Estimating resilience of evolving epileptic brain networks

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Epilepsy

Greek term for *seizure;* disease first mentioned ~ 1750 BC

~ 50 Mio people suffer from epilepsy (~ 0.8 % of world population)*

seizure: short-lasting dysfunction of central nervous system

epilepsy: recurrent (> 2/a) seizures without acute cause

famous people suffering from epilepsy:

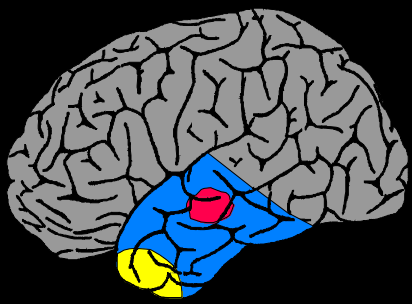
Sokrates, Alexander the Great, Julius Caesar, Lenin, Flaubert, Dostojevski, Carroll, Poe, Berlioz, Paganini, Händel, van Gogh, Newton, Pascal, Helmholtz, Nobel

** WHO fact sheet, Feb 2017*

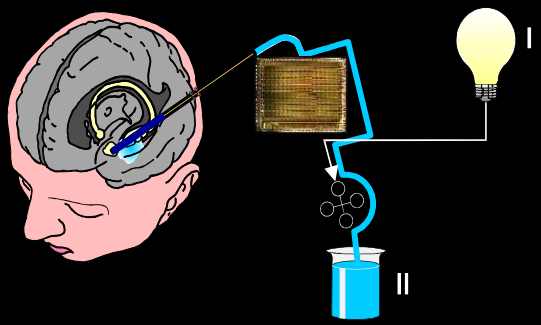
Treatment of Epilepsy

- **antiepileptic drugs**; primary therapy
  success: ~ 70 %
  side effects, long-term treatment

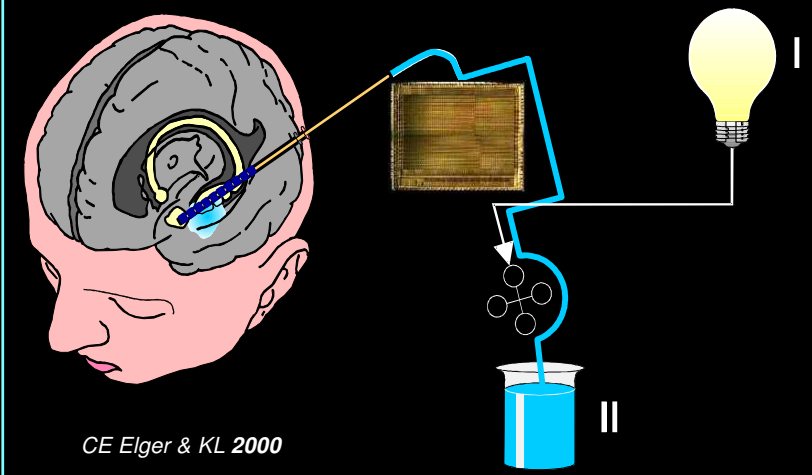
- **epilepsy surgery**; option for ~ 5 – 10 % of patients
  requirement: localize and delineate epileptic focus from functionally relevant brain areas
  success: ~ 60 % (15 % – 85 %)
  long-term outcome, surgery-induced alterations?



- **alternative therapies;** for ~ 22 % of patients
  seizure prediction, seizure control
  success: ?



New Treatment Options through Seizure Prediction



*CE Elger & KL **2000***

on demand:

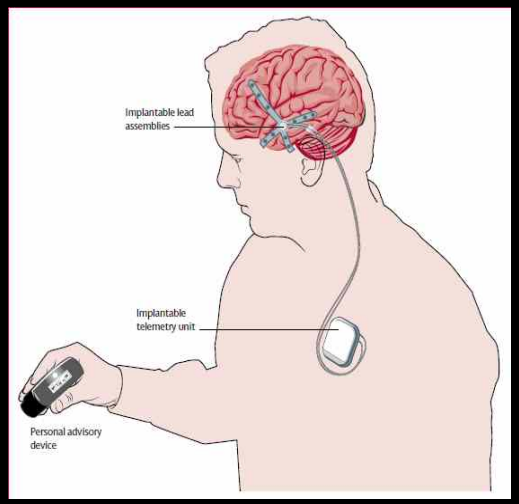
warning / self-control

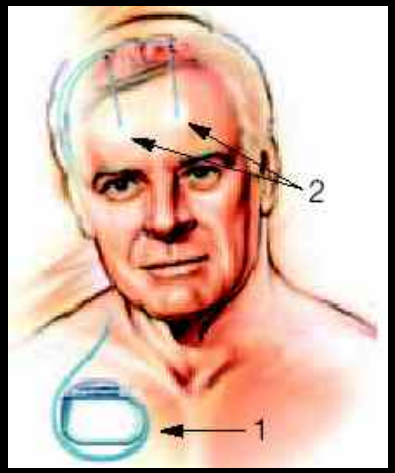
local drug administration

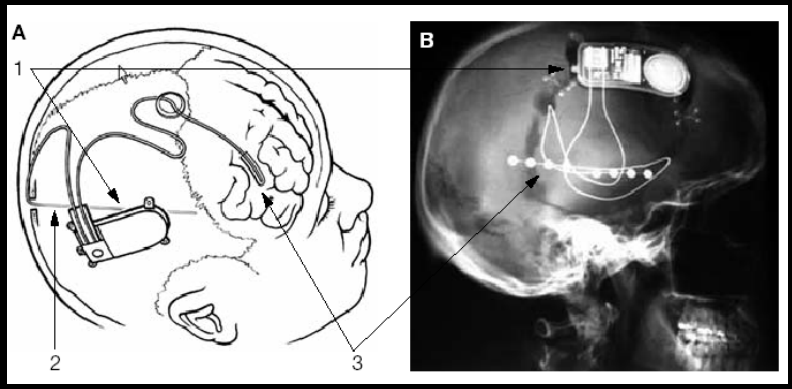
local cooling

stimulation

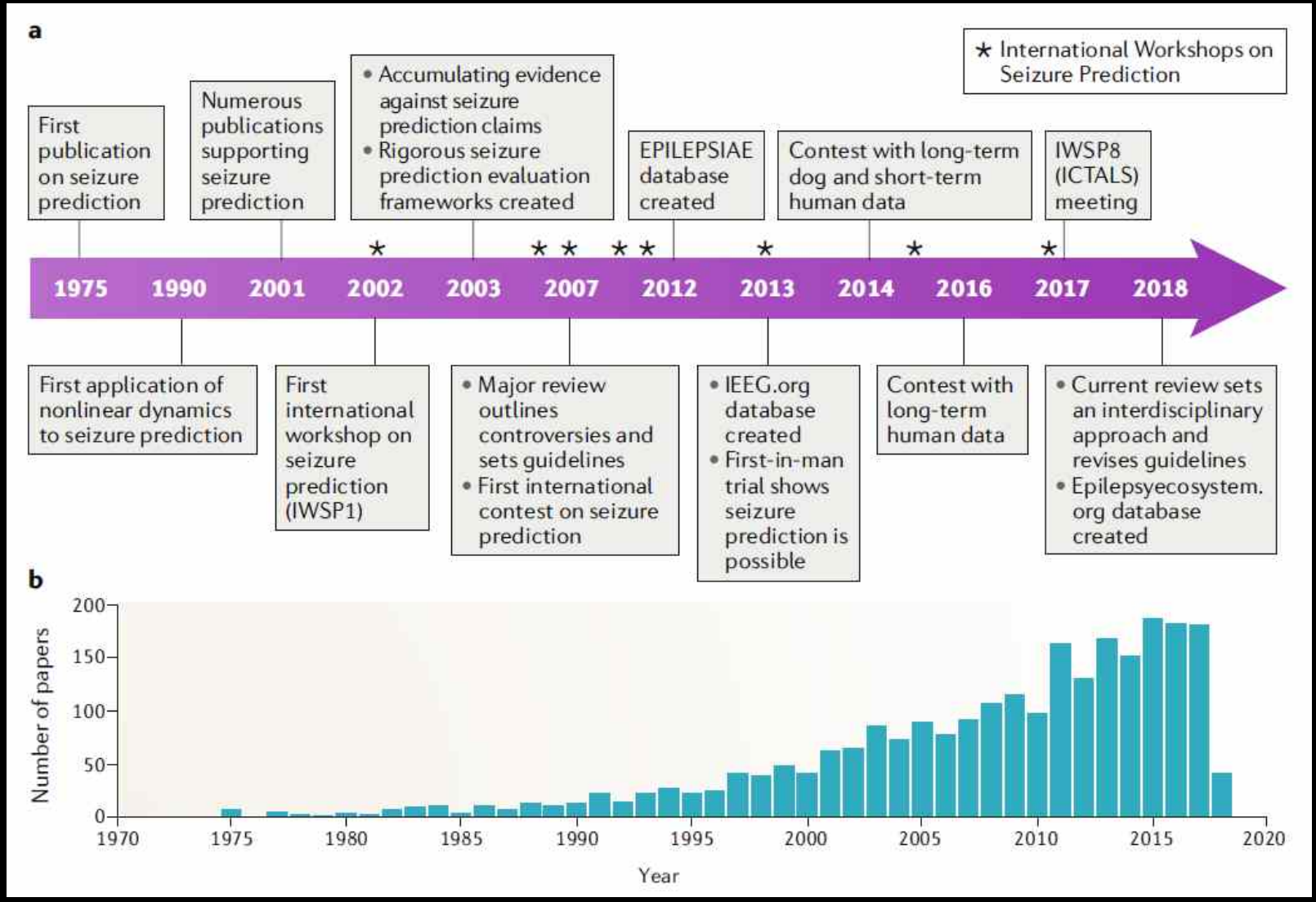
…





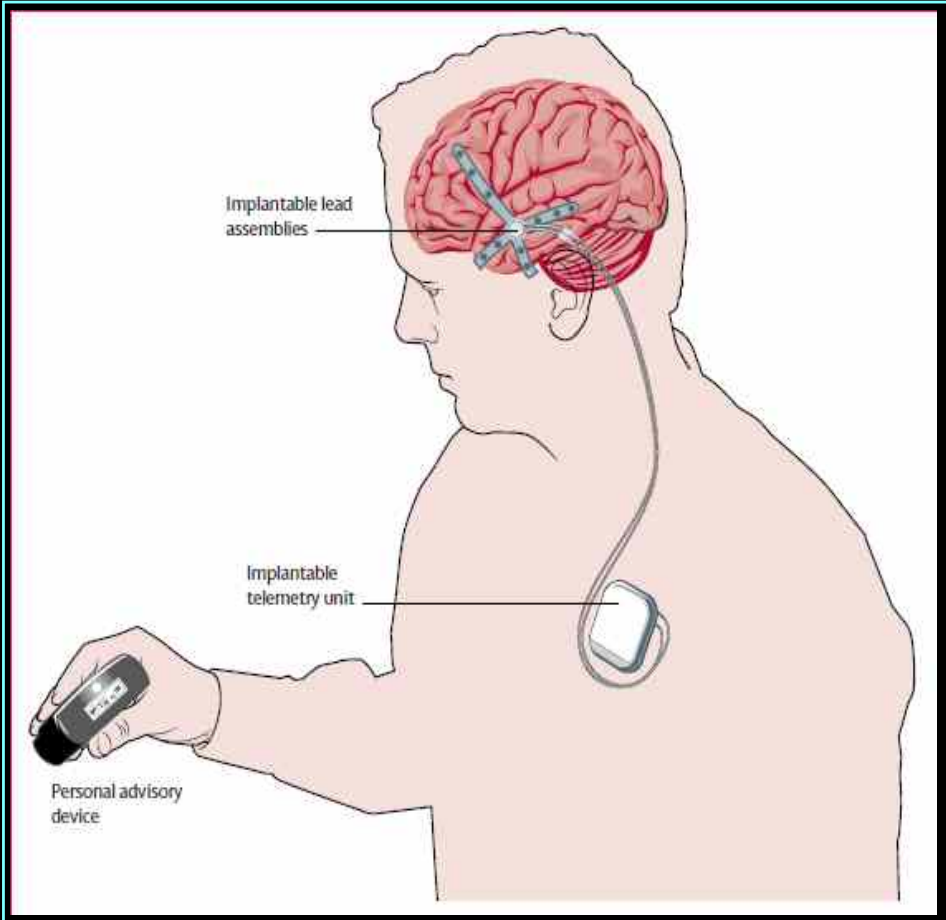


Evolution of Seizure Prediction



L. Kuhlmann, KL et al., ***Nat Rev Neurol****, 14, 618, 2018*

Implantable Seizure Prediction System



Cook et al., Lancet Neurol 2013; 12: 563

- 15 patients
- Australian feasibility study
- NeuroVista Corp. (USA)
  "Seizure Advisory System"

- up to 3 yrs of continuous recording (16 channels @ 400 Hz)

prediction is feasible, but …
… not in all patients
… not in all seizures

reasons ?

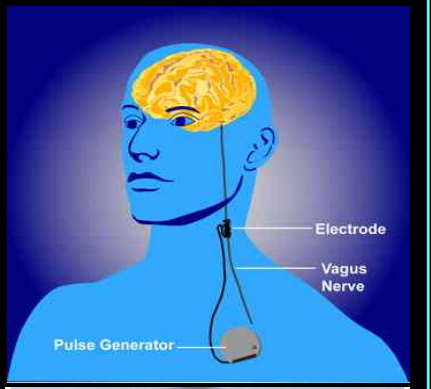
Neuromodulation in Epilepsy

not better than drugs

Vagal Nerve Stimulation (VNS)

unspecific activation of N. vagus

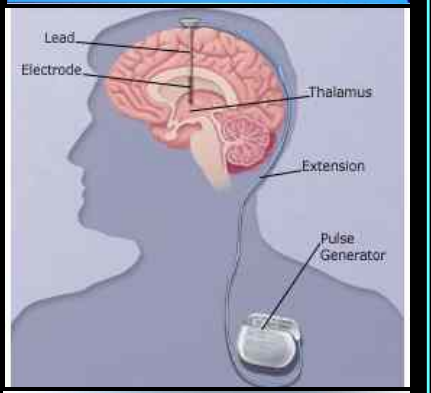
seizure reduction ~35 % (1. yr) – ~ 43% (3. yr)



Deep Brain Stimulation (DBS)

targeted stimulation of thalamic nuclei

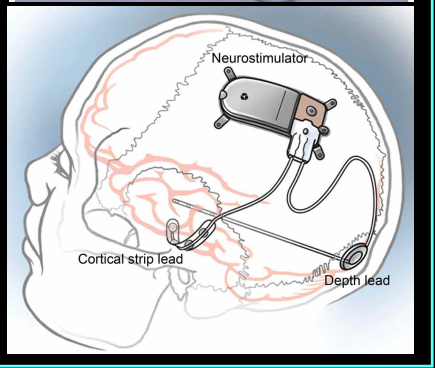
seizure reduction ~ 41 % (1. yr) – ~ 56% (2. yr)



Responsive Neurostimulation (RNS)

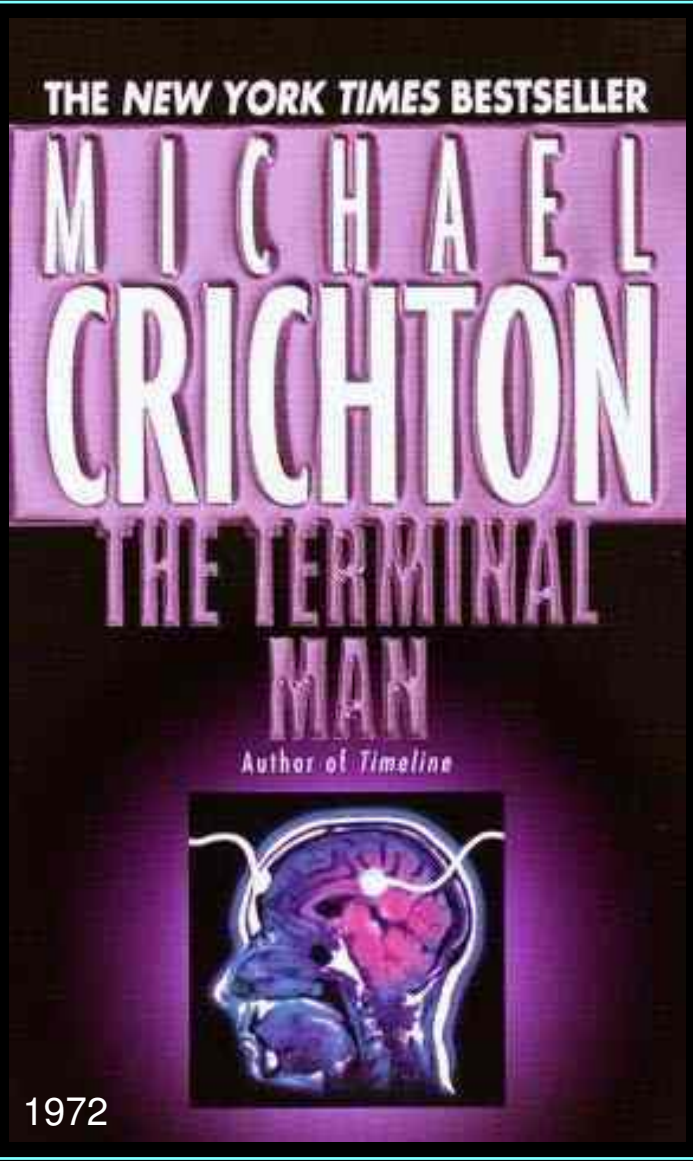
targeted elect. stimulation of epileptic focus at seizure onset

seizure reduction: ~ 44 % (1. yr) – 48-66 % (3-6 yr)



side effects, long-term success ?

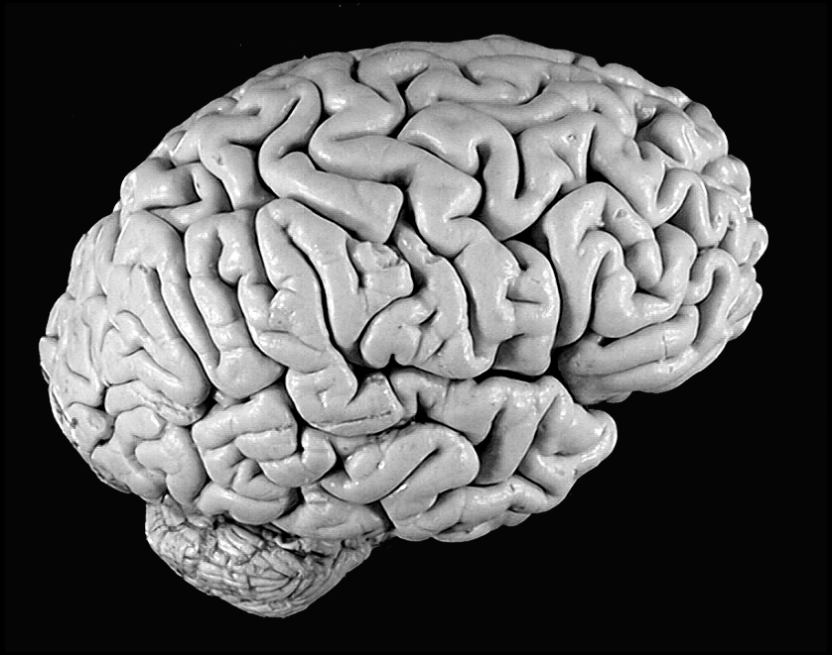
Seizure Prediction and Prevention



nonlinear, open, dissipative

adaptive

plasticity



can the epileptic brain be controlled?

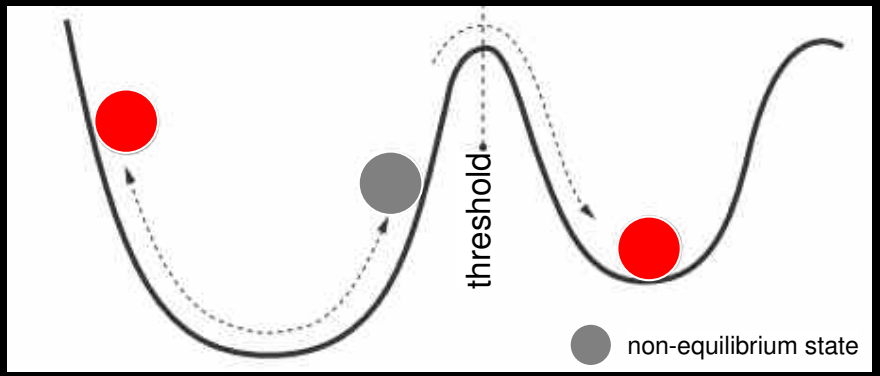
(or: does it want to be controlled?)

Resilience and Dynamical Systems

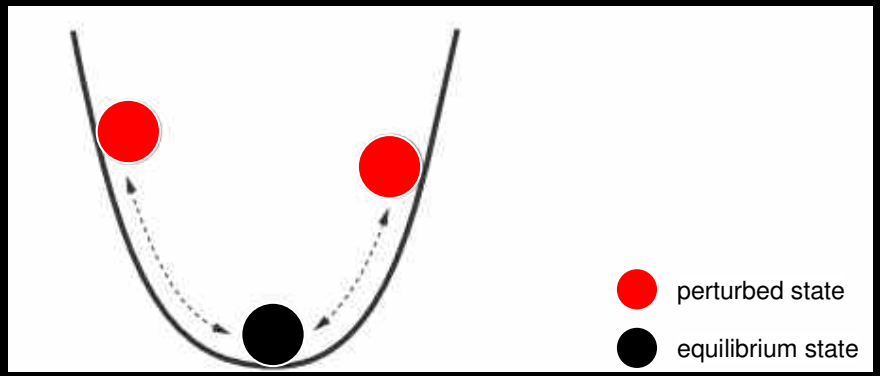
"the capacity of a system to absorb disturbance and reorganize while undergoing change so as to still retain essentially the same function, structure, identity, and feedbacks"

Crawford S. Holling: *Resilience and stability of ecological systems.*
In: *Annual Review of Ecology and Systematics* (1973)

ecological resilience (Holling)



engineering resilience (Pimm)



Resilience in Different Domains

engineering resilience Pimm (1984)	system's speed of **return to equilibrium** following a **shock**
ecological resilience Holling (1973, 1996)	ability of system to withstand **shock** and **maintain** critical relationships and functions
social-ecological resilience Carpenter et al. (2001)	(i) amount of **disturbance** a system can **absorb and remain** within a domain of attraction; (ii) capacity for learning and adaptation, (iii) degree to which system can self-organize
social resilience Adger (2000)	ability of groups or communities to **cope with external stresses and disturbances** as a result of social, political and environmental change
development resilience Pasteur (2011); Barrett & Constas (2014)	capacity of a person, household or other aggregate unit **to avoid poverty** in the face of various **stressors** and in the wake of myriad **shocks** **over time**
socio-economic resilience Mancini et al. (2012)	refers to the policy-induced ability of an economy to **recover from or adjust to** the negative impacts of adverse exogenous **shocks** and to benefit from positive **shocks**
community resilience Norris et al. (2008)	process linking a set of adaptive capacities to a positive trajectory of **functioning** and **adaptation** after a **disturbance**
psychological resilience Tugade, Fredrickson & Feldman Barrett (2004)	an individual's ability to **adapt to stress and adversity**; resilience is a process and can be learned by anyone using positive emotions

e.g. Quinlan et al., J Appl Ecol 2016

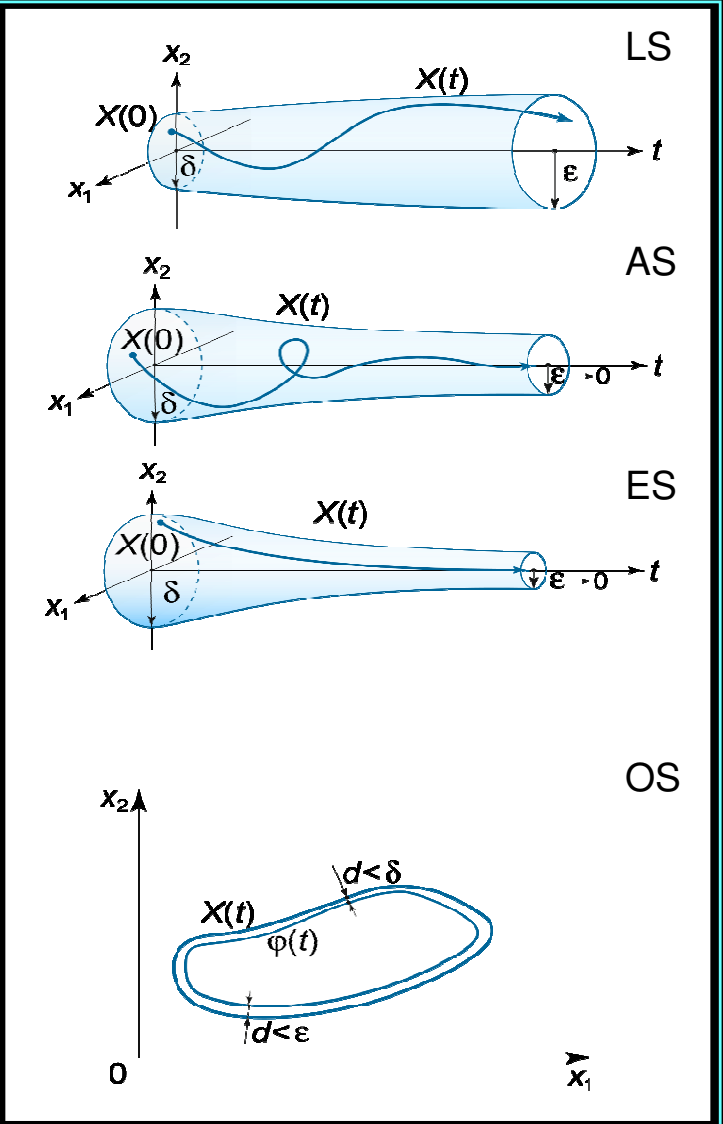
Stability of Dynamical System (I)

- differential (or difference) equations describing dynamical system
- infinitesimal (**small**) perturbations

stability of system near equilibria
- Lyapunov stability (LS)
- asymptotic stability (AS)
- exponential stability (ES)

stability of trajectory
- orbital stability (OS)

stability of system itself
- structural stability



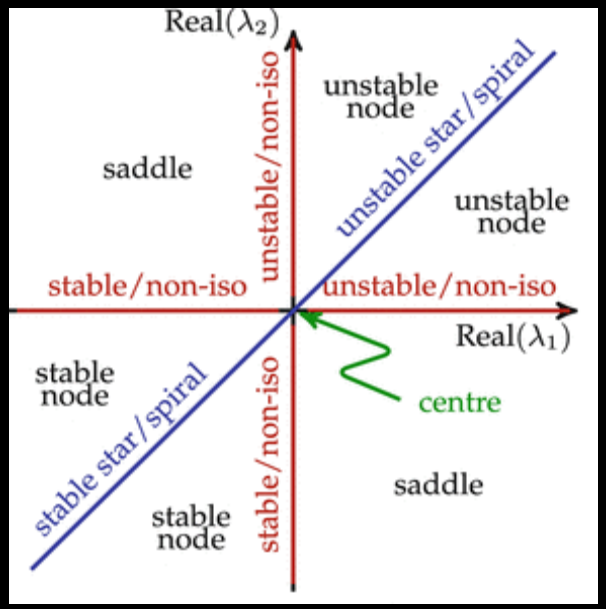
adopted from: math24.net

Lyapunov, 1892; Andronov and Pontryagin. 1937

Stability of Dynamical System (II)

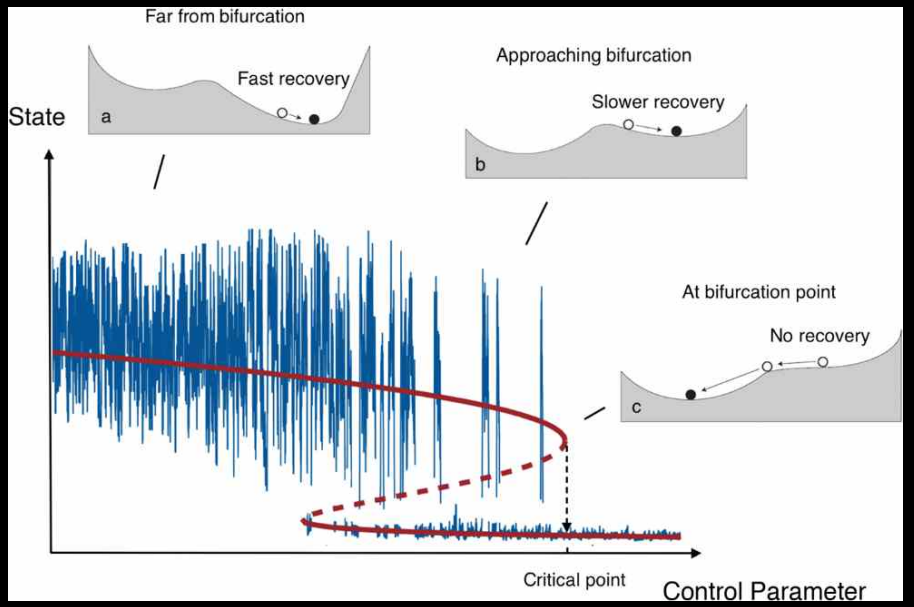
Methods and Extensions small perturbations

- linear stability analysis
- evaluate eigenvalues of Jacobian at equilibrium



from: P. Fieguth: An Introduction to Complex Systems, 2017

- tipping (bifurcation) points
- critical slowing down (not universal)
- relevance for epilepsy unclear



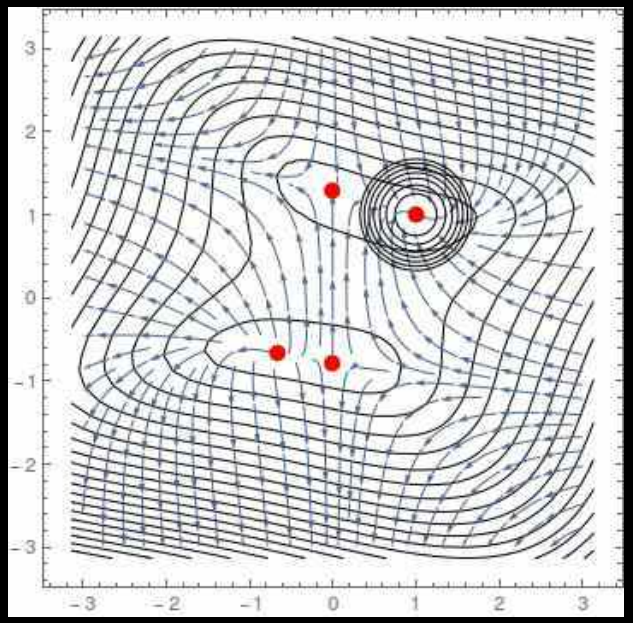
from: C. Diks et al., Emp Econ., 2018

Stability of Dynamical System (III)

Methods and Extensions

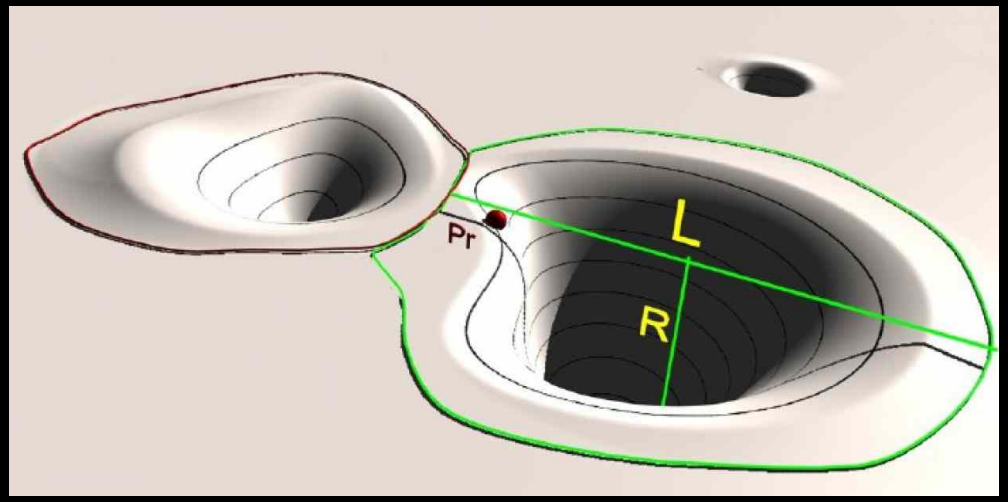
large, non-local perturbations, multistable systems

- Lyapunov stability criterion
- Lyapunov functions
- LaSalle invariance principle



from: math.stackexchange.com

- basin of attraction
- volume
- prob. to return to attractor, return time
- latitude, resistance, precariousness



from: Leuteritz & Ekbia, 2008

e.g. Walker et al., 2004, Menck et al. 2014

Stability of Dynamical System (IV)

most methods require exact knowledge of equations of motion

perturbations:

- small vs. large
- local vs. non-local
- control parameter vs. state variables

data-driven methods rare; strong claims

Network Resilience

complex system $\rightarrow$ complex network

- robustness against attacks (micro $\rightarrow$ macro), mostly endogenous*

- multi-dimensional system $\rightarrow$ effective one-dimensional dynamics: ***resilience patterns & functions***, impact of topology, (ongoing research)

$$\dot{x}_i = F(x_i) + \sum_{j=1}^{N} A_{ij} G(x_i, x_j)$$

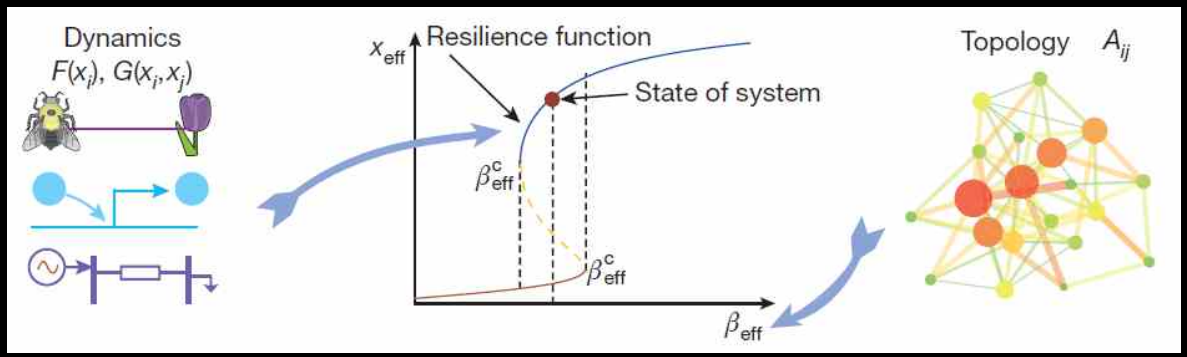
$$\Downarrow$$

$$\boxed{\dot{x}_{\text{eff}} = F(x_{\text{eff}}) + \beta_{\text{eff}}\, G(x_{\text{eff}}, x_{\text{eff}})}$$

$$\text{where } x_{\text{eff}} = \frac{\sum_{ij} A_{ij} x_j}{\sum_{ij} A_{ij}}$$

$$\text{and } \beta_{\text{eff}} = \frac{\sum_{ij} A_{ij} A_{ji}}{\sum_{ij} A_{ij}}$$

perturbations affect network structure only



from: *Gao et al., Nature 530, 307, 2016*

*e.g., S. Havlin, R Cohen: Complex Networks: Structure, Robustness and Function, 2010

Data-driven Estimation of Resilience

system representation: $\dot{x}_i = F(x_i) + \sum_{j=1}^{N} A_{ij} g(x_i, x_j; t)$

ansatz:

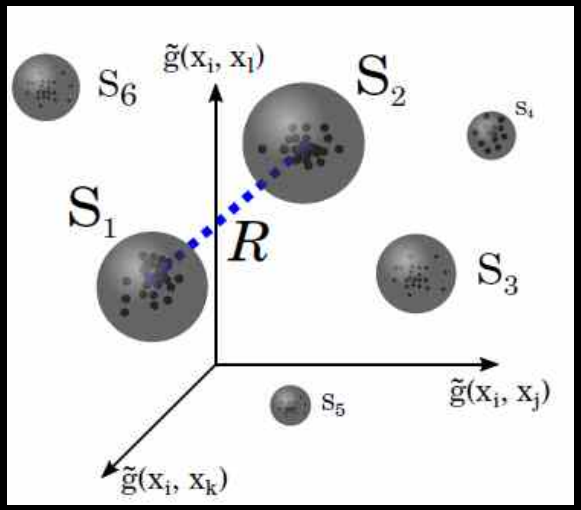
- estimate time-resolved coupling structure $\tilde{g}(t)$
  (e.g., via pairwise estimations of strength of interaction)

- recurring coupling structures* indicate dynamical regimes

$$\xi(t_1, t_2) = \|\tilde{g}(t_1) - \tilde{g}(t_2)\|_2$$

- identify dynamical regimes with
  hierarchical clustering

- minimum distance R between dynamical
  regimes as proxy for resilience

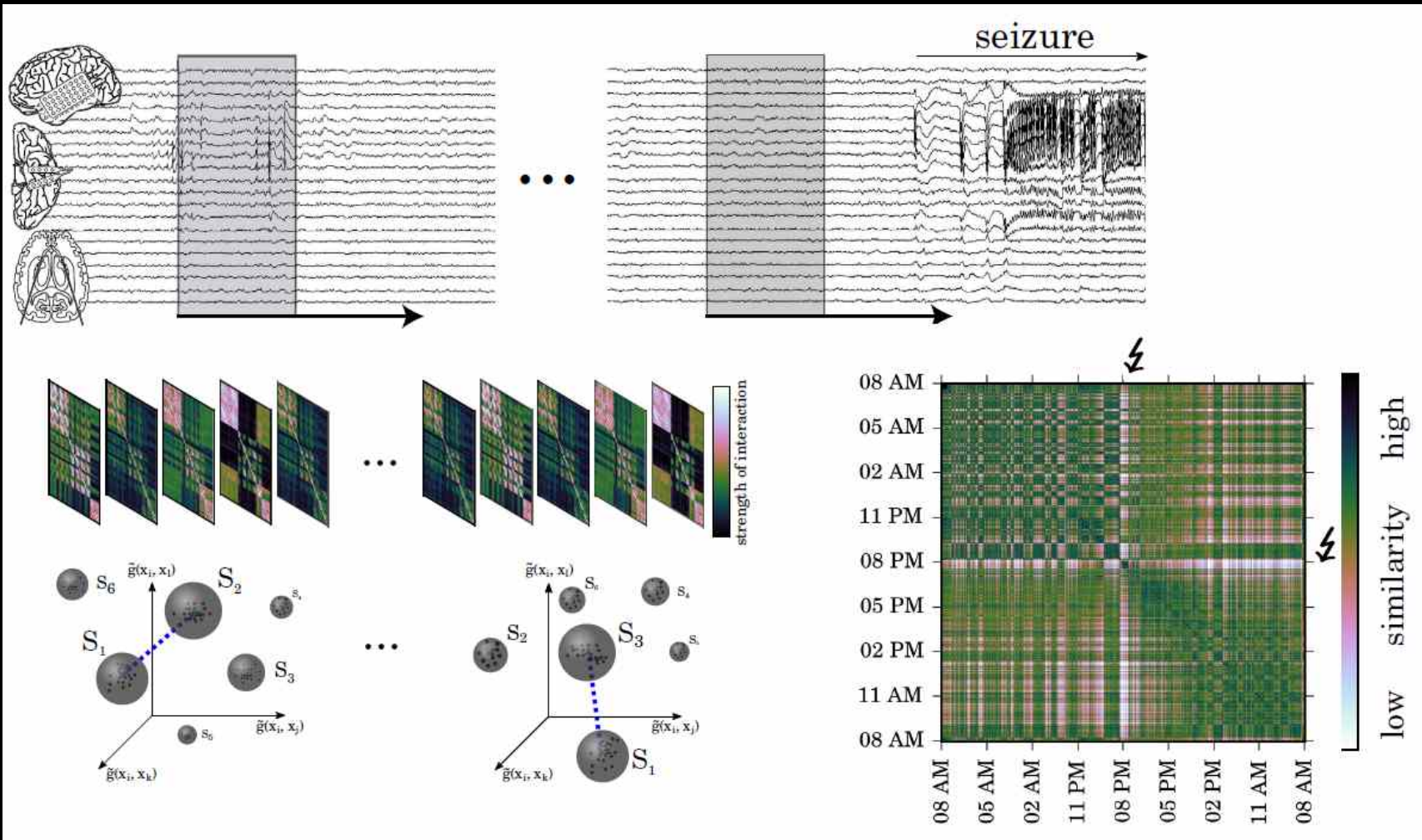


T Rings et al., Sci Rep 9, 1744, 2019

* Münnix et al., Sci Rep 2, 644, 2012

Data-driven Estimation of Brain Resilience

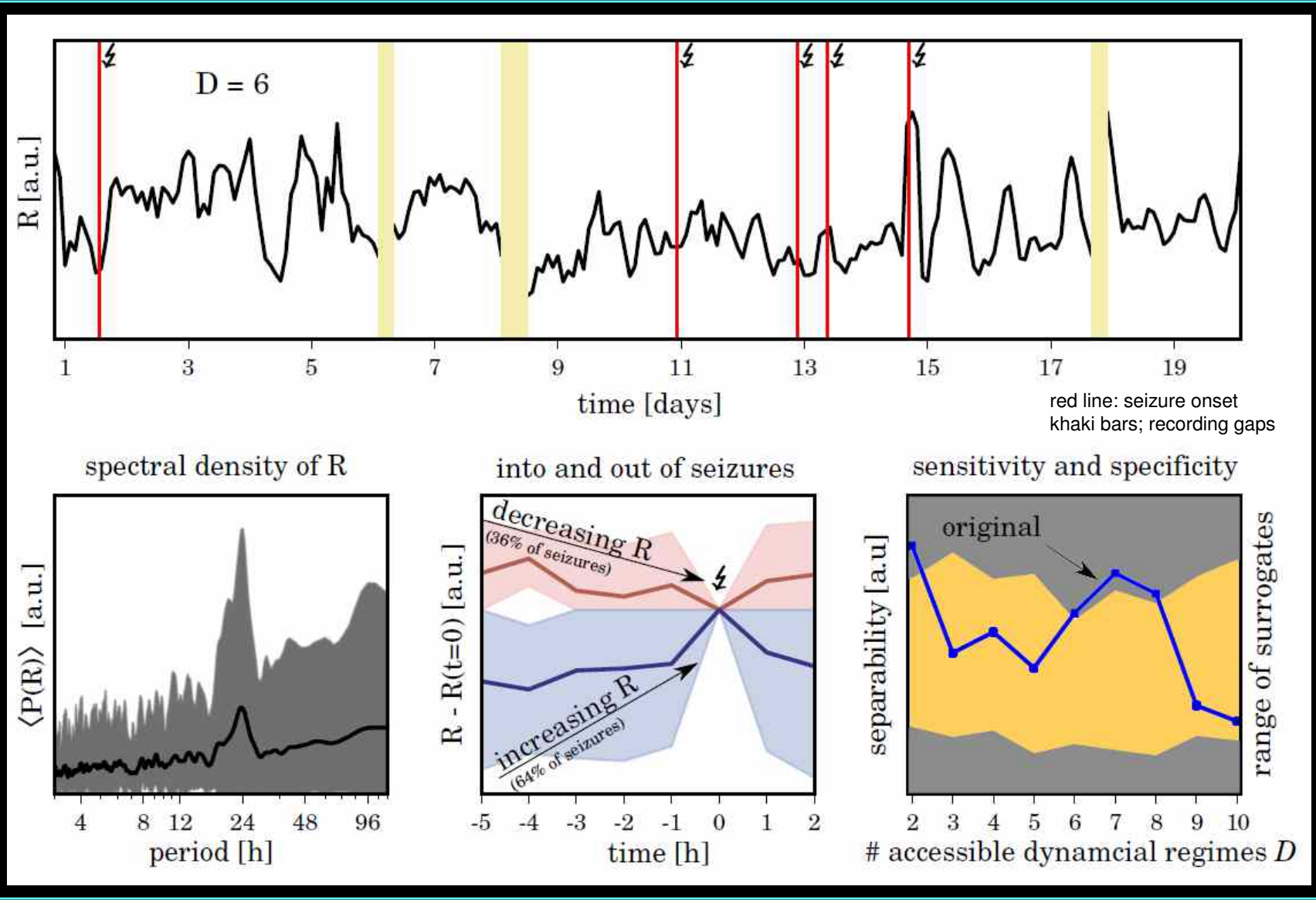
43 subjects, 109 seizures, drug-resistant epilepsies, 4000 h iEEG recording



temporal resolution for clustering: 1 h

T Rings et al., Sci Rep 9, 1744, 2019

Data-driven Estimation of Brain Resilience



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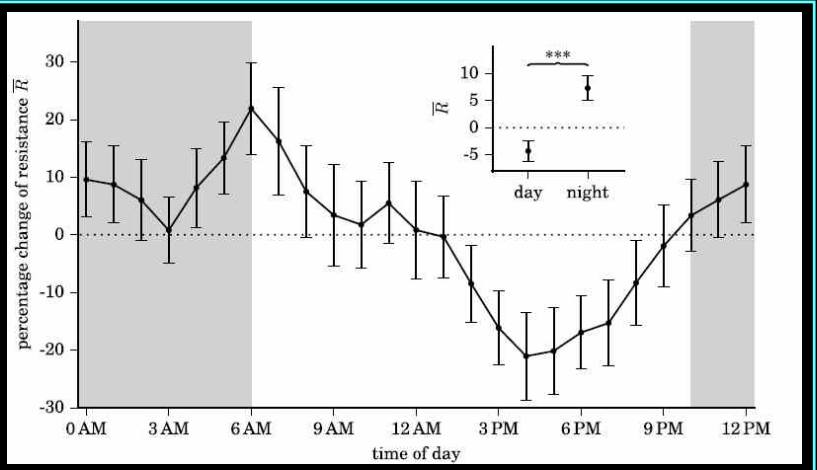
Summary and Outlook

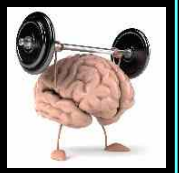
- brain resilience is higher during night times

- brain resilience increases prior to seizures
  - unexpected !
  - more than two thirds of cases



- pre-seizure increase possibly reflects drug-resistance

- pre-seizure increase possibly reflects an abnormal learned response of the brain to certain repeated provocations*



- tracking brain resilience
  improve understanding of seizure-generating mechanisms
  improve control strategies

T Rings et al., Sci Rep 9, 1744, 2019

*Hsu et al. "An open hypothesis: is epilepsy learned, and can it be unlearned?." Epilepsy & Behavior 13 , 511-522, 2008