Numerické simulace v diagnostice onemocnění mozku

Computational modeling in epilepsy intervention & diagnosis

12/02/2020, Neurofyziologie, CVUT, Prague

Isa Dallmer-Zerbe, PhD student in Neuroscience

Supervision: Jaroslav Hlinka, PhD and Prof MUDr Přemysl Jiruška, PhD

INSTITUTE OF COMPUTER SCIENCE
The Czech Academy of Sciences

INSTITUTE OF PHYSIOLOGY CAS

2. LF UK

Part I: Background

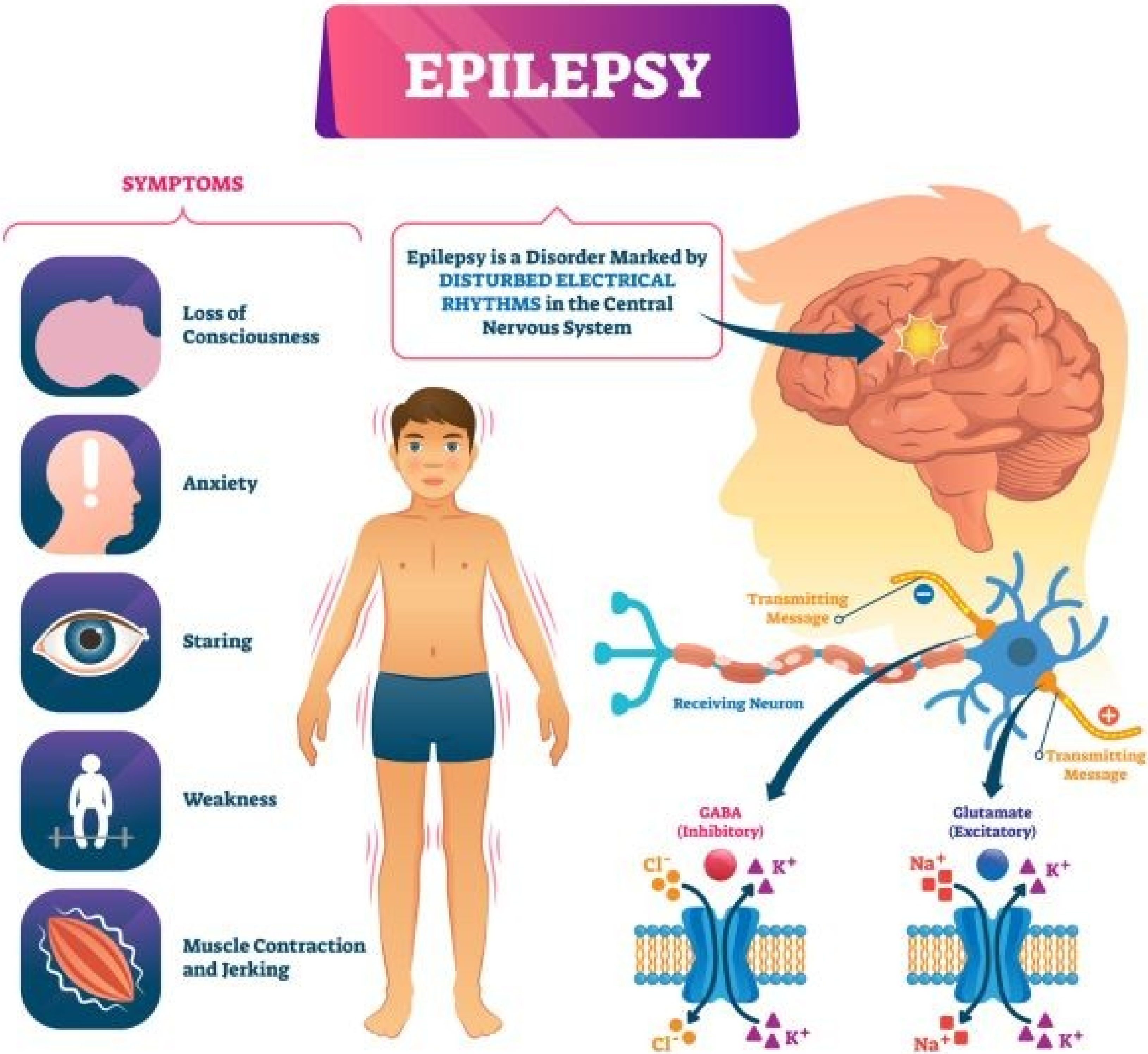
- Epilepsy
- Computational Modeling

Part II: Computational modeling in epilepsy intervention

- Why model?
- Network models for brain surgery: know-how
- Network models for brain stimulation: know-how

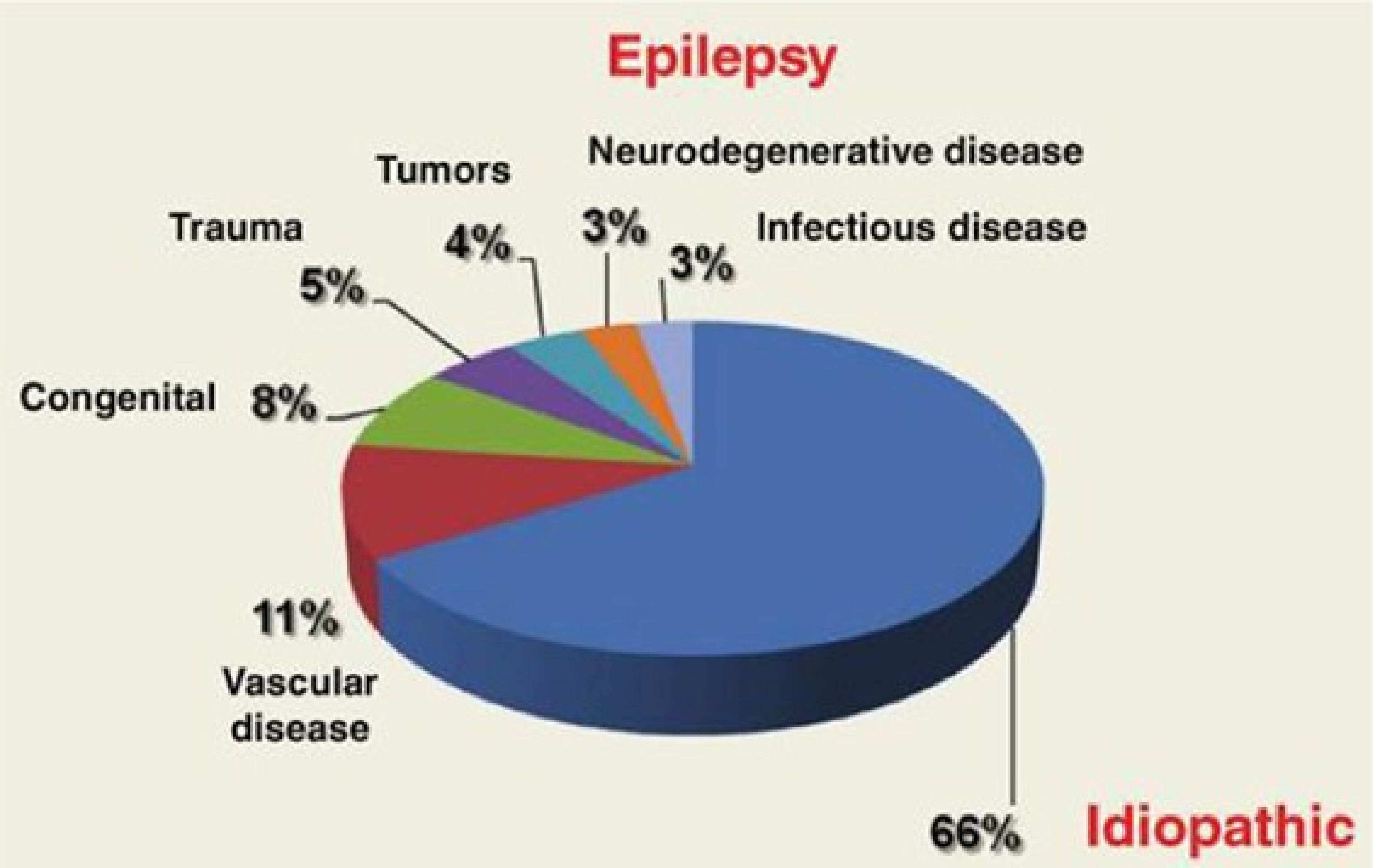
Part III: Current state of the art & future outlook

Epilepsy

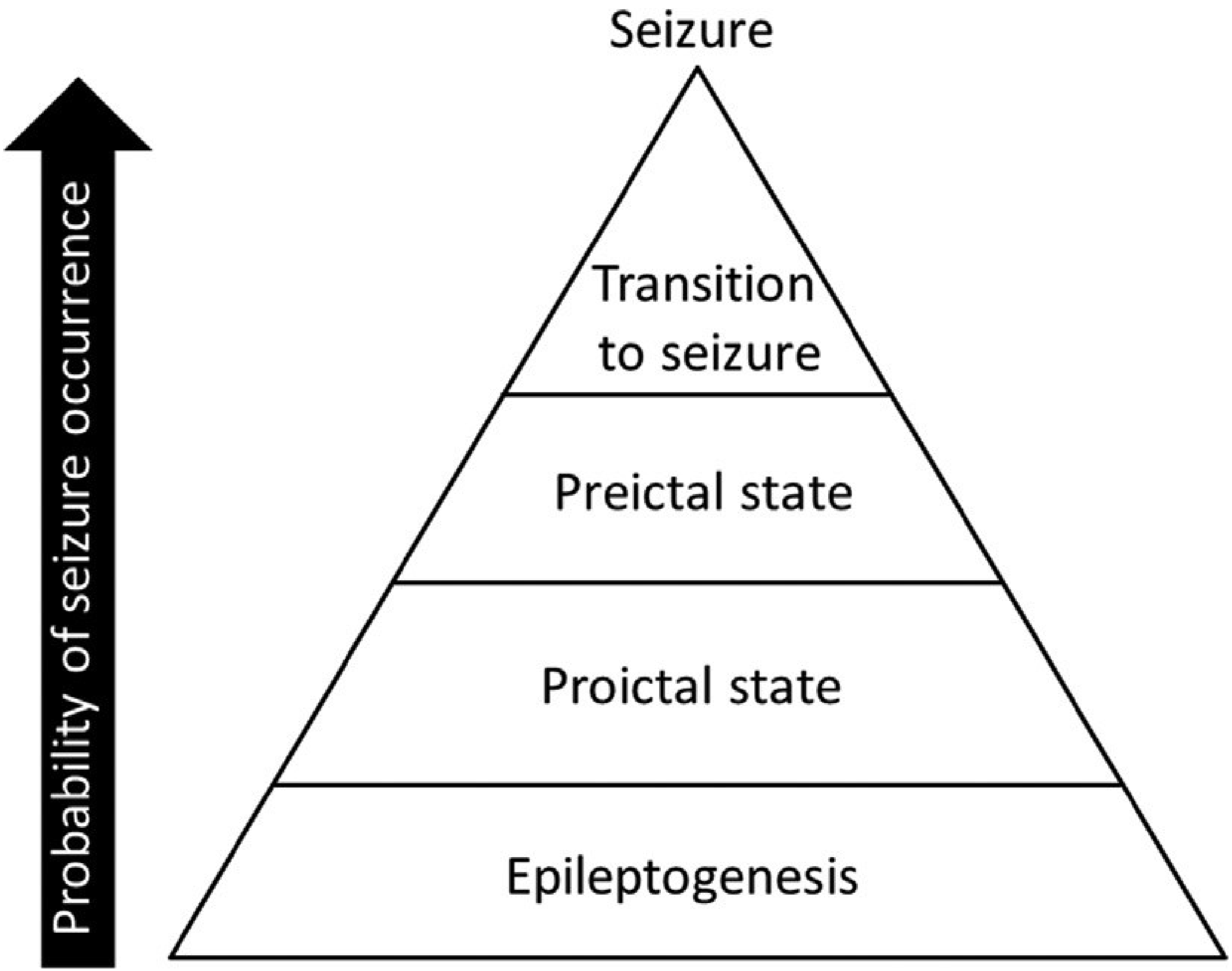


EPILEPSY
SYMPTOMS
Loss of Consciousness
Anxiety
Staring
Weakness
Muscle Contraction and Jerking
Epilepsy is a Disorder Marked by DISTURBED ELECTRICAL RHYTHMS in the Central Nervous System
Transmitting Message
Receiving Neuron
Transmitting Message
GABA (Inhibitory)
Glutamate (Excitatory)
Cl⁻
K⁺
Na⁺

Etiology



Epilepsy
Neurodegenerative disease
Tumors
Trauma
4%
3%
Infectious disease
3%
5%
Congenital
8%
11%
Vascular disease
66%
Idiopathic



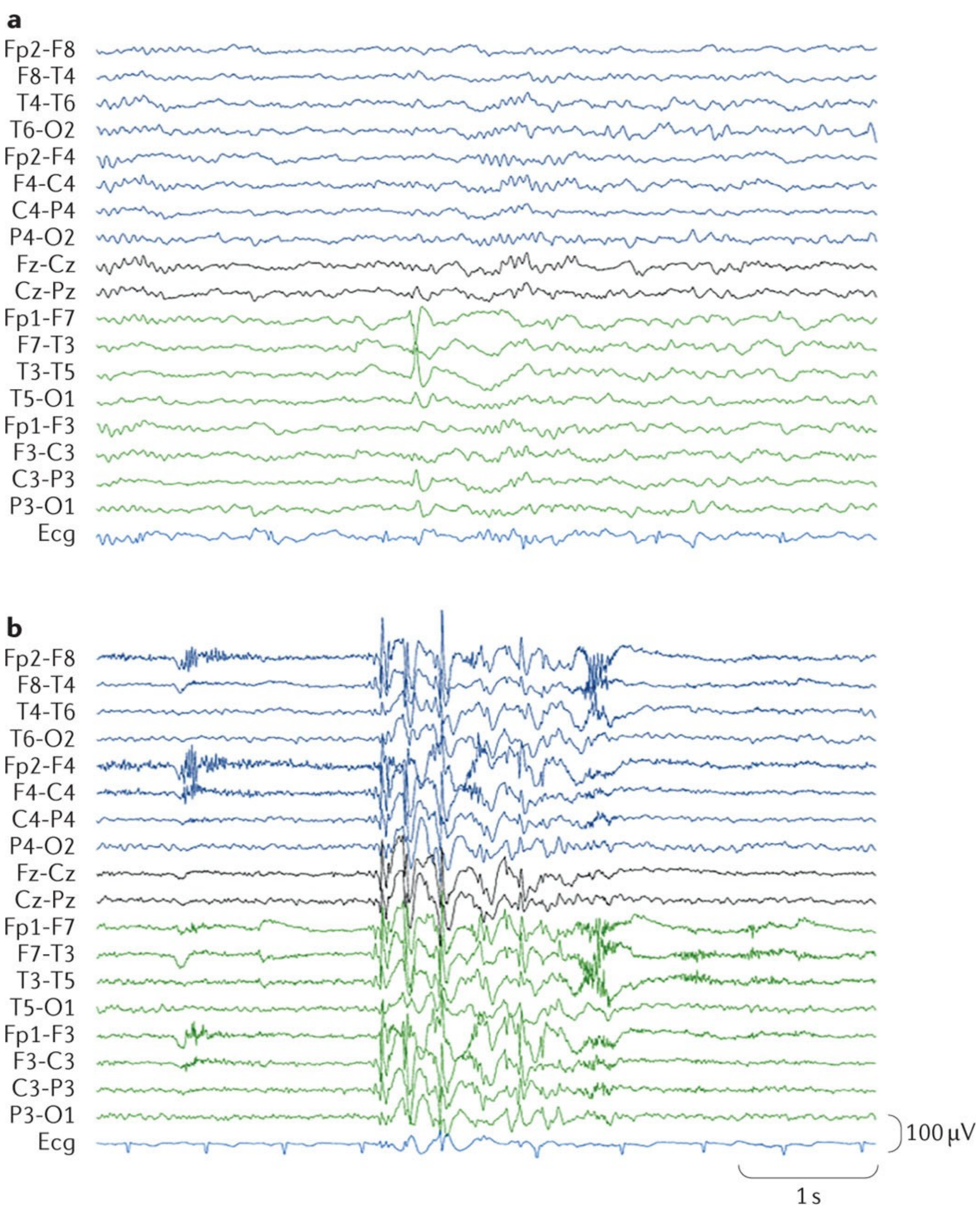
Etiology ⟷ Epileptogenesis ⟷ Ictogenesis

Focal

Generalized

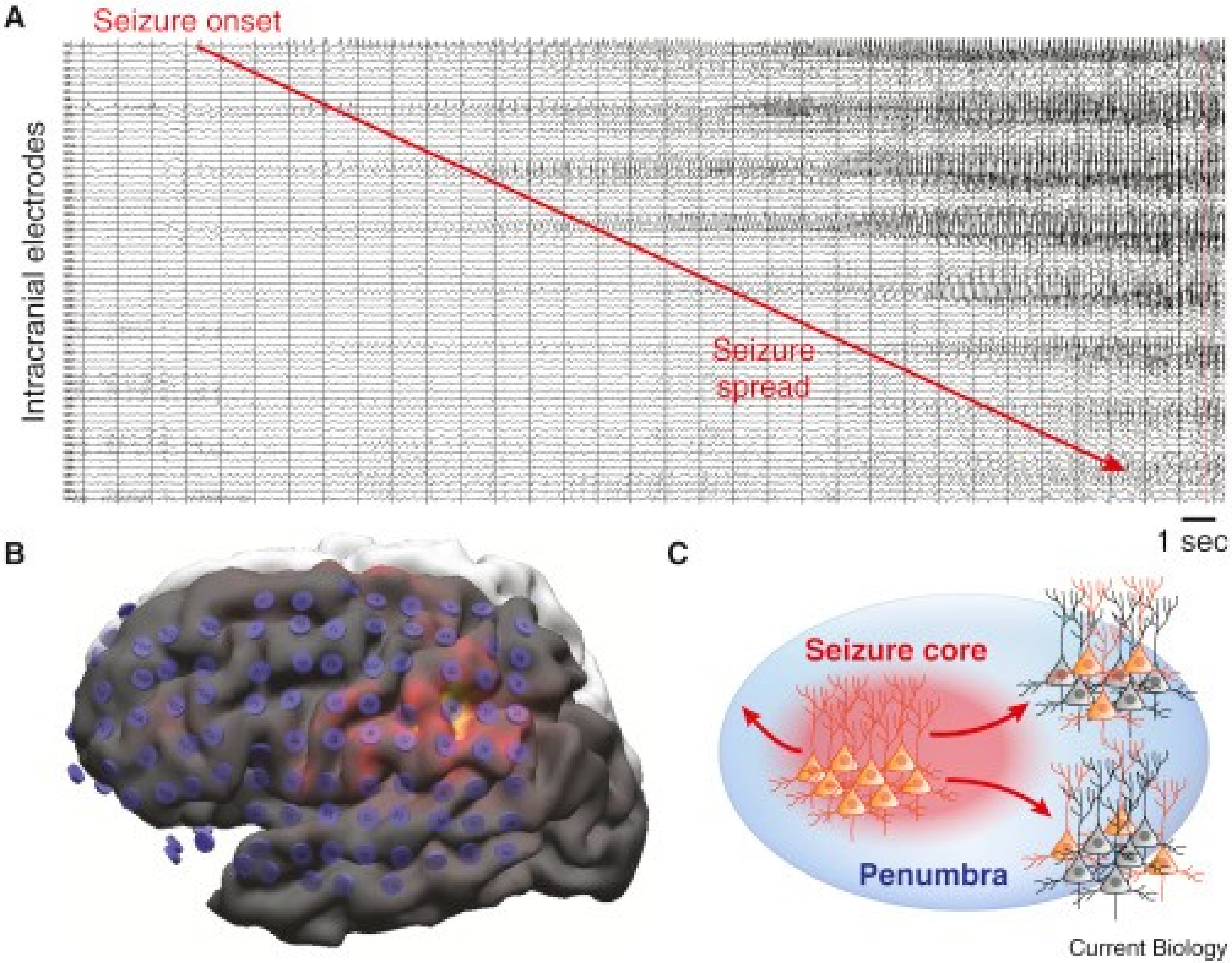
Unknown

Interictal Events

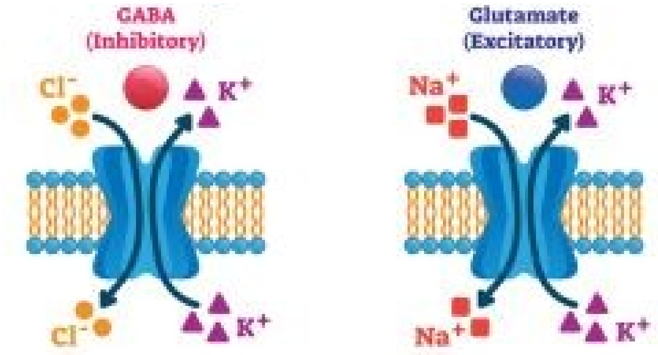


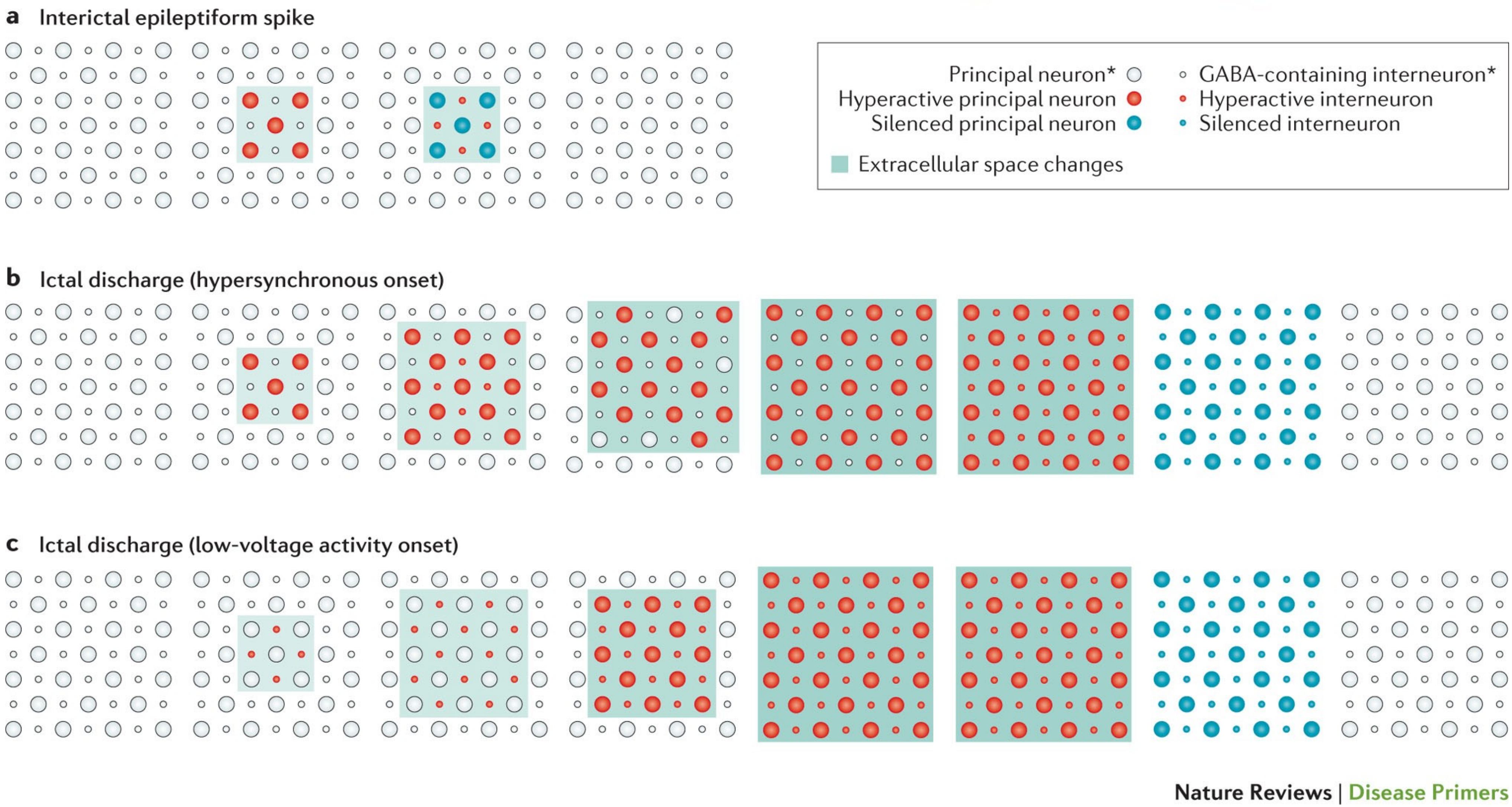
Nature Reviews | Disease Primers

Focal Seizure



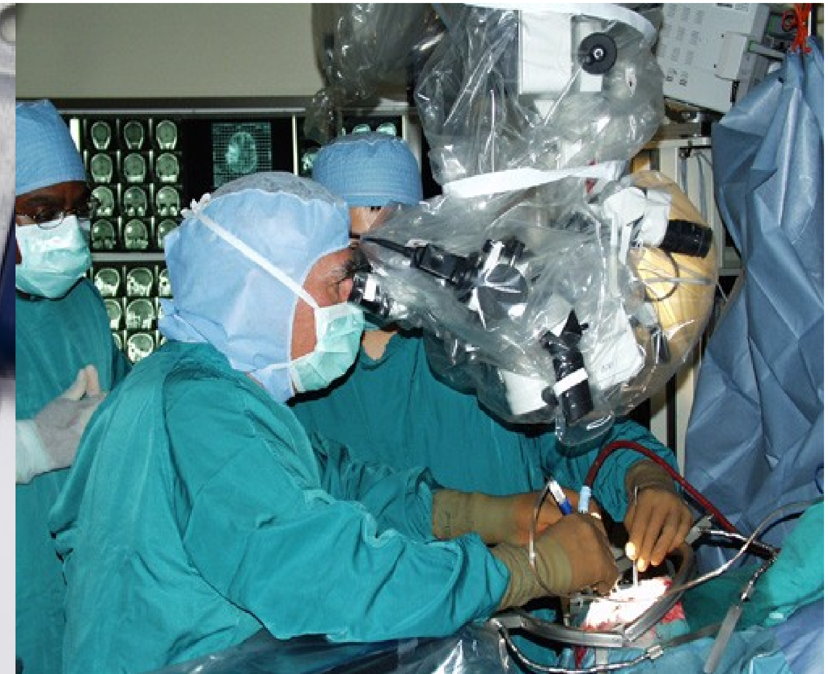
Seizure Mechanisms

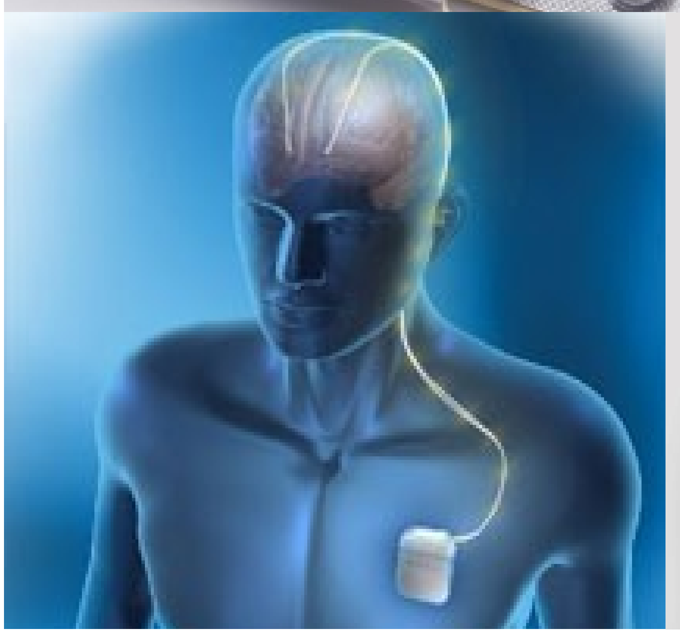


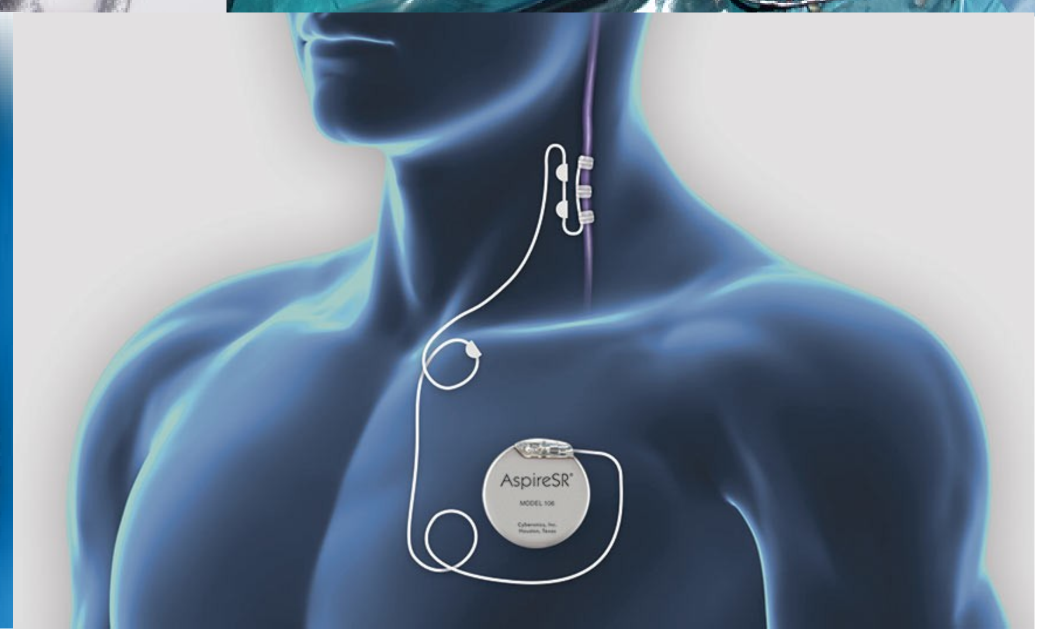


Treatment


Anticonvulsant
Medication
Tablets
500 mg
dispense with patient
leaflet provided separately
reach and sight of children
Rx only
30
tablets






AspireSR

Summary

Symptoms: manifold, dependent on involved brain area

Seizure types: focal, generalized, unknown

Etiology, Epileptogenesis & Ictogenesis: complex mechanisms acting across different spatial and time scales

Ictogenesis Mechanisms: disrupted inhibition/excitation balance in neural networks leads to spreading hyper-synchronization

Treatment: 30% of patients pharmacoresistant, surgery requires markers for the identification of the zone to be resected (epileptogenic zone), brain stimulation needs better stimulation parameter adjustment

Computational Modeling

What is a model?

A computational model is a set of equations that describe how a neuron, a network, a cortical area, or clinical behavior changes as a function of some variable, such as time.

- **variables and parameters**

- **retrospective modeling vs. prospective modeling**

What is a model?

A computational model is a set of equations that describe how a neuron, a network, a cortical area, or clinical behavior changes as a function of some variable, such as time.

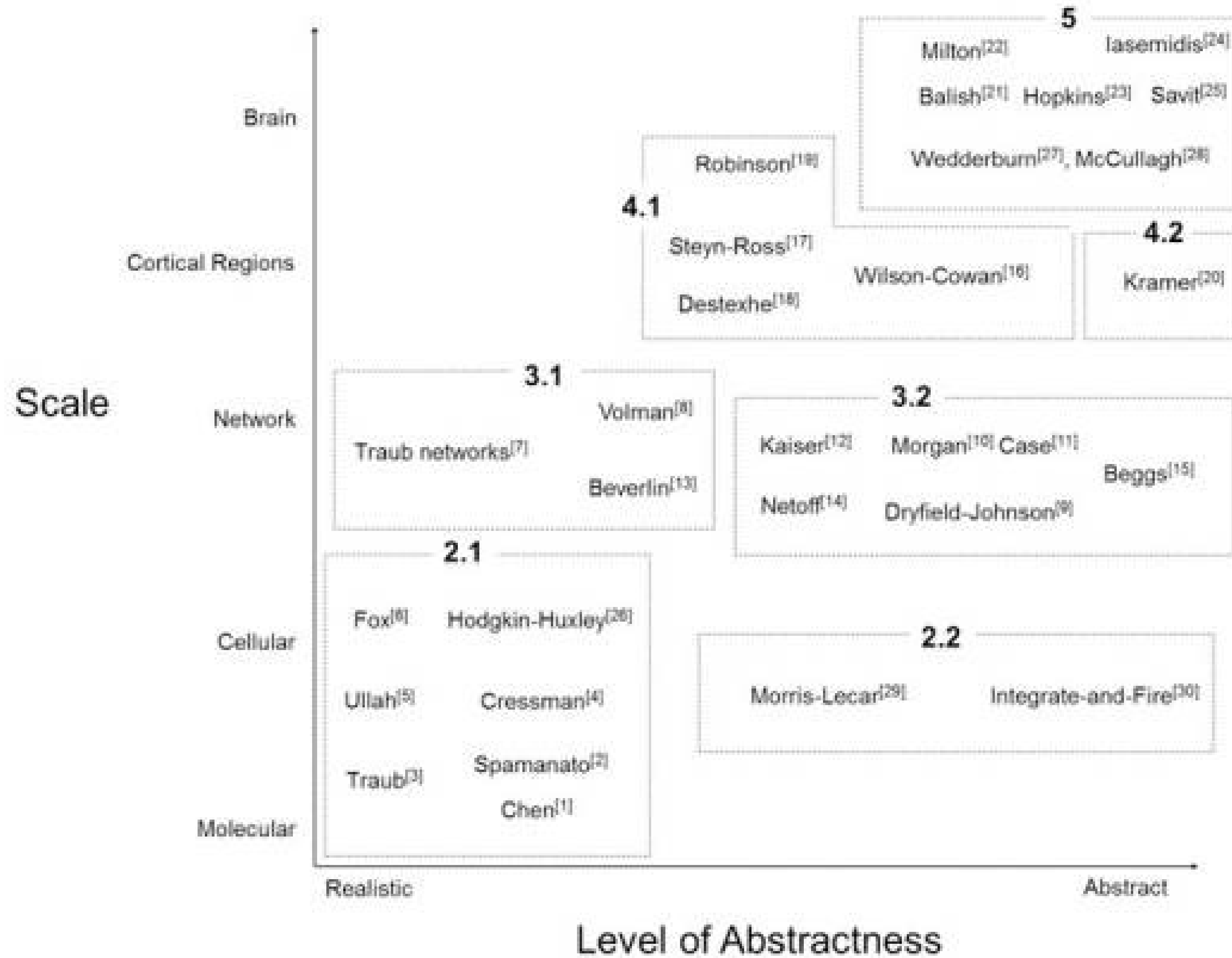
- variables and parameters

- retrospective modeling vs. prospective modeling

"The true test of a model is in prospective modeling, where the model is verified by examining whether it correctly predicts the experimental outcome."

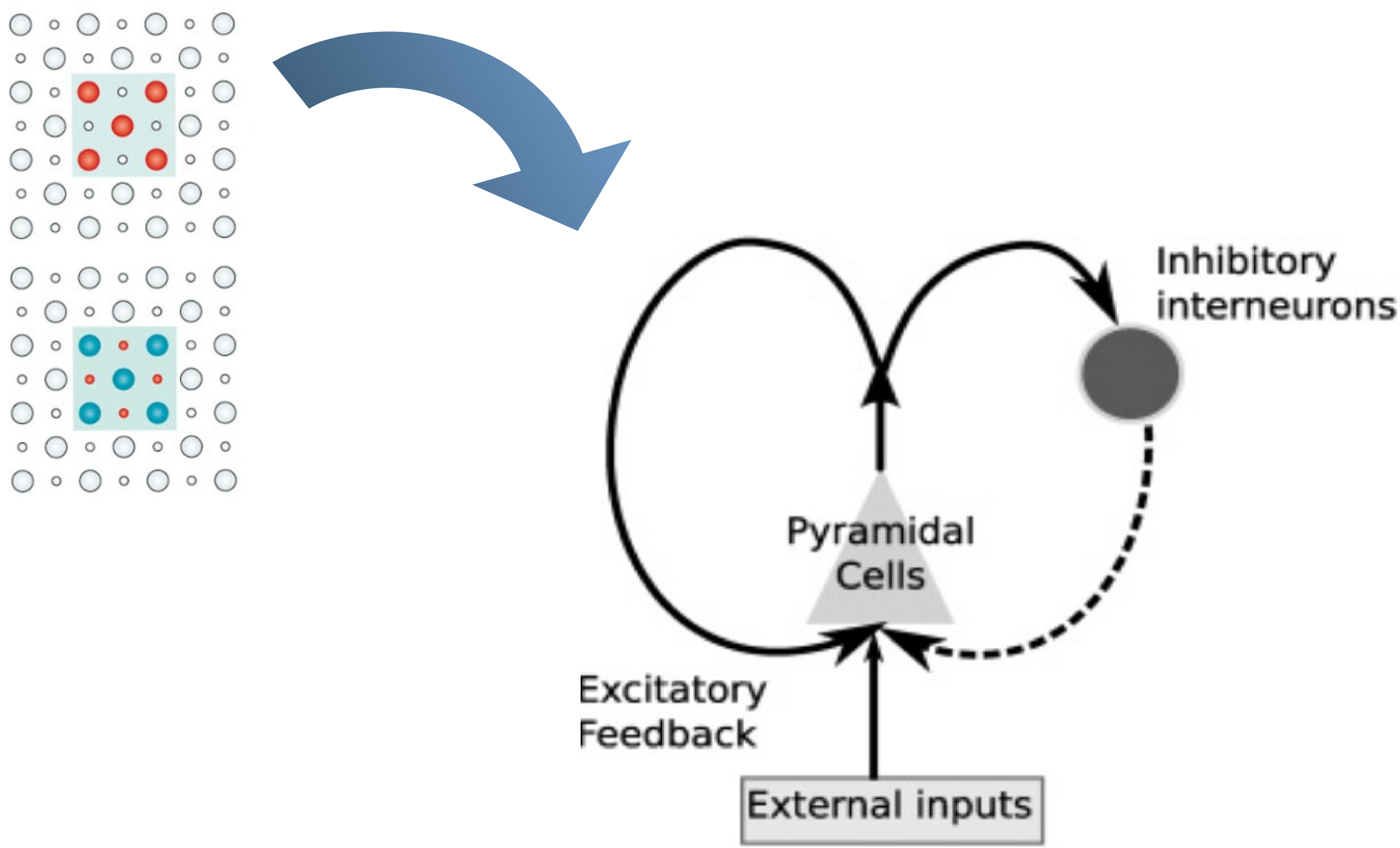
Holt, & Netoff 2013

Different types of models



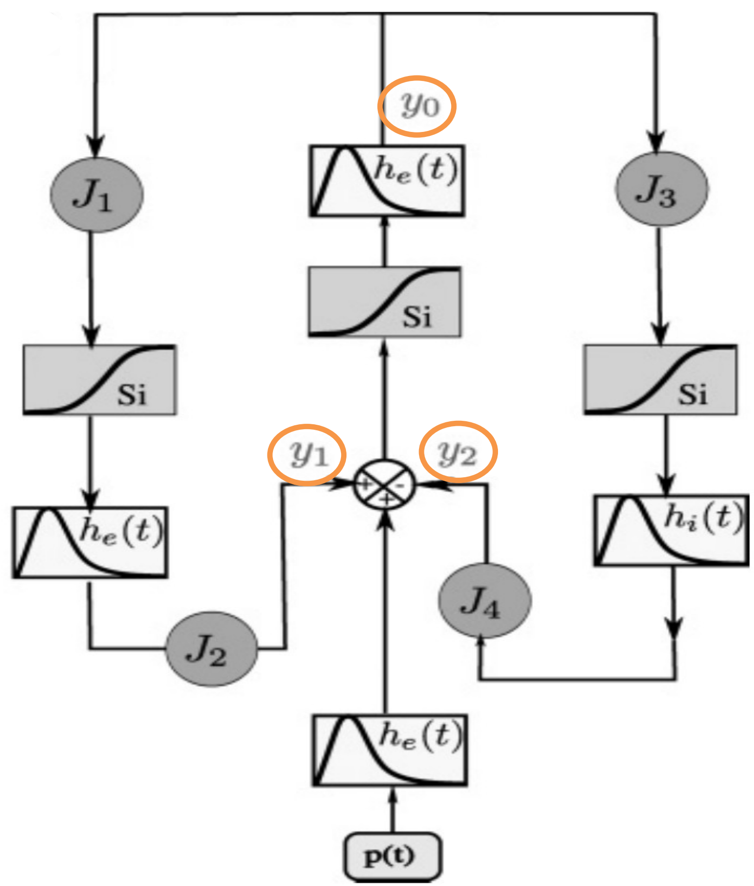
Jansen and Rit model

Realistic temporal dynamics such as those found in EEG



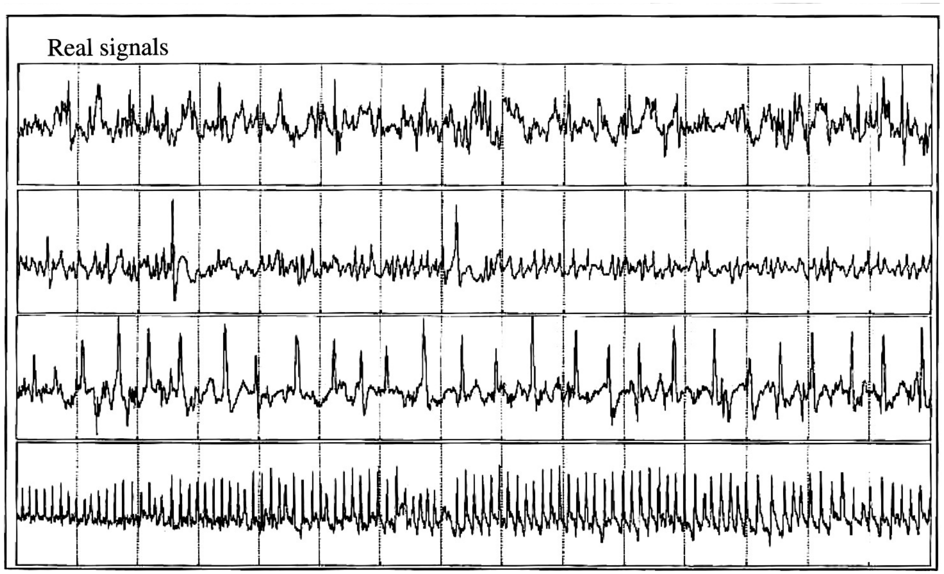
Jansen and Rit model

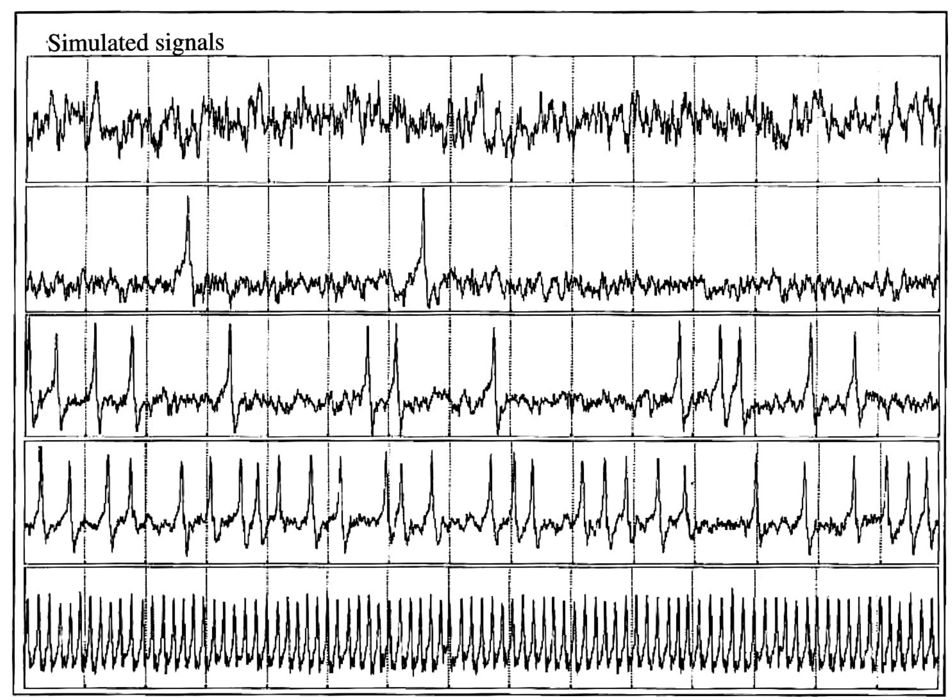
$$\begin{cases} \ddot{y}_0(t) = A\,a Si\left(y_1(t) - y_2(t)\right) - 2\,a\,\dot{y}_0(t) - a^2\,y_0(t) \\ \ddot{y}_1(t) = A\,a\left\{p(t) + J_2 Si\left(J_1 y_0(t)\right)\right\} - 2\,a\,\dot{y}_1(t) - a^2\,y_1(t)\,. \\ \ddot{y}_2(t) = B\,b\,J_4 Si\left(J_3 y_0(t)\right) - 2\,b\,\dot{y}_2(t) - b^2\,y_2(t) \end{cases}$$



Jansen and Rit model

Parameter	Interpretation
A	Average excitatory synaptic gain
B	Average inhibitory synaptic gain
$1/a$	Time constant of excitatory PSP
$1/b$	Time constant of inhibitory PSP
α_1, α_2	Average probability of synaptic contacts in the feedback excitatory loop
α_3, α_4	Average probability of synaptic contacts in the slow feedback inhibitory loop
J	Average number of synapses between populations
v_0	Parameters of the sigmoid (amplitude)
ν_{max}	(threshold)
r	(slope)





Jansen and Rit model

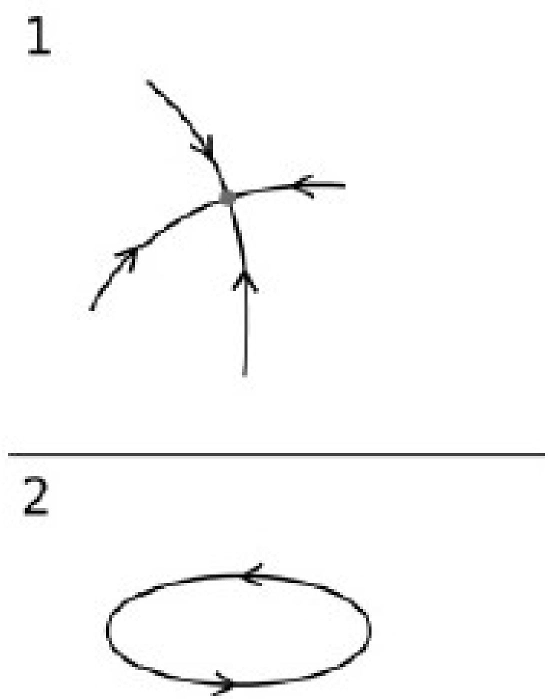
Relationship between bifurcations and excitability properties

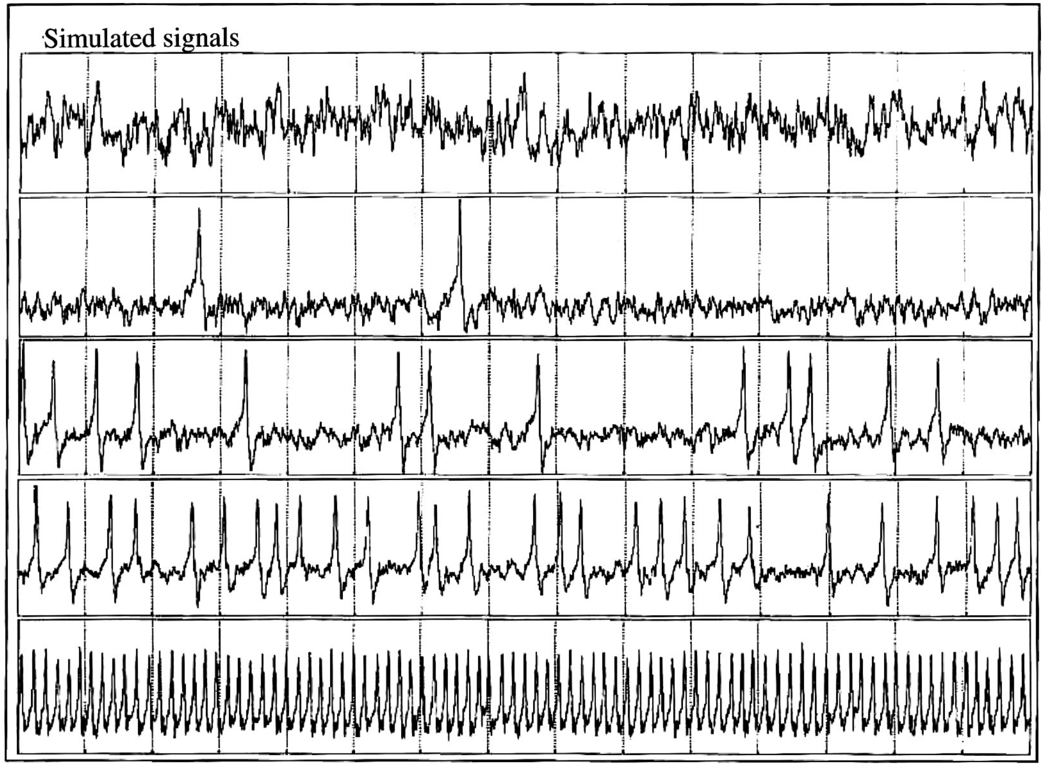
Table 3: EEG-Neural Mass Dictionary.

EEG	Neural Mass
Normal (background)	Stable fixed point
Oscillations	Limit cycle $\Leftarrow$ Hopf bifurcation
Bistable	Two stable fixed points/ limit cycles $\Leftarrow$ Cusp bifurcation
Low-frequency, large-amplitude oscillations (epilepsy?)	Saddle homoclinic $\Leftarrow$ Bogdanov-Taken bifurcation

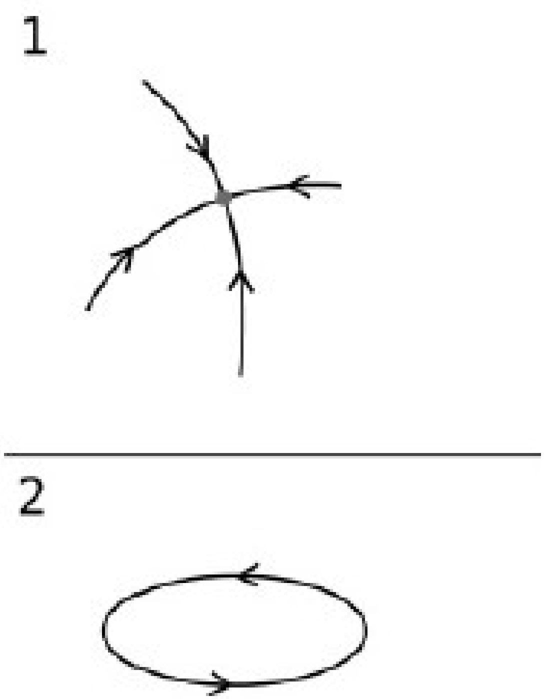
Note: EEG behavior in relation to dynamical systems properties and bifurcations generically related to such properties when relevant.

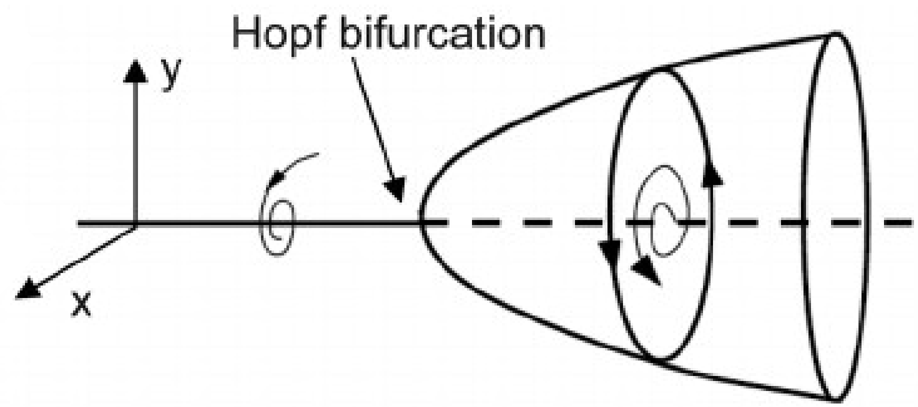
Attractors in the dynamical system

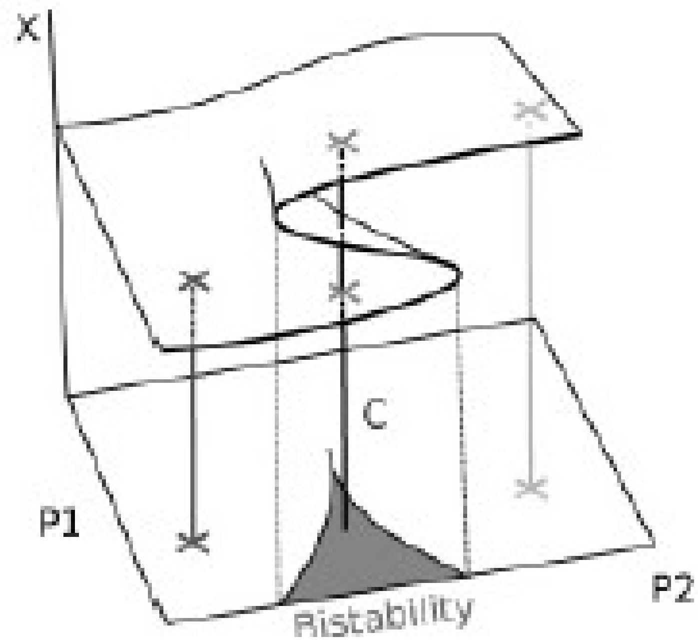




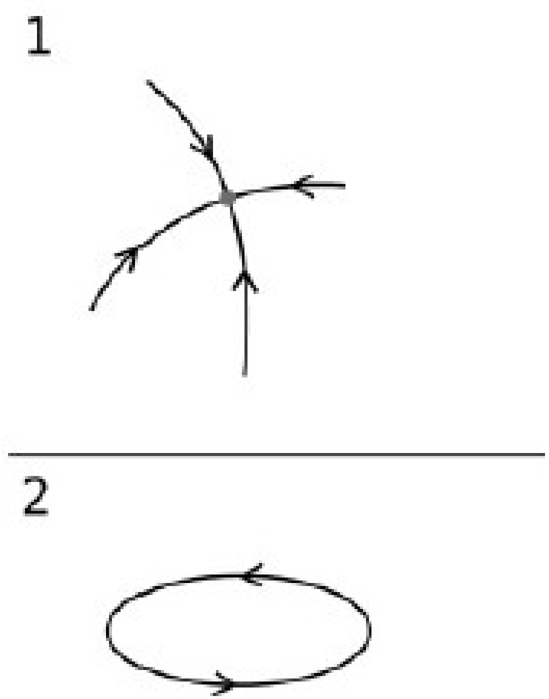
Transitions in the dynamical system

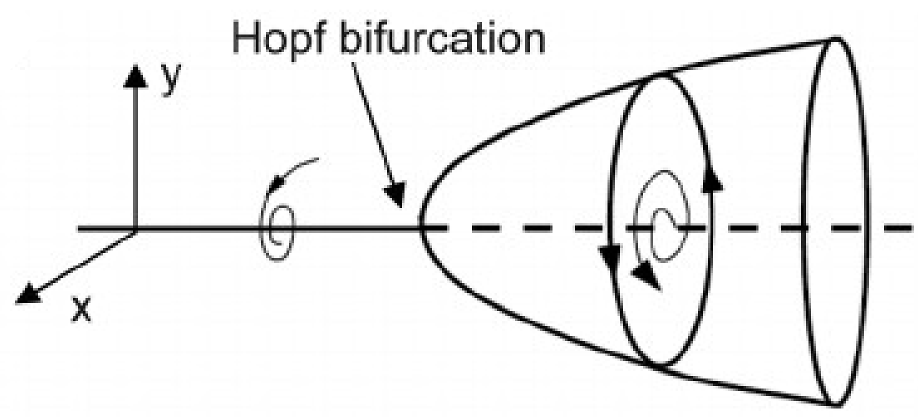


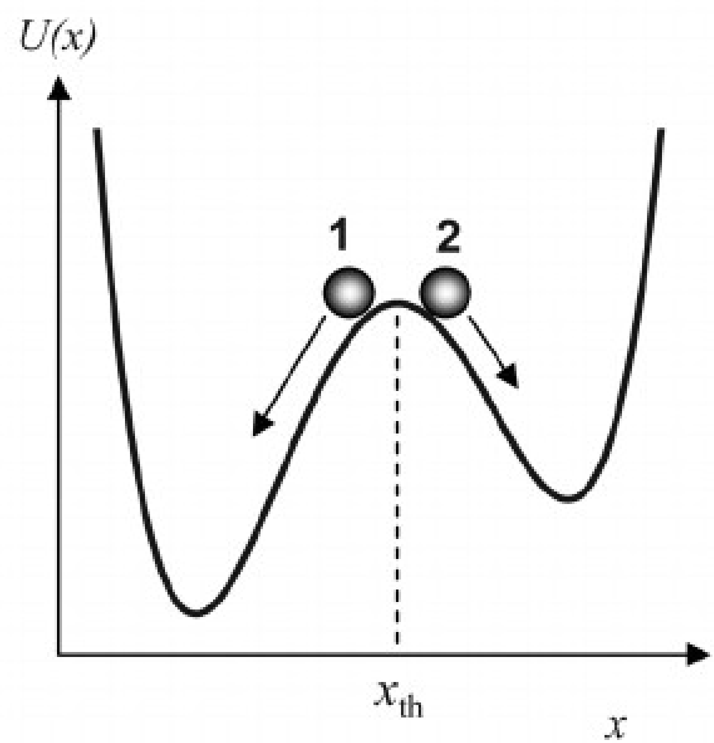




Transitions in the dynamical system

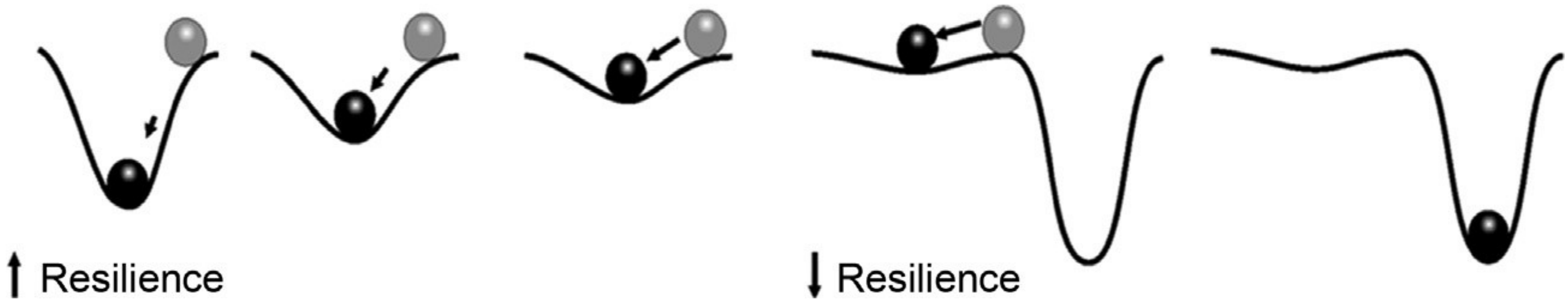






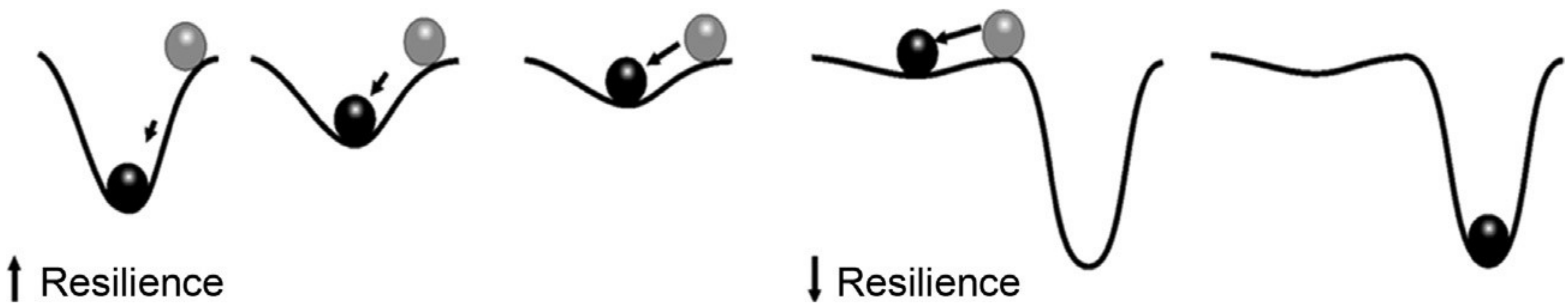
Attractors in the dynamical system

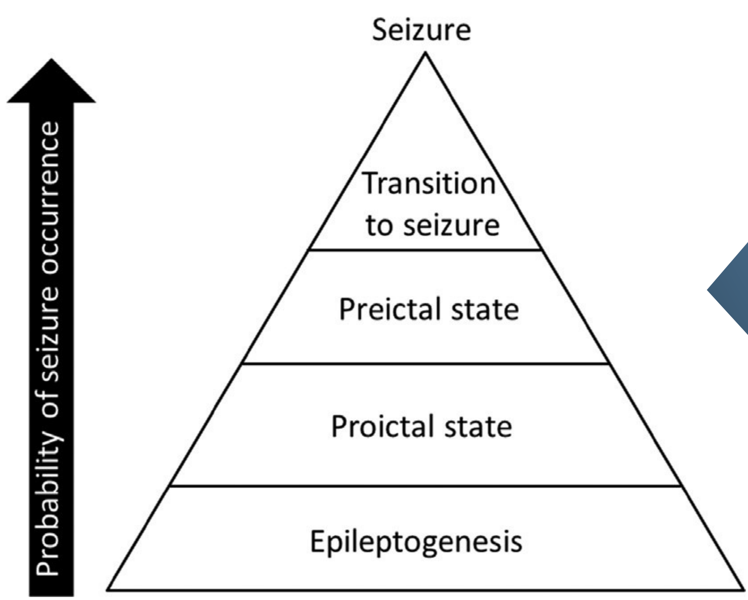
Relationship between bifurcations and excitability properties



Attractors in the dynamical system

Relationship between bifurcations and excitability properties





Summary

What is a model: variables and parameters, retro-/ prospective modeling

Different types of models: abstract/ realistic, micro- to macroscale

Jansen Rit model: lumped neural mass model with interacting pyramidal and interneuron populations, realistic replication of LFP/ EEG data

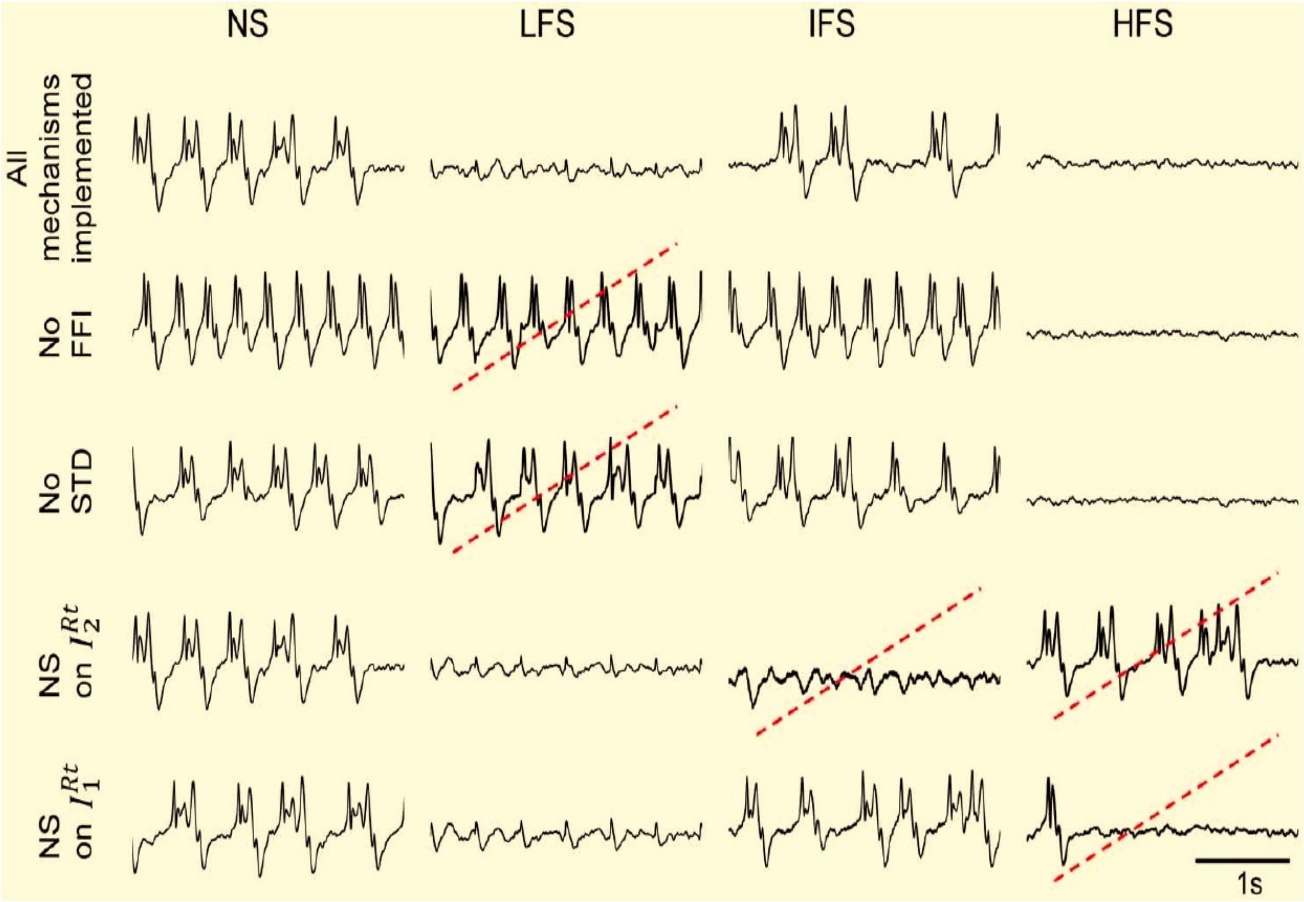
Dynamical systems: attractors, basins of attraction, bifurcations, relationship between bifurcations and excitability properties

Computational Modeling
in Epilepsy

Why model?

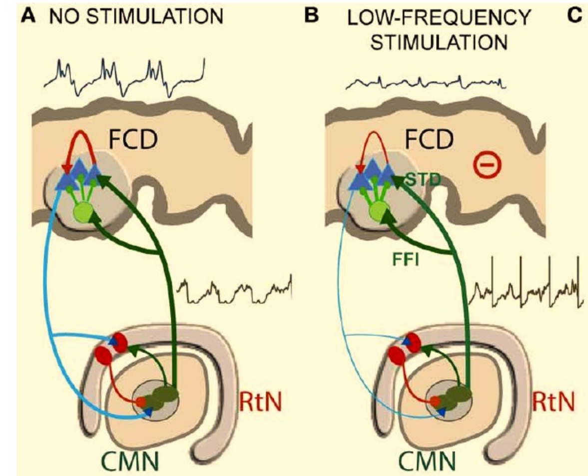
Mechanism study

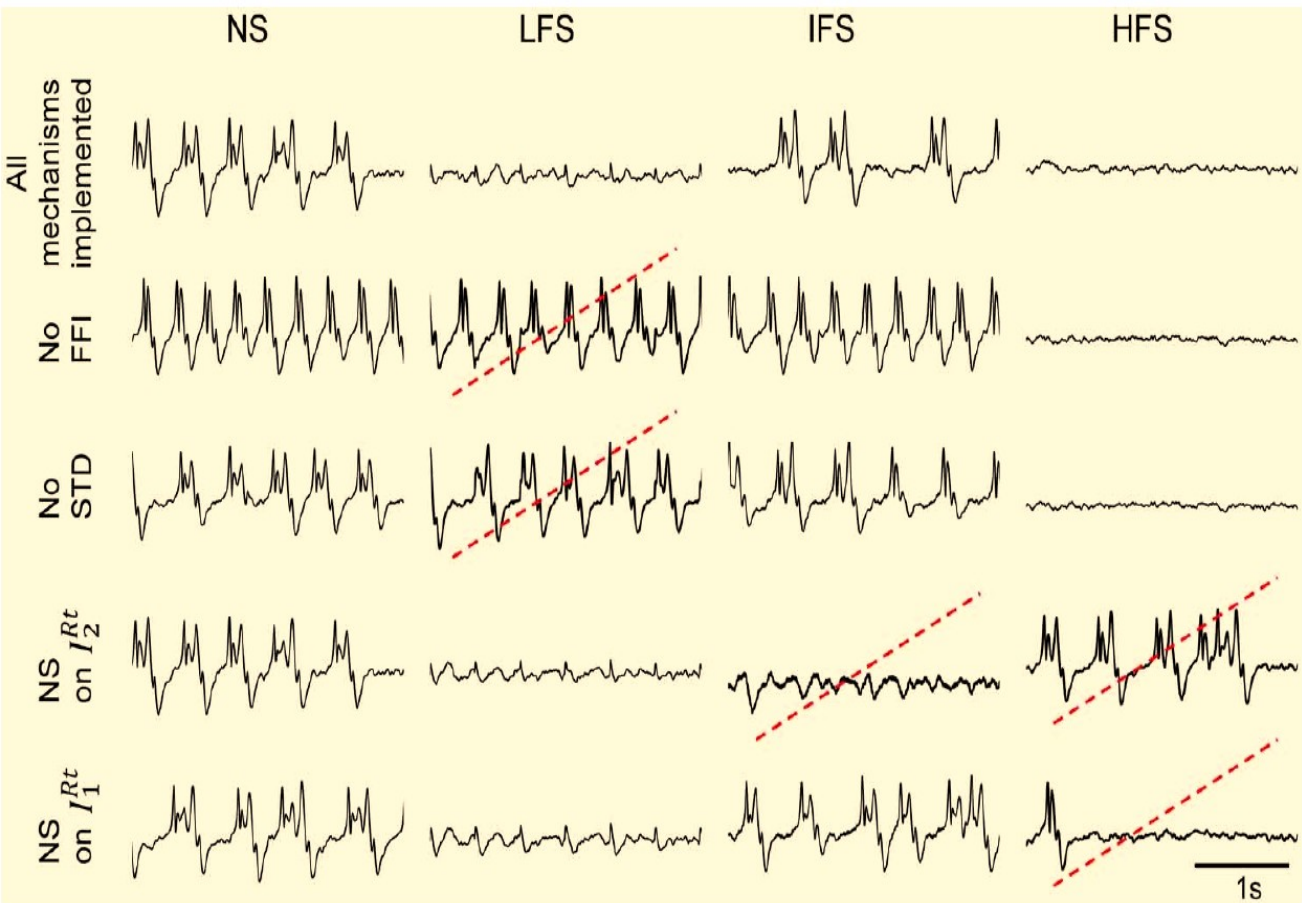
e.g. Mina et al., 2013



Mechanism study

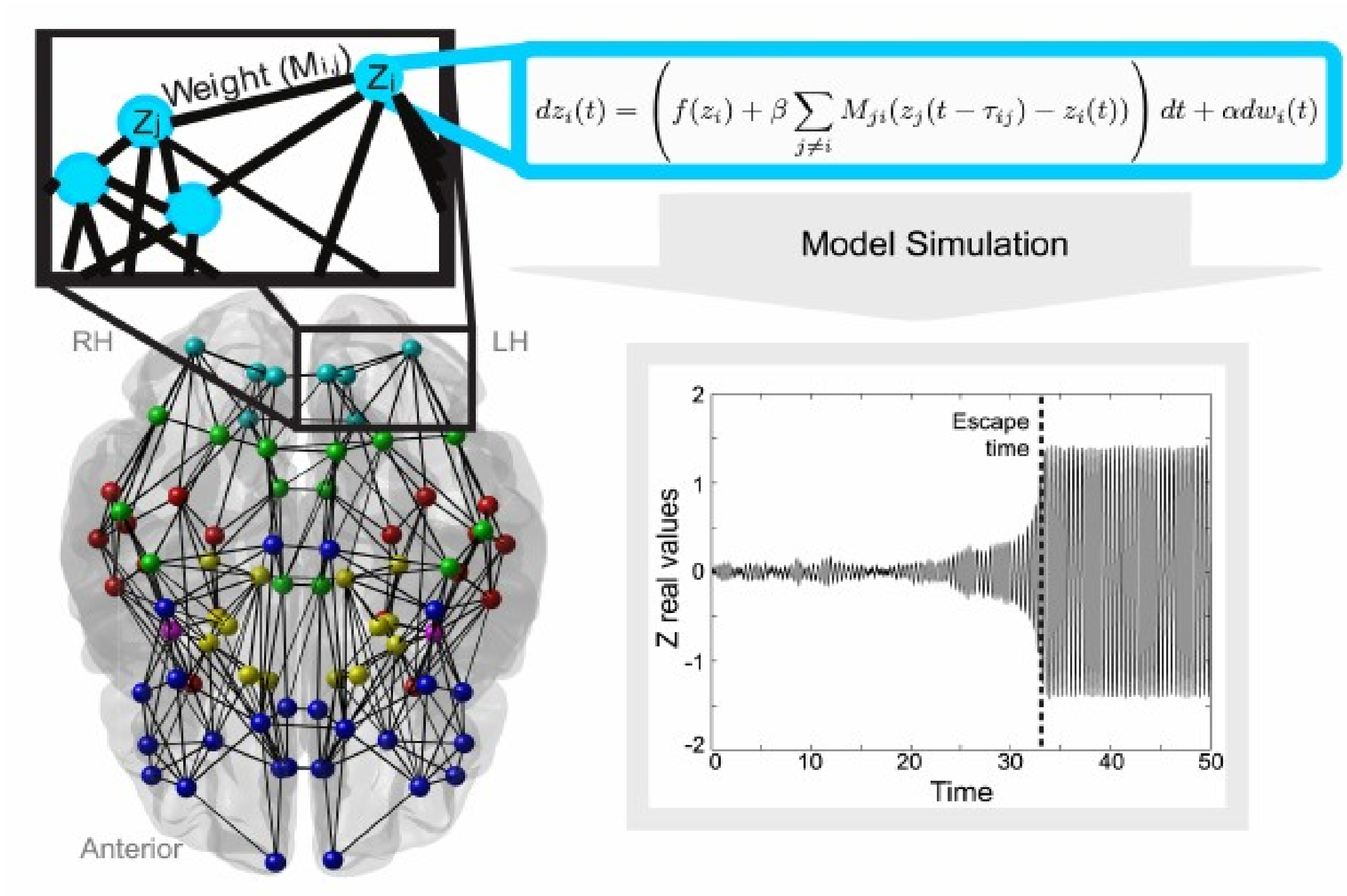
e.g. Mina et al., 2013





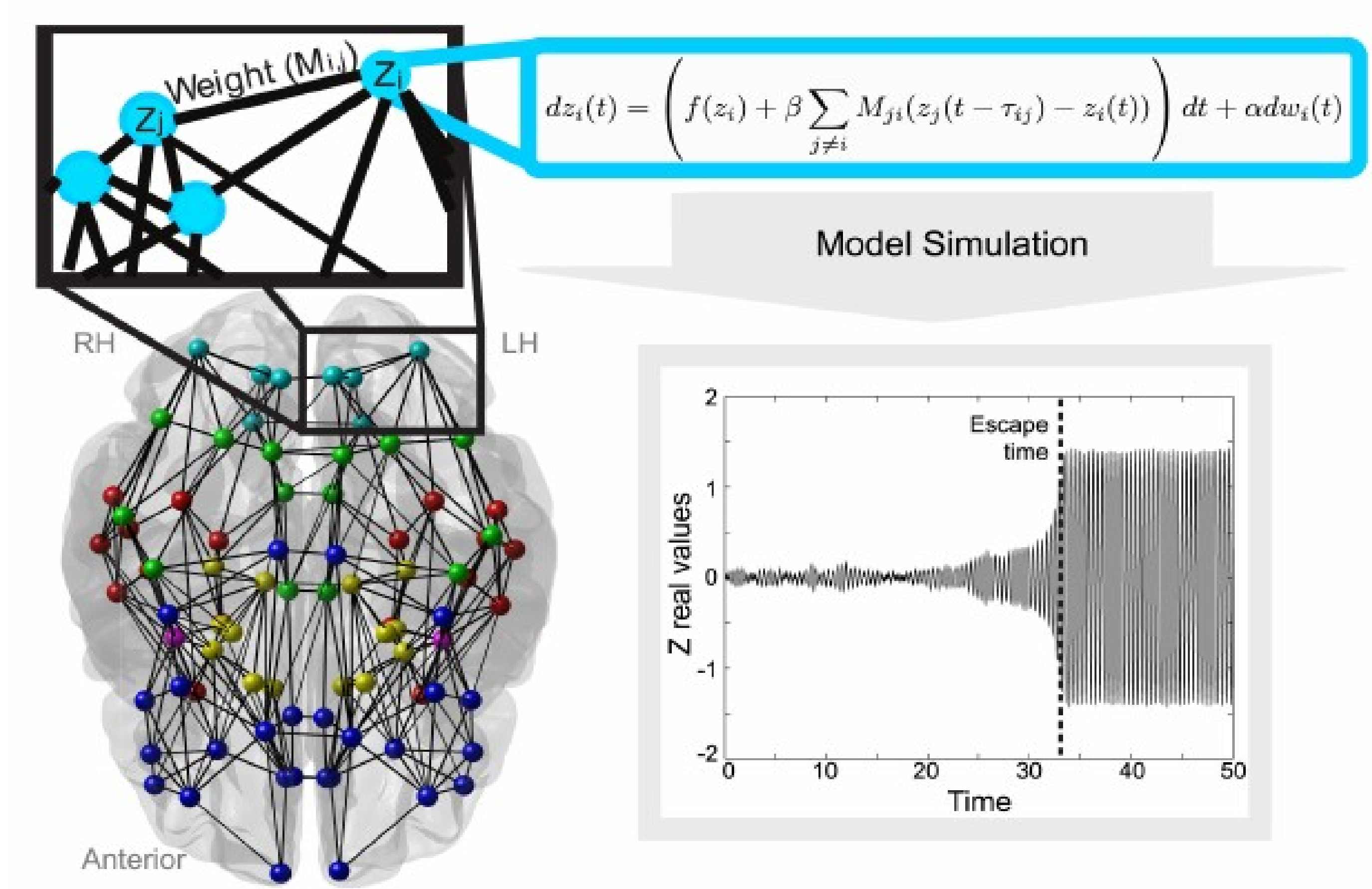
In silico testing

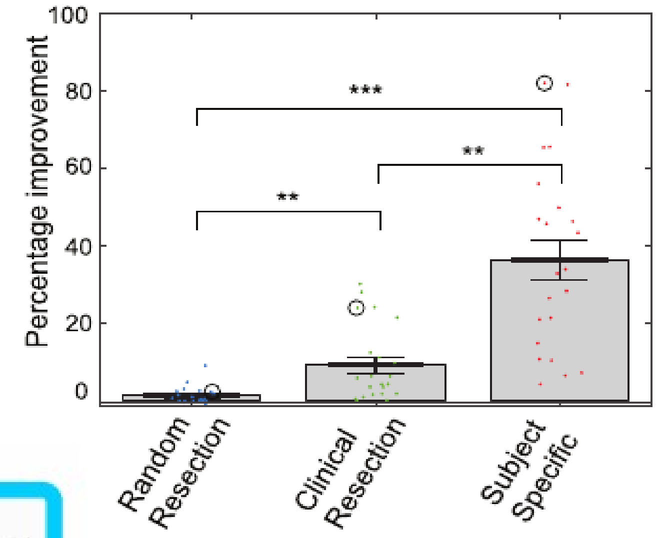
e.g. Hutchings et al., 2015



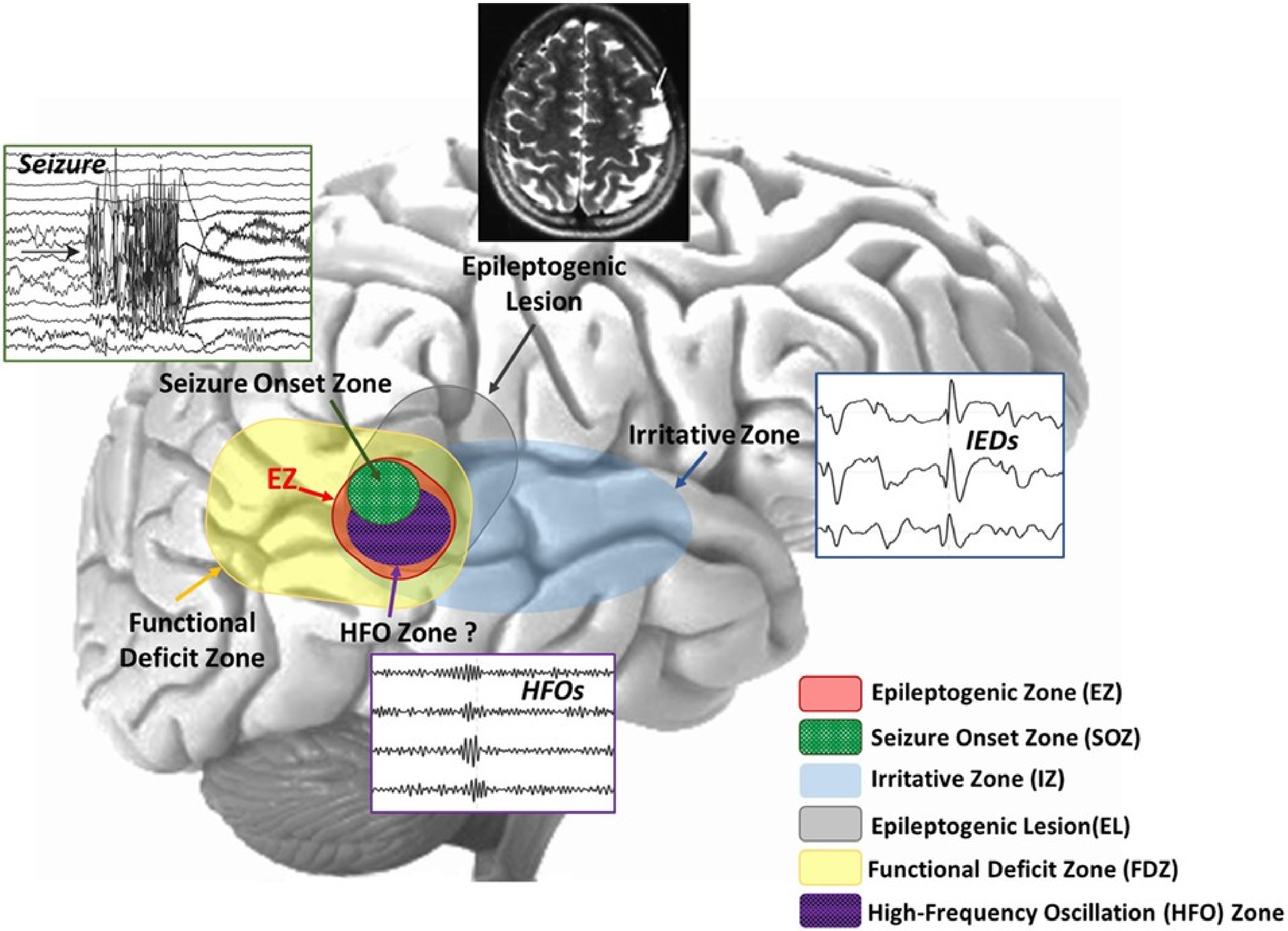
In silico testing

e.g. Hutchings et al., 2015

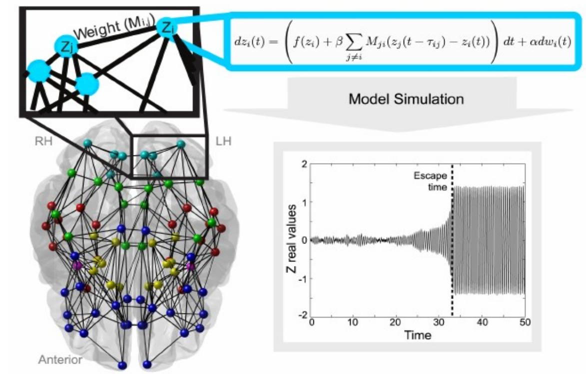


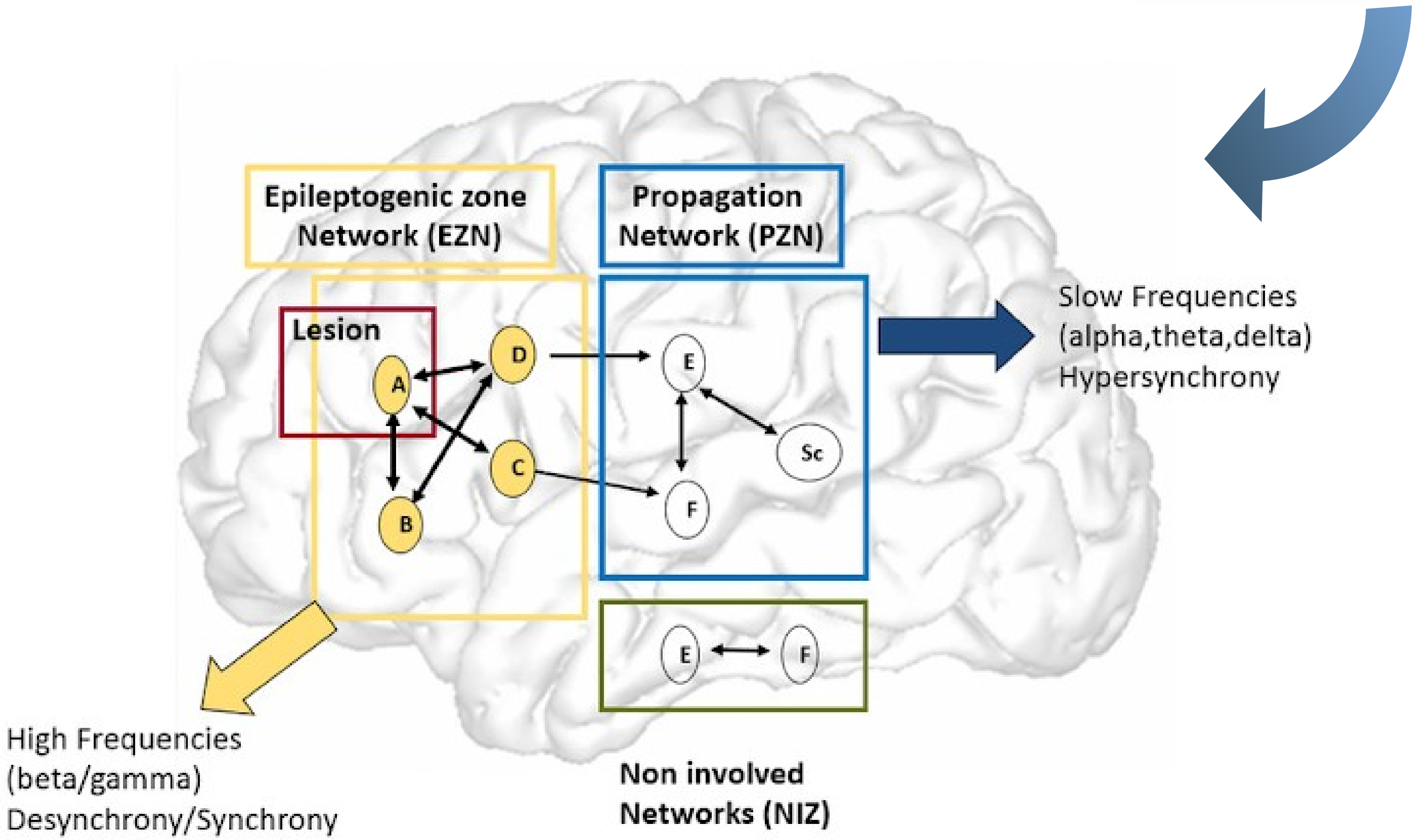


Network models for brain surgery



Network models for brain surgery





Advantages of brain network modeling

- ✔Identification of “epileptogenic zone” through resection testing
- ✔Patient-specific predictions of optimal/alternative resection zone
- ✔Feasibility, safety, no ethics restrictions, testing of unobservables
- ✔Insight into dynamical principles in the epileptic brain

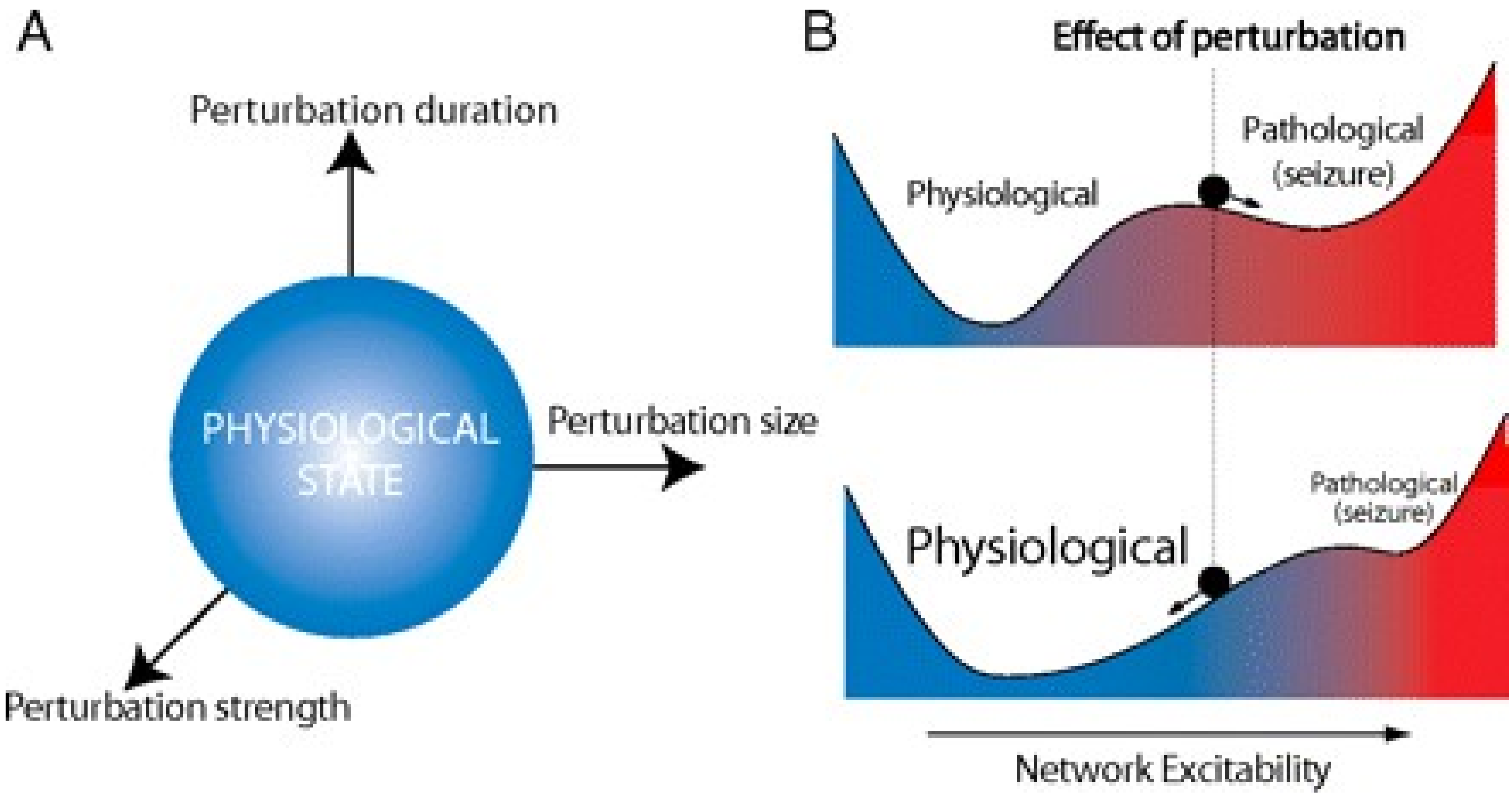
Advantages of brain network modeling

- ✔Identification of “epileptogenic zone” through resection testing
- ✔Patient-specific predictions of optimal/alternative resection zone
- ✔Feasibility, safety, no ethics restrictions, testing of unobservables
- ✔Insight into dynamical principles in the epileptic brain

Correctness of predictions depends on MODEL VALIDITY

Network models for brain stimulation

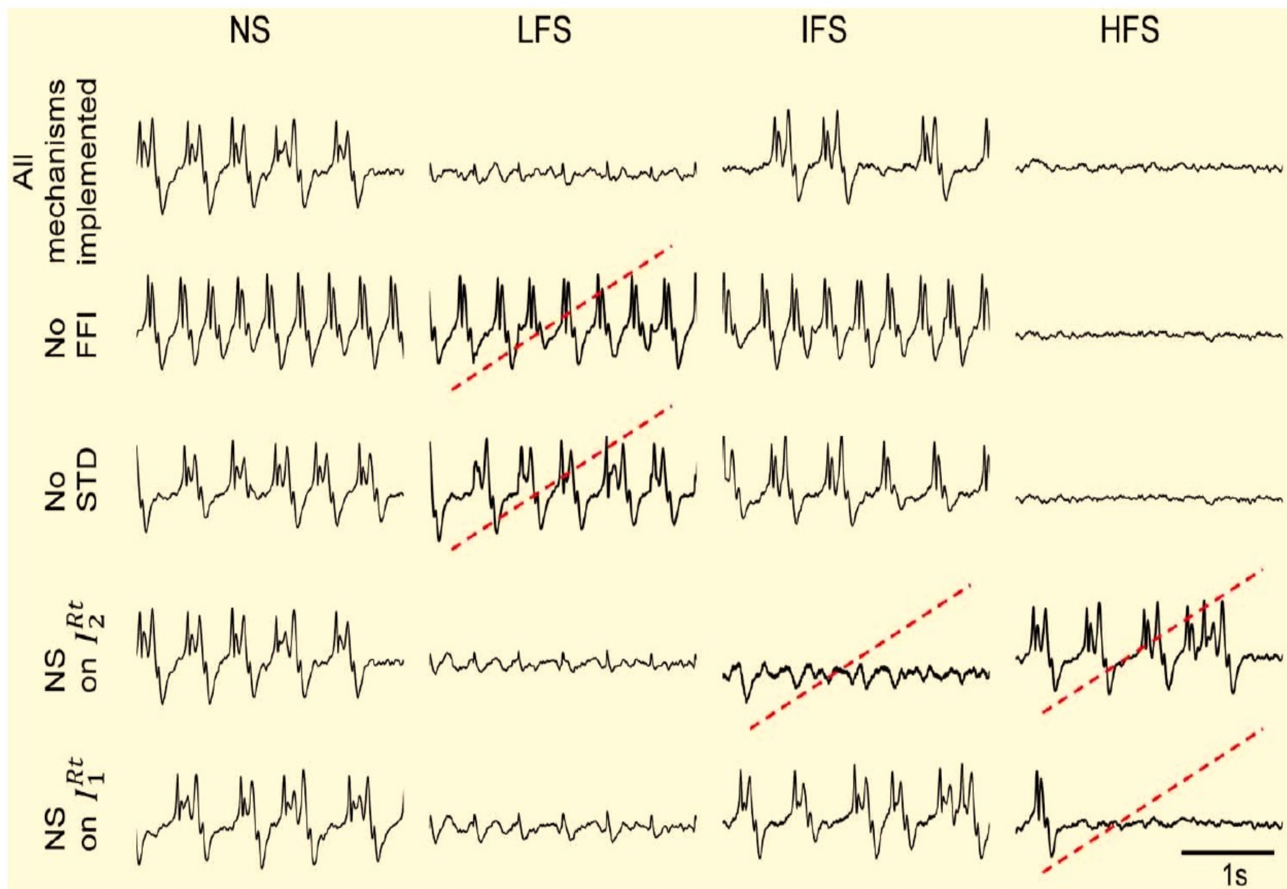
Stimulation timing – a crucial parameter in brain stimulation



Network models for brain stimulation

Stimulation timing – a crucial parameter in brain stimulation

model tuning to time series



Advantages of brain network modeling

✔Mechanism insight

✔Rational stimulation parameter choice

✔Feasibility, safety, no ethics restrictions, testing of unobservables

✔Insight into dynamical principles in the epileptic brain

Correctness of predictions depends on MODEL VALIDITY

Summary

Why model: mechanism study (biomarkers, new treatment targets, ...), in silico testing (safe, efficient, unrestricted by ethics and feasibility, ...)

Network models for brain surgery: virtual resection for epileptogenic zone identification, patient-specific predictions of optimal/alternative resection sites

Network models for brain surgery: timing as a critical, additional parameter in brain stimulation, model tuning to individual patient time series

Current State of the Art and Future Outlook

Network models for brain surgery

10 studies, 111 patients, different types of epilepsy, structural/functional connectivity data, model information + prediction validation

- ✔**New diagnostic markers**
- ✔**successful prediction of individual surgery outcome**
- ✔**in silico replication of the established EZ resection**
- ✔**improvement to conventional diagnosis procedures and surgical approaches**: especially reduction of invasivenes
- ✔**first clinical trials ongoing**

Network models for brain stimulation

7 studies, 38 patients, different types of epilepsy, structural/functional connectivity and time series data, model information + validation, diverse objectives and methods

- ✔ **in silico optimization of stimulation parameters**: mainly optimal frequency of stimulation, and closed-loop stimulation
- ✔ **study of stimulation induced brain mechanisms**: especially for frequency (low intermediate, high), random noise and timing
- ✔ **next step: comparison of blinded model predicted stimulation efficiency against actual stimulation efficiency**

Summary

review: pubmed, <August 2020, human neuroimaging

Achievements	Future Directions
✔ New markers for epilepsy	✚ Clinical trials
✔ Successful prediction	✚ Retrospective vs. (quasi-) prospective
✔ Potential improvement	✚ "Virtual brain pharmacology"
✔ Personalization	✚ Potential for stimulation → *in silico* testing
✔ Mechanism insight	

The Human Brain Project

https://www.youtube.com/watch?v=JqMpGrM5ECo

Sources & Thank you

brainsurgery-6aa3.kxcdn.com/wp-content/uploads/2012/05/brain-surgery-300x240.jpg | www.epilepsysociety.org.uk/sites/default/files/deep-brain-stimulation.jpg | www.epilepsysociety.org.uk/sites/default/files/vns-forweb_0.jpg | c3.thejournal.ie/media/2017/09/epilepsy-drug-2-390x285.jpg | https://www.doctorshealthpress.com/wp-content/uploads/2017/02/Lecompte_Focal-Seizure_020117.jpg | https://sa1s3optim.patientpop.com/assets/images/provider/photos/1781941.png

Blauwblomme, T., Jiruska, P., & Huberfeld, G. (2014). Mechanisms of Ictogenesis. In International Review of Neurobiology (Vol. 114, pp. 155–185). Elsevier.

Devinsky, O., Vezzani, A., O'Brien, T. J., Jette, N., Scheffer, I. E., de Curtis, M., & Perucca, P. (2018). Epilepsy. Nature Reviews Disease Primers, 4(1), 18024.

Grimbert, F.; Faugeras, O. (2006). Bifurcation Analysis of Jansen's Neural Mass Model. Neural Computation, 18(12), 3052–3068.

Touboul, J., Wendling, F., Chauvel, P., & Faugeras, O. (2011). Neural Mass Activity, Bifurcations, and Epilepsy. Neural Computation, 23(12), 3232–3286.

Qu, Z., Xie, L.-H., Olcese, R., Karagueuzian, H. S., Chen, P.-S., Garfinkel, A., & Weiss, J. N. (2013). Early afterdepolarizations in cardiac myocytes: Beyond reduced repolarization reserve. Cardiovascular Research, 99(1), 6–15.

Hutchings, F., Han, C. E., Keller, S. S., Weber, B., Taylor, P. N., & Kaiser, M. (2015). Predicting Surgery Targets in Temporal Lobe Epilepsy through Structural Connectome Based Simulations. *PLOS Computational Biology*, *11*(12), e1004642.

Mina, F., Benquet, P., Pasnicu, A., Biraben, A., & Wendling, F. (2013). Modulation of epileptic activity by deep brain stimulation: a model-based study of frequency-dependent effects. Frontiers in Computational Neuroscience, 7.

Tamilia, E., Madsen, J. R., Grant, P. E., Pearl, P. L., & Papadelis, C. (2017). Current and Emerging Potential of Magnetoencephalography in the Detection and Localization of High-Frequency Oscillations in Epilepsy. Frontiers in Neurology, 8.

Bartolomei, F., Lagarde, S., Wendling, F., McGonigal, A., Jirsa, V., Guye, M., & Bénar, C. (2017). Defining epileptogenic networks: Contribution of SEEG and signal analysis. Epilepsia, 58(7), 1131–1147.

Frohlich, F., Sejnowski, T. J., & Bazhenov, M. (2010). Network Bistability Mediates Spontaneous Transitions between Normal and Pathological Brain States. Journal of Neuroscience, 30(32), 10734–10743.

Thank you for your attention!

dallmer-zerbe@cs.cas.cz

INSTITUTE OF COMPUTER SCIENCE
The Czech Academy of Sciences

INSTITUTE OF PHYSIOLOGY CAS

2. LF UK