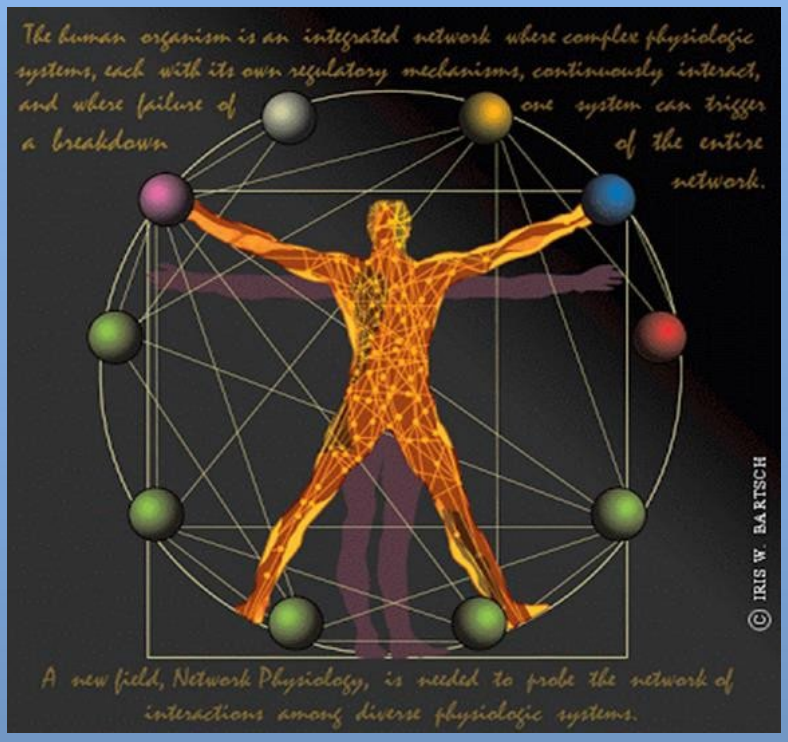
Fourth International Summer Institute on Network Physiology (ISINP)

Lake Como School of Advanced Studies, 27 July – 1 August, 2025



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Frontiers in Network Physiology

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Welcome to ISINP 2025

The human organism is an integrated network, where multi-component organ systems, each with its own regulatory mechanism, continuously interact to coordinate their function. Physiological interactions occur at multiple levels and spatiotemporal scales to produce distinct physiologic states, e.g. wake and sleep, consciousness and unconsciousness. Disrupting organ communications can lead to dysfunction of individual systems or collapse of the entire organism, as observed under clinical conditions such as sepsis, coma and multiple organ failure. Yet, despite its importance to basic physiologic functions, the nature of interactions between diverse organ systems and sub-systems, and their collective role in maintaining health is not known. Further, there are no adequate analytic tools and theoretical framework to probe these interactions.

Despite the vast progress and achievements in systems biology and integrative physiology in the last decades, we do not know the basic principles and mechanisms through which diverse physiological systems and organs dynamically interact and integrate their functions to generate a variety of physiologic states at theorganism level.

The emerging new interdisciplinary field of *Network Physiology* aims to address this fundamental question. In addition to defining health and disease through structural, dynamical and regulatory changes in individual physiological systems, the new conceptual framework of Network Physiology focuses on the coordination and network interactions among diverse organ systems and sub-systems as a hallmark of physiologic state and function.

Novel concepts and approaches derived from recent advances in network theory, coupled dynamical systems,statistical and computational physics, signal processing and biological engineering show promise to provide new insights into the complexity of physiological structure and function in health and disease, bridging sub- cellular level signaling with inter-cellular interactions and communications among integrated organ systems and sub-systems. These advances form first building blocks in the methodological formalism and theoreticalframework necessary to address the problems and challenges in the field of Network Physiology.

This international summer institute will integrate empirical and theoretical knowledge across disciplines with the aim to understand in different contexts, from extensive data analysis and modeling approaches to clinical practice, how diverse physiological systems and sub-systems dynamically interact to produce health and disease.

This will be an interactive event with lectures ranging from physics and applied mathematics to neuroscience, physiology and medicine, covering a range of physiological systems from the cellular to the organ level, and will discuss the challenges, current frontiers and future developments in the emerging field of Network Physiology.

Presentations on basic research will be combined with lectures by leading physiologists and clinicians, working with large medical and ICU databases.

This International Summer Institute aims to provide a relaxed setting where lecturers and attendees interact throughout the course of the week. We have speakers, prominent leaders in their respective fields, who will present new directions in the theory of networks of dynamical systems, brain and neuronal dynamics, tissues and cell assemblies, pair-wise and network interactions of organ systems and sub-systems, and advanced methods from non-linear dynamics and synchronization phenomena.

The Summer Institute will address a diverse audience of graduate students, postdoctoral fellows, research scientists and faculty across a broad range of disciplines and fields from physics, applied mathematics and biomedical engineering to neuroscience, physiology and clinical medicine.

We look forward to a product meeting in Como!

Plamen Ch. Ivanov, Ph.D., D.Sc.

Director, Keck Laboratory for Network Physiology, Boston University
Director, Fourth International Summer Institute on Network Physiology (ISINP)
Field Chief Editor, Frontiers in Network Physiology

26 July 2025, Como, Italy

Sponsors

Frontiers in Network Physiology

is the only journal publishing rigorously peer-reviewed research dedicated to furthering our understanding of network physiology. This multidisciplinary, open-access journal is at the forefront of communicating impactful scientific discoveries to academics and clinicians.

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Fondazione Alessandro Volta

"The Foundation makes available the energy of Alessandro Volta for the City of Como, to promote science and culture at all levels, to enhance human capital, to put man back at the center and create a useful foundation for the concrete development of the city."

W.M. Keck Foundation

The ISINP international institute builds on groundbreaking research at the Boston University Keck Laboratory for Network Physiology that pioneered the new field of Network Physiology. This has been made possible by support from the W.M. Keck Foundation.

School Director

Plamen Ch. Ivanov

Professor Ivanov, PhD, DSc, is Director of the Keck Laboratory for Network Physiology at Boston University.

He has introduced innovative ways to analyze and model physiological systems, adapting and developing concepts and methods from modern statistical physics, nonlinear dynamics and networks theory. He has investigated the complex dynamics and underlying control mechanisms of a range of physiological systems, including studies on cardiac and respiratory dynamics, sleep-stage transitions, circadian rhythms, locomotion and brain dynamics, and has uncovered basic laws of physiologic regulation.

Professor Ivanov has pioneered the study of dynamic network interactions of physiological and organ systems. He is the originator and founder of the interdisciplinary field of Network Physiology. His current work focuses on developing methods of data analysis to investigate interactions among diverse organ systems and build a theoretical framework to understand how physiologic states and functions at the organism level emerge out of organ network interactions, and how diverse organ systems coordinate and integrate their functions to produce health or disease. His work lays the foundation of the Human Physiolome, a new type of BigData, containing streams of continuously recorded, high frequency, synchronized physiological signals under various states and clinical conditions, with an associated Atlas of network maps representing interactions among physiological systems at different levels in the human organism.

His discoveries have been broadly featured in the Media, including Scientific American, Science News, Nature Science Update, New Scientist, Physics World, Nature Medicine Research Highlights, Washington Post, Futurity Magazine, The Boston Globe.

Professor Ivanov is the Field Chief Editor of the journal Frontiers in Network Physiology. He is the founding Director of the International Summer Institute on Network Physiology (ISINP), Lake Como School of Advanced Study. Professor Ivanov is one of nine founding members of PhysioNet — the first NIH-sponsored data sharing research resource with millions of users and data downloads. He has served as editorial and advisory board member for several leading journals, including New Journal of Physics, EPL (Europhysics Letters), EPJ Nonlinear Biomedical Physics, Journal of Biological Physics (JOBP), Physiological Measurement and Frontiers in Physiology. His research has been funded by NIH, the W.M. Keck Foundation, the Office of Naval Research (ONR) and the US-Israel Binational Science Foundation (BSF).

For his pioneering applications of statistical physics and nonlinear dynamics to physiology and biomedicine, and for uncovering fundamental scaling and multifractal properties, self-organized criticality, sleep- and circadian-related phase transitions in physiologic dynamics, Professor Ivanov was elected Fellow of the American Physical Society in 2010. He is recipient of the Sustained Research Excellence Award of the Biomedical Research Institute, Brigham and Women's Hospital, Harvard Medical School (2009-2011); the Georgi Nadjakov Medal of the Bulgarian Academy of Sciences (2012), the Pythagoras (Pitagor) Prize for high achievements in interdisciplinary research bestowed by the President of Bulgaria (2014), and $ 1 milion W.M. Keck Foundation Award (2015).

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Organizing Committee

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Speakers

Krasimira Tsaneva-Atanasova

Professor Krasimira Tsaneva-Atanasova is Vice-President and Deputy Vice-Chancellor for Research and Impact and Professor of Mathematics for Healthcare. She is an internationally recognised expert in mathematical modelling, data analysis and applications of dynamical systems theory to addressing biomedical and health challenges. As Vice-President and Deputy Vice-Chancellor (Research and Impact), Professor Tsaneva-Atanasova oversees a total research portfolio of over £500 million and leads the research and impact strategy for the University. Her overarching responsibilities include our preparation and submission for the Research Excellence Framework in 2029; interdisciplinary institutes, networks and centres; strategic leadership of our Doctoral College, the University Ethics Committee and the Research and Impact Executive Committee; and ensuring our research is utilised and impacts positively on the wider world. Professor Tsaneva-Atanasova represents the University externally via a number of research-related groups including GW4, our regional alliance of the Universities of Bristol, Bath, Cardiff and Exeter, and as Chair of the UUKi Global Research and Innovation Network (GRIN) (2024 – 2025). Currently she also serves as a member of the BBSRC Commitee E, the UKRI Talent Panel College and the EPSRC Peer Review College. Among other positions, she is Director of the EPSRC Hub for Quantitative Modelling in Healthcare, an associate member (since February 2020) of the Bulgarian Academy of Sciences, Institute of Biophysics and Biomedical Engineering, Bioinformatics and Mathematical Modelling and a Fellow of the Institute of Mathematics and its Applications (since April 2020). She held a Hans Fischer Senior Fellowship at the Technical University of Munich, Institute for Advanced Study (2019-2023). Professor Tsaneva-Atanasova's research addresses open questions in Health and Life Sciences by means of mathematical modelling and analysis including advanced data analytics. The ultimate goal is to be able to propose novel applications of mathematics to enable the development of quantitative methods for healthcare and healthcare technologies. She is an expert in data-informed biophysical modelling with particular focus on biomedical and healthcare applications. She has a long-standing interest in developing patient-specific (personalised) computational approaches to complex disease prognosis and progression to inform clinical decision making. This is reflected in her experience in modelling neuroendocrine, neuropsychiatric, and chronic respiratory disorders.

Natàlia Balagué

Professor of Exercise Physiology at INEFC (University of Barcelona) and coordinator of the Complex Systems and Sport Research Group. She participates in education programs addressed to professional soccer coaches under the auspices of Football Club Barcelona and the Spanish Soccer Federation. Her research applies complex systems tools to biobehavioural sciences with particular focus on sport related phenomena. Her main aim is to understand the general principles of adaptive behavioral and experiential dynamics of human beings. She has published numerous works and is co-author of the first books applying complex systems science to sport. She founded the international conference Complex Systems in Sport, has been member of the scientific committee of the European College of Sport Science and is Editor-in-chief of Frontiers in Network Physiology of Exercise.

Ronny P. Bartsch

Ronny Bartsch studied physics in Konstanz, Germany, and at Bar-Ilan University, Israel, where he received his Ph.D. in 2009. From 2008 to 2013, he was a post-doctoral fellow at the Division of Sleep Medicine, Harvard Medical School, and then joined the faculty as an Instructor in Medicine. In April 2014, Ronny became a Research Assistant Professor in the Physics Department at Boston University. Later that year, he became a faculty member at the Department of Physics at Bar-Ilan University, where he has been an Associate Professor since October 2020. Ronny's research interests include investigating physiologic dynamics, sleep regulation, and how physiologic transitions affect the networked interactions between organ systems. He received the 2012 Young Investigator of the Year Prize from the German Society of Sleep Medicine and prestigious fellowships from Germany (DAAD, 2010-2012) and the European Union (Marie Curie, 2014-2016). Since 2021, he has been on the editorial board of Physiological Measurement and Frontiers in Network Physiology.

Thomas Beyer

Thomas Beyer holds a PhD in Physics and is co-developer of combined PET/CT imaging systems. He has a background in research and project management in academia and imaging industry. Thomas graduated in Physics from the Leipzig University (Germany) and got his PhD in Medical Physics from Surrey University (UK). During his US-based studies he became involved in the development and clinical testing of the first PET/CT prototype (1992-2000) before joining Siemens/CTI PET Systems as an International PET/CT specialist. In 2002 he became a Research Associate in Nuclear Medicine and Radiology and PET/CT project manager at Essen University Hospital (Germany). In 2006 he became Teaching Professor (Priv.-Doz.) for Experimental Nuclear Medicine at Essen, and joined timaq medical imaging Inc, a Zurich-based Imaging CRO. In 2007 Thomas moved to Philips Medical Systems as International Manager Clinical Science Nuclear Medicine. In 2008 he set up a Zurich-based consulting company for expert advise in cross-modality imaging and applications. He was appointed full professor of Physics of Medical Imaging at the Medical University of Vienna in March 2013. Since then, he has co-founded two University spin-offs and proliferated collaborative research in whole-body and total-body PET/CT imaging with a focus on multi-organ interactions in health and disease. Thomas is a member of various national and international Medicine organizations, a founding member of the European Association of Nuclear Medicine (EANM) Physics Committee, the European Society of Hybrid Imaging and past Head of the New Technology working group at the Association of Imaging Producers and Equipment Suppliers (AIPES).

Paul Bogdan

Paul Bogdan is the Jack Munushian Early Career Chair and Associate Professor in the Ming Hsieh Department of Electrical and Computer Engineering at University of Southern California. He received his Ph.D. degree in Electrical & Computer Engineering at Carnegie Mellon University. His work has been recognized with a number of honors and distinctions, including the 2021 DoD Trusted Artificial Intelligence (TAI) Challenge award, the USC Stevens Center 2021 Technology Advancement Award for the first AI framework for SARS-CoV-2 vaccine design, the 2019 Defense Advanced Research Projects Agency

(DARPA) Director's Fellowship award, the 2018 IEEE CEDA Ernest S. Kuh Early Career Award, the 2017 DARPA Young Faculty Award, the 2017 Okawa Foundation Award, the 2015 National Science Foundation (NSF) CAREER award, the 2012 A.G. Jordan Award from Carnegie Mellon University for an outstanding Ph.D. thesis and service, and several best paper awards. His research interests include cyber-physical systems, computational cognitive neuroscience tools for deciphering biological intelligence, network physiology, quantification of the degree of trustworthiness and self-optimization of AI systems, machine learning techniques for complex multimodal data, control of complex time-varying networks, modeling and analysis of biological systems and swarms, control of multi-fractal characteristics, performance analysis and design methodologies for heterogeneous manycore systems.

Luca Faes

Luca Faes is Professor of Biomedical Engineering at the University of Palermo, Italy. He obtained his MS and PhD in Electronic Engineering at the University of Padova (1998) and at the University of Trento (2003), Italy, respectively. He was with the Dept. of Physics (2004-2013) and the BIOtech Center (2008-2013) of the University of Trento, and with the Bruno Kessler Foundation (FBK, Trento, 2013-2017). He has been visiting scientist at the State University of New York (2007), Worcester Polytechnic Institute (MA, USA, 2010), University of Gent (Belgium, 2013), University of Minas Gerais (Brazil, 2015), and Boston University (MA, USA, 2016). He is Senior Member of the IEEE, and member of the IEEE Engineering in Medicine and Biology Society (IEEE-EMBS), for which he serves in the Technical Committee of Biomedical Signal Processing and regularly organizes symposia and invited sessions at the Annual EMBC Conference. He is member of the European Study Group on Cardiovascular Oscillations (ESGCO), and was organizer and Program Chair of the 8th ESGCO conference (Trento, Italy, 2014). He is Specialty Chief Editor of the Section "Information Theory" of Frontiers in Network Physiology, and serves as editor at several peer-review journals, including Entropy, Frontiers in Physiology, and Computational and Mathematical Methods in Medicine. His teaching activity includes Biosensors, Biomedical Devices and Statistical Analysis of Biomedical Signals: His research activity is focused on the development of methods for multivariate time series analysis and system modeling, with applications to cardiovascular neuroscience, cardiac arrhythmias, brain connectivity and network physiology. Within these fields, he has authored eight book chapters and more than 200 peer-reviewed publications, receiving more than 5700 citations (h-index: 50; font: Scholar).

Flavio H. Fenton

Flavio H. Fenton is a Professor in the School of Physics at Georgia Tech, specializing in nonlinear dynamics and chaos, with focus on their applications to biological and physiological systems. He is deeply involved in computational physics and high-performance computing. His research uses an equally combined approach of theoretical work, experiments, and computer simulations involving network-based approaches. Dr. Fenton has been recognized as a Fellow of the American Physical Society for his groundbreaking contributions to the understanding of the nonlinear dynamics of cardiac arrhythmias. He has also received the prestigious Douglas P. Zipes Lectureship Award from the Heart Rhythm Society. Dr.

Fenton's work has been supported by grants from the National Science Foundation (NSF), National Institutes of Health (NIH), and the American Heart Association (AHA). In addition to his research, Dr. Fenton is passionate about teaching and outreach. He has designed and delivered numerous graduate and undergraduate workshops and has received several teaching awards.

Susanna Gordleeva

Susanna Gordleeva received the M.Sc. and Ph.D. degrees in physics and mathematics from the Lobachevsky State University of Nizhny Novgorod, Nizhny Novgorod, Russia, in 2010 and 2015, respectively, and the D.Sc. (Habilitation) degree in biophysics from the Institute of Theoretical and Experimental Biophysics RAS, Pushchino, Russia, in 2022. Since 2015, she has been serving as an Assistant Professor in computational neuroscience at Lobachevsky State University, Nizhny Novgorod. In 2021, she became the Head of the Laboratory of Neurodynamics and Cognitive Technologies, Institute of Neuroscience, Lobachevsky State University. In 2022, she was appointed as a Professor in computational neuroscience. She is currently a Professor at the Department of Neurotechnologies and Director of the Neuroscience Research Institute at the Lobachevsky State University. Her research interests encompass theoretical neuroscience, computational neurobiology, neurotechnology, and mathematical biology. In 2023, she received the Russian Presidential Prize for Young Scientists in the field of Science and Innovation for her development of neuromorphic AI technologies.

Nandu Goswami

Dr Goswami is a medical doctor, with a PhD in cardiovascular/integrative Physiology. Dr Goswami's special research interests are in the field of cardiovascular regulation, cerebral blood flow, orthostatic intolerance and the effects of bedrest induced deconditioning. As orthostatic intolerance is a clinical problem as well as a major problem in spaceflight, Dr Goswami combines clinical research related to syncope, autonomic function and falls with spaceflight research. He has extensive experience in the usage of lower body negative pressure (LBNP). His expertise also includes vascular function assessments in health and disease. He is professor of Physiology and the co-director of the Center for Space and Aviation Health at the Mohammed Bin Rashid University of Medicine (MBRU) at Dubai, Dubai Health, and is also the head of the research unit "Gravitational Physiology and Medicine" at the Medical University of Graz, Austria. He has published over 160 papers in the field of cardiovascular system and vascular function assessments in health and diseases. Dr Goswami is a PI on several Mohammed Bin Rashid Space Center (MBRSC) and European Space Agency (ESA) approved projects. Dr Goswami is a member of the ESA bedrest scientific committee, a full member of the international Academy of Astronautics (IAA) and immediate past-president of the Austrian Physiological Society.

Sallie Gregson

Sallie Gregson is the Journal Manager for Frontiers in Network Physiology, the only scientific journal dedicated to the field. Sallie has over 10 years experience in managing journals and supporting researchers

to publish their work. At Frontiers she is responsible for the development of Frontiers in Network Physiology, which was only launched in 2021 and has already been indexed by Web of Science, Scopus, and PubMed Central. Frontiers is a leading research publisher, Frontiers journals provide a trusted open access platform for well-established and emerging research communities. Directed by experienced chief editors, they ensure a continuous stream of high quality, openly available research in their field.

Shlomo Havlin

Professor Shlomo Havlin made fundamental contributions to the physics of complex systems and statistical physics. These discoveries have impacted many other fields such as medicine, biology, geophysics, and more. He has over 70,000 citations on ISI Web of Science and over 120,000 in Google Scholar. His h-index is 118 (151) in Web of Science (Google Scholar). Havlin has been a Highly Cited Scientist in the last 3 years. He is a professor in the Physics Department at Bar-Ilan University. He received his Ph.D. in 1972 from Bar Ilan University and he has been a professor at BIU since 1984. Also, between the years of 1999 – 2001 he was the Dean of the Faculty of Exact Sciences and from 1996 to 1999 he was the President of the Israel Physical Society. Havlin won the Israel Prize in Physics (2018), Order of the Star of Italy, President of Italy (2017), the Rothschild Prize for Physical and Chemical Sciences, Israel (2014), the Lilienfeld Prize for "a most outstanding contribution to physics", APS, USA (2010), the Humboldt Senior Award, Germany (2006), the Distinguished Scientist Award, Chinese Academy of Sciences (2017), the Weizmann Prize for Exact Sciences, Israel (2009), the Nicholson Medal, American Physical Society, USA (2006) and many others. His main research interests are in the fields of statistical physics and complex networks, with a focus on interdependent networks, cascading failures, networks of networks and their implications to real world problems. The real-world systems he studied include physiology, climate, infrastructures, finance, traffic, earthquakes and others.

James W. Holsapple

James Holsapple is the Chair of the Department of Neurological Surgery at Boston University School of Medicine and Chief of Neurological Surgery at Boston Medical Center. He is a graduate of the University of Kansas School of Medicine. Dr. Holsapple completed residency training in neurological surgery at SUNY Syracuse where he also served as an intern in general surgery and participated in a NRSA research training fellowship in neuroscience. His research interests include primate motor system anatomy, non-vesicular mechanisms of synaptic acetylcholine storage and secretion, scaling effects of visual stimuli in primate V1, and most recently cerebral blood flow autoregulation and development of non-invasive measurements of intracranial pressure, blood flow, and compliance. Dr. Holsapple is the residency program director for the Beth Israel Deaconess Medical Center/Boston Medical Center training program in neurological surgery. He also serves as the program director of the undergraduate summer program in neuroscience (SPIN) at Boston University School of Medicine.

Yaron Ilan

Dr. Yaron Ilan is a Professor of Medicine at the Faculty of Medicine of the Hebrew University and the

Chairman of the Department of Medicine at the Hadassah Medical Center in Jerusalem. Dr. Ilan served as the Vice Dean of the Hebrew University-Hadassah Medical School. Dr. Ilan was a Visiting Professor at Harvard University, focusing on innovative oral immunotherapies and the relationship between the brain and gut. Dr. Ilan's primary research areas include the development of artificial intelligence-based algorithms for healthcare, immunomodulatory therapies for fatty liver disease, diabetes, and inflammatory bowel diseases, as well as drugs targeting primary liver cancer. He holds over 50 patents for innovative discoveries and has authored over 350 peer-reviewed articles and two books. His book, "Improve with Noise," has achieved bestseller status on Amazon. Dr. Ilan is the inventor of various drugs, medical devices, and AI-based algorithms developed in collaboration with several pharmaceutical companies. Many of his innovations have successfully reached the clinical market. He is also the founder of several companies and serves as a medical director and advisor for various biotech firms. Dr. Ilan's research in network physiology focuses on using biological noise to improve the effectiveness and functionality of complex systems. He has developed the concept of constrained disorder, which characterizes complex systems by their inherent variability. This variability is limited by dynamic boundaries that help regulate the noise range for optimal adaptation to internal and external disturbances. This work created the Constrained Disorder Principle and a second-generation artificial intelligence platform. Algorithms based on this principle integrate physiological and pathological variability patterns into therapeutic regimens to address system malfunctions. This platform helps patients overcome the unresponsiveness of target organs to treatments by utilizing artificial intelligence processes that take advantage of biological noise.

Plamen Ch. Ivanov

Professor Ivanov, PhD, DSc, is Director of the Keck Laboratory for Network Physiology at Boston University. He has introduced innovative ways of analyzing and modeling physiologic systems, adapting and developing concepts and methods from modern statistical physics and nonlinear dynamics. He has investigated the complex dynamics and underlying control mechanisms of a range of physiological systems, including studies on cardiac and respiratory dynamics, sleep-stage transitions, circadian rhythms, locomotion and brain dynamics, and has uncovered basic laws of physiologic regulation. He is the originator and founder of the multidisciplinary field of Network Physiology, to address the fundamental question of how diverse organ systems and sub-systems in the human body interact as a network and continuously coordinate, synchronize and integrate their functions to produce health and disease. Prof. Ivanov has published more than 180 peer-reviewed articles, books and book chapters. He is one of the nine founding members of PhysioNet, an NIH sponsored data sharing research resource. His research has been funded by the W. M. Keck Foundation, NIH, Office of Naval Research (ONR) and the US-Israel Binational Science Foundation (BSF). For his discoveries and achievements, Prof. Ivanov was elected Fellow of the American Physical Society in 2010. He is recipient of the Sustained Research Excellence Award (2009-2011) of the Biomedical Research Institute, Brigham and Women's Hospital, Harvard Medical School; of the Georgi Nadjakov Medal, Bulgarian Academy of Sciences (2012), and of the Pythagoras Award for significant achievements in interdisciplinary research (2014). He served on several Editorial and Advisory Boards, including EPL (Europhysics Letters), EPJ Nonlinear Biomedical Physics, Journal of

Biological Physics (JOBP), Frontiers in Fractal Physiology, Physiological Measurement. Professor Ivanov is the Field Chief Editor of the journal Frontiers in Network Physiology. He is the founding Director of the International Summer Institute on Network Physiology (ISINP), Lake Como School of Advanced Study. Keck Lab Network Physiology website: https://sites.google.com/site/labnetworkphysiology/home

Viktor Jirsa

Viktor Jirsa is Director of Research at the Centre National de la Recherche Scientifique (CNRS) in France. He serves as Director of the Inserm Institut de Neurosciences des Systèmes (UMR1106 Inserm) at Aix-Marseille University and Chief Science Officer of the federated European digital neuroscience infrastructure EBRAINS (https://ebrains.eu). 1999 to 2005 he served as faculty member at the Center for Complex Systems and Brain Sciences, as well as the Physics Department of Florida Atlantic University. He joined the CNRS in Marseille, France in 2006 and co-founded the Institut de Neurosciences des Systèmes (INS), UMR1106 Inserm, Aix-Marseille University in 2012. Today INS is a research institute comprising 150 researchers and faculty of various disciplines including theoretical, cognitive and clinical neurosciences. INS is recognized as one of the leading centers in digital health in France. Since the late 90s Dr. Jirsa has made pioneering contributions to the understanding of how network structure constrains the emergence of brain activity using methods from nonlinear dynamic system theory and computational neuroscience. He leads the neuroinformatics platform The Virtual Brain (www.thevirtualbrain.org) with a focus on applications of digital twins in personalized medicine. He is Scientific Director of the French large-scale multi-site clinical trial EPINOV testing Virtual Brain technologies in Epilepsy surgery with 400 prospective patients. Dr. Jirsa has been awarded several international and national awards for his research including the Early Career Distinguished Scholar Award (NASPSPA, 2004), the Francois Erbsmann Prize in 2001, the first HBP Innovation prize (2021) and Grand Prix de Recherche en Provence (2018). He is invited regularly to major international conferences and has given more than 200 invited lectures, including various keynote addresses and plenary lectures. Dr. Jirsa serves on multiple Editorial and Scientific Advisory Boards and has published more than 200 scientific articles and book chapters with more than 20,000 citations, as well as co-edited several books including the Handbook of Brain Connectivity.

Boris P. Kovatchev

Boris Kovatchev, Ph.D. is the Madge M Jones Professor of Diabetes at the University of Virginia School of Medicine, Adjunct Professor at the School of Data Science, and the founding Director of the UVA Center for Diabetes Technology. Kovatchev has 32-year track record in data analysis, modeling, biosimulation, and algorithm development. He is Principal Investigator of several projects dedicated to diabetes data science and the development of automated insulin delivery (AID) systems, known as the “artificial pancreas.” His research team has been involved in the AID field, since its beginning back in 2005. In 2008, Kovatchev and colleagues introduced the first (and so far only) simulator of the human metabolic system accepted by the FDA as a substitute to animal trials. Since then AID algorithms are being developed and evaluated fast and cost effectively in silico – animal trials have been abandoned – and this accelerated the development of AID by years. In 2011, his team introduced the first wearable AID system – UVA’s DiAs (Diabetes

Assistant) – which enabled the earliest outpatient AID trials in the U.S. and Europe. During 2016-2020, Kovatchev led the multi-center NIH/NIDDK International Diabetes Closed-Loop (iDCL) Trial. This study resulted in the FDA approval for clinical use of a new AID system – Control-IQ (Tandem Diabetes Care) – which is based on a control algorithm developed at UVA. Control-IQ is now used by nearly 500,000 people with type 1 diabetes in the U.S. and 25 other countries. Today, AID is the standard of care for type 1 diabetes. Each AID user collects a data vector every 5 minutes, for life, rapidly turning the treatment of diabetes into a Data Science problem. As a result, in 2024, Kovatchev's team introduced a new class of AID algorithms – a Neural-Net Artificial Pancreas that is entirely based on data-driven machine learning methods, instead of traditional differential-equation models. The Neural-Net Artificial Pancreas became the first "black box" insulin controller approved by the FDA to automatically regulate in real time the blood sugar levels of people with diabetes. To date, two clinical trials confirmed its effectiveness, opening the AID field to new Artificial Intelligence applications. Kovatchev is author of over 240 peer-reviewed publications cited 37,000 times and holds over 40 U.S. and international patents. For his translational work, he was named the University of Virginia's Edlich-Henderson Inventor of the Year, and was elected Fellow of the U.S. National Academy of Inventors.

Jürgen Kurths

Jürgen Kurths is a mathematician and a physicist. He received the Ph.D.degree from the GDR Academy of Sciences and his Dr. habil. from the university of Rostock.. He was a Full Professor with the University of Potsdam, from 1994 to 2008. He has been a Professor of Nonlinear Dynamics at the Humboldt University, Berlin, and the Chair of the Research Domain Complexity Science of the Potsdam Institute for Climate Impact Research, since 2008. He is a Fellow of the American Physical Society, of the Royal Society of Edinburgh and of the Network Science Society and a member of the Academia Europaea. He received an Alexander von Humboldt Research Award in 2005 and 2021, the Richardson award from the European Geoscience Union in 2013, the Lagrange Award in 2022, and the SigmaPhi Prize of the European Physical Society in 2023 (together with Nobel Prize winner Michael Kosterlitz). He is Chapman Chair of the university of Fairbanks and Distinguished Adjunct Professor at KENTECH (Korea). He was the German Speaker of the International Research and Training Group (IRTG 1740): Dynamical and Transport Phenomena on Complex Networks (Germany and Brazil, DFG&FAPESP), is a highly-cited researcher (Clarivate) since 2017 without interruptions and got eight Honorary Doctorates and Honorary Professorships. He is Editor-in-chief of CHAOS – A Journal of Nonlinear Science and editor of further journals. The primary research interests of Jürgen Kurths include complex systems science, in particular synchronization, complex networks, extreme events and time series analysis and its applications in Earth Sciences, Physiology, engineering and others.

Ying-Cheng Lai

Ying-Cheng Lai is a Regents Professor (the highest possible faculty award in Arizona), the ISS Endowed Professor of Electrical Engineering, and a Professor of Physics at Arizona State University. He received the Presidential Early Career Award for Scientists and Engineers (PECASE) award in 1997 from the White

House and has been a Fellow of the American Physical Society since 1999. In 2016, he was selected by the Department of Defense for the Vannevar Bush Faculty Fellowship. In 2018, he was elected as a Foreign Member of the National Academy of Science and Letters of Scotland. In 2020, he was elected as a Foreign Member of Academia Europaea (The Academy of Europe) and as a Fellow of the American Association for the Advancement of Science (AAAS). His current research interests are Machine Learning as applied to Complex Physical Systems, Nonlinear Dynamics, Complex Networks, Mathematical Biology, Quantum Chaos, Data Analysis and Signal Processing.

Helene M. Langevin

Dr. Helene Langevin holds an M.D. degree from McGill University, Montreal. She completed a postdoctoral research fellowship in neurochemistry at the MRC Neurochemical Pharmacology Unit in Cambridge, England, and a residency in internal medicine and fellowship in endocrinology and metabolism at The Johns Hopkins Hospital, Baltimore. In November 2018, Dr. Langevin was sworn in as director of the National Center for Complementary and Integrative Health (NCCIH). Prior to her arrival, she was director of the Osher Center for Integrative Medicine, jointly based at Brigham and Women's Hospital and Harvard Medical School, Boston, and professor in residence of medicine at Harvard Medical School. She also was a visiting professor of neurological sciences at the University of Vermont Larner College of Medicine, Burlington. Dr. Langevin is interested in exploring how to keep connective tissue flexible and free from pain, slow aging, and increase the health of the whole body. Connective tissue is a body-wide network that connects all its systems and parts, making it important for the integrated functioning of the whole body. Dr. Langevin's previous work has focused on the role of connective tissue in chronic pain and the mechanisms of acupuncture, manual, and movement-based therapies. Her goal at NIDCR is to understand how mechanical forces may help connective tissue stay strong and flexible, allow for successful healing after injury, reduce inflammation, and prevent cancer.

Klaus Lehnertz

Professor Lehnertz, PhD, is a Physicist and Director of the Neurophysics Group at the Department of Epileptology at Bonn University Medical Center. In addition, he is Co-Director of the Interdisciplinary Centre for Complex Systems and an affiliated member of the Helmholtz-Institute for Radiation and Nuclear Physics at Bonn University. He is Co-initiator of the International Seizure Prediction Group, which brings together researchers from a wide range of backgrounds including epileptology, neurosurgery, neurosciences, physics, mathematics, computer science, and engineering to deepen scientific and medical understanding of epilepsy and to develop new diagnosis, treatment and intervention options for patients with epilepsy. For more than two decades, his research group has been developing methods of data analysis and a theoretical framework to understand how brain sub-systems dynamically interact and coordinate functions under physiological and pathophysiological activities. His research interests include nonlinear dynamics, complex networks, statistical physics, neurophysics, computational physics, physics of imaging, medical physics, and epilepsy. He is the author of more than 200 original publications in international peer-reviewed journals, reviews, book chapters, and books.

Joseph Loscalzo

Dr. Loscalzo is the Samuel A. Levine Professor of Medicine and the Hersey Distinguished Professor of the Theory and Practice of Medicine at Harvard Medical School as well as Physician-in-Chief Emeritus and former Chair of the Department of Medicine at Brigham and Women's Hospital. He is a summa cum laude graduate of the University of Pennsylvania, where he also obtained his M.D. and Ph.D. in biochemistry. He trained in internal medicine and cardiology at Brigham and Women's Hospital, after which he was appointed to the hospital staff and Harvard Medical School faculty. After ten years on the Harvard faculty, Dr. Loscalzo moved to Boston University as Director of the Whitaker Cardiovascular Institute and Chief of Cardiology; in 1997, he was appointed Wade Professor and Chair of the Department of Medicine. In July, 2005, he returned to the Harvard faculty. Author of over 1,200 articles, 54 books, and 33 patents, he is internationally recognized for his work on the vascular biology of nitric oxide, redox biology, systems pathobiology, and network medicine, a field he helped establish. He has received many awards including election to the American Society for Clinical Investigation, the Association of American Physicians, the American Association for the Advancement of Science, National Academy of Medicine, the American Academy of Arts and Sciences, and the Académie Royale de Médecine de Belgique. He holds three honorary degrees. He is the recipient of a MERIT Award from the National Institutes of Health, the Research Achievement Award and a Merit Award from the American Heart Association, the Outstanding Investigator Prize from the International Society for Heart Research, the William Silen Lifetime Achievement Award in Mentoring from Harvard Medical School, and the International Pericle d'Oro Prize. He is a past member of the Advisory Council of the National Heart, Lung, and Blood Institute, and of the Council of Councils of the National Institutes of Health; has served on several NIH study sections and editorial boards, including the New England Journal of Medicine, and as Editor-in-Chief of Circulation; and is currently Editor-at-Large for the New England Journal of Medicine, a senior editor of **Harrison's Principles of Internal Medicine**, and the lead editor of **Network Medicine: Complex Systems in Human Disease and Therapeutics.**

Alan Macy

Alan Macy is currently the Research and Development Director of Biopac Systems, Inc. In 1984, shortly after graduating MSEE from UCSB, Macy co-founded Biopac Systems. Biopac developed and manufactured novel, life-science oriented, hardware and software-based, data acquisition peripherals for the original Macintosh computer, and shortly thereafter, the first Microsoft Windows computers. Since then, Biopac has expanded worldwide and primarily serves the academic research and education community that focuses on human physiology and psychophysiology. Biopac data acquisition and analysis systems are used in nearly all Universities around the world. Biopac's physiology data acquisition and analysis systems have been referenced and utilized in over 53,000 academic research publications and in over 7500 patents. Macy designs data collection and analysis systems, used by researchers in the life sciences, that help identify meaningful interpretations from signals produced by life processes. Macy orients to analog electronics, sensor design and digital signal processing. Trained in electrical and biomedical engineering

and physiology, with over 40 years of product development experience, Macy is currently focusing on network physiology, psychophysiology, emotional and motivational state measures, magnetic resonance imaging-based sensors and augmented/virtual reality investigations. Macy presents in the areas of network physiology, affect and emotion. Macy's talk "Beauty and the Origins of Electrophysiology, Telecommunications and the Global Theater" has been delivered at TEDx Hong Kong, Google, UCSB, Dalhousie and others. As an applied science artist, Macy focuses on technological extensions of the human nervous system and specializes in the creation of cybernated art, interactive sculpture and environments. Macy is a visiting scholar and research specialist at UCSB's Psychological and Brain Sciences - Memory, Emotion, Thought, Awareness (META) Lab. Macy is also the founder of the Santa Barbara Center for Art, Science and Technology (SBCAST), a live-work arts residency in Santa Barbara, CA. This residence / laboratory provides infrastructure for emerging cooperative working models. SBCAST has relationships with the UCSB Media Arts and Technology Program, UCSB Neuroscience and UCSB Psychology to provide working development space and laboratory resources. Macy is also the founder of PIVOT, a Santa Barbara based incubation and development working studio for artists and scientists that's presently in building development. Alan Macy website: www.alanmacy.com

Rosario Mantegna

Rosario N. Mantegna is professor of Applied Physics at Palermo University, Palermo, Italy and external faculty member of the Complexity Science Hub, Vienna, Austria. He was professor of Economics and Network Science at Central European University, Budapest, Hungary and honorary professor of Computer Science at University College London, London, UK. He is associated with the UCL Centre for Blockchain Technologies. His research concerns interdisciplinary applications of statistical physics. In 1995 he investigated the statistical properties of coding and non-coding regions of complete chromosomes and complete genomes with methods inspired by statistical physics, stochastic processes, and information theory. He is a leading expert in Lévy stable processes. He co-introduced the Truncated Lévy processes and devised the fastest algorithm known to simulate symmetrical Lévy processes. He was a pioneer in the field of econophysics. In 1991 he wrote the first econophysics paper and in 1999, he coauthored the first book on econophysics. The same year, he published the first paper on similarity-based networks proposing to use the minimum spanning tree as a filtering tool in multivariate complex systems. The methods of information filtering introduced by him and his collaborators are widely used by academicians and applied scientists in the analysis and modeling of complex systems. In 1999, he founded the Observatory of Complex Systems, a research group of Palermo University. In 2011, his team introduced the concept of statistically validated networks to highlight links of a projected network that aren't compatible with a null hypothesis assuming heterogeneity of the elements. His recent interests of research concerns (a) statistical validation of hyperlinks, (b) co-morbidity networks, (c) higher order processes and structures in neuroscience, (d) investment decisions of single legal entities, and (e) underlying patterns of high frequency trading. Mantegna has participated in several national and international research projects contributing to the management and coordination of them. Examples are the COST P10 action "Physics of Risk", the GIACS (General Integration of the Applications of Complexity in Science) coordination action of

the EU, the CRISIs project of EU, and the INET project on systemic risk interlinkages. In 2008, within the GIACS coordination action, he promoted the “Jerusalem Declaration on Data Access, Use and Dissemination for Scientific Research”. Currently he is the PI of two national Italian research projects (i) PRIN 2022 PNRR project “Higher-order complex systems modeling for personalized medicine”, and (ii) PNRR MNESYS cascade project “Network science for neuroscience”.

J. Randall Moorman

Randall Moorman, M.D., is Professor of Medicine, Physiology, and Biomedical Engineering at the University of Virginia where he is a clinical cardiologist and founding Director of the UVa Center for Advanced Medical Analytics. He completed his undergraduate and medical degrees at the University of Mississippi, did clinical training at Duke Hospital where he was Chief Medical Resident, and undertook basic science research training at Baylor in molecular electrophysiology and membrane biophysics. His research focuses on bedside prediction of subacute, potentially catastrophic illnesses using advanced mathematical and statistical pattern recognition analyses of time series data from clinical monitors. His work initially centered on neonatal sepsis, a life-threatening infection of the bloodstream, and now on adult patient deterioration in ICUs and hospital wards. He developed sample entropy for use in physiological time series, and he introduced coefficient of sample entropy for detection of atrial fibrillation. He is an inventor on 9 issued US patents, the 2014 UVa Innovator of the Year, and Chief Medical Officer of Advanced Medical Predictive Devices, Diagnostics, and Displays. He is vice-president of the Society for Complex Acute Illness and Editor-in-Chief of Physiological Measurement.

Ulrich Parlitz

Ulrich Parlitz is a research scientist at the Max Planck Institute for Dynamics and Self-Organization, Göttingen (Germany) and an adjunct professor of Physics at the University of Göttingen. He received his PhD in 1987 at the University of Göttingen. From 1989 to 1994 he was with the Institute for Applied Physics at the Technical University of Darmstadt, Germany, and in 1994 he became a scientific assistant at the Third Institute of Physics of the University of Göttingen where received his habilitation in 1997. His main research areas are nonlinear dynamics and data analysis with applications in life sciences, nonlinear oscillators, networks, cavitation, and laser dynamics. In 2010 Ulrich Parlitz joined the Research Group Biomedical Physics at the Max Planck Institute for Dynamics and Self-Organization. There he is involved in theoretical and experimental studies for understanding the nonlinear dynamics of the heart focusing on cardiac arrhythmias. This research includes numerical studies of (transient) spatio-temporal chaos in excitable media and the application of data assimilation methods for fusing experimental measurements (e.g., multichannel ECG time series) with mathematical models of electro-mechanical excitation waves in cardiac tissue. Ulrich Parlitz has published over 200 peer-review publications, including 13 papers in Physical Review Letters (Web of Science H-index 49). He served as a panel member of the German Science Foundation (DFG) for Statistical Physics, Soft Matter, Biological Physics and Nonlinear Dynamics, and in the Editorial Board of Phys. Rev. E. He is Speciality Chief Editor for Networks in the Cardiovascular System (Frontiers in Network Physiology), member of the Editorial Board of Frontiers in Applied Mathematics and Statistics (Dynamical Systems) and the Editorial Advisory Board of Chaos: Int. J. of Nonlinear Science, and

member of the Advisory Committee of the conference series “Dynamics Days Europe”.

Sergi Garcia-Retortillo

Dr. Sergi Garcia-Retortillo is an Assistant Professor in the Department of Health and Exercise Science at Wake Forest University (USA) and a member of the Complex Systems in Sport Research Group at the University of Barcelona (Spain). He holds a BS in Exercise Science from the University of Barcelona, a BS in Physical Therapy from University Ramon Llull, an MSc in Physical Activity and Health, and a Ph.D. in Exercise Science from the University of Barcelona. Dr. Garcia-Retortillo’s research focuses on the application of Network Physiology to Exercise Science. He explores how networks within and between skeletal muscles, as well as between muscles and other organs like the heart and lungs, function during exercise. His work aims to develop innovative fitness assessment systems using novel network-based markers. The primary markers in his research include: (i) inter- and intra-muscular coordination (muscle—muscle sEMG), (ii) cardio-muscular coordination (heart EKG—muscle sEMG), and (iii) cardio-respiratory coordination. These markers offer have the potential to open new horizons in exercise testing and rehabilitation by providing a comprehensive understanding of how the body, as a network, adapts to fatigue, training, and injury. Dr. Garcia-Retortillo has published over 30 scientific articles and book chapters and has received several awards, including recognition from the Southeast Chapter of the American College of Sports Medicine (SEACSM). In 2020, the American Physiological Association (APA) highlighted one of his works as one of the top published articles in physiological research. He has also served as an Associate Guest Editor for Frontiers in Network Physiology and holds positions on several editorial boards. With over a decade of experience in the fitness and wellness industry, Dr. Garcia-Retortillo has worked as both a strength and conditioning coach and a physical therapist, serving a diverse range of athletes and patients.

Rossella Rizzo

Rossella Rizzo is a mathematician and assistant professor in Applied Mathematics at the Department of Engineering, University of Palermo, Italy, awarding a grant on European Funds. She currently works on Turing instability and pattern formation for reaction-diffusion (RD) systems in brain dynamics. Her primary research goal is to study chemotactic RD systems to model multiple sclerosis lesions formation and understand under which conditions the system evolves towards coherent structures corresponding to the lesions visible in the brain magnetic resonance images (MRI). Dr Rizzo completed her PhD in Science and Engineering (specialization in Applied Mathematics) at University of Calabria, Cosenza, Italy, with excellent grades in 2020, working on the identification of brain structures to improve the knowledge of cerebral morphometry and the processing capacity of software for brain imaging. In 2018 Rossella joined Prof. Robert Whelan’s group at the Trinity Institute of Neuroscience (TCIN) as Visiting Researcher to conduct research on unhealthy ageing within the BrainPAD project. Between 2018 and 2020 Rossella worked, and since then collaborates with Prof. Plamen Ivanov’s group at the Keck Laboratory for Network Physiology at Boston University, applying cross-correlation functions and statistical analysis to understand dynamical interactions between the brain and the locomotor system during different sleep stages in healthy and Parkinson’s subjects. Between 2020 and 2021 Dr Rizzo worked as a Postdoctoral Research Fellow in the FRAILMatics Research Group, under the direction of Prof. Roman Romero–Ortuno, at The Irish Longitudinal

Study on Ageing (TILDA). There, she worked on cognitive data for older people, applying big data analysis, computational modeling and machine learning techniques to identify in a large population-based study participants who are at high risk of mobility and cognitive decline and consequential loss of independence. Dr Rizzo contributed to various conferences with talks, posters, and abstracts, organized conferences and summer schools, has received international awards, and has published on different high impact factor peer-reviewed journals. She is review editor in Frontiers in Network Physiology and Frontiers in Fractal Physiology, and referee for Physiological Measurements, Scientific Report and Physics in Medicine.

Eckehard Schöll

Is Professor of Theoretical Physics at TU Berlin (Berlin Institute of Technology), Guest Scientist at the Potsdam Institute for Climate Impact Research, and Principal Investigator of the Bernstein Center for Computational Neuroscience Berlin. He studied physics at the University of Tübingen (Germany), and holds PhD degrees in mathematics from the University of Southampton (UK, 1978) and in physics from RWTH Aachen (Germany, 1981), and an Honorary Doctorate from Saratov State University (Russia, 2017). In 2018 he received the Badge of Honor from the German Physical Society (DPG). He held a Visiting Professorship of the London Mathematical Society, and a Fulbright Senior Scholar Award at Duke University, USA. He is President of the International Physics and Control Society (IPACS), a member of the German Physical Society (DPG), and a member of the Italian Society for Chaos and Complexity (SICC). He is Speciality Chief Editor of the new open access Journal Frontiers in Network Physiology: Networks of Dynamical Systems, which was launched on April 1, 2021. He has authored more than 570 publications in peer-reviewed journals (Hirsch index h=71, google scholar) and 3 books, and is editor of 5 books (among these the Handbook of Chaos Control) and 10 topical journal issues, among which the latest is the Research Topic “Adaptive Networks in Functional Modeling of Physiological Systems” in Frontiers in Network Physiology. Since 2005 he has been a Member of the International Advisory Board of Dynamics Days Europe, which he chaired 2016-18, and the Organizer of International Conferences on Control of Complex Systems and Networks Usedom 2016, Warnemünde 2014; Toronto 2015, Palma de Mallorca 2012, and the Local Chairman of the 72nd, 76th, and 79th Annual Meeting and Spring Meeting of the Condensed Matter Division of DPG, Berlin 2008, 2012, and 2015, and of the Joint meeting of the DPG and EPS Condensed Matter Divisions, Berlin 2018. He was Deputy Chairman and Principal Investigator of the Collaborative Research Centers on Semiconductor Nanostructures (SFB 296, 1994-2002), on Complex Nonlinear Processes (SFB 555, 1998-2010), and Founder and Chairman of SFB 910 on Control of Self-Organizing Nonlinear Systems (2011-2018). Eckehard Scholl is an expert in the field of nonlinear dynamical systems and head of the group Nonlinear Dynamics and Control. His work pertains to a wide area of research in the fields of mathematics and physics, particularly semiconductor physics, laser physics, neurodynamics, complex systems and networks, synchronization, time-delayed feedback control, and bifurcation theory. His latest research is also related to topics in biology and the social sciences, e.g. simulation of the dynamics in socioeconomic, physiological, or neuronal networks and power grids. He is one of the forerunners into the research of chimera states.

Sebastiano Stramaglia

Dr. Stramaglia is a Professor of Applied Physics at the University of Bari, Italy, and External Scientific Member of the Basque Center for Applied Mathematics, Bilbao, Spain. He received his Ph.D. in Statistical Mechanics of random surfaces from the University of Bari in 1995, and the Laurea degree in models of strongly correlated electronic systems in 1991. Since 2001 he is a member of the Center of Excellence "Innovative Technologies for Signal Detection and Processing", funded by the Italian Ministry for Scientific Research, since 2002 he is a member of the V National Scientific Commission of INFN-Istituto Nazionale di Fisica Nucleare, Italy. He chaired several international events, including "Modeling Migraine: from nonlinear dynamics to clinical neurology" July 2009, Berlin, and "Nonlinear dynamics in electronic systems" July 2013, Bari. Editor of the books "Modelling Biomedical Signals", World Scientific 2002, and "Emergent Complexity from Nonlinearity, in Physics, Engineering and the Life Sciences", Springer 2017. He has been visiting scientist at the Institute for Theoretical Physics NORDITA and at the Department of Data Analysis of the University of Gent, Belgium, and visiting professor at Biocruces Health Institute, Bilbao, Spain. Since 2003 he is team leader of the INFN project "Biological applications of Theoretical Physics Methods". His research focuses on dynamical networks and Granger causality approaches to physiological interactions, in particular he developed a kernel approach for the inference of nonlinear coupling among dynamical systems with applications to brain function and brain-heart interactions.

Misako Takayasu

Misako Takayasu is a professor in the School of Computing at the Institute of Science Tokyo (formerly Tokyo Institute of Technology) in Japan. She is also a member of the Science Council of Japan. Trained in theoretical physics at Nagoya University, she received her Ph.D. in non-equilibrium statistical physics from Kobe University. She has studied various statistical properties such as dynamical phase transition behavior in wide areas of complex systems in the real world through data analysis and numerical simulations, including automobile traffic, information packet traffic in the Internet, financial Brownian motions, business firms' trade relationship networks, rumor diffusion in cyberspace, and human mobility based on mobile phone GPS data. As well as publishing scientific papers and books, her mathematical model for estimating money flows in the transaction network of about 1 million firms has been used in the RESAS (Regional Economy Society Analyzing System) platform provided by the Cabinet Office of Japan. She is a member of the International Advisory Committee of the StatPhys conference and on the editorial boards of scientific journals such as Scientific Reports, Entropy, Complexity and Physica A. Since 2022, she has been involved in a scientific grant project supported by the Japan Science and Technology Agency, "Decoding the host-gut microbiota crosstalk by developing an automated sample collection platform for use in high-resolution time series analysis". It is known that there are about 10 to the 11th power microbiomes in just one gram of feces, and these microbiomes control the health status of the host. She is developing new data analysis methods for metagenomic time series and building numerical models to elucidate microbiome interaction networks.

Robert J. Thomas

Robert Joseph Thomas, M.D., M.M.Sc, is Associate Professor of Medicine, Harvard Medical School & The

Division of Pulmonary, Critical Care & Sleep, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, His background includes Internal Medicine, Neurology and Sleep Medicine. His research spans mood, cognition (translational and epidemiology), sleep epidemiology, signal analysis in sleep medicine, and sleep-breathing outcomes, and functional imaging of cognition in sleep disorders. He has articulated a new approach to sleep physiology termed “sleep effectiveness”, which is a cross-physiology, networked, integrative approach to characterizing sleep state using cardiopulmonary coupling estimates (patented). His laboratory generates novel approaches and analysis tools for probing several sleep signals – ECG, EEG, respiration and multi-signal integration approaches. He funding sources are the NHLBI, NINDS and the American Sleep Medicine Foundation. He was key in the development of a FDA approved wearable device, the M1/SleepImage system, for dynamic sleep quality tracking. He is an acknowledged expert in the area of treatment of central and complex sleep apnea and periodic breathing, utilizing CO2 regulation approaches (patented). He studies brain health in the context of sleep disorders in the USA and South Korea. He directs the AASM accredited clinical sleep center and sieep laboratory, and the sleep medicine training program at the Beth Israel Deaconess Medical Center. I worked in the development and implementation (patented) of auto CPAP algorithms from concept through regulatory submission, which are now in FDA approved products

Bettina Weigelin

Bettina Weigelin holds a professorship in Preclinical Imaging of the Immune System at the Werner Siemens Imaging Center, Department of Preclinical Imaging and Radiopharmacy at the University of Tübingen, Germany. Her research group ‘Multiscale Immunoimaging’ combines advanced microscopic techniques with macroscopic PET/MR imaging to gain mechanistic insights into the immune system in inflammation and cancer. Her work focuses on visualizing immune cell function across scales, from cellular mechanisms to systemic effects, with the goal of identifying strategies for improved immunotherapies. Dr. Weigelin received her diploma in biology from the Julius-Maximilians-University of Würzburg, Germany, in 2007 and her Ph.D. in medical sciences from Radboud University Nijmegen, the Netherlands, in 2015. In her PhD research she applied intravital multiphoton imaging to study cancer invasion and immune function in solid tumors. Supported by an NWO Rubicon Young Investigator Award in 2016, she conducted postdoctoral research at MD Anderson Cancer Center, Houston, TX, USA, where she developed strategies to target prostate cancer metastases in bone, a critical clinical challenge. In 2019, she accepted a Junior Research Group position at the Werner Siemens Imaging Center at the University of Tübingen, Germany and in 2021 received a professorship at the University of Tübingen. Her research record includes several pioneering contributions to science, including the discovery of additive cytotoxicity by cytotoxic T cells, the implementation of third harmonic generation microscopy to understand tissue-guided cancer invasion, and novel insights into the immune-enhancing effects of hyperthermia. In recognition of her research, Dr. Weigelin has received several awards, including the 2024 DGHT Society Award, the 2021 Best Publication Award in Cancer Research from Radboud University, and the 2017 Young Investigator Award from the Society for Thermal Medicine. She also serves on the editorial board of the Journal of Molecular Imaging and Biology and holds leadership roles in international societies, including board member of the European Society for Molecular

Imaging (ESMI) and advisory board member of the German Bioimaging Society (GerBi). Her commitment to diversity and mentorship is reflected in her leadership roles, including her role on the Executive Committee of the iFIT Cluster of Excellence as Coordinator for Diversity and Equal Opportunity. Beyond academia, Dr. Weigelin is actively involved in science communication, organizing outreach events and lectures for Kids University and Science and Innovation Days to inspire the next generation of scientists.

Alexey Zaikin

Alexey Zaikin has a Chair in Applied Mathematics and Systems Medicine at UCL, holding a shared appointment between Department of Mathematics and Institute for Women's Health. Currently funded by MRC and CR-UK, he has published more than 140 papers in multidisciplinary areas, especially in the field of complex systems and data analysis, and has long experience of collaboration with wet biologists and clinicians. He studied physics at Moscow State University, and received an MS in Physics with distinction and the Khoklov Award for Excellence in Research. He got his PhD in 1998 in Moscow and Habilitation in 2003 in Potsdam, Germany. In 2008 he joined UCL and worked on analysis of clinical data, to find new oncomarkers for ovarian cancer, to investigate new methods for the analysis of DNA methylation, to study association of sex-steroid hormones with breast cancer risk, to investigate sex-hormone system in BRCA1/2 mutation carriers, to study early detection of colorectal and pancreatic cancer or aberrant regulation of RANKL/OPG in developing breast cancer. In addition to data analysis, he devoted a significant amount of time to the development of new statistical and AI methodologies, including development of algorithms for the detection of network community oncomarkers, parameter estimation methods, Bayesian change point methods for the analysis of longitudinal oncomarkers, or new methods to analyse trends in longitudinal oncomarkers. These works confirmed the power of longitudinal algorithms over the analysis of single time points. Recently he started to utilize parenclitic and developed synolitic network analysis methodology. For the past 5 years, his research interests have included the study of intelligence and consciousness in genetic and neuronastrocyte networks, investigating the role of astrocytes and a generation of Integrated Information.

Xiyun Zhang

Dr Zhang is Associate Professor at the Department of Physics, Jinan University, Guangzhou, China. Dr. Zhang received his PhD in theoretical physics at East China Normal University in June 2016. He was a W.M. Keck Foundation post-doctoral fellow at the Keck Laboratory for Network Physiology, Boston University from 2016 till 2019. In December 2019 he joined Jinan University, Guangzhou China. Dr. Zhang's main research interest is to understand complex phenomena and collective behaviors in physical, physiological and biological systems utilizing methods and concepts from nonlinear dynamics and statistical physics. His research focuses on synchronization in complex networks of dynamical systems; novel time series analysis methodology to infer network interactions among physiological systems; developing novel network-based biomarkers of organ interactions for early diagnosis and prognosis; uncovering regulatory mechanisms underlying distinct physiological states and functions at the organism level through the Network Physiology framework.

Scientific Program

Registration		**12:00-13:00**	**Sunday, 27 July, 2025**
Opening	**Plamen Ch. Ivanov**	**13:00-13:15**	**Sunday, 27 July, 2025**
Session Chair:	**Plamen Ch. Ivanov**		
Plamen Ch. Ivanov		**13:15–13:50**	**Sunday, 27 July, 2025**

Title: ***The new field of Network Physiology: Building the Human Physiolome***

Abstract: The human organism is an integrated network where complex physiological systems, each with its own regulatory mechanism, continuously interact to optimize and coordinate their function. Organ-to-organ interactions occur at multiple levels and spatiotemporal scales to produce distinct physiologic states: wake and sleep; light and deep sleep; consciousness and unconsciousness. Disrupting organ communications can lead to dysfunction of individual systems or to collapse of the entire organism (coma, multiple organ failure). Yet, we know almost nothing about the nature of interactions among diverse organ systems and sub-systems, and their collective role as a network in maintaining health.

The emerging new field of Network Physiology aims to address these fundamental questions. In addition to defining health and disease through structural, dynamical and regulatory changes in individual systems, the network physiology approach focuses on the coordination and interactions among diverse organ systems as a hallmark of physiologic state and function.

Through the prism of concepts and approaches originating in statistical and computational physics and nonlinear dynamics, we will present basic characteristics of individual organ systems, distinct forms of pairwise coupling between systems, and a new framework to identify and quantify dynamic networks of organ interactions.

We will demonstrate how physiologic network topology and systems connectivity lead to integrated global behaviors representative of distinct states and functions. We will also show that universal laws govern physiological networks at different levels of integration in the human body (brain-brain, brain-organ and organ-organ), and that transitions across physiological states are associated with specific modules of hierarchical network reorganization.

We will outline implications for new theoretical developments, basic physiology and clinical medicine, novel platforms of integrated biomedical devices, robotics and cyborg technology.

The presented investigations are initial steps in building a first Atlas of dynamic interactions among organ systems and the Human Physiolome, a new kind of BigData of blue-print reference maps that uniquely represent physiologic states and functions under health and disease.

[1] Bashan A, Bartsch RP, Kantelhardt JW, Havlin S, Ivanov PCh. Network physiology reveals relations between network topology and physiologic function. Nature Communications 2012; 3: 702.

[2] Bartsch RP, Liu KKL, Bashan A, and Ivanov PCh. Network Physiology: how organ systems dynamically interact. Plos One, 2015; 10(11): e0142143

[3] Ivanov PCh and Bartsch RP. Network Physiology: Mapping Interactions Between Networks of Physiologic Networks. In "Networks of Networks: the last Frontier of Complexity", edited by D'Agostino G and Scala A. Book Series: Understanding Complex Systems Springer, Cham; 2014; p.203-222

[4] Ivanov PCh, Liu KKL, and Bartsch RP. Focus on the emerging new fields of network physiology and network medicine. New Journal of Physics, 2016; 18: 100201.

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Network Physiology, 2021; 1: 711778.

James W. Holsapple **13:50–14:25** **Sunday, 27 July, 2025**

Title: ***Network Physiology: An emerging tool in the clinical neurosciences?***

Abstract: Neurosurgeons, neurologists and neuro-intensivists confront the difficult task of treating life-threatening neurological diseases with incomplete visualization or understanding of bedside physiologic data. Typical problems include characterization of the type, severity and effect of disease, identifying dynamic sub-system interactions relevant to optimizing treatment and identifying changes corresponding to deterioration or recovery. Network physiology provides a promising framework to address and potentially solve these problems. A range of common neurological disorders provide an important testing ground of this perspective including acute stroke, traumatic brain injury, concussion, intractable epilepsy, movement disorders and chronic pain. Present and future applications of network physiologic methods to the management of these complex clinical problems will be discussed.

J. Randall Moorman **14:25–15:00** **Sunday, 27 July, 2025**

Title: ***How can the study of network physiology improve patient care***

Abstract: Doctors follow patients with repeated measurements of organ function using vital signs and laboratory tests. We realize though, that diverse organ systems dynamically coordinate their function to maintain health, and that there is extra information in our data that can signal disease. Many recent efforts have shown that applied mathematical analyses can lead to effective early detection of disease resulting in improved patient outcomes.

While traditional approaches focus on individual physiological subsystems, and machine-learning-based diagnostics extract correlations without mechanistic insight, neither offers a holistic, interpretable framework for understanding how systemic failures emerge. Network Physiology provides a new paradigm, integrating well-established physiological principles with concepts from statistical physics, information theory, and nonlinear dynamics to model human physiology as a coordinated network. This approach offers new ways to detect synthesize useful clinical insights from ubiquitously available clinical data.

Why might bedside tools based on Network Physiology approaches be better than those based on traditional machine learning and deep learning for doctors who take care of patients? The major advantage is that they are mechanistically based on well-understood principles of human physiology integrated across systems. Unlike blackbox AI algorithms, they are understandable and therefore Intuitively, appealing to clinicians.

We already know that organ interactions exhibit phase transitions, with changes in connectivity reflecting shifts in autonomic regulation, sleep states, aging, and pathological conditions. For example, studies have shown that cardiorespiratory phase synchronization (CRPS), a measurable form of network coordination, undergoes a large increase from wakefulness to deep sleep, providing a new physiological marker for autonomic function. Similarly, work in network topology of physiological interactions has demonstrated that physiological networks undergo rapid structural shifts within minutes, indicating high network flexibility in response to perturbations such as transitions between sleep stages, stress, or early illness [illegible]. These findings suggest that the loss of stable network connectivity may serve as an early biomarker of disease progression, potentially preceding traditional clinical symptoms.

For quantitative scientists, Network Physiology presents a rich set of well-defined, tractable problems in dynamical systems, network science, and information theory. Unlike many AI-driven medical models that rely on opaque correlation-based outputs, Network Physiology is rooted in first principles and directly testable. The scientific credibility is very good because it is built on rigorous mathematical models and established physiological mechanisms. There are many clinical applications, especially in acute and critical care hospital settings. Since the field bridges physics, applied mathematics, machine learning, and clinical medicine, it brings together cross-disciplinary teams.

Network Physiology is a research area with both foundational and translational impact. The theoretical groundwork is solid, empirical validation is actively progressing, and computational tools now allow real-

time monitoring of physiological networks.

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Coffee Break **15:00-15:20** **Sunday, 27 July, 2025**

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Helene M. Langevin **15:20–15:55** **Sunday, 27 July, 2025**
Title:
Abstract:

Rosario Mantegna **15:55-16:30** **Sunday, 27 July, 2025**
Title: ***Comorbidity networks***
Abstract: We investigate a large set of electronic health records (EHRs) collected by wellbeing services county of Southwest Finland (Varha). These data can be accessed for research purposes via Auria Clinical Informatics. Auria Clinical Informatics is a company situated in Turku, Finland. Specifically, we investigate the overall comorbidity networks empirically detected for different cohort of patients characterized by their age and sex over a time period about sixteen years. This is one of the largest-scale study of comorbidity networks obtained from EHRs covering all diseases for several age and sex cohorts [1].
Different diseases have different prevalence in a given population. For this reason, the observation of a specific comorbidity in a given patient could be just the result of a random co-occurrence of two unrelated diseases. Therefore a comorbidity network of diseases obtained from EHR data can in principle mix comorbidity occurrences originating either from random or from biological/medical origin. To extract from EHR data information on biologically or medically induced comorbidity we perform the detection of so-called statistically validated networks [2,3]. In this approach, all links of a projected network obtained starting from a bipartite network are subject to a statistical test. In the present case, the bipartite network is a patient-disease network and the projected (PROJ) and statistically validated networks (SVN) are networks of diseases. Each link in the PROJ network of diseases is therefore subjected to a statistical test able to discriminate whether the presence of a link can be seen as an indication of comorbidity of unknown origin (i.e. in technical terms the co-occurrence is compatible with a so-called "null hypothesis") or as an indication of potential comorbidity of biological/medical origin (for those pairs of diseases rejecting the "null hypothesis"). Defining and testing a "null hypothesis" is the process of hypothesis testing in statistics.
Hypothesis testing is a statistical method used to determine if there is enough evidence in a sample data to draw conclusions about a population. It involves formulating two competing hypotheses, the so-called "null hypothesis" and the "alternative hypothesis". In our statistical design, the "null hypothesis" assumes random co-occurrence of each pair of diseases taking into account the different prevalence of the two diseases. The "alternative hypothesis" rejects random co-occurrence. By performing the same statistical test for all diseases' pairs present in the PROJ network we extract what we address as a SVN. The SVN is providing a selection of those comorbidities that cannot be statistically explained only by random co-occurrence of diseases of different prevalence.

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Eckehard Schöll **16:30-17:15** **Sunday, 27 July, 2025**
Title:

Abstract:

Poster Session I **17:15-18:30** **Sunday, 27 July, 2025**

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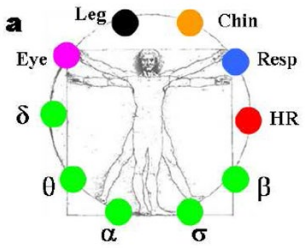
Registration **08:00-09:00** **Monday, 28 July, 2025**

Session Chair:

Shlomo Havlin **09:00–09:35** **Monday, 28 July, 2025**

Title: ***Theory of Interdependent Networks: Applications in physics and physiology***



Interdependent Physiological Networks

Abstract: Interdependent networks appear in all aspects of nature and technology. Examples include our physiological systems in our body and infrastructures. A theoretical framework for percolation theory of interdependent networks will be presented. In interdependent networks, such as infrastructures or physiology, when nodes in one network fail, they cause dependent nodes in other networks to also fail. This will happen recursively and can lead to a cascade of failures and to an abrupt collapse of the system of systems. This contrasts with a single network where the percolation transition due to failures is continuous. I will present analytical solutions based on percolation theory, for the general case, the functional network of n interdependent networks, the cascading failures and the microscopic mechanisms behind the collapse transitions. Our analytical results show that percolation theory of a single network studied for over 90 years is just a limited case, n=1, of the general and a significantly richer case of n>1.

I will also show that interdependent networks embedded in space are extremely vulnerable and have significantly richer behavior compared to non-embedded networks. I will finally show that the abstract interdependent percolation theory and its novel behavior in networks of networks can be realized and proven in controlled experiments, performed by Aviad Frydman on real physical systems, the interdependent superconducting networks. I will also show how the theory of interdependent networks explains the broad power law distribution of death and recovery times of bacteria under pressure.

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[8] Orr Levy et al to be published (2025)

Bettina Weigelin **09:35–10:10** **Monday, 28 July, 2025**

Title: ***Multiscale immuno-imaging and network physiology: from immune cell function to systemic immune response in cancer***

Abstract: A successful anti-cancer immune response depends on a dynamic network of diverse immune cell populations interacting at multiple levels - from local tumor environments to systemic regulation. Rather than the mere presence of tumor-targeting immune cells, their spatial distribution within tumors and the clustering of specific immune subpopulations in distinct cellular neighborhoods are decisive for therapeutic outcomes. Comprehensive monitoring of anti-tumor effector cells, inhibitory immune cell populations, and their interactions in tissues require multiscale, multiplexed imaging approaches.

In this talk, I will present our development, application and remaining challenges of multimodal and multiplex 3D imaging methods that allow to correlate information about cell-cell interactions with tissue- and whole-organ microscopic imaging. To understand systemic immune response against cancer, we established a multiscale imaging pipeline, including live-cell imaging in vitro, intravital microscopy in live

tumors and whole-organ and whole-mouse light-sheet microscopy of systemic cancer metastasis. In combination, the multiscale workflow allows us to map anti-cancer immune response across scales, ranging from mechanistic in vitro studies of immune cell dynamics, monitoring immune cell behavior in live tissues to ex vivo mapping of immune response in intact organs and tracing systemic immune activation. Such comprehensive imaging allows us to reveal previously hidden crosstalk among different tissue compartments, ultimately bridging the gap between cellular-scale events and systemic physiological responses.

Thus, multiscale imaging offers insights into how local and systemic immune mechanisms are governed by regulatory networks spanning cellular, tissue, and organ systems. By placing immuno-imaging within a Network Physiology framework, we demonstrate how understanding immune cell function at multiple scales can inform the broader regulatory architecture of the immune system and facilitate more effective cancer immunotherapy strategies.

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Coffee Break **10:10-10:40** **Monday, 28 July, 2025**

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Joseph Loscalzo **10:40–11:15** **Monday, 28 July, 2025**

Title:

Abstract:

Jürgen Kurths **11:15–11:50** **Monday, 28 July, 2025**

Title: ***Synchronization phenomena in coupled oscillators and complex adaptive networks: from complete to partial synchronization***

Abstract: Complex systems science is often regarded as a rather new field of research. But even its scientific roots go back much to the past where basic phenomena and concepts of recurrence (more than 2300 years ago), synchronization (17th century), chaos, and graphs (18th century) were found and developed. But the very rapid evolution started about 50 years ago and it is ongoing.

In this talk I will i) give a short historic journey of milestones on synchronization phenomena starting with Huygens´ work and then ii) to recent findings of different synchronization phenomena in coupled chaotic systems and in adaptive complex networks. In particular such phenomena will be discussed for multistable systems. Another main direction are adaptive systems where we find coexisting regimes of synchronization and disorder.

James W. Holsapple **11:50–12:25** **Monday, 28 July, 2025**

Title:

Abstract:

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Lunch Break **12:30-14:00** **Monday, 28 July, 2025**

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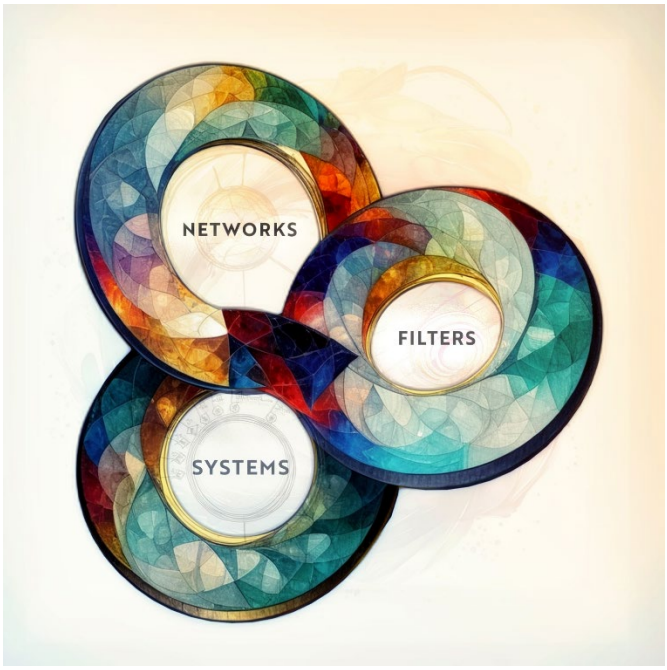
Session Chair:

Alan Macy **14:00–14:35** **Monday, 28 July, 2025**

Title: ***Advancing Network Physiology: Challenges and opportunities in developing integrated medical device platforms for high-frequency multisystem monitoring***

Abstract: The future of medicine lies in understanding the human body as a dynamic, interconnected network. Unlocking this requires integrated medical platforms and wearable sensor networks capable of capturing high-frequency, synchronous data from multiple physiological systems in real time. This talk will

explore the challenges of developing these systems — from data synchronization and real-time analysis to system dynamics and control. We'll examine how networked devices, large-scale data streams, and advanced computational models can decode the hidden language of physiological networks, revealing how different systems communicate and adapt under stress, disease, and recovery. Monitoring and analyzing these complex interactions at scale will transform both clinical medicine and our understanding of human physiology as a living, adaptive network.



Flavio H. Fenton **14:35–15:10** **Monday, 28 July, 2025**

Title: ***Simultaneous optical mapping of voltage and calcium dynamics in myocardial cell networks of whole ex-vivo human explanted hearts to investigate emergent behavior in arrhythmias***

Abstract: In the heart, connections between cells—from 1D to 2D and 3D—give rise to new network emerging behaviors, which can lead to the initiation of arrhythmias in cardiac tissue. In this talk, we present experimental results from both in live animal and human explanted hearts, as well as numerical simulations, demonstrating how network connectivity between cells can generate emerging dynamical behaviors. Using dual recordings of voltage and calcium, coupled with numerical simulations, we show how the complexity of dynamics increases as the system transitions from a single cell to 1D, 2D, and 3D tissue. Experimental data, obtained through optical mapping in live explanted animal and human hearts under approved IACUC and IRB protocols from Georgia Tech and Emory Hospital, reveal the emergence of complex spatiotemporal dynamics in tissue and the mechanisms underlying these phenomena. Specifically, we present results on a period-doubling bifurcation that develops from a single cell and leads to complex spatiotemporal patterns, which ultimately contribute to the initiation of complex spatiotemporal arrhythmias in the heart.

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Coffee Break **15:10-15:40** **Monday, 28 July, 2025**

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Bettina Weigelin **15:40–16:15** **Monday, 28 July, 2025**

Title: ***Thermal tuning of immunity: Fever-range temperature modulation of cancer immunity and network physiology***

Abstract: Temperature is a fundamental regulator of cellular processes and, consequently, a strong modulator of systemic physiology. The homeostatic temperature of mammals is thus tightly controlled, and temperature variations have profound cellular and systemic effects. The most prominent example is the rise in temperature during inflammation and fever, which enhances the ability of the immune system to control

infection. At the cellular level, an increase in temperature modulates gene expression and cell signaling while at the tissue level, temperature e.g. increases vascular permeability and vasodilation modulating the local microenvironment by increasing oxygenation, nutrient delivery and immune cell infiltration. The controlled application of fever-range temperature is thus a potential strategy to increase anti-cancer immune effector function or to convert immunosuppressive into proinflammatory microenvironments.
In this talk, I will present our findings on how controlled fever-range temperature impacts cytotoxic T cell (CTL) effector function against metastatic melanoma and breast cancer - at the cellular level, within the tumor microenvironment and systemically in metastases. Using live-cell microscopy combined with multiplexed immunofluorescence, we identified a temperature-dependence of CTL killing based on more stable CTL-tumor cell contacts and impaired repair mechanisms in cancer cells under mild heat stress. Intravital microscopy in live melanoma lesions further demonstrated that temperature modulation can enhance CTL killing in vivo and induce senescence in the tumor cell population that was sub-lethally damaged by CTL. In metastatic sites in lungs and liver, immuno-thermal combination treatment however showed marginal effects with great variability depending on the anatomical tissue niche. In lymph nodes, the hyperthermia treatment induced increased expression of proliferation markers in T cell areas, indicating a systemic immune activation.
Multiscale imaging allowed us to monitor and quantify the thermal regulation of CTL function and trace how cellular effects were integrated in complex tissue- and organ-level functions. Our data thus shows how multiscale imaging can be used to study the immune system as interconnected physiological network which mediates local and systemic immunity.

Sergi Garcia-Retortillo **16:15–16:40** **Monday, 28 July, 2025**
Title: ***Network Physiology of exercise: Inter-muscular networks in rest, exercise, fatigue and aging***
Abstract: The human organism comprises various physiological systems that continuously interact across a range of spatio-temporal scales. Synchronization and integration among physiological systems is essential to generate distinct physiological states (e.g., health, and disease) and, therefore, unraveling the underlying principles of physiological systems integration as a network is crucial to understand physiological functions. Inspired by the multi-disciplinary field of Network Physiology and Complex Systems Science, Network Physiology of Exercise (NPE) emerges to transform the theoretical assumptions, the research program and the current practical issues of current Exercise Physiology. By advancing research on the horizontal integration of key organ systems—heart, muscles, brain— during exercise, NPE has the potential to enhance our understanding of fundamental physiology and contribute to various fields, including Exercise and Sports Physiology, Sports Medicine, Physical Therapy and Rehabilitation.
This dynamic network approach is leading to the development of novel network-based markers that offer groundbreaking insights into multilevel inter-muscular and muscle-organ interactions. These markers provide a new lens to study diverse exercise-related phenomena such as performance, fatigue, or aging. Some of the most relevant network-based markers include: (i) inter- and intra-muscular coordination, (ii) cardio-muscular coordination, (iii) cortico-muscular coordination, and (iv) cardio-respiratory coordination. This talk will specifically focus on inter-muscular coordination, exploring its physiological principles and how it adapts across different states, including rest, exercise, fatigue, and aging, addressing a fundamental question in muscle physiology—how distinct muscles synchronize and integrate as a network to generate fine tune movements.
Over the past years, we have uncovered basic physiological principles of inter-muscular coordination, and reported the first empirical evidence that different muscles dynamically synchronize their activity following distinct patterns of cross-frequency communication, that depend on muscle histochemical characteristics and on the role muscles play during the movement (i.e., primary, secondary, compensatory). Moreover, we established how the global inter-muscular network reorganizes with transition from rest to exercise and with an accumulation of fatigue during consecutive exercise bouts. We discovered that each pair of muscles in the global inter-muscular network forms a distinct sub-network that is characterized by a specific signature of cross-frequency communication. Remarkably, our findings indicate the existence of general physiological patterns of inter-muscular coordination for different fundamental movement patterns (e.g., squats, push-ups…), so that muscle network interactions and their reorganization with fatigue do not depend on the

specific movement but rather reflect the role that pairs of muscles play during each movement. Thus, an infinite variety of movements involving various combinations of muscles could be represented by a few classes of muscle interaction networks.
Building upon this framework, we recently assessed the effects of aging on inter-muscular coordination. Assessing inter-muscular coordination in older adults is crucial, as it directly impacts an individual's ability for independent functioning, falls prevention, and active engagement in daily activities. Our results show an overall reduction of the degree of inter-muscular coordination and increased stratification of the inter-muscular network in older adults compared to their younger counterparts. These findings suggest that as individuals age, the global inter-muscular network becomes less flexible and adaptable, hindering its ability to respond and reorganize effectively in the face of fatigue or other stimuli.
By integrating principles from Network Physiology into Exercise Physiology, this approach offers a new perspective on how muscle networks function, adapt to exercise, and change with aging. Understanding these network dynamics can help refine training approaches, improve rehabilitation strategies, and provide insights into the mechanisms behind fatigue and aging.

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[4] Garcia-Retortillo S and Ivanov PC (2022) Inter-muscular networks of synchronous muscle fiber activation. Front. Netw. Physiol. 2:1059793. doi: 10.3389/fnetp.2022.1059793
[5] Garcia-Retortillo S, Abenza O, Vasileva F, et al. (2024) Age-related breakdown in networks of inter-muscular coordination. GeroScience. doi: 10.1007/s11357-024-01331-9

Sallie Gregson **16:40–17:05** **Monday, 28 July, 2025**
Title:
Abstract:

Poster Session II **17:15-18:30** **Monday, 28 July, 2025**

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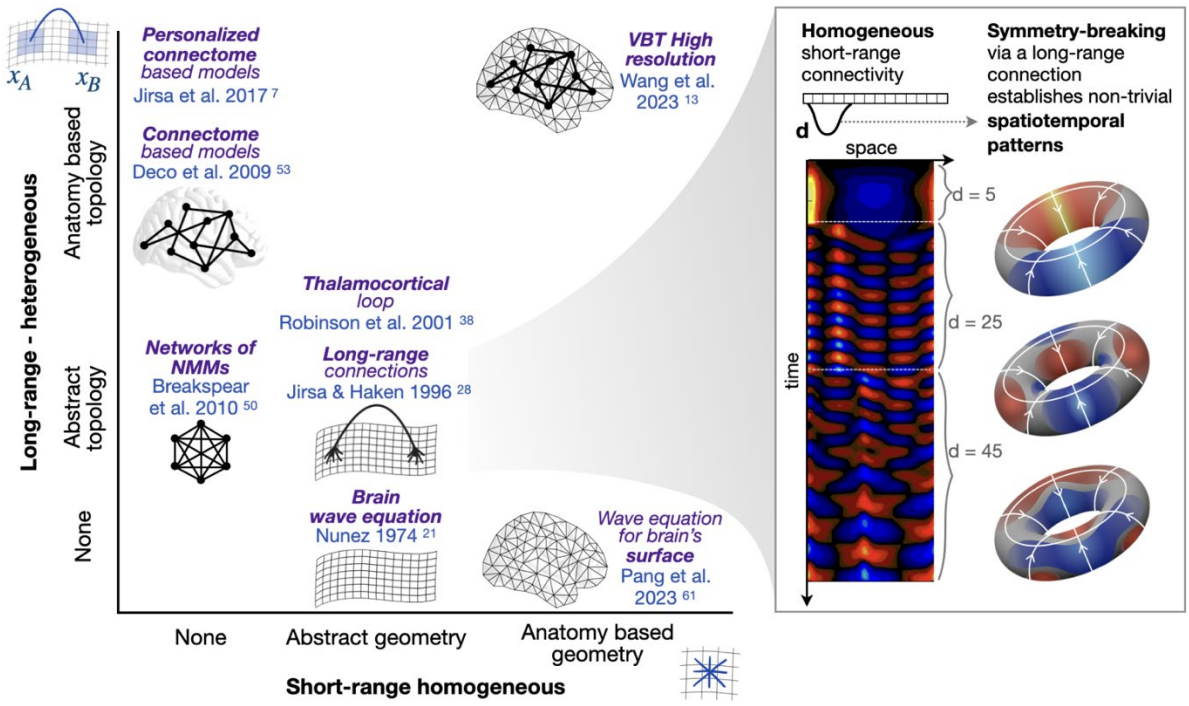
Session Chair:

Viktor Jirsa **09:00–09:35** **Tuesday, 29 July, 2025**
Title: ***On the space-time structure of large-scale brain networks and their dynamics***

Abstract: Neuroscience encompasses concepts and theories rooted in various domains, including information theory, dynamical systems theory, and cognitive psychology. However, not all of these can be coherently linked—some concepts are incommensurable, and domain-specific language creates barriers to integration. Conceptual integration, however, provides intuition and consolidation, guiding progress that might otherwise remain unguided. In this talk, we bring together computational modeling, dynamical systems analysis, and cognitive neuroscience perspectives to offer a mechanistic account of how resting-state and task-based manifolds emerge via network connectivity. We demonstrate that symmetry breaking within connectivity structures generates a characteristic flow on the manifold, producing key data features across scales and imaging modalities. These include spontaneous high-amplitude co-activations, neuronal cascades, spectral cortical gradients, multistability, and distinctive functional connectivity dynamics. When aggregated across cortical hierarchies with short- and long-range connectivity within the same brain network, these features align with and explain empirical functional brain imaging data. The emergent perspective illustrates how neurotheoretical frameworks—such as the free energy principle—can be linked

to internal cognitive models and how these models arise from the neural substrate.



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[2] P Triebkorn, V Jirsa, PF Dominey (2025) Simulating the impact of white matter connectivity on processing time scales using brain network models. Communications Biology 8 (1), 197, 2025

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Robert J. Thomas **09:35–10:10** **Tuesday, 29 July, 2025**
Title:
Abstract:

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Coffee Break **10:10-10:40** **Tuesday, 29 July, 2025**

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Yaron Ilan **10:40–11:15** **Tuesday, 29 July, 2025**
Title:
Abstract:

Ulrich Parlitz **11:15–11:50** **Tuesday, 29 July, 2025**
Title: ***Challenges of the complex dynamics of cardiomyocyte networks in heart tissue***
Abstract: The myocardium is an excitable medium that can exhibit complex dynamics, such as spatiotemporal chaos associated with (fatal) cardiac arrhythmias. On a small scale, cardiac tissue consists of a network of cardiomyocytes embedded in an extracellular matrix. The beating cardiomyocytes form a dynamic network of electromechanically coupled oscillators that enable the propagation of excitation waves that lead to contraction of the heart muscle. These waves can turn into spiral or scroll waves, leading to

tachycardia with impaired pumping or to chaotic wave dynamics associated with a complete loss of pumping function, which is immediately life-threatening in the case of ventricular fibrillation.
In the talk, we will present measurement data and numerical simulations addressing various aspects of complex cardiac dynamics, the role of electromechanical interactions of cells in the network, and novel concepts to control and terminate arrhythmias.

Krasimira Tsaneva-Atanasova **11:50–12:25** **Tuesday, 29 July, 2025**
Title:
Abstract:

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Lunch Break **12:30-14:00** **Tuesday, 29 July, 2025**

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Session Chair:

Verkhratsky or Semyanov **14:00–14:35** **Tuesday, 29 July, 2025**
Title:
Abstract:

Thomas Beyer **14:35–15:10** **Tuesday, 29 July, 2025**
Title: ***Dual-modality PET-based whole-body imaging for systemic phenotyping***
Abstract: The global burden of complex diseases, including cancer, cardiovascular disorders, neurodegenerative conditions, and metabolic syndromes, continues to rise, underscoring the critical need for early diagnosis and personalized treatment strategies to improve patient outcomes. Diagnostic tools, particularly blood-based biomarkers and non-invasive imaging techniques, play a pivotal role in this endeavour. Among these, the integration of Positron Emission Tomography (PET) and Computed Tomography (CT) into a dual-modality PET/CT system has revolutionized diagnostic imaging by combining high-resolution anatomical visualization with molecular-level functional insights [1]. PET/CT has demonstrated exceptional sensitivity and specificity in detecting and characterizing malignant diseases, making it indispensable for diagnosis, monitoring disease progression, and predicting therapeutic responses [2].
Today, over 80% of PET scans are performed for oncology indications, primarily using 2-deoxy-2-[18F]fluoro-D-glucose (FDG) as the tracer of choice. FDG-PET highlights regions of increased glucose metabolism, a hallmark of cancer tissue, and is commonly employed in whole-body PET (WB-PET) imaging to detect metastatic lesions. However, current analytical methods often treat organs in isolation, overlooking the intricate metabolic interactions between them. This reductionist approach limits the potential of PET imaging, particularly in assessing systemic diseases that disrupt metabolic homeostasis across multiple organs [3].
The advent of total-body (TB) PET/CT represents a significant technological advancement, offering unprecedented insights into systemic metabolic interactions and inter-organ communication [4]. By capturing the entire body in a single scan, TB-PET/CT provides a comprehensive view of both pathological and physiological FDG uptake patterns. This systemic perspective holds immense potential for innovating research, enabling the detection of subtle metabolic deviations that precede overt disease manifestation, such as in early-stage cachexia or chronic conditions.
This presentation will explore the evolution of PET/CT imaging, introduce TB-PET/CT as a transformative technology, and highlight its implications for advancing research and clinical practice. Examples of TB-PET/CT imaging in systemic diseases and health will be discussed, illustrating its potential to redefine our understanding of metabolic interactions and improve diagnostic precision.

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Coffee Break **15:10-15:40** **Tuesday, 29 July, 2025**

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Susanna Gordleeva **15:40–16:15** **Tuesday, 29 July, 2025**

Title: ***Thermal tuning of immunity: Fever-range temperature modulation of cancer immunity and network physiology***

Abstract: In a condensed timeframe, diverse discoveries have unveiled the significant role of astrocytes in modulating neuronal signaling, information processing, and memory formation [Santello et al., 2019; Kol et al., 2020; Adamsky, A. et al. 2018; de Ceglia et al., 2023; Doron et al., 2022; Miguel-Quesada et al., 2023; Andrade-Talavera et al., 2023; Noh et al., 2023]. Recent advancements in measuring and manipulating astrocyte signaling have illuminated key subcellular mechanisms, such as the generation of Ca2+ signals in astrocytes [Semyanov et al., 2020; Bindocci et al., 2017], spatio-temporal Ca2+ dynamics of astrocytes in response to sensory stimulation [Stobart et al., 2018; Lines et al., 2020], and the morphological organization of the tripartite synapse [Arizono et al., 2020], a key concept for synapse-specific communication between neurons and astrocytes. Collective research underscores the active role of astrocytes in synaptic wiring and plasticity [Adamsky, A. et al. 2018; de Ceglia et al., 2023], information processing [Miguel-Quesada et al., 2023], and memory function [Adamsky, A. et al. 2018; de Ceglia et al., 2023; Kanaya et al., 2023], revealing their crucial involvement in brain function and neural computation.

Despite recent progress, several longstanding questions remain [Hirrlinger & Nimmerjahn, 2022]. A widely accepted paradigm suggests that astrocytes re-encode fast synaptic information, which is then transmitted back to neurons. However, the computational benefits of this feedback mechanism remain unclear. The algorithms by which astrocytes participate in information processing and memory formation – using their proven ability to integrate and process synaptic information and regulate synaptic transmission and plasticity – are still poorly understood. How, and to what extent, does astrocyte-induced modulation of neural circuit dynamics across various temporal and spatial scales enhance computational power, flexibility, and the robustness and stability of learning and memory organization? Moreover, although the relatively slow temporal dynamics of astrocytes (but see Stobart et al., 2018) may allow them to participate in calculations on longer, behaviorally significant time scales, such as working memory, the functional significance of synapse-triggered astrocyte outputs compared to neurons has yet to be fully resolved.

My talk will focus on my experience with mathematical modeling of astrocyte signaling within neural circuits in the context of information processing, learning, and memory. I will present results from the construction and investigation of biologically plausible mathematical models, ranging from single-cell Ca2+ signaling [Gordleeva et al., 2019; Wu et al., 2019] to neuron-astrocyte interactions in two-cell models [Gordleeva et al., 2012; Pankratova et al., 2019] and multicellular networks [Kanakov et al., 2019; Makovkin et al., 2022]. We will discuss how incorporating astrocytes into traditional recurrent neural networks has demonstrated multi-item working memory capabilities [Gordleeva et al., 2021; Tsybina et al., 2022]. Furthermore, I will present results showing how the interplay of synaptic changes by STDP and astrocyte-induced modulations improve memory performance [Gordleeva et al., 2023]. Finally, I will discuss the instrumental role of

astrocytic involvement in neural network signaling for the development of brain-like artificial intelligence [Roy et al., 2019].

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Natàlia Balagué **16:15–16:40** **Tuesday, 29 July, 2025**

Title: ***Network Physiology may reveal sex differences in the response to exercise with relevant implications for health and performance***

Abstract: Due to the general under-representation of females in clinical trials, less is known about their acute and adaptive response to exercise and training. This leads to inadequate and non-personalized exercise interventions, similar to what happens with medical treatments and their adverse reactions. The exclusion of females from clinical trials has been justified by the need for sample stability and homogeneity in traditional research based on group data means comparisons. Network Physiology offers methodological approaches that help to reveal individual differences in the response to exercise and contributes to personalize training and rehabilitation strategies.

The temporal variability of the inter-muscular coordination during exercise has remained underexplored in relation to sex differences. This study investigates sex differences in inter-muscular network interactions and their temporal variability during a squat test. Eleven males and twenty-seven females performed bodyweight squats at a regular pace (1 squat every 6seconds) until exhaustion. Simultaneous surface electromyography (sEMG) recordings were taken from the left and right vastus lateralis (leg) and erector spinae longissimus (back) muscles. The sEMG signals were decomposed into ten frequency bands [F1-F10]. Pairwise coupling (cross-correlation C) for each pair of sEMG spectral power frequency bands across all leg and back muscles was quantified. Finally, to assess the temporal variability of the inter-muscular network, cross-correlation moving averages with 3-second resolution were computed for each pair of sEMG frequency bands across all leg and back muscles, and the coefficient of variation (CV) of the resulting time series was calculated. Females exhibited: a) stronger link strength within the inter-muscular network and b) lower temporal variability in network dynamics, particularly when higher sEMG frequency bands were involved. The lower temporal variability in the inter-muscular network in females may suggest reduced flexibility and adaptability to the imposed exhausting effort compared to males. The inter-muscular coordination approach applied in this research provides a novel framework for quantifying the interactions among physiological network components and their dynamics during exercise and could play a crucial role in implementing personalized exercise and rehabilitation interventions.

Xiyun Zhang **16:40–17:05** **Tuesday, 29 July, 2025**

Title:

Abstract:

Round Table Discussion I **17:15-18:30** **Tuesday, 29 July, 2025**

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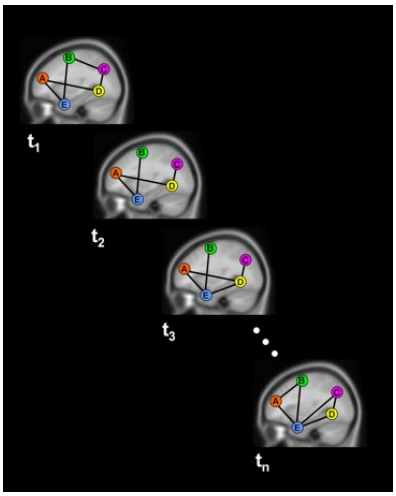
Session Chair:

Joseph Loscalzo **09:00–09:35** **Wednesday, 30 July, 2025**
Title:
Abstract:

Shlomo Havlin **09:35–10:10** **Wednesday, 30 July, 2025**
Title: ***Time Persistence of Brain Networks***



Brain networks persistence

Abstract: Time persistence is a fundamental property of many complex physiological and biological systems. Thus, understanding this phenomenon in the brain is of high importance. Time persistence has been explored at the level of stand-alone neural time-series, but since the brain functions as an interconnected network, it is essential to examine time persistence at the network level. Changes in resting-state networks have been previously investigated using both dynamic (i.e., examining connectivity states) and static functional connectivity (i.e., test-retest reliability), but no systematic investigation of the time persistence as a global network has been conducted, particularly across different time-scales (i.e., seconds, minutes, dozens of seconds, days) and different brain subnetworks. Additionally, individual differences in network time persistence have not been explored. Here, we devised a new framework to estimate network time persistence at both the link (i.e., connection) and node levels. In a comprehensive series analysis of three functional MRI (fMRI) resting-state datasets including both sexes, we established that: a) The resting-state functional brain network becomes gradually less similar to itself for the gaps up to 23 minutes within the run and even less similar for the gap between the days; b) Network time persistence varies across functional networks, while the sensory networks are more persistent than non-sensory networks; c) Participants show stable individual characteristic persistence, which has a genetic component; and d) Individual characteristic persistence could be linked to behavioural performance. Overall, our detailed characterization of network time persistence sheds light on the potential role of time persistence in brain functioning and cognition.

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Coffee Break **10:10-10:40** **Wednesday, 30 July, 2025**

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Boris P. Kovatchev **10:40–11:15** **Wednesday, 30 July, 2025**
Title: ***Controlling the Human Glucose-Insulin Metabolic Network: the Neural Network AI artificial pancreas and the contemporary treatment of diabetes***

Abstract: In the 1970s, the first trials of continuous subcutaneous insulin delivery (CSII) using insulin pumps to control the blood sugar levels of people with type 1 diabetes were reported, and in the beginning of the 21st century, continuous glucose monitoring (CGM) was introduced. In 2004-2006, first steps were made towards automated insulin delivery (AID), known as the “artificial pancreas” – a system connecting CGM and CSII via an algorithm controlling insulin delivery, typically every 5 minutes, for life. In 2009 JAMA wrote “Artificial pancreas may soon be a reality,” and by 2010 AID became a global research topic. In May 2012, a Diabetes Outlook published in Nature highlighted AID, and Science then featured the same topic.

The Figure below depicts the progress of AID over the years, and the more recent transition from model-based to data-driven control algorithms:
Today, AID is the gold-standard treatment for type 1 diabetes, and is expanding to people with type 2 diabetes on insulin treatment. Several commercial systems are available in the U.S., including: Medtronic's MiniMed™ 670G, 770G, and 780G; t:slim X2 and Mobi with Control IQ Technology™ by Tandem Diabetes Care; OmniPod 5™ hybrid closed loop system, Insulet Corporation; the iLet Bionic Pancreas system by Beta Bionics, CamAPS FX (CamDiab Ltd., Cambridge, UK), and the twiist™ AID system by Sequel. Other systems are available in Europe, e.g., Diabeloop DBLG1 (Diabeloop France) and Inreda AP (Inreda Diabetic B.V., the Netherlands).
A major difference between AID configurations is the control algorithm, which directs insulin delivery based on CGM readings and other factors, such as insulin on board. To date, most AID algorithms are equation-based using models of the metabolic system, simplified enough to be tractable in real time, to calculate control actions. With the accumulation of large data sets and the increasing ability of contemporary CGM/CSII systems to track individuals across long periods of time, data-driven controllers are emerging based on techniques that fall in the domain of data science, such as machine learning and artificial intelligence (AI). This transition has already begun, with first studies of a Neural Network AID conducted at the University of Virginia in 2024.
By design, AI is capable of real-time learning, adaptation, and problem solving, all of which are critical to the real-time control of the continually changing human metabolic system and human behavior. Thus, the movement towards the AI AP of the near future is likely inevitable (see the Figure above).

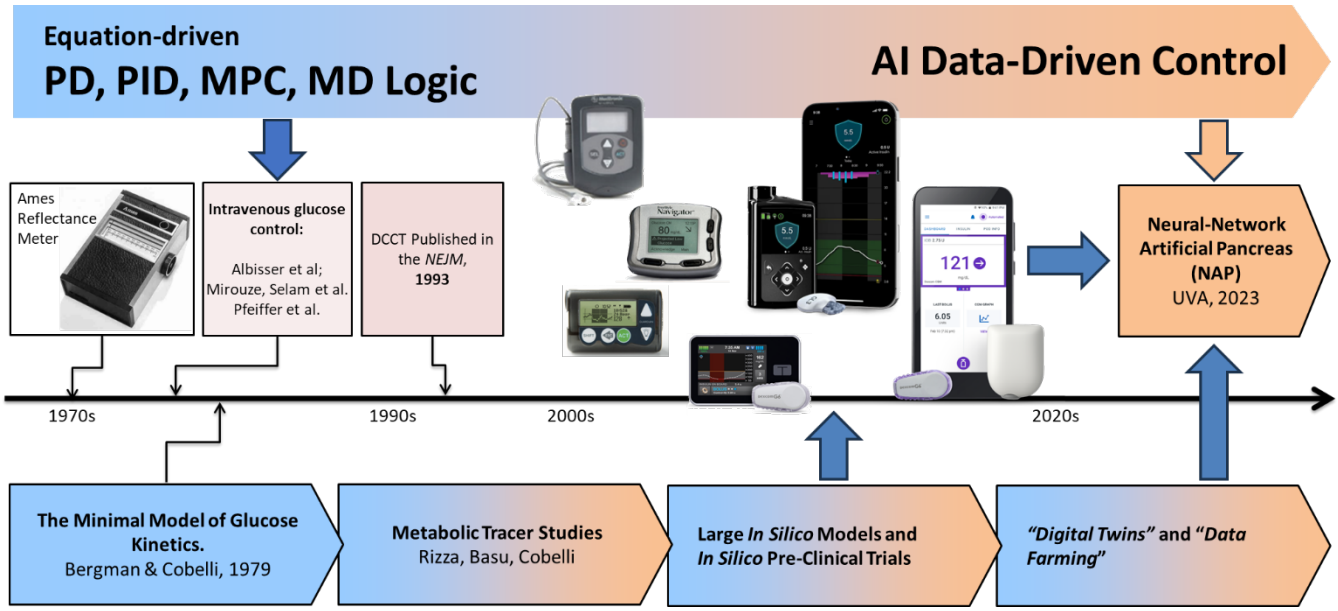
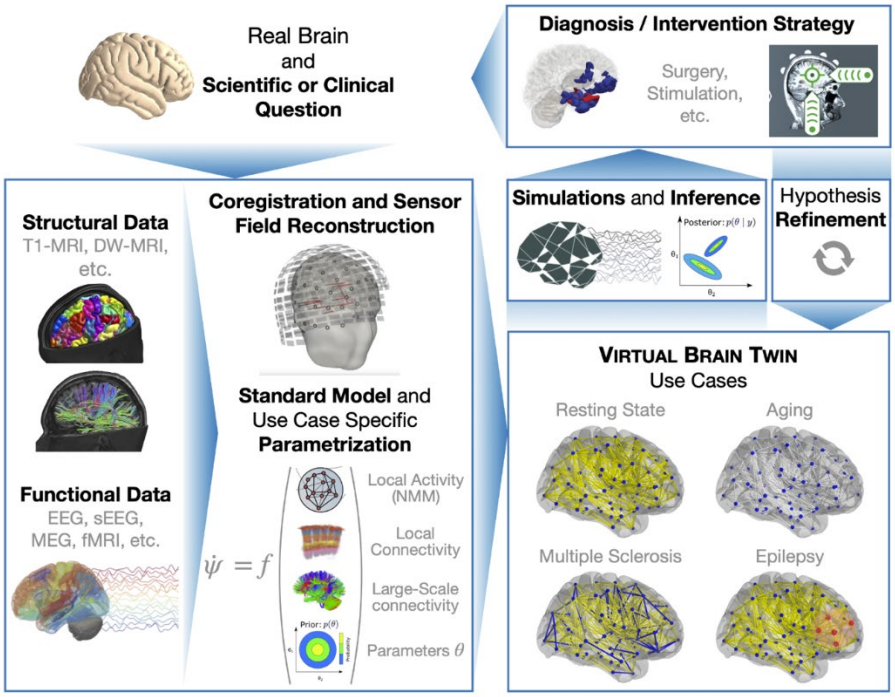


Figure: The progress of AID, from first insulin pumps and sensors, to commercial systems. A recent trend in the field is the transition from equation-based to data-driven control algorithms

Viktor Jirsa **11:15–11:50** **Wednesday, 30 July, 2025**
Title: ***Principles and operation of virtual brain twins***



Abstract: Current clinical methods often overlook individual variability by relying on population-wide trials, while mechanism-based trials remain underutilized in neuroscience due to the brain's complexity. A Virtual Brain Twin (VBT) is a personalized digital replica of an individual's brain, integrating structural and functional brain data into advanced computational models and inference algorithms. By bridging the gap between molecular mechanisms, whole-brain dynamics, and imaging data, VBTs enhance the understanding of (patho)physiological mechanisms, advancing insights into both healthy and disordered brain function. Central to VBT is the network modeling that couples mesoscopic representation of neuronal activity through white matter connectivity, enabling the simulation of brain dynamics at a network level. This transformative approach provides interpretable predictive capabilities, supporting clinicians in personalizing treatments and optimizing interventions. This Review outlines the key components of VBT development, covering the conceptual, mathematical, technical, and clinical aspects. We describe the stages of VBT construction–from anatomical coupling and modeling to simulation and Bayesian inference–and demonstrate their applications in resting-state, healthy aging, multiple sclerosis, and epilepsy. Finally, we discuss potential extensions to other neurological disorders, such as Parkinson's disease, and explore future applications in consciousness research and brain-computer interfaces, paving the way for advancements in personalized medicine and brain-machine integration.

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Ying-Cheng Lai **11:50–12:25** **Wednesday, 30 July, 2025**

Title: ***Controllability of nonlinear dynamical networks***

Abstract: There has been tremendous development in linear controllability of complex networks. Real-world systems are fundamentally nonlinear. Is linear controllability relevant to nonlinear dynamical networks? A common trait underlying both types of control exists: the nodal "importance". For nonlinear and linear control, the importance can be determined, respectively, by physical/biological considerations and the probability for a node to be in the minimum driver set. For empirical mutualistic networks and a gene regulatory network, the nonlinear nodal importance can be quantified by the ability of individual nodes to restore the system from the aftermath of a tipping-point transition. A finding was that the nodal importance ranking for nonlinear and linear control exhibits opposite trends: for the former large-degree nodes are more important but for the latter, the importance scale is tilted towards the small-degree nodes, suggesting strongly the irrelevance of linear controllability to these systems.
The speaker is not familiar with Network Physiology. Therefore, discussions with conference participants on potential applications of network control in Network Physiology will be appreciated.
Main collaborators: Prof. Jun-Jie Jiang, Prof. Wen-Xu Wang, and Dr. Shirin Panahi.

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Lunch Break **12:30-14:00** **Wednesday, 30 July, 2025**

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Session Chair:

Helene M. Langevin **14:00–14:35** **Wednesday, 30 July, 2025**
Title:
Abstract:

J. Randall Moorman **14:35–15:10** **Wednesday, 30 July, 2025**
Title: ***How Anti-Aircraft Gunnery Helps the Network Physiologist***
Abstract: During World War II, the urgent need to defend against rapidly maneuvering enemy aircraft spurred a series of breakthroughs in control systems theory. Engineers and mathematicians—including Norbert Wiener—developed new methods to predict and counteract unpredictable target movements using feedback, error signals, and adaptive algorithms. This work, which revolutionized anti-aircraft gunnery, also laid the groundwork for cybernetics: the science of communication and control in machines and living organisms.
At its core, anti-aircraft gunnery demanded an integrated system: radar to detect aircraft, predictive algorithms to forecast flight paths, servomechanisms to reposition guns, and human operators to oversee the entire process. Each component had a feedback loop, continually refining its performance based on real-time error signals (e.g., tracking discrepancy between predicted and actual flight paths). The system's overall success depended on interconnected controls that functioned cooperatively, demonstrating how

multiple feedback mechanisms interact to optimize a response under uncertain conditions.

Today's network physiologist faces an analogous challenge in understanding how organ systems coordinate to maintain homeostasis under constant internal and external perturbations. Just as a single anti-aircraft gun could not succeed without cooperating radar, computational models, and feedback sensors, no single organ can maintain health independently. Instead, the heart, lungs, kidneys, brain, and other systems must synchronize their operations, each continuously monitoring and adjusting functions through feedback loops.

Arthur Guyton's pioneering work on the circulation is a salient example of using WWII-era control principles in physiology. He described how the kidney, vasculature, and heart form a multi-loop control network, each component sensing changes (e.g., blood volume) and adjusting outputs (e.g., sodium excretion, vascular resistance, cardiac output). In doing so, Guyton implemented the very logic of predictive correction and feedback from anti-aircraft defense systems, showing that physiological stability emerges from interacting control loops across organ systems.

Modern Network Physiology expands on these foundations, blending cybernetics and nonlinear dynamics to capture the complex orchestration of multiple feedback loops at different scales. As with wartime gunnery, success depends on detecting small deviations quickly and responding effectively. When these loops fail to coordinate, just as a miscommunication in anti-aircraft targeting leads to missed shots or friendly-fire incidents, physiologic dysregulation ensues—manifesting as hypertension, arrhythmias, or systemic breakdowns.

Indeed, the same principles of adaptivity, feedback, and error correction refined for anti-aircraft targeting are central to analyzing and predicting network behaviors in physiology. By examining timing delays, control gains, and coupling strengths, scientists can quantify how robust or fragile multi-organ interactions may be. In real clinical contexts, this can translate to early detection of disease, optimized interventions, and more personalized medical strategies.

In essence, the lessons of WWII gunnery reveal how to harness feedback loops efficiently in complex environments. By interpreting organ systems as coordinated control circuits—each sensing, anticipating, and correcting for perturbations—the network physiologist can uncover the roots of health and disease. That a historical effort in ballistics and control should illuminate today's approaches to organ network integration reminds us of the timeless value in cross-disciplinary synergy.

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Coffee Break **15:10-15:40** **Wednesday, 30 July, 2025**

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Sebastiano Stramaglia **15:40–16:15** **Wednesday, 30 July, 2025**

Title: ***Higher order interactions, in physiological networks, assessed by gradients of O-information and decomposition of the transfer entropy.***

Abstract: The study of high order dependencies in complex systems has recently led to the introduction of statistical synergy, a novel quantity corresponding to a form of emergence in which patterns at large scales are not traceable from lower scales; its application in the analysis of physiological networks is the topic of this talk. Two computational tools will be described, gradients of O-information and the decomposition of the transfer entropy: their application on cardiovascular and cardiorespiratory interactions, as well as on heart-brain interaction, will be described. The structure of anticorrelated networks in the human brain will eventually be discussed.

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Rossella Rizzo **16:15–16:40** **Wednesday, 30 July, 2025**

Title: ***Network physiology of cortico-muscular interactions: mathematical framework and implications for physiological regulation, sleep and neurodegenerative disorders***

Abstract: The human organism consists of diverse physiological systems, which synchronously interact among each other through an integrated network of physiological interactions, which occur at multiple spatio-temporal scales and multiple levels. The new field of Network Physiology, has emerged to investigate interactions among diverse systems and how networks of networks (e.g. the brain as a neuronal network, muscles as fibers network) change across physiological states . Here, we focus on the network of brain-muscle interactions, essential in facilitating vital body functions. Traditional approaches to cortico-muscular coordination focus on associations between movement tasks or exercises and the activation of particular brain waves at specific cortical areas. However, neural control of the muscular system is continuously present even at rest. We hypothesize that network interactions between brain waves and rhythms embedded in muscle activity may also reflect changes in physiologic regulation as a function of physiological states. Moreover, it is hypothesized that PD starts years before appearance of evident symptoms related to locomotor dysfunction. Non-motor symptoms, related to autonomic nervous system dysfunction with effects on sleep, mood, cognition, indicate a higher-than-average risk of developing motor symptoms and a diagnosis of PD in the future. Thus, mapping the neuronal activation on the muscular system can lead to novel biomarkers for PD early diagnosis.

We investigate the coupling between synchronous bursts in physiologically relevant brain waves at distinct cortical locations and peripheral EMG activity in different frequency bands across four major, well defined physiological states – Wake, REM, Light Sleep (LS), Deep Sleep (DS). Particularly, in the first part we analyze cortical EEG signals and surface chin and leg muscle tone EMG signals from 36 healthy young subjects; secondly, we consider data from 97 healthy subjects and 33 PD sub age matched. Utilizing a novel approach based on the Network Physiology framework we develop a mathematical method, time delay stability (TDS), and we find that i) each physiological state is characterized by a unique network of cortico-muscular interactions with specific hierarchical organization and profile of links strength; ii) particular brain waves play role as main mediators in cortico-muscular interactions during each state; iii) PD leads to muscle-specific breakdown of cortico-muscular networks, altering the sleep-stage stratification pattern in network connectivity and links strength. Specifically, for young healthy subjects we find high connectivity and high network link strength during wake, intermediate during REM and LS, and low during DS, a sleep-stage stratification that indicates high sensitivity of cortico-muscular control to changes in autonomic regulation, even at low levels of physical activity and muscle tone during sleep. Healthy old subjects exhibit stronger links during wake and LS, and weaker links during REM and DS. In contrast, network interactions reorganize in PD with decline in connectivity and links strength during wake and non-REM sleep, and increase during REM, leading to markedly different stratification with gradual decline in network links strength from wake to REM, LS and DS. Further, the links strength profiles specific for each sleep stage are altered with PD, indicating disruption in the synchronous activity and network communication among brain waves and muscle rhythms.

Our empirical findings demonstrate previously unrecognized basic principles of brain-muscle communication, network integration and control, with potential clinical implications for neurodegenerative, movement and sleep disorders. However, it is evident the importance and the necessity of developing a mathematical formalism, capable of capturing the emerging behavior of networks of interactions among physiological systems. As first step, we develop a model of PDE to describe the space-time evolution of the electrical impulse, which travels from neuron to neuron in a complex integrated network of long-range interactions. Particularly, we study the formation of Turing patterns for a FitzHugh-Nagumo (FHN) model combined with anomalous diffusion terms. The model supports a wide scenario of stationary coherent structures, which could represent different scenarios in networks of interactions across physiological states. Our aim is to compare our findings for the model with the empirical observations of network physiology dynamics.

Our studies provide new insights on the laws of organ systems cross-communication, and shed light on a unifying theoretical framework to describe the complex coordination and network integration among cortical rhythms and rhythms in muscle activity that respond to changes in autonomic regulation, with potential for novel network-based markers for early diagnosis, and for guiding treatment strategies.

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Ronny P. Bartsch **16:40–17:05** **Wednesday, 30 July, 2025**

Title: ***Coexisting forms of coupling and networks of physiological interactions***

Abstract: Physiological systems can exhibit multiple independent forms of coupling, each operating on different time scales. These interactions are transient, with varying forms of coupling coexisting simultaneously and reflecting various aspects of physiological regulation. Specifically, we identify a network of interactions between the brain and other organ systems across physiologic states with distinct neuro-autonomic regulation. Our findings highlight how this network transitions under physiological and pathological changes, demonstrating a strong link between structure and function. These empirical investigations shed light on the mechanisms of physiological interactions and establish associations between patterns of network interactions and physiological states.

Round Table Discussion II **17:15-18:30** **Wednesday, 30 July, 2025**

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Session Chair:

Plamen Ch. Ivanov **09:00–09:35** **Thursday, 31 July, 2025**

Title: ***Physiologic network interactions: Novel hallmark of physiological state and function***

Abstract: The new framework of Network Physiology aims to understand states and functions at the organism level as emergent coordination among physiological sub-systems and systems, each of which exhibits unique dynamics characterized by non-stationary, noisy and even scale-invariant output. In this framework, transitions across physiologic states involve hierarchical reorganization of the networks of physiologic interactions. Despite the rapid development of Network Physiology as a new field, the specific question of how key physiologic systems continuously interact and collectively behave as a dynamic

network to generate distinct functions remains elusive. I will discuss a general strategy to approach this fundamental question. I will outline the typical challenges encountered in probing physiologic interaction and present some recently developed techniques suitable to address these challenges. By applying these new methods to empirical physiologic recordings, I will present some new findings regarding communications among distinct brain cortical rhythms as well as their feedback control on key organ systems with focus on plasticity of brain wave network interactions and brain-heart regulation.

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Ulrich Parlitz **09:35–10:10** **Thursday, 31 July, 2025**

Title: ***Data driven modelling, control, and dynamical networks***

Abstract: Understanding the interplay of different dynamic components in network physiology requires novel and efficient approaches for analyzing the interrelationships between different types of measurement data and methods for establishing links between observations and mathematical models that allow a better understanding of the underlying mechanisms and causalities. In the talk we will present novel methods for time series analysis, prediction, classification and parameter estimation. In particular, we will discuss features and applications of reservoir computing, where the response of networks of dynamic elements to a given input signal is used for prediction and control. When applied in network physiology, the networks play a dual role in this case: they are both the object and a tool of analysis.

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Coffee Break **10:10-10:40** **Thursday, 31 July, 2025**

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Klaus Lehnertz **10:40–11:15** **Thursday, 31 July, 2025**

Title: ***Time-Evolving functional brain networks - Insights from epilepsy***

Abstract: Functional brain networks are abstractions of interactions among brain regions reflecting normal and diseased functioning of the human brain. Networks consist of vertices and edges associated with brain regions and their time-dependent interactions that can be characterized with appropriate bivariate time-series-analysis techniques [1,2]. Long-term electroencephalographic measurements – e.g. in subjects with epilepsy – enable investigating the evolution dynamics of functional brain networks over longer periods of time (days to weeks) with high spatial and temporal resolution. Metrics based on concepts and methods

from graph theory then allow characterizing the networks' topological and spectral properties as well as their internal organization [1,2]. Time series of such metrics form the basis for in-depth studies of time-evolving functional brain networks which can potentially provide more detailed information about the networks' temporal fluctuations and their complex interplay with ongoing physiologic activities – such as biological rhythms [3,4] – compared to what can be achieved with snippets of recordings of brain dynamics that usually last only a few tens of seconds. I will illustrate this approach at the example of time-evolving epileptic brain networks [5], highlighting the relevance of the approach for basic physiology and for clinical practice, in particular as a novel tool for diagnosis and treatment [6,7,8].

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Luca Faes **11:15–11:50 Thursday, 31 July, 2025**

Title: ***Measuring integration and emergence in dynamic physiological networks: an information-theoretic approach***

Abstract: The complexity of physiological systems stems for the richness of the interactions among their units. To address such complexity, a variety of systems (e.g., the brain or the human organism) has been described as networks whose interacting pairs of nodes (e.g., neural units or organ systems) are connected by links mapping functional dependencies (e.g., brain connectivity or cardiovascular interactions). Beyond this very popular, yet basic description, a mounting body of evidence is showing that interactions within physiological networks can occur in groups of three or more nodes and cannot be fully described just in terms of simple dyads. Accordingly, several methods rooted in probability and information theory are being developed to quantify polyadic, higher-order interactions in dynamic network systems, that is, patterns of activity that can be explained in terms of the whole but not the parts. In this context, a crucial role is played by the concept of statistical synergy, measuring the information conveyed to the collective state of a network system by all its units considered together but none of them individually.

This presentation introduces an approach, based on the emerging framework of information dynamics, to quantify two fundamental properties of network systems which arise from high-order interactions among their units, i.e. integration and emergence. Both these properties refer to how much better a dynamic network system is at predicting its own future when it is considered as a whole compared to when it is considered as the sum of its parts, leveraging synergy: integration evaluates how much predictive information (PI) is generated by the system over and above the PI generated by its units considered alone; emergence evaluates how much combining the present states of the units generates irreducible PI, i.e. information about the future evolution of the system that cannot be imputed to any unit considered alone. Here, these concepts are formalized in the context of network systems mapped by multivariate random processes, computing the PI between the present and the past network states and dissecting it into

amounts quantifying the unique, redundant and synergistic information shared by the present of the network and the past of each unit. The decomposition of the PI is performed exploiting the popular frameworks of Partial Information Decomposition and Integrated Information Decomposition, from which quantitative measures of integration and emergence capacity are defined.

The proposed tools are implemented in practice using vector autoregressive models fitted on multivariate time series and validated in simulated network systems with known dynamics, determining how the integration and emergence capacity of the system are influenced by the complex interplay between internal dynamics and connectivity structure. Then, the measures are applied in a paradigmatic case study in Network Physiology, i.e. the network of interactions between the beat-to-beat spontaneous variability of heart rate, arterial pressure and respiration measured in resting conditions and during postural and mental stress. Our results point out the proposed measures of integration and emergence as hallmarks of the integrated short-term autonomic control in cardiovascular and respiratory networks.

Recent theoretical works in the field of information theory a mounting body of evidence is showing that taking the higher-order structure of these systems into account can greatly enhance our modeling capacities and help us to understand and predict their emerging dynamical behaviors

In this context, a crucial role is played by the statistical concepts of redundancy and synergy, measuring respectively the information conveyed to the collective state of a network system simultaneously by its units, and the information conveyed by all units together but none of them individually. Data-driven methods for the analysis of complex physiological systems pay a key role in the field of Network Physiology. Such methods are typically devised to build. out of a set of physiological time series, a network model encoded by a graph where the observed system (e.g., the brain or the human organism) is represented by distinct nodes (e.g., neural units or organ systems) connected by edges mapping functional dependencies (e.g., brain connectivity or cardiovascular interactions).

The framework of information dynamics offers a set of tools, grounded within the solid basis of information theory, to quantify several aspects of the dynamic interactions observed at the nodes of complex network systems. These tools, including measures of information storage, Granger causality and higher-order interactions, are extensively used to assess regulatory mechanisms, coupled activity and emergent behaviors in physiological networks studied from multiple simultaneously measured biosignals. Nevertheless, the framework of information dynamics has been developed mostly to assess interactions from discrete-time processes studied in the time domain, and this constitutes a limitation for the analysis of physiological systems where interactions occur at different levels of horizontal and vertical integration within the human body. For instance, the standard formulation of information dynamics is inappropriate to study the frequency-specific interactions occurring among the physiological rhythms of different organ systems.

This contribution illustrates some developments of the framework of information dynamics whereby we move from the analysis of pairwise interactions between coupled processes to the study of higher-order interactions involving more than two processes, and from the time-domain to the frequency-domain analysis of physiological time series. Our developments exploit the spectral representation of linear vector autoregressive models to quantify pairwise and higher-order interactions for multivariate rhythmic processes interacting in distinct frequency bands. The new framework will be first formulated theoretically and implemented through data-efficient estimators. Then, its performance and peculiarities will be illustrated on simulations of stochastic oscillatory processes. Finally, applications to physiological networks explored at different levels of vertical and horizontal integration will be reported, including human cardiovascular, cardiorespiratory and cerebrovascular oscillations studied in different physio-pathological states, electrocorticographic signals acquired in an animal experiment during anesthesia, and multichannel EEG recordings acquired during a motor execution task.

Rosario Mantegna **11:50–12:25** **Thursday, 31 July, 2025**

Title: ***Clustering and dismantling of comorbidity networks***

Abstract: We investigate clusters of diseases both in PROJ and in SVN networks. PROJ networks are so dense that Infomap, a widely used community detection algorithm [1], is unsuccessful in detecting distinct clusters of diseases. On the other hand, the same algorithm applied to SVN networks is highlighting clusters of diseases that are informative about different groups of comorbidities occurring for different

cohorts of patients. To quantify similarity between pairs of diseases' communities we compute the Jaccard similarity J(Ca,Cb) of each pair of communities Ca and Cb. The value of Jaccard similarity ranges from zero (observed when no common link is present between the two communities) to one (observed when the two communities presents the same links). For all pairs of communities, the Jaccard similarity is running from 0 to the maximum value of 0.609. The Jaccard matrix computed between all pairs of 380 diseases' communities present a number of pairs of communities with a value close to 0.6 that is indicating a large overlap of edges in several communities. Starting from the Jaccard similarity we define a distance for each pair of communities as d(Ca,Cb) and using this distance we perform a hierarchical clustering procedure with the average linkage algorithm. The average linkage hierarchical tree shows several distinct branches indicating that the SVNs have diseases' communities of different patient cohorts that cluster together.
In our analysis of comorbidity networks, we also consider a so-called dismantling procedure, i.e., the successive removal of nodes (i.e., diseases) from networks with a procedure based on global network properties, both on the PROJ and SVN networks. In this procedure, we highlight the categories of diseases that contribute to the backbone of comorbidity relationships. Again, we verify that the approach of SVN diseases' networks provide information that is not obtainable using only the information present in the PROJ networks. Moreover, this information is cohort specific and is consistent with known conclusions obtained in epidemiological studies.
The knowledge of diseases' categories that are fragmenting the largest connected component of SVN comorbidity network give us information on the diseases' categories to target to minimize the effects of comorbidity for different cohorts of sex and age. For each cohort, we select the diseases whose removal reduces the size of the largest connected component of SVN to 10% of its original size. Having highlighted a set of diseases, for each cohort, we count the fraction of diseases belonging to each category and we compare this fraction with the fraction observed by randomly sampling a set of diseases of the same size from the corresponding PROJ network. With this comparison we are able to detect the over-expression or under-expression of diseases of a specific category for each cohort.

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Lunch Break **12:30-14:00** **Thursday, 31 July, 2025**

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Session Chair:

Jürgen Kurths **14:00–14:35** **Thursday, 31 July, 2025**

Title: ***Various Synchronization Phenomena in Neural Systems with Time Delay and Complex Noise***

Abstract: We study effects synchronization phenomena in different models of many coupled neurons. The foci are on systems with partial time delays, on complex noise and on those with excitatory and inhibitory synapses their resulting dynamics. We discuss various resulting dynamics, especially synchronization phenomena and how one can control different regimes via time delays and noise parameters.
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Krasimira Tsaneva-Atanasova **14:35–15:10** **Thursday, 31 July, 2025**

Title:

Abstract:

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Coffee Break **15:10-15:40** **Thursday, 31 July, 2025**

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Nandu Goswami **15:40–16:15** **Thursday, 31 July, 2025**

Title: ***Risk of thromboembolism in space: System interactions, challenges and perspectives***

Abstract: Spaceflight has effects on many important physiological systems. These include the musculoskeletal system, the cardiovascular system, cerebral autoregulatory control, and, recently, the coagulation system. In 2020, a diagnosis of deep venous thrombosis (DVT) was made during a long-duration ISS mission, which may lead to a potentially fatal pulmonary embolism (PE). Interestingly, jugular DVT is rarely reported on Earth but is associated with relatively poor outcomes. It remains to be clarified, however, whether the poor outcomes are due to underlying comorbid disease is usually associated with central venous lines or cancer, or due to the clot itself. While DVTs can occur without PEs, the latter is almost always preceded by a DVT. Diagnosis of DVT can be challenging and may even be missed, even when PE is diagnosed. Thus, clinicians usually use Venous Thromboembolism (VTEs) to describe a pathology that includes DVT and PE. When PE occurs, lung circulation can be compromised, causing varying degrees of respiratory and cardiovascular insufficiency, leading to mortality. While DVT can occur without PE, the latter is believed to be preceded by a DVT. Diagnosis of DVT can be challenging due to the fact its clinical manifestations can vary over time, spontaneously resolve, or are not observable, even when PEs have already been diagnosed. As a result, clinicians usually use the term Venous Thromboembolism (VTE), which refers to both DVT and PE, considering them as different stages of the same pathology.

VTE formation on Earth depends on the interaction of hypercoagulability, blood stasis, and vessel injury, commonly termed the Triad of Virchow. Blood coagulation depends on a finely controlled balance of pro- and anti-coagulant factors. While some aspects of the venous system and blood coagulation have been investigated in microgravity, there is a paucity of data. Furthermore, the reported changes in CSF dynamics in microgravity and the compensatory action of venous flow and CSF flow to keep the intracranial volume constant is a potential predisposing factor for the higher incidence of jugular DVT in space when compared to jugular DVT on Earth. As a result, a complete picture of how the Triad is affected in microgravity remains to be determined.

Presented in this talk will be how a given adverse event such as thrombosis emerges from interactions of processes and systems in the human body and provide a perspective/ outlook on how Network Physiology can help resolve current challenges and lead to new knowledge and treatment procedures before, during and after space flight. Specifically, the systems-interactions findings from an ESA-expert topical team, coordinated by Prof Goswami, examined the gaps in this research field via extensive literature reviews. Aspects such as how network physiology as a framework and as a field can help evaluate health and diagnose abnormal conditions during space flight will be presented. Original data from ongoing clinical studies will be presented, considering the interactions of the system, especially aspects such as pro- and anti-coagulatory factors, -omics, and the genomics associated with coagulation, as well as the role of circadian rhythms in coagulatory events. Domains of venous system status, hemodynamics, coagulation physiology, cerebral spinal fluid (CSF) dynamics, and the constraints of spaceflight to define a (operationally-focused) research and technological/procedural evaluation roadmap will be presented.

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Paul Bogdan **16:15–16:40** **Thursday, 31 July, 2025**

Title: ***Artificial Intelligence for Network Physiology***

Abstract: Network physiology explains how different organ systems within a living organism interact and dynamically coordinate with each other as a complex network sustaining life. The deciphering of the principles of collective (physiological) intelligence, emerging from the interactions among organs, calls for defining the theoretical foundations for (i) understanding how multiscale physiological processes interact to contribute to various network physiological states; (ii) modeling, analyzing and detecting the disease signatures or the change points corresponding to the onset of diseases; and (iii) discovering noninvasive efficient, robust and agile control strategies for medical therapies. The biological processes, enabling the coupling and information transfer among organ systems to sustain life, exhibit a pronounced non-stationary, non-Markovian and non-Gaussian behavior. To contribute to the definition of theoretical foundations for network physiology, we will discuss a general and comprehensive mathematical framework capable to infer couplings among physiological processes, model the network dynamics among physiological processes, and efficiently control such adaptive networks of dynamical systems. A special emphasis will be put on capturing the multi-fractal / non-Markovian, non-stationary and non-Gaussian behavior of biological networks and identifying the laws of time-varying and nonlinear network interactions that drive these adaptive networks of dynamical systems. More precisely, to infer the “unknown unknowns” influencing time varying complex physiological networks, we will discuss mathematical techniques for jointly estimating the fractional latent node activities, and unknown drivers, as well as iteratively infer the complete model (latent + observed). To efficiently control adaptive networks of dynamical systems, we will discuss mathematical models and algorithms to determine the minimum number of driven nodes and their placement within a specific time-horizon (i.e., the ‘time-to-control’). Remarkably, we demonstrate that controlling non-Markovian dynamical networks requires considerably fewer driven nodes to steer the network’s state to a desired goal for any given time-to-control as compared with Markov dynamical networks. Finally, we discuss and exemplify how multifractal and non-Markovian modeling of network physiology leads to novel (biological geometry-aware) artificial intelligence (AI) for disease detection. More precisely, we will discuss how a fractional-order dynamics deep learning analysis can predict the stage of chronic obtrusive pulmonary disease (COPD) with over 98% accuracy from a variety of physiological processes. In conclusion, this mathematical framework can uncover the multiple forms of coupling and feedback loops among biological processes enabling us to derive principles of coordination and network integration among dynamical systems in association with network states and functions. We will also review the remaining challenges related to this framework for adaptive networks of dynamical systems across several neuroscience case studies and highlight several problems to be addressed by our community in order to define the theory of adaptive networks of dynamical systems and their applications to physiology and medicine.

Sergi Garcia-Retortillo **16:40–17:05** **Thursday, 31 July, 2025**

Title: ***Networks of Cardio-Muscular coordination – Evolution with exercise and fatigue***

Abstract: A fundamental question in cardiovascular and muscle physiology is how the heart operates in

synchrony with distinct muscles to maintain homeostasis, facilitate movement and adapt to exercise demands and fatigue. The utilization of reductionist approaches has led to great advances in the understanding of the autonomic regulation of the heart, as well as basic muscle physiology at the cellular and molecular levels, with a focus on the microscopic scale of individual muscles. However, the precise mechanisms regulating cardio-muscular coupling remain unknown. Specifically, we do not know the functional forms and physiological principles of dynamic coupling and network communication between the heart and distinct muscles, and how these network interactions adapt to exercise and fatigue.

To establish the first building blocks of cardio-muscular coordination, we present here a novel analytical approach to assess the direct coupling between cardiac activity (EKG, heart rate variability (HRV)) and activation of distinct muscles (EMG). Specifically, we analyze the degree of cross-correlation between time series of instantaneous HR and EMG spectral power for different frequency bands (amplitude–amplitude coupling). This method allows us to identify basic physiological principles of direct coupling and network communication between autonomic regulation of cardiac function and distinct muscles, and how these network interactions evolve over time, adapting to exercise and fatigue. Notably, this method has been successfully utilized to assess how distinct frequency bands embedded in muscle dynamics synchronize with each other and integrate as a network across muscles during exercise, and to establish how the network of inter-muscular interactions reorganizes with fatigue

Accordingly, our aim was to investigate how autonomic regulation of cardiac function synchronizes and integrates as a network with the activity of distinct muscles during exercise, and establish how the network of cardio-muscular interactions reorganizes with fatigue. In summary, (1) we uncovered the first profiles of cardio-muscular network interactions during exercise; (2) these profiles depend on the role muscles play during the specific movement and on muscle histochemical characteristics; (3) the degree of cardio-muscular coupling decreases with fatigue due to parasympathetic withdrawal and neuro-muscular fatigue; (4) cardio-muscular profiles of link strength show similar characteristics and response to fatigue across timescales, featuring complex transitions from synchronous to asynchronous behavior at short timescales of a few seconds. The Network Physiology of Exercise framework that we utilize in this study introduces new avenues for the development of novel network-based markers, with the potential to characterize cardio-muscular, inter-muscular and inter-organ network interactions during exercise, assess levels of fatigue, fitness status, or the effectiveness of cardiovascular and muscle injury rehabilitation programs.

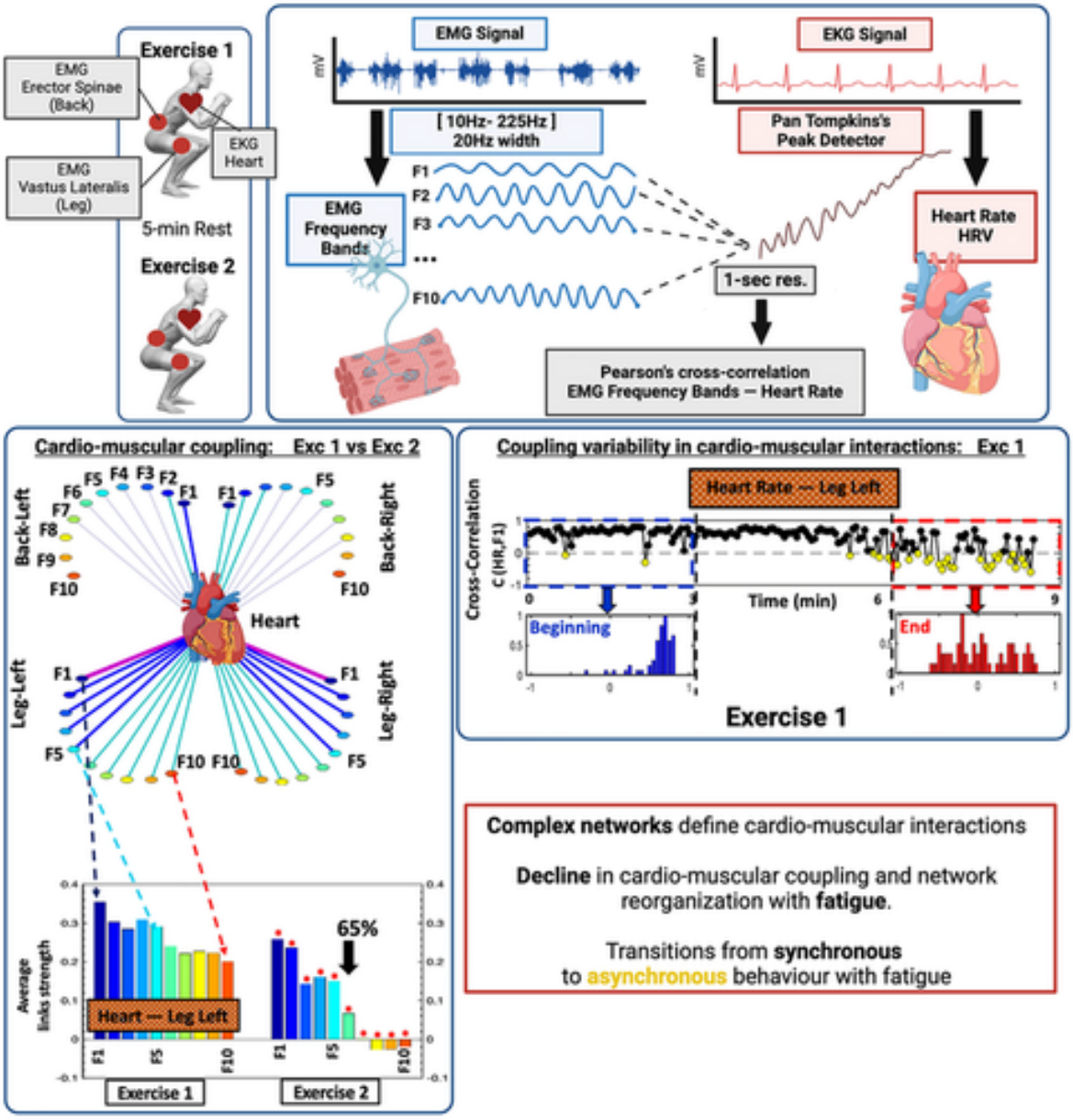

Figure 1. This study introduces a pioneering approach to assess cardio-muscular network interactions by examining the synchronization of cardiac function with muscle activity during exercise and fatigue. Participants performed two sets of bodyweight squats until exhaustion, with a 5 min rest period between sets. During the protocol, electrocardiogram (EKG) signals were recorded alongside electromyography (EMG) signals from the left and right vastus lateralis (Leg Left, Leg Right) and erector spinae (Back Left, Back Right) muscles. We decomposed EMG signals into 10 frequency bands (F1–F10) and then cross-correlated these bands with heart rate derived from the EKG. We uncover the first profiles of cardio-muscular interactions characterized by specific hierarchical organization of link strength. We observed a significant decline in the degree of cardio-muscular coupling with fatigue (~65%), marked by complex transitions from synchronous to asynchronous behavior.

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Social Event

Concert, Classical music, Sala Bianca	**19:00**	**Thursday, 31 July, 2025**
Dinner, Ristorante Sociale	**20:30**	

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Session Chair:

Alexey Zaikin **09:00–09:35** **Friday, 01 August, 2025**

Title: ***Analysis of multidimensional medical data with synolitic networks***

Abstract: Advancements in modern physiology have led to an unprecedented surge in data availability, spanning genomic, proteomic, epigenetic, and other -omics data. These datasets can be integrated with high-frequency time series from EEG, ECG, or MEG, as well as imaging modalities such as ultrasound, MRI, and fMRI. The sheer volume of this data has already surpassed our analytical capabilities. More recently, single-cell data have become available, allowing for the ultra-high-dimensional characterization of individual patients, where features are not only numerous but also dynamic over time. Fortunately, the rapid progress of AI has equipped us with a diverse range of tools, from convolutional neural networks for computer vision to bidirectional transformers and large language models (LLMs) such as ChatGPT and Gemini. However, training such models requires large datasets—an obstacle in clinical practice, where data collection is both expensive and ethically challenging. A promising approach to addressing the challenges of high-dimensional, low-sample-size data is the use of ensemble methods, which combine multiple low-dimensional classifiers. This principle underlies the efficiency of DeepSeek compared to models like ChatGPT. This can be also done by uncovering the underlying network structure within complex datasets—an approach that we explore through Synolitic or Ensemble Graph Network analysis. In Synolitic networks, class labels alone are used to reconstruct an inherent network structure in data that lack an a priori defined topology [1]. These networks belong to the broader class of parenclitic networks, first introduced by Zanin and Boccaletti, which infer connections between parameters or nodes without requiring prior knowledge of their interactions [2]. This is achieved by leveraging residual distances from linear regression models constructed between every pair of analytes to generate a graph. In [4], we applied this methodology to machine learning classification for identifying cancer development signatures from human DNA methylation data. Recognizing that biological interactions are often nonlinear, we further proposed using two-dimensional kernel density estimation (2DKDE) to model control distributions [5]. Synolitic networks can be interpreted as an ensemble of classifiers in graph form, representing a specialized type of correlation network in which correlations capture changes between two conditions (e.g., disease vs. non-disease) [6]. These networks have been successfully employed to identify age-related trajectories in Down syndrome [7] and to predict survival outcomes for critically ill COVID-19 patients [8]. A key advantage of the Synolitic network approach is its compatibility with Graph Neural Networks (GNNs) [1], making it applicable not only to structured data but also to imaging analysis, including fMRI [9]. Future research will focus on developing Synolitic networks with enhanced feature engineering capabilities and extending their application to time-varying data, which remains an ongoing challenge.

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Flavio H. Fenton **09:35–10:10** **Friday, 01 August, 2025**

Title: ***Spatiotemporal synchronization in networks of cardiac cells during arrhythmias and defibrillation***

Abstract: Approximately 6.57 million cardiac arrests, caused by ventricular fibrillation, occur out-of-hospital worldwide each year, yet survival rates remain low, with fewer than 10% of patients surviving to hospital discharge. This highlights the urgent need for effective and timely defibrillation, both through emergency interventions and long-term solutions such as implantable cardioverter-defibrillators (ICDs), which are implanted in over 200,000 patients globally each year to prevent sudden death. Defibrillation shocks typically deliver energies ranging from 20-100 joules for internal defibrillation and up to 300 joules for external defibrillation. In this talk, we demonstrate that ventricular fibrillation is chaotic, not random, and as such, it is possible to identify unstable periodic orbits within the dynamics.Therfore. by locating spsssssssecific times as well as precise excitations in phase space, we can achieve defibrillation using much lower energies (order of 90% rduction. We experimentally demonstrate this concept in two-dimensional systems and in 3D in vivo preparations.

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Coffee Break **10:10-10:40** **Friday, 01 August, 2025**

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Boris P. Kovatchev **10:40–11:15** **Friday, 01 August, 2025**

Title: ***How in silico models of the human glucose-insulin metabolic network across organ systems made animal trials obsolete***

Abstract: In health, glucose metabolism is tightly controlled by a hormonal network including the gut, the liver, the pancreas, and the brain to ensure stable fasting blood sugar levels, brief post-meal increases, and transient fluctuations with exercise. In diabetes, this network control is disrupted by deficiency or absence of insulin secretion. The figure below depicts the glucose-insulin control network. The conduits disrupted by diabetes are marked red:

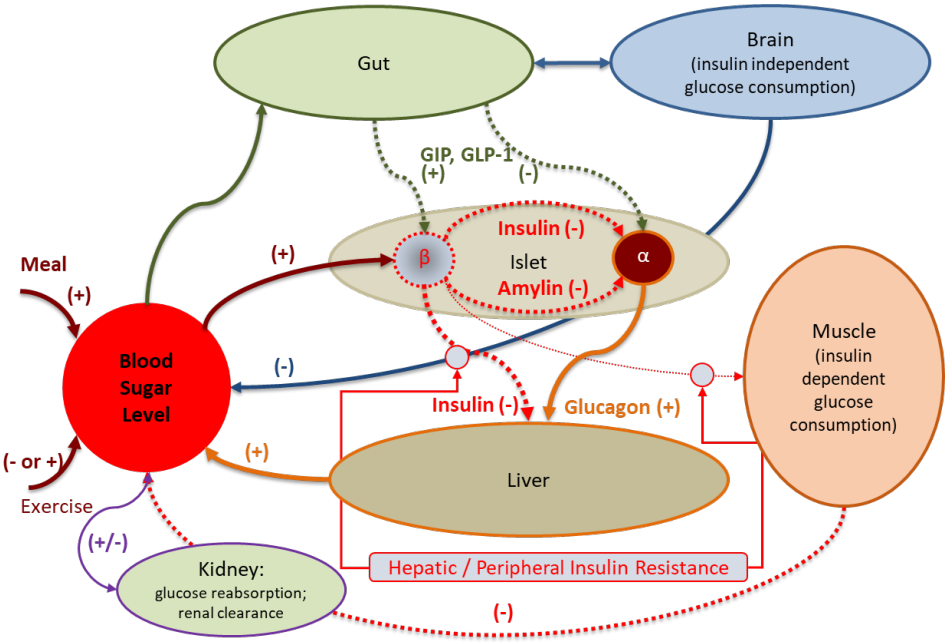

Figure: The human glucose-insulin control network

Type 1 diabetes is characterized by absolute deficiency of insulin secretion resulting from autoimmunity targeting the β–cells in the islets of Langerhans of the pancreas – the site of insulin secretion and synthesis. Affected individuals require insulin therapy to control hyperglycemia and sustain life. In type 2 diabetes, insulin resistance (hepatic and/or peripheral) is typically accompanied by diminished insulin responsivity of the β–cells, leading to overall increase in both fasting and postprandial blood sugar levels.

During the past 50 years, this network has been modeled extensively: In 1979, Bergman and Cobelli introduced the Minimal Model of Glucose Kinetics – a compartmental model providing basic description of the human metabolic network. By 2006, the minimal model concept has evolved into elaborate multi-compartment models described by systems of nonlinear differential equations with multiple parameters, such as rates of endogenous glucose production, whole body glucose disappearance, and appearance of meal carbohydrates in the bloodstream.

Based on one of these “maximal” models, in 2007 we introduced a computer simulator of the human metabolic system equipped with a “population” of N=300 in silico “subjects” with type 1 diabetes. Each in silico “subject” was defined by a specific physiologically plausible combination of model parameters. In January 2008, in an unprecedented decision, the U.S. Food and Drug Administration (FDA) accepted this simulator as a substitute to animal trials for the pre-clinical testing of insulin treatment strategies. This opened the field for rapid and cost-effective development and pre-clinical testing of new treatment approaches.

In the years that followed, the metabolic simulation environment, now known as the UVA/Padova simulator, has grown to a collection of over 7,000 in silico “individuals” with type 1 and type 2 diabetes. Countless in silico experiments allowed the development and pre-clinical testing of new treatment strategies, including but not limited to, automated closed-loop control of diabetes, a.k.a., the artificial pancreas. Meanwhile, animal experiments for the purpose of designing new insulin treatment algorithms, have been abandoned.

Paul Bogdan **11:15–11:50** **Friday, 01 August, 2025**

Title: ***Network Physiology-inspired theoretical foundations of neuroAI: Challenges and a Gedanken modeling framework of living neuronal networks dynamics***

Abstract: Brains build compact models or discover governing laws of the world from just a few noisy and possibly conflicting observations. Biological brains can also predict uncanny events via memory-based analogies especially when resources are limited. The ability of biological intelligence to discover, generalize, hierarchically reason and plan, and complete a wide range of unknown heterogeneous tasks calls for a comprehensive understanding of how distributed networks of interactions among neurons, glia, and vascular systems enable animal and human cognition. Such an understanding can serve as a basis for advancing the design of artificial general intelligence (AGI). In this talk, inspired by network physiology, we

will discuss the challenges and potential solutions for inferring the theoretical foundations of biological intelligence and NeuroAI. To infer networks from very scarce and noisy data, we propose a new mathematical framework capable of learning the emerging causal fractal memory from biological neuronal spiking activity. This framework offers insight into the topological properties of the underlying neuronal networks and helps us predict animal behavior during cognitive tasks. We will also discuss an AI framework for mining the optical imaging of brain activity and reconstructing the weighted multifractal graph generators governing the neuronal networks from very scarce data. This network generator inference framework can reproduce a wide variety of network properties, differentiate varying structures in brain networks and chromosomal interactions, and detect topologically associating domain regions in conformation maps of the human genome. We will discuss how network science-based AI can discover the phase transitions in complex systems and help with designing protein–nanoparticle assemblies. To infer the objectives and rules by which distributed networks of neurons attain intelligent decisions, we discuss an AI framework (multiwavelet-based neural operator) capable of learning, solving, and forecasting sets of coupled governing laws. We thus learn the operator kernel of an unknown partial differential equation (PDE) from noisy scarce data. For time-varying PDEs, this model exhibits 2-10X higher accuracy than state-of-the-art machine learning tools. Inspired by the multifractal formalism for detecting phase transitions in biological neuronal networks, we explore the principles of self-organization in Large Language Models (LLMs). We reveal the intricate dynamics of neuron interactions, showing how self-organization facilitates the emergence of complex patterns and intelligence within LLMs.

Misako Takayasu **11:50–12:25** **Friday, 01 August, 2025**
Title: ***Analysis of high-resolution metagenomic time series and modelling of the microbiome interaction network***
Abstract: Although feces has a common image as a dirty substance to be discarded, it is now attracting attention and is rapidly being studied from a variety of scientific perspectives, including medicine, the immune system, ecology and complex systems. This new scientific trend is being driven by a new observational technique called metagenomic analysis. It is now possible to read the DNA of gut bacteria in feces in parallel and quantitatively measure the reality of the complex microbial ecosystem in the gut. Using our newly developed instrument, we observed mouse feces at high frequencies and obtained time series of fluctuations in the number of about a thousand species. As this time series data is highly non-stationary and the frequency distribution has characteristics similar to a power law distribution, and therefore cannot be adequately characterized by ordinary data analysis, we have developed a new data analysis method that is just right for this data set. This allowed us to observe the actual interactions between species and to represent complex networks of interactions such as cooperative and exclusive relationships. We are also building a mathematical model that will reproduce the whole characteristics of this time series.

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Lunch Break **12:30-14:00** **Friday, 01 August, 2025**

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Session Chair:

Eckehard Schöll **14:00–14:35** **Friday, 01 August, 2025**
Title:
Abstract:

Robert J. Thomas **14:35–15:10** **Friday, 01 August, 2025**
Title:
Abstract:

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Coffee Break **15:10-15:40** **Friday, 01 August, 2025**

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Ying-Cheng Lai **15:40–16:15** **Friday, 01 August, 2025**

Title: ***Reservoir computing and dynamical networks: recent results and open questions***

Abstract: Reservoir computing has been exploited to solve a variety of challenging problems in nonlinear and complex dynamical systems. The speaker will review some recent works from his group in this area: predicting tipping point, digital twins of nonlinear dynamical systems, parameter and trajectory tracking, and associative memory for complex dynamical patterns. Some open questions will discussed.
The speaker is not familiar with Network Physssssiology. Therefore, discussions with conference participants on potential applications of reservoir computing in Network Physiology will be appreciated.
Main collaborators: Dr. Shirin Panani, Dr. Ling-Wei Kong, and Mr. Zheng-Meng Zhai.

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Alexey Zaikin **16:15–16:40** **Friday, 01 August, 2025**

Title: ***Emerging of intelligence in complex physiological networks***

Abstract: The human body is a supernetwork—a network of networks—where each individual network exhibits sufficient complexity to generate intelligence. Moreover, these networks communicate in an intelligent manner. This raises fundamental questions: What are the principles governing the emergence of intelligence in complex physiological networks? How can we measure it? And how does intelligence interact with other properties of complex networks, such as multiplexing or even consciousness? In the human brain alone, there are approximately 86 billion neurons, each with up to 10,000 dynamic synapses, interwoven with a network of astrocytes and other glial cells. Calcium events in astrocytes can be triggered by neural activity, subsequently modulating synaptic neurotransmitters and facilitating local, transient synchronization. Recently, we demonstrated that astrocytes, through this localized integration, can organize associative working memory [1,2] and even enable situation-based neuromorphic memory in spiking neuron-astrocyte networks [3]. Furthermore, in a simple yet biologically realistic neuro-glial model, we showed that the presence of astrocytes contributes to positive Integrated Information, suggesting that their evolutionary emergence may have played a crucial role in the development of consciousness [4,5]. Thus, astrocytes and genetic networks may influence not only intelligence but also the emergence of consciousness. Beyond the neural network, each cell contains multiple complex and interacting networks, and even the genome alone possesses enough complexity to exhibit perceptron-like properties [6]. Intelligence can emerge in genetic networks through various mechanisms [7], and some theories even suggest a role in the generation of consciousness [8]. However, a key open question remains: How is learning organized in genetic-neuron-astrocyte networks? Another intriguing discovery is that stochasticity can induce artificial intelligence-like behavior by altering the effective phase space of the system. Specifically, noise can induce excitability—a fundamental requirement for AI-like properties in neuron-

astrocyte systems—through noise-induced phase transitions [9]. A critical challenge is developing methods to measure the ability of a dynamical network to contribute to the intellectome of a physiological system. Even more intriguing is the relationship between the intellectome and the system's capacity to generate consciousness. In an effort to quantify consciousness, the Integrated Information Theory of Consciousnesshas been proposed, controversially claiming not only to measure brain complexity but also to estimate the level of consciousness itself.

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Closing **16:40-17:00** **Friday, 01 August, 2025**
Plamen Ch. Ivanov

Poster Session I

17:15-18:30 Sunday, 27 July, 2025

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1. Ensemble of coupling profiles and dynamic networks of brain wave interactions as hallmark of health and neurodegenerative disorders

William Drury[1], **Yaopeng J.X. Ma[1*]**, Marie-Helene Saint-Hilaire[2], James W. Holsapple[3] and Plamen Ch. Ivanov[1*]
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Introduction

Brain rhythms across cortical regions are dynamically modulated across physiologic states and disrupted by neurodegenerative disorders. The traditional paradigm in brain research emphasizes the role of individual dominant brain rhythms, their spatiotemporal organization, and pairwise interactions in association with diverse physiological states and pathological conditions. However, interactions among physiological systems as a network are essential to facilitate physiological functions and conditions and to maintain health. The field of Network Physiology provides an alternative integrative approach and theoretical framework to understand how physiological states and functions emerge out of complex dynamic networks of systems interactions, and the mechanisms through which breakdown in physiological networks leads to pathological states and disease [1-4]. Recent studies using the network physiology approach reveal that all cortical brain rhythms continuously coordinate their activity to sustain physiological states and functions [5, 6]. Further, different cortical rhythms play role as major mediators of interactions and control of peripheral organ systems [7, 8, 9]. Neurodegenerative disorders, such as Parkinson's disease (PD), disrupt physiological networks like the cortico-muscular network [10], leading to hierarchical disorganization and altered link strengths. However, how neurodegenerative disorders affect the interaction network of distinct physiologically relevant brain rhythms within and across cortical regions across physiological states remains unknown.

Hypothesis and Method

We hypothesize that brain rhythms within and across cortical regions coordinate as a complex network to generate basic states under autonomic regulation such as wakefulness, sleep, and sleep stages and that the hierarchical network organization and dynamics are altered by neurodegenerative disorders. Further, we hypothesize that the effects of neurodegenerative diseases on interaction network among cortical rhythms maybe heterogeneous for physiological states with different mechanisms of autonomic regulation.

To quantify the degree of synchronous (or asynchronous) activity in the spectral power of all (dominant and non-dominant) cortical rhythms at each physiological state (wake/sleep stages), we derive the degree of positive and negative cross-correlation within short epochs of time throughout the duration of the state to obtain cross-correlation distribution profiles for each pair of cortical rhythms ($\delta, \theta, \alpha, \sigma, \beta$ and γ) from normalized EEG power at six cortical locations representing the frontal, central, occipital left and right hemisphere. Links strength in the network of cortical rhythms is derived from the functional form of the cross-correlation distribution profile for each pair of rhythms. Coupling profiles, links strength, and fractions of significant positive and negative correlated links, and network connectivity patterns of inter-hemispheric and intra-hemispheric subnetworks and modules were compared between healthy subjects and PD patients across all sleep stages.

Results

We discovered that cortical rhythms interact through an ensemble of coupling forms, universally observed across individuals. Further, the ensemble of coupling forms uniquely defines each physiological state (wake/sleep, sleep stages). We find that Parkinson's neurodegeneration leads to amplified synchronous and asynchronous activity of cortical rhythms, leading to significant modulation in the functional forms of coupling profiles and links strength, with corresponding reorganization of network structure and dynamics within subnetworks and modules.

Our empirical analyses show that PD leads to heterogeneous reorganization of the brain waves network, where certain subnetworks and modules are more affected than others, and that the degree of network reorganization depends on the specific physiological states (sleep stages). Specifically, in PD patients networks of both positive (synchronous) and negative (asynchronous) interactions across distinct cortical areas exhibit a significant increase in links strength, while network interactions within cortical areas do not change significantly. In the inter-cortical networks, the average link strengths of horizontal links are at a similar level, while the average strengths of other links show a significant increase. Notably, we find that the overexpression of network links strength with Parkinson's is more pronounced during deep sleep, light sleep, and REM compared to wake, resulting in an altered sleep stage stratification pattern in network structure and dynamics compared to healthy subjects.

Conclusion

Our findings demonstrate that the dynamic network of cortical rhythms interactions across cortical regions serves as a hallmark of physiological states and functions, as well as a marker of neurodegeneration. The Network Physiology approach to study the dynamics of physiological interactions, sheds new light on the complex regulatory mechanisms of basic physiological states, such as sleep and wake, and how these mechanisms are modulated under neurodegenerative disorders leading to the empirically observed alterations in the functional forms of coupling and network organization of cortical rhythms interactions.

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2. You don't need symmetric plasticity for forward and reverse delay-driven replay

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Study Objectives Neuronal replay is a phenomenon observed in mammals and songbirds where cor- tical and hippocampal cell activation sequences experienced during wakeful periods are repeated during rest or sleep. Replay is believed to play a crucial role in episodic memory consolidation, planning, and memory retrieval [1]. Importantly, these replays are not simple repetitions of the observed sequences. Despite only experiencing stimuli at real-world speed in a predefined order, neural circuits learn to replay sequences both in the original order and in reverse. These replays also occur at various speeds, sometimes compressing the duration of the original events by up to twenty times [2].

Sequence learning has traditionally been modeled by temporally asymmetric Hebbian plasticity rules, which explain replay as a chain of activity. The inability of such rules to strengthen backward connections in feed-forward networks has led to the widespread belief that it cannot account for bidirectional replay [3]. Existing theoretical work therefore explains reverse replay through symmetric connections [4] which would be formed through symmetric plasticity rules [5]. This assumption does not fully align with biological evidence on CA3 circuit structure and plasticity. Our goal is therefore to provide an alternative explanation of bidirectional replay, without symmetric connections.

Methods In our model, neural activity evolves as a nonlinear response to external and recurrent inputs with a fixed transmission delay. Synaptic weights evolve as the product of presynaptic and the time derivative of postsynaptic activity, a plasticity rule that is the rate-based version of asymmetric STDP. External input is given as a periodic traveling wave, which results in equilibrium weights that can be described by a kernel of the neuron phase difference. With a Heaviside neural activation function, we derive a solution for activity in the externally-driven regime.

During replay, there is no external stimulus and neural activity is driven by its own time-delayed recurrent signal on a learned circular neural field. We derive a lowdimensional description with the fundamental spatial Fourier component of activity, and find solutions for various replay speeds in both directions. Furthermore, we analyze the stability of possible replay speeds and verify our theory in simulations.

Results In this contribution, we show both analytically and by simulations that an asymmetric rule is sufficient to learn replay in both forward and backward directions, and with varying speeds. The analytical stability condition of replay speed is determined by the stimulus and biophysical properties of the circuit such as its firing rate time constant and transmission delay. We also demonstrate that the effects of neuromodulation on plasticity enable our model to learn to replay a pattern after only a single exposure with noise.

Conclusions Our study reveals that a temporally asymmetric learning rule is indeed capable of sup- porting both forward and reverse replay. This model integrates various experimental observations on learning and replay in the hippocampus under minimal assumptions and complexity.

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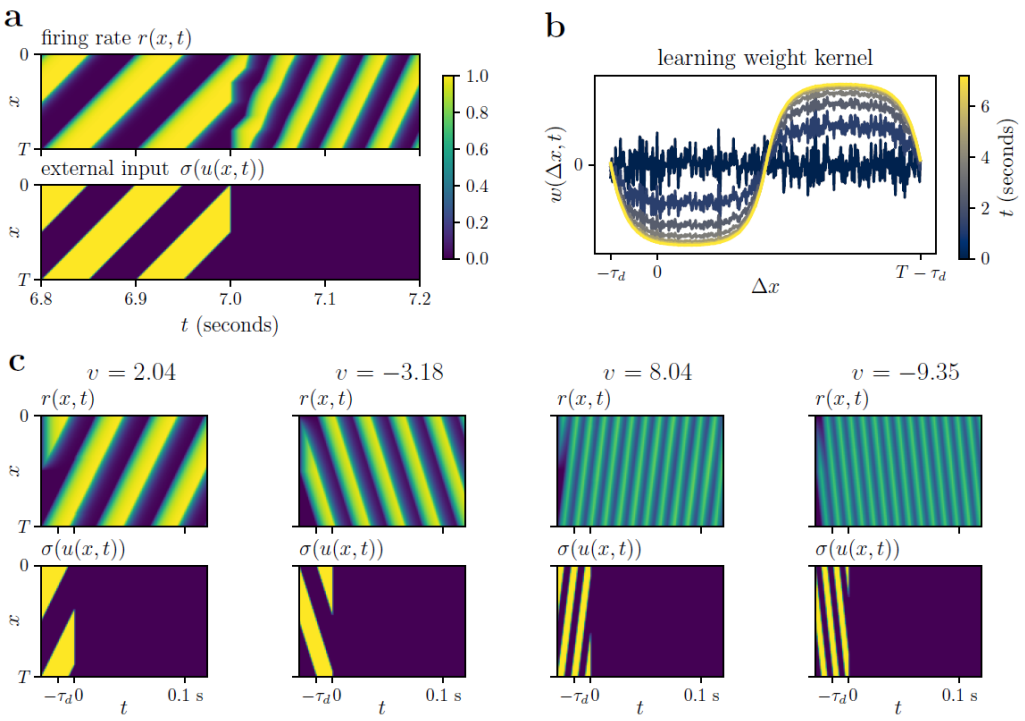

Figure 1 (a) Model is stimulated with a periodic traveling wave, then replays it at a faster speed. (b) Evolution of synaptic weights during stimulation. Given a random initialization, the weights quickly learn the pattern and saturate after around 70 stimulation cycles for our chosen parameters. (c) Analytically determined stable replay speeds v of model from (a) and (b), activated by short initial stimulus.

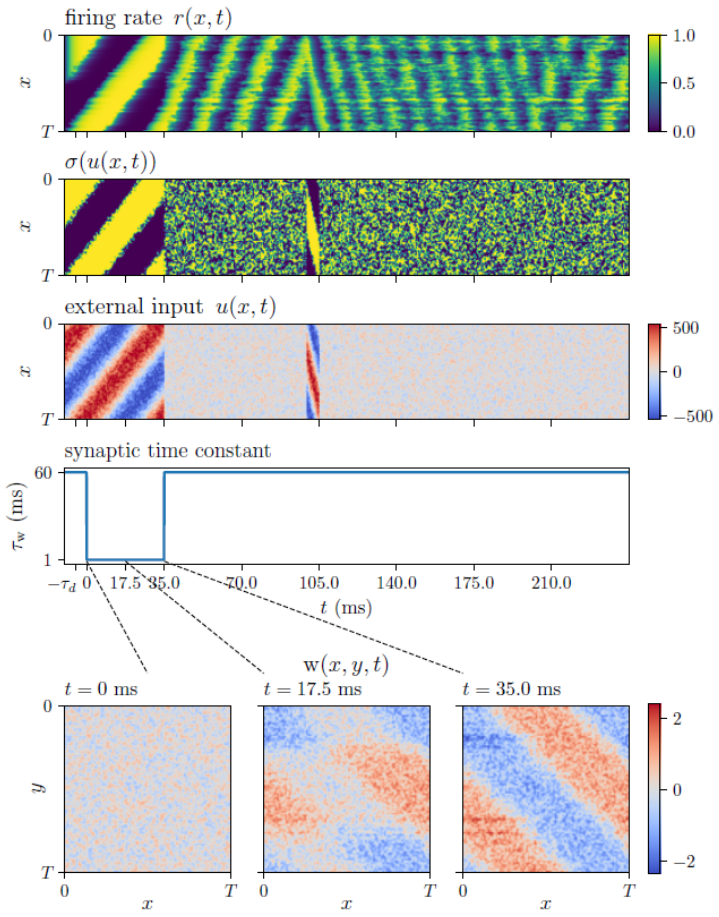

Figure 2: In this scenario, the stimulus is only shown once. During this stimulus presentation, we consider neuromodulation to decrease the synaptic time constant. We also add coarse-grained noise to the initial synaptic weight matrix and to the external stimulus. At around 100 ms, the reverse stimulus is shown for 6 ms. Despite the noise, the model can already perform replay in both directions after a single experience of the stimulus. Due to the external noise, the model switches back to the more stable forward replay after some time.

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3. Network interactions of wearables-derived movement and skin temperature covary with conditions associated with peripheral vascular blood flow deficits and peripheral arterial resistance

Jamison Burks, Stephan Dilchert PhD, Wendy Hartogensis PhD, Ashley Mason PhD, Benjamin Smarr PhD
Shiu Chen – Gene Lay Department of Bioengineering, University of Califonia, San Diego, USA

Study Objectives

Skin temperature is influenced by various conditions, including thyroid and endocrine disorders, infections, mental health, and aging, as well as by other factors. [1] These conditions indirectly act upon skin temperature by affecting upstream components of distal skin thermoregulation, including autonomic and endocrine associated vascular tone, cardiac output, and peripheral blood perfusion.[2] This suggests that, with appropriate signal processing, continuous skin temperature measurement could reveal signs of physiological changes associated with peripheral blood perfusion deficits.

The proliferation of wearable devices capable of measuring physiological signals presents an opportunity to passively monitor skin temperature across large, diverse populations under real-world conditions.[3] This capability holds promise for detecting the onset or presence of various health conditions. However, the uncontrolled environment in which wearable data are generated introduces significant challenges to analyzing skin temperature measurements. Specifically, observed skin temperature is the output of a dynamic process involving core body temperature, ambient temperature, adiposity, sweat, and vasodilation. These overlapping influences make it difficult to separate changes in skin temperature linked to long-term biological states from those driven by external factors.

In this work, we use distal skin temperature and activity signals sampled every minute, across multiple nights, from roughly 40,000 Oura Ring owners to construct a mathematical model that incorporates the nonlinear effects of activity on temperature during sleep. There were three primary objectives of the work: 1) show that first-principles thermodynamics can be applied to uncontrolled wearables data; 2) use the residual (unexplained) temperature trajectories to infer the dynamics of nonlinear activity perturbations; 3) evaluate how the parameters of the combined mathematical model of activity and temperature separate cohorts with and without conditions affecting peripheral blood perfusion.

Methods

Data from subjects participating in the TemPredict [4] study were used for the construction of the models as well as the subsequent separation of the personalized model parameters by participant conditions and comorbidities. To evaluate the effects of isolated activity perturbations during sleep, 20-minute windows of skin temperature data during sleep were only selected as candidate trajectories if they met the following criteria: there was no observed activity 20 minutes prior to the activity perturbation, as well as no observed activity 20 minutes after the activity perturbation. Therefore, any non- zero activity level that met that criteria could be viewed as an “instantaneous” effect on the observed temperature dynamics 20 minutes (20 samples) following each perturbation.

Assuming that the decay constant for skin temperature back to steady state remains constant near the tail end of each temperature trajectory, the decay constant for the last 10 samples was approximated using least-squares curve fitting of a first-order exponential decay against the observed data with

$$T(t) = T_{end} - (T_{end} - T_n)e^{-k_1 t}$$

where $T(t)$ is the skin temperature as a function of time, $Tend$ is the final temperature, T_0 is the starting temperature, and k_1 is the decay constant (Figure 1A). However, due to the effects of activity, skin temperature will return to baseline in a state dependent manner and not a first-order time dependent manner. The residual activity effect was recovered by using the approximated decay constant to estimate the ΔT (rate of change of temperature) at each time step based on the prior observation to generate the expected state-space trajectory, and then subsequently subtracting that trajectory from the observed data. The hypothesized activity effect was then the residual temperature curve (Figure 1A) – the parameters of

which were approximated using a time-dependent exponential decay (Figure 1B):

$$MET\_Effect(t) = aM_0t^ne^{-k_2t}$$

where a is the amplitude modulation of the activity level at time zero, M_0, n is the curve ascent steepness relative to time, and k_2 is the decay constant for the activity effect.

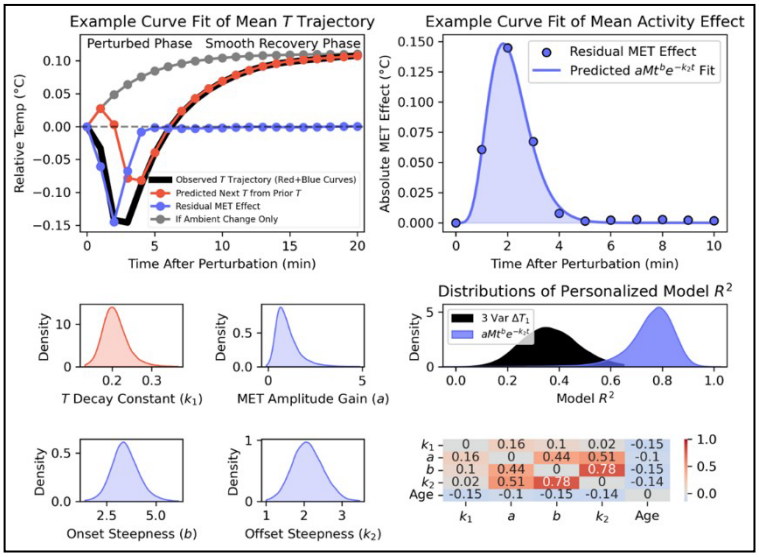

Figure 1: A. Temperature and residual temperature curves across time. B. Residual MET effect curve and model fit. C-F. Distributions of the coefficients for each participant's model. G. Distribution of a simple, 3-variable linear model and the time-dependent model. H. Heatmap of population coefficients to each other as well as age.

Results

The personalized model parameters for both the temperature decay and activity effects are all narrowly distributed (leptokurtic) (Figure 1C-2F). The time- dependent model of activity perturbations drastically outperforms a 3-variable linear model that only predicts the ΔT at time 1 (Figure 1G). The personalized model coefficients also covary with patient age in negative rank- order fashion ($p < 0.001$ for all comparisons; Figure 1H). While age appeared to convey a small proportion of rank- order variance in the model parameters (consistent with the concept of observed "critical slowing down" in elderly populations), we then evaluated how well the nonlinear model coefficients separate cohorts who reported having atrial fibrillation (AF), hypertension without diabetes (H), diabetes without hypertension (D), the combination of hypertension and diabetes (H+D), and coronary artery disease (CAD) – accounting for age and sex.

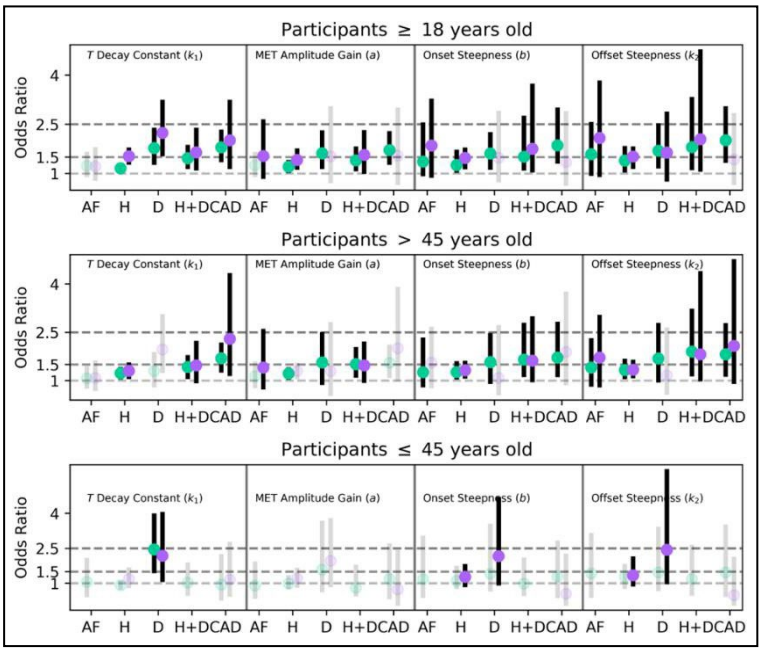

Figure 2: A. 95th percentile ranges (black lines) of odds-ratio when comparing cohort with a condition to a Monte-Carlo sampled (with replacement), equal-sized subset from the control cohort. Non- transparent lines are significant results ($p < 0.0125$). Median odds-ratios for each comparison are cyan and magenta for male and female groups, respectively. B. Same analysis but only in an older cohort. C. Same analysis but only in a younger cohort.

When grouping all participant ages, the model parameters significantly separate male and female cohorts across all conditions with the exception of temperature decay constant in AF (Figure 2A). The temperature decay constant, onset steepness, and offset steepness coefficients are all lower in the D, H+D, and CAD from control (no reported conditions) with moderate effect sizes (Odds-Ratio > 1.5). When comparing only the older cohort (older than 45 years), the 95th percentile for odds-ratio in CAD improves substantially in the female population coefficients for temperature decay constant and offset steepness, indicating a greater deficit in the cohort (Figure 2B). Furthermore, most of the significant effects appear to be found in the older sample, and are lost when comparing only the younger sample (at or younger than 45 years) (Figure 2C). Interestingly, the offset steepness, onset steepness, and temperature decay constant coefficients have large (Odds-Ratio > 2.5), medium, and medium effect sizes, respectively in the younger female cohorts with diabetes

Conclusion

Our findings indicate that incorporating MET into a causal model effectively filters out transient influences of

activity on temperature and further highlights the importance of quantifying network interactions between these variables. This enables us to focus on residual temperature changes and model parameters, which can help differentiate individuals with and without conditions that affect thermoregulation. Additionally, these parameters allow for a more nuanced classification of individuals, not just based on absolute temperature values but on how their temperature dynamics respond to activity perturbations over time. This approach demonstrates the potential of using skin temperature as a practical biomarker for cardiovascular health monitoring and disease detection, laying the groundwork for broader clinical applications.

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4. The heart-brain connection: How cardiac rhythms support neural function and mental health

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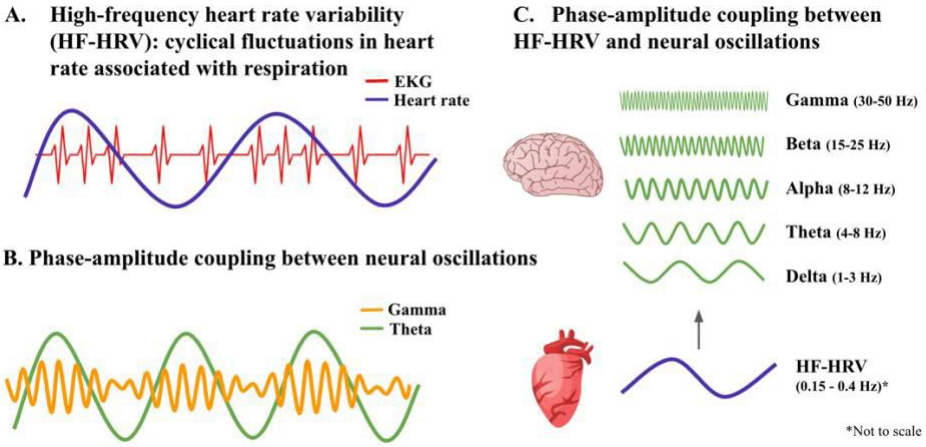
Study Objectives: An accumulating body of evidence indicates that peripheral physiological rhythms help regulate and organize large-scale brain activity. Previous work from our group has found that oscillations in heart rate, an aspect of heart rate variability (HRV), modulate the amplitude of neural oscillations through phase-amplitude coupling (PAC; Sargent et al., 2024). PAC is a mechanism of organization and communication typically studied in the brain whereby the phase of a slower oscillation modulates the amplitude of a faster oscillation, fostering the integration of neural assemblies across spatiotemporal scales. Our findings demonstrate that PAC serves as a mechanism of oscillatory coupling not only within the brain, but between the brain and body.



Schematic illustration adapted from Sargent et al., 2024.

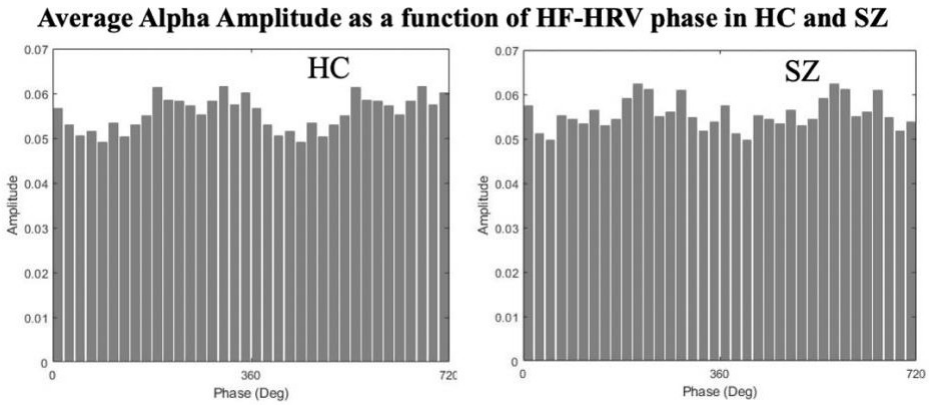
Importantly, Granger causality analyses indicated much stronger directional effects from heart to brain than vice versa, suggesting that heart rhythms play a causal role in modulating neural activity. We suggest that the influence of cardiac rhythms on neural activity may partially account for robust relationships

between HRV and various domains of psychological function, including emotion regulation, cognitive function, and overall mental wellbeing (Beauchaine & Thayer, 2015).

To explore the possibility that heart-brain coupling may be relevant for mental health and illness, we examined HRV-EEG coupling among individuals diagnosed with first- episode schizophrenia. Schizophrenia (SZ) is characterized by marked abnormalities in oscillatory cortical activity as well as changes in autonomic function, particularly reductions in HRV. We hypothesized that central and autonomic nervous system deficits may be mechanistically related through HRV-EEG PAC.

Methods: PAC was measured between high-frequency heart rate variability (HF-HRV) as an index of parasympathetic activity and EEG oscillations in 36 individuals with first-episode SZ and 38 healthy comparison participants. EEG and EKG were recorded during rest, and R- wave peaks were identified and used to compute a timeseries of interbeat-intervals (IBI) for each participant. IBI and EEG timeseries were filtered and Hilbert transformed to obtain phase and amplitude timeseries for HF-HRV and EEG oscillations, respectively. The modulation index (MI; Tort et al., 2010) was computed to quantify systematic variation in EEG amplitude as a function of phase of HF-HRV oscillation, reflecting PAC.

Results: HRV-EEG coupling was lower in SZ in the alpha ($F(1,72) = 7.08$, $p = .01$) and theta ($F = 4.95$, $p = .03$) bands. In binary hierarchical regression models, HRV-EEG coupling uniquely predicted group membership (alpha MI: $\Delta R2 = .11$, $p = .02$; theta MI: $\Delta R2 = .09$, $p = .04$), whereas HRV and EEG power alone did not predict group. HRV-EEG coupling in the alpha band correlated with measures of sustained attention in SZ ($r = .40$, $p = .01$) Granger causality analyses indicated a stronger heart-to-brain effect than brain-to-heart effect, consistent across groups.



Conclusions: Lower HRV-EEG coupling provides evidence of deficient autonomic regulation of cortical activity in SZ. We suggest that cardiac autonomic rhythms provide a scaffold for the spatiotemporal organization of neural activity, and that dysregulated autonomic rhythms contribute to a breakdown in neural organization with consequences for mental health and cognitive function. As lower HRV is observed across a number of mental health disorders, our work suggests that autonomic disruption may in fact contribute to changes in cognitive and psychological function. Further work should investigate patterns of heart-brain coupling in other clinical populations and explore the use of therapies that specifically target autonomic function to improve mental health. Taken together, our work on heart-brain coupling suggests that psychological function depends not only on precisely orchestrated brain dynamics, but on a complex interplay between the brain and body.

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5. Characterizing brain-wide interactions in different states of consciousness: EEG analysis with ordinal patterns

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Objectives

Recent advances in neurophysiological brain network analysis have demonstrated novel potential for diagnosis and prognosis of disorders of consciousness [1, 2, 3]. In the majority of previous studies, networks were derived from electroencephalographic (EEG) recordings, concentrating on the strength of interactions between pairs of sampled brain regions. However, to further support the Global Workspace Hypothesis that consciousness emerges by information processing [4, 5], a thorough characterization of both strength and direction of information flow would be desirable [6]. To do so, we investigate long-lasting multichannel EEG recordings from nine subjects with unresponsive wakefulness syndrome (UWS) and from nine healthy controls making use of ordinal-pattern-based analysis techniques.

Methods

We derive ordinal-pattern-based quantifiers [7, 8, 9] for strength, complexity and direction of interactions from multi-channel EEG data using a moving window approach with non-overlapping windows of 20 s duration. We investigate the spatial distributions of group medians of the respective temporal means of interaction quantifiers from subjects with UWS and compare them to those from healthy controls during wakefulness and sleep.

Results

The spatial distributions of the ordinal-pattern-based quantifiers differ between the investigated states of consciousness, i.e. sleep, wakefulness and UWS, however, to a different extent. Interestingly, parts of the distributions seen for healthy subjects during wakefulness appear to resemble parts of the default- mode-network.

Conclusion

Our findings provide first promising evidence for ordinal-pattern-based investigations of brain-wide interactions to further disentangle spatial and temporal aspects of information flow during different states of consciousness.

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6. Characterization of inter-organ metabolic networks in healthy females and breast cancer patients using whole-body [18F]FDG-PET/CT

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Study Objectives

Inter-organ interactions are fundamental to maintaining systemic homeostasis. Mapping the underlying metabolic connections could offer valuable information about the mechanisms by which health is preserved and provide a reference for identifying disease-specific metabolic disruptions. Whole-body [18F]FDG-PET/CT imaging enables a non-invasive approach to assess glucose metabolism and signaling pathways at the systemic level. This study aims to define the characteristics of the metabolic network in healthy females and investigate how these networks are altered in breast cancer (BC) patients at different stages of the disease.

Methods

Patients and imaging procedure

Three cohorts were studied: 25 healthy women (HW, 38±15 y/o), 147 women with early BC, and 285 women with advanced BC. Among the advanced BC cohort, 101 women had triple-negative BC (TNBC) (52±13 y/o) and 184 women had hormone receptor-positive BC without HER2 overexpression (HR+) (53±14 y/o). This HR+ group was randomly divided into 2 subsets of 92 patients each, to get 3 groups of advanced BC patients of comparable size. The early BC cohort included 98 TNBC patients (50±12 y/o) and 49 HR+ patients (52±12 y/o). All participants underwent [18F]FDG-WB-PET/CT imaging: two dynamic scans (test and retest) 3 months apart for healthy women using a Siemens Vision Quadra PET/CT scanner at Medical University of Vienna from which the 55-60 min post-injection scan was generated, and one baseline static scan 60 min post-injection for women with BC using different PET/CT scanners at Institut Curie.

Data analysis

Seven anatomical volumes of interest (VOIs)—lungs, pancreas, liver, spleen, spinal cord, skeletal muscles, and subcutaneous fat (fatSC)—were segmented from WB CT scans with TotalSegmentator [1] and registered with the corresponding PET images. Mean standardized uptake value normalized to lean body mass (SULmean) was calculated using LIFEx [2] for each VOI. Advanced BC cases with metastases in the selected VOIs were excluded.

First, to identify “healthy” inter-organ interactions, metabolic networks between SULmean in all 7 VOIs were built independently for the test and retest groups of the HW, using 8 group-level methods: 2 methods identifying undirected links (Spearman correlation, partial Spearman correlation adjusted for age, BMI, height, and weight) and 6 directed acyclic graph methods yielding directed links [3]: Greedy Equivalence Search (GES), Peter-Clark algorithm (PC), DirectLiNGAM, ICALiNGAM, Notears, and Joint-Notears. In addition, the Kullback-Leibler Divergence Similarity Estimation (KLDSE) [4] individual-level method that identifies undirected links was used. For each network identification method, reproducibility between test and retest networks was assessed via Wilcoxon signed-rank tests.

Second, to compare HW and BC metabolic networks, HW test and retest groups were merged (n=50), and the Spearman correlation method was applied to all groups. Correlations with a p-value < 0.05 after Benjamini-Hochberg correction were retained. The metabolic dialogue score (MDS), defined as the sum of all significant correlation coefficients within the network, was calculated for each subject group and compared. In addition, each link in the network was classified according to its presence in the different subject groups

Results

“Healthy” metabolic network

The different methods identified significant links between VOI SULmean in both the test and retest groups. Wilcoxon signed-rank tests indicated no significant differences between test and retest networks regardless of method. Averaging between test and retest groups, 4 links were detected by at least half of the methods: the fatSC – lungs and liver – spleen links were identified by 8/9 methods in test and retest groups. The fatSC – pancreas was identified 4/9 times in the test group and 8/9 in the retest group. Last, the spinal cord – spleen link was identified 4/9 times in the test group and 5/9 in the retest group. The metabolic activity of the skeletal muscle did not show any significant connections with other VOIs.

Alterations of the metabolic network in BC patients

Comparing HW and BC networks, the number of inter-organ links using Spearman correlation varied significantly (χ^2 test p-value<10^{-5}). Age was significantly different between HW and BC patients, making it impossible to distinguish between the effect of age and the effect of BC. However, the number of significant inter-organ links increased from HW (7 significant links) to early-stage BC (18 for TNBC, 16 for HR+), and advanced BC (17 for TNBC, 20 and 21 for HR+ groups 1 and 2, respectively). Similarly, HW had a lower MDS (1.34) than early-stage BC (6.54 for TNBC and 7.91 for HR+) and much smaller than advanced-stage BC patients: TNBC and HR+ groups 1 and 2 had values of 7.18, 9.37, and 10.85, respectively. In addition, the metabolic networks of HR+ patients consistently showed higher MDS compared to TNBC patients, regardless of disease stage. Six links were common to all groups, including three of the four reproductible links found in the “healthy” test and retest metabolic network analysis, and nine links were specific to all BC patients (Table 1). The liver-spleen correlation (Fig 1) was consistently the highest across all groups and was similar in HW and TNBC patients. The correlation between the spleen and spinal cord SULmean (Fig 1) was found in all groups but with higher spinal cord SUVmean in BC patients (0.97±0.16) compared to HW (0.87±0.08, p-value<10^{-5}). The correlation between the spleen and skeletal muscles SULmean (Fig 1) was found in all groups but was negative in the HW and positive in all BC groups.

Conclusions

Whole-body [18F]FDG-PET/CT imaging revealed four metabolic links between selected key organs in healthy females: fatSC-lungs, liver-spleen, fatSC-pancreas and spleen-spinal cord. These links were repeatedly identified in test and retest scans and were found significant by most of the nine network analysis methods used for this exploration. Three of these four links persisted in BC groups, calling for further characterization to determine whether and how their strength changes in the presence of the disease and at different stages of the disease. Our results also suggest that the metabolic dialogue increases as BC advances, with young healthy individuals exhibiting much simpler metabolic networks compared to early- and advanced-stage BC patients. The higher metabolic dialogue observed in HR+ patients compared to TNBC patients further suggests disease- specific variations in inter-organ interactions.

Further investigations will explore the physiological reasons of these metabolic networks and their implications for disease progression.

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VOI1	VOI2	Healthy	Advanced TNBC	Advanced HR+ group1	Advanced HR+ group2	Early TNBC	Early HR+
FatSC	Muscles		0.51	0.56	0.69	0.45	0.35
FatSC	Spleen		0.29	0.55	0.57	0.33	0.35
Muscles	Liver		0.46	0.61	0.61	0.40	0.51
Muscles	Spinal cord		0.41	0.51	0.48	0.38	0.63
Pancreas	Liver		0.27	0.56	0.64	0.39	0.52
Spinal cord	Liver		0.45	0.60	0.47	0.61	0.62
Spinal cord	Lungs		0.43	0.35	0.32	0.29	0.52
Spinal cord	Pancreas		0.38	0.35	0.41	0.38	0.35
Spleen	Lungs		0.40	0.38	0.48	0.23	0.44
FatSC	Liver		0.29	0.52	0.53	0.25	
Muscles	Pancreas		0.47	0.26	0.54	0.30	
FatSC	Pancreas	0.50	0.35	0.38	0.62	0.40	0.48
Lungs	Liver	0.44	0.37	0.35	0.42	0.33	0.44
Muscles	Spleen	-0.39	0.41	0.54	0.60	0.30	0.47
Spleen	Liver	0.58	0.56	0.74	0.75	0.62	0.66
Spleen	Pancreas	0.35	0.57	0.65	0.73	0.57	0.56
Spleen	Spinal cord	0.41	0.56	0.58	0.62	0.65	0.61
FatSC	Spinal cord			0.38	0.36		
Pancreas	Lungs			0.25	0.27		
Muscles	Lungs			0.25	0.43		0.41
FatSC	Lungs	-0.55			0.30	-0.35	
Metabolic dialogue		1.34	7.18	9.37	10.85	6.54	7.91

cancer specific	cancer specific except for early HR+	common	advanced HR+ specific	HR+ specific	not classified

Table 1: Significative Spearman correlation values for each pair of VOIs and each group. The last row shows the metabolic dialogue defined as the sum of all significant correlation coefficients within a group. The row colour indicates in which group the link is significant.

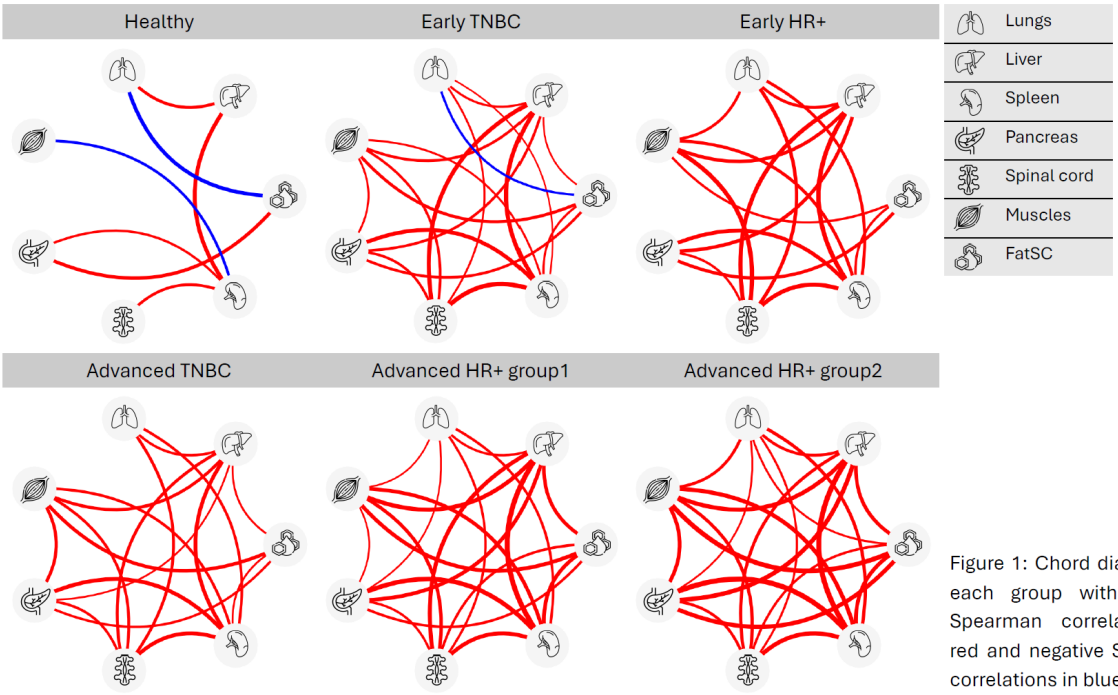

Figure 1: Chord diagrams of each group with positive Spearman correlations in red and negative Spearman correlations in blue.

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7. Uncovering brain hemodynamics through fNIRS: Insights from time-resolved information-theoretic analysis

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Study objectives

Functional near-infrared spectroscopy (fNIRS) is a non-invasive imaging technique which relies on the use of light at specific wavelengths for measuring the hemodynamic activity of brain tissue. fNIRS signal contains various background physiological components (e.g., cardiac, respiratory, and blood pressure fluctuations) that influence brain dynamics beyond purely neural activity [1]. These physiological signals are often considered "noise" in traditional analyses of brain connectivity, as they can obscure the detection of evoked neural responses. However, their impact on brain function remains underexplored, with most techniques primarily aiming to remove them from the fNIRS signal. Recent advances in network physiology suggest a shift in perspective, interpreting these background fluctuations not as mere artifacts but as meaningful physiological interactions. Within this framework, the human body can be seen as an integrated network, where each physiological system, despite having its own regulatory mechanisms, continuously interacts with others to coordinate functions and generate distinct physiological states in both health and disease [2]. In this context, cardiorespiratory dynamics arise from the coordination of respiratory, cardiovagal, and sympathetic functions, which operate across various levels of the nervous system. These interactions play a critical role in maintaining physiological equilibrium and have only recently been shown to have a direct impact on neural activity signals in specific clinical conditions [3]. To further investigate these complex interactions, we designed a protocol based on the breath-holding task, in which the presence of respiratory signals is systematically modulated, allowing for a detailed assessment of the influence of respiratory activity on brain dynamics.

Methods

The acquisitions of fNIRS signal (16 channels, sampling frequency 130 Hz) were obtained from six healthy subjects performing a breath-holding task, during which two different phases (apnea and breathing) were alternated for five times in an observation window of five minutes. The aim was to characterize the

modulation due to the task performed on the dynamical behavior of brain system, in terms of predictability. In the field of information theory, it is possible to dissect the information processed in a dynamical system into meaningful elements to quantify its complexity and predictability. Let us consider a dynamic stochastic process, assumed as a Markov process, with X_n representing the random variable sampling the process at time n and $W_n = [X_{n-1}, \dots, X_{n-p}]^T$ the vector of its past history truncated up to a lag p. The measure of Information Storage (IS), referred to a specific time instant *n,* quantifies the amount of information contained in the present state that can be predicted by the knowledge of its past state, and can be defined as [4]:

$$S_{X_n} = I(X_n; W_n) = \mathbb{E}\left[\log \frac{p(x_n \mid w_n)}{p(x_n)}\right]$$

where x_n and w_n refer respectively to a realization of X_n and W_n, $\mathbb{E}[\cdot]$ is the expectation operator, $p(x_n)$ is the probability density function of X_n measured for the outcome x_n, and $p(x_n|w_n)$ defines the conditional probability of observing these states. In this work, starting from the assumption of gaussianity, a time resolved estimation of the IS was obtained using a time-varying autoregressive model of the fNIRS signal, modeled as a realization of a zero-mean stochastic process X. The pre-processing pipeline of fNIRS signal adopted for this study involves the following step: i) raw intensity signals were converted to optical density (OD) signals using the equation $OD = -\ln(I(t)/I_0)$, where $I(t)$ is the time-dependent recorded signal intensity and I_0 is its initial value; ii) the Temporal Derivative Distribution Repair method was applied to the OD signals to correct motion artifacts; iii) the corrected OD signals were converted to oxyhemoglobin HbO_2 and deoxyhemoglobin (HHb) concentration signals using the modified Beer-Lambert law; iv) lowpass filtering (0.5 Hz), downsampling to 1 Hz and then high-pass autoregressive filtering (0.018 Hz); v) normalization to zero mean and unit variance. Afterwards, the time resolved IS was estimated for each fNIRS channel and averaged within each time window corresponding to the analyzed experimental condition (apnea and breathing). The obtained values were further averaged across the five available windows for each experimental condition to obtain a representative value for each of the six subjects. Statistically significant differences between the apnea and breathing conditions were evaluated using the Wilcoxon test for paired data ($\alpha < 0.05$).

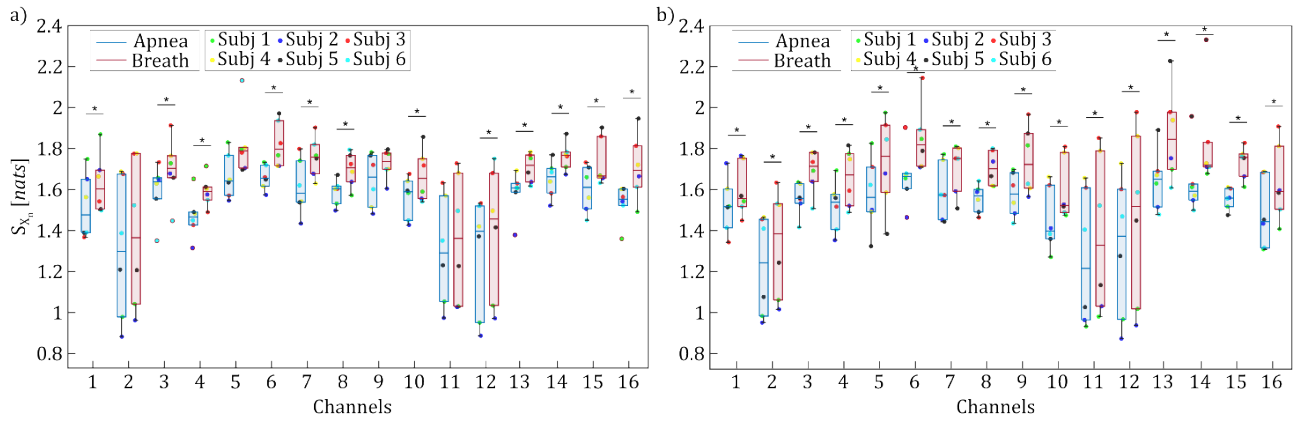

Figure 1 *Boxplot distributions and individual values of the time-resolved information storage (S_{X_n}) for HbO_2 (panel a) and HHb (panel b), computed for each channel and displayed separately for the apnea (blue) and breath (red) phases. Statistically significant differences between the breath and apnea windows are marked with $*$ ($p < 0.05$, Wilcoxon signed rank test).*

Results and Discussion

Figure 1 shows the boxplot distributions of the time-resolved information storage, averaged across five different time windows relevant to the apnea (blue) and breath (red) phases, computed separately for HbO_2 (panel a) and HHb (panel b). The results suggest a modulation of uncertainty in the oxyhemoglobin and deoxyhemoglobin time series. Particularly, the IS is significantly higher when subjects resume breathing, for

almost all channels, indicating that respiratory activity modulates brain function [3], leading to more predictable dynamics. These results highlight the importance of accounting for the system's past history, as they indicate an increase in predictability during the breath compared to the apnea condition. Few studies exploited time-resolved information-theoretic measures, primarily investigating the dynamics of brain and physiological systems [5]. Some of these studies have shown that the emergence of a predominant oscillation, driven by synchronization phenomena, is directly associated with increased predictability of brain dynamics, even across different contexts. Moreover, since a transition occurs after the onset of apnea, we can link the observed decrease in predictability during apnea to previous studies, which have highlighted that such transitions are associated with a reduction of the time-resolved information storage [5].

Conclusions

Our results highlight that time-resolved measure of information dynamics, although still little used in literature, can reveal subtly varying properties of physiological dynamics. In this work, the variability of the information storage evidenced alterations in the patterns of information of the fNIRS signals due to the breath holding task. This result suggests that respiratory activity influences the predictability of the fNIRS signal dynamics. These findings underscore the complementary value of combining fNIRS with sophisticate analytical frameworks to unravel dynamics of brain function, opening the way for broader applications in neuroimaging and clinical diagnostics.

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8. Brain-heart interactions underlying movement disorder symptoms in Parkinson's Disease

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Introduction

The interaction between the brain and interoceptive signals, such as heartbeats, plays a key role in maintaining internal balance and regulating neural dynamics, shaping cognition and behavior [1]. Recent methodological advances suggest that examining the covariation between cardiac rhythms and the formation of functional brain networks offers a promising approach to understanding various dimensions of bodily self- awareness, including the sense of control over body movements [2].

Many pathologies manifest disruptions in brain-body interactions, making these physiological manifestations valuable biomarkers for diagnosing, monitoring, and predicting neurological disorder outcomes. Parkinson's disease, which affects neurons throughout the body, significantly impacts brain-heart interactions [3]. While these interactions have been linked to dysautonomia, our recent studies using non-invasive electrophysiology (EEG, ECG) in diverse cohorts demonstrate that brain-heart dynamics can effectively track motor symptoms, such as tremors and freezing of gait.

Methods

We quantified the brain-heart couplings from EEG and ECG recordings from Parkinson's disease, at rest and under episodes of freezing of gait. Time-resolved analysis of cardiac dynamics was performed using a robust estimator that combines heart rate and heart rate variability dynamics, based on the correlation of the Poincaré plot descriptors of interbeat intervals from the ECG [4], allowing an estimation of cardiac sympathetic-vagal activity.

We proposed two new frameworks for assessing the functional interplay between cortical networks and cardiac dynamics from noninvasive electrophysiological recordings. In one framework, we quantified the relationship between cardiac sympathetic–vagal activity and the formation of functional brain connections [5], ultimately identifying the brain networks dynamically forming as a function of changes in cardiac rhythmicity in a defined condition.

In another framework, we focused on fluctuating network metrics obtained from connectivity matrices of EEG data. Specifically, we quantified the coupling between cardiac sympathetic–vagal activity and brain network metrics of clustering, efficiency, assortativity, and modularity [6].

Results

Using our two distinct frameworks, we demonstrated that Parkinson's disease alters resting-state brain-heart physiology. Specifically, we identified distinctive couplings between cardiac rhythms and the dynamic formation of brain connections, as well as global measures of brain integration and segregation. Additionally, we tracked how these couplings change with and without dopaminergic therapy, revealing that the degree of coupling change correlates with motor symptom improvement. Expanding this research, we investigated brain-heart interactions during freezing of gait episodes, with preliminary results indicating that cardiac rhythmicity predicts these episodes. Our ongoing work aims to uncover links between heart activity and functional brain networks during these events.

Conclusions

Studying brain-heart interactions provides an integrative perspective that could enhance the accuracy of physiological evaluations. This research opens new avenues for targeted interventions, tailored to the specific physiological responses observed during neurorehabilitation procedures.

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9. Unveiling the intrinsic brain-heart interplay: multimodal HRV-fMRI studies in major depressive disorders

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Introduction

According to the neurovisceral integration model [1], the interplay between the brain and the heart is a well-established phenomenon, with the central autonomic network (CAN) playing a crucial role in regulating cardiac function through autonomic nervous system (ANS) pathways [2]. This regulation involves a network of key brain structures, including the insula, amygdala, hypothalamus, as well as more recently identified regions, such as medial prefrontal cortex, anterior cingulate cortex, and cerebellum [3]. Advancements in neuroimaging, particularly functional magnetic resonance imaging (fMRI), have significantly improved our understanding of brain function by detecting blood oxygenation level-dependent (BOLD) signal changes. Complementarily, electrocardiography (ECG) provides insights into heart rate variability (HRV), a key indicator of autonomic balance through sympathetic and parasympathetic activity [4]. However, traditional approaches focusing on single physiological parameters provide a limited perspective on the hierarchical structure and regulation within CAN, highlighting the need for integrated brain-level investigations.

Despite growing interest in the brain-heart connection, multimodal studies remain limited probably due to the complexity of the physiological phenomenon, and the technical and computational challenges associated with acquiring and analyzing multimodal datasets [5]. Specifically, research investigating the interplay with autonomic modulation via HRV is particularly limited in psychopathology. HRV analysis holds significant potential for assessing ANS function in both healthy individuals and clinical conditions, including psychiatric disorders. Major depressive disorder (MDD) is a debilitating psychiatric condition frequently associated with autonomic dysfunction, as evidenced by reduced HRV [6], yet the nature of the reciprocal influence between alterations in brain function and HRV remains poorly understood.

Within this context, the primary aim of my PhD project is to deepen our understanding of the dynamic relationship between brain activity and cardiac autonomic modulation, thanks to ECG-fMRI simultaneous acquisition and through different HRV-fMRI integrated approaches. Multimodal analyses are applied to both healthy controls and patients with adult-onset MDD to investigate potential differences in central autonomic regulation. Investigating the brain-heart connection in this context may offer novel insights into pathophysiological mechanisms underlying MDD and identify potential biomarkers for more targeted, potentially combined, therapeutic interventions.

Methods

This study included HC and patients affected by adult-onset MDD [7]. All participants underwent a multimodal 3T MRI session, including T1-weighted structural scan for morphological reference, diffusion tensor imaging (DTI), and resting-state fMRI. ECG recording was performed simultaneously with the fMRI acquisition.

fMRI preprocessing. fMRI preprocessing was performed using HALFpipe toolbox [8] and included volumes realignment, co-registration with anatomical image, brain tissue segmentation, and spatial normalization to the Montreal Neurological Institute (MNI) standard space. Additionally, widely used steps were applied, including spatial smoothing, grand mean scaling, and temporal filtering. To enhance data quality, a multi-metric comparison of denoising techniques was conducted, and mean signals from white matter, cerebrospinal fluid, and global signal were regressed out [9].

HRV analysis. ECG signals were processed to remove the gradient artifacts from the MRI

environment. R peaks were semi-automatically identified to compute HRV time series as their difference in time. An ECG-derived respiration was estimated and sampled at each R peak to obtain the respirogram. A time-varying bivariate autoregressive model was applied to the tachogram and respirogram for cross-spectral analysis, enabling the identification of linear frequency relationships between the signals [10,11]. Sympathetic activity was estimated as the low-frequency power in the tachogram, removing respiration- driven spectral components. Vagal activity was estimated by computing the power in the spectrum explaining respiration's influence on HRV. This interaction is linked to respiratory sinus arrhythmia, reflecting vagal activity at the respiration rate, typically within the HRV high-frequency range. These time-varying estimates were convolved with the canonical hemodynamic response function to account for the neurovascular coupling delay.

Multimodal HRV-fMRI integration. Unimodal fMRI and HRV information were integrated using complementary approaches to explore the brain-heart interplay from different perspectives.

An HRV-driven fMRI analysis was performed to study the brain hemodynamic and metabolic correlates of cardiac autonomic-related variability. Time-varying HRV parameters were used as regressors of interest within a general linear model to explain voxel-level fMRI data and to identify the cortical and subcortical regions with a significant BOLD response to sympathetic and vagal modulation [12].

A trimodal HRV-fMRI-DTI framework was defined and applied on a pilot sample. After standard DTI preprocessing, the clusters of voxels derived from the HRV-driven fMRI activation maps were used to drive the DTI analysis and estimate structural connectivity streamlines of HRV-related brain activity by means of probabilistic tractography [13].

In another study, fMRI and HRV were integrated into a joint symmetric framework. We computed whole-brain dynamic functional connectivity (dFC), and then dFC features (ROI-to-ROI-to-ROI dFC) were correlated with both time-varying sympathetic and vagal estimates to investigate the strength of the coupling between dFC and autonomic dynamics [14].

Results

The HRV-driven fMRI analysis enabled us to identify brain regions exhibiting significant BOLD response to sympathetic and vagal activity. Group-level results showed activation and deactivations in key CAN structures, including anterior and middle cingulate cortex, precuneus, parietal cortex, superior medial frontal gyrus, parahippocampus, and thalamus. Significant differences between MDD patients and HC were found in the insula, inferior temporal gyrus, postcentral gyrus, precuneus, middle cingulum, hippocampus, hypothalamus, vermis, and cerebellum, many of which are central to CAN function.

In the pilot study, integrating DTI-derived white matter connectivity with HRV-related brain activity allowed for a more comprehensive characterization of the structural underpinnings of autonomic regulation. This approach enabled the exploration of structural-functional relationships within the CAN. The symmetric dFC-HRV approach identified brain regions triplets whose dFC was coupled with sympathetic or vagal dynamics in a fully data-driven manner. The results suggested a CAN subdivision in sympathetic and vagal activity modulation and in subnetworks that are devoted to excitatory and inhibitory roles separately or in combination.

Conclusion

In the present studies, we adopted novel multimodal and multi-organ approaches for the investigation of the intrinsic interplay between brain activity and autonomic regulation in physiological and psychopathological conditions. The application for the first time of dynamic HRV-fMRI approaches on MDD patients allowed to identify brain-level functional alterations in regulating autonomic mechanisms compared to HC. Notably, the findings suggest an overlap between brain regions modulating autonomic activity, which resulted altered in MDD, and those implicated in MDD psychopathology (i.e., mood regulation), supporting the hypothesis of a shared neurobiological source underlying the heterogeneous symptoms of MDD. Further integrated HRV-fMRI analyses will provide a more comprehensive overview on the autonomic and central neural bases of MDD, bridging the gaps among its heterogeneous clinical

features and allowing to characterize this disabling disorder from a new and different point of view.

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10. Temporal variability of inter-muscular and cardio-muscular interactions during exercise

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INTRODUCTION

The human organism is a complex and dynamic system composed of multiple organs interacting as a network across distinct spatial and temporal scales to optimize physiological function. Each physiological system exhibits complex structural organization and regulatory mechanisms that lead to dynamic fluctuations in their signals, representing variability containing physiologically relevant information about the health status of the system. While significant progress has been made in understanding physiological variability within individual systems, such as heart rate variability (HRV) or other neuromuscular outputs, the mechanisms regulating variability in the coupling between distinct organ systems — i.e., how physiological coupling changes and varies over time—remain not understood. In particular, the functional forms and physiological principles underlying the temporal variability of network communication among distinct muscles and the heart, as well as how these interactions dynamically adapt to exercise and aging, are still unknown.

OBJECTIVES

This study aims to investigate the temporal variability of cardio-muscular and inter- muscular coupling under resting conditions and assess how this coupling variability responds to exercise and aging.

METHODS

A total of 97 participants performed a bodyweight squat test to exhaustion at a controlled squatting pace (3:3 tempo: 3 sec. for eccentric and concentric phases, respectively). To assess inter-muscular interactions, electromyographic (EMG) signals were recorded simultaneously from selected leg and back muscles. The EMG signals were decomposed into ten frequency bands ([F1-F10]). Inter-muscular coordination was quantified through pair-wise coupling (cross-correlation *C*) for each pair of EMG spectral power frequency bands across all Leg and Back muscles. To assess cardio-muscular coupling, additional recordings of a 3-lead electrocardiogram (EKG Lead II) were obtained during the squat test, with instantaneous heart rate (HR) derived using the Pan-Tomkins QRS detection algorithm. Pairwise coupling was then quantified between the HR time series and all EMG spectral power frequency bands in each Leg and Back muscle. Finally, to assess the temporal variability of inter-muscular and cardio-muscular interactions, we computed cross-correlation moving averages with a 3-second resolution for each pair of EMG frequency bands across all Leg and Back muscles (inter-muscular), and for each pair of HR and EMG frequency bands across all muscles (cardio-muscular). We computed distinct metrics to assess the magnitude (standard deviation, kurtosis) and complexity (Hurst Exponent through Detrended Fluctuation Analysis) of the inter-muscular and cardio-muscular coupling time series.

RESULTS

Overall, at rest, participants exhibited significantly higher standard deviation (SD_{MEAN} = 0.38; *SD* = 0.02), lower kurtosis (K_{MEAN} = 2.23; *SD* = 0.42), and lower Hurst Exponent values (H_{MEAN} = 0.61; *SD* = 0.02) in the inter-muscular coupling time series compared to exercise condition (SD_{MEAN} = 0.24; *SD* = 0.04; K_{MEAN} = 4.83; *SD* = 1.50; H_{MEAN} = 0.75; *SD* = 0.03; $p < 0.05$ in general), suggesting that rest is characterized by

higher variability degree. When analysing the effects of aging, older participants presented significantly higher standard deviation (SD_{MEAN} = 0.21; SD = 0.05) and lower kurtosis (K_{MEAN} = 5.15; SD = 1.05) in inter-muscular coupling compared to younger participants (SD_{MEAN} = 0.09; SD = 0.01; K_{MEAN} = 6.11; SD = 2.22; p < 0.05 in general). Similarly, in cardio-muscular coupling, older participants exhibited higher standard deviation (SD_{MEAN} = 0.35; SD = 0.01) and lower kurtosis (K_{MEAN} = 2.79; SD = 1.26) compared to their younger ones (SD_{MEAN} = 0.30; SD = 0.01; K_{MEAN} = 4.50; SD = 0.45; p < 0.05 in general).

CONCLUSIONS

These findings emphasize the importance of examining physiological variability not only at the level of individual systems (e.g., HRV) but also in the coupling between distinct organ systems, to gain a comprehensive understanding of the mechanisms regulating dynamic network interactions. This network-based approach provides a novel framework for quantifying physiological network dynamics, enabling the observation of inter-organ communication across timescales. This perspective offers a nuanced understanding of the network functioning and its implications for adaptability and health.

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11. Multiscale Synchronization in Beta Cell Networks: Connecting Cellular Oscillations to Hormone Secretion

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Study Objectives

Within the islets of Langerhans, beta cells orchestrate synchronized insulin secretion, a key process for maintaining metabolic homeostasis. Studying these cells poses significant challenges, as their functionality arises from intricate cell-cell interactions and exhibits complex multicellular behavior. This, coupled with a growing recognition that coordinated cellular dynamics are essential for proper function, has led to the application of network science approaches for a quantitative assessment of cellular activity in islets [1,2]. This complexity extends beyond network-level interactions of individual cells, whose oscillatory activity unfolds across three interconnected timescales. The first timescale involves slow, metabolically driven oscillations with periods of several minutes, which regulate the periodicity of insulin secretion at the organismal level. The second consists of electrically driven fast oscillations, or bursts, with periods of a few seconds, which are believed to modulate the amplitude of insulin release. The third timescale features ultrafast spikes, reflecting electrical depolarizations of the cellular membrane with periods of tens of microseconds. These spikes govern individual secretion events at the microscale and have only recently become experimentally accessible at the multicellular level [3]. The mechanisms by which cells synchronize across different timescales, and how rapid individual events interfere with one another to form pulsatile secretion patterns at the organismal level, remain unknown. Additionally, due to technical constraints, experimental data alone provide only limited insight. To address this, we developed in our study a multicellular computational model to simulate the multimodal collective activity of beta cells examining how dynamic cellular interactions across different timescales manifest at the macroscopic level of hormone secretion.

Methods

$[Ca^{2+}]_{IC}$ time series were obtained from acute pancreatic tissue slices which were prepared from 3-6-months-old male NMRI mice and loaded with the CalbryteTM calcium-sensitive dye as described in [3]. For $[Ca^{2+}]_i$ imaging, we transferred an individual slice into a recording chamber of Leica TCS SP5 AOBS Tandem II upright confocal system. To resolve the ultrafast $[Ca^{2+}]_i$ dynamics, we recorded a line scan at 165 Hz sampling rate. During off-line analysis, data from individual ROI were smoothed and binarized. The extracted binary signals were then used to assess signaling parameters and intercellular activity by means

of coactivity coefficients and functional networks [3].

Since our experimental measurements are limited to line scans, we developed a phenomenological multicellular model to gain a more holistic insight into beta cell behavior. This model incorporates the fundamental features of beta cell dynamics and consists of coupled slow and fast oscillatory units. The slow metabolic oscillatory activity is modeled using the paradigmatic Stuart-Landau oscillator, while the fast electrical activity is simulated with the Izhikevich model, which captures both fast bursts and superimposed spikes. Additionally, we integrated an insulin secretion model into this framework, which probabilistically and spike-dependently governs insulin release from granules. This approach enables us to simulate secretion patterns at the scale of the entire micro- organ and investigate the parameters that shape these processes.

Results

Despite the rather phenomenological nature of our model, it effectively captures the dynamic patterns observed in experiments (Figure 1). An analysis of the synchrony between different oscillatory components revealed that ultrafast spikes exhibit the weakest correlations and decay most rapidly with distance, indicating that their activity reflects highly localized interactions. Functional networks constructed from bursts and spikes appear highly segregated and closely resemble the structural network that governs intercellular information transfer. In contrast, the network formed by the slow oscillatory component displays a greater number of long-range connections, suggesting that connectivity is largely determined by intrinsic cellular profiles rather than the structural intercellular network. Further analysis of the secretory dynamics in the model demonstrated that insulin secretion occurs in a pulsatile manner at the network level, with the period of secretion being dictated by the period of metabolic oscillations. The amplitude of secretion, on the other hand, depends on the number of spikes, which in turn is influenced by the level of stimulation. In this regard, our simple model aligns with existing hypotheses regarding the nature of insulin secretion under *in vivo* conditions. Notably, these findings are strongly dependent on the degree of intercellular coupling—when coupling is reduced, synchrony is lost, and the pulsatile pattern of secretion disappears, mirroring what is observed in diabetes.

Conclusions

In summary, our computational and network-based approach provides valuable insights into the functional organization of beta cell populations, complementing the latest experimental findings on islet networks [3]. Moreover, our study contributes to a deeper understanding of how collective processes at the micro- and mesoscopic scales drive complex endocrine regulation at the macroscopic level, ensuring normal physiological function.

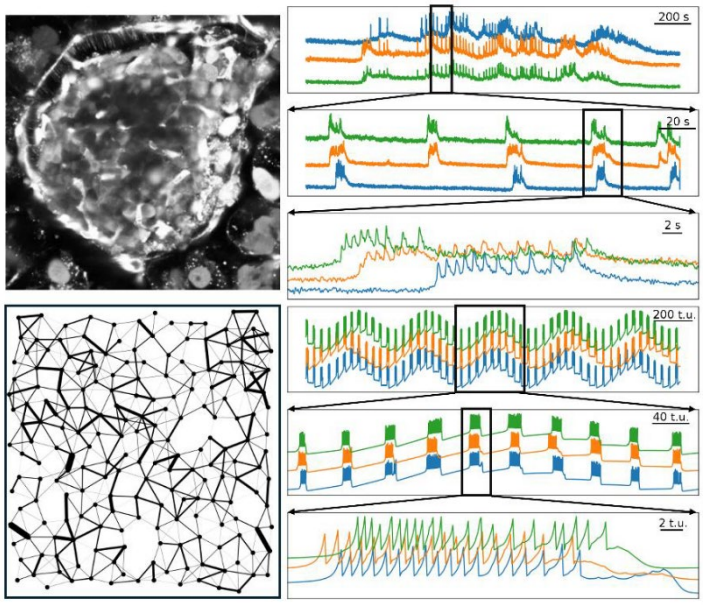

Figure 1. Experimentally measured (upper row) and simulated (lower row) multicellular and multimodal beta cell activity. Three representative traces from calcium imaging and model data are shown at different temporal scales. The experimental data are from Ref. [3].

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12. Illuminating GABA-Mediated Coordination in Pancreatic Beta Cells via Multicellular Imaging, Network Analyses and Computational Modelling

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Study Objectives: Gamma-aminobutyric acid (GABA) is a key inhibitory neurotransmitter in the central nervous system, but its functions extend beyond synaptic transmission, playing crucial roles in various peripheral tissues, including the endocrine pancreas. In pancreatic islets, beta cells release GABA, which influences islet cell activity through autocrine and paracrine signaling. GABA acts via ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors, modulating beta cell excitability, calcium signaling, and insulin secretion, while also regulating alpha and delta cell function by inhibiting glucagon release and modulating somatostatin secretion. Additionally, GABA is metabolized through the GABA shunt, linking it to cellular metabolism and mitochondrial function, where it contributes to redox balance and energy homeostasis [1].

Recent evidence indicates that GABA is released in a rhythmic, pulsatile manner with a period of 4 to 10 minutes, closely mirroring the oscillatory secretion of insulin. While GABA secretion is metabolically regulated, it is not directly triggered by high glucose levels. Instead, GABA release is tightly coupled to its biosynthesis and catabolism, with alterations in these processes directly affecting secretion dynamics [2]. The pulsatile nature of GABA release raises the question of whether it plays a role in regulating the rhythmic secretion of insulin. Experimental manipulation of GABA metabolism supports this idea—blocking GABA biosynthesis with allylglycine reduces secretion amplitude and leads to insulin oversecretion, while inhibiting GABA catabolism with vigabatrin increases GABA release and suppresses insulin secretion. Notably, both interventions disrupt the periodicity of insulin pulses, suggesting that GABA signaling contributes to the coordinated timing of islet activity [2].

The interplay between GABA, collective cellular activity, and insulin secretion is incompletely understood. To date, no studies have investigated how GABA-mediated signaling contributes to islet synchronization that governs hormone secretion and systemic metabolic homeostasis. Inspired by concepts from network physiology and functional connectivity, we addressed these questions in our study by combining advanced multicellular imaging techniques with network analyses. Furthermore, as experimental data alone provide only limited insight, we developed a mathematical model to explore the mechanisms on how GABA affects collective cellular function and secretory responses in further detail.

Methods: Ca^{2+} time series were recorded from acute pancreatic tissue slices prepared from 8–25-week-old male NMRI mice, which were loaded with the CalbryteTM calcium-sensitive dye, as described in [3,4]. In our experiments, tissue slices were placed in a continuously perifused bath chamber with oxygenated ECS containing stimulatory 8 mM glucose plus GABA receptor antagonists in the experimental protocol, and 8 mM glucose alone in the control protocol. The exported time series were first subjected to band-pass filtering to extract the electrically-driven fast and metabolically-driven slow metabolic component [3]. The fast component oscillations were binarized and used to identify individual Ca^{2+} waves and to calculate various cellular signaling parameters, such as oscillation frequency, duration of oscillations, and relative

active time. For both protocols, we also identified and compared the cellular activation patterns. Finally, to assess the effect of GABA inhibitor we constructed multiplex functional networks in which cells represent nodes and connections functional associations in the fast and slow oscillatory components.

To gain a more mechanistic insight into GABA-mediated cellular activity, we designed a computational model based on the framework by Grubelnik et al. [5], investigating GABA metabolism, particularly the role of GABA shunt in regulating cellular energy balance. Our model examines GABA metabolism and secretion in relation to Ca^{2+} dynamics during oxidative and cataplerotic phases of beta cell metabolic activity, corresponding to the slow component of Ca^{2+} oscillations.

Results: The experimental part of the study is still at a preliminary stage. Our initial analyses suggest that the presence of GABA blockers accelerates cell recruitment in response to glucose stimulation. We also observed that cells under the influence of a GABA antagonist oscillate at a higher frequency. At the level of the fast component, we did not detect any significant differences in intercellular-wave-mediated synchronicity. The intercellular waves do appear somewhat more heterogeneous, but additional experiments are needed to confirm this. More pronounced differences were noted in the patterns of functional connectivity among cells at the level of the slow, metabolically driven component, which may be associated with intensified slow-component oscillations.

Further analyses based on our computational model have shown that GABA shunt activity is maximal during the oxidative phase. Preliminary model predictions also suggest that GABA metabolism modulates the frequency of slow Ca^{2+} oscillations. Specifically, inhibiting the GABA shunt results in a decrease in their frequency. In terms of collective cellular activity, the model predicts that GABA-mediated modulation of slow oscillations contributes to enhanced synchrony between neighboring beta cells. These results suggest that GABA plays a role not only in individual cell activity but also in maintaining the collective synchronization that is critical for the coordinated release of insulin.

Conclusions: In our study we have systematically explored GABA's role in orchestrating beta cell network activity, a key component of hormone secretion at higher organizational levels. Given the well-established link between disrupted islet synchronization and metabolic disorders such as diabetes, a deeper investigation into GABA's role in orchestrating beta cell network activity could offer new perspectives on islet dysfunction.

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13. Investigating Cardiorespiratory Coupling Through RSA Index and Mutual Correlation Coefficient*

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* This work supported by Center for Higher Education Funding and Assessment Ministry of Higher Education, Science, and Technology of Republic Indonesia

Abstract—The study of cardiorespiratory interactions has attracted substantial research interest in recent years, as it has proven to be beneficial and has demonstrated practical applications, such as serving as an indicator for specific medical conditions or monitoring intensive physical activities. However, analyzing physiological signals raises a significant challenge due to their inherent complexity and the unique characteristics of research subjects. The objectives of this study are to gain knowledge to characterize the cardiorespiratory coupling by selecting appropriate tools or indicators. The study evaluates two tools, the Respiratory Sinus Arrhythmia (RSA) Index and the Mutual Correlation Coefficient (MCC) to determine their capacity to define the systems interaction. The analysis began by using a one-directional Van der Pol oscillator, mimicking heart and lung signals, in order to explore the interpretation of the coupling parameter. The coupling parameters were changed, and the tools were applied and studied to gain insights into the strengths and limitations associated with the coupling. The results from the modelled signals indicate that MCC effectively detects the presence of coupling, whereas RSA provides insights into the coupling strength. The subsequent step is to apply the same analytical tools to the recorded physiological signals with different breathing patterns to validate whether the tools provide an informative characterization of the cardiorespiratory coupling.

STUDY OBJECTIVES Cardiorespiratory interaction is a topic that has been studied for many years. Their connection is evident and beneficial in many practices, for example, Cardiorespiratory Fitness (CRF) in sports used to monitor the physical activity related to oxygen consumption during exercise or Cardiorespiratory Coupling (CRC) used in sleep stage studies [1]. Referring to the physiological signals profile, it is challenging to comprehend the system itself, as well as the interaction. Other than the system's self-sustained oscillators, the signals also carry a number of noises from enclosed multiple systems as well as beneficial interactions that we are interested in.

The study of cardiorespiratory interaction has been performed in many ways, using various techniques with specific subject profiles and health conditions. One of the tools that is commonly used is the Respiratory Sinus Arrhythmia (RSA) analysis. In the physiological signals, the modulation manifests itself as the RSA effect when the heart rate (HR) changes to meet the metabolic demands. The RSA influenced by the breathing pattern in mental attention task, as mentioned in the Mortola et al. study. The findings demonstrates that the cardiorespiratory mechanism regulated the blood circulation around the lungs with the air flows. Rosenblum et al. [2] discussed the potential of using the mutual correlation analysis to identify this interaction. Correlation analysis is recommended as an initial standard for analyzing the pres- ence of interaction between variables.

There are numerous tools available for characterizing the cardiorespiratory coupling. However, the value of each tool is unclear. Specifically, we need to clarify the robustness (insensitivity) of the tools to the non-stationarity of physio- logical signals. Therefore, we consider the cardiorespiratory coupling for different respiratory patterns and develop an approach for the coupling characterization that takes into account the respiratory dynamics.

METHODS Rather than immediately applying the tools to the complex physiological signals, we initially explored testing the tools using the model of coupled Van der Pol oscillators as a preliminary step to have a better understanding of the tools behavior related to the coupling strength. To model changing the heart rate due to the RSA, the signal from one Van der Pol oscillator acts on a parameter of the second signal. The self-oscillators imitate the coupling between the heart and respiratory systems, which is represented by the mathematical model as in Equation (1,2) [3]:

$$\ddot{x} + \mu x(1 - x^2)\dot{x} + ((\Omega_0)^2 + ky)x = 0 \qquad (1)$$

$$\ddot{y} + \mu y(1 - y^2)\dot{y} + \left(\left(\Omega_y\right)^2\right) y = 0 \qquad (2)$$

The initial differential equation (1) generates a signal that simulates cardiac activity $x(t)$, whereas Equation (2) produces respiratory activity $y(t)$. The value k represents the coefficient of unidirectional

coupling, whereby the second self-oscillator (respiration) influences the first (heart) oscillator without any reverse influence. The parameters are selected to ensure that the relaxation oscillations of the initial self-oscillator are evident, while the oscillations of the subsequent one approximate a sine wave. The parameters $\Omega^2 = 1.0$ and $\Omega^2 = 0.085$ designate the natural frequencies of self-oscillator oscillators. The frequencies of the primary and secondary approximate a 3:1 ratio. In the absence of coupling $k = 0$, both self-oscillators exhibit periodic oscillations. For $k > 0$, the signal $y(t)$ regularly alters the parameter Ω_x and modulates the oscillation frequency of the primary self-oscillator, emulating the RSA effect. This approach aims to replicate the frequency variations inside the cardiac system.

Two techniques were used to further investigate the modeled signals to describe the system's coupling. The range dataset of the iHP signal dataset is determined in order to do modulation analysis or RSA. A different approach employed to examine system interactions is the Mutual Correlation Coefficient (MCC). The analysis was used to characterize the coupling of these two systems. However, the actual signals exhibit greater complexity. Applying the methods to real physiological signals to investigate the nature of their interaction is the next analytical step.

The physiological signals were obtained from 13 subjects exhibiting varied breathing patterns. Unlike the modeled signal, real signals are complex and require prior preprocessing. The R-peak signifies the heartbeat, and the respiratory signal's zero crossing quantifies the respiration interval. The same approach was conducted in the physiological signal, the RSA, and the MCC analysis. The modelled signal interpretation from the tools applied was then used to characterize the coupling from the physiological signal.

RESULTS Figure 1. (a) depicts the MCC for $k \in [0.0,0.54]$ in the modeled signal. In the analysis, we utilized paired respiratory and iHP signals. The MCC has a near-zero correlation for $k = 0$, however it displays around -1 for $k \neq 0$. The MCC will yield a value in the presence of coupling, whereas in the absence of coupling, the value approaches zero. This tool can be utilized to detect the existence of the coupling. Figure 1. (b) illustrates the behavior of RSA derived from the dataset range of the iHP signal is increased when the coupling strength is monotonically increased. The graph indicates that an increase in coupling results in a corresponding increase in RSA. This picture indicates that the RSA may represent the strength of the coupling. The interpretation of these two tools is used to identify the coupling of real physiological signals.

The similar approaches applied to the physiological signal with different breathing patterns. The recording consists of spontaneous and controlled breathing with different frequencies. The aim of controlled breathing is to reduce the variability of the respiratory interval.

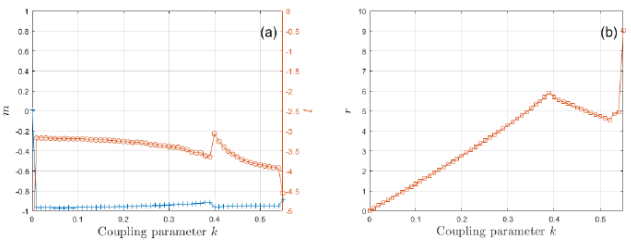

Fig. 1. Figure 1. (a) The dependences of the mutual correlation coefficient, m, (marker $+$) and the time lag, l, (marker $\circ$) on the coupling parameter k. (b) The dependence of the RSA index, r, on the coupling parameter k.

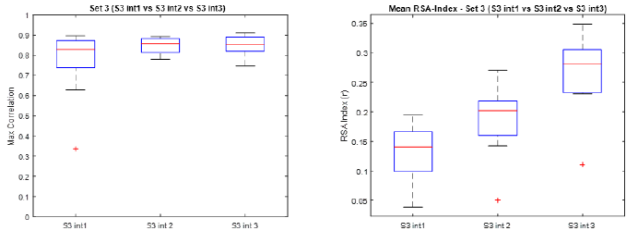

Fig. 2. Figure 1. (a) Maximum MCC of respiratory and iHP signals. (b) RSA index

The physiological signals differ from the modeled signal in that they are non-stationary; therefore, a one-minute window is utilized in the MCC analysis. The maximum correlation from each observed window is selected instead of including the entire data calculation, as presented in Figure 2.a. The data indicates the highest correlation of controlled breathing across three different frequencies: S3 int1 aligns with the subject's normal breathing frequency, S3 int2 reflects a breathing rate that is 30% slower, and S3 int3 corresponds to a breathing rate that is 150% slower.

The three sets depicted in the picture demonstrate correlation, although it is not as strong as that observed in the modeled signal. In this situation, we assume the presence of coupling; however, due to the interconnection of these two systems with other systems within the physiological network, the MCC value does not approach one. However, the respiratory system predominantly influences the heart, as indicated by a correlation value between 0.8 and 0.9.

The RSA analysis with the same breathing profile is analyzed by calculating the mean of the RSA index for the entire recording shows in Figure 1.b. The RSA index is obtained by calculating the range of the dataset of each respiratory cycle, then calculating the mean. The result shows that the RSA index increases when the subject slows their breath. Refer to what is obtained in the modelled signal; the RSA increased when the coupling strength increased. We can conclude that in this breathing set, the subject increased the coupling strength

CONCLUSION RSA index and MCC are beneficial tools to characterize the coupling; the presence, and the strength. These two tools are robust indicators that can be used to build a model to characterize the coupling.

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14. Effects of Menstrual Cycle on Hemodynamic and Autonomic Responses to Central Hypovolemia

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Background: Estrogen and progesterone levels undergo changes throughout the menstrual cycle. Existing literature regarding the effect of menstrual phases on cardiovascular and autonomic regulation during central hypovolemia is contradictory.

Aims and study: This study aims to explore the influence of menstrual phases on cardiovascular and autonomic responses in both resting and during the central hypovolemia induced by lower body negative pressure (LBNP).

Methods: The study protocol consisted of three phases: 1) 30 minutes of supine rest; 2) 16 minutes of four LBNP levels; and 3) 5 minutes of supine recovery. Hemodynamic and autonomic responses (assessed via heart rate variability, HRV) were measured before-, during-, and after-LBNP application using Task Force Monitor® (CNSystems, Graz, Austria). Blood was also collected to measure estrogen and progesterone levels.

Results: We have exclusively assessed 14 females: 8 in the follicular phase of the menstrual cycle (mean age 23.38 ± 3.58 years, height 166.00 ± 5.78 cm, weight 57.63 ± 5.39 kg and BMI of 20.92 ± 1.96 25 kg/m^2) and 6 in the luteal phase (mean age 22.17 ± 1.33 years, height 169.83 ± 5.53 cm, weight 62.00 ± 7.54 kg and BMI of 21.45±2.63 kg/m^2). Baseline estrogen levels were significantly different from the follicular phase as compared to the luteal phase: (33.59 pg/mL, 108.02 pg/mL, respectively, $p<0.01$). Resting hemodynamic variables showed no difference across the menstrual phases. However, females in the follicular phase showed significantly lower resting values of low- frequency (LF) band power (41.38 ± 11.75 n.u. and 58.47 ± 14.37 n.u., $p=0.01$), but higher resting values of high frequency (HF) band power (58.62 ± 11.75 n.u. and 41.53 ± 14.37 n.u., $p=0.01$), as compared to females in the luteal phase. During hypovolemia, the LF and HF band powers changed only in the follicular phase $F(1, 7) = 77.34$, $p<0.0001$ and $F(1,7) = 520.06$, $p<0.0001$, respectively.

Conclusions: The menstrual phase had an influence on resting autonomic variables, with higher sympathetic activity being observed during the luteal phase. Central hypovolemia leads to increased cardiovascular and autonomic responses, particularly during the luteal phase of the menstrual cycle, likely due to higher estrogen levels and increased sympathetic activity.

Disclosure statement: Parts of this abstract have been published as a full paper in *Frontiers in Cardiovascular Medicine* (Shankhwar 2024, article in press).

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15. Wavelet Analysis of Laser Doppler Flowmetry Signals: Assessing the Effects of Acute Hyperglycemia on Skin Microvascular Reactivity in the Context of Network Physiology

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Study objectives

Laser Doppler Flowmetry (LDF) is widely recognized as a gold standard for non-invasive assessment of skin microvascular function. However, the laser Doppler (LD) microcirculatory signal reflects the complex, dynamic interactions within the broader physiological networks of the body. Wavelet analysis (WA) is a powerful spectral technique that provides both time and frequency localization of measured signals, allowing for a detailed exploration of these dynamic interactions. WA of LD signals has revealed distinct frequency intervals (0.005–2 Hz), each corresponding to oscillations related to specific physiological influences that modulate skin microcirculatory responses [1]. These oscillations can be considered as components of a broader physiological network, whose components—such as endothelial (endo) nitric oxide-independent (NOi) and NO-dependent (NOd) mechanisms—are all interconnected and contribute to the regulation of skin microvascular function [2,3]. In this study, we aim to evaluate the scarcely-

investigated impacts of acute hyperglycemia on skin microvascular reactivity by examining these oscillatory patterns using WA of LD-measured microcirculatory signals. To take a step further and include an additional parameter in our network model, we coupled LDF analysis with heart rate variability (HRV) analysis. This approach allows us to gain a more thorough insight into the dynamic interactions underlying complex vascular regulation under glycemic conditions, providing a more comprehensive view of the interconnected physiological components involved in microvascular function.

Methods

Skin microvascular reactivity was assessed in 28 participants (16 females, 12 males) at three time points: before and after glucose or water loading protocols (45 minutes and 120 minutes, respectively). LDF was used to monitor changes in forearm basal perfusion and microvascular responses to provocations, specifically iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP). Simultaneously, ECG recordings from standard precordial leads were continuously monitored.

WA was employed to assess spectral components related to endothelium-independent nitric oxide (endo NOi), endothelium-dependent nitric oxide (endo NOd), and myogenic activity, as these components are particularly sensitive to changes in glycemic conditions. Additionally, time-domain HRV parameters (root mean square of successive differences, RMSSD and standard deviation of normal-to-normal intervals, SDNN) were assessed from the lead II ECG recordings to evaluate autonomic regulation throughout the protocol.

A two-way repeated measures ANOVA was conducted to assess the effects of intervention (glucose vs. control), time (0, 45, and 120 minutes), and their interaction on selected wavelet spectral components and HRV metrics.

Results

Our main finding was a significant interaction between time and intervention (glucose/water loading) in the endo NOi ($p=0.014$) and myogenic ($p=0.029$; two-way repeated measures ANOVA) bands evaluated from the SNP response, indicating that the glucose and water loading had a significantly different effect on these components over time, whereas no effect was shown for the endo NOd component. No significant interactions were observed for basal LD flow or ACh iontophoresis. In addition, significant interaction was observed in the time-domain HRV measures (RMSSD: $p = 0.009$, SDNN: $p = 0.008$; two-way repeated measures ANOVA), with both measures showing a trend of decrease over time.

Conclusions

By employing wavelet analysis (WA) to examine the microcirculatory response within the context of broader physiological networks, we demonstrated that acute hyperglycemia affects microcirculation in healthy humans. The primary mechanisms likely involve the modulation of endo NOi signaling, altered autonomic regulation, and changes in vascular smooth muscle responsiveness. These interconnected and time-dependent effects reflect the complex, dynamic interactions within the broader physiological networks that regulate microvascular function. Our findings provide a more comprehensive understanding of how glycemic conditions affect the interconnected regulatory systems, highlighting the need to study complex physiological interactions in an integrated manner.

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16. How Technical Choices Shape Functional Connectivity Patterns in Islet Networks

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Study objectives

The analysis of functional connectivity patterns represents a powerful and increasingly popular tool for quantifying collective activity in complex coupled systems, including the islets of Langerhans. The most abundant cells within these islets are beta cells, which secrete insulin—a process essential for maintaining metabolic homeostasis [1]. Although individual beta cells exhibit considerable heterogeneity in their electrical and calcium signaling activities, gap junctional coupling ensures synchronized multicellular responses. Due to their highly heterogeneous nature, the presence of distinct subpopulations, and an ever-changing environment, beta cells display intricate yet coherent intercellular activity patterns, which become disrupted in diabetes [2]. These are the main reasons why the application of network-based tools in this field has become so popular [3, 4]. However, due to variations in experimental preparations, microscopic imaging techniques, the nature of recorded signals, subsequent signal processing methods, and the approaches used to derive functional connectivity patterns, each of which may differ across research groups, comparing results and integrating them into a unified, comprehensive framework becomes challenging, even for experts in islet research. This motivated us to systematically investigate how various experimental and analytical approaches influence the characterization of functional connectivity patterns in pancreatic islets [5].

Methods

Functional beta cell networks were constructed from multicellular calcium imaging of acute pancreatic tissue slices of male NMRI, C57BL/6J, and C57BL/6N mice or from isolated mouse islets. The cells were loaded with the calcium-sensitive dye and continuously perifused with solutions containing glucose concentrations between 8 and 12 mM. Imaging was performed using confocal microscopy or CCD camera microscopy at various spatial resolutions and sampling frequencies. Extracted calcium signals were band-pass filtered to isolate fast or slow oscillatory components. The processed signals were binarized to quantify cellular activity. Network construction involved Pearson's correlation coefficients (PCC), Coactivity (CA) or Mutual information (MI), for determining functional connectivity. Three network thresholding methods were compared: fixed threshold, fixed average degree, and multilayer minimum spanning tree (MST). Network attributes such as clustering coefficient, modularity, global efficiency, node degree, and small-worldness were calculated to assess network topology and cellular synchronization, and the Jaccard similarity was computed to compare different types of networks [5].

Results

The analysis showed that functional connectivity patterns were largely unaffected by the choice of similarity metrics (PCC, CA, MI), but significantly influenced by the thresholding method used to construct networks. Employing a fixed similarity threshold resulted in considerable inter-islet variability, obscuring pharmacological intervention effects such as those observed with GLP-1 receptor agonist treatments. Adaptive thresholding, maintaining a fixed average node degree, facilitated consistent inter-islet

comparisons. Further examination demonstrated notable differences in network topology depending on the type of oscillatory calcium activity analyzed. Networks based on fast calcium oscillations were characterized by strong local clustering and shorter connections, more closely resembling the physical gap-junction coupling patterns. In contrast, networks derived from slow calcium oscillations showed extensive long-range connections, higher global efficiency, and reduced clustering and modularity. Analysis of different mouse strains (NMRI, C57BL/6J, and C57BL/6N) revealed no significant strain- dependent differences in network attributes, including clustering, modularity, global efficiency, and small- worldness. These results indicate consistency across mouse strains, suggesting robustness of functional connectivity measures. Comparative analysis between tissue slices and isolated islets revealed distinct but consistent structural features. Isolated islet networks generally resembled networks derived from slow oscillatory signals in tissue slices, exhibiting higher global connectivity with longer-range interactions and lower local clustering compared to fast-oscillation networks. Despite these differences, both tissue slices and isolated islet networks confirmed the positive correlation between node connectivity and cellular activity, with hub cells consistently exhibiting higher relative active time [5].

Conclusions

Our systematic methodological analysis [5] underscores the importance of standardizing experimental and analytical procedures for functional connectivity studies in pancreatic islets. Network topology is significantly influenced by the selection of signal preprocessing methods and the chosen type of oscillatory calcium activity. The findings confirm that adaptive thresholding methods such as maintaining a fixed average node degree facilitate robust inter-islet comparisons, reliable interpretations of pharmacological effects while also enhancing and clarifying the identification and characterization of cellular subpopulations such as hub cells. By refining network connectivity analysis, this study advances our understanding of multicellular dynamics in pancreatic islets, highlights caveats in the interpretation of collective activity analysis employing different experimental and/or analysis techniques and has broader applicability to other multicellular systems exhibiting complex signaling patterns [5].

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Poster Session II

17:00-18:30 Tuesday, 28 July, 2025

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1. Dynamic network interactions among cortical rhythms in rats and the effect of ventrolateral preoptic nucleus (VLPO) lesion on these interactions

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It is well understood in modern neuroscience that sleep stages can be defined by dominant brain waves. However, an EEG signal has much more complexity than this simple observation of which brain wave is dominant. Embedded within these signals are patterns of interaction between cortical rhythms: a given brain wave does not fluctuate independently of the others. In previous research by Lin et al., the communication between cortical rhythms has been shown to be coordinated at a very high level, and the patterns of these dynamic interactions have been shown to define physiological state (i.e. sleep stage).[1] In this work we consider if these coordinated interactions are unique to the human brain, and if physiological perturbations like neurodegenerative diseases affect network communication.

We start by analyzing EEG data taken from healthy rats in order to determine if nonhuman EEG recordings exhibit the same dynamic network interactions uncovered by Lin et al., or if this is a finding unique to humans. We demonstrate the presence of dynamic network interactions between brain waves in EEG data from rats, where previously this network analysis has only been done with human data. This indicates a degree of species universality that would be better understood by future work on EEG data of other species.

Next, we look beyond the existence of dynamic interactions among brain waves in healthy rats and consider the effect of a brain lesion on these networks as a model of neurodegenerative disease. This data looks at rats with ventrolateral preoptic nucleus (VLPO) lesions. The VLPO is a subdivision of the lateral preoptic area in the anterior hypothalamus and is a key

sleep-promoting center in the brain.[2] The VLPO functions by sending inhibitory projections to the major arousal-promoting regions of the brainstem and hypothalamus, which results in promotion of sleep.[2] Thus, lesioning the VLPO is a model of insomnia, since sleep promotion is diminished.

In the comparison of the interaction profiles of the control and VLPO rats, many of our results were surprising. First of all, there was not a complete restructuring of network profiles as may have been expected for such a profound neurological disruption: many links change but not all do. We had expected NREM to have the most brain wave pairs that exhibited significant changes in the strength of their coupling due to the increased activation of VLPO neurons during NREM,[2] but the opposite was observed. This suggests that, instead of altering the characteristics of deep sleep, the cortical cross communication during “active” states like REM and wake is altered by regulation from the VLPO, which in turn leads to the onset of sleep, a “quiet” state.

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*

2. Deciphering brain network dynamics in(between) pathological and nonpathological Brain Functioning

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Objectives

Network physiology offers a transformative perspective on understanding the brain as a dynamic, interconnected system. By examining time-evolving func- tional brain networks through properties from a local to a global scale, we can uncover subtle patterns and characteristics – such as stability, robustness, and communication efficiency – that may be invisible or inaccessible through tradi- tional methods. The network physiological framework holds immense potential for advancing the diagnosis and treatment not only for neurological and psy- chogenic disorders, but also for disambiguating and disentangling the dynamics and brain states between healthy and diseased functioning.

Methods

Deriving time-evolving weighted functional brain networks from multi-day, multi- channel electroencephalographic data recorded continuously from large and di- verse subject groups allows differentiation of different brain states and dynamics. We use a moving window approach with non-overlapping windows, associating vertices with sampled brain regions and deriving edges from estimating the strength of interaction between the dynamics of pairs of brain regions. For each snapshot network in the time-dependent sequence of functional brain networks, we assess both global and local characteristics, revealing insights into the brain's functional organisation and its deviations in pathological states. This allows the diagnosis of central nervous system disorders [1, 2, 3], probing their stability, robustness, and communication efficiency.

Results

Our initial results demonstrate the potential of the functional network approach in distinguishing (in)between physiological and pathophysiological states. By analyzing time-evolving functional brain networks across multiple scales – lo- cal (centrality measures), intermediate (network substructures and constituent groups), and global (integration, segregation, and stability) – we reveal key dif- ferentiating network properties. We propose a dynamic state space framework that enables the comparison and positioning of brain states along a continuum, ranging from extreme physiological states (e.g., sleep and wakefulness) to ex- treme pathophysiological conditions (e.g., healthy and diseased states). Within this framework, global network properties reveal that individuals with psy- chogenic non-epileptic seizures (PNES) occupy an intermediate position between healthy controls and people with epilepsy [4]. Furthermore, subject-specific alter- ations in local network properties correlate with neuropsychological responses, including stress, emotional dysregulation, and dissociative mechanisms [5].

Our findings also suggest the potential to distinguish between different types of epileptic seizures (and possibly types of epilepsy), as well as to differentiate between disorders of consciousness, sleep stages, and drug-induced alterations of consciousness (cf. Fig. 1).

Conclusion

Overall, our study underscores the promise of network-based diagnostics within the framework of network physiology, offering deeper insights into the mech- anisms underlying both healthy and pathological brain states. This approach holds potential for refining differential diagnoses in conditions with overlap- ping clinical presentations. Understanding disease-specific alterations, patterns, and properties in and of time-evolving functional brain networks could bridge the gap between normal brain function and pathophysiological disorders – such as epilepsy – offering new insights into the neurophysiological underpinnings of several pathological and non-pathological phenomena and improving clinical differentiation and diagnosis [6].

Acknowledgements

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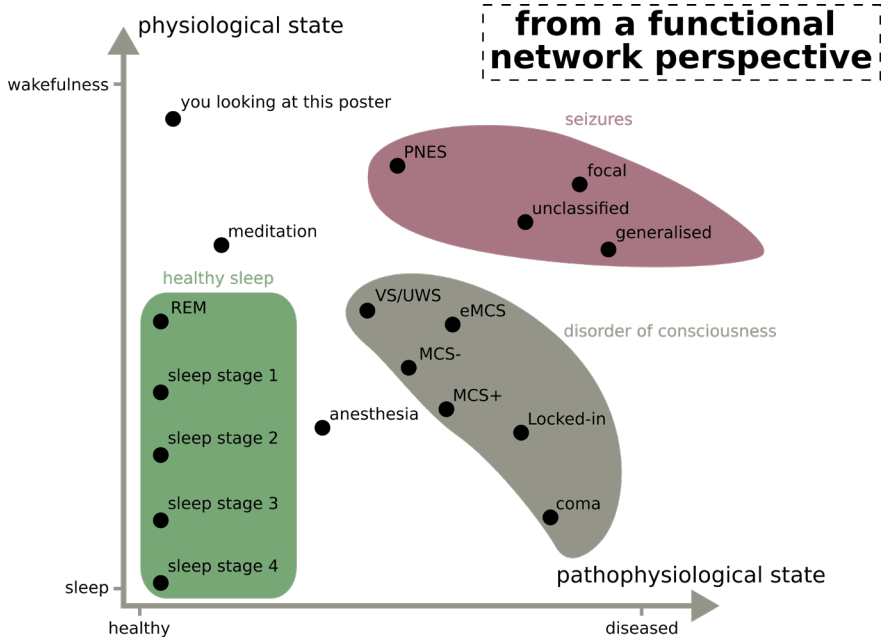

Figure 1: Schematic state space of brain states from a functional network perspective. The state space is spanned by extreme pathological states and extreme pathophysiological states.

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3. Pulse optimization for low-energy defibrillation using virtual electrodes

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The cardiac muscle represents a fascinating example of a system that can be modeled as an excitable medium. The interplay of billions of electrically as well as mechanically coupled cardiomyocytes gives rise to a variety of highly complex dynamical states.

The crossing of an electrical excitation threshold causes an action potential eventually leading to mechanical contraction of a cardiac cell. The coupling of cells enables the formation of excitation waves that drive the periodic heart beat and therefore the heart's pumping function.

In case the normal signal conduction is disturbed so that nonlinear dynamical phenomena arise so called *cardiac arrhythmias* occur. They affect the heart's pumping function and represent one of the major causes of mortality worldwide. Life-threatening cases such as ventricular fibrillation are commonly treated with a single high-energetic shock that causes traumatic pain, tissue damage and a worsening prognosis for the patients. Low-energy defibrillation techniques that apply a sequence of weak electrical pulses reduce the necessary energy while still being able to control the fibrillation.

Throughout the whole journey of improving defibrillation techniques since they were first used in a clinical context around 1950 [1, 2] the mechanisms that lead to successful termination are not fully understood up to today. By now it is known that *virtual electrodes* play an essential role for defibrillation. This has been indicated by theoretical studies [3] and shown experimentally [4, 5].

They consist of heterogeneities in conductivity within cardiac tissue. In the presence of an external electrical field these less or non-conductive defects act as wave emitters. They cause a counterwave or an obstacle to the fibrillation signal eventually terminating the arrhythmia. Thus, an essential criteria for successful defibrillation techniques depends on the activation of virtual electrodes in the cardiac tissue.

Since defibrillation techniques have been used in a clinical context they have undergone a constant process of improvement leading next to other aspects to a transition of convention from using monophasic pulse forms to biphasic pulse forms and later to asymmetric, biphasic pulses.

A variety of experimental as well as numerical studies finds biphasic pulse forms to be more effective in regards to applied energy and defibrillation success. Here, the focus mainly lies on conventional single high energy shock defibrillation. In this numerical study we shed a light on the energy optimizing pulse form in the context of low-energy defibrillation methods.

We conduct simulations in a two dimensional model of excitable media in a monodomain as well as bidomain framework modeling the local dynamics with the Fenton-Karma as well as the Ten-Tusscher-Panfilov model.

For different sizes of heterogeneities and pulse forms we identify the minimal energy needed for activation of virtual electrodes. By optimizing the pulse du- ration and form, the necessary energy is significantly reduced. Furthermore, we find that for larger virtual electrodes a monophasic pulse form is more effective compared to a biphasic pulse form. This might have major implications for the optimal pulse form differing for low-energy defibrillation methods (were especially large heterogeneities are recruited) compared to conventional defibrillation.

With our work, defibrillation protocols that apply sequences of weak, energetic electrical pulses can be further optimized. Therefore, we provide valuable insights for the further development of improved defibrillation techniques.

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4. Digital organoid: A biologically inspired neural network for image classification

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I. STUDY OBJECTIVES

The design of Artificial Neural Networks (ANNs) emulates the nervous system, passing information between neurons (nodes) through axons (edges). ANNs lack the temporal component of these signals. SNNs improve upon this design by transforming signals to temporal inputs [1]. Neither ANNs nor SNNs capture the temporal dynamics of signals passing between nodes, however. To capture these dynamics, we introduce the Digital Organoid, a spherical graph network that models the signals between neurons as traveling waves. Our design takes inspiration from brain organoids: 3-dimensional cultures of pluripotent stem cells that have grown in popularity in the past decade for studying neural development [2]. Their spherical shape is a simple starting point for a 3-dimensional machine learning algorithm. Both the Hodgkin and Huxley model and cable equation do not capture the inductive forces of neural signaling. We use the telegraper's equation, developed by Oliver Heaviside [3], to model neural signaling over time and space while capturing the inductive forces. The Digital Organoid extends SNNs to capture the dynamics of signals between neurons over time and distance as a result of their physiological characteristics.

II. METHODS

The Digital Organoid's neurons are evenly distributed along 5 sphere layers of decreasing diameter: Input (I), Convolutional 1 (C1), Convolutional 2 (C2), Pooling (P), and Out (O). The largest diameter matches the maximum diameter of Lancaster protocol organoids [2]. The resulting layers are shown in Figure 1a. The physical dimensions of the system determine the electrophysiological properties of the edges. The nodes are regular spiking Izhikevich neurons. Each edge has a g-ratio: the ratio of the inner diameter of the membrane ($d_{i,j}$) to the outer diameter of the myelin ($D_{i,j}$). The g-ratio and $d_{i,j}$ determine the $D_{i,j}$, velocity (θ), internodal distance (ℓ) [4], resistance (R), conductance (G), and capacitance (C) of each edge. The wave signal along an edge is modeled using these electrical properties in the telegrapher's equation.

We test the model on a set of six 9x9 dice faces with white dots on a black background. We project images onto the network using UV Mapping as shown in Fig. 1b. Image pixels are assigned U and V values according to their width and height coordinates. We plug U and V into the parametric equation of a sphere to project the image onto the surface. Pixels are assigned to their closest node in angular space. Rate encoding transfers pixel values to input spike probabilities [1]. For each time step, white and black pixels have Bernoulli spike probabilities of 1 and 0, respectively. A spike event injects 15 *mv* of applied current into the neuron. For each input image, the network runs for 100 *ms* in discrete time steps of 0.01 *ms*. At each time step, neurons are either spiking or resting. If spiking, injected current is added to the postsynaptic node. The amount of injected current is the integral of the signal wave in the last 10% of the axon. The network learns through synaptic timing-dependent plasticity (STDP) using Eq. 1 [5]. This method approximates the classic behavior that neurons that fire together, wire together.

$$\Delta w = \eta\left(x_{pre} - x_{tar}\right)(w_{max} - w)^{\mu} \quad (1)$$

III. Results

We analyze the output nodes of the network in three ways. First, we identify the node that fires first and then most, shown in Fig. 2a, following two SNN output classification methods: latency and rate encoding [1]. Second, we analyze the output node voltages over time and frequency to capture the network's temporal dynamics. Magnitude spectrograms are created for each output node and averaged across presented stimulus classes. The resulting spectrogram is found in Fig. 2b. Third, we measure the

organoid's network assortativity and average degree strength after each image presentation in Fig 2c.

IV. CONCLUSIONS

The provided results show systematic alteration in network structure over time. We plan to extend this work to include modifying node positions to manipulate signal speeds. Reinforcement learning will be employed as an evolutionary process to identify the optimal node configuration. This extension will result in a system whose learning process is governed by conformational changes in the Digital Organoid's shape rather than changes to the numerical weights.

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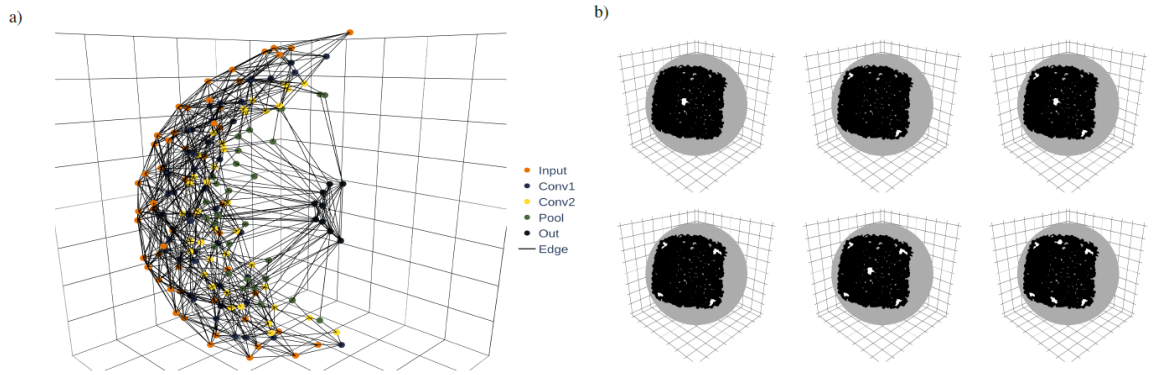

Fig. 1: **Network Architecture**: The network connections and UV Mapping of images onto the surface. **a)** Wiring configuration of the Digital Organoid network color coded by node type. Only a quarter of the network is shown for visualization purposes. **b)** Six 28x28 dice faces projected onto the Digital Organoid surface through UV Mapping. Grey nodes have no pixel assignment. Note: a larger image size is used for visual demonstration.

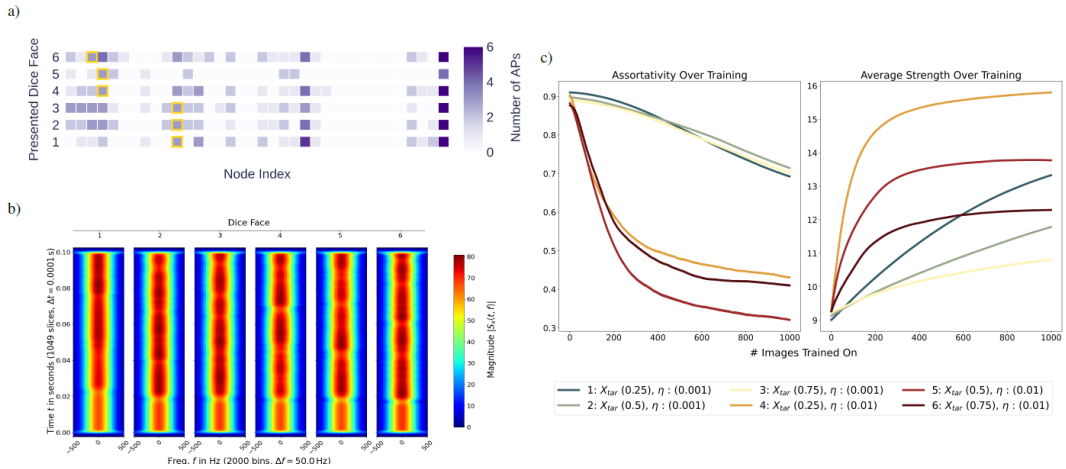

Fig. 2: **Network Analysis**: After training, the network is analyzed in three ways. **a)** Output node firing analysis identifies nodes that underwent the most action potentials (APs), indicated by color, and fired first, indicated by yellow outline. **b)** An averaged spectrogram analysis of the output node firing captures the time and frequency dynamics of the network. Each column is a dice face and color indicates the average magnitude of the signal. **c)** Network assortativity and average degree strength across training for different values of target pre-synaptic trace

($Xtar$) and learning rate (η) in STDP show systematic alteration.

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5. Estimation of coexisting or exclusive interactions from population dynamics of gut microbiome of mice

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We introduce a new data analysis method of gut microbiota population time series to clarify coexisting or exclusive interaction networks among about hundreds of species [1]. It is known that the population of species of gut microbiota generally follows a fat-tailed distribution typically aproximated by a power law, and therefore, a lot of species have only small population with many zero values in the integer compositional abundance time series. In order to analyze such time series data we transform the time series to 0 (absence) and 1 (presence), and statistical tests are applied to extract significant coexistence and mutual exclusion relationships. For a given pair of time series of species i and j, we count the number of (0,0), (0,1), (1,0), and (1,1) appearing at the same time. Let these numbers be a, b, c, and d, and we apply Fisher's exact test to estimate the P-value that characterizes whether co-occurrence events, (0,0) and (1,1), or exclusive events, (0,1) and (1,0), are statistically significant or not. In the case ad-bc>0 with significantly small P- value (typically less than 10^{-5}) we judge that species i and j are coexisting, and in the case ad-bc<0 the pair is judged as exclusive. Methods have been developed for estimating p-values by integrating experimental data from different mice and for eliminating false correlations through conditioning with a third species.

We applied this method to real data of the gut microbiota by analysing mouse faeces. In a typical case with 420 species (more precisely, Operational Taxonomic Unit (OTU)), we found that almost all species (419 out of 420) have at least one significant correlation, i.e. in terms of the interaction network where nodes represent microbial species, there is a giant coonnecting network with about 90% of coexisting and 10% of exclusive relations. This observation suggests that the knowledge of complex network analysis will play an important role in the future to understand the ecology of the gut microbiota.

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6. A Synergetic Repertoire of Whole-Brain Network Dynamics

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Objectives

The human brain is an extraordinary complex system operating at both flexibility and complexity (Chialvo, 2010), whose function is achieved through the orchestrated coordination of many specialized subsystems. Given the high spatial resolutions and sub-second temporal precision of functional Magnetic Resonance Imaging (fMRI) that enables rich spatiotemporal measurements of brain activity, a viable approach to ascertain the intricacy of large-scale brain dynamics is through dimensionality reduction (Cunningham et al., 2014) while preserving the critical features of neural interactions. Over the years, both parameterized and non- parameterized methods have been widely adopted on fMRI data; from statistical inference and pattern recognition, for example, principal or independent component analysis, to decompose brain spatiotemporal or spectral modes in neurobiological contexts, the dynamic orchestration of which underpins brain function. Despite the remarkably consistent connectivity patterns that have been uncovered, challenges persist in interpreting the brain modes and assessing their falsifiability, particularly given the absence of ground truth inherent to black-box investigative approaches.

To address the challenges, this study aims to disentangle brain network dynamics derived from fMRI activity using a novel approach to define low-dimensional manifolds, and to characterize the functional significance of the modes informed by complex systems principles (Breakspear, 2017) that have been extensively explored across disciplines but less applied and tested in the human brain. Furthermore, by applying the analysis to individuals with neuropsychiatric disorders, this research also endeavors to offer important insights into disrupted dynamics, shedding light on the potential pathological mechanisms underlying brain disease.

Methods

We developed a novel approach to identify brain modes evolving over time, also termed “brain states” that represent the basic building blocks constituting a dynamic repertoire of brain operating, by using inputs corresponding to time-varying graph theory metrics. This highly customized approach, in principle, enables a non-linear mapping onto the low dimensional manifolds (Gao et al., 2021), where a limited number of latent variables capture the essential features of large-scale neural activity. By applying this approach to preprocessed fMRI data of healthy population, this study first validates this new approach through its capability to discriminate distinct and meaningful brain states by associating with well-defined properties observed across various complex systems. The approach is next extended to disease data to investigate how the dynamics may be disrupted within and between the identified brain states.

Specifically, instead of recruiting structured techniques to deploy the decomposition of brain dynamics, we take time-resolved brain networks within the empirical sliding-window framework and extract network features (i.e. graph theory metrics, such as clustering coefficient, closeness centrality, participation coefficient, etc.) for input into an unsupervised clustering algorithm. We adapt an analysis from modern network science that characterizes brain network topology across micro-, meso- and macro-scales to facilitate non-linear dimensionality reduction. To address challenges in parameter selection, particularly the optimal number of brain states, we employ Gaussian mixture model inferred using Variational Bayes, in which brain states are modeled as data sampled from probabilistic components, to allow automatic parameters approximation from empirical posterior provided by an infinite Dirichlet Process prior.

Results

The most important findings of our approach applied to resting state and task fMRI-derived brain networks are summarized in Fig 1. Our results indicate that the identified brain states can be meaningfully interpreted by a divergent bifurcation pattern, delineated in two fan-shaped branches with an intermediate overlapping region, forming three fundamental configurations that govern dynamic transitions within the brain system. By mapping the discovered states to the graph theory indices, our results not only show consistency with the well-established integration and segregation processing across the whole brain but also demonstrate superior discriminative power in distinguishing between states. Further interpretation of the brain states can also be inferred from network organizations that exhibit a marginal yet consistent increase in global efficiency. This suggests a unified principle in terms of connection wirings, which remains invariant across

metastable latent states. Building on the concept of metastability in dynamical systems (Ibanez et al., 2024), our framework introduces an embedded manifold structure, that is represented in a reduced space derived from the original high dimensional connectivity data across hundreds of brain parcellations, and the distribution of brain dynamic activity samples over time in this space reveals a structured flow that encapsulates the brain transitions between in a whole.

Conclusions

This study reveals that the brain exhibits inherent, scale-invariant manifold patterns, whose structured visitation constitutes a dynamic repertoire that can be characterized by synergetic, which *per se* emerge from multi-scale interactions spanning the whole brain, including cortical and subcortical regions. With the advanced neuroimaging techniques offering unprecedented access to brain activity signals, our study presents great potential for quantifying complex system properties, bridging dynamic model and computations of the human brain as a self- organizing living system rooted in human physiology.

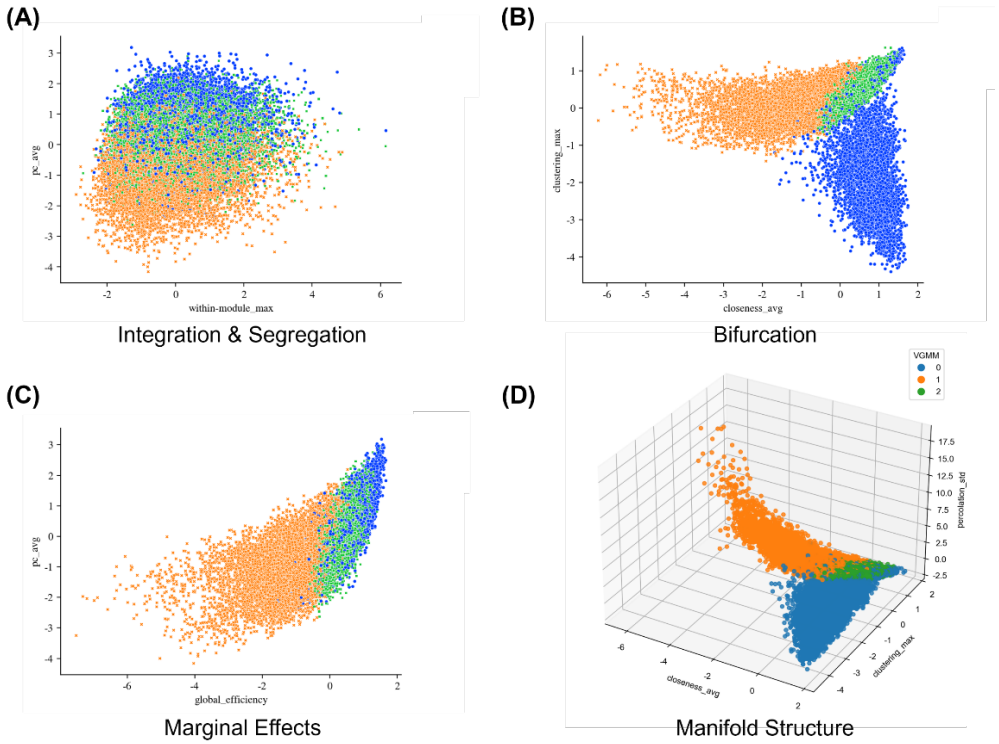

Fig 1. Network-informed manifold patterns in decoding consistent and critical brain dynamics. (A) Manifold projections onto the key features of participation coefficient (integration proxy) and within-module degree (segregation proxy) reveals a low-dimensional manifold encoding the brain's empirically validated trade-off between **segregation** (specialized modular processing) and **integration** (global information synthesis), showcasing model consistency with canonical findings in network neuroscience. **(B)** Manifold projections onto the clustering coefficient (local efficiency) and closeness centrality (global integration) uncover **bifurcation** structure that marks critical phase transition, and the overlapping state near bifurcation points reflect metastability and state ambiguity. In some contexts, the emergent order parameters are used to quantify symmetry-breaking dynamics. (C) Manifolds projections onto the global efficiency and participate coefficient reveal diminishing returns ($\Delta E/\Delta C \rightarrow 0$ as wiring cost C↑) in efficiency gains. The manifold's curvature presents Pareto-optimality that balances metabolic constraints with communication efficacy, serving as a hallmark of evolved, scale-free neural architectures. **(D)** Manifold represented in reduced 3D landscape (closeness centrality, clustering coefficient and percolation) highlights critical transitions as inflection points in the manifold's curvature. It is noticed that while these patterns describe emergent dynamics, they arise from intrinsic interactive collective mechanisms rather than explicit control parameters. All the panels use the same coloring scheme according to assignments of brain states for time-resolved brain networks.

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7. Metastability and transient dynamics in neuroscience

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Metastability, characterized typically as a variability of dynamical regimes over time, is a ubiquitous behavior in many systems, particularly in the brain. We examine this behavior using dynamical systems theory to provide a consistent and accessible framework for explaining different forms of metastability. We provide a general and clear definition of the behavior, which is typically missing in the neuroscience literature. Furthermore, we discuss many possible dynamical mechanisms that can generate metastability and show, how known experimental and theoretical studies can be explained by those various mechanisms. Special emphasis is given to transient dynamics which is one of the key features of metastability since it focusses on the transitions from metastable state to another. Particular role is played by chaotic saddles which are often the backbone of such transitions. We explain the mechanisms how chaotic saddles appear, their dynamical and statistical properties and their possible role in the dynamics of neuronal systems. To demonstrate the associated dynamics, we employ a network of FitzHugh-Nagumo oscillators and show how metastability can occur as a hopping dynamics between different space-time patterns like low- amplitude oscillations, nonlinear waves and extreme events.

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8. Amygdala GABA Neurons: Gatekeepers of Stress and Reproduction

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Study Objectives

Stress can cause disruptions to the menstrual cycle and normal reproductive function via the suppression of the gonadotropin-releasing hormone (GnRH) pulse generator, which regulates luteinizing hormone (LH) production. The posterodorsal medial amygdala (MePD) has been implicated in mediating stress-induced suppression of GnRH pulsatility through its modulation of GABAergic neurons within the amygdaloid circuit [1]. However, the precise neural mechanisms underlying stress processing in the MePD remain poorly understood. The objective of this study is to understand the role of MePD GABAergic neurons in stress processing by combining in vivo calcium imaging, data analysis, and computational modelling. Specifically, we investigate how distinct subpopulations of MePD GABA neurons interact to relay stress-related information and regulate downstream reproductive neuroendocrine activity.

Methods

To investigate the dynamics in vivo calcium activity of MePD GABA neurons has been measured under acute stress and under the optogenetic stimulation of urocortin (UCN3) neurons, which are believed to be involved in stress processing in the MePD. Calcium activity is analysed using functional connectivity metrics, such as signed lagged cross-correlation (SLxCorr) and K-means clustering. We use results from the data analysis to inform the parametrisation of our previously developed MePD circuitry mathematical modelling framework [2]. The framework then is coupled to the model of the GnRH pulse generator [3] to investigate the eSects of various MePD interventions (stimulation of MePD UCN3 neurons, stimulation of MePD GABA neurons, simultaneous stimulation of MePD UCN3 neurons and suppression of MePD GABA neurons) as well as eSects of stress. These predictions are then validated with in vivo intersectional strategies.

Results

Our findings show that MePD GABAergic neurons consist of two functionally distinct, anti- correlated subpopulations. Both SLxCorr and K-means clustering identified these clusters under optogenetic UCN3 stimulation and acute stress (Fig. 1**A**). We parametrized our MePD circuit model to reproduce this anti-correlation (Fig. 1**B**), requiring mutually inhibitory GABA interactions and self-inhibition. Additionally, shared input entrains both populations to a common stimulus, necessitating distinct streams for anti-correlation.

Coupling the MePD circuit showed that MePD UCN3 and GABA excitation increases LH pulse periods, highlighting their role in GnRH modulation (Fig. 2**A**,**B**). Suppressing GABA interactions alongside UCN3 stimulation had little eSect on GnRH pulsatility (Fig. 2**C**), suggesting UCN3's impact depends on GABA. All aforementioned predictions were experimentally validated using intersectional strategies, supporting the underlying circuit mechanisms. Simulating acute stress in the model reproduced the loss of pulsatile dynamics (Fig. 2**D**), which also observed in vivo[4].

Conclusions

Our study identifies the critical role of both UCN3 and GABAergic neurons in stress processing within the MePD. Using calcium imaging and computational modelling, we uncover two distinct, anti-correlated GABAergic sub-populations regulated by mutual inhibition. Our mathematical model of the MePD circuit reproduces experimental findings, identifying potential mechanisms underlying the modulation of the LH pulsatility by the MePD. Furthermore, we highlight the functional orthogonality between UCN3 and GABA neurons, emphasizing the complexity of MePD's role in stress-induced reproductive suppression.

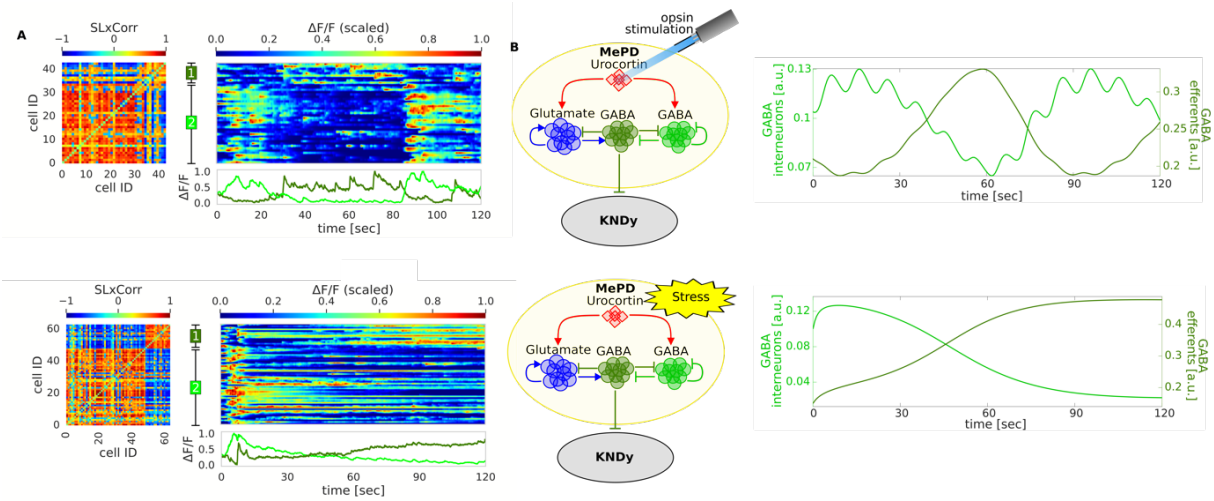

Figure 1: (**A**) Representative example of a clustered connectivity matrix and associated calcium time- traces of MePD GABA neurons during optogenetic stimulation of UNC3 neurons (top) and acute stress (bottom). (**B**) *In*

silico simulation of the activity in the GABAergic neuronal populations in the MePD under the increased excitatory input from UCN3 neurons (top) and under acute stress (bottom).

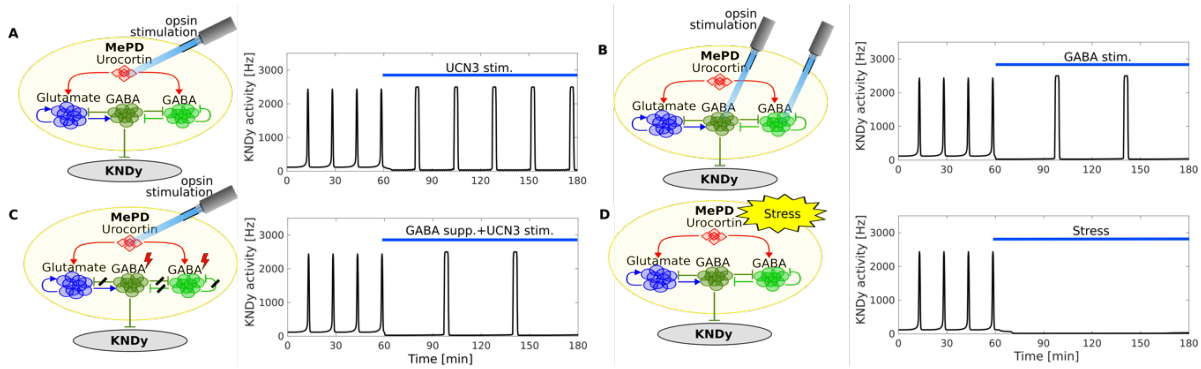

Figure 2: Coupled MePD - KNDy model predictions for the eHect of stress and stimulation of UCN3 neurons on GnRH pulse generator activity and hence LH pulsatility. (**A**) Simulation of the optogenetic stimulation of the UCN3 neurons leads to the increase of the KNDy IPI 15.18 min to 23.97 min. (**B**) Optogenetic stimulation of the MePD GABA neurons (providing excitatory input to both GABAergic populations) increases KNDy IPI from 15.18 min to 42.65 min. (**C**) Optogenetic stimulation of the UCN3 neurons and simultaneous inhibition of GABAergic neuronal populations do not significantly aHect KNDy IPI, where it changes from 15.18 min to 17.32 min. (**D**) Simulating the eHects of stress leads to the cessation of the pulsatile dynamics.

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9. Combining Machine-Learning and Dynamic Network Models to enhance Sepsis Scores

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Background

As the most extreme course of an infectious disease, sepsis poses a serious health threat, with a high mortality rate and frequent long-term consequences for survivors. In 2017, an estimated 48.9 million people worldwide suffered from sepsis and the same year, 11.0 million deaths were associated with sepsis [3]. Untreated, the disease is always fatal and even with successful treatment, around 75% of those affected suffer long-term consequences. Overall, untreated septic diseases in particular represent an enormous burden on the global healthcare system. The triggers for sepsis are varied, but almost half of all sepsis-related deaths occur as a secondary complication of an underlying injury or non-communicable disease, highlighting the importance of early recognition and treatment of infections in patients with pre-existing health conditions. Faster recognition of the septic condition significantly increases the chance of survival [5],

it urges to develop accurate and robust detection and prediction methods, i.e. reducing the time to receive the appropriate medical attention.

So-called sepsis scores have been established to simplify the early detection of sepsis in people at risk and to support medical personnel in making a diagnosis. In recent years, machine and deep learning methods have also been increasingly developed to further increase the effectiveness of sepsis predictions [1]. Despite good prediction results, these approaches often suffer from a lack of interpretability, making them difficult to accept in clinical practice.

Objectives and Methodology

In this project, we want to enhance the interpretability of sepsis detection and prediction models by integrating machine-learning techniques with a specialized dynamical system designed to model septic conditions. The “Dynamic Network Model” (DNM), introduced in [4], represents the interaction between parenchymal cells (functional organ cells, opposed to stroma, the structural cells) and immune system of patients using a two-layered partly adaptive oscillator framework. Communication between the two layers in the biological system via Cytokines is modeled by adaptive coupling weights. By analyzing synchronization patterns and other dynamic states within this system valuable information about the patient’s condition can be obtained [4].

To utilize the DNM for detection and prediction of sepsis, our approach involves the learning of patient-specific DNM parameters from historical data, enabling the classification of the evolving clinical status of patients as healthy, vulnerable or pathological (*Detection*). Tracking a patient’s trajectory through the lower dimensional parameter-space is proposed to reflect clinical progression over time. This potentially allows the extrapolation of pathological developments, treatment responses and prediction of critical conditions (*Prediction*). As data sources we primarily rely on the publicly available “MIMIC Clinical Databases” (versions III and IV) [2], which is a widely accepted database to train sepsis prediction models of various flavors. The specific research questions involve:

- **Usability of the DNM**: How and to what extent can the ML-determined trajectories of the DNM be used for detection and prediction, especially of critical infection states and mortality.
- **Comparison with data-based approaches**: How can the model-based predictions be compared with those of purely data-based approaches in terms of predictive power and interpretability.

Generated results will be compared with conventional purely data-based machine learning sepsis detection and prediction approaches, such as random forests, gradient boosting or deep learning [1]. Established comparative metrics will be used to assess the interpretability and general task performance of each method.

Implementation and Results

Regarding the sepsis detection we mainly project high dimensional patient condition – including various bio- and health-markers – into the low-dimensional parameter space of the DNM.

To achieve this we are using modern machine-learning techniques alongside an appropriate numerical integrator for simulation of the dynamical system. The prediction phase is expected to include sequence-to-sequence modeling with deep neural networks, such as recurrent or transformer based architectures, which are well-suited for time-series analysis and extrapolation tasks.

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10. Ionic models of atrial fibrillation in stem-cell derived atrial cardiomyocytes

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Atrial fibrillation is the most common form of cardiac arrhythmia. Prolonged atrial fibrillation significantly increases the risk of stroke, as well as heart disease. To treat and prevent it, studying the causes of atrial fibrillation is vital. Experimentally, this has often been done in extracted animal hearts, which are not always adequate models of the human cardiac electrophysiology. An alternative for conducting experiments are stem-cell derived human atrial cardiomyocytes. These cells can be artificially generated in the laboratory to imitate the electrophysiological properties of human atrial cells.

Based on experimental measurements on single stem-cell derived atrial cardiomyocytes, we extend an existing ionic model [1] of induced pluripotent stem-cell derived cardiomyocytes to model atrial stem-cell derived cardiac muscle cells by incorporating the ultra-rapid delayed rectifying potassium current, known to be relevant in atrial cells, into the model. Together with adjusting the model based on laboratory measurements of individual currents, this allows us to make predictions of drug effects on the electrophysiology of the cells and validate these predictions using tissue level optical mapping measurements.

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11. 3-body synergistic dynamics of EEG functional networks during an arithmetic task experiment

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The study of the interactions and statistical constraints present in neural activity across different parts of the brain is one of the most well-established areas of research in neuroscience. These interactions have been studied mainly via the application of statistical tools designed for the detection of pairwise interrelationships between pairs of variables, such as Pearson's correlation or Mutual Information.

Although these tools have yielded significant insights for pairwise relationships, the investigation of potential interactions involving more than two brain regions, specifically those that cannot be reduced to diadic coupling,is inherently unfeasible using standard bivariate methods.

In the present work we report preliminary results on a study of changes in the functional networks of 3rd order obtained from 35 participants of a cognitive task vs rest experiment [1].

To build the 3rd order functional networks, we measured the synergistic term of the Partial Information Decomposition (PID) [2,3] for every triplet of EEG channels of each hemisphere of the brain.

The synergies were statistically validated with random permutation surrogates to test against random occurrences of synergy and with Cholesky factorization surrogates to test against deviations from the synergistic structure that is expected in a Gaussian system.

The results obtained so far seem to indicate that the most intense increases in synergistic interaction are in the left temporal and left parietal lobes but that these changes are negatively correlated with the intensity of synergistic interactions measured at rest.

Further work will include the topological study of hypergraphs induced by the 3rd order synergistic activities.

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12. Information dynamics of heart rhythm, repolarization and amplitudes time series in Long QT Syndrome

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Study Objective. In the study, we focused on Long QT Syndrome (LQTS). It is a genetically determined dysfunction of ion channels or the proteins that regulate them. LQTS leads to severe symptoms, including fainting or sudden cardiac arrest. The disease is characterized by arrhythmias caused by prolonged cardiomyocyte repolarization. The clinical classification of the disease depends on gene mutation. For example, in LQTS type 1, the mutation disrupts the slow potassium current.

One goal is to stratify the risk of arrhythmia in LQTS patients, especially in the asymptomatic group. The symptoms of LQTS may be due to the condition of the heart or the activity of the autonomic nervous system. A complete risk analysis requires prospective studies, and such data are not widely available. A preliminary step to justify the usefulness of certain measures as clinical indicators is a retrospective study showing that they discriminate pathological cases from normal cases.

Methods. Two databases from the THEW Project were used: E-HOL-03-0202-003 (202 ECG of healthy individuals [1]) and E-HOL-03-0480-013 (480 ECGs of the Long QT Syndrome patients with 4 subgroups of genotype [2]). However, in this study, we analyzed only part of the recordings: 195 LQTS patients (132 women, LQTS1: 109 records, LQTS2: 60 cases, LQTS3: 9 cases, other: 17 cases) and 150 healthy individuals (74 women). The age of the participants was limited to 18-60 years. The limited number of recordings is caused by not satisfying quality of T-wave end determination. From ECG recordings RR, QT, DI intervals as well as QRS and T wave amplitude were extracted. For the analysis nighttime segments were selected. All signals were divided into non-overlapping windows of length 1200 intervals, and in all windows, we checked if the signal is stationary (ADF test). Non-stationarity in the form of trends was removed by .tting a third-degree polynomial.

The aim of this study was to investigate the information .ow between cardiac rhythm and repolarization processes using conditional entropies [3,4,5]. Bivariate and trivariate entropies were estimated using ITS

Toolbox for RR, QT and DI intervals and for R and T wave amplitudes. As a result, 23 variables were obtained, as only information flows with values significantly different from zero were considered.ssssss

Determining the optimal values of hyperparameters for Support Vector Machine (SVM) and Random Forest (RF) models was performed in Python using GridSearchCV. The data was divided into training and test sets, with the size of the test set being 33% of the size of the total data. The number of cross-validation was set to 5.

Results. The results obtained using the RF approach demonstrate that entropy-based methods allow the construction of a classi.er capable of distinguishing recordings from LQTS patients with 97.4% accuracy, 97.4% sensitivity and 95.9% specificity. The SVM-based classi.er achieved an accuracy of 94.7%, with a sensitivity of 94.7% and a specificity of 93.9%. Figure 1 shows the ROC curves for both classifiers to illustrate their performance.

The best result for test sets we obtained using the following set of parameters:

- SVM: gamma = 0.01, C = 50, kernel = ‘rbf’,
- RF: criterion = ‘gini’, max_depth = 8, n_estimators = 100.

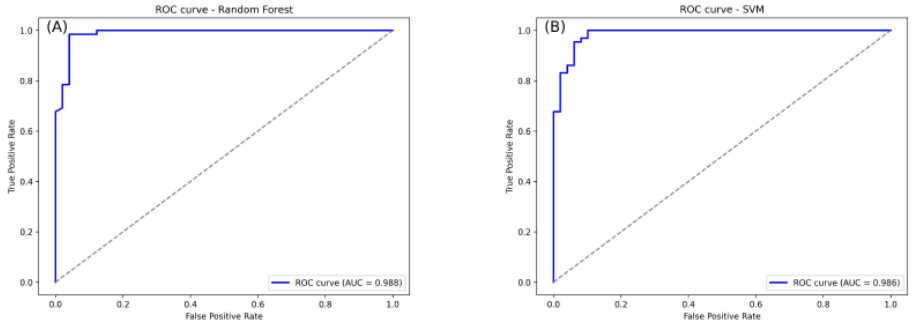

Fig. 1: ROC curves for RF (A) and SVM (B) classifiers for the specified parameters in the binary classification task of patients with LQTS and healthy individuals.

Conclusions. The estimated values of information dynamics show promising potential to distinguish the complex dynamics of cardiac repolarization and heart rhythm between healthy individuals and LQTS patients. These results serve as a promising proof of concept, demonstrating the feasibility of developing an automated model to assist clinicians in disease diagnosis. Although the information .ow parameters were determined from univariate ECG recordings, they do allow for the study of time series classification. Furthermore, multivariate analysis supports the detection of arrhythmic symptoms using standard ECG.

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13. Potential Clinical Benefits of the Time-Evolving Brain Network Approach in Di↵erentiating Disorders of Consciousness

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1 Objectives

Complex network analysis of EEG data has demonstrated novel potential for diagnosis and prognosis of disorders of consciousness (DOC). This approach offers advantages over traditional methods by providing a more holistic and comprehensive evaluation of brain dynamics, considering the integrity of brain-wide networks. Unlike traditional methods that measure localized brain activity, network-based analyses capture dynamic interactions between brain regions, offering valuable insights into how brain networks evolve across different states [1]. Investigating time-evolving functional brain networks can significantly aid in understanding and differentiating between various stages of consciousness (coma, under anesthesia, asleep, and awake), as well as neurological and psychogenic disorders. We present findings obtained from applying network-based EEG analysis to elucidate time-dependent changes in brain dynamics, associated with DOC, providing a more nuanced perspective on brain dynamics and its relation to consciousness.

2 Methods

We investigate changes in time-evolving weighted functional brain networks from continuous multi-day, multi-channel EEG data collected from large, diverse subject groups. We associate brain regions with vertices and estimated the strength of interactions between pairs of brain regions associated with weights of edges that evolve in time. For each snapshot network in the temporal sequence of functional brain networks, we evaluated both global and local characteristics, providing insights into the brain's functional organization. We assess deviations from normal functioning, which enables the diagnosis of and differentiation between central nervous system disorders [2, 3, 4], via examining their stability, robustness, and communication efficiency. Patients were assessed twice, 3–6 weeks apart, with EEG, multisensory stimulation and neuropsychological evaluation of states of consciousness [5].

3 Results

We observe changes in network characteristics on various network scales that allow to differentiate states of consciousness. Notably, interindividual variability in network characteristics aided in distinguishing between subjects with unresponsive wakefulness syndrome (UWS) from healthy controls despite clinical uniformity [5]. Decreasing age-corrected global network characteristics reflected both short-term stimulation e↵ects and long-term therapeutic intervention, indicating a shift towards less segregated brain networks, potentially signaling recovery. The network approach also identified subject-specific differences in local and global network characteristics, offering a more precise method for tracking recovery in subjects with UWS. In a separate study, we examined differences in functional network properties of healthy controls, individuals with psychogenic non-epileptic seizures (PNES), and those with epilepsy [6]. This analysis revealed distinct network differences between the groups. People with PNES showed higher network integration and lower segregation compared to individuals with epilepsy, suggesting more diffuse network dynamics.

4 Conclusion

Our findings stress the potential of this approach as practical method for monitoring disorders of consciousness during early rehabilitation, as well as the differentiation between physiological and pathophysiological brain states. We hypothesizes that our approach supports more accurate diagnoses and the development of personalized treatment plans. Ultimately, monitoring the recovery trajectory of subjects with DOC, as well as assessing the impact of therapeutic interventions in the time-evolving functional brain network framework allows to advance clinical decision-making, improve diagnostic accuracy, and optimize individualized care strategies for consciousness disorders.

5 Acknowledgements

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17. Analysis of Ventricular Fibrillation in Human using 4D Echocardiography

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Study Objectives

Cardiovascular disease is the leading cause of death worldwide and ventricular fibrillation (VF) remains a major cause of sudden cardiac arrest. This is caused by a dyssynchronous dynamics within the complex network of coupled, electro-mechanically oscillating cardiomyocytes in the cardiac tissue. Spiral waves or rotors have been described as the organizing centers of the dynamics [1], however, their intramural and mechanical dynamics remain elusive. In the animal model, the co-localisation of electrical and mechanical rotors has been shown [2]. In human however, the investigation of the spatiotemporal dynamics underlying VF is strongly limited due to the need for immediate termination of this malignant arrhythmia.

We performed the translation of 3D rotor mapping of VF from animal model to human using epicardial high-resolution 4D echocardiography during spontaneous VF in patients undergoing on-pump cardiac surgery.

Methods

Spontaneous ventricular fibrillation was examined in 35 patients with preserved left ventricular ejection fraction undergoing elective coronary artery surgery. Patients were supported by cardiopulmonary bypass and thus the additional burden due to recording was low. Ethics approval was granted by the local ethics committee in accordance with the declaration of Helsinki and the ICH guidelines for good clinical practice. 4D (3D + time) high resolution ultrasound imaging (>100 volumes/s) of the left ventricular wall was performed epicardially with simultaneous recording of the Lead-II ECG. In the echocardiograms, motion tracking was performed and the strain rate was computed from the obtained displacement fields. Activation maps were defined as the time since the last onset of contraction and period duration as the time between two activations. For analyzing mechanical rotors, the phase was computed from the analytic signal of the strain rate. Rotor centers were identified as phase singularities and tracked in time.

Results

We observed 3D mechanical rotors in human ventricular fibrillation with filament-like phase singularities across the entire depth of the ventricular wall. The rotor dynamics is characterized by multiple short-lived centers of rotation, which propagate at a fast pace, and frequently interact, altering their morphology.

Furthermore, we could resolve intermittent states with different levels of organization and synchronicity of cardiac mechanics. Mechanical motion was predominantly observed as undirected, low-amplitude motion and low, rather fractionated strain rates. During intermittent intervals, displacement fields showed high

synchronisation with a directed, strong motion and large areas of the ventricle showed simultaneous onset of contraction (fig. 1). This change in dynamics could not be observed by evaluating the ECG alone.

Conclusions

This first in-human analysis of the intramural cardiac motion during VF using 4D echocardiography showed to be capabe of resolving intramural 3D rotor dynamics. Notably, intermittent changes in the mechanical dynamics can be observed with the high spatial resolution of ultrasound imaging, which are not observable in ECG.

We anticipate these results to be a starting point for more detailed analysis regarding anatomical locations and interactions of rotors as well as synchronizity in the complex network of oscillating and moving cardiomyocytes. A more detailed characterisation of varying cardiac dynamics bears the potential for novel strategies in arrhythmia prevention and termination, involving ablation, defibrillation and pharmacological interventions.

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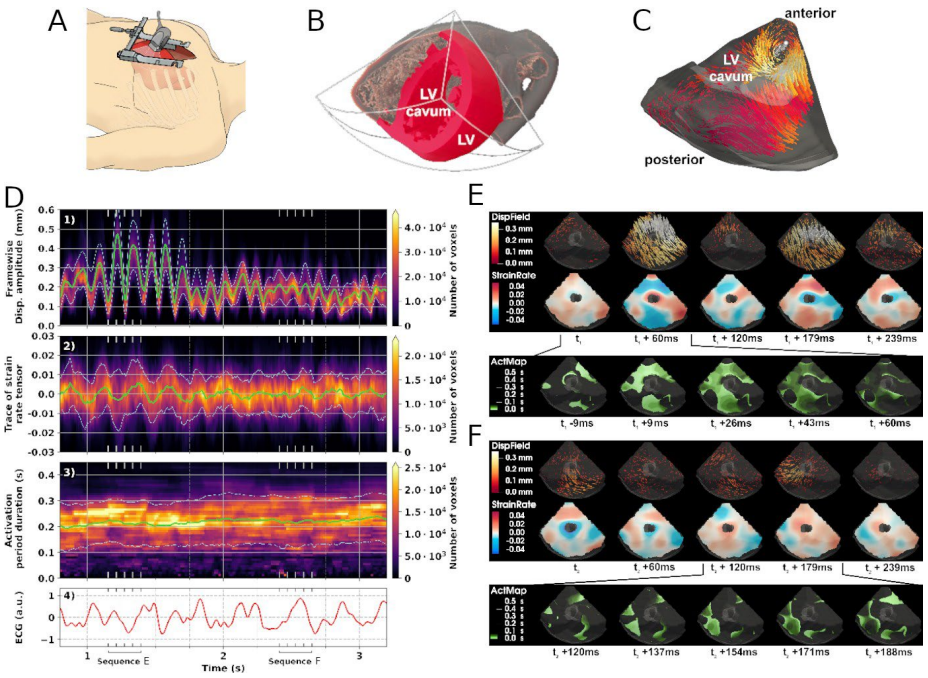

Figure 1: A Ultrasound acquisition in the operating room during open- chest surgery on cardiopulmonary bypass. B Exemplary representation of the recorded 3D-ultrasound field of view focused on the LV in a model of the human heart. C Displacement vector field derived from the reference frame-based registration showing a displacement vortex with central phase singularity filament. D Histograms of displacement fields (1), strain rate (2), period duration derived from the activation map (onset of contraction) (3), revealing two distinct dynamic states alongside temporal evolution of ECG (4). E Time series illustrating high synchronisation with directed, high-amplitude motion in the displacement field and large coherent regions of similar strain rates. The activation wavefront shows simultaneous activation over a large area before one cycle of directed motion. F Time series illustrating less synchronisation with undirected, low-amplitude motion in the displacement field and fractionated, smaller regions of coherent strain rates. The activation wavefronts lack simultaneous activation of large areas over a similar time sequence.

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18. Exploring the temporal variability of muscle oxygen saturation: A key variable for physiological networks during exercise?

L.Montull, P.Vázquez, M. Petelczyc, N. Balagué

Objectives: The temporal variability of physiological and kinematic variables, extracted at meso- and macroscopic levels during exercise, has demonstrated potential for the early detection of acute fatigue. The sensitivity of microscopic variables, such as muscle oxygen saturation, which provide insight into muscle metabolism dynamics, remains underexplored (Barstow, 2019). This study aimed to investigate the temporal variability structure of the tissular saturation index (TSI) during a graded maximal exercise test performed until exhaustion.

Methods: Nineteen participants began running at 8 km/h, with a 1 km/h increase every 100 seconds until they could no longer maintain the prescribed velocity. The temporal variability of TSI, recorded from the quadriceps, was analyzed using Detrended Fluctuation Analysis (DFA) and Sample Entropy (SampEn) over the first and last 2048 recorded data points. Wilcoxon tests and Cohen's d were applied to compare the initial and final segments of the test.

Results: Results showed a significant decrease in the Hurst exponent (from H = 0.66 ± 0.12 to H = 0.49 ± 0.09; $p < 0.01$; d = -2.88) and a corresponding increase in SampEn (from 1.31 ± 0.28 to 1.81 ± 0.18; $p < 0.01$; d = 3.21). See an example in Fig.1 of TSI dynamics between the initial and final parts of the graded exercise.

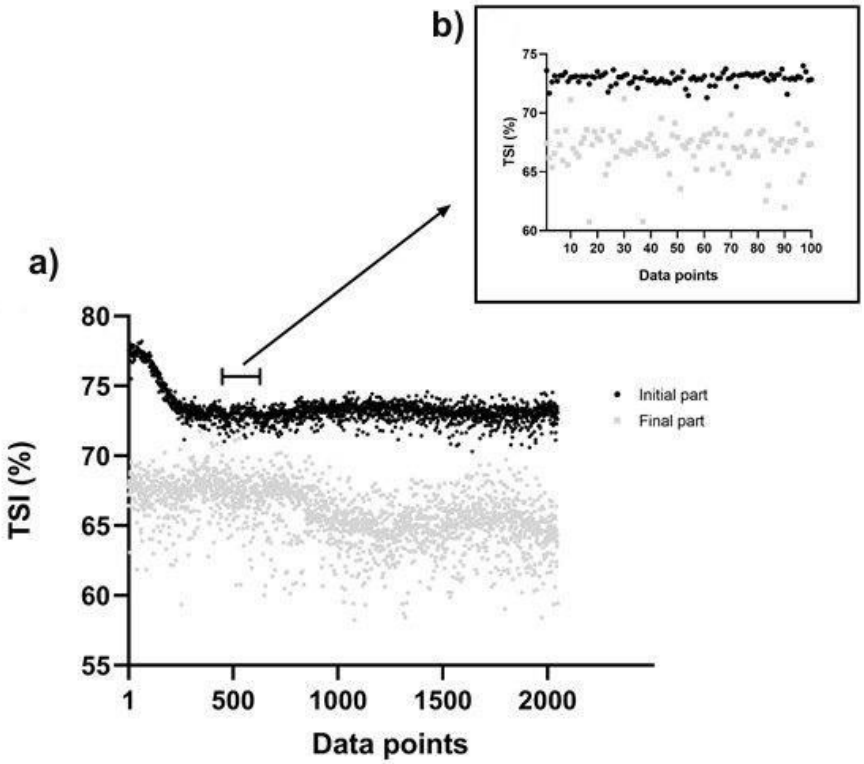

Fig. 1 Example of TSI fluctuations during the initial (black, higher values) and final (grey, lower values) phases of the graded maximal exercise test for one participant (a: analyzed 2048 data points; b: zoomed-in view of 100 data points).

Conclusions: These findings indicate a shift towards uncorrelated white-noise as exhaustion approached, suggesting a decline in the efficacy of oxygen transportation with increasing workloads. The temporal variability of muscle oxygen saturation appears to be a promising variable for assessing acute fatigue during exercise and investigating physiological networks. Future research should focus on a comprehensive network analysis of the temporal variability structure of multilevel physiological variables, including muscle

oxygen saturation, to better understand their synergistic interactions, potential time delays, and how these insights might collectively reflect the system's adaptability to exercise fatigue, pathologies, injuries rehabilitation, among others (Balagué et al., 2020; Ivanov, 2021; Manchado-Gobatto et al., 2022).

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19. Higher Order Functional Connectivity in Autism reveals atypical synergistic patterns

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Study Objectives: Autism Spectrum Disorder (ASD) is a complex and multifaceted neurodevelopmental disorder characterized by challenges (primarily deficits) in social interaction, communication, and behavioral patterns (e.g., restricted interests, and repetitive behaviors). Autism has been extensively studied using functional neuroimaging revealing alterations in several regions and neural circuits (e.g. the default mode network (DMN), primary motor and sensory regions). However, most fMRI studies have often focused on pairwise relationships between regions, whilst recent evidences suggest that studying how more than two regions work interactively might be critical to get a full understanding of the complexity of brain, especially in the presence of multiple brain disorders.

Here, we used Higher-Order Functional Connectivity (HOFC) to characterize the relationship between two regions. Considering one region as the target and the other as the driver, it is possible to decompose the predictability of the target as the sum of a unique contribution from the driver (U), plus the redundant (R) and synergistic (S) contributions that measure the cooperation of the driver with other brain regions. This decomposition allows the identification of higher-order brain patterns that differ between typically developing controls (TDC) and individuals with ASD.

Methods: Participants (884 TDC and 657 ASD) were selected from the ABIDE-I and ABIDE- II repositories. Functional and anatomical data were preprocessed using established neuroimaging softwares (e.g., FSL, Freesurfer). Each individual anatomical parcellation (Desikan-Killiany atlas: 9 subcortical and 34 cortical structures in each hemisphere) was projected onto the corresponding functional data, and the mean functional time series of each region was used to estimate the HOFC. The HOFC is estimated via predictability decomposition [1] based on Leave One Covariate Out (LOCO) [2] approach. LOCO quantifies the decrease in predictive power when feature X is removed from the regression model at hand, $L_{\mathbf{Z}}(X \to Y) = \epsilon(Y \mid \mathbf{Z}) - \epsilon(Y \mid X, \mathbf{Z})$, where $\epsilon(Y \mid X, \mathbf{Z})$ represents the mean squared prediction error of *Y* based on all input variables, *X* and **Z**. $L_{\mathbf{Z}}(X \to Y)$ has a similar role in predictability as conditional mutual information $I(X; Y \mid \mathbf{Z})$ does in entropy reduction, and the maximal predictive power of X to Y is expressed as $L_{\mathbf{Z}_{max}}(X \to Y) =$

$U + R + S$.

The HOFC brain patterns were computed in each subject considering each brain region as a target, and for a fixed target all other regions were considered as drivers. For each target-driver pair, the LOCO measure was estimated using a linear regression (including the global signal as a covariate in order to reduce spurious connections influenced by heart rate and respiratory fluctuations) in an iterative greedy algorithm up to multiplets of length 20 regions. The decomposition of a driver region was then measured by unique and redundant/synergy (based on the minimum/maximum LOCO value across the 20 added regions) components, yielding a directed (but not effective) connectivity matrices (target x driver regions). Prior to group-level analyses, HOFC data were harmonized to overcome interscanner variability, and effects of no interest (i.e., age, sex, and displacement) were removed.

Results: Summing over drivers, gives the total incoming influence for each region (In). Conversely, summing over targets gives the total outgoing influence from each region (Out). Significant differences between ASD and TDC (Benjamini corrected, q = 0.05) for both synergistic contributions and encoded cortical regions are shown in Figure 1 which includes several temporal, visual, and frontal regions. Synergistic contributions suggest that these regions perform integration by projecting to other regions, and that such integration increases with the pathology, perhaps as a compensatory effect. Interestingly, synergistic encoded regions also involved left/right amygdala and cerebellum, left hippocampus and right nucleus accumbens subcortical regions. There were no significant differences in redundancy.

Using the same subtype partitioning of the ASD group from [3], to assess the differences between these two subtypes respect to TDC group in the overall HOFC per participant, we performed a global connectivity analysis, defined as the average of the redundancy and synergy matrices (see Figure 2). For redundancy, subtype 1 showed significant hypo-connectivity to TDC (β = -0.04, t_{1232} = -14.86, p < .001). The opposite was true for subtype 2 (β = 0.02, t_{1168} = 6.75, p < .001), thus corresponding to hyper-connectivity. This result reproduced the finding in [3] obtained by averaging the functional connectivity matrices estimated by the Pearson correlation measure. For synergy, a completely opposite pattern was found: hyper-connectivity in subtype 1 (β = 0.05, t_{1232} = 17.78, p < .001) and hypo- connectivity in subtype 2 (β = -0.03, t_{1268} = -9.72, p < .001).

Conclusions: Increased synergistic information between ASD and TDC was found in default mode and sensory networks, as well as in regions involved in the integration of sensory, emotional and cognitive information. This finding is consistent with the Intensive World Theory [4], which proposes a hyper-functioning of local neural microcircuits. However, the differences between the subtypes will be investigated further.

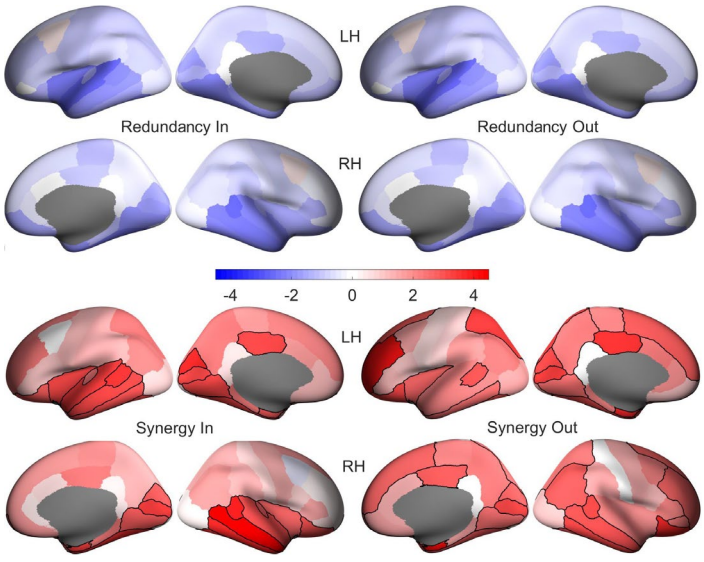

Figure 1: T-statistic values for redundant and synergistic In and Out measures in each region. No significant differences between ASD and TDC groups for redundancy were found. Black lines delineate significant regions for In (target regions with synergistic contributions in ASD from other driver regions) and Out (regions whose state is synergistically encoded in other target regions more in ASD than in controls).

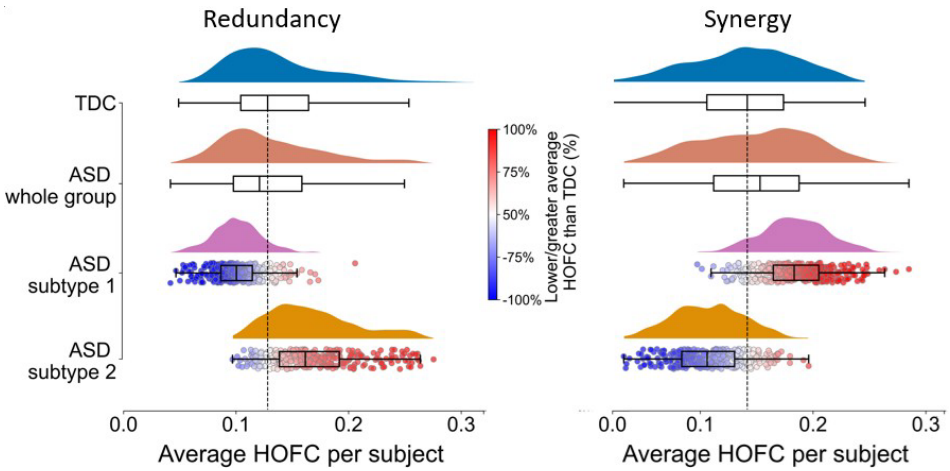

Figure 2: The ASD subtypes showed an opposite hypo/hyper connectivity. Subtype 1 is dominated by hypo and subtype 2 by hyper redundant connectivity, whereas the opposite pattern emerge from the synergistic connectivity.

References:

[1] Ontivero-Ortega, M., et al.Phys. Rev. E 111, (2025).
[2] Lei, J., et al. J. Am. Stat. Ass. 113, 1094 (2018).
[3] Rasero, J., et al. Biological Psychiatry 94.10, (2023).
[4] Markram, K., and Markram, H. Frontiers in human neuroscience 4, 2224 (2010)

Round Table Discussion I

17:15-18:30 Wednesday, 30 July, 2025

Panel participants:

Krasimira Tsaneva-Atanasova, *Ph.D., Professor*
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Jürgen Kurths, *Ph.D., Professor*
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Potsdam Institute for Climate Impact Research, Germany

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Shlomo Havlin, *Ph.D., Professor*
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Eckehard Schöll, *Ph.D., Professor*
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Bernstein Center for Computational Neuroscience Berlin, Germany

Viktor Jirsa, *Ph.D., Professor*
CNRS, France
Institut de Neurosciences des Systèmes, Aix-Marseille University, France

Paul Bogdan, *Ph.D., Associate Professor*
Ming Hsieh Department of Electrical and Computer Engineering,
University of Southern California, USA

Round Table Discussion II

17:15-18:30 Thursday, 31 July, 2025

Panel participants:

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Department of Medicine, Hadassah Medical Center, Israel

Boris P. Kovatchev, *Ph.D., Professor*
School of Medicine, University of Virginia, USA

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Announcements

Special Issues in the journal Frontiers in Network Physiology

In parallel with the ISINP-2025 meeting, we organize several special issues in the journal ***Frontiers in Network Physiology***, published by Frontiers Media SA:

"Self-Organization of Complex Physiological Networks: Synergetic Principles and Applications — In Memory of Hermann Haken"
"Cortico-Muscular Network Interactions"
"Mathematical Methods and Models of Systems Interactions and Network Dynamics"
"Networks during sleep in physiological and pathological conditions",
"Stress recognition and classification in network interactions of physiological systems from biosignals: recent trends and novel approaches"
"Advancing Network Physiology: Data-Driven Exploration of Brain-Body Interactions"

Despite the vast progress and achievements in systems biology and integrative physiology in the last decades, we do not know the basic principles and mechanisms through which diverse physiological systems and organs dynamically interact as a network and integrate their functions to generate a variety of physiologic states and pathological conditions at the organism level.
These special issues will focus on both empirical and theoretical interdisciplinary work with contributions ranging from applied math, statistical physics, nonlinear dynamics and complex networks to biomedical engineering,neuroscience, physiology and clinical medicine, and is now open for manuscript submissions.

We invite all ISINP attendees and speakers to contribute work related to Network Physiology in the multidisciplinary journal, ***Frontiers in Network Physiology***.

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Social Event

Classical Music Concert 19:00-20:00 Thursday, 31 July, 2025

Location:

Teatro Sociale di Como – Sala Bianca

Performers:

Dr. Christina Wright-Ivanova – Piano
http://www.christinajwright.com/

Ms. Egle Jarkova – Violin
https://www.eglejarkova.com/

Christina Wright-Ivanova,

Dr. Christina Wright-Ivanova**,** hailed by critics as “a brilliant pianist” (Wiener Zeitung, Vienna) and an “ideal partner” (Huffington Post), is an Associate Professor of Music and Coordinator of Keyboard Studies at Keene State College. From 2014-2024 she served as the Artistic Director for the North End Music & Performing Arts *Winter Concert Series* in Boston. She recently held the Interim Artistic Director position at the Redfern Arts Center and served on faculty as an art song coach for graduate students at New England Conservatory.

As a chamber musician, she has been heard in over 25 countries throughout North & South America, UK, Europe, Asia and Australia, appearing in recital with many established artists, including Tchaikovsky Competition Bronze-medal cellist Bion Tsang, virtuoso violinist Yevgeny Kutik, Israel Philharmonic violinist Sharon Cohen, and Joachim Intl. Violin competition winner Dami Kim. She enjoys frequent performances with orchestral musicians, including members of the Boston Symphony Orchestra, Pittsburgh Symphony, Las Vegas Philharmonic, Civic Orchestra of Chicago, Kansas City Symphony, San Antonio Symphony, Boulder Philharmonic, and with the Apple Hill, Lydian, and Mivos Quartets. She has given master classes across the US, Europe, and China. An upcoming release of diverse American cello and piano music, ‘American Vignettes’, with cellist Aron Zelkowicz will be heard on Toccata Classics in 2025.

Dr. Wright-Ivanova spends her summers at Colorado’s *Summer Institute for Contemporary Performance Practice* and has premiered over 150 works by living composers.She has performed both solo and collaborative new works in such venues as Boston’s Museum of Fine Arts, Isabella Stewart Gardner Museum, Berklee School of Music, MIT, The Harvard Club, Opera America (NY), Jordan Hall, Tanglewood’s Ozawa Hall, Old North Meeting House, and in the Clutch New Music Series in Austin TX and the NEXTET series in Las Vegas.

She has enjoyed working with composers such as Jo Kondo, Augusta Read Thomas, Steve Reich, Julian Anderson, Joan Tower, Daniel Brewbaker, Tristan Murail, Robert Beaser, Jennifer Bellor, Heather Gilligan, Daron Hagen, Paul Chihara, Virko Baley and more. She has worked with several ensembles in new music, including the Callithumpian Consort, MIVOS Quartet (NEON Festival), HUB New Music, Juventas New Music Ensemble, and at the Academie für Neue Musik with the Arditti Quartet. She also recorded a series of demos for Jonny Greenwood’s (Radiohead) soundtrack for the 2012 movie ‘The Master’ (Western LLC).

Egle Jarkova

Lithuanian born violinist Egle Jarkova is a top prize winner of several national and international competitions in Europe and United States of America, she holds the name of Queen Morta Premium Laureate in Lithuania, and is the winner of the Boston Conservatory Chamber Music and String Department Competitions.

Ms. Jarkova studied at the National M. K. Ciurlionis Art School in Vilnius (Lithuania) and at the United World College of the Adriatic (Italy) where she obtained International Baccalaureate Diploma and received Diploma in Chamber Music from “Scuola Superiore Internazionale di Musica da Camera del Trio di Trieste”. She then completed her studies with full scholarship and as Shelby Davis scholarship recipient at the Boston Conservatory, where she received her Bachelor in Violin in 2012, and Graduate

Performance Diploma in 2014; and received her Masters from Boston University in 2016.

Ms. Jarkova has performed widely in Europe and America, including countries such Albania, Austria, Croatia, Italy, Poland, Russia, Slovenia, Puerto Rico, and more; and concert venues such as Carnegie Hall, Beethoven Hall, Wiener Saal, Sala Tripkovich, and others. She participated in “Kodaly – Bartok World Youth Orchestra”, “International Frenkel Villa Festival”, “International Summer Academy Mozarteum”, and was featured as a guest artist in International Music Festival “A Tempo”. Ms. Jarkova worked with V. Oistrakh, J. Silverstein, L. Chilingirian, D. Kim, M. Frischenschlager, A. Schnarch, Y. Berick, P. Frank, A. Cardenes, J. Fleezanis, among others. Her principal teachers include Lynn Chang and Bayla Keyes (Boston), Massimo Belli (Trieste), and Ingrida Armonaite (Vilnius).

Most recently Ms. Jarkova debuted with the Albanian National TV and Radio Orchestra playing Brahms Violin Concerto, performed Piazzolla “Four Seasons of Buenos Aires” with Boston Conservatory String Orchestra, and Beethoven Triple Concerto with LAB Orchestra and Quincy Orchestra. Ms. Jarkova was assistant to the Boston Conservatory chamber music department director, and performed with JEMUR PIANO TRIO (with pianist Rui Urayama, and cellist Edevaldo Mulla). She teaches in Boston, and plays with various orchestras around.

Ms. Jarkova is a founder of International Summer Music Festival “Vivace Vilnius” in Lithuania since 2012. The festival offers intensive master classes for young professional musicians and presents free concerts performed by the faculty and guest artists. The faculty members travel from the USA representing American musical culture and esthetics to the participants and Lithuanian audience.

Concert Program:

Dinner 20:30-22:30 Thursday, 31 July, 2025

Ristorante Sociale,
Address: Via Rodari, 6, 22100 Como CO, Italy

https://www.ristorantesociale.it/

Thank you for joining this Fourth International Summer Institute on Network Physiology (ISINP-2025), and for being part of a growing society of scholars, clinicians and biomedical engineers working in this new field.

We look forward to meeting you again in 2027!