University of Maribor

Faculty of Medicine

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Faculty of Natural Sciences and Mathematics

Javna agencija za raziskovalno dejavnost Republike Slovenije

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Network science as a gateway to understanding of emerging dynamics and function of multicellular systems

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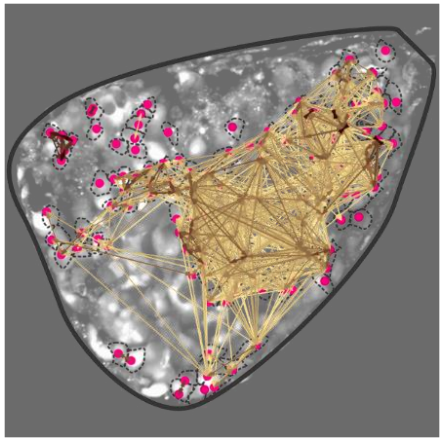
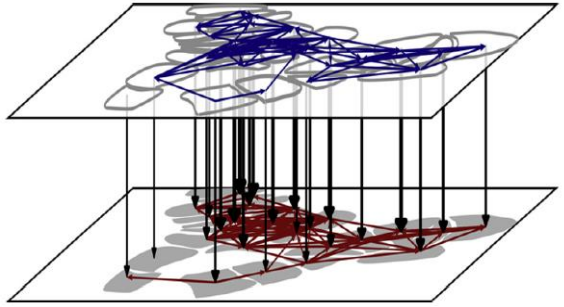
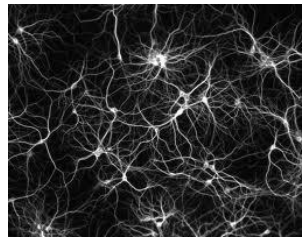
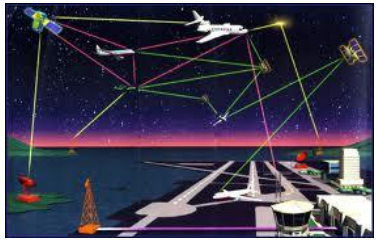
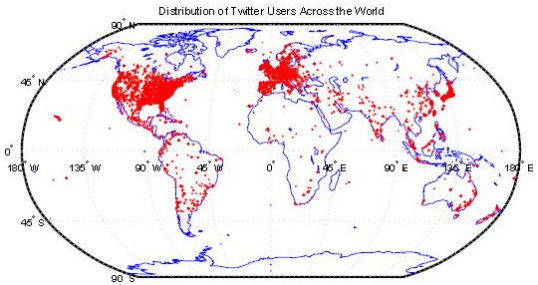


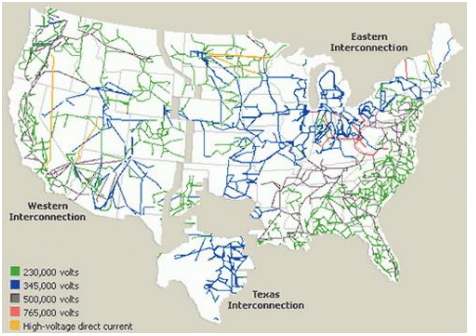


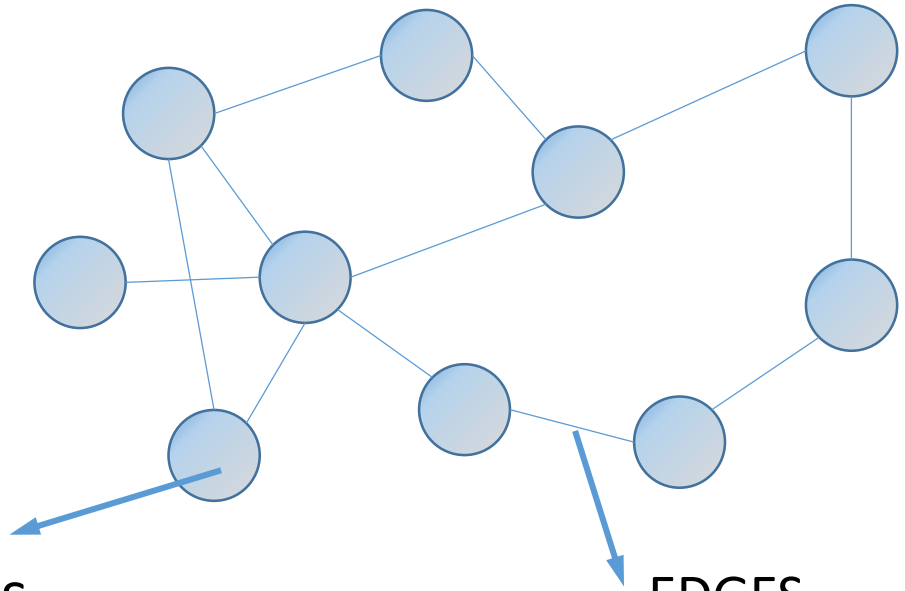
Network science – a hot topic since 1998











NODES
humans, companies, computers, web-pages, airports, power stations, cells, metabolites, etc.

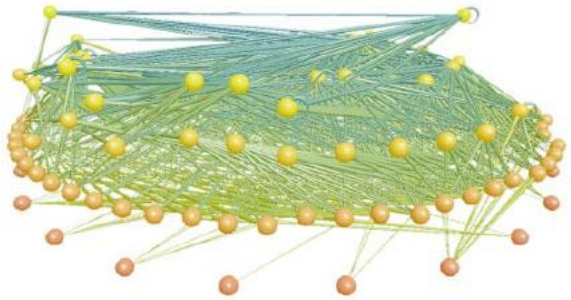
EDGES
friendship, collaboration, direct links, power lines, chemical interactions, etc.

Seminar papers: Watts&Strogatz, Nature 1998 & Barabási&Alberts, Science 1999
~ 65000 citations!

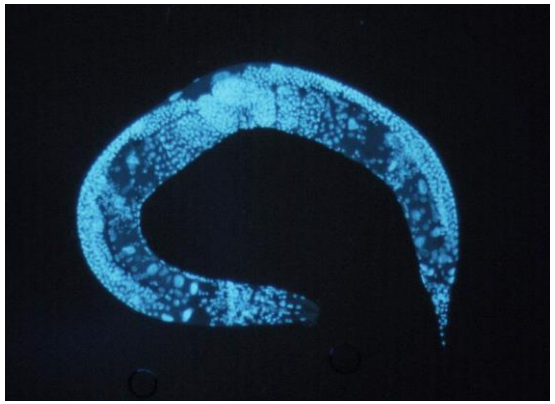
Network science
The study of network representations of physical, biological, and social phenomena.

Complex networks and biological systems

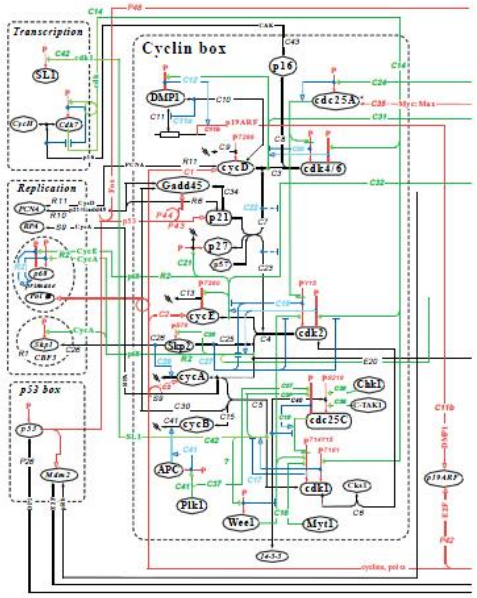
Food webs:



Neuronal networks:

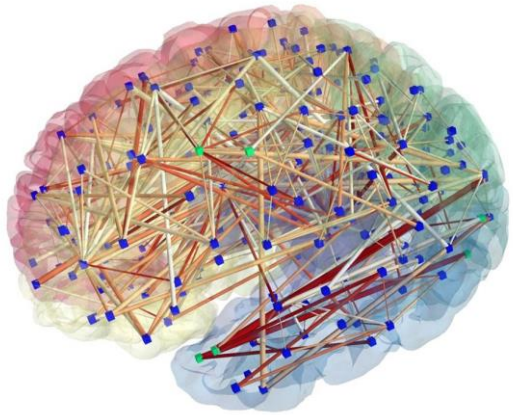


Subcellular molecular networks:

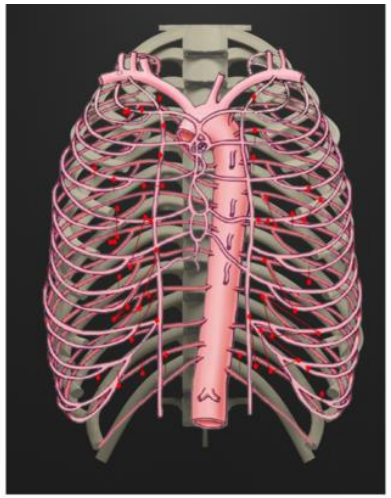


Disease spreading networks:

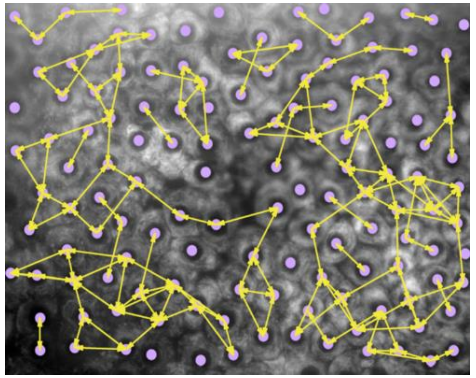
Brain networks:



Vascular networks:



Intercellular networks:



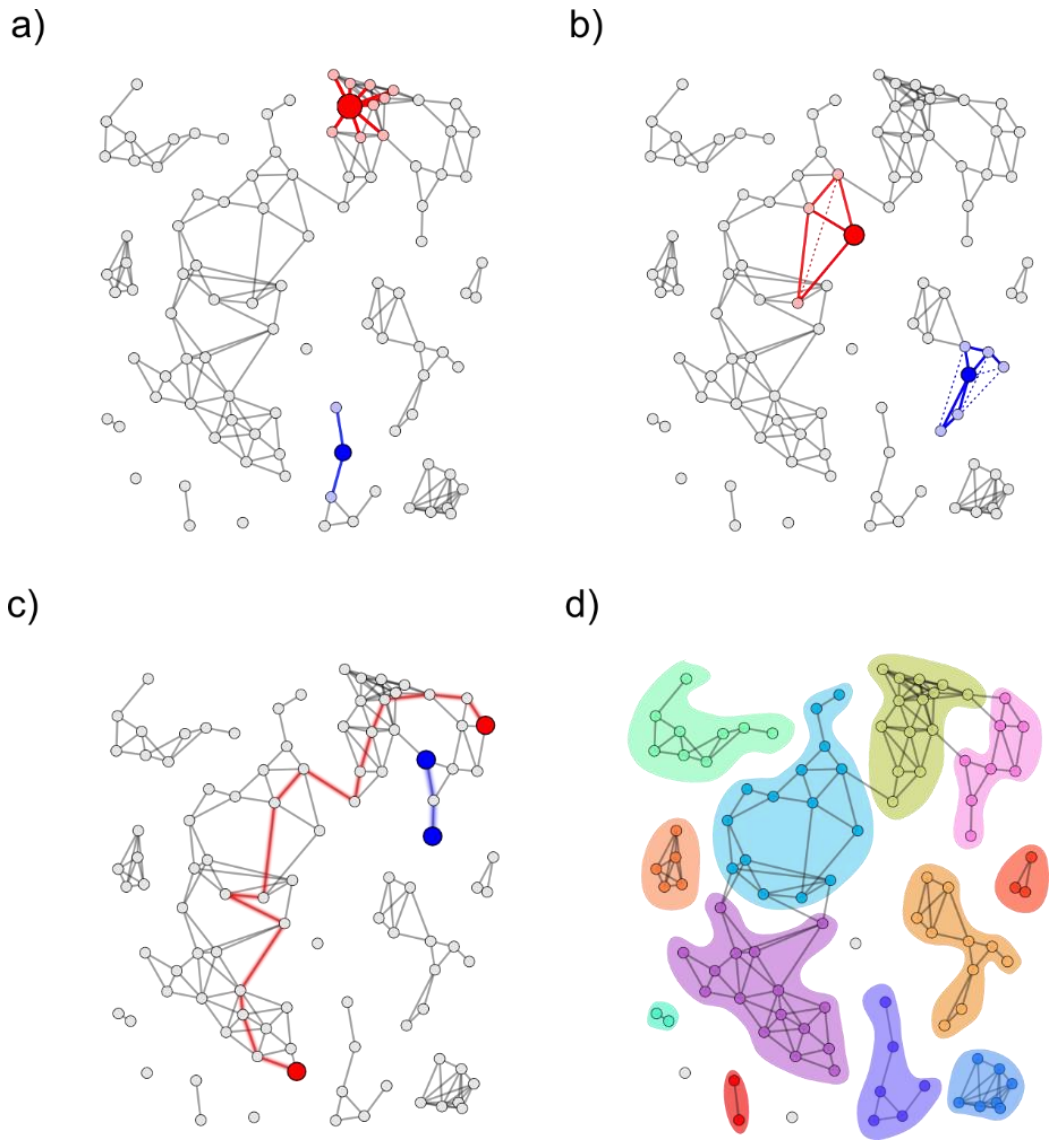
Basic metrics for the characterization of the network‘s structure

a) Node degree and degree distribution.

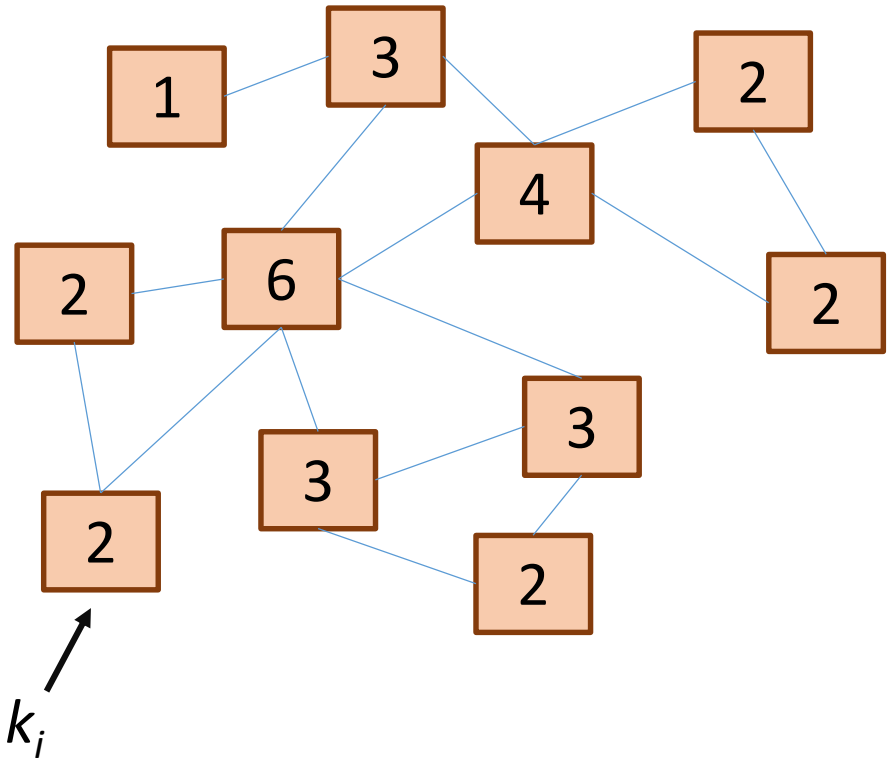
b) Clustering coefficient.

c) Average shortest path length (global efficiency).

d) Modularity (the presence of communities).

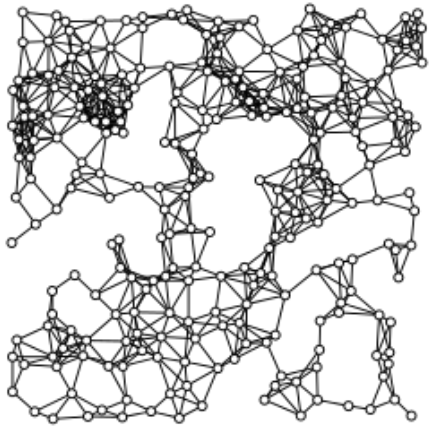


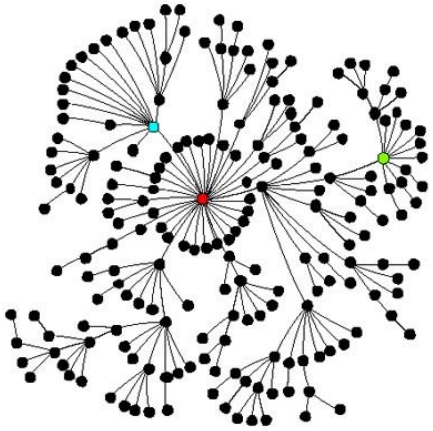
a) Node degree and degree distribution.



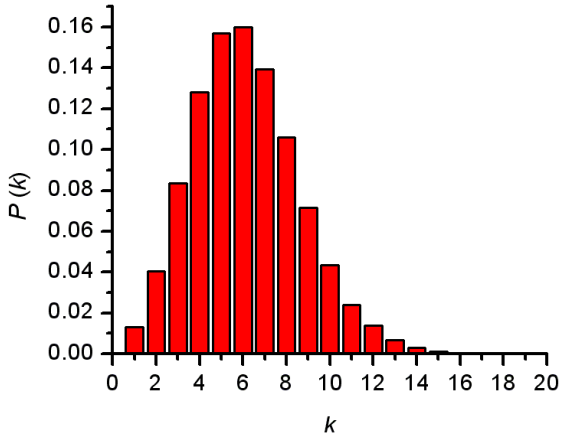
Average degree: $k_{\text{avg}} = \frac{1}{N}\sum_{i=1}^{N} k_i$

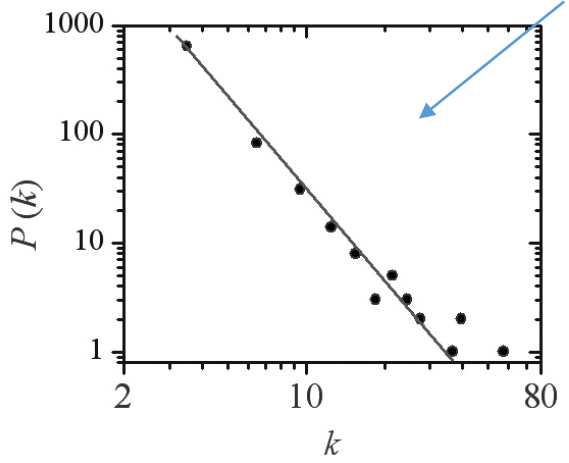
Degree distribution – a global network‘s measure:





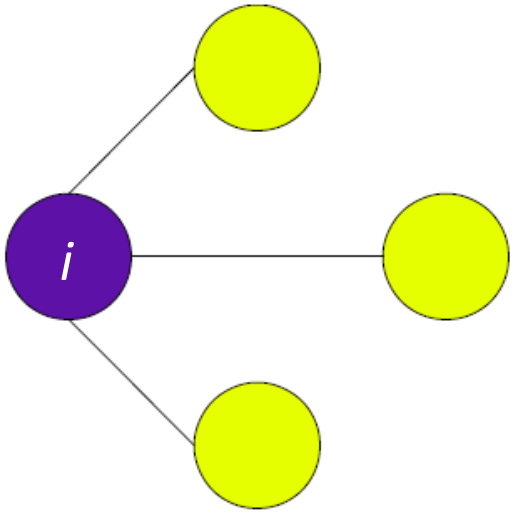
Scale-free property

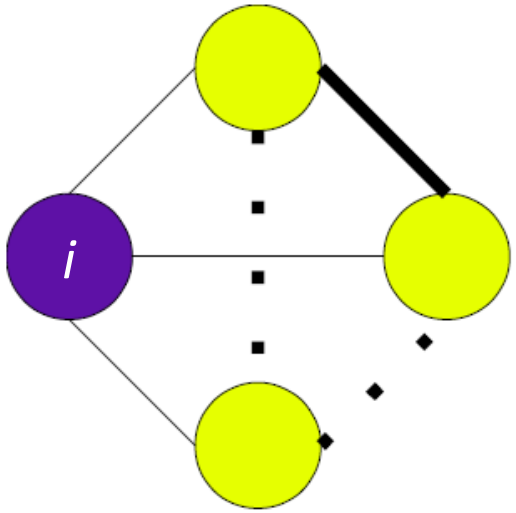


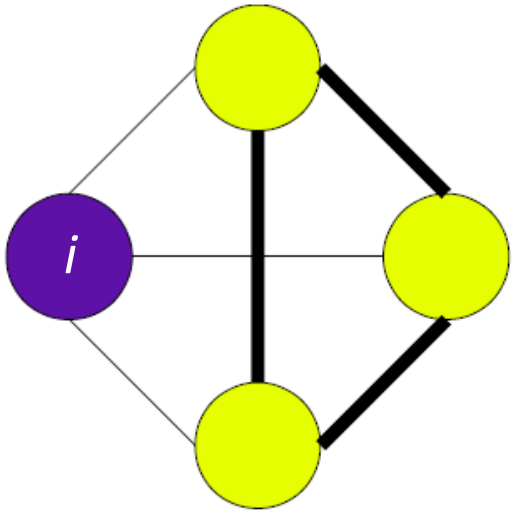


Homogeneous & heterogeneous networks

b) The average clustering coefficient







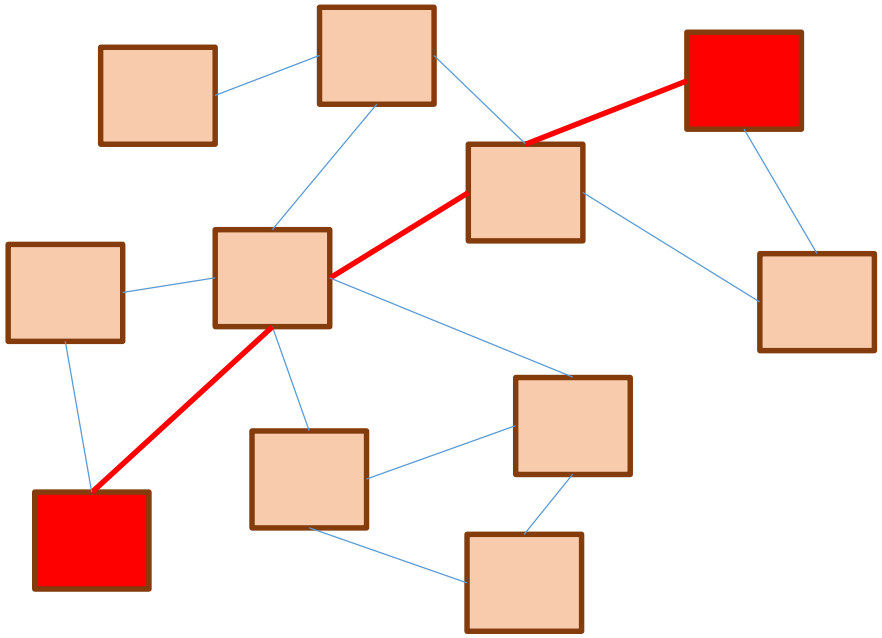
$c_i = 0$ $c_i = 1/3$ $c_i = 1$

$$C_i = \frac{2n_e}{k_i(k_i - 1)}$$

… ratio between existing and all possible connections between neighbors.

The average over all pairs: a global measure for local interconnectness.

c) Average shortest path length (global efficiency)



$l_{ij} = 3$

The shortest path is the relevent one!

Average over all node pairs signifies the network‘s global communication ability:

$$E_{\text{avg}} = \frac{1}{N(N-1)} \sum_{i \neq j}^{N} \frac{1}{l_{ij}}$$

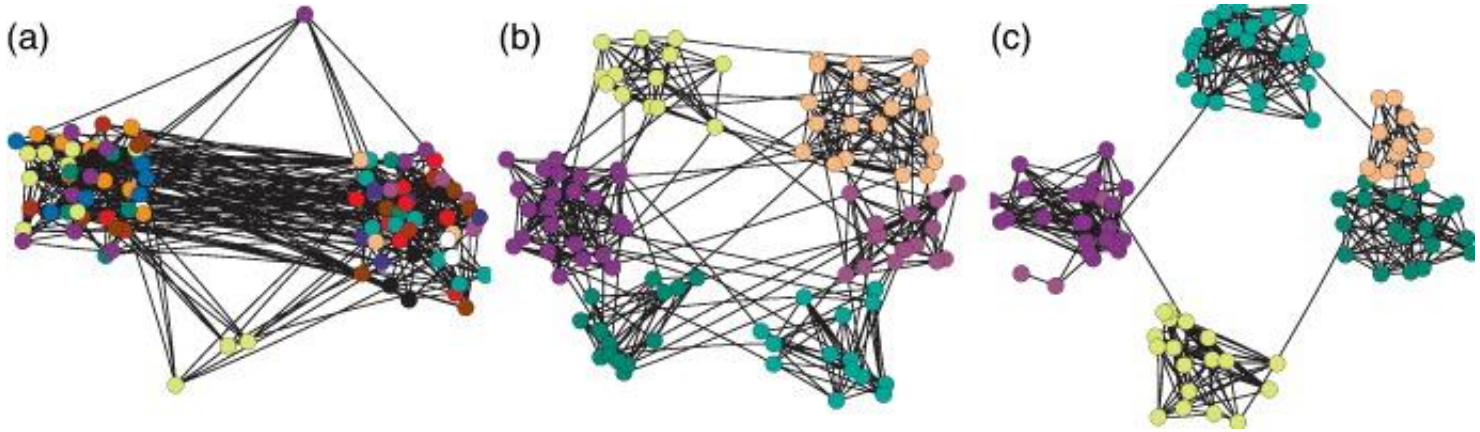
d) Network‘s modularity (community structure)

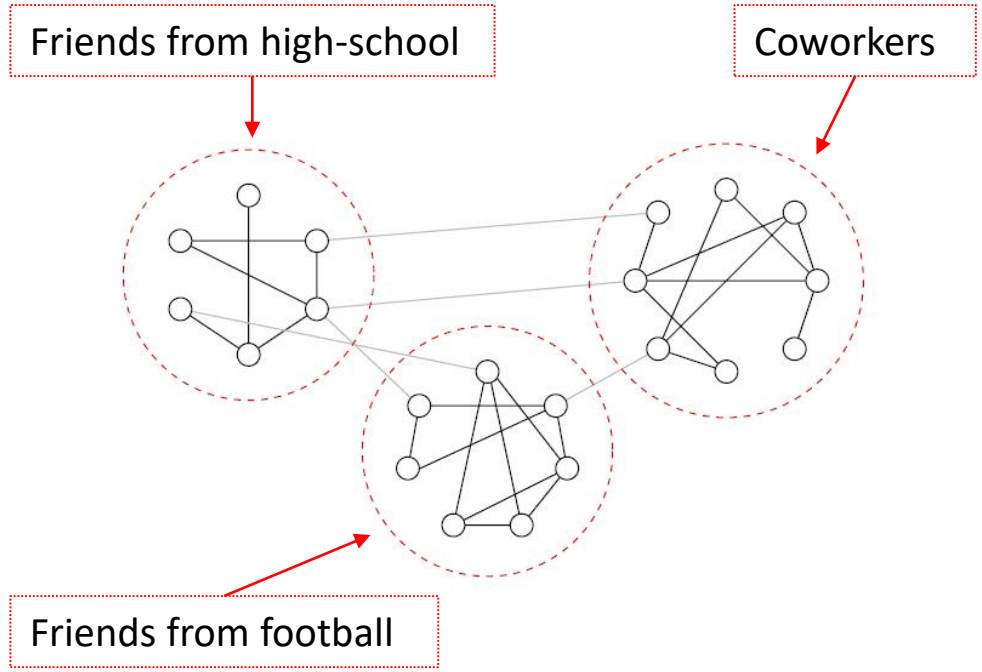
Modularity – a measure that quantifies the partitioning of a network:

A community is a partition of a network or a sub-graph in which the nodes are more densely interconnected as in the rest of the network.

$$Q = \frac{1}{2m}\sum_{i,j}\left[d_{ij}(t) - \frac{k_i(t)k_j(t)}{2m}\right]\delta(c_i, c_j)$$

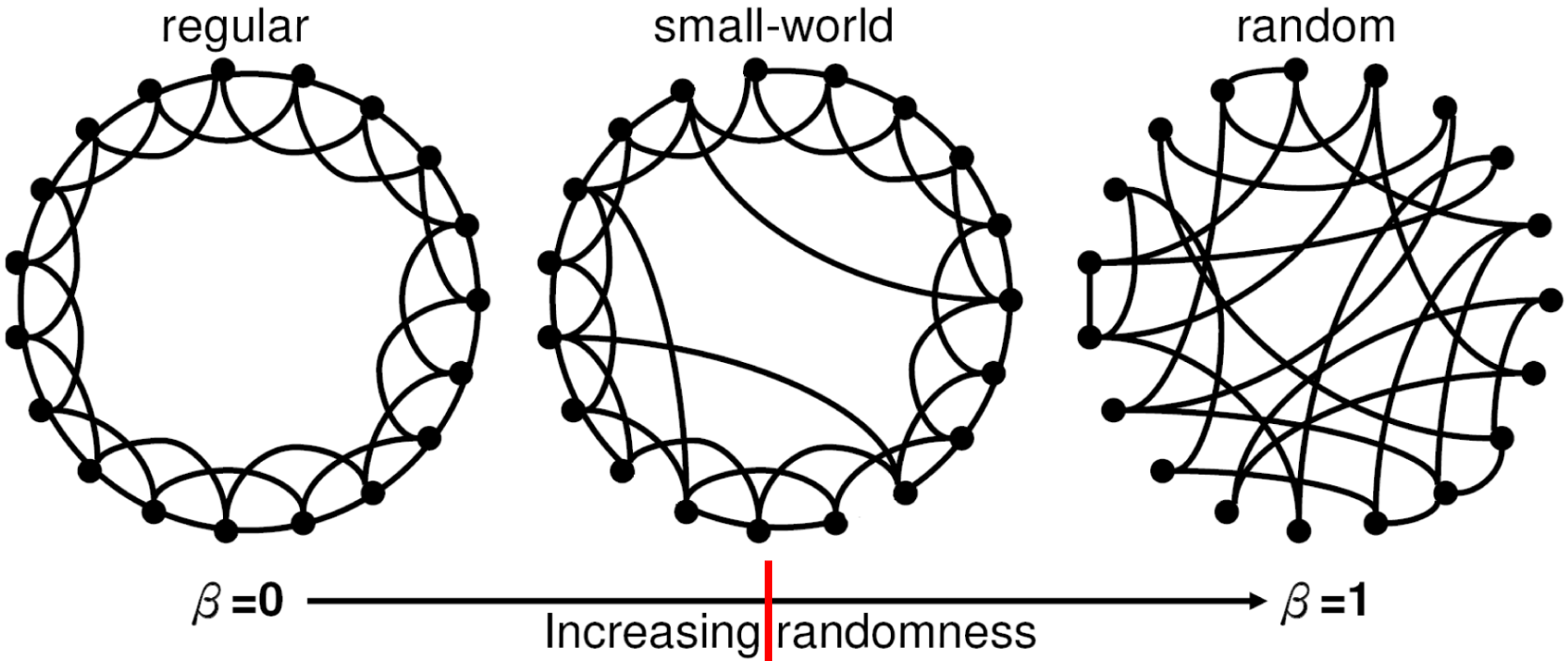
Low modularity ⟶ High modularity





Small-world networks

Watts&Strogatz, Nature 1998



High clustering, low efficiency

Low clustering, high efficiency

High clustering, high efficiency

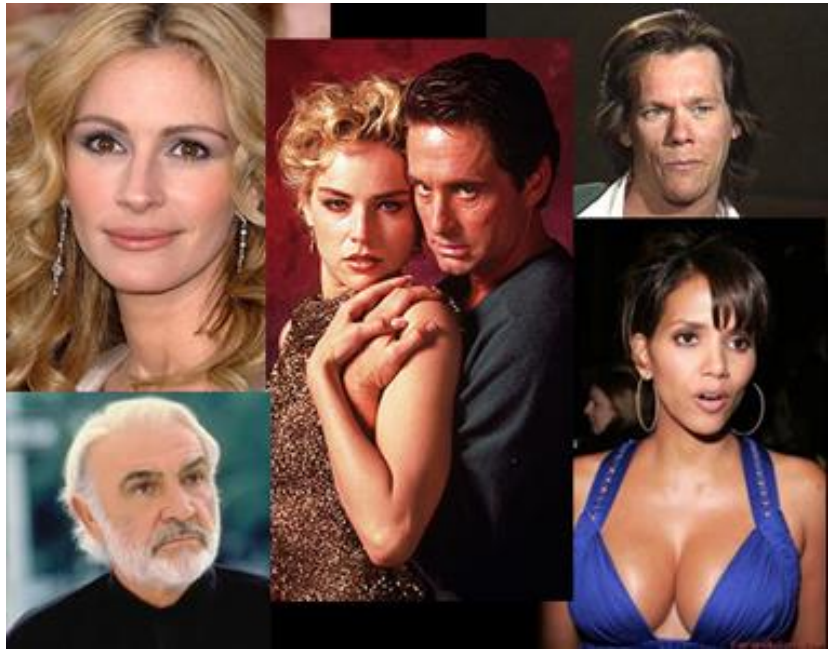
Example: the network of movie actors

nodes = actors

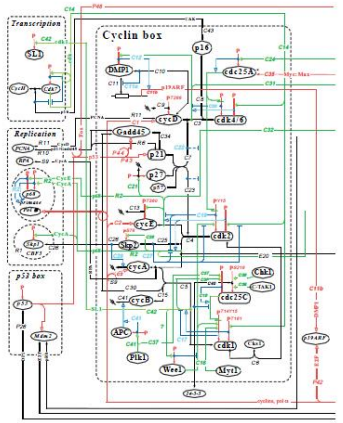
connection = two actors played in the same film

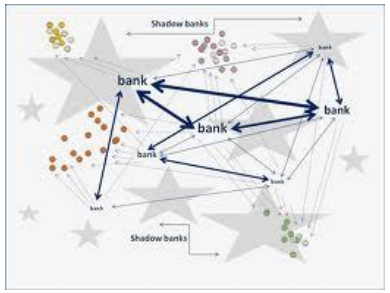
N = 225 226; $\langle k \rangle$ = 61

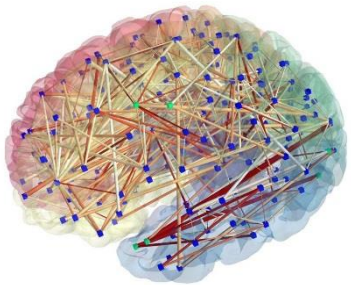
l	l_{rand}	C	C_{rand}
3,65	2,92	0,79	0,00027



Small-world network!







The same topological structures were identified in scientific collaboration networks, power grid networks, metabolic networks, neuronal networks, etc..

Watts&Strogatz, Nature 1998

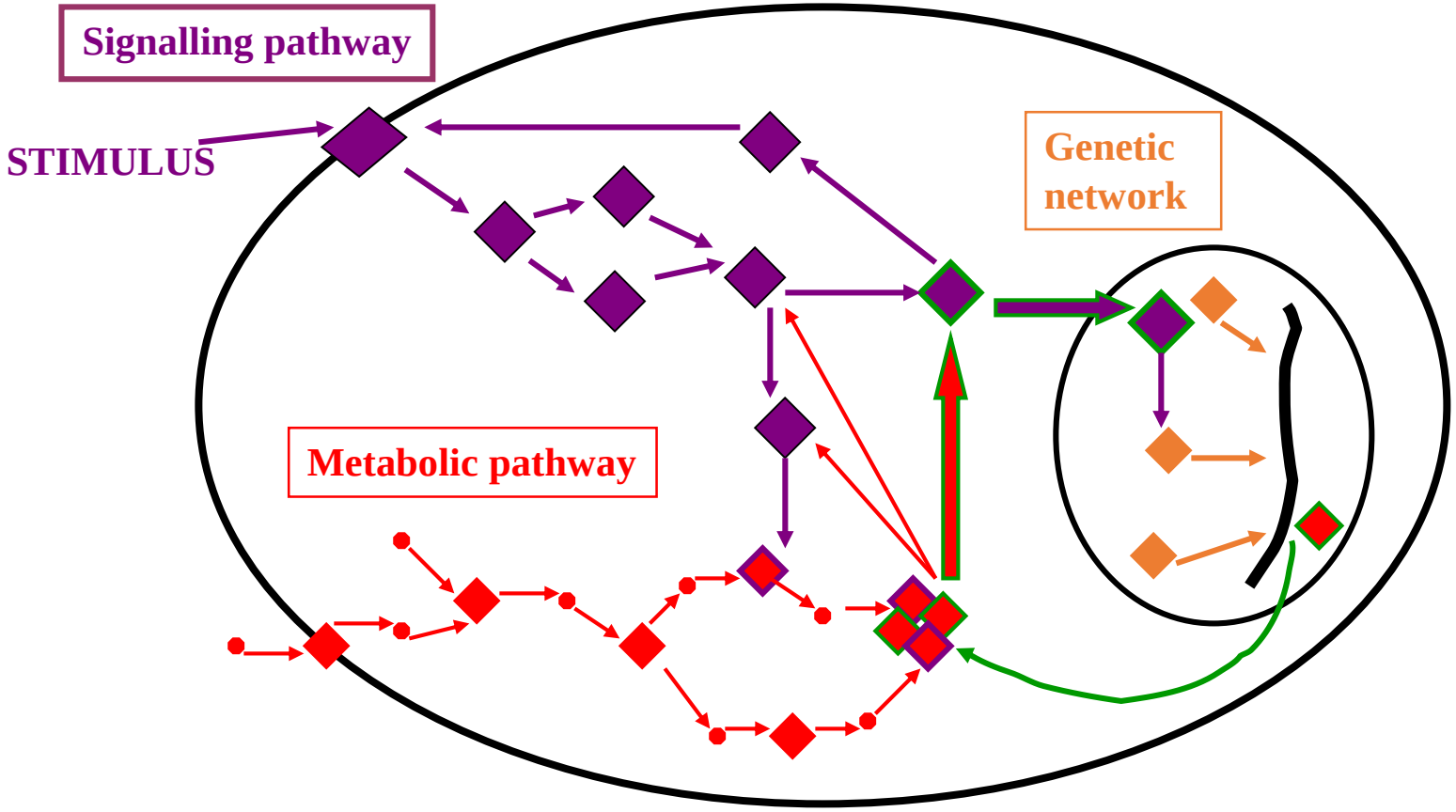
Subcellular molecular networks

Molecular interaction networks provide a framework to investigate cellular processes.
Complex topological features (small-worldness, heterogeneity and modularity).

Genetic regulatory networks

Protein-protein intetraction networks (PPI)

Metabolic networks



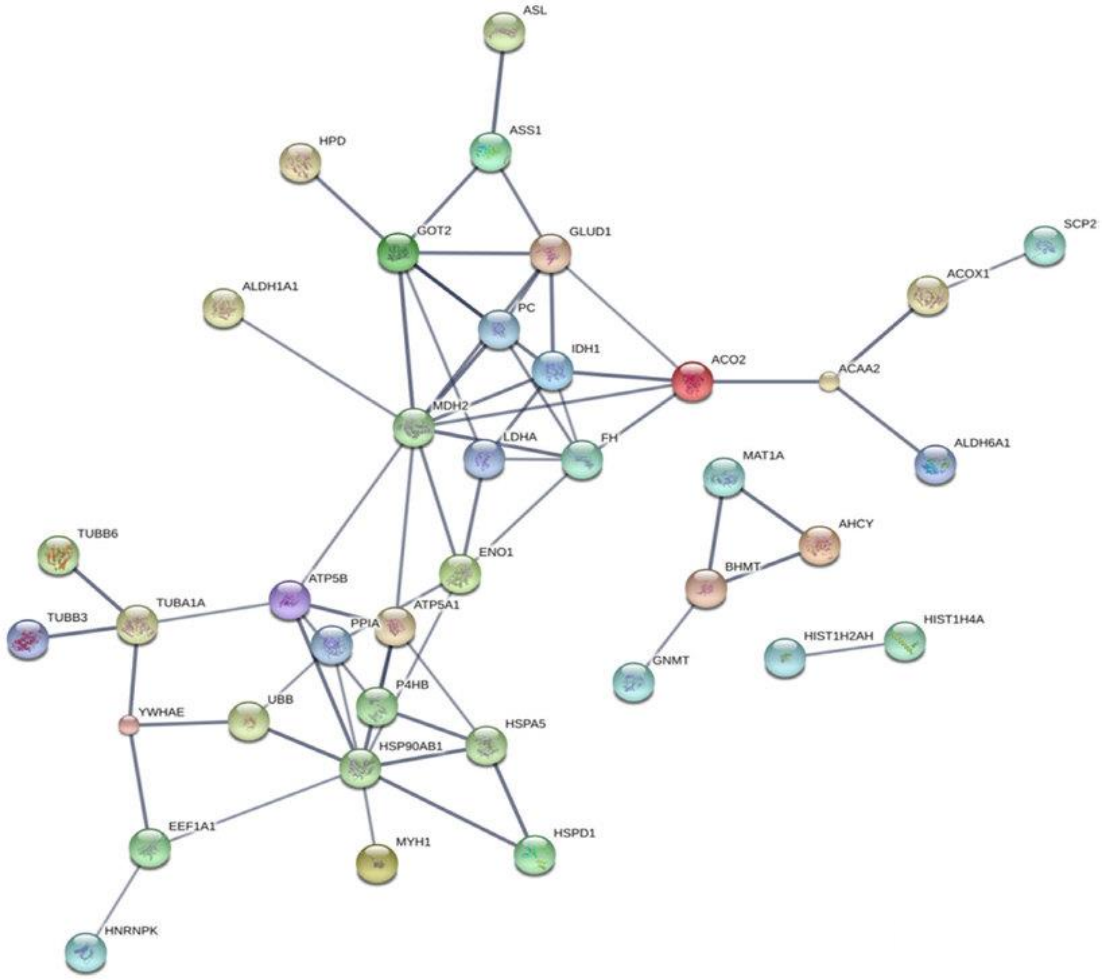
Barabasi & Oltvai, Nature Rev Gen 2004
Klosik et al., Nature Communications 2017

Protein-protein interaction (PPI) network

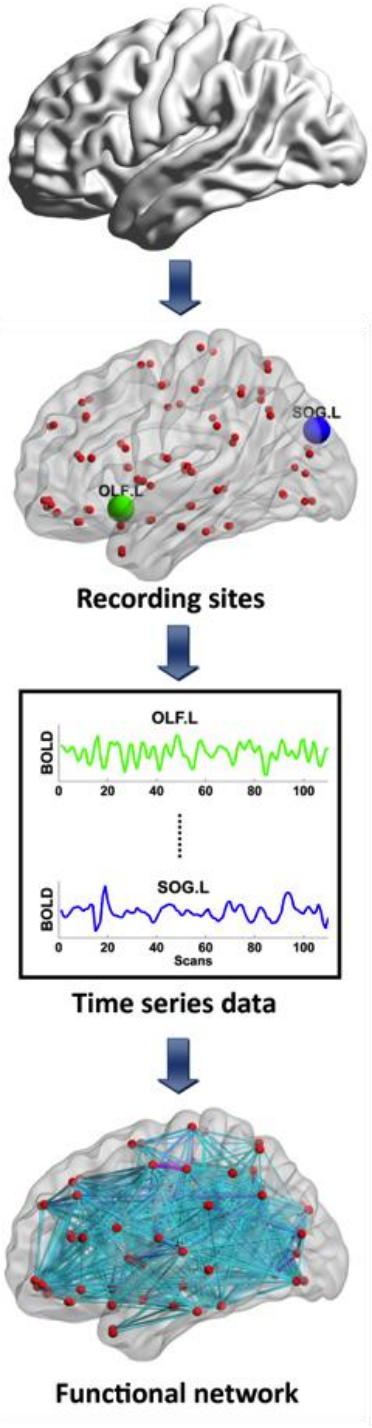
- Protein connectivity at proteome-scale.
- Node = specific protein
- Edge = interaction between two proteins.

Establishing connections:

- The proteins interact physically and form large complexes
- The proteins are enzymes that catalyze two successive chemical reactions in a pathway
- One of the proteins regulates the expression of the other.



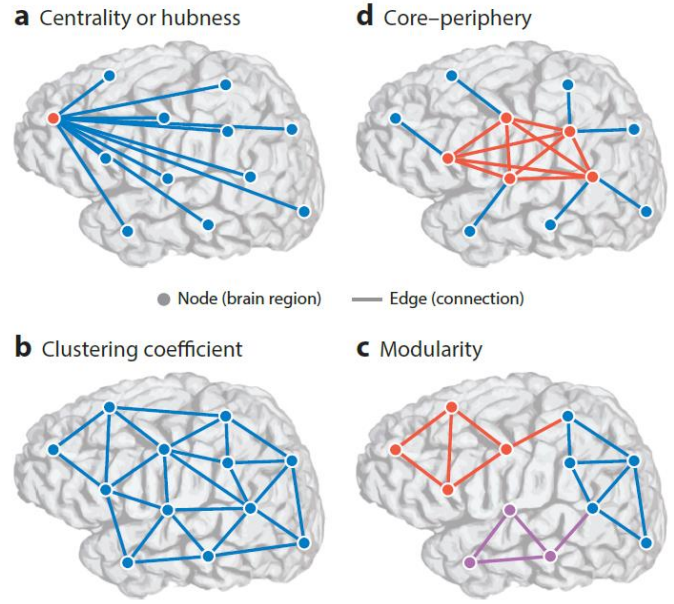
Vykoukal et al., 2017



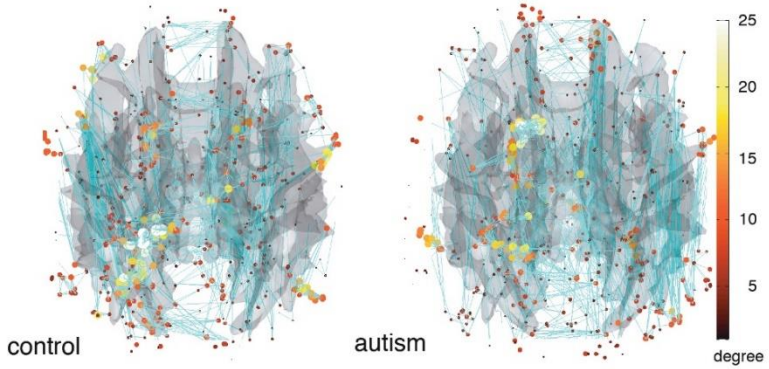
Functional connectivity of brain networks – extracting interaction patterns out of dynamics

- Parts of the brain are (functionally) connected and work synchronous.
- The interconnectness between regions can be regarded as a network.
- For the description and analysis of brain networks we can use theoretical tools from the complex network theory.

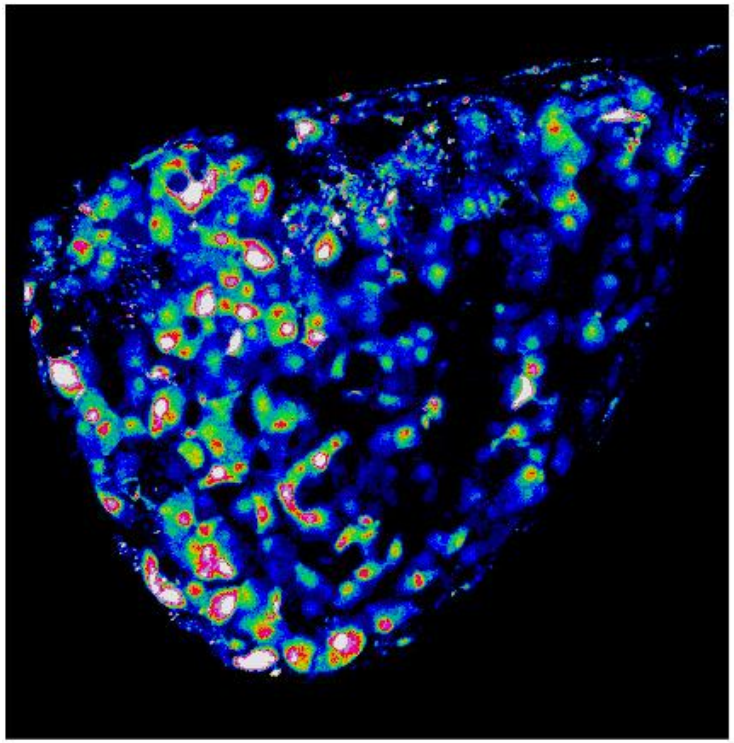
Under pathological conditions – the network structure changes

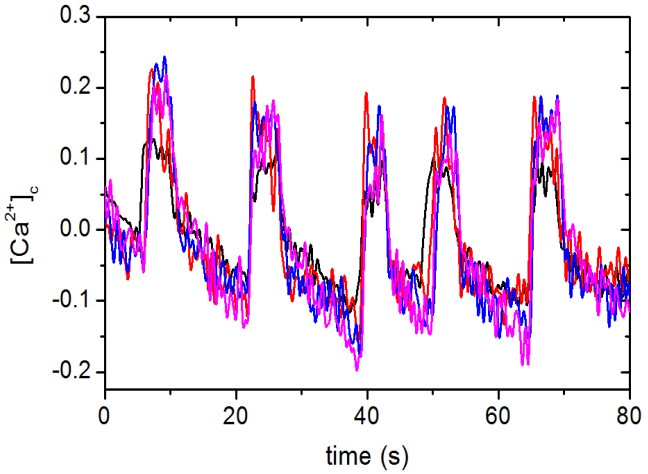


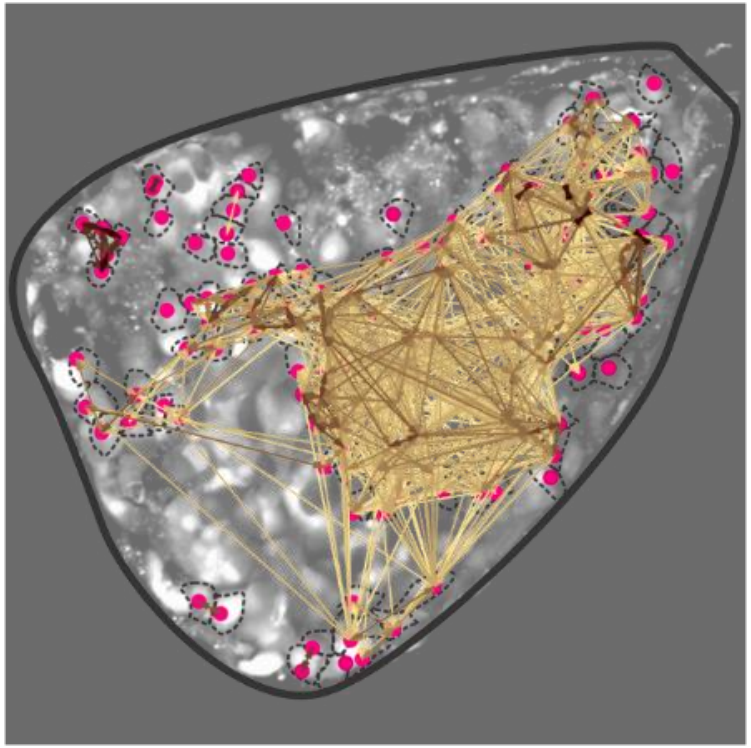
Bassett et al., Annu Rev Biomed Eng 2017



Our work: Connectivity within the islets of Langerhans -> complex network



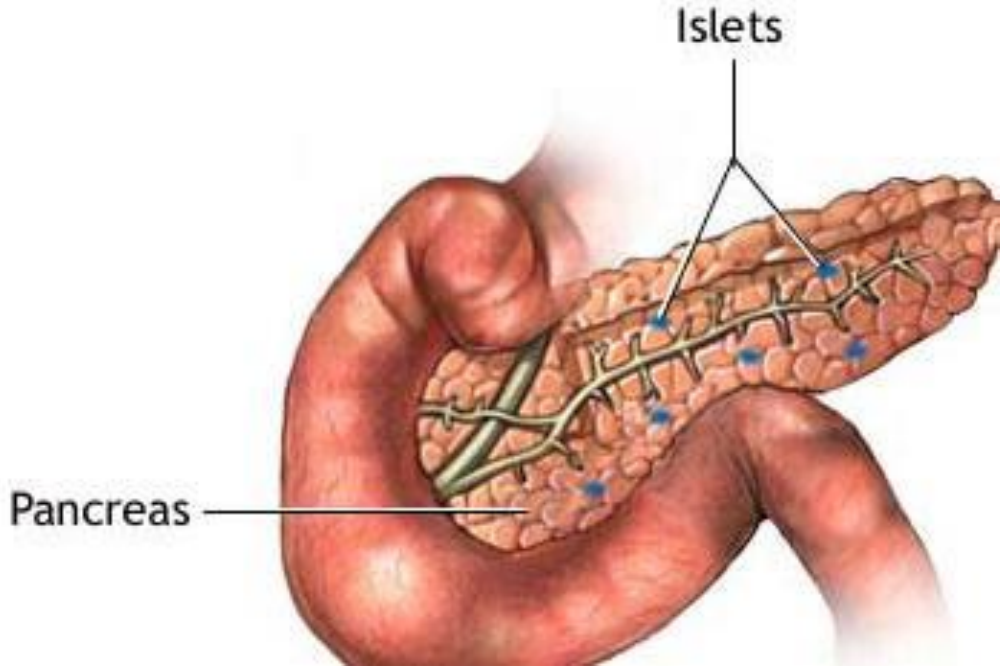




Our goal: to quantify intercellular interaction patterns within living tissues.

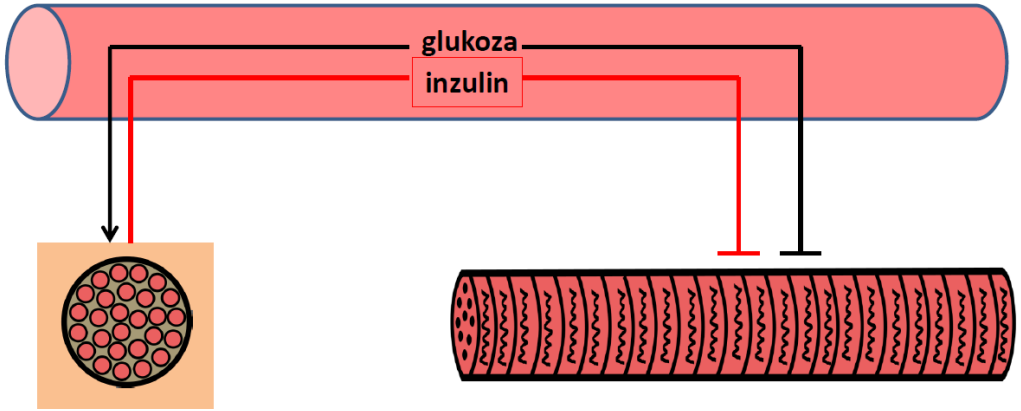
Regulation of blood glucose level by pancreatic islets

- Pancreas – the key organ for the regulation of blood sugar.
- Islets of Langerhans; beta cells -> sensors for level of blood glucose.
- Beta cells -> at higher glucose concentration they become active and secrete insulin.
- Insulin-> hormone, that lowers blood glucose levels.
- Disruptions of beta cell functioning -> impaired insulin production -> diabetes.

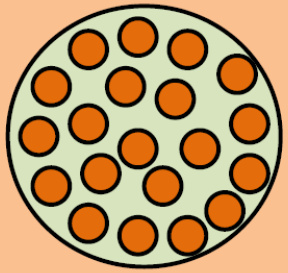


Why is it important to study the physiology of beta cells?

- Disruptions in beta cell function lead to diabetes mellitus.
- App. 8.5 % of world‘s population suffer on diabetes, the number is increasing.
- 550 billions is the global economic cost of diabetes.
- Diabetes decreases the quality of life.
- People suffering on diabetes are more susceptible the other diseases.

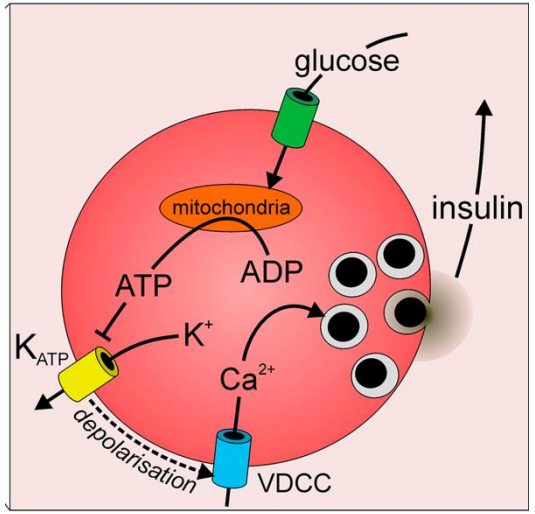


Studying *in vitro* on **tissue slices**.

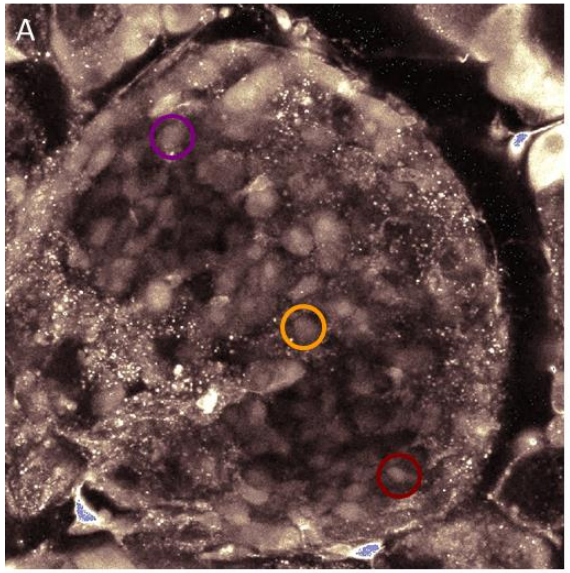


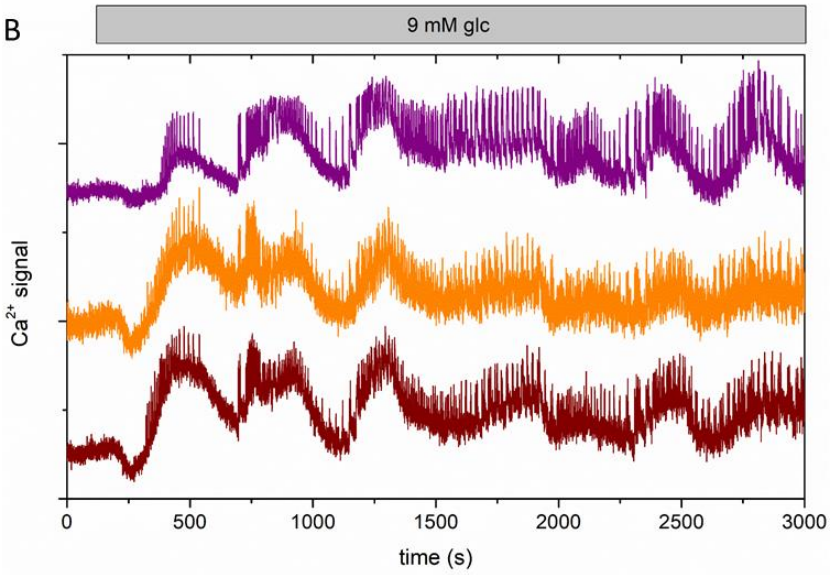
Cellular mechanisms for blood sugar regulation

- Glucose acts as a stimulus that depolarizes the beta cell.
- Depolarization leads to metabolic processes, which in turn provoke the (periodic) rise in intracellular Ca^{2+}.
- Ca^{2+} activity leads to insulin secretion.



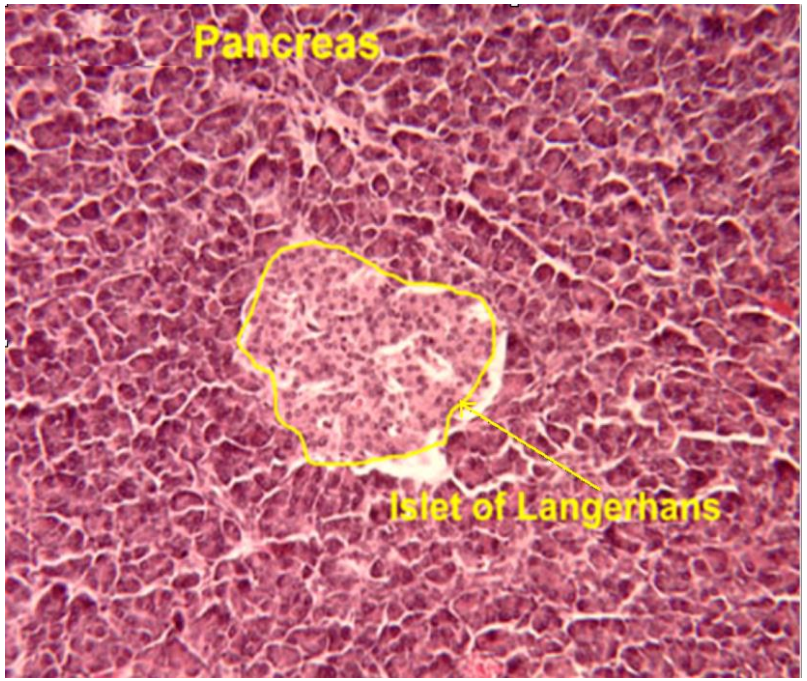
Typical Ca^{2+} signal of a pancreatic beta cell after stimulation with glucose (switch from 6 mM to 9 mM):

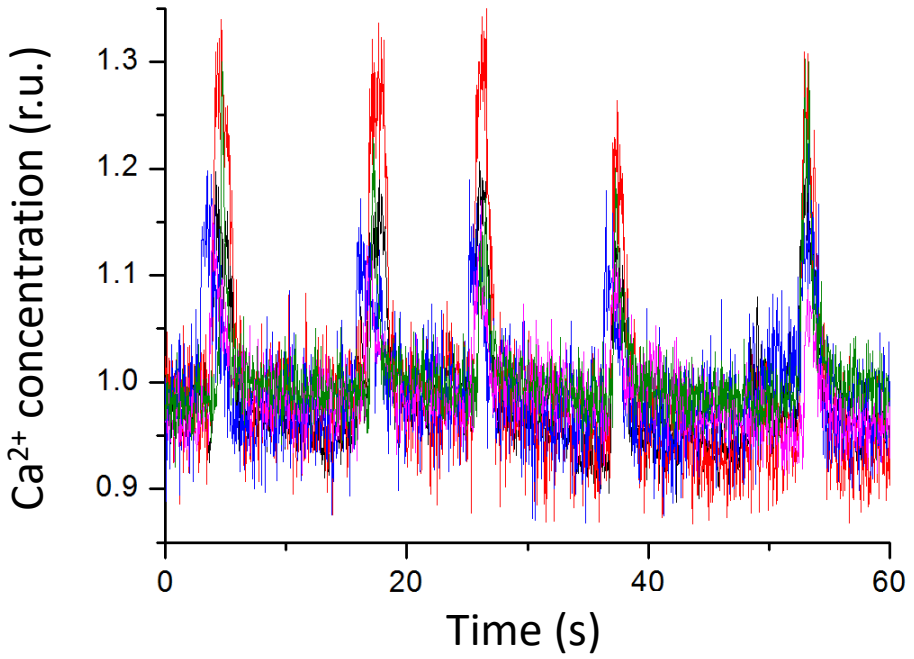




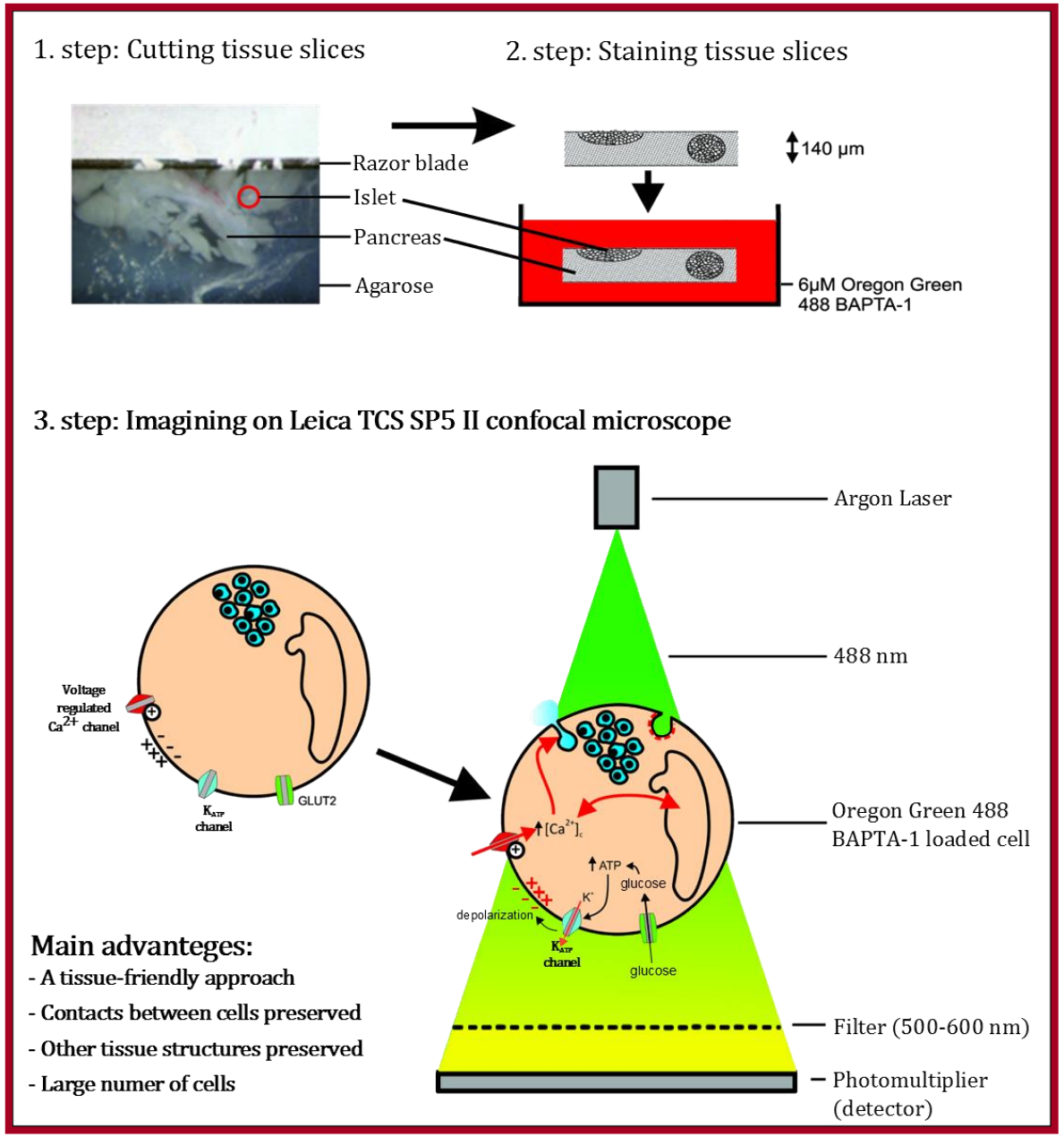
Motivation: Regulation of insulin secretion is a collective process!

- Intercellular communication and coordinated cellular activities are necessary for secreting insulin on a global scale.
- Impairments in the intercellular communication lead to failures in insulin secretion.

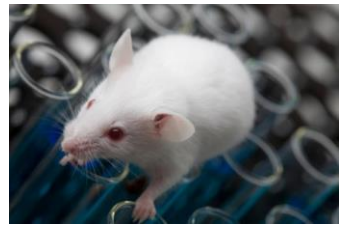


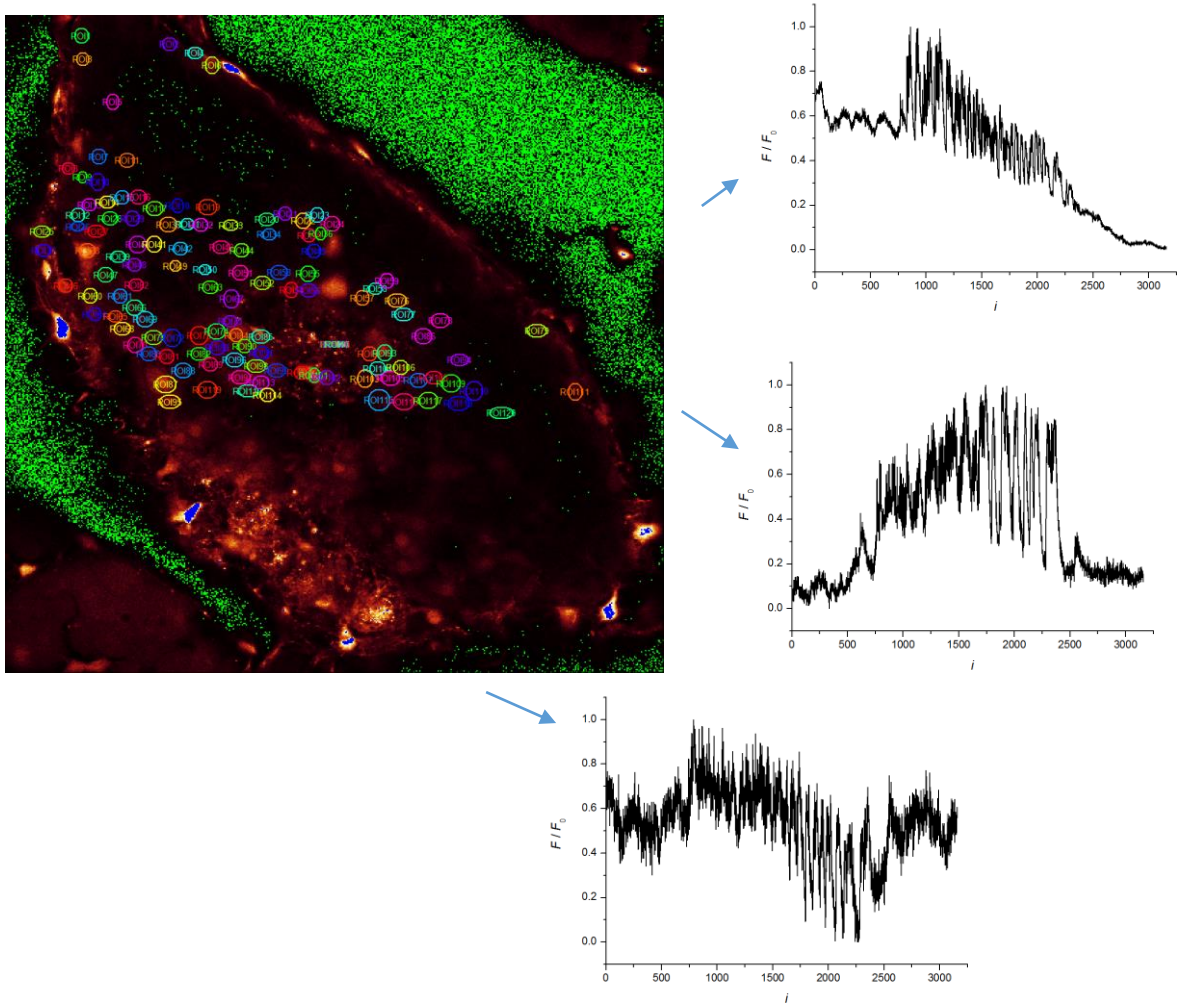


Multicellular confocal imaging in acute tissue slices:

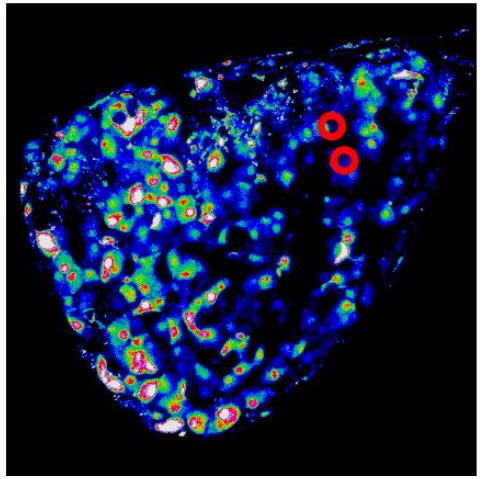


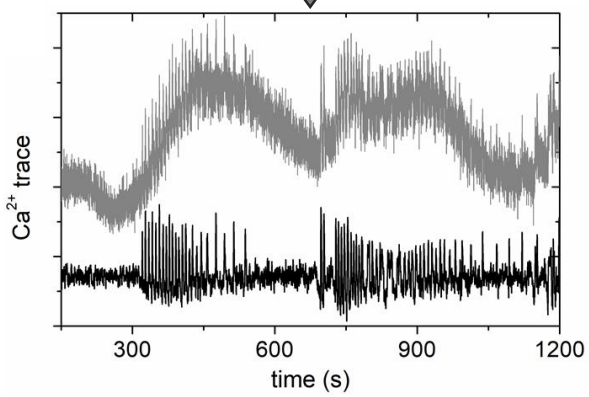
Measuring the Ca^{2+} dynamics in beta cells

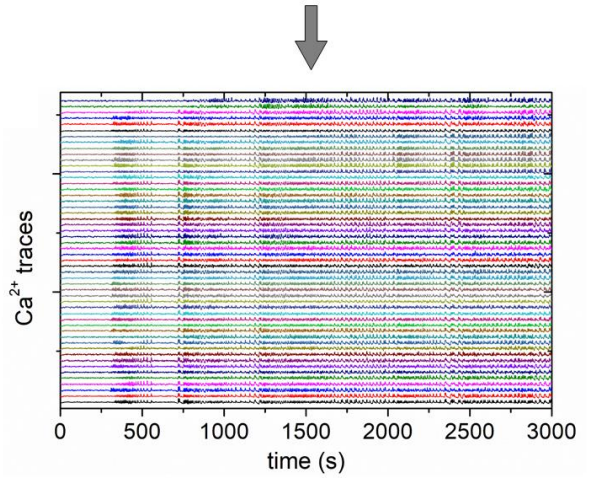


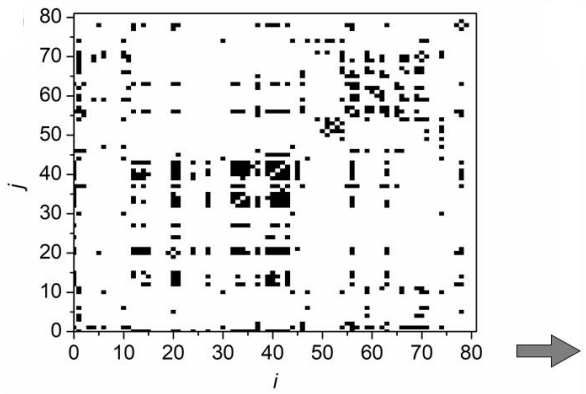


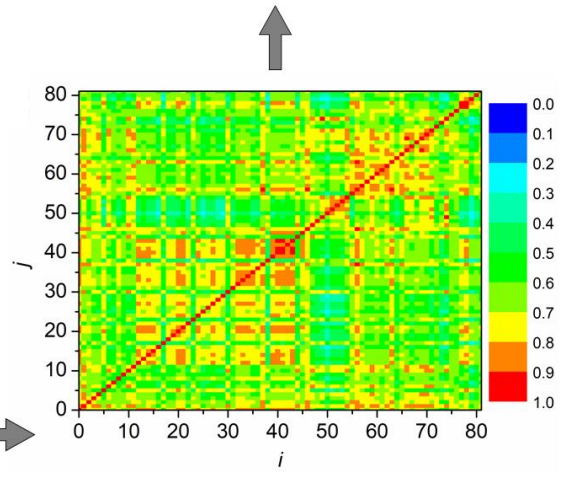
Extracting the functional connectivity patterns between beta cells

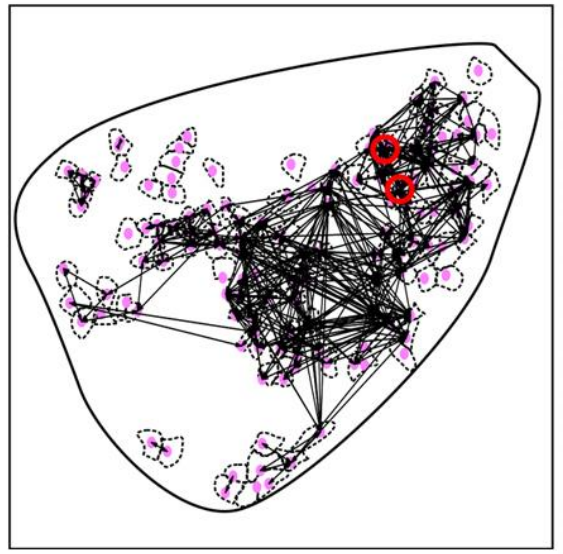








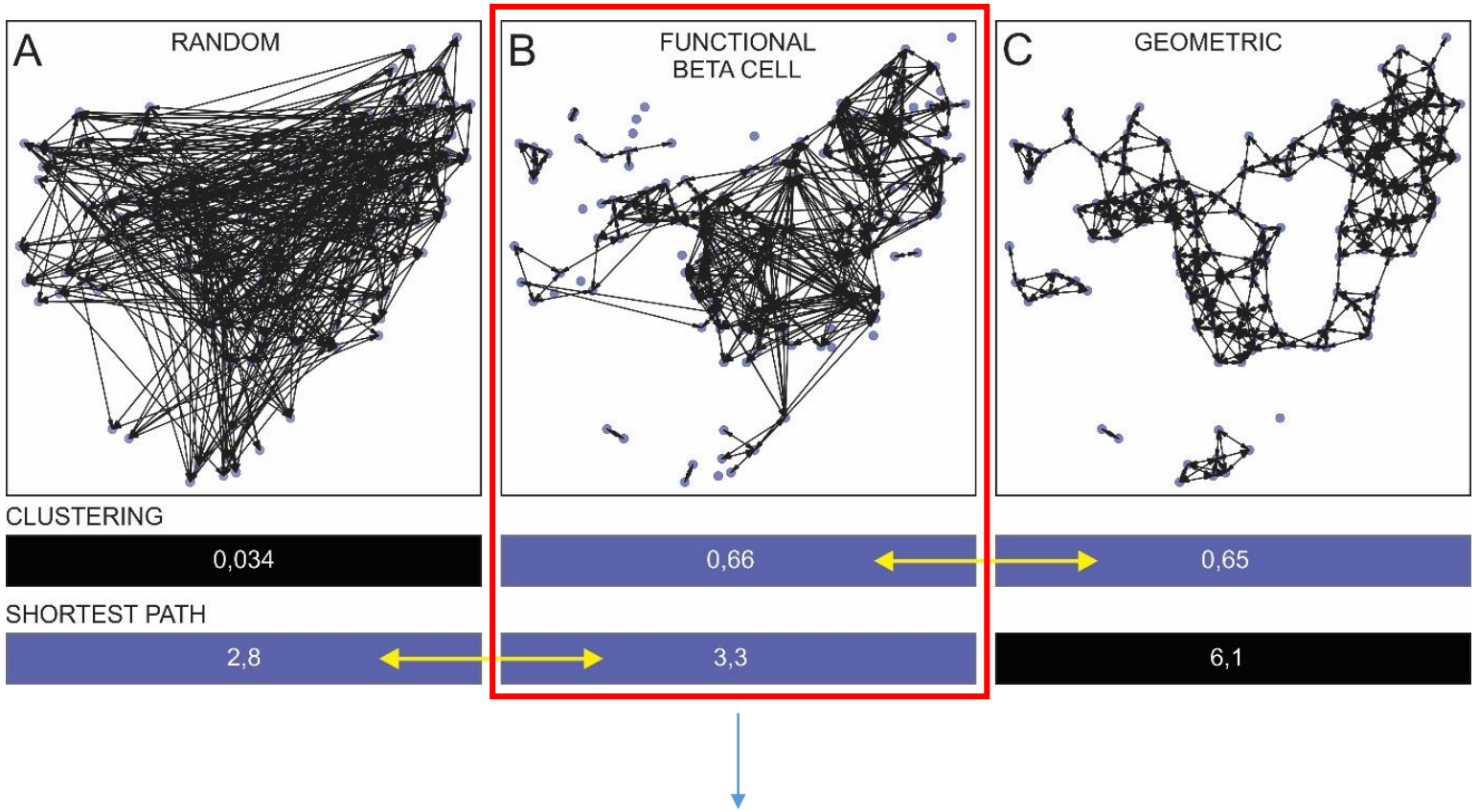




Network metrics:					
N	k_{avg}	C_{avg}	E_{glob}	SW	Q
82	6.83	0.48	0.26	3.63	0.46

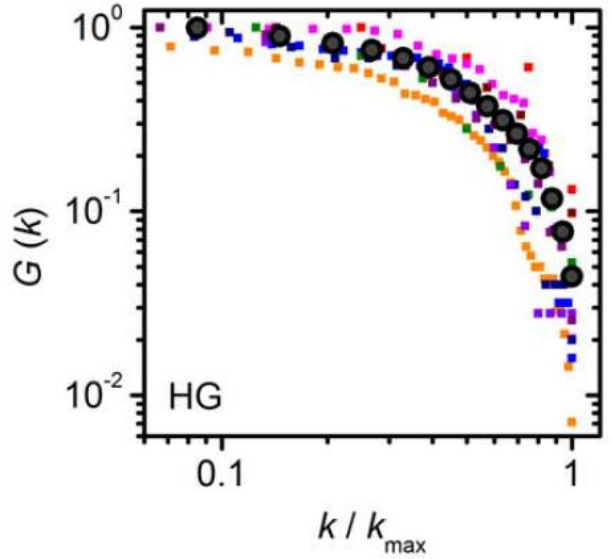
Is two cells are synchronized enough they are considered as connected.

Functional connectivity between beta cells reflects small-world properties



small-world network characteristics

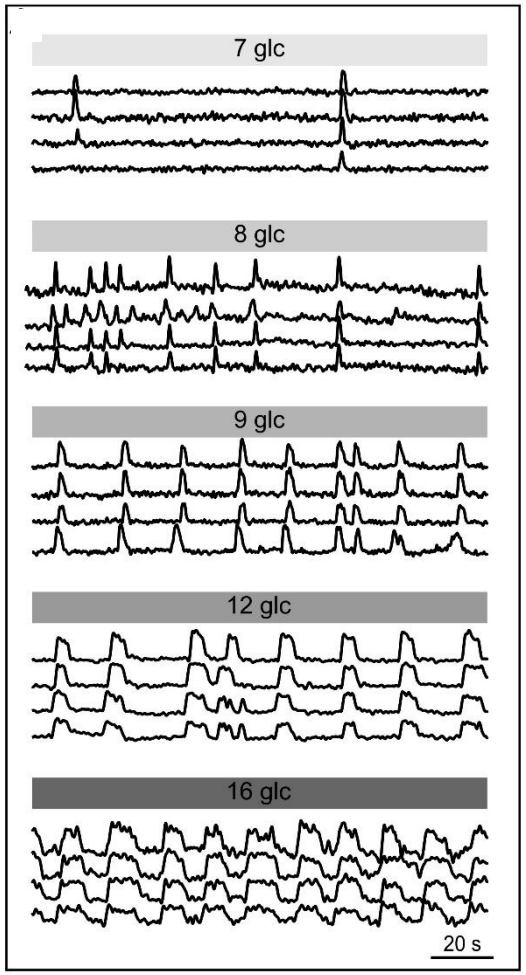
Cumulative degree distribution:



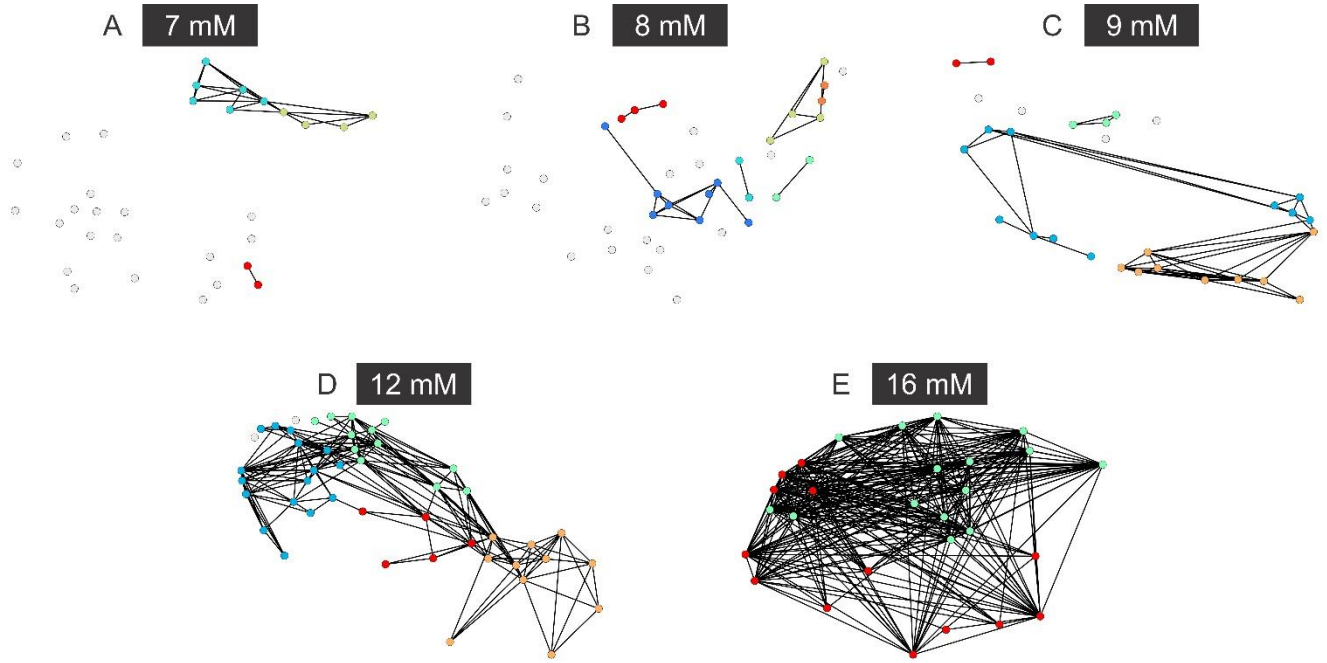
The beta cell functional network is a broad-scale small-world network!

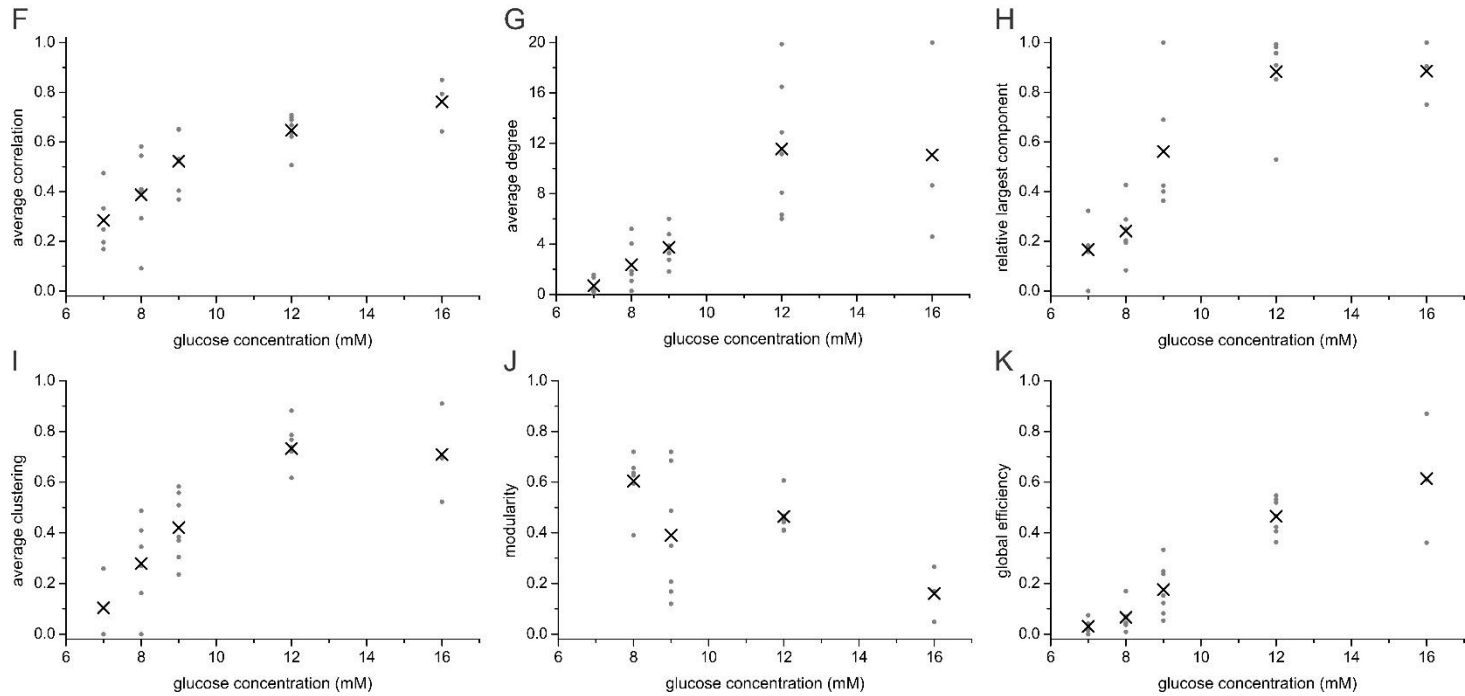
Stožer, Gosak, Dolenšek, et al., PLoS Comput. Biol. 2013

Intra- and inter-cellular beta cell activity under different glucose concentrations



Markovič, Stožer, Gosak, et al., Sci Rep 2015
Gosak, Dolenšek, Markovič, ASTE 2015



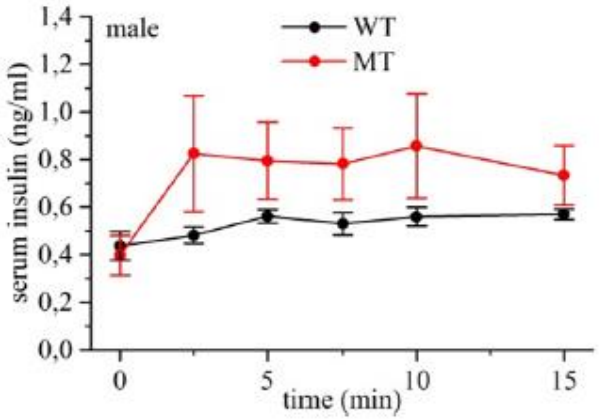


Assessing the beta cell network functionality in pre-diabetic animal models

SNAP-25b-deficienct mice:

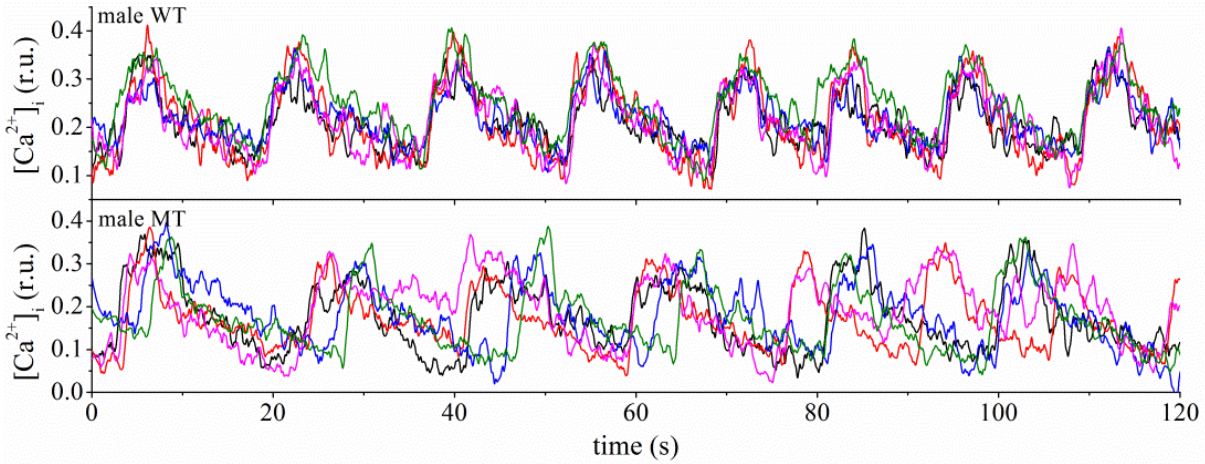
- Increased insulin secretion,
- Modified morphology of islets.

In vivo measurements of insulin secretion:

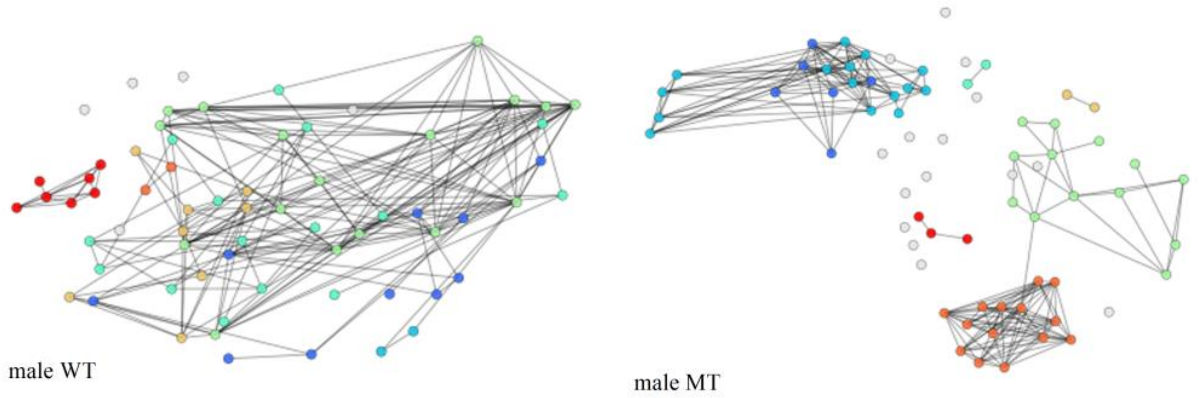


In collaboration with the Department of Molecular Medicine and Surgery, Karolinska Institut, Sweeden

Ca^{2+} traces after stimulation with 12 mM glucose:



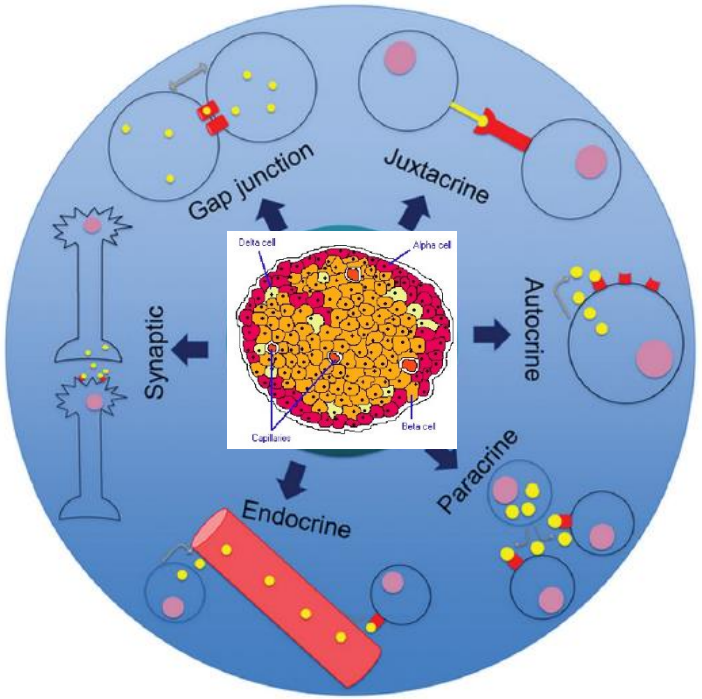
Functional networks – wildtype vs. mutant:



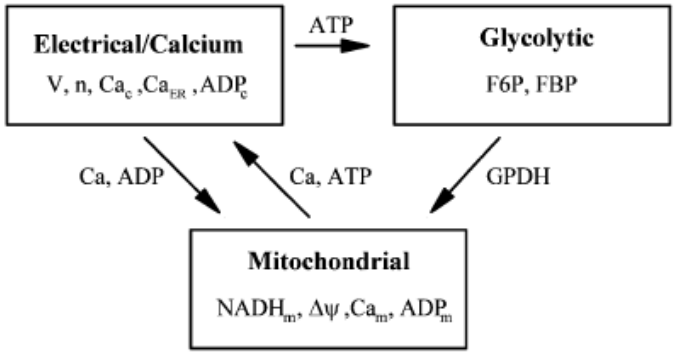
Daraio, Bombek, Gosak, et al., Sci Rep 2017

Is the „standard“ network approach an oversimplification?

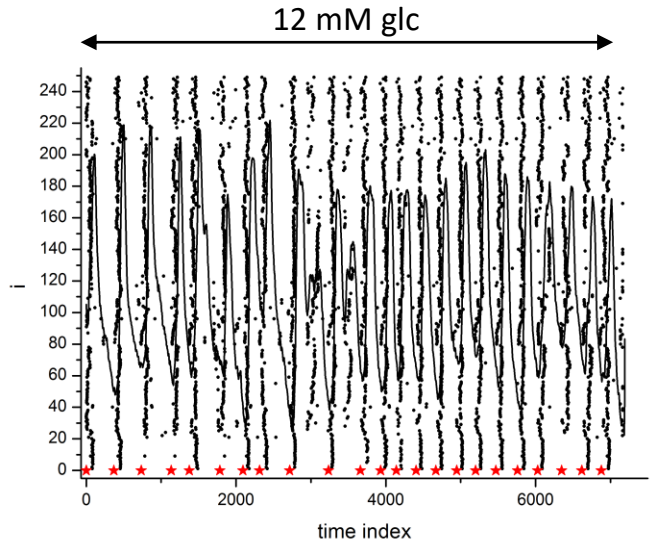
Several (interdependent) communication mechanisms; multiple types of intercellular interactions



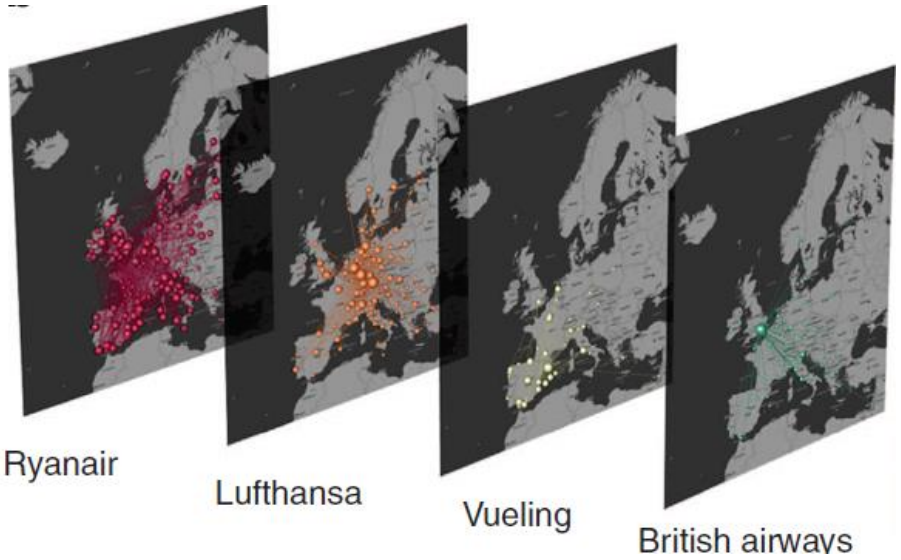
Beta cell dynamics is governed by feedback interactions of different oscillatory subsystems



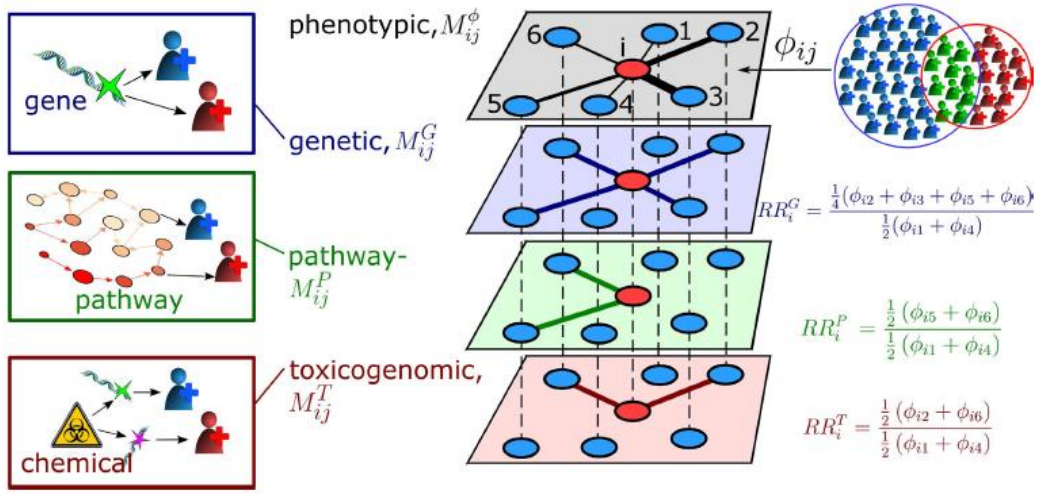
Beta cell activity is nonstationary even under constant stimulatory conditions



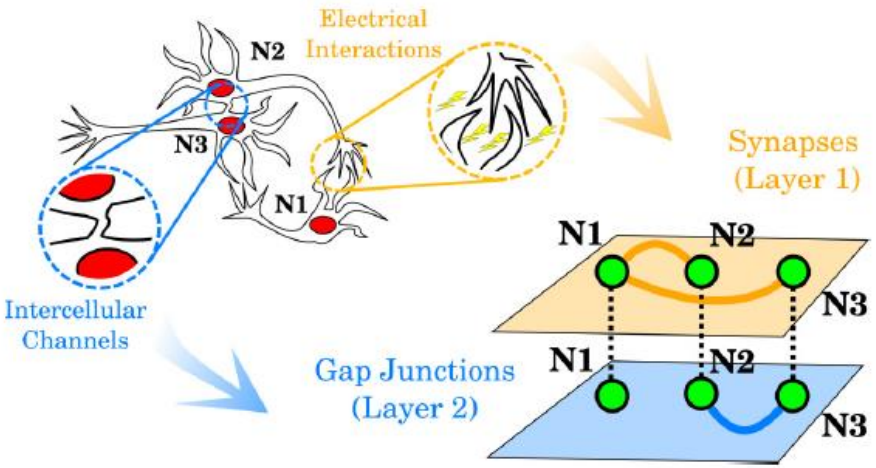
The multilayer network formalism



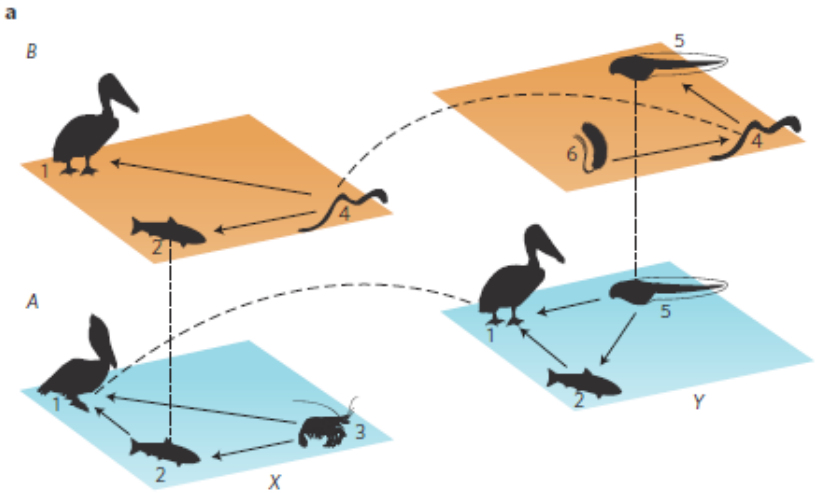
Domenico et al., Nature commun. 2015



Klimek et al, Sci Rep 2016



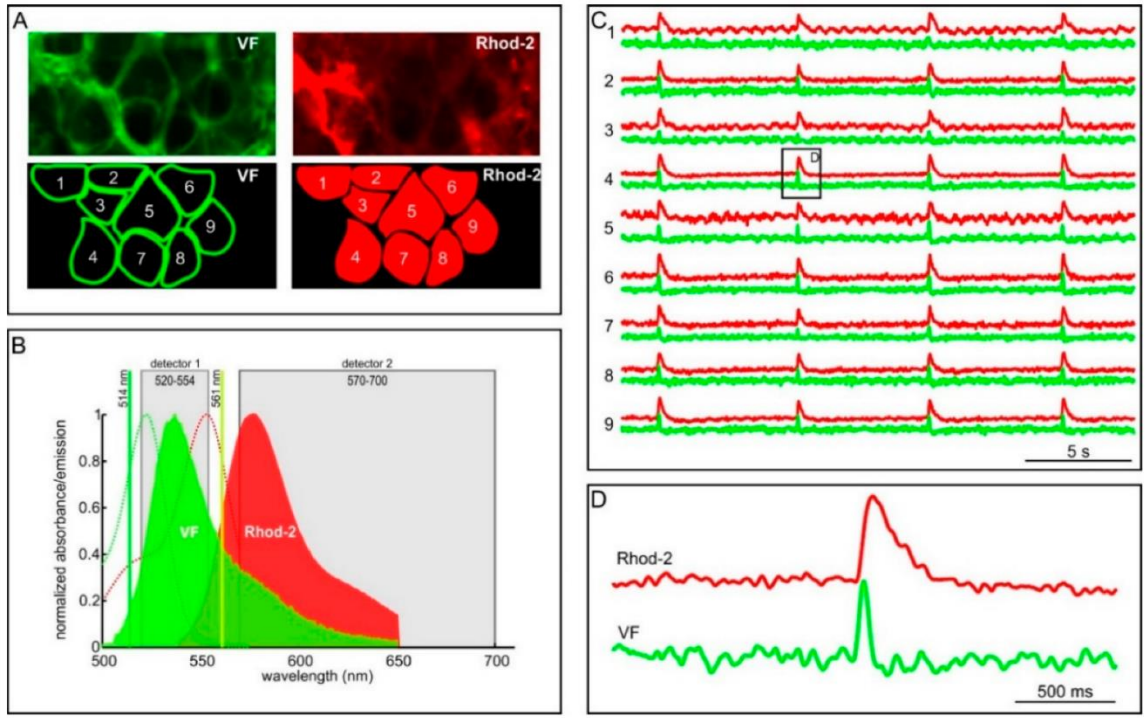
Battistion et al., PRE 2014



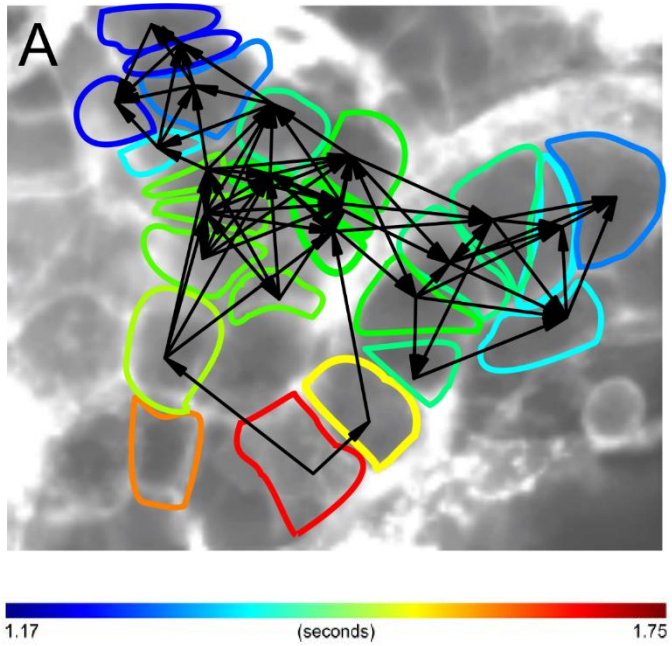
Pilosof et al., Nature Ecol. Evol. 2017

Studying the relationship between membrane potential and Ca^{2+} dynamics in beta cell syncytium by means of multiplex network representation

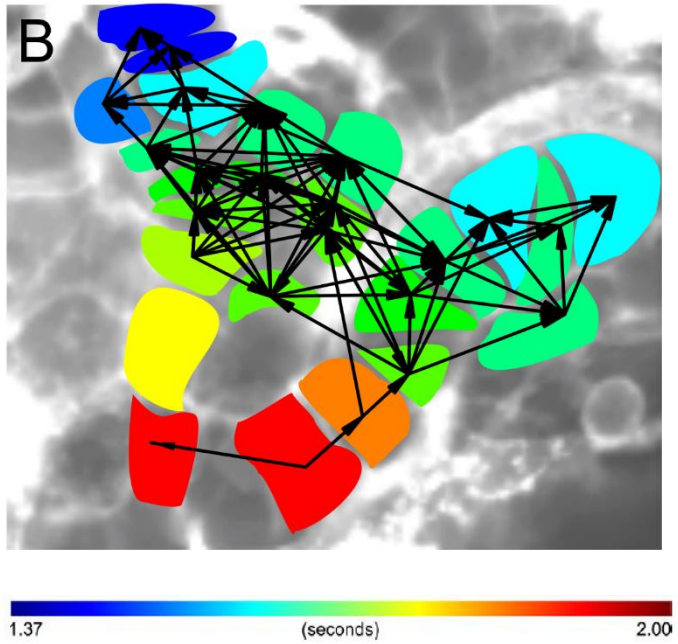
Simultaneous measurments of membrane potential (VoltageFluor dyes) and Ca^{2+} concentration (Rhod-2 marker):



Spreading of the MP signal:



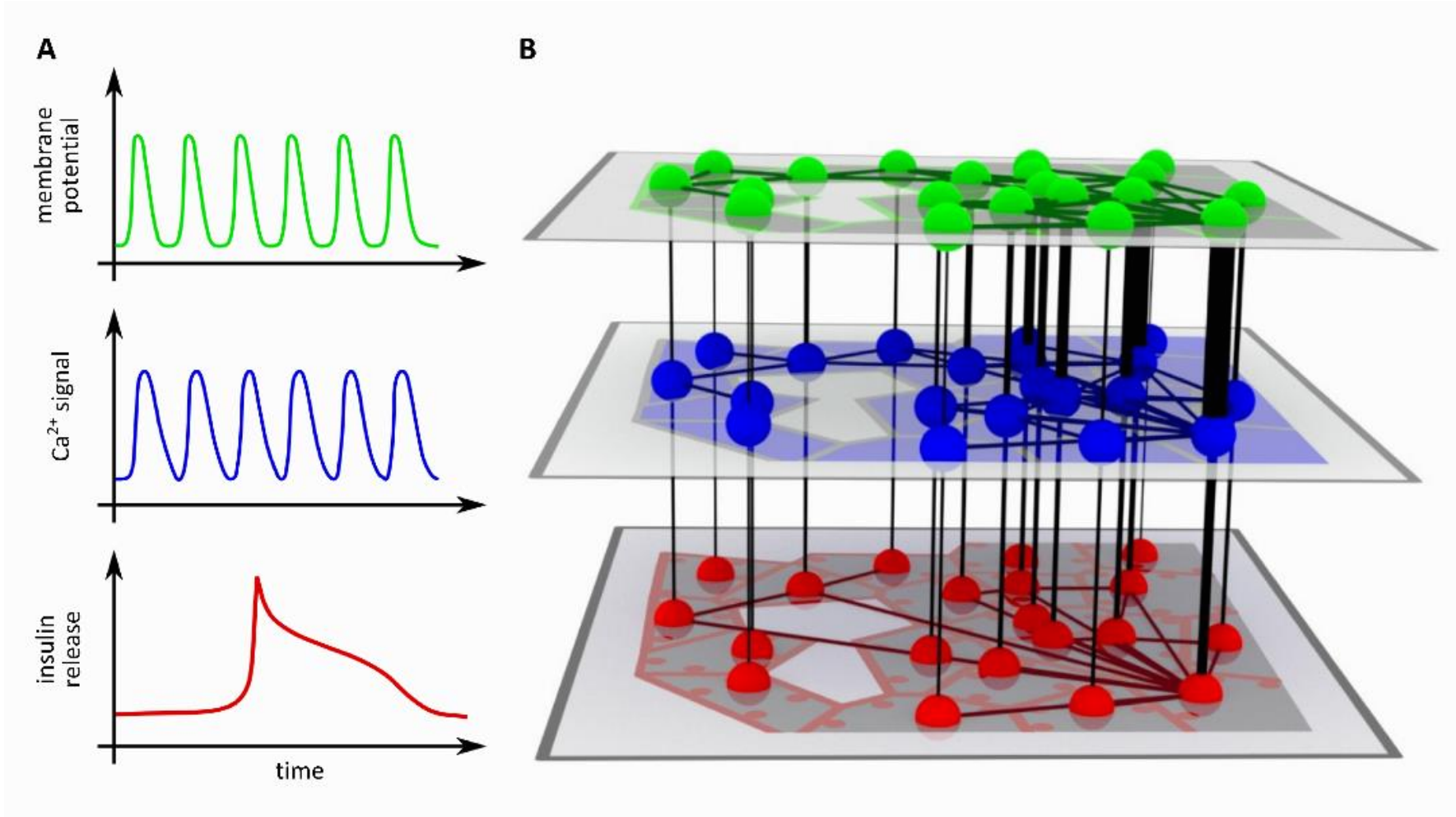
Spreading of the Ca^{2+} wave:



Dolenšek, Stožer, Skelin, et al., PLoS one 2013
Dolenšek, Špelič, Klemen, et al., Sensors 2015
Gosak, Dolenšek, Markovič, et al., Chaos, Solitons & Fractals 2015

Multilayered intercellular beta cell networks

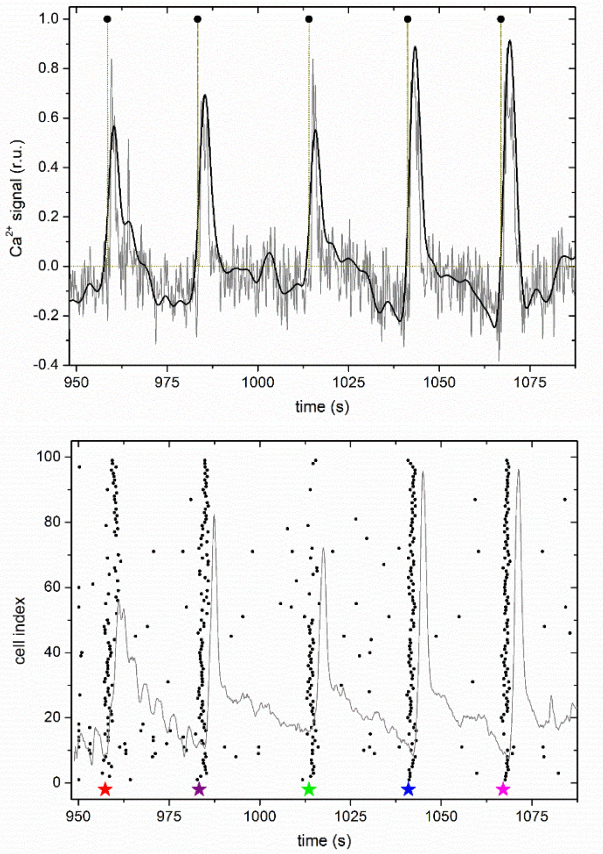
Hypothetical multiplex beta cell network: functional interactions based on simultaneously recorded membrane potential (green), calcium (blue), and exocytotic event dynamics (red). The thickness of interlayer connections reflects the time lag between individual signals.

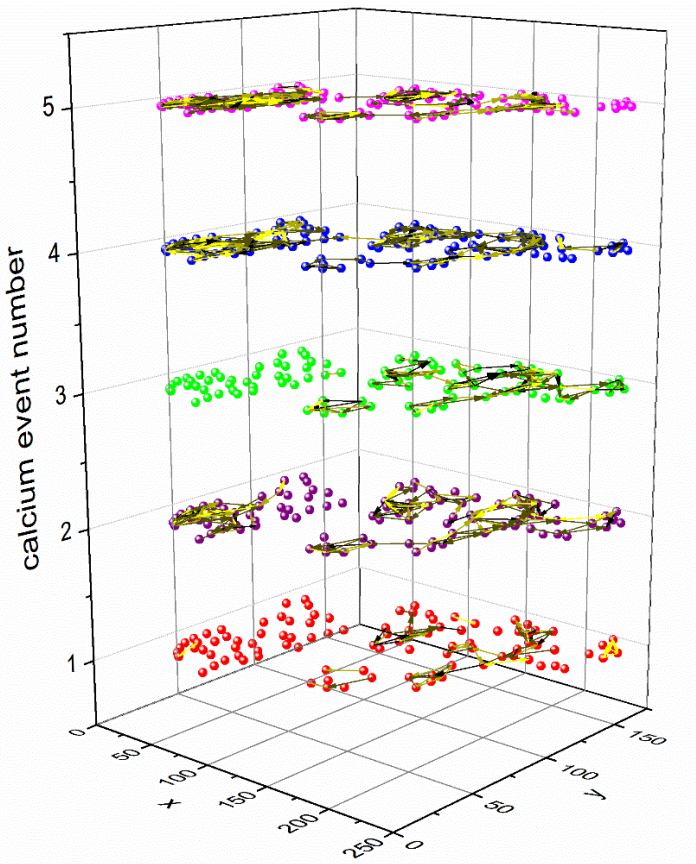


Gosak, Markovič, Dolenšek, et al., Phys. Life Rev. 2018

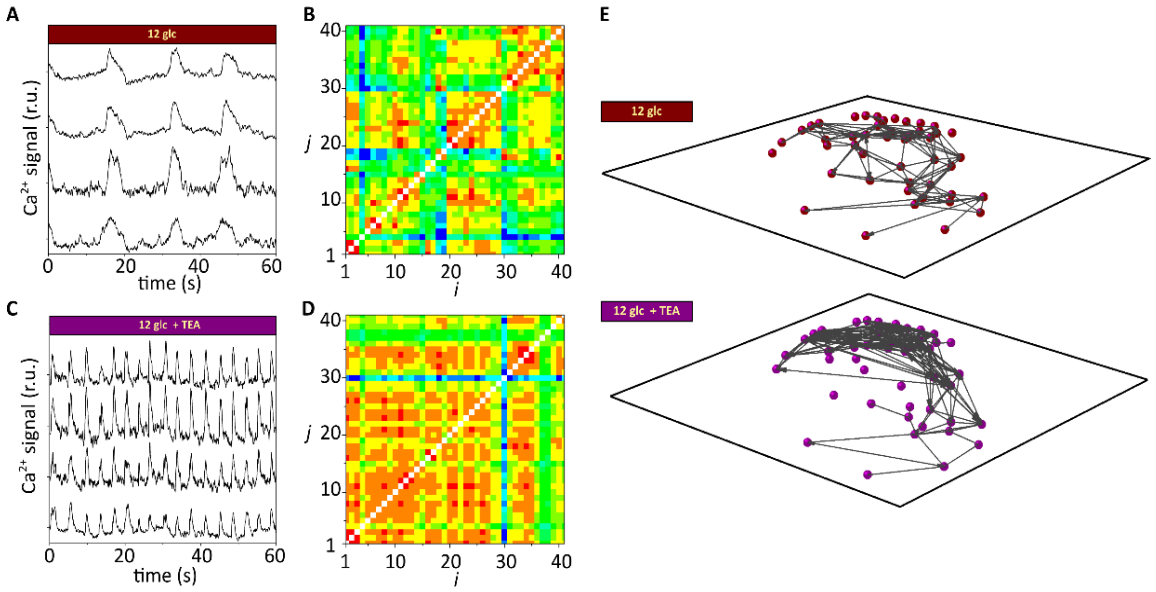
Assessing the temporal nature of intercellular communication by means of multilayer network analysis

Individual Ca^{2+} events as temporal network layers:





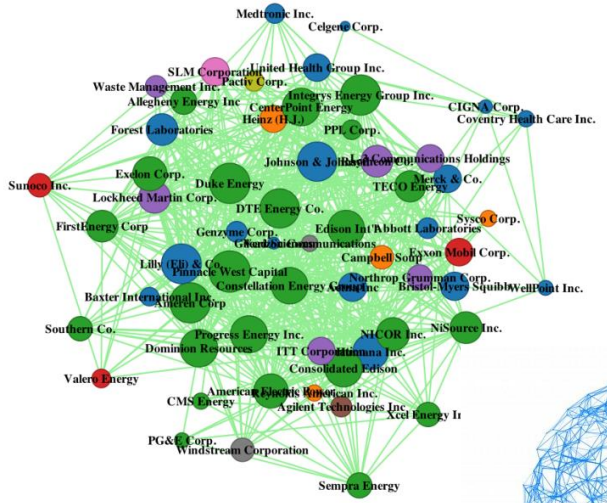
Quantifying the changes in intercellular interactions provoked by pharmacological interventions:

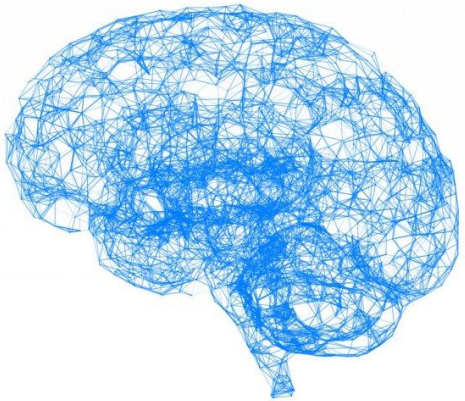


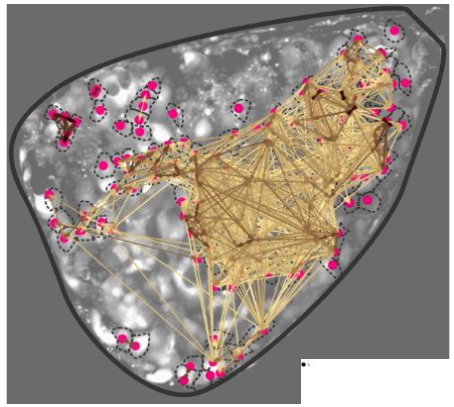
Gosak, Markovič, Dolenšek, et al., Phys. Life Rev. 2018

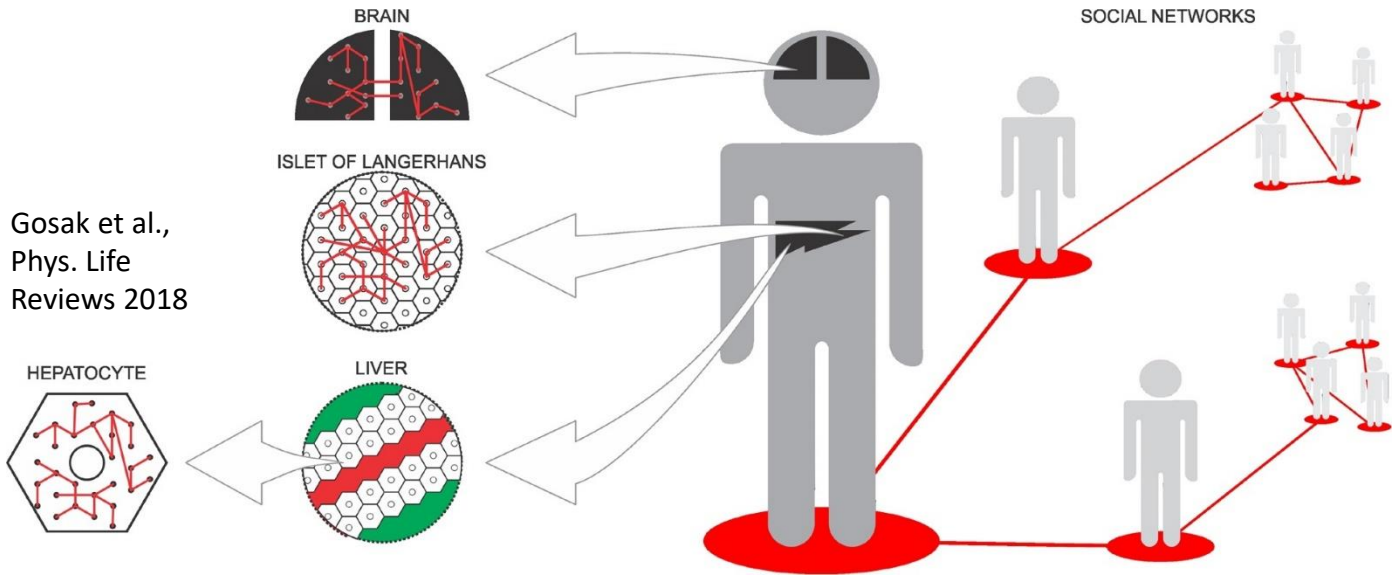
We live in a world of networks

- Complex biomedical systems are constituted by many nonlinear dynamical elements, which interact in a non-trivial manner.
- Understanding their functional organization is a great challange.
- Network science offers a huge potential to address these issues.

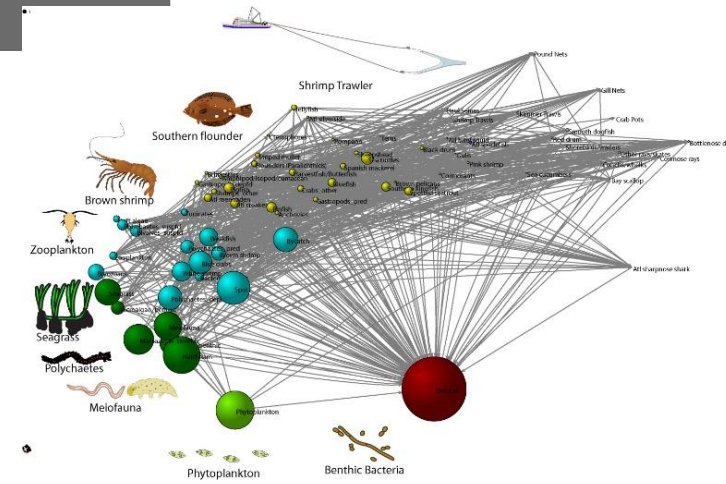








Gosak et al., Phys. Life Reviews 2018



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