A new information-theoretic framework to analyze neural spike trains and physiological point processes

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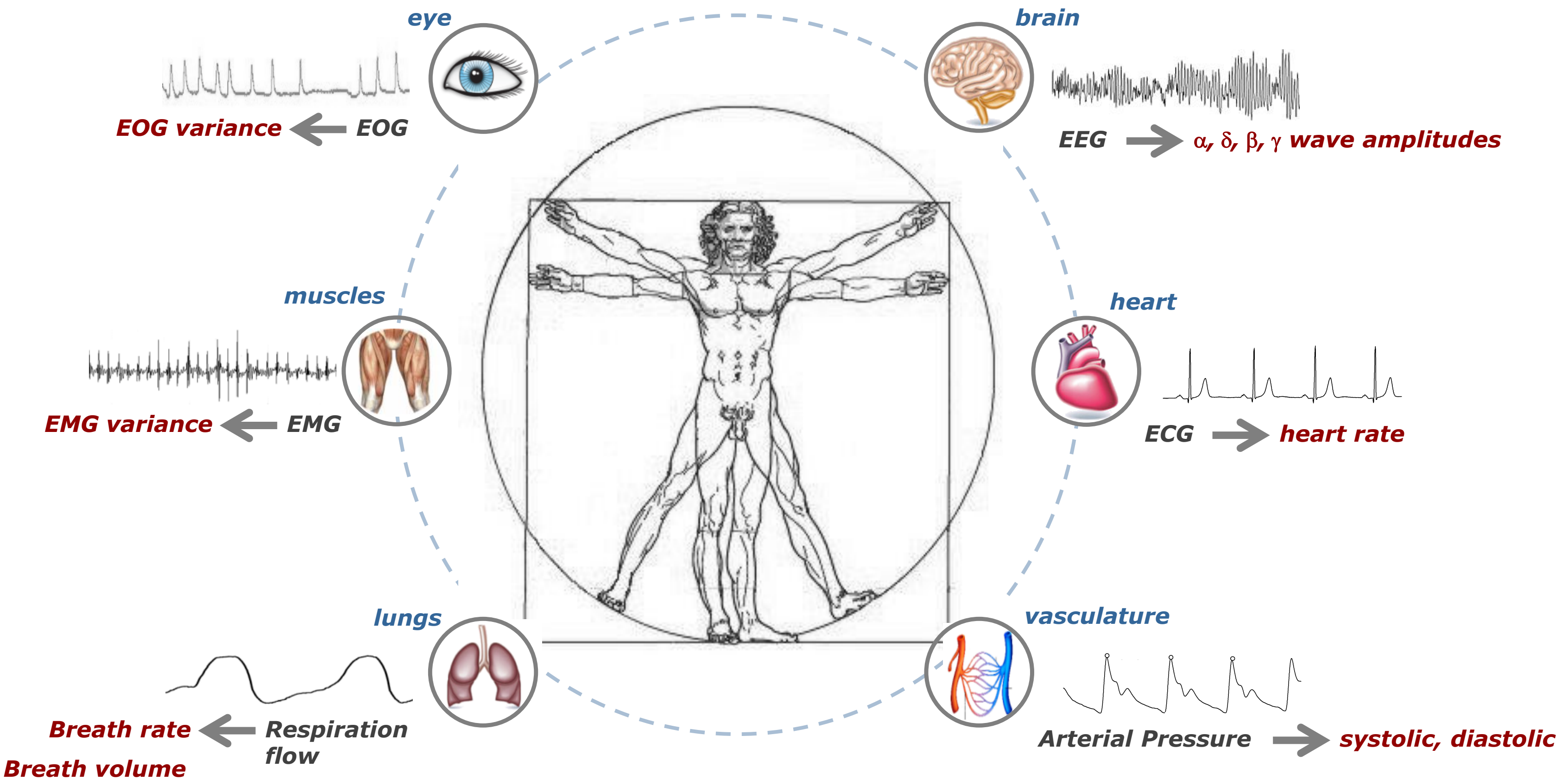
The Field of Network Physiology

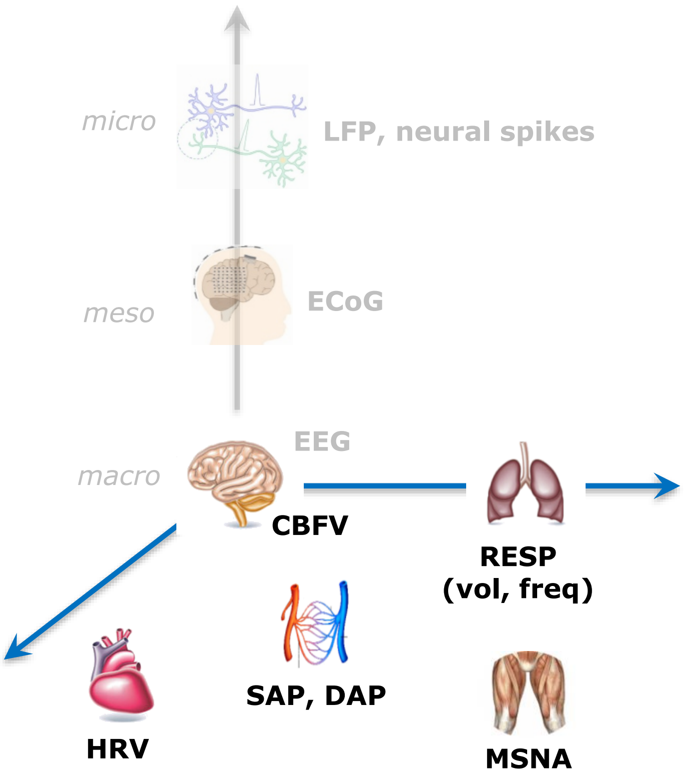


Organ Systems → *Biomedical Signals* → *Time Series*

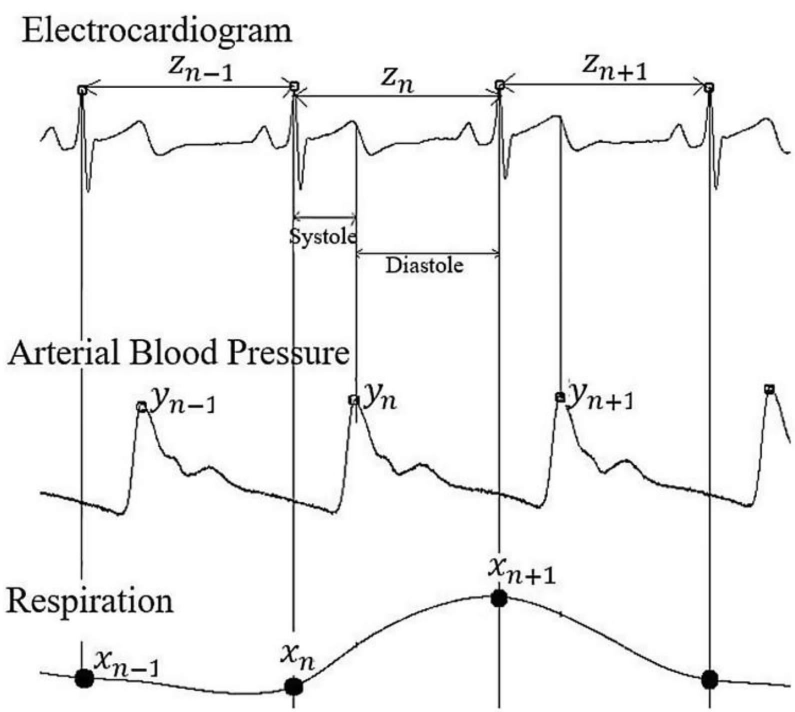
The Field of Network Physiology

Vertical and Horizontal Network integration of Physiologic Systems

Horizontal system integration



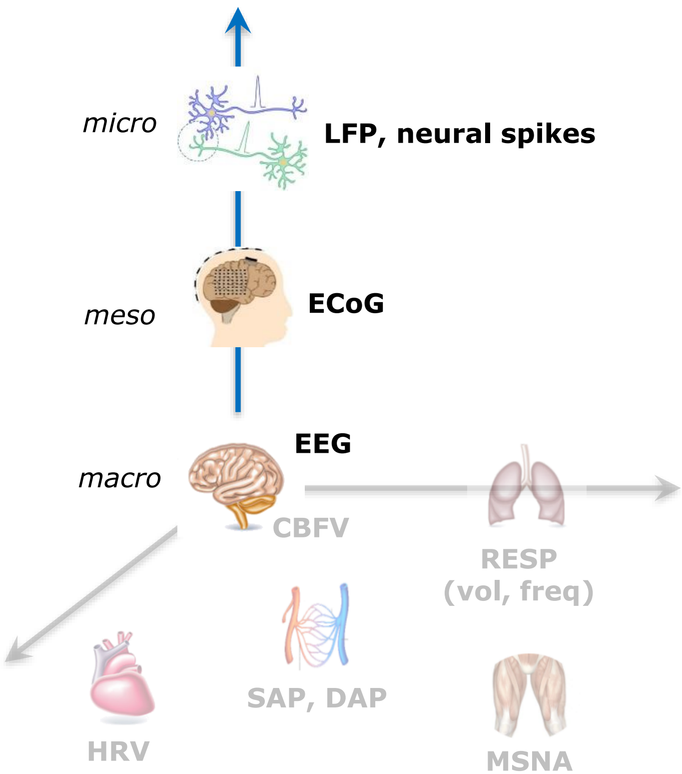
Physiological signals and time series



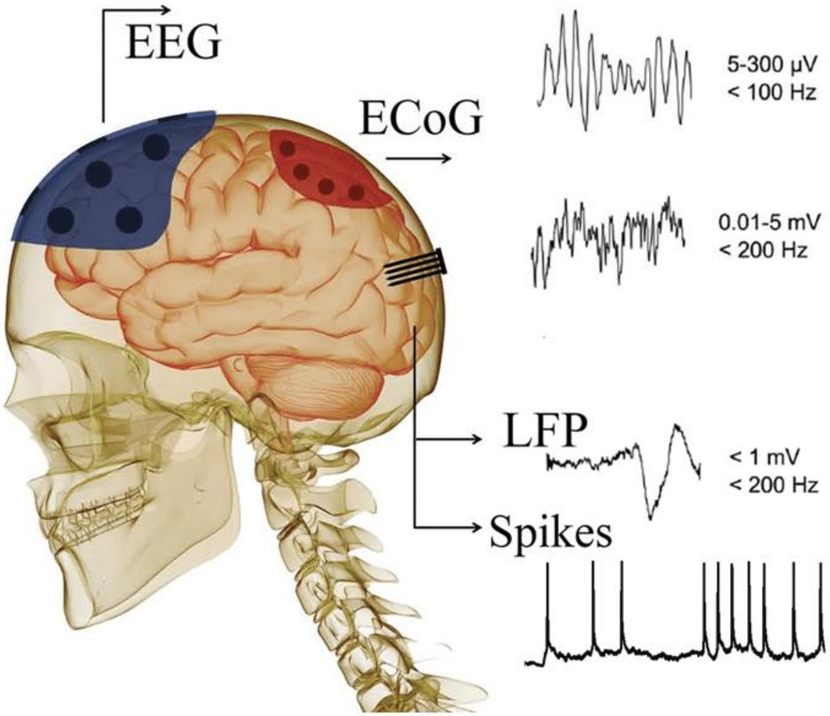
The Field of Network Physiology

Vertical and Horizontal Network integration of Physiologic Systems

Vertical system integration

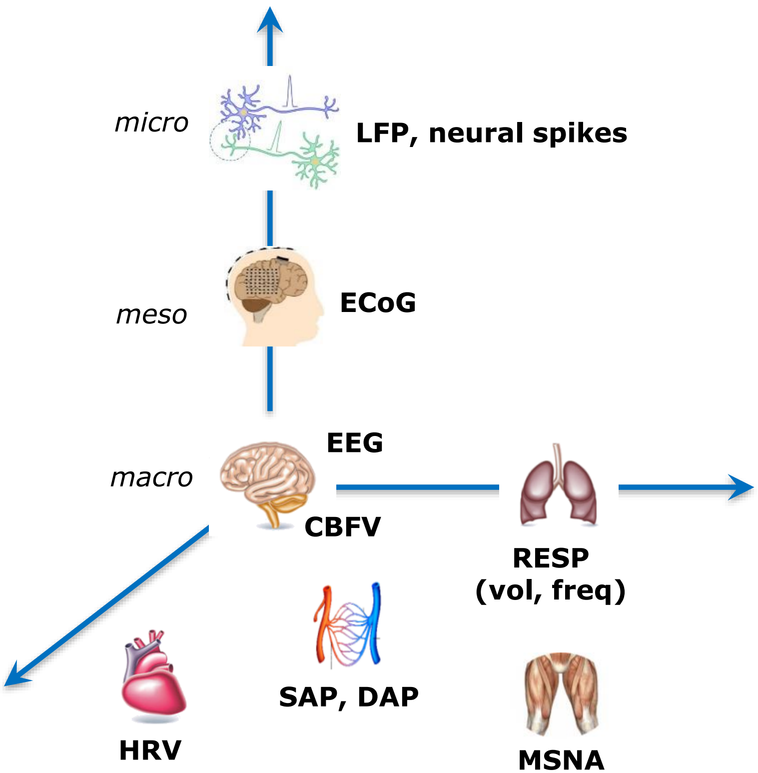


Physiological signals and time series

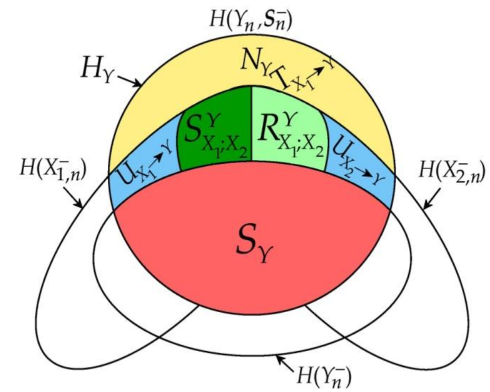


Information Theory for Network Physiology

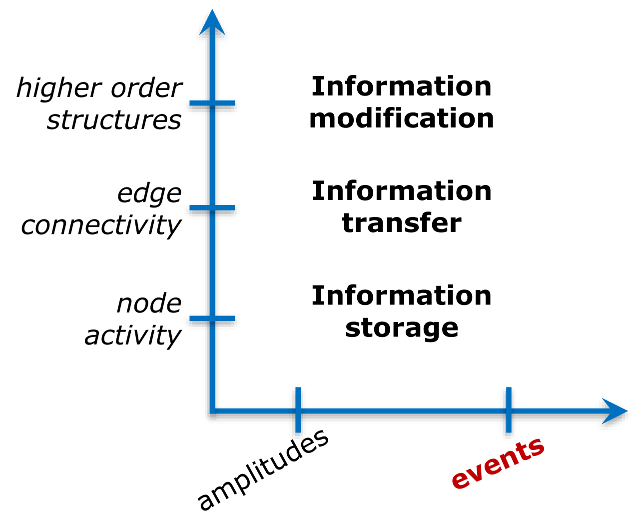
Levels of system integration



Information Theory



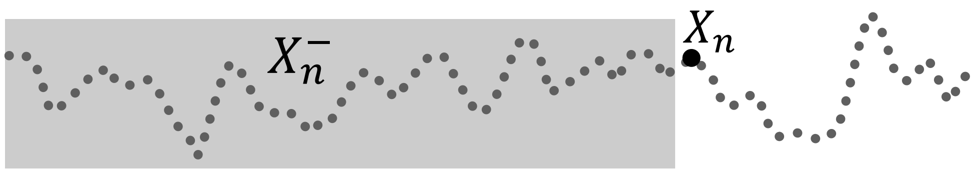
Levels of system description



- **AIM: to introduce an approach for the assessment of information dynamics in physiological systems described by spike train data (point processes)**

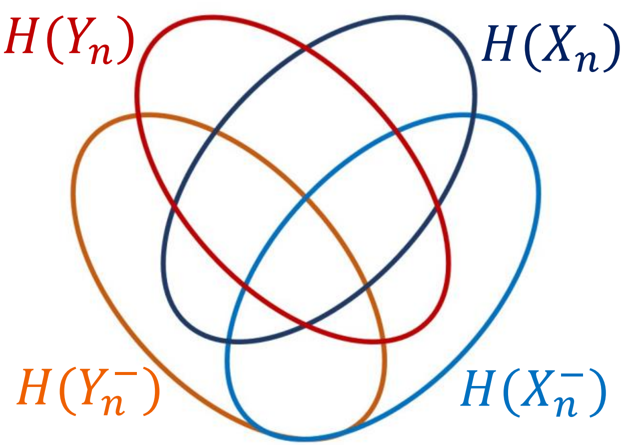
Mutual Information Rate for Discrete-Time Processes

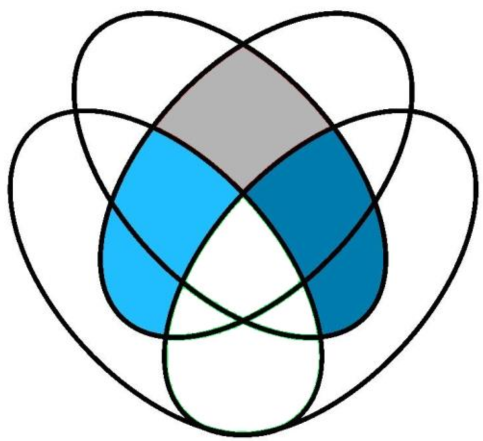
- **Discrete-time stochastic processes:** $X = \{X_n\}, Y = \{Y_n\}, n \in \mathbb{Z}$



- **Mutual Information rate (MIR):** $\dot{I}_{X;Y} \triangleq \lim_{N\to\infty} \frac{1}{N} I(X_{n:n+N}; Y_{n:n+N})$

- **MIR expansion:**





Transfer Entropy:

$I(X_n; Y_n^- | X_n^-) = T_{Y\to X}$

$I(Y_n; X_n^- | Y_n^-) = T_{X\to Y}$

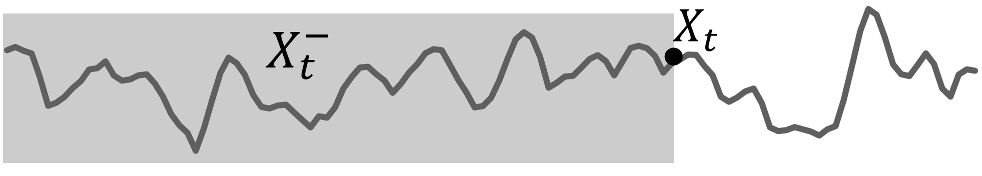
Instantaneous causality:

$I(X_n; Y_n | X_n^-, Y_n^-) = I_{X\cdot Y}$

$$\underbrace{\dot{I}_{X;Y} = I(X_n, X_n^-; Y_n, Y_n^-) - I(X_n^-, Y_n^-)}_{\text{coupling}} = \cdots = \underbrace{T_{X\to Y} + T_{Y\to X}}_{\text{causal interactions}} + \underbrace{I_{X\cdot Y}}_{\text{instantaneous causality}}$$

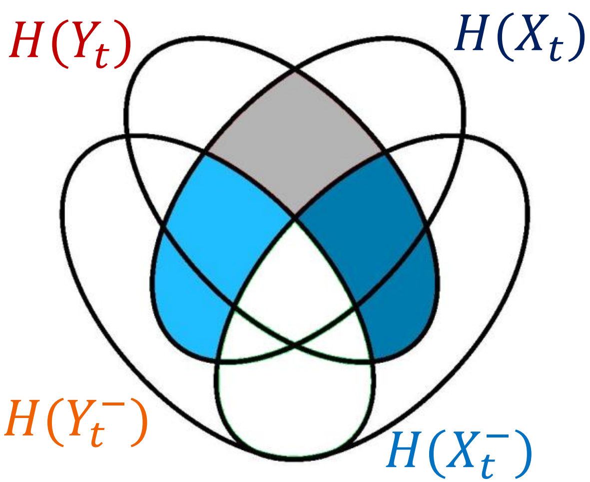
Mutual Information Rate for Continuous-Time Processes

- **Continuous-time stochastic processes:** $X = \{X_t\}, Y = \{Y_t\}, t \in \mathbb{R}$



- **Mutual Information rate (MIR):** $\dot{I}_{X;Y} \triangleq \lim_{\tau\to\infty} \frac{1}{\tau} I(X_{t:t+\tau}; Y_{t:t+\tau})$

- **Information decomposition of the Mutual Information Rate (MIR)**



Transfer Entropy rate:

$$\dot{T}_{Y\to X} = \lim_{\Delta t\to 0} \frac{1}{\Delta t} I(X_t; Y_t^- | X_t^-)$$

$$\dot{T}_{X\to Y} = \lim_{\Delta t\to 0} \frac{1}{\Delta t} I(Y_t; X_t^- | Y_t^-)$$

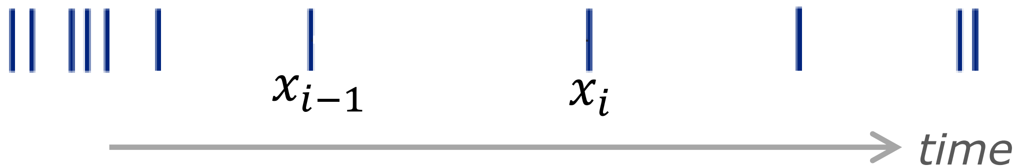
Instantaneous causality rate:

$$\dot{I}_{X\cdot Y} = \lim_{\Delta t\to 0} \frac{1}{\Delta t} I(X_t; Y_t | X_t^-, Y_t^-)$$

$$\underbrace{\dot{I}_{X;Y}}_{\text{coupling}} = \underbrace{\dot{T}_{X\to Y} + \dot{T}_{Y\to X}}_{\text{causal interactions}} + \underbrace{\dot{I}_{X\cdot Y}}_{\text{instantaneous causality}}$$

Mutual Information Rate for Spike Train Processes

- **Point processes:** $X = \{x_i\}, Y = \{y_i\}, i \in \mathbb{Z}$



- **Information decomposition of the Mutual Information Rate (MIR)**

G. Mijatovic, Y. Antonacci, T. Loncar-Turukalo, L. Minati and L. Faes, "An information-theoretic framework to measure the dynamic interaction between neural spike trains", ***IEEE Transactions on Biomedical Engineering***, 68(12), 3471-3481, **2021**.

Assumption: simultaneous events are not possible

$$\dot{I}_{X \cdot Y} = 0 \longrightarrow \dot{I}_{X;Y} = \dot{T}_{X \to Y} + \dot{T}_{Y \to X}$$

- **Formulation of the Transfer Entropy Rate (TER) for point processes:**

R. E. Spinney at al, "Transfer entropy in continuous time, with applications to jump and neural spiking processes**", Physical Review E,** 95(3), 032319, **2017.**

$$\dot{T}_{Y \to X} = \lim_{T \to \infty} \frac{1}{T} \sum_{i=1}^{N_X} \ln \frac{\lambda_{X,x_i | X_{x_i}^-, Y_{x_i}^-}}{\lambda_{X,x_i | X_{x_i}^-}} = \bar{\lambda}_X \mathbb{E}\left[\ln \frac{\lambda_{X,x_i | X_{x_i}^-, Y_{x_i}^-}}{\lambda_{X,x_i | X_{x_i}^-}} \right]$$

Transfer Entropy Rate for Spike Train Processes: **estimation**

- **Formulation of the Transfer Entropy Rate (TER) for point processes:**

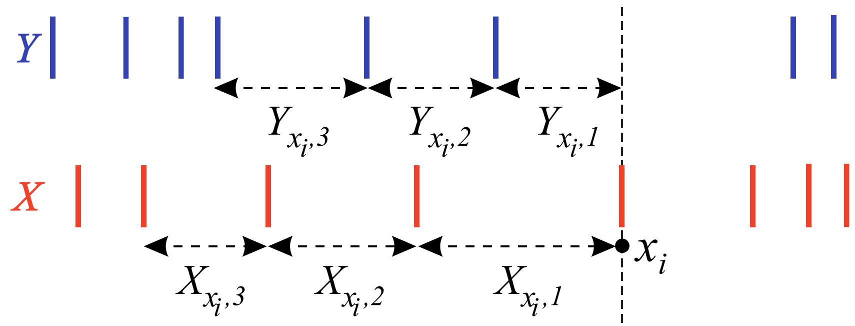
D Shorten at al, 'Estimating transfer entropy in continuous time between neural spike trains or other event-based data', .**PLoS Comput. Biol.** 17(4): e1008054, **2021.**

$$\dot{T}_{Y\to X} = \bar{\lambda}_X \mathbb{E}\left[\ln \frac{p_x(X^-_{x_i}, Y^-_{x_i})}{p_u(X^-_{x_i}, Y^-_{x_i})} \cdot \frac{p_u(X^-_{x_i})}{p_x(X^-_{x_i})}\right]$$

- **Embedding at target spiking times x_i, for the computation of p_x**

$$Y^-_{x_i} \approx Y^l_{x_i}$$

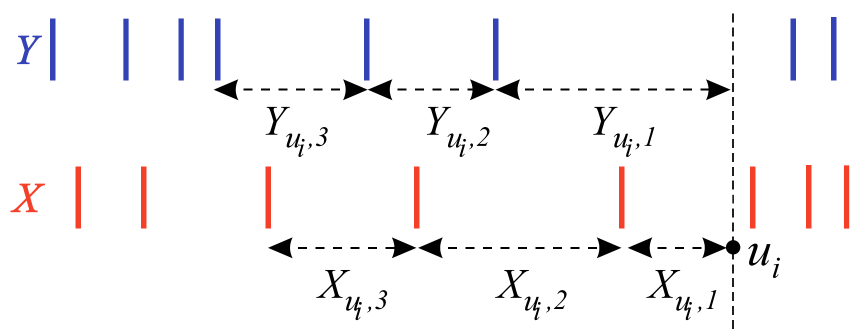
$$X^-_{x_i} \approx X^l_{x_i}$$



- **Embedding at random times u_i , for the computation of p_u**

$$Y^-_{x_i} \approx Y^l_{x_i}$$

$$X^-_{x_i} \approx X^l_{x_i}$$



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Transfer Entropy Rate for Spike Train Processes: **estimation**

- **Formulation of the Transfer Entropy Rate (TER) for point processes:**

$$\dot{T}_{Y\to X} = \bar{\lambda}_X \left[H_{p_u}\left(X^-_{x_i}, Y^-_{x_i}\right) - H_{p_x}\left(X^-_{x_i}, Y^-_{x_i}\right) + H_{p_x}\left(X^-_{x_i}\right) - H_{p_u}\left(X^-_{x_i}\right)\right]$$

D Shorten at al, 'Estimating transfer entropy in continuous time between neural spike trains or other event-based data', .**PLoS Comput. Biol.** 17(4): e1008054, **2021.**

- **Nearest neighbor entropy estimator:**

L. Kozachenko and N. N. Leonenko, 'Sample estimate of the entropy of a random vector'**, Problemy Peredachi Informatsii,** 23(2), 9–16, **1987.**

$$\mathbf{W} \in \mathbb{R}^{(N\times d)} \longrightarrow \widehat{H}_{p_w}(W) = \ln(N-1) - \psi(k) + \frac{d}{N}\sum_{i=1}^{N} \ln \varepsilon^k_{w_i,\mathbf{W}} \longrightarrow H_{p_x}$$

$$\mathbf{V} \in \mathbb{R}^{(M\times d)} \longrightarrow \widehat{H}_{p_v}(W) = \ln(M) - \psi(k) + \frac{d}{N}\sum_{i=1}^{N} \ln \varepsilon^k_{w_i,\mathbf{V}} \longrightarrow H_{p_u}$$

- **Estimator of the Transfer Entropy Rate: model-free way!**

$$\hat{\dot{T}}_{Y\to X} = \frac{\bar{\lambda}_X}{N'_X}\sum_{i=1}^{N'_X}\left\{\begin{matrix}\psi\left(k_{X^l_{x_i},\mathbf{X}^l_u}\right) - \psi\left(k_{X^l_{x_i},\mathbf{X}^l_x}\right) + \psi\left(k_{J^l_{x_i},\mathbf{J}^l_x}\right) - \psi\left(k_{J^l_{x_i},\mathbf{J}^l_u}\right) \\ +l\cdot\ln\dfrac{\varepsilon_{X^l_{x_i},\,k_{X^l_{x_i},\mathbf{X}^l_x},\mathrm{X}^l_x}\cdot{\varepsilon^2}_{J^l_{x_i},\,k_{J^l_{x_i},\mathbf{J}^l_u},\mathrm{J}^l_u}}{\varepsilon_{X^l_{x_i},\,k_{X^l_{x_i},\mathbf{X}^l_u},\mathrm{X}^l_u}\cdot{\varepsilon^2}_{J^l_{x_i},\,k_{X^l_{x_i},\mathbf{J}^l_x},\mathrm{J}^l_x}}\end{matrix}\right\}$$

R. E. Spinney at al, "Transfer entropy in continuous time, with applications to jump and neural spiking processes**", Physical Review E,** 95(3), 032319, **2017.**

Estimation of Mutual Information Rate and bias compensation

- **Estimation of the MIR starting from TER:**

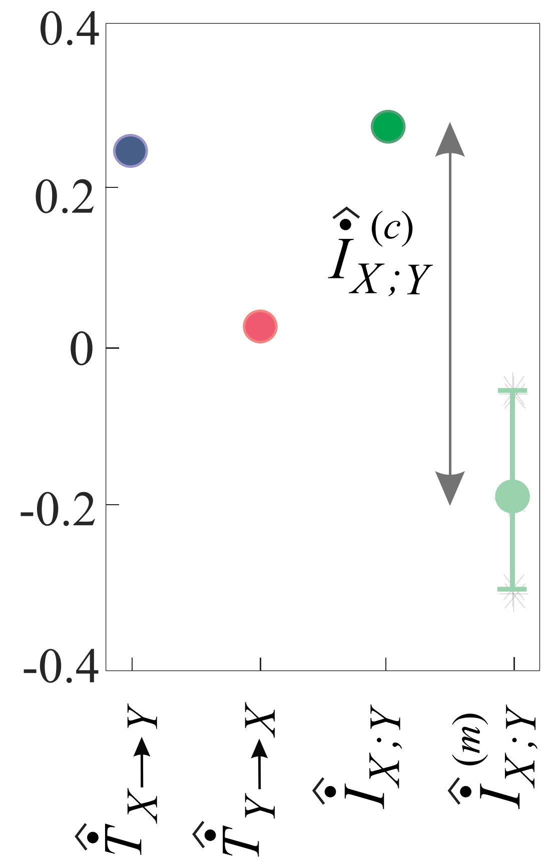
$$\hat{\dot{I}}_{X;Y} = \hat{\dot{T}}_{X\to Y} + \hat{\dot{T}}_{Y\to X}$$

- **Bias compensation and corrected MIR:**
  - *Generation of surrogate spike trains* (*):

$$\hat{\dot{I}}^{(s_1)}_{X;Y}, \dots, \hat{\dot{I}}^{(s_{100})}_{X;Y} \longrightarrow \text{median: } \hat{\dot{I}}^{(m)}_{X;Y}$$

  - *Corrected MIR (**):*

$$\hat{\dot{I}}^{(c)}_{X;Y} = \hat{\dot{I}}_{X;Y} - \hat{\dot{I}}^{(m)}_{X;Y}$$



(*) L. Ricci at al, "Generation of surrogate event sequences via joint distribution of successive inter-event intervals", **Chaos: An Interdisciplinary Journal of Nonlinear Science,** 29(12), p. 121102**, 2019.**

(**) G. Mijatovic, R Pernice, A Perinelli, Y Antonacci, M Javorka, L Ricci, L Faes, "Measuring the rate of information exchange in point-process data with application to cardiovascular variability", ***Frontiers in Network Physiology***; 1:765332, **2022.**

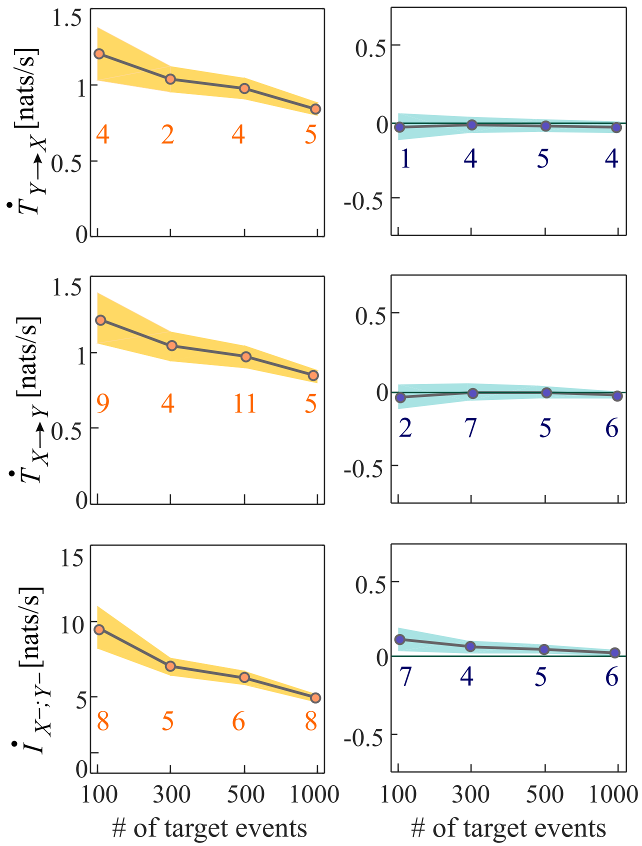
Validation on simulated neural spike trains

- **Pairs of Poisson spike trains with mean firing rate 1 spike/s**

Comparison between continuous-time and discrete-time estimates (based on time discretization)

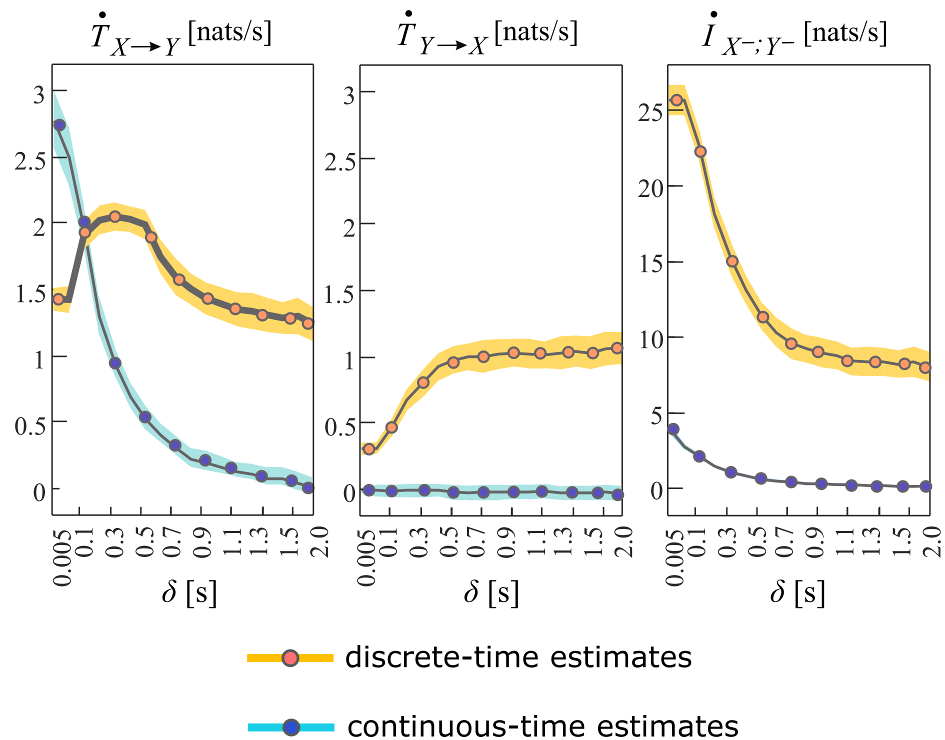
Independent processes:

$\dot{I}_{X;Y} = \dot{T}_{Y\to X} = \dot{T}_{X\to Y} = 0$



Coupled processes: $y_i = x_i + \tau + u_i$

τ: propagation delay $u_i \in \mathcal{U}(-\delta, \delta)$ random time jitter



G. Mijatovic, Y. Antonacci, T. Loncar-Turukalo, L. Minati and L. Faes, "An information-theoretic framework to measure the dynamic interaction between neural spike trains", ***IEEE Transactions on Biomedical Engineering***, 68(12), 3471-3481, **2021**.

Validation on simulated cardiovascular point processes

Process X reproduces the heartbeat times, generated as a point process following the history-dependent inverse Gaussian (HDIG) model:

R Barbieri at al, "A point-process Model of Human Heartbeat Intervals: New Definitions of Heart Rate and Heart Rate Variability", *Am. J. Physiol.-Heart Circ. Physiol. 288,* **2005**

Given any event x_i (heartbeat times), the waiting time until the next event w_i (IEI) is drawn:

mean

$$p(w_i, X^p_{x_i}, \theta, \lambda) = \sqrt{\frac{\lambda}{2\pi w_i^3}}\, e^{-\frac{\lambda\left[w_i - \mu(X^p_{x_i}, \theta)\right]^2}{2\mu(X^p_{x_i}, \theta)^2 w_i}} \qquad X^p_{x_i} = (w_{i-1}, w_{i-2}, \ldots, w_{i-p})$$

scale

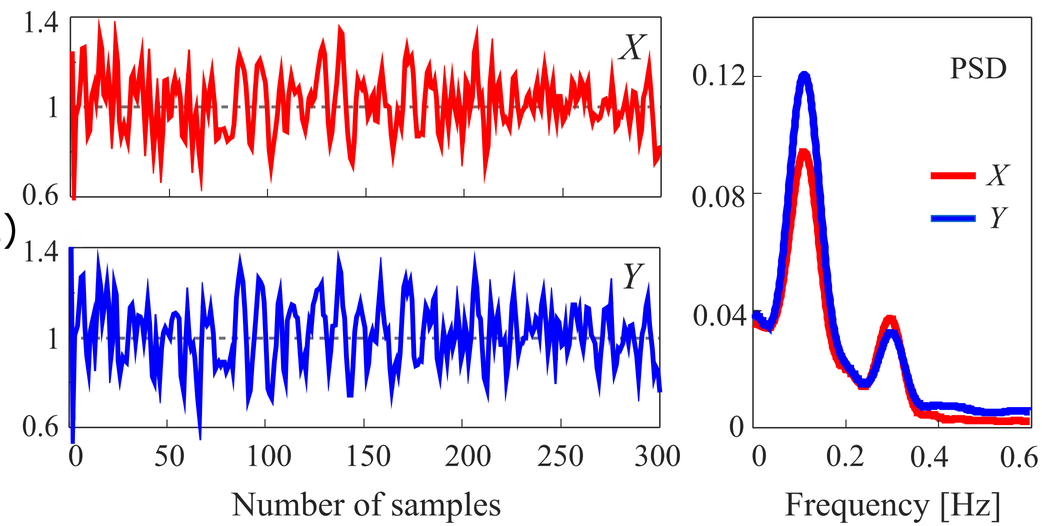
$$\mu(X^p_{x_i}, \theta) = \theta_0 + \sum_{j=1}^{p} \theta_j w_{i-j}; \quad \theta = (\theta_0, \theta_1, \ldots, \theta_p)$$

Oscillations of w_i:

VLF (< 0.04 Hz)

LF (0.04–0.15 Hz)

HF (0.15–0.4 Hz)



Blood pressure arrival times:

$$y_i = x_i + \tau_i$$

Propagation delay simulating PAT

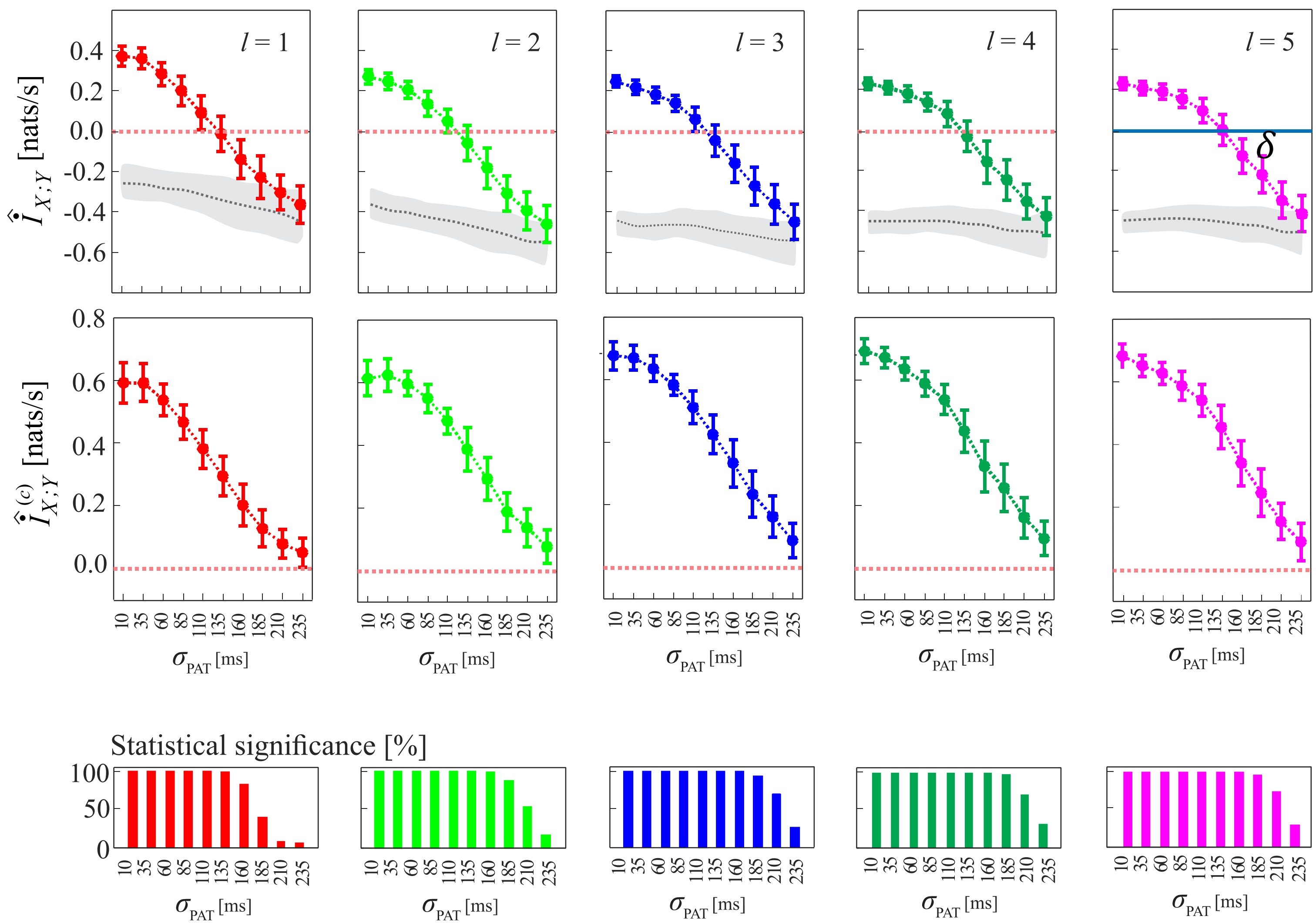
300 ms

$\boldsymbol{\sigma}_{\mathbf{PAT}}$

$$\tau_i = a_0 + a_1\tau_{i-1} + a_2\tau_{i-2} + u_i$$

G Mijatovic, R Pernice, A Perinelli, Y Antonacci, M Javorka, L Ricci, L Faes, 'Measuring the rate of information exchange in point-process data with application to cardiovascular variability', ***Frontiers in Network Physiology***; 1:765332, **2022.**

Validation on simulated cardiovascular point processes



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Application to neural spike trains

EXPERIMENTAL PROTOCOL: in-vitro cultures

- ❖ Public available dataset: dissociated neural cultures of cortical cells harvested from the brains of rat embryos and plated on glass culture wells.

D. A Wagenaar et al, "An extremely rich repertoire of bursting patterns during the development of cortical culture", **BMC Neuroscience**, 7(1), **2006**.

- ❖ Various stages of neural development designated by days in-vitro, **DIV**.

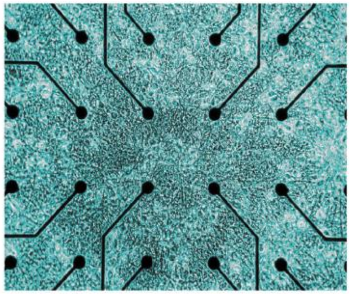
- ❖ Spontaneous, daily activity
- ❖ High-density: 2500 cells/μL
- ❖ 30 cultures

EARLY (≈ 7 DIV)

INTERMEDIATE (≈ 15 DIV)

MATURE (≈ 25 DIV)

Multi-Electrode Array**, MEA**

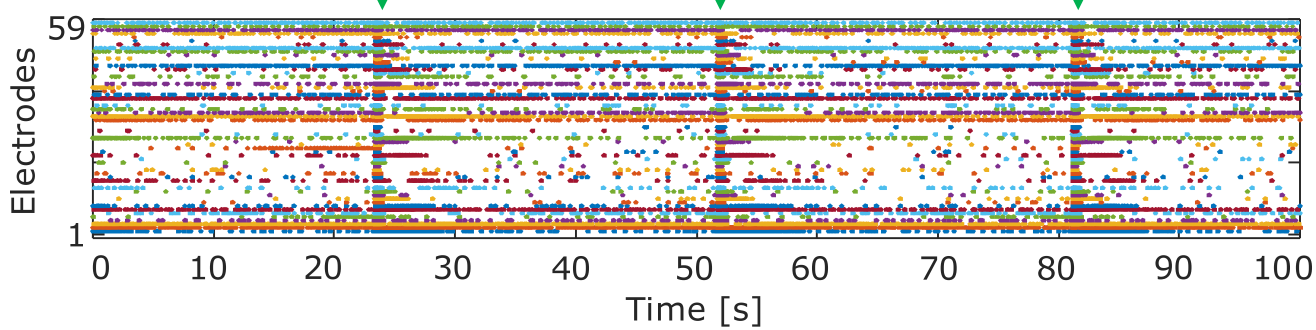


grid of 8×8 electrodes; electrodes not positioned on the corners; one electrode used as the ground ⟶ total number of electrodes is **59**.

each electrode captures the ensemble spiking activity approximately between 100 and 1000 neurons ⟶ multi-unit activity (**MUA).**

Synchronized bursting

MATURE STAGE



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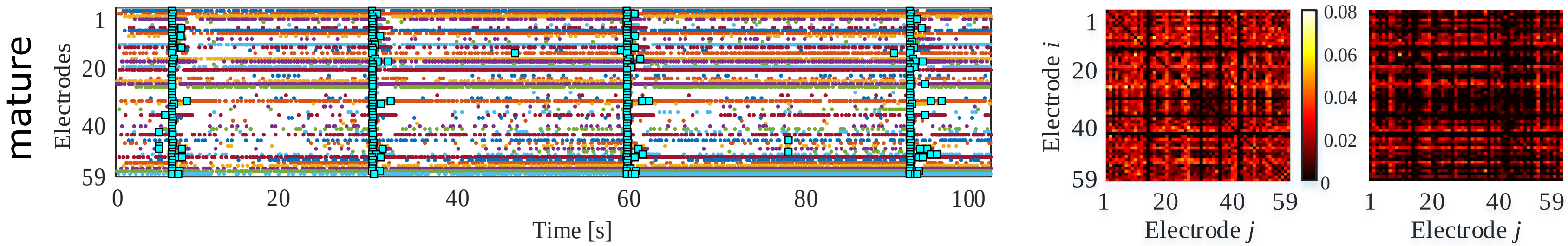
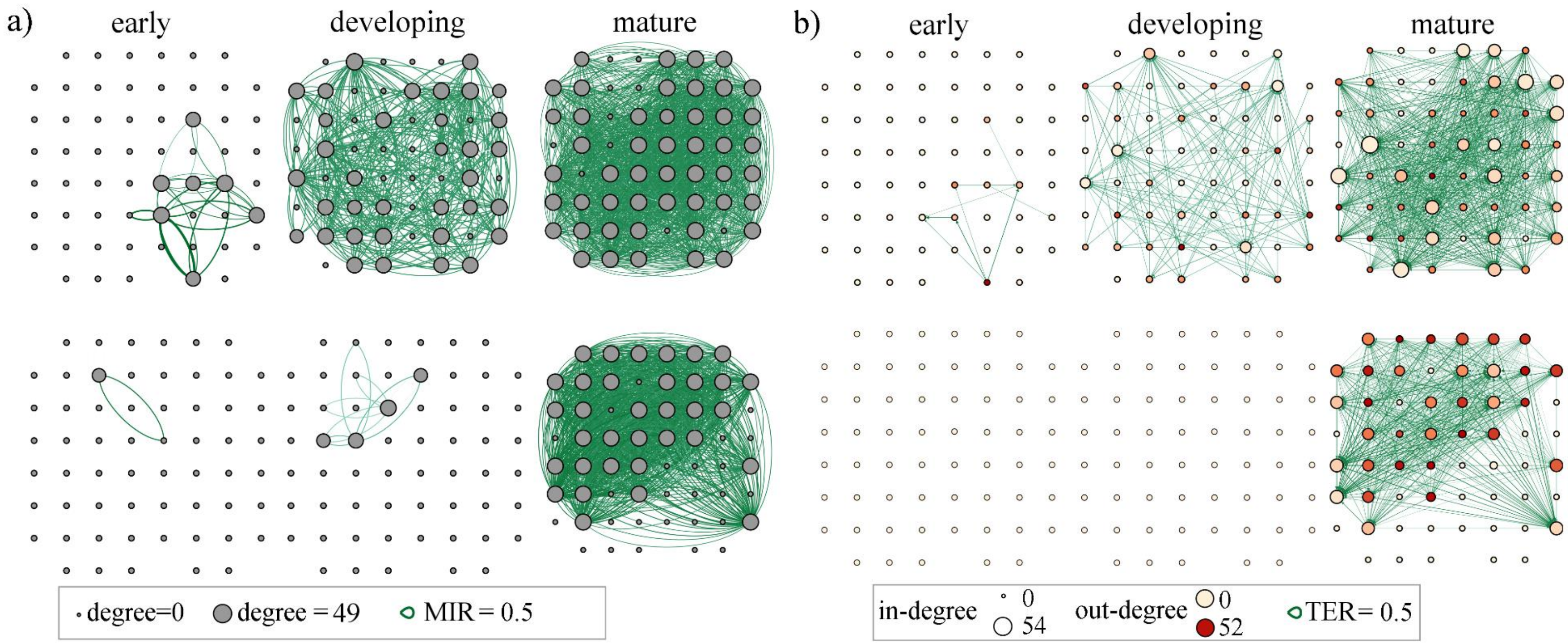
Application to neural spike trains

Statistically significant symmetric (MIR) and directed (TER) links in two cultures at different maturation ages



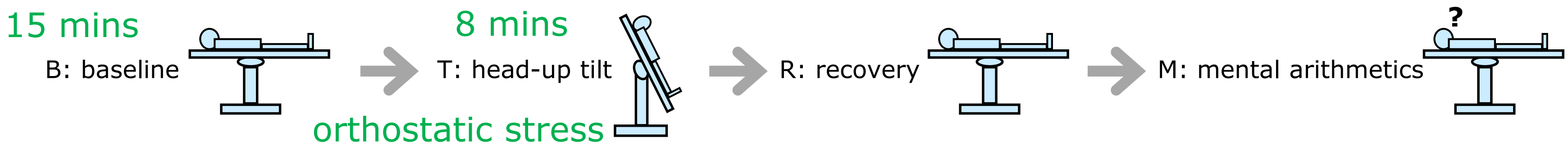


Both the MIR and the TER can detect the expected larger involvement of the neuronal units in the establishment of networked functional interactions occurring as DIV increases.

G Mijatovic, Y Antonacci, T Loncar-Turukalo, L Minati and L Faes, 'An information-theoretic framework to measure the dynamic interaction between neural spike trains', ***IEEE Transactions on Biomedical Engineering***, 68(12), 3471-3481, **2021**.

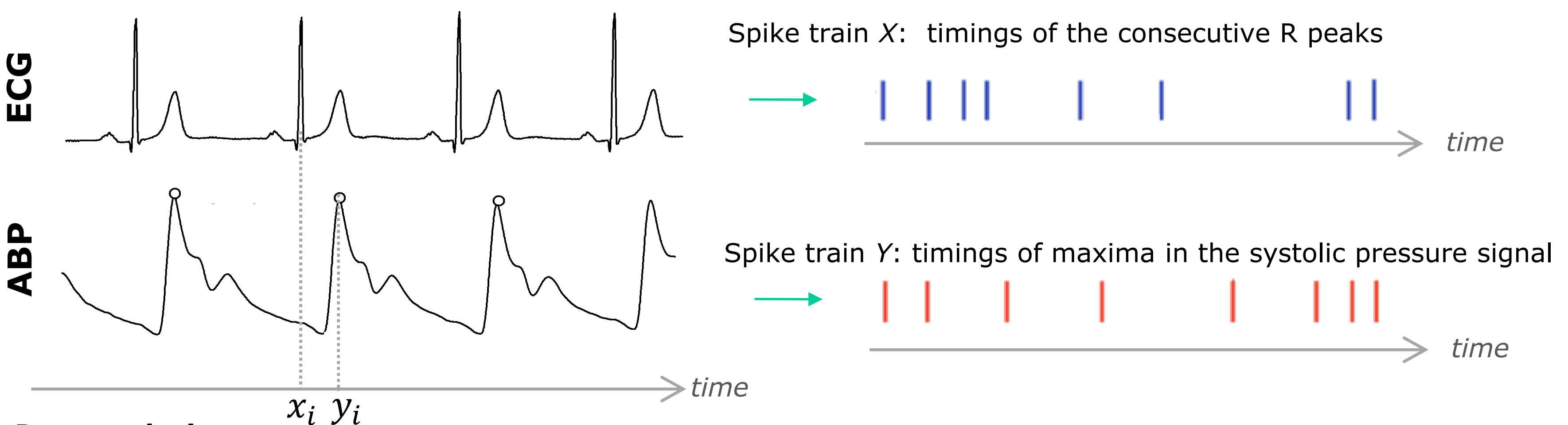
Application to cardiovascular point processes

- ***Protocol: 76 young healthy subjects during head-up tilt and mental stress tasks***



M. Javorka et al, "Basic cardiovascular variability signals: mutual directed interactions explored in the information domain", **Phys. Meas**, 38 (877), **2017.**

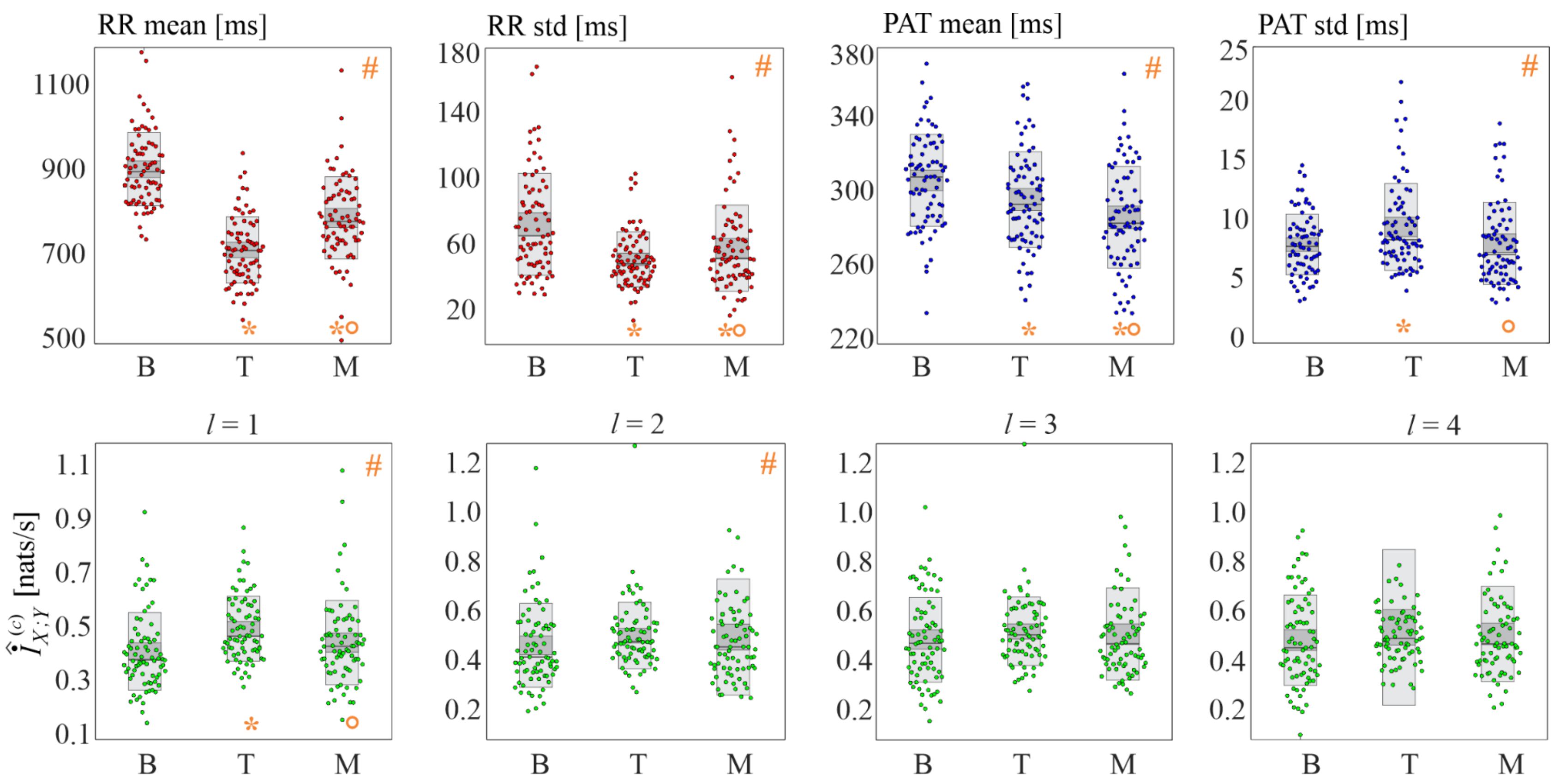
- ***Signals and measurement of point process data:***



- ***Data analysis:***
  - ✓ Measurement of heart period (RR interval) time series: $RR_i = x_{i+1} - x_i$
  - ✓ Measurement of Pulse Arrival Time (PAT) time series: $PAT_i = y_i - x_i$
  - ✓ Computation of the corrected MIR (N=300 events)

G Mijatovic, R Pernice, A Perinelli, Y Antonacci, M Javorka, L Ricci, L Faes, 'Measuring the rate of information exchange in point-process data with application to cardiovascular variability', ***Frontiers in Network Physiology***; 1:765332, **2022**

Application to cardiovascular point processes



- *The **higher cMIR** during tilt, together with the lower mean and higher STD of PAT, suggest that common mechanisms of **sympathetic activation** drive the increased exchange of information during postural stress.*

G Mijatovic, R Pernice, A Perinelli, Y Antonacci, M Javorka, L Ricci, L Faes, 'Measuring the rate of information exchange in point-process data with application to cardiovascular variability', ***Frontiers in Network Physiology***; 1:765332, **2022**

Thank you for your attention!