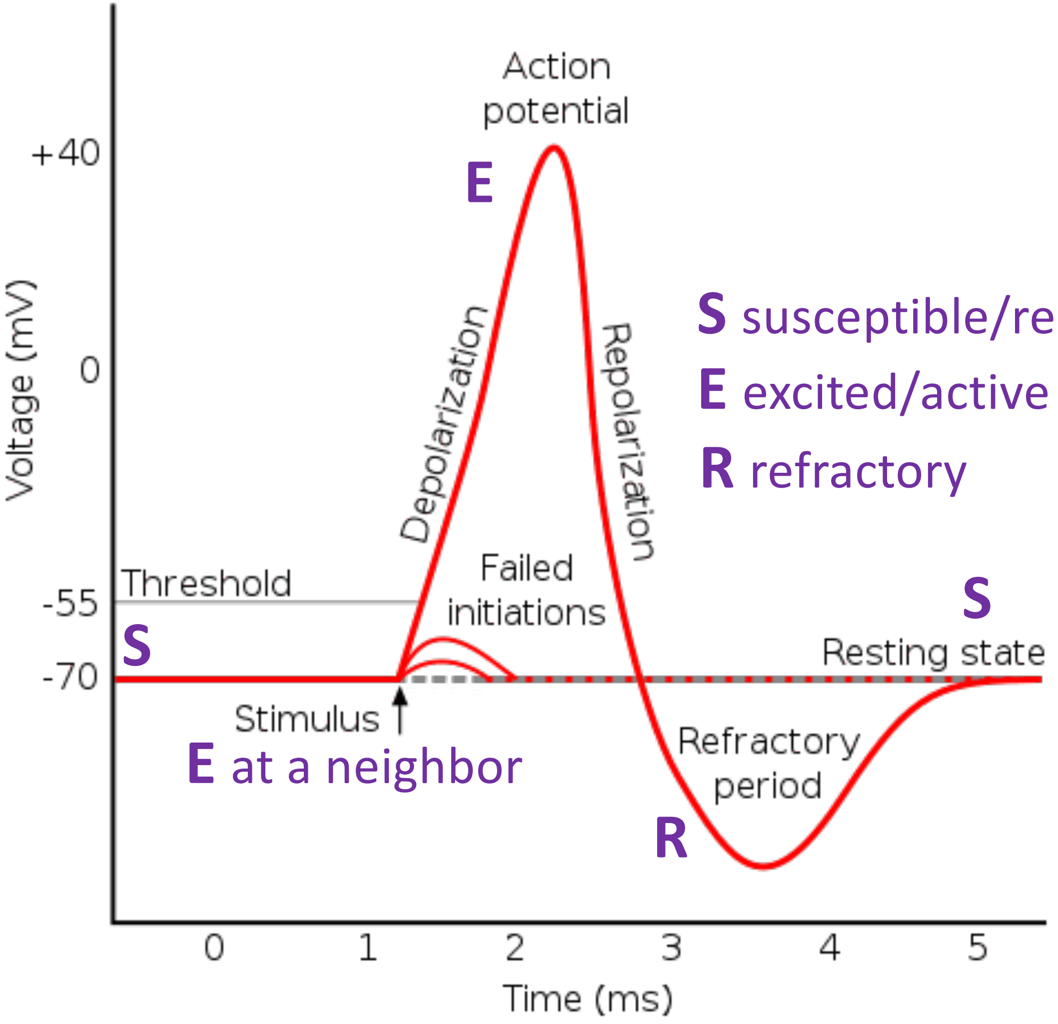
Simple models and complex networks

Marc-Thorsten Hütt
Constructor University
Bremen/Germany

Computational
Systems Biology



S susceptible/resting
E excited/active
R refractory

Action potential of a neuron (taken from *teachmephysiology.com*)

typical mathematical model

- two coupled differential equations
- continuous time, continuous states
- 5 to 7 parameters

radically simplified model

- discrete time, discrete states
- 0 to 2 parameters

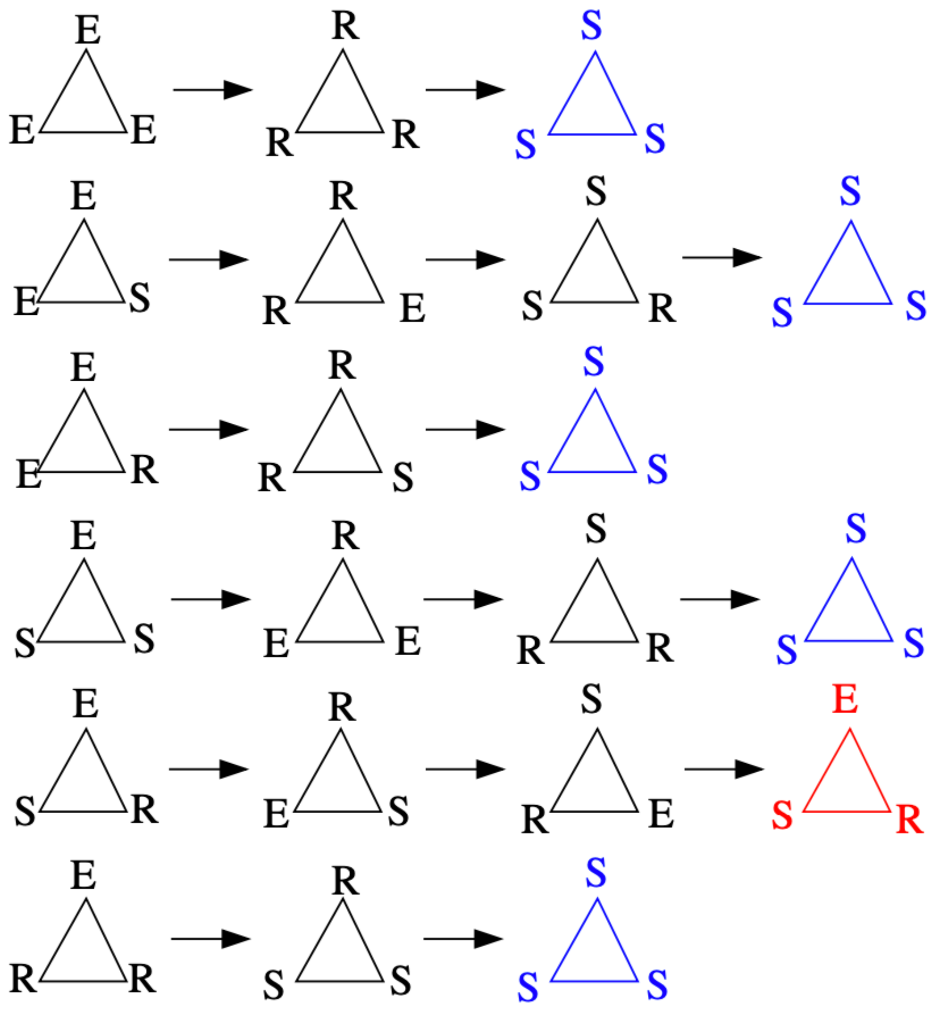
$$E \longrightarrow R$$

$$S \xrightarrow{\exists E \text{ in } NB} E$$

$$R \longrightarrow S$$

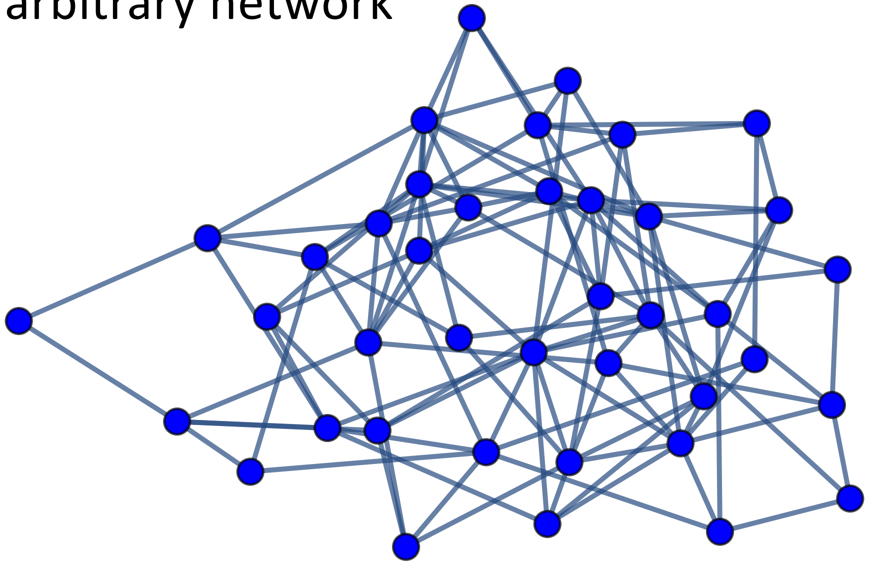
(deterministic, zero parameter)
SER model

triangle, simplest SER model



Garcia, Lesne, Hütt, Hilgetag (2012)
Frontiers in Computational Neuroscience 6, 50.

arbitrary network



more complicated excitation patterns

collective excitation patterns

Which functional connectivies are possible on a given structural connectivity?

network architecture

▶ Structure of the talk

'Complex networks'

'Simple models'

Example 1: Self-organized excitation waves in networks
joint work with Claus Hilgetag (Hamburg), Paolo Moretti (Nürnberg), joint work with Annick Lesne

Example 2: Networks as structural models
to interpret high-throughput data in
Biology and Medicine
joint work with Annick Lesne

Example 3: The digital-analog duality in biology: how network and non-network
mechanisms jointly shape biological data and hence systemic function
joint work with Annick Lesne

Brief remark 1: 'The bigger picture'

Brief remark 2: Some next steps

Intro 1: Complex networks

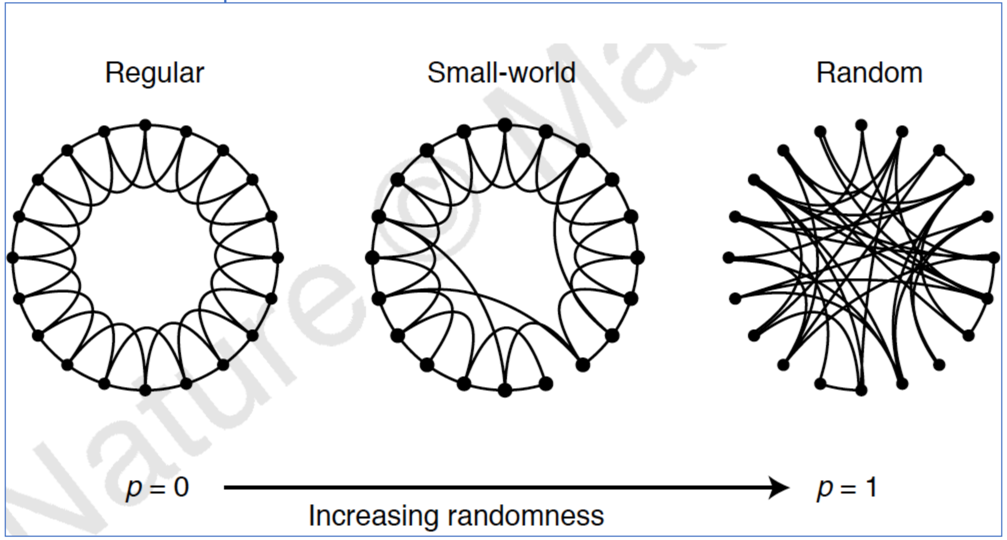
Complex networks

Collective dynamics of ‘small-world’ networks

Duncan J. Watts* & Steven H. Strogatz

NATURE | VOL 393 | 4 JUNE 1998

> 55.000 google scholar citations

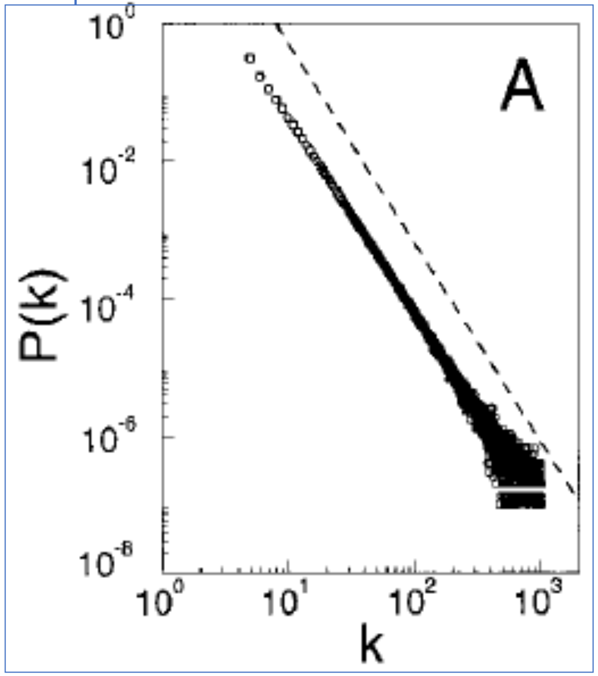


Emergence of Scaling in Random Networks

Albert-László Barabási* and Réka Albert

SCIENCE VOL 286 15 OCTOBER 1999

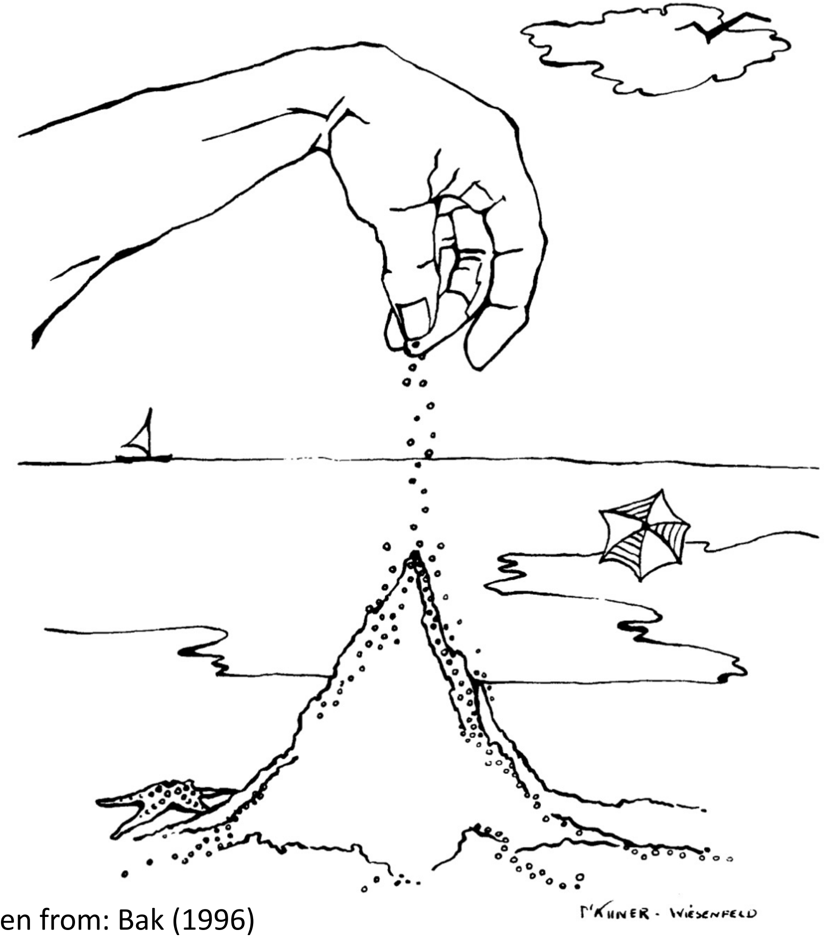
>47.000 google scholar citations



Intro 2: Simple models or 'Toy models'

Simple models

The BTW sandpile model

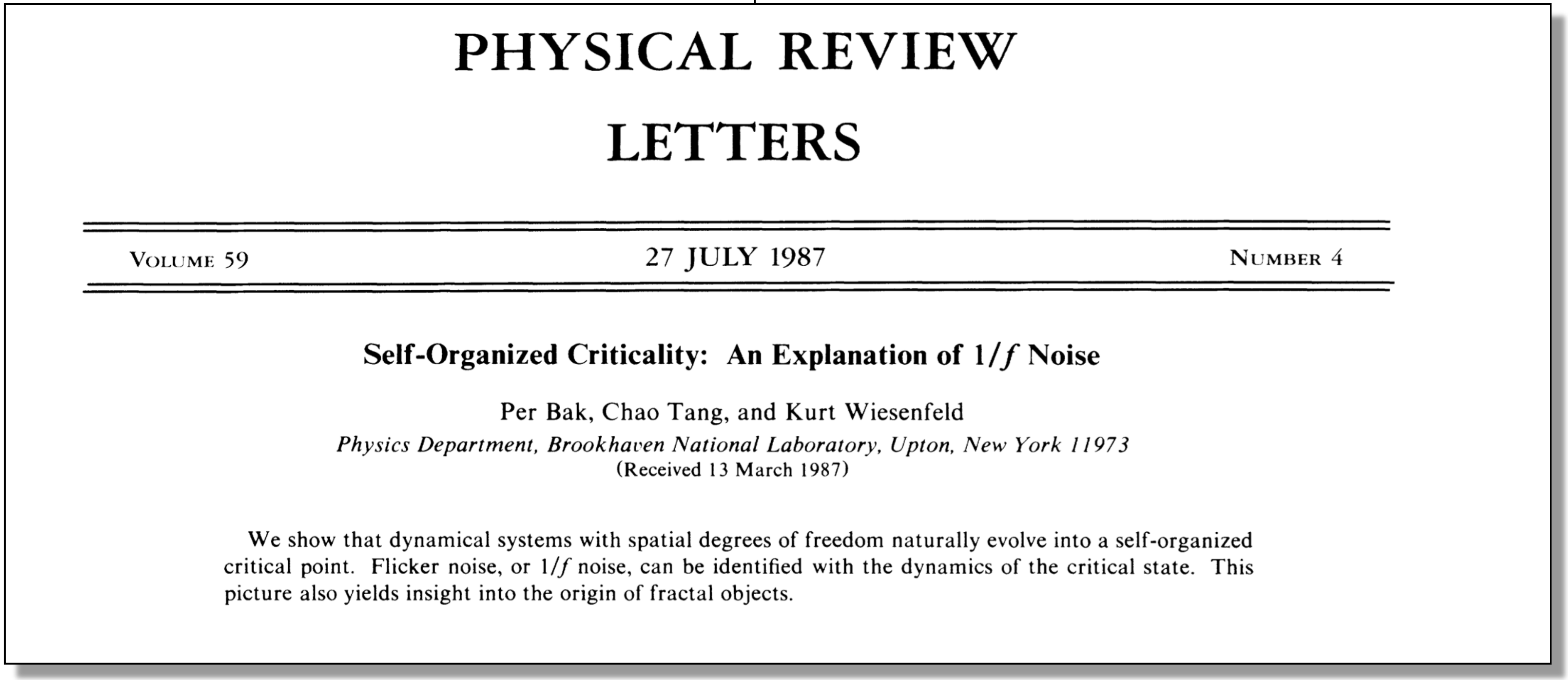


Taken from: Bak (1996)

Simple models

The BTW sandpile model

→ Self-organized criticality



PHYSICAL REVIEW
LETTERS

VOLUME 59 27 JULY 1987 NUMBER 4

Self-Organized Criticality: An Explanation of $1/f$ Noise

Per Bak, Chao Tang, and Kurt Wiesenfeld
Physics Department, Brookhaven National Laboratory, Upton, New York 11973

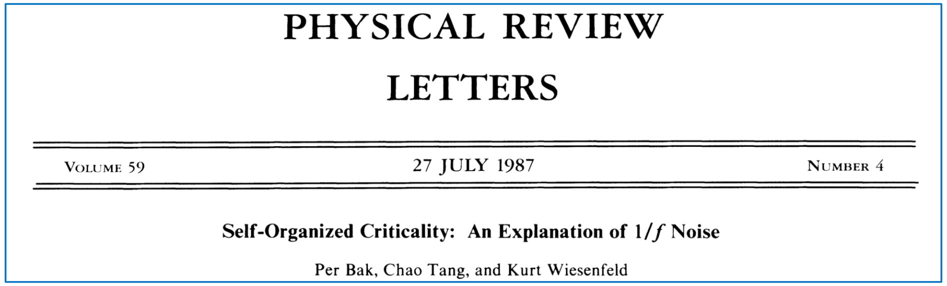
(Received 13 March 1987)

We show that dynamical systems with spatial degrees of freedom naturally evolve into a self-organized critical point. Flicker noise, or $1/f$ noise, can be identified with the dynamics of the critical state. This picture also yields insight into the origin of fractal objects.

Simple models

The BTW sandpile model

→ Self-organized criticality



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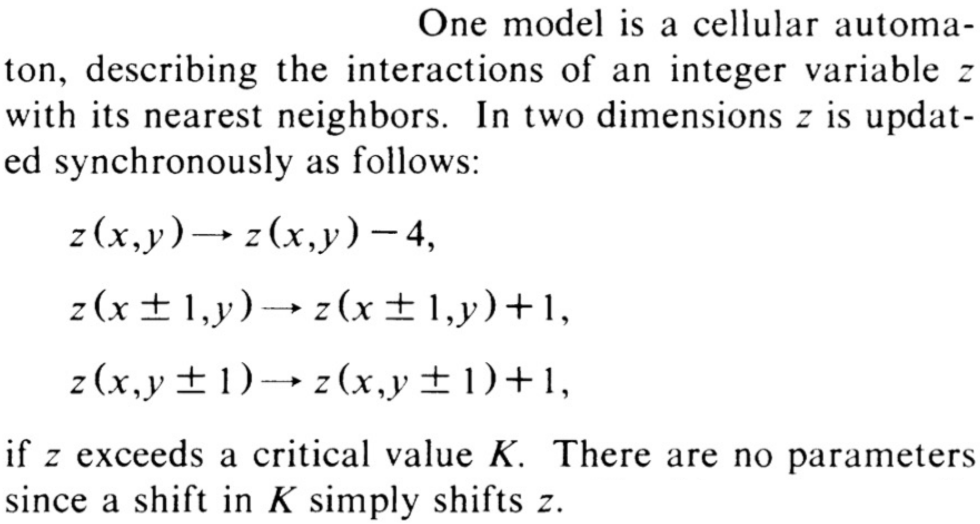


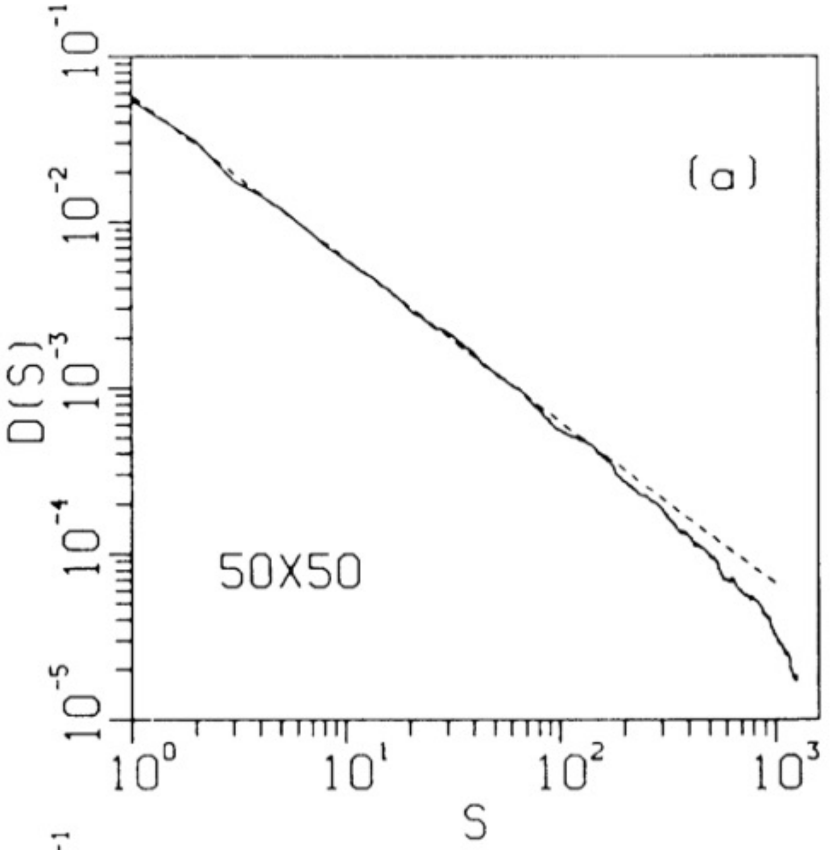
One model is a cellular automaton, describing the interactions of an integer variable z with its nearest neighbors. In two dimensions z is updated synchronously as follows:

$$z(x,y) \to z(x,y) - 4,$$

$$z(x \pm 1,y) \to z(x \pm 1,y) + 1,$$

$$z(x,y \pm 1) \to z(x,y \pm 1) + 1,$$

if z exceeds a critical value K. There are no parameters since a shift in K simply shifts z.

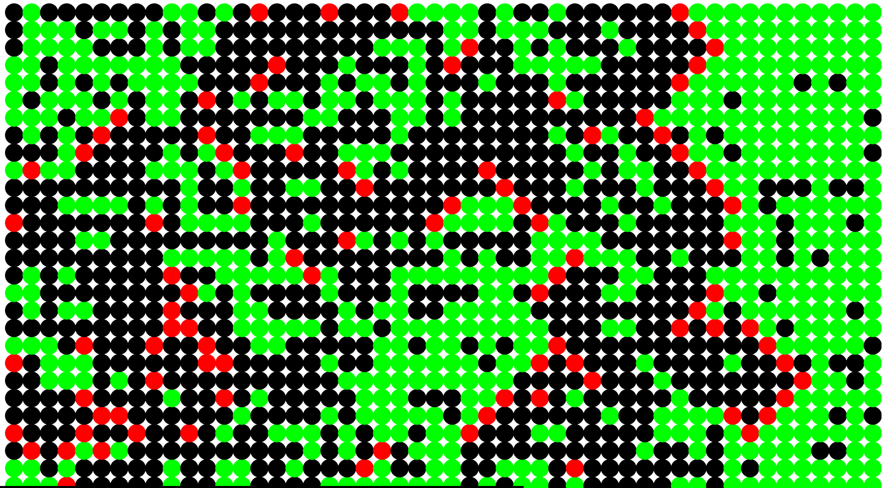


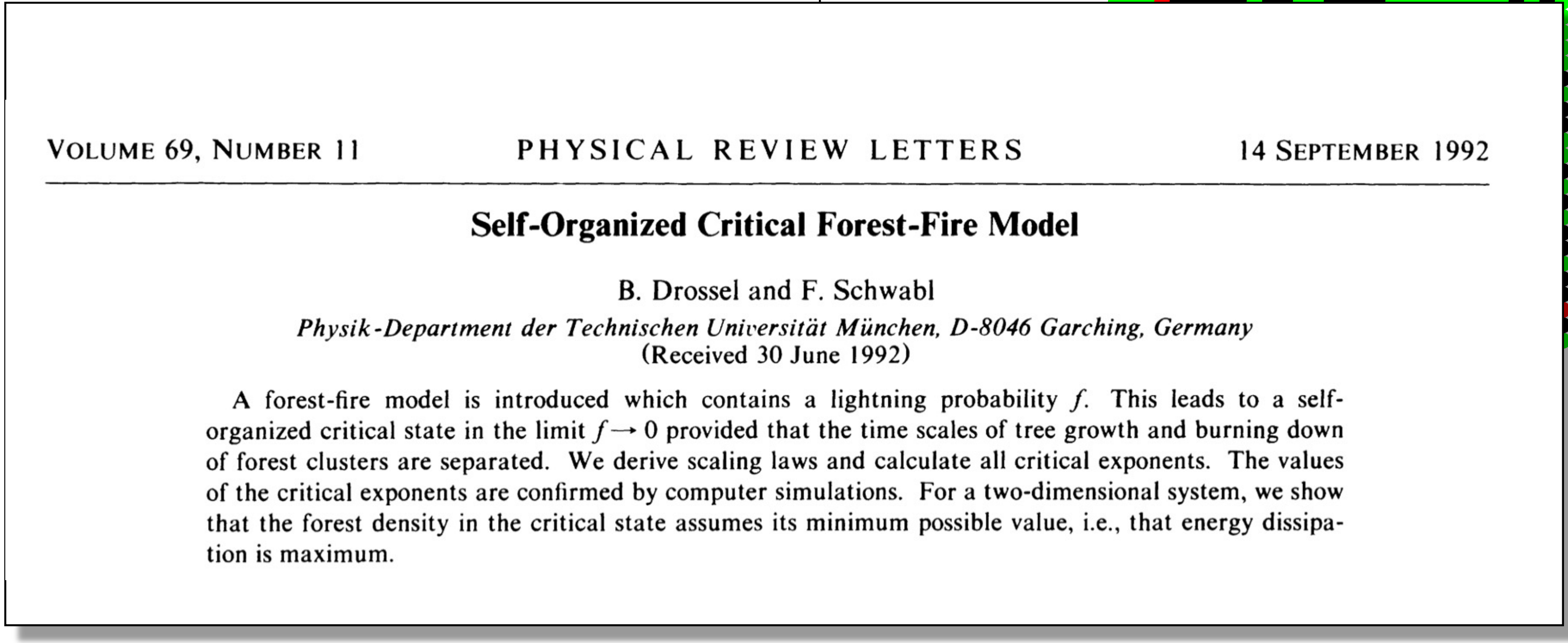
A first example

The BTW sandpile model

→ Self-organized criticality

→ Forest fire model





VOLUME 69, NUMBER 11 PHYSICAL REVIEW LETTERS 14 SEPTEMBER 1992

Self-Organized Critical Forest-Fire Model

B. Drossel and F. Schwabl
Physik-Department der Technischen Universität München, D-8046 Garching, Germany

(Received 30 June 1992)

A forest-fire model is introduced which contains a lightning probability f. This leads to a self-organized critical state in the limit $f \to 0$ provided that the time scales of tree growth and burning down of forest clusters are separated. We derive scaling laws and calculate all critical exponents. The values of the critical exponents are confirmed by computer simulations. For a two-dimensional system, we show that the forest density in the critical state assumes its minimum possible value, i.e., that energy dissipation is maximum.

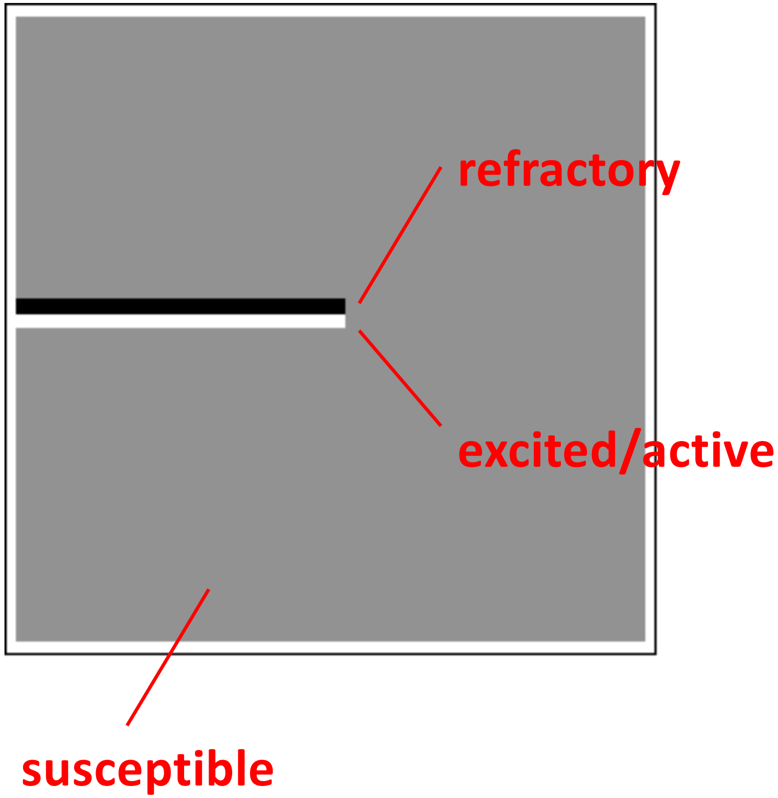
Digression: Spiral waves

$$E \longrightarrow R$$

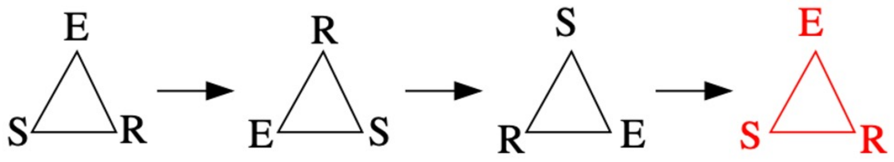
$$S \xrightarrow{\exists E \text{ in } NB} E$$

$$R \longrightarrow S$$

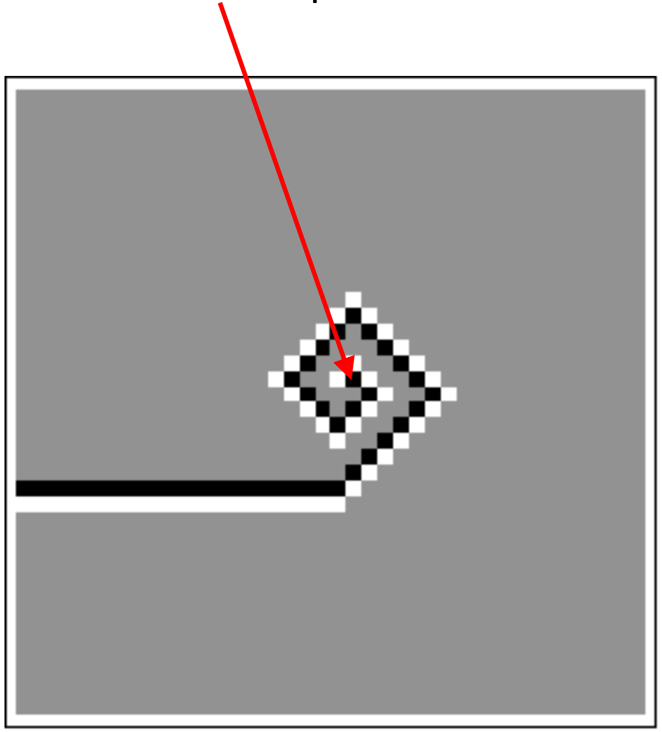
E: excited/active
R: refractory
S: susceptible



Digression: Spiral waves



self-sustained spiral core



$$E \longrightarrow R$$

$$S \xrightarrow{\exists E \text{ in } NB} E$$

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E: excited/active
R: refractory
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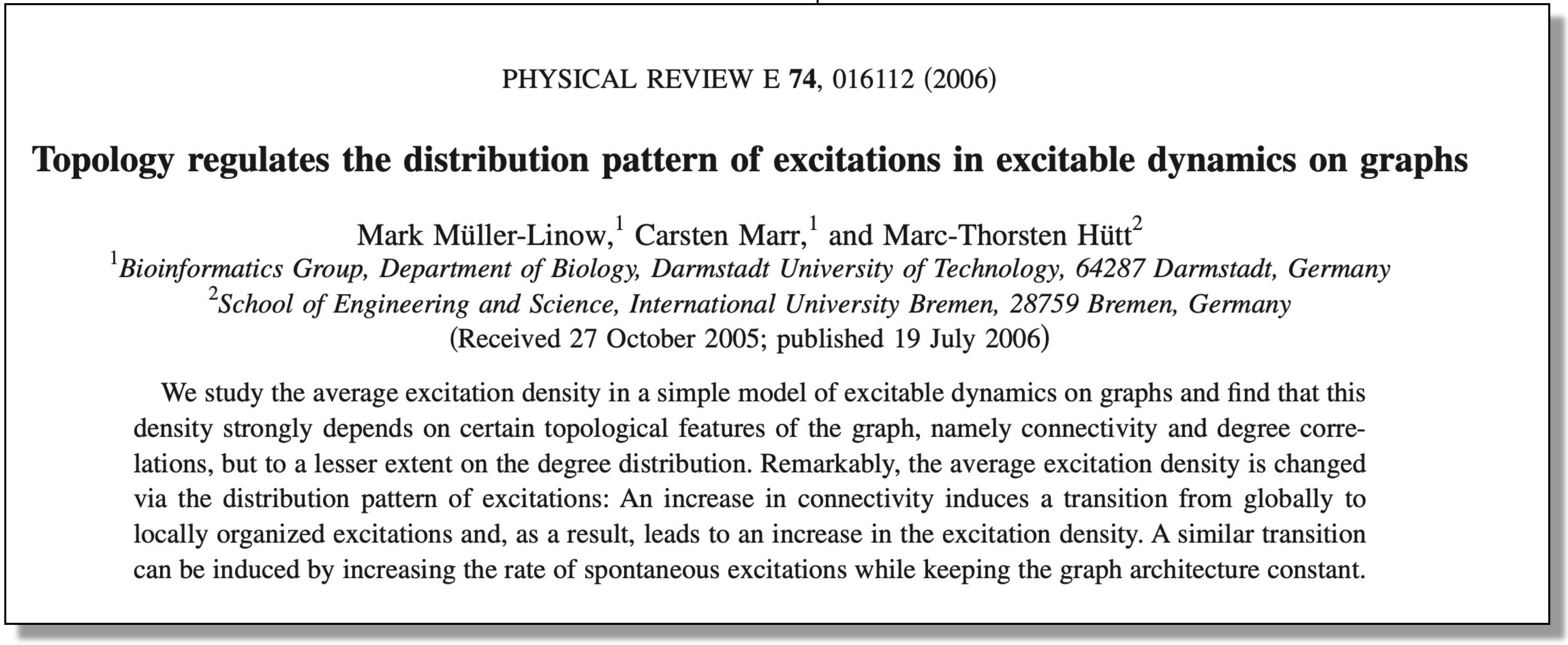
A first example

The BTW sandpile model

- → Self-organized criticality
- → Forest fire model
- → SER model



PHYSICAL REVIEW E **74**, 016112 (2006)

Topology regulates the distribution pattern of excitations in excitable dynamics on graphs

Mark Müller-Linow,[1] Carsten Marr,[1] and Marc-Thorsten Hütt[2]
[1]*Bioinformatics Group, Department of Biology, Darmstadt University of Technology, 64287 Darmstadt, Germany*
[2]*School of Engineering and Science, International University Bremen, 28759 Bremen, Germany*

(Received 27 October 2005; published 19 July 2006)

We study the average excitation density in a simple model of excitable dynamics on graphs and find that this density strongly depends on certain topological features of the graph, namely connectivity and degree correlations, but to a lesser extent on the degree distribution. Remarkably, the average excitation density is changed via the distribution pattern of excitations: An increase in connectivity induces a transition from globally to locally organized excitations and, as a result, leads to an increase in the excitation density. A similar transition can be induced by increasing the rate of spontaneous excitations while keeping the graph architecture constant.

Example 1: Self-organized excitation waves in networks

How can we use minimal models to contribute to neuroscience?

Trends in Cognitive Sciences

CellPress REVIEWS

April 2020, Vol. 24, No. 4

Review

Linking Structure and Function in Macroscale Brain Networks

Laura E. Suárez,[1] Ross D. Markello

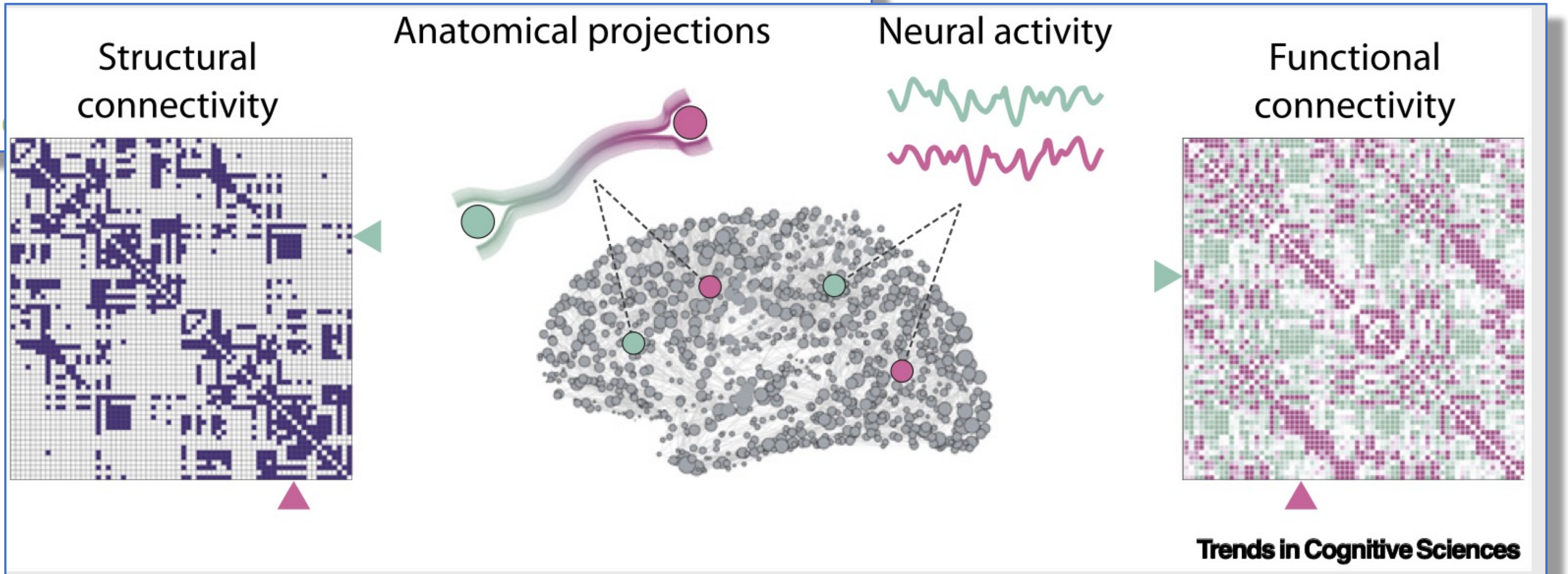


Figure I. Measuring Structural and Functional Connectivity. At the macroscale level, structural and functional networks are derived by first parcellating the brain into grey matter nodes. For structural connectivity networks, edges are defined by reconstructing white matter projections between network nodes. For functional networks, edges are defined by estimating statistical associations between node time courses.

How can we use minimal models to contribute to neuroscience?

Trends in Cognitive Sciences

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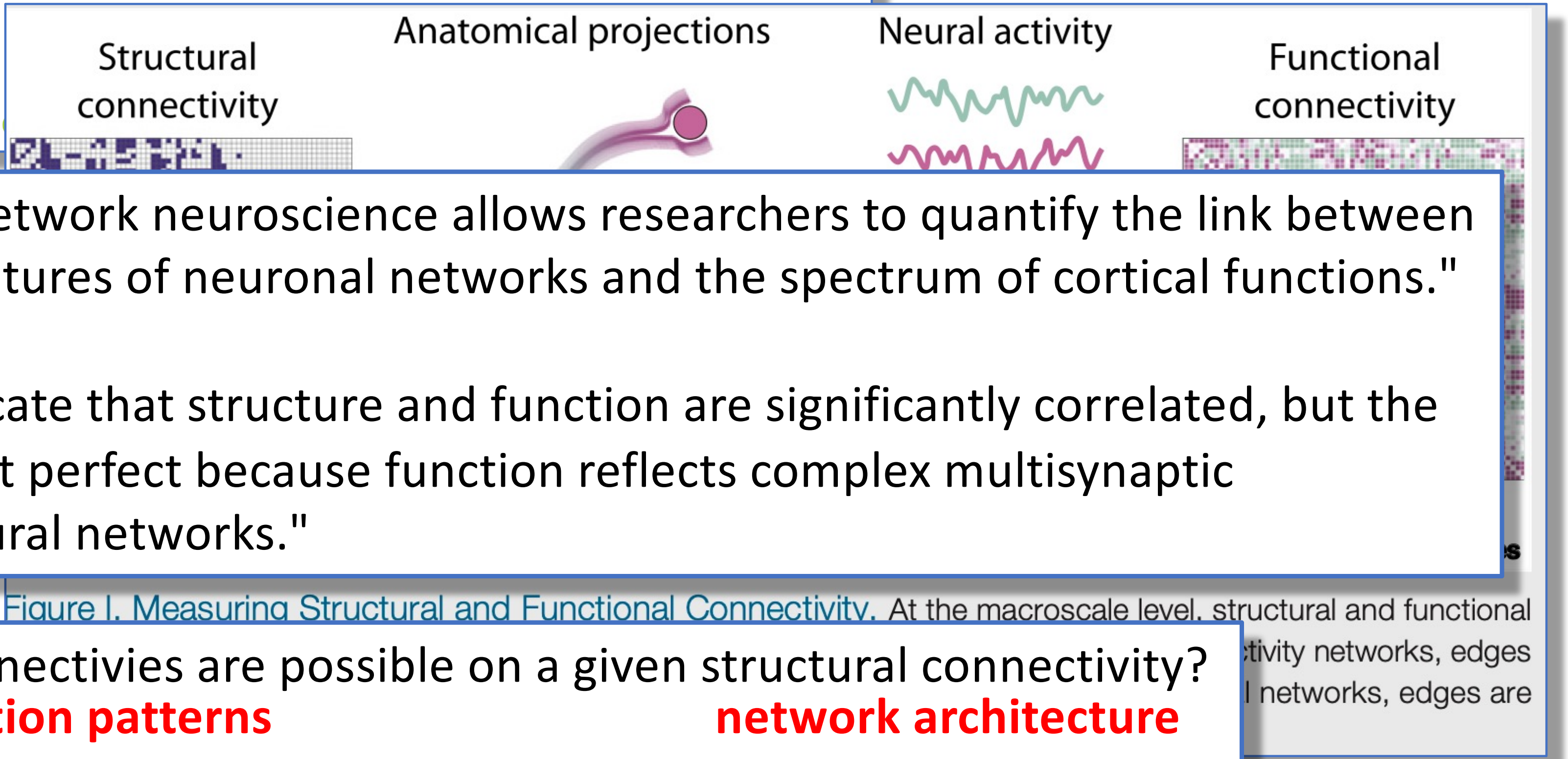


Figure I. Measuring Structural and Functional Connectivity. At the macroscale level, structural and functional

tivity networks, edges

l networks, edges are

"The emergence of network neuroscience allows researchers to quantify the link between the organizational features of neuronal networks and the spectrum of cortical functions."

"Current models indicate that structure and function are significantly correlated, but the correspondence is not perfect because function reflects complex multisynaptic interactions in structural networks."

Which functional connectivies are possible on a given structural connectivity?

collective excitation patterns — network architecture

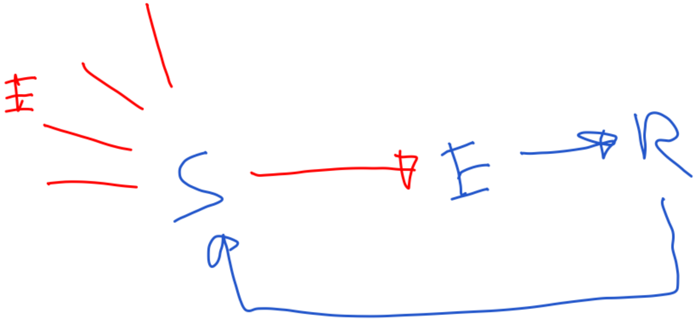
How can we use minimal models to contribute to neuroscience?

$$E \longrightarrow R$$

$$S \xrightarrow{\exists E \text{ in } NB} E$$

$$R \longrightarrow S$$

deterministic SER model



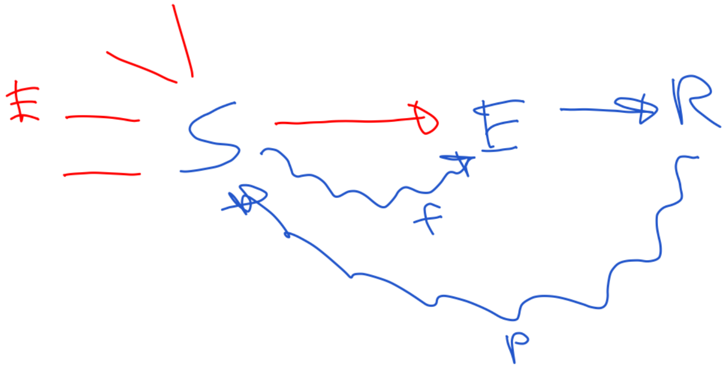
$$E \longrightarrow R$$

$$S \xrightarrow{\exists E \text{ in } NB} E$$

$$R \xrightarrow{p} S$$ recovery probability *p*

$$S \xrightarrow{f} E$$ rate of spontaneous activity *f*

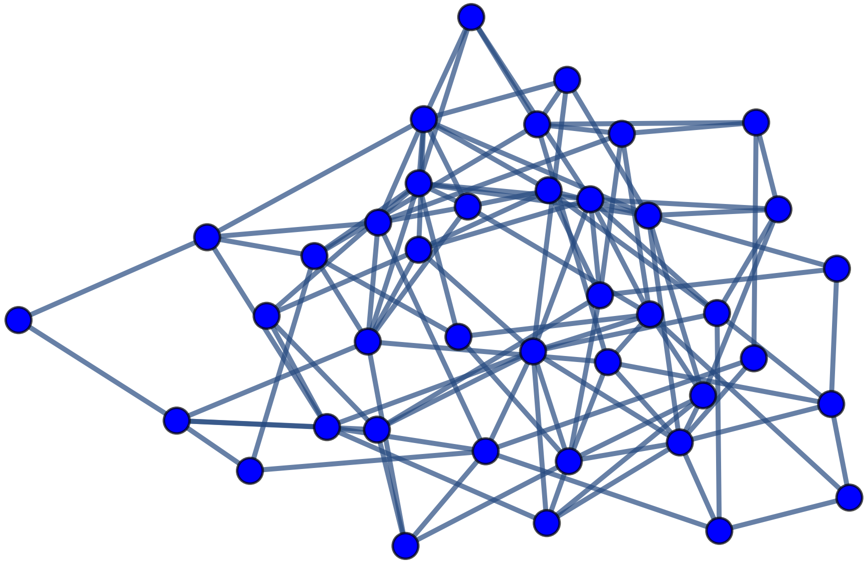
(standard [stochastic]) SER model



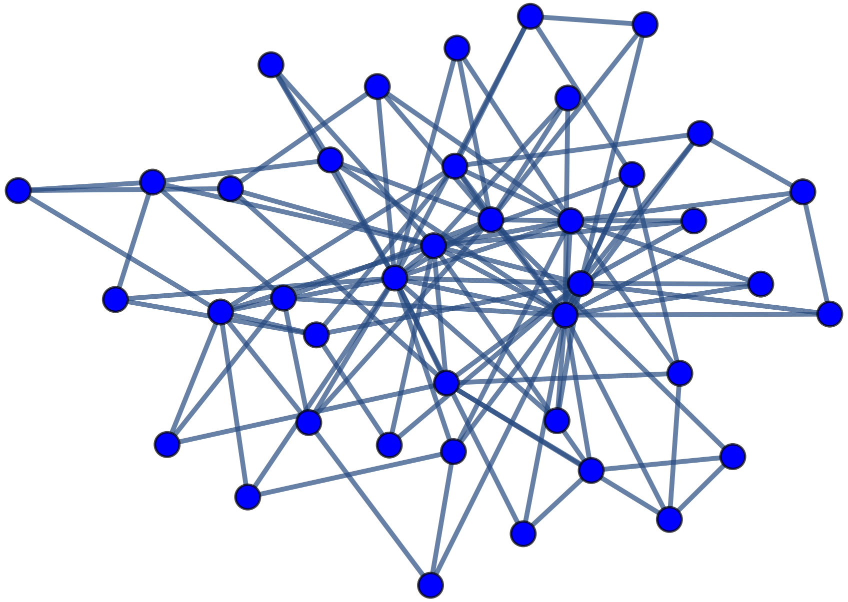
● = network
● = local
→ = deterministic
⇝ = stochastic

How can we use minimal models to contribute to neuroscience?

ER graph

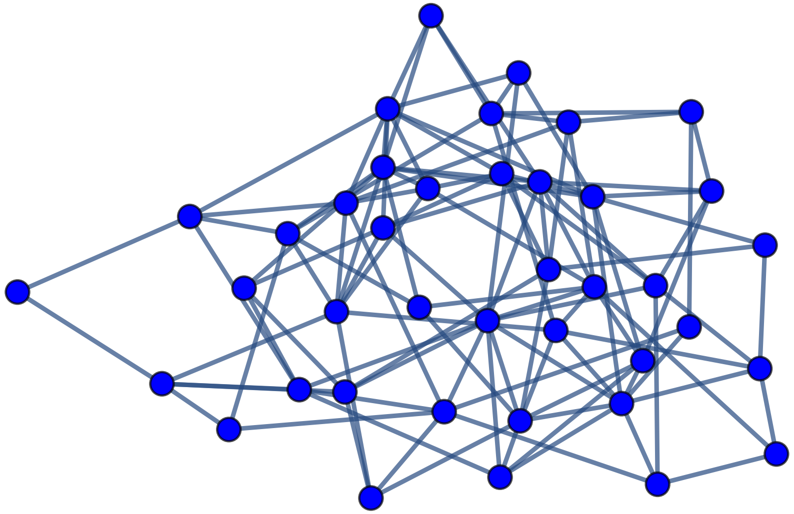


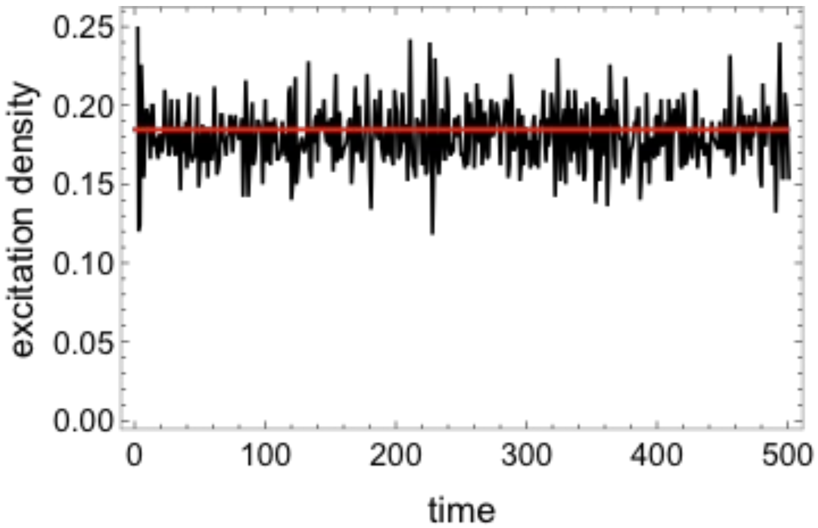
BA graph



How can we use minimal models to contribute to neuroscience?

ER graph





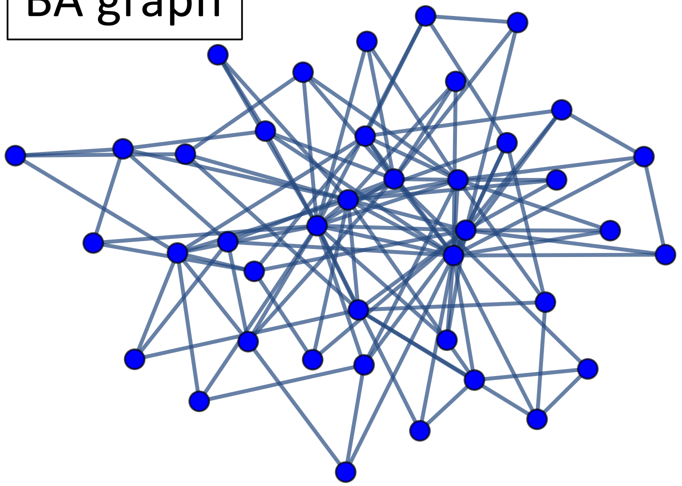
N= 500
p = 0.3
f = 0.01

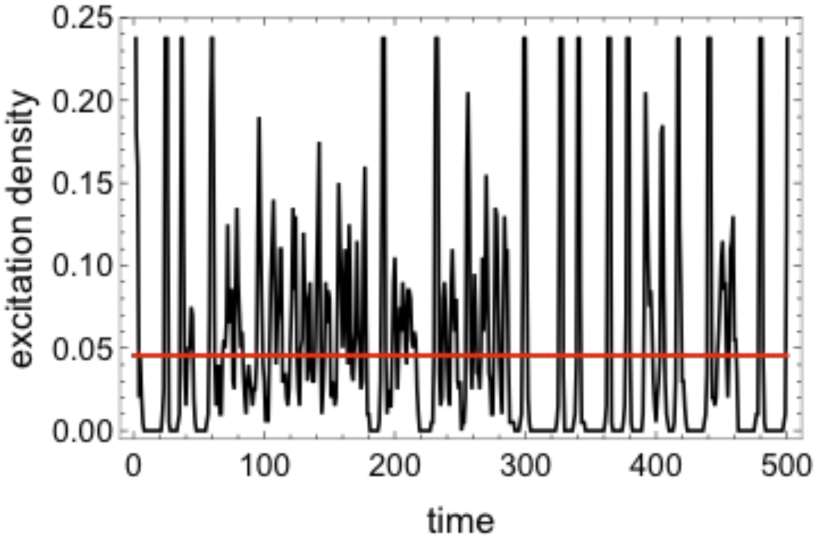
— steady-state prediction from the mean-field model

Mean-field model from:
Hütt and Lesne (2009). Frontiers in Neuroinformatics, 3, 578.
Hütt and Lesne (2020). In: Atay et al. (eds) Discrete and Continuous Models in the Theory of Networks. Operator Theory: Advances and Applications, vol 281. Birkhäuser

How can we use minimal models to contribute to neuroscience?

BA graph

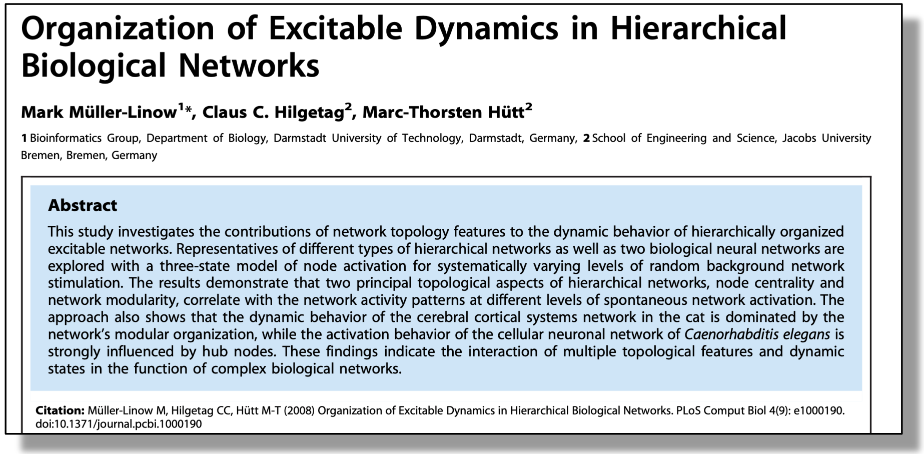




N= 500
p = 0.3
f = 0.01

steady-state prediction from the mean-field model

→ evidence for self-organized waves around hubs



Organization of Excitable Dynamics in Hierarchical Biological Networks

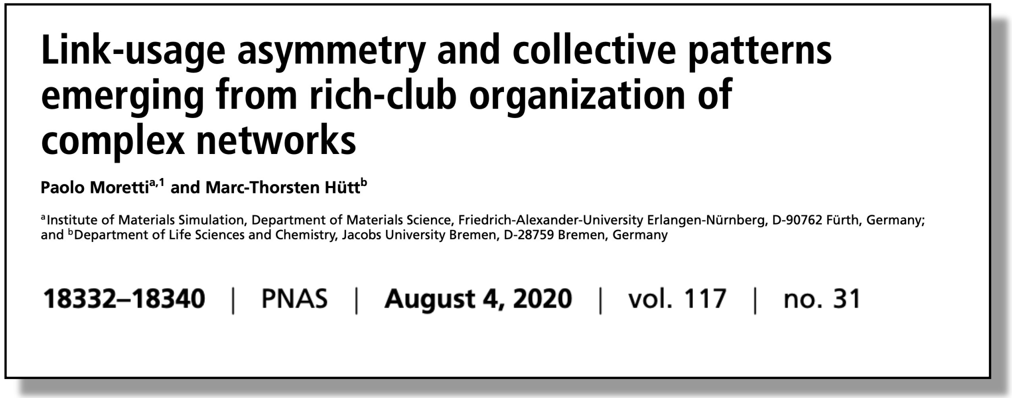
Mark Müller-Linow[1]*, Claus C. Hilgetag[2], Marc-Thorsten Hütt[2]

1 Bioinformatics Group, Department of Biology, Darmstadt University of Technology, Darmstadt, Germany, 2 School of Engineering and Science, Jacobs University Bremen, Bremen, Germany

Abstract

This study investigates the contributions of network topology features to the dynamic behavior of hierarchically organized excitable networks. Representatives of different types of hierarchical networks as well as two biological neural networks are explored with a three-state model of node activation for systematically varying levels of random background network stimulation. The results demonstrate that two principal topological aspects of hierarchical networks, node centrality and network modularity, correlate with the network activity patterns at different levels of spontaneous network activation. The approach also shows that the dynamic behavior of the cerebral cortical systems network in the cat is dominated by the network's modular organization, while the activation behavior of the cellular neuronal network of *Caenorhabditis elegans* is strongly influenced by hub nodes. These findings indicate the interaction of multiple topological features and dynamic states in the function of complex biological networks.

Citation: Müller-Linow M, Hilgetag CC, Hütt M-T (2008) Organization of Excitable Dynamics in Hierarchical Biological Networks. PLoS Comput Biol 4(9): e1000190. doi:10.1371/journal.pcbi.1000190



Link-usage asymmetry and collective patterns emerging from rich-club organization of complex networks

Paolo Moretti[a,1] and Marc-Thorsten Hütt[b]

[a]Institute of Materials Simulation, Department of Materials Science, Friedrich-Alexander-University Erlangen-Nürnberg, D-90762 Fürth, Germany; and [b]Department of Life Sciences and Chemistry, Jacobs University Bremen, D-28759 Bremen, Germany

18332–18340 | PNAS | **August 4, 2020** | vol. 117 | no. 31

Example 2: Networks as structural models to interpret high-throughput data in Biology and Medicine

An example of a network-based interpretation of medical high-throughput data

Agreement of transcriptome data with a given biological network

Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature

Haberman et al.

J Clin Invest. 2014;124(8):3617–3633. doi:10.1172/JCI75436.

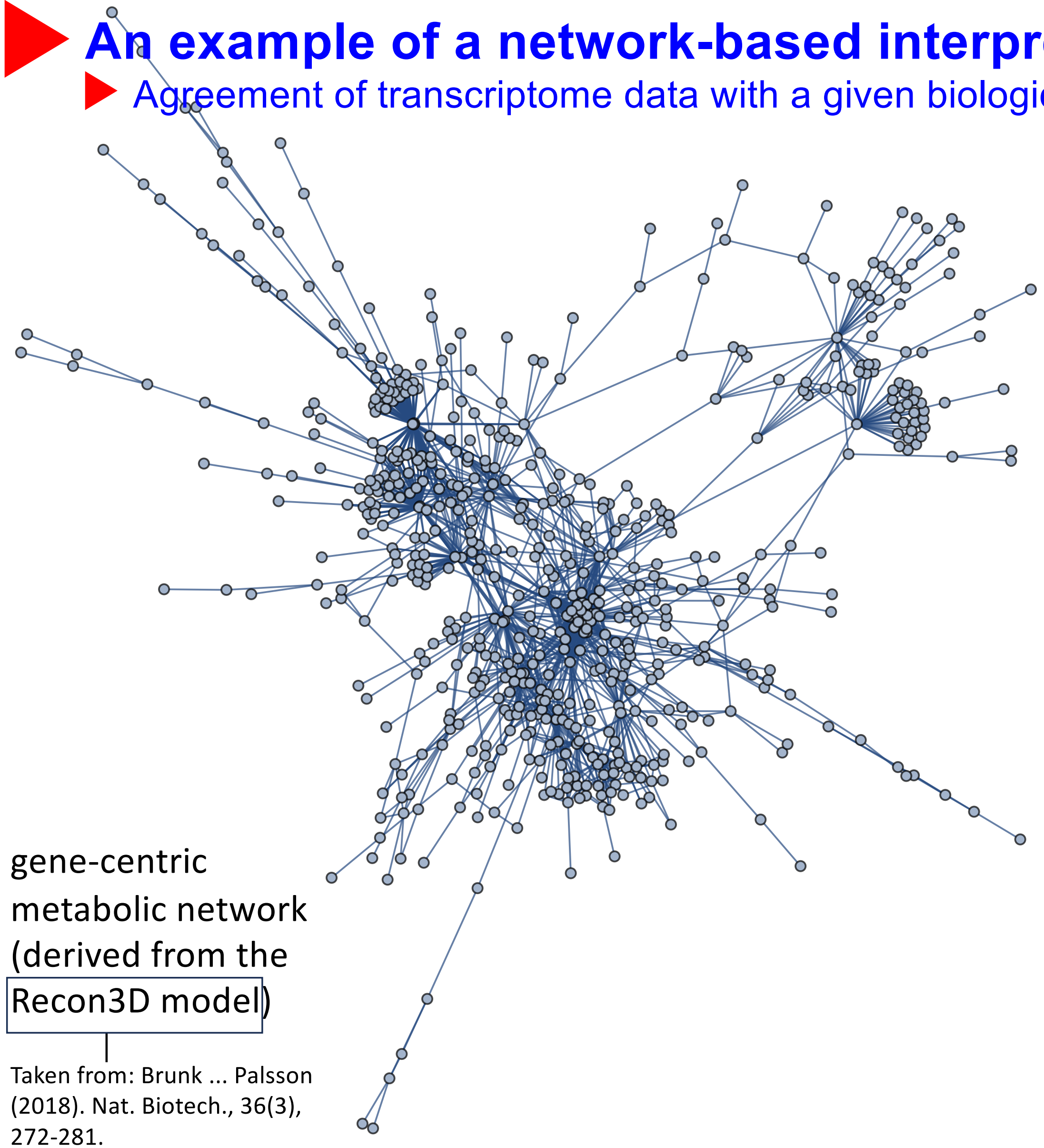
Some features of the data set

- treatment-naive pediatric patients
    - Crohn's disease (CD)
    - ulcerative colitis (UC)
    - no inflammatory bowel disease (notIBD)

- 321 samples (with an age range from 2 to 17 years)
- gene expression measured via RNA-Seq

An example of a network-based interpretation of medical high-throughput data

Agreement of transcriptome data with a given biological network

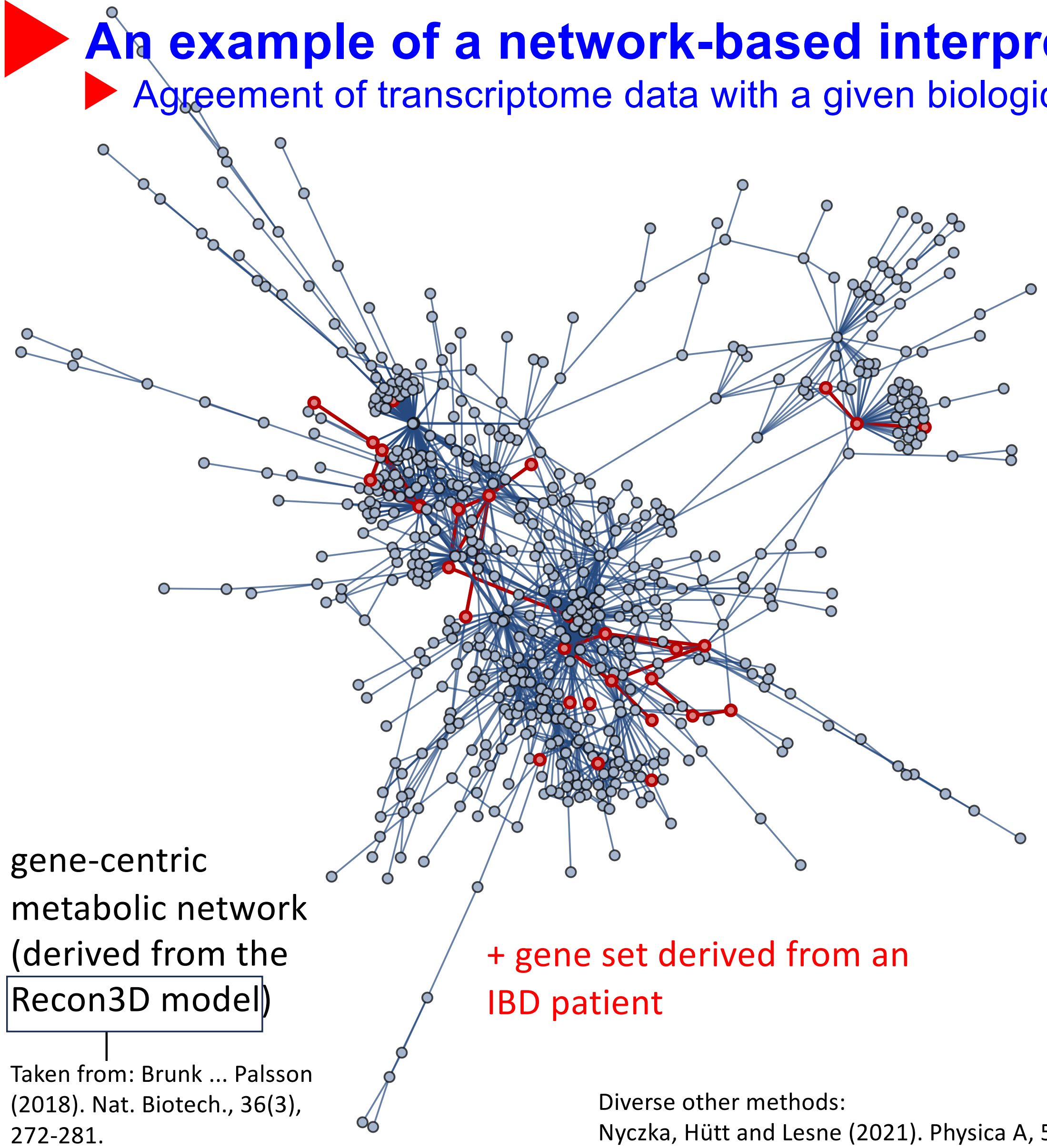


gene-centric metabolic network (derived from the Recon3D model)

Taken from: Brunk ... Palsson (2018). Nat. Biotech., 36(3), 272-281.

An example of a network-based interpretation of medical high-throughput data

Agreement of transcriptome data with a given biological network



gene-centric metabolic network (derived from the Recon3D model)

Taken from: Brunk ... Palsson (2018). Nat. Biotech., 36(3), 272-281.

+ gene set derived from an IBD patient

$G' = (V', E'),$

$V' \subseteq V$ differentially expressed genes

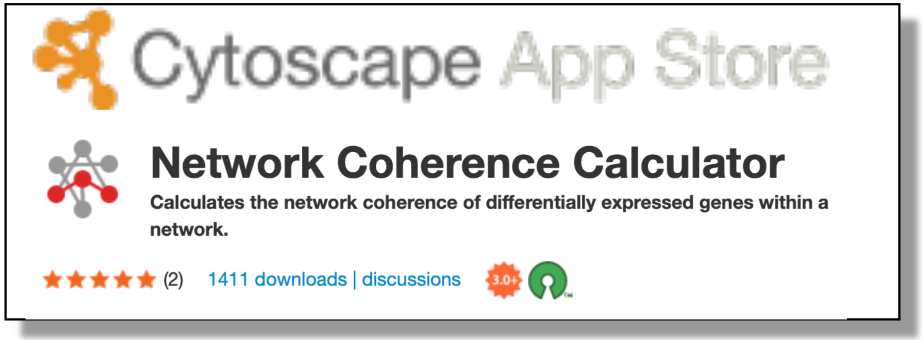
$E' \subseteq E$ all edges in G among vertices in V'

$$R = \frac{|\{v_i \in V' | k(v_i) > 0\}|}{|V'|}, \quad k(v_i) \text{ degree of node } v_i$$

z-score (with respect to random vertex sets)

'network coherence'

Method from:
Sonnenschein, Geertz, Muskhelishvili and Hütt (2011). BMC Systems Biology, 5, 1-13.
Sonnenschein, Golib Dzib, Lesne, Eilebrecht, Boulkroun, Zennaro, Benecke and Hütt (2012). BMC Systems Biology, 6, 1-13.



Cytoscape App Store

Network Coherence Calculator

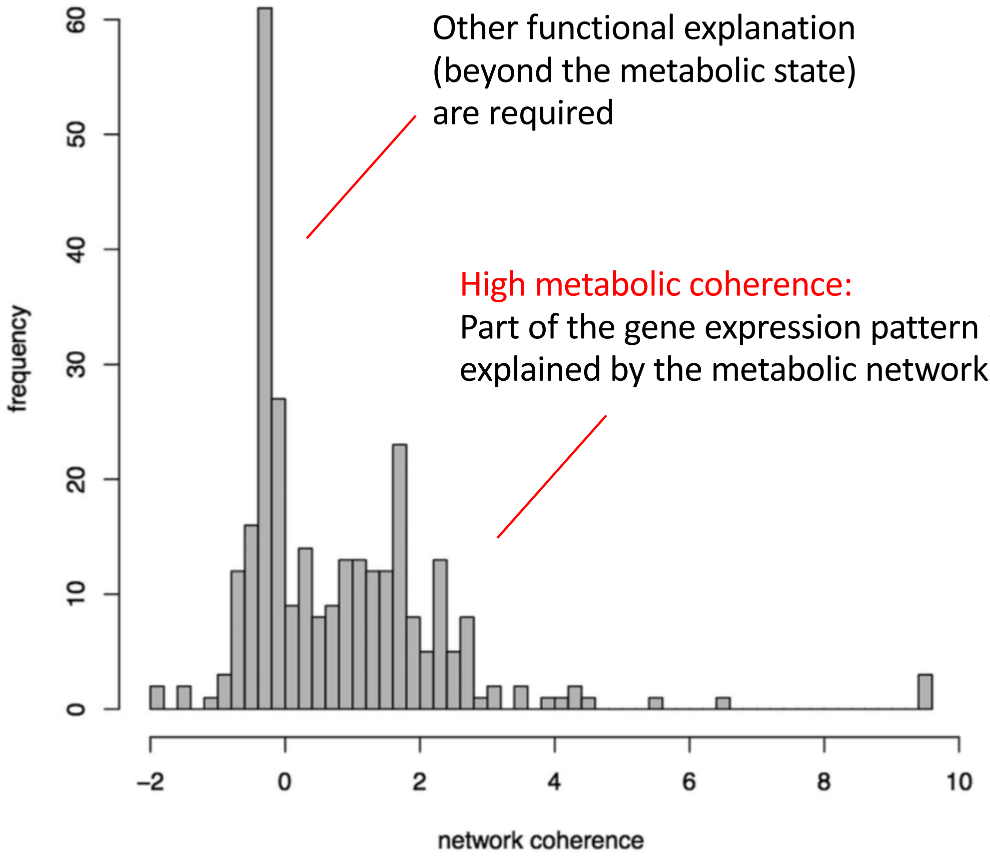
Calculates the network coherence of differentially expressed genes within a network.

★★★★★ (2) 1411 downloads | discussions

Diverse other methods:
Nyczka, Hütt and Lesne (2021). Physica A, 566, 125631.

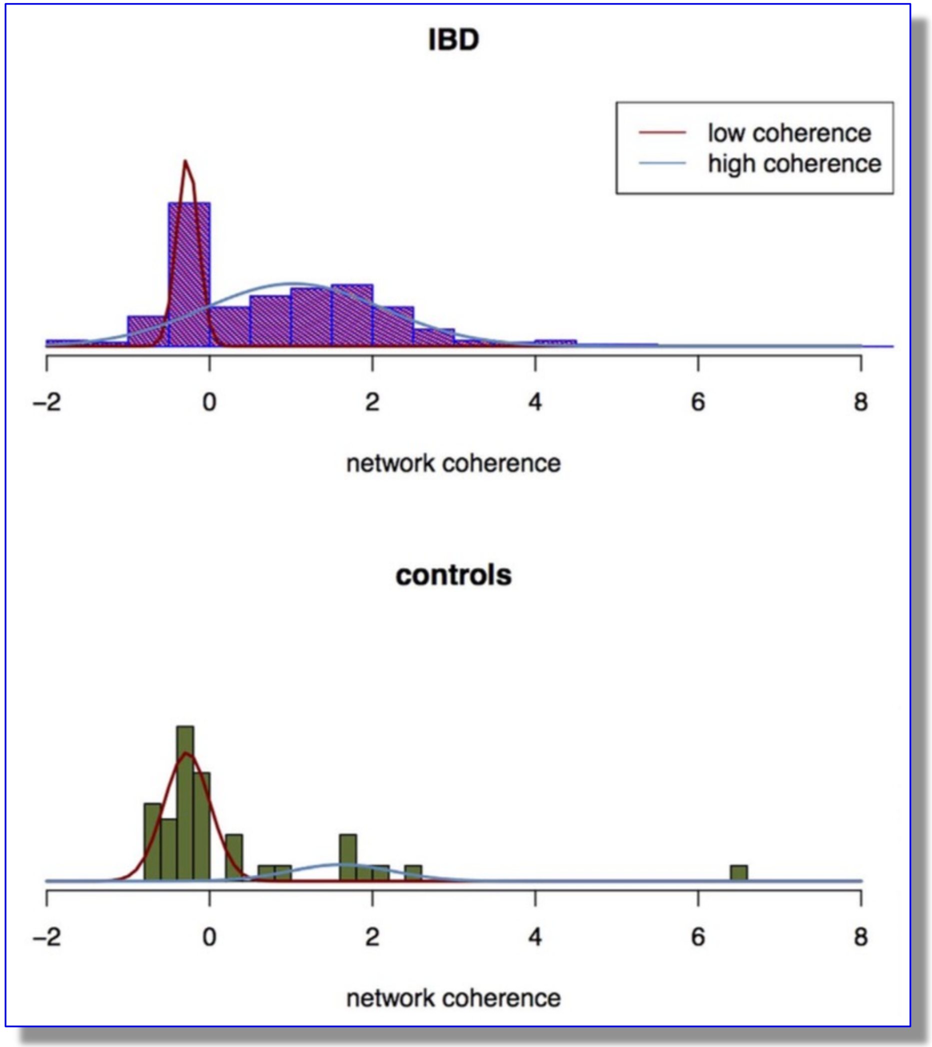
An example of a network-based interpretation of medical high-throughput data

Agreement of transcriptome data with a given biological network



Low metabolic coherence:
Other functional explanation
(beyond the metabolic state)
are required

High metabolic coherence:
Part of the gene expression pattern is
explained by the metabolic network



Knecht, Fretter, Rosenstiel, Krawczak and Hütt (2016) Scientific Reports 6, 32584.

Example 3: The *digital-analog duality* in biology: how network and non-network mechanisms jointly shape biological data and hence systemic function

Biological and medical data are complicated

One complication:

Biology operates via the interplay of analog (rather gradual) and digital (discrete, symbolic) information.

> "The observation I wish to make is this: processes which go through the nervous system may, as I pointed out before, change their character from digital to analog, and back to digital, etc., repeatedly."

von Neumann, J. (1958) The Computer and the Brain. Yale University Press.

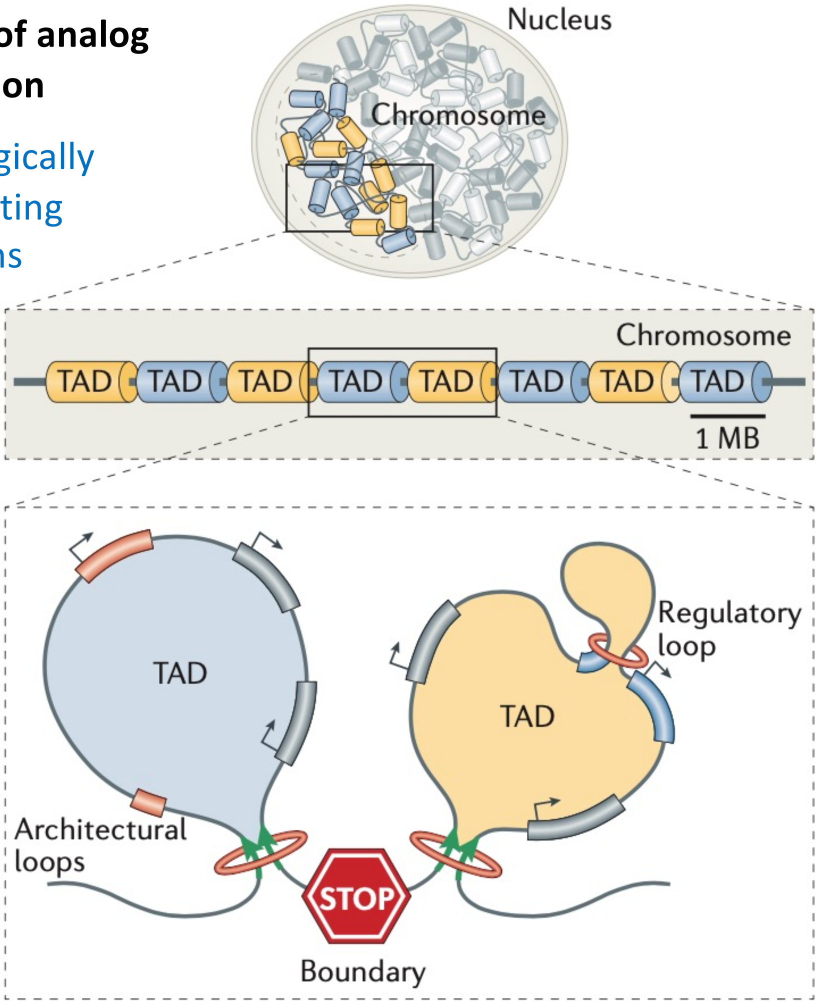
Mathematical and computational approaches (modeling, data analysis, machine learning) are challenged by this interplay of digital and analog information.

Biological and medical data are complicated

Interpretation of disease-associated SNPs via analog information

Concept of analog information

Topologically associating domains (TADs)



Taken from: Krijger and de Laat (2016) Nat. Rev. Mol. Cell. Biol. 17, 771.

Data resources

TAD data

Rao et al. (2014) A 3D map of the human genome at kilobase resolution reveals principles of chromatin looping. Cell 159, 1665–1680.

Disease-associated SNPs from GWAS catalog

GWAS Catalog

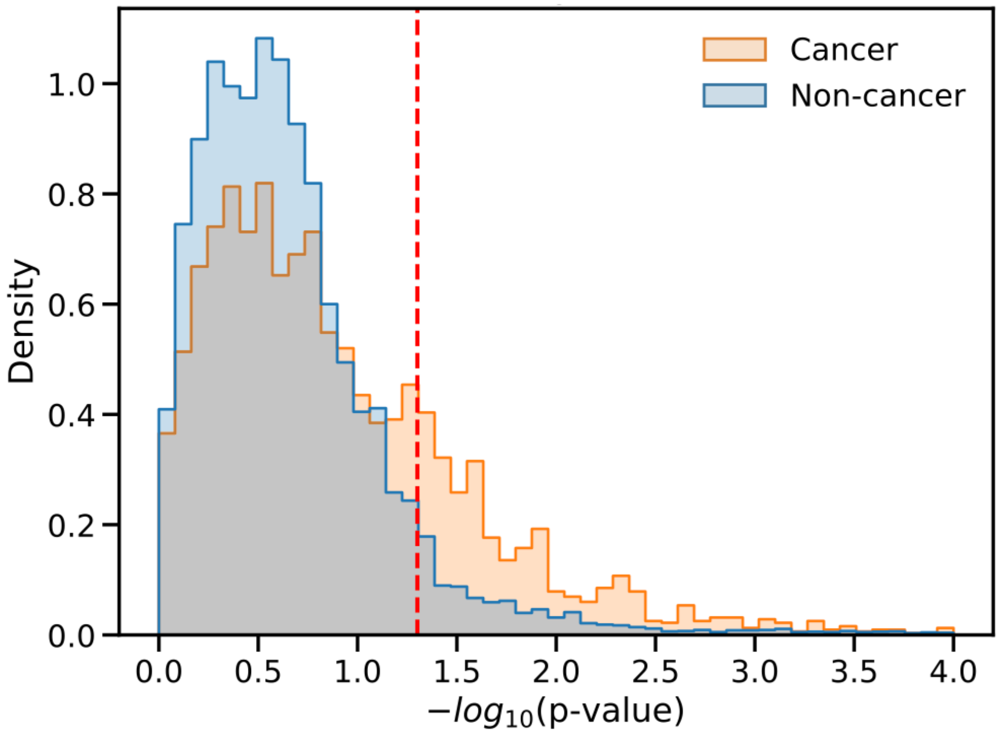
Statistical question

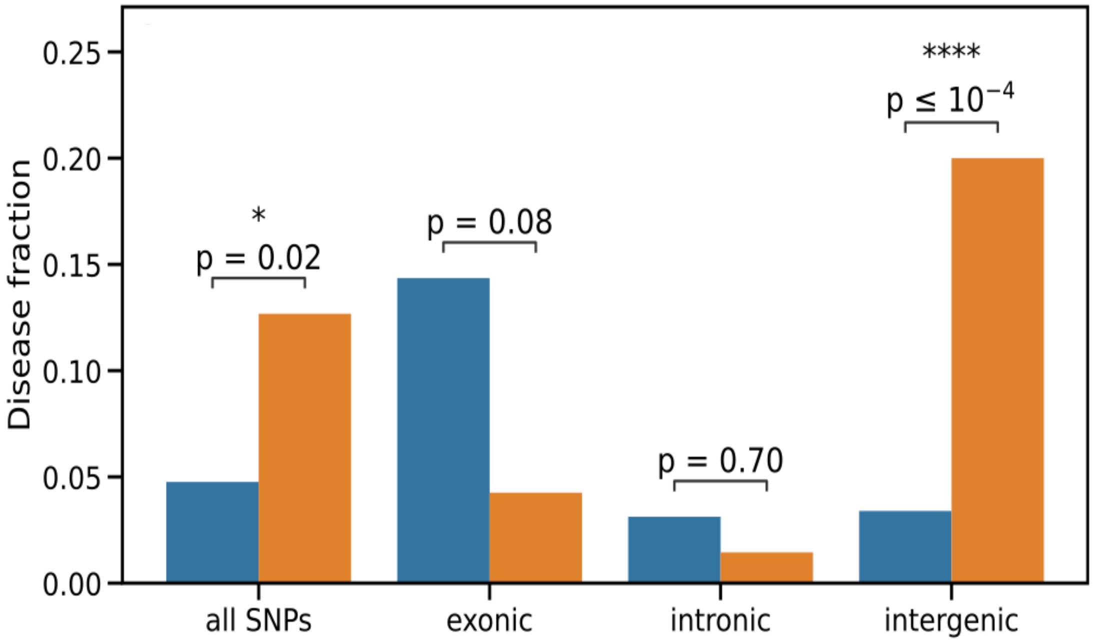
Are there diseases, for which the disease-associated SNPs are significantly often located in TAD boundaries?

Biological and medical data are complicated

Interpretation of disease-associated SNPs via analog information

enrichment of SNPs in TAD borders





associated with
specific genes

SNPs with often
unclear gene
association

Jablonski, Carron, Mozziconacci, Forné, Hütt, Lesne (2022). Human Genomics, 16(1), 2.

Brief remark 1: The 'bigger picture'

What is scientific understanding (in times of AI)?

Definition (attempt)

A **minimal model** (also: 'toy model', 'cartoon model', 'stylized model') is the simplest mathematical representation of a universal behavior.

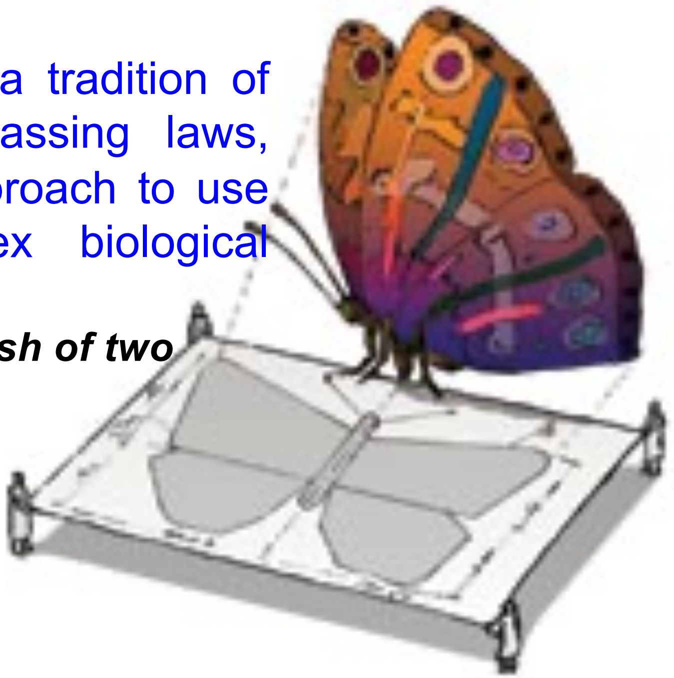
It points to deep order in some of the most complex (fluctuating, nonlinear) systems.

general principles behind a large set of phenomena

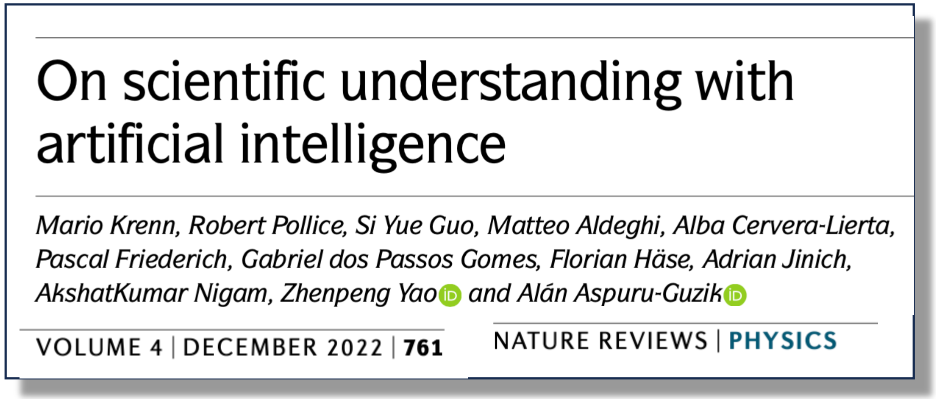
Debate about the theoretical foundations of Biology

"Physicists come from a tradition of looking for all-encompassing laws, but is this the best approach to use when probing complex biological systems?"

E. Fox Keller (2007) ***A clash of two cultures*****.** ***Nature*** **445, 603**



AI-driven scientific discovery ('digital discovery')



On scientific understanding with artificial intelligence

Mario Krenn, Robert Pollice, Si Yue Guo, Matteo Aldeghi, Alba Cervera-Lierta, Pascal Friederich, Gabriel dos Passos Gomes, Florian Häse, Adrian Jinich, AkshatKumar Nigam, Zhenpeng Yao and Alán Aspuru-Guzik

VOLUME 4 | DECEMBER 2022 | **761**

NATURE REVIEWS | **PHYSICS**

Brief remark 2: Some next goals

Some next goal

'Complex networks'

'Simple models'

Example 1: Self-organized excitation waves in networks
joint work with Claus Hilgetag (Hamburg), Paolo Moretti (Nürnberg), joint work with Annick Lesne

Analysis of SER model variants

Spiral waves in networks

Example 2: Networks as structural models to interpret high-throughput data in Biology and Medicine
joint work with Annick Lesne

Extending the data analysis to more disease

Using simple models to obtain a mechanistic understanding of disease genes in networks

Example 3: The digital-analog duality in biology: how network and non-network mechanisms jointly shape biological data and hence systemic function
joint work with Annick Lesne

Understanding how this digital-analog duality affects modeling and data analysis (including machine learning)

Using simple models to obtain a mechanistic understanding of the interplay of digital and analog mechanisms in biology

Brief remark 1: 'The bigger picture'

Brief remark 2: Some next steps