Networks and stability

Part 1 – Network topology

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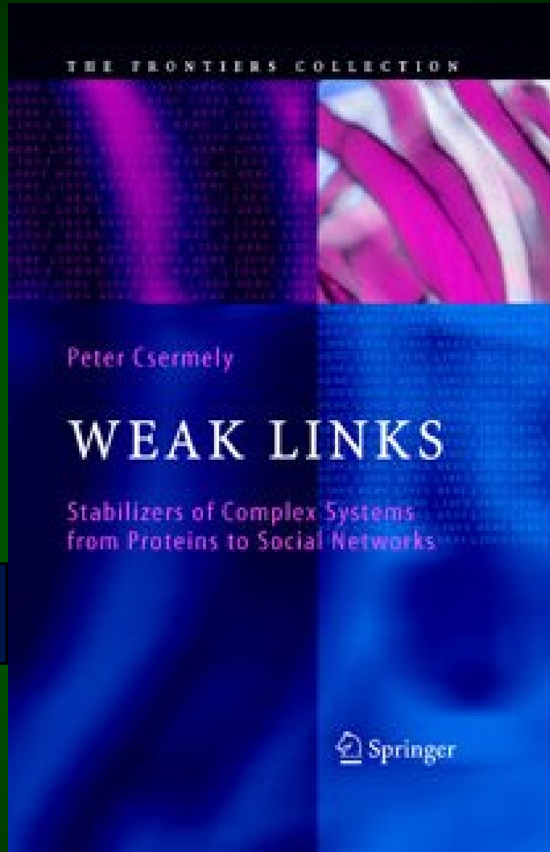
Péter Csermely and
the Turbine team

www.weaklink.sote.hu/halozat.html

Hungarian

Vince Publisher, Budapest, 2005-2007



English

Springer, 2006-2009

www.weaklink.sote.hu/weakbook.html + Google

Information explosion
- data explosion
- connection explosion

„we are drowning in a sea of data and starving for knowledge"

Sydney Brenner, Nobel Lecture

Left → right hemisphere dominance + the role of the unconsciousness

~~**Gutenberg-galaxy**~~
~~Enlightment~~
~~left hemishpere~~

- ✓ **visual image**
  right hemisphere
- ✓ **emotions**
  subconsciousness

New synthesis: networks

✓ both visual and

✓ logical

Newest synthesis: subconscious + emotions…

Traditional view

cause → effect

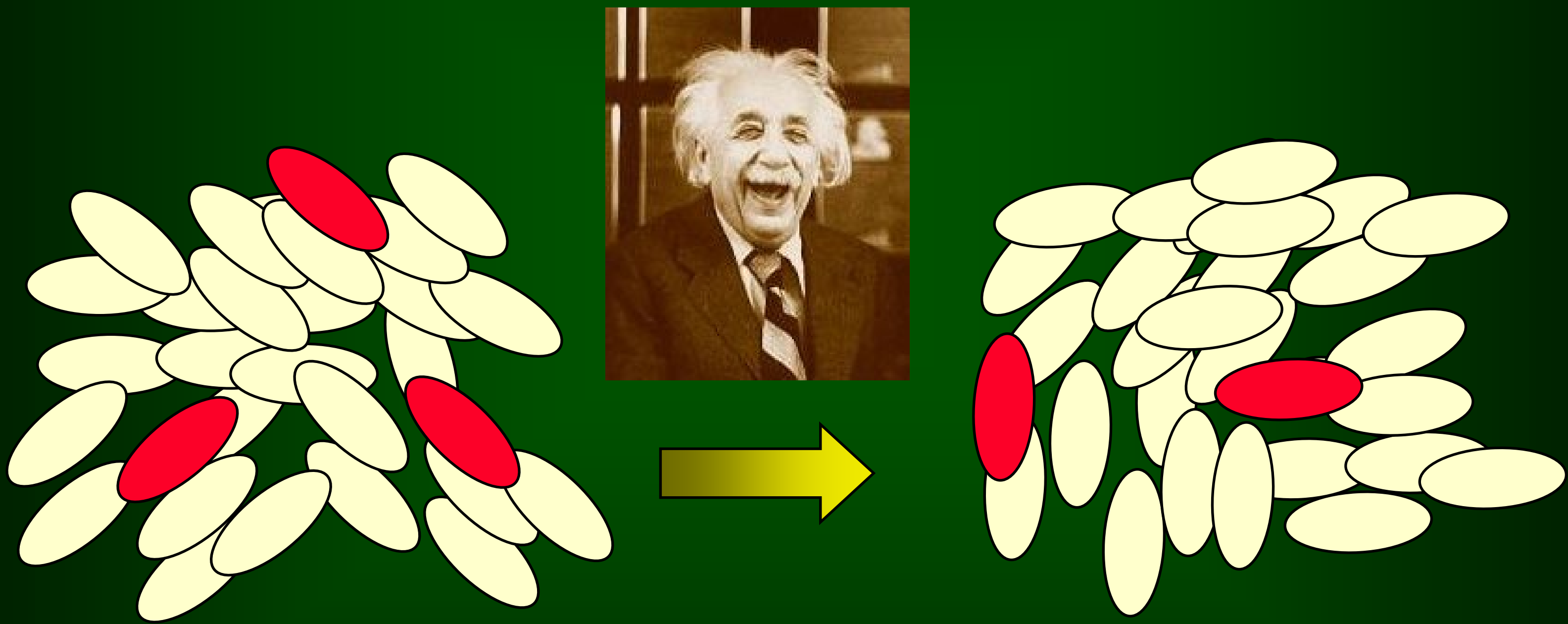
(Paul Ehrlich's magic bullet)

Recently changed view

100 causes

100 effects

Networks may help!



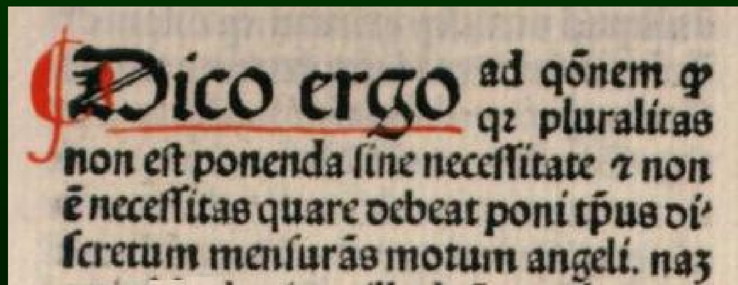
major causes

major effects

Occam’s razor

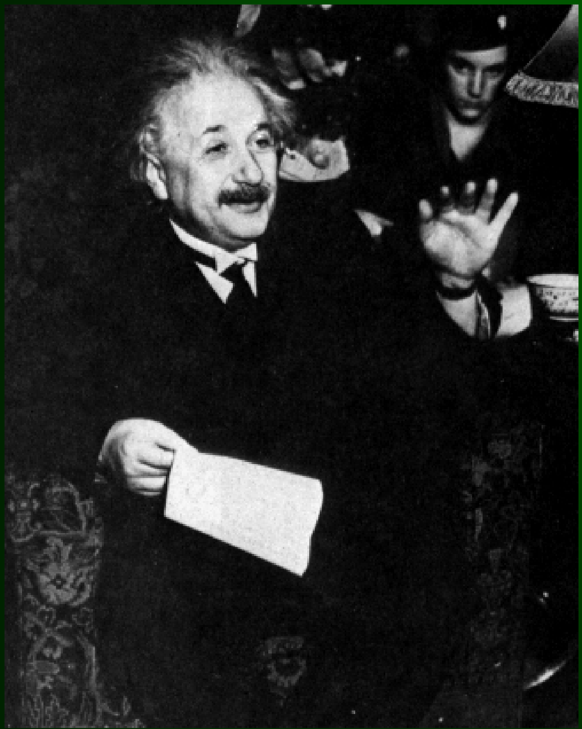
” ... plurality is not to be posited without necessity…”

William of Occam (1285-1349)



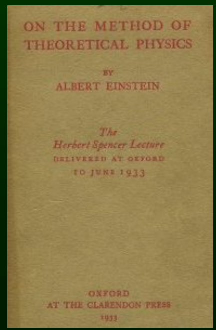
Dico ergo ad q̃onem q̃ qz pluralitas non eſt ponenda ſine neceſſitate ⁊ non ē neceſſitas quare debeat poni tp̃us di- ſcretum menſurãs motum angeli. naz

Einstein's razor



" ... the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience"

The Herbert Spencer Lecture (1933)



Warren Weaver (1948)
American Scientist
36:536-544

1. **problems of simplicity**
   Leibnitz, Newton
2. **disorganized complexity**
   Boltzmann, Maxwell, Gibbs
3. **organized complexity**

natural sciences	physician	social sciences
point, node, exact	⟷	identity, context, fuzzy

Definition of networks

• nodes: parts of the system
which have common properties
• edges: connections of nodes
(weighted, directed, signed, coloured)

Caution: Extreme data reduction!
– based on background knowledge

Emergent properties of complex systems

emergent property: a property which can not be predicted from the properties of the parts (e.g. life, consciousness, God)

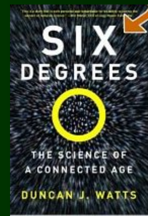
Novikoff, Science 101:209-215 (1945)

Networks can break conceptual barriers

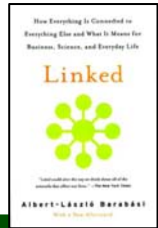
Networks have general properties

- small-worldness (6 degrees of separation)
- hubs (scale-free degree distribution)
- nested hierarchy
- stabilization by weak links

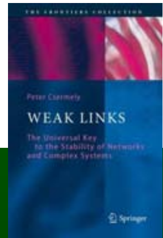
Karinthy 1929



Watts/Strogatz 1998



Albert & Barabasi, 1999



Csermely, 2004

Generality of network properties offers

- judgment of importance
- innovation-transfer across different layers of complexity

Crisis-prevention in different systems:
example to break conceptual barriers

Early-warning signals for critical transitions

Marten Scheffer[1], Jordi Bascompte[2], William A. Brock[3], Victor Brovkin[5], Stephen R. Carpenter[4], Vasilis Dakos[1], Hermann Held[6], Egbert H. van Nes[1], Max Rietkerk[7] & George Sugihara[8]

ecosystem, market, climate
- slower recovery from perturbations
- increased self-similarity of behaviour
- increased variance of fluctuation-patterns

Nature 461:53

Aging is an early warning signal of a critical transition: **death**

Prevention: elements with less predictable behaviour
- omnivores, top-predators
- market gurus
- stem cells

Farkas *et al.*, Science Signaling 4:pt3

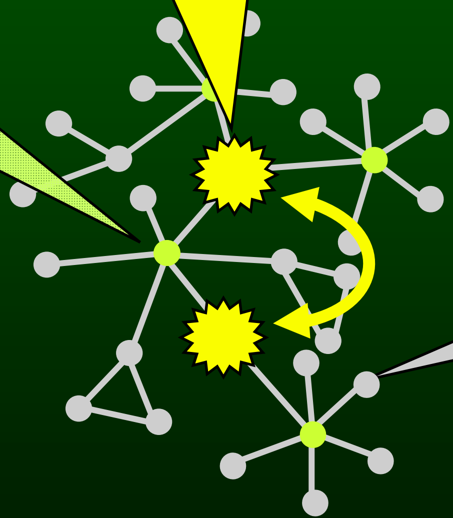
Creative nodes

(as possible targets of anti-aging therapies)

Creative: few links to hubs, unexpected re-routing, flexible, **unpredictable**

Why is such a behavior creative?

Distributor: hub, specialized to signal distribution, **predictable**

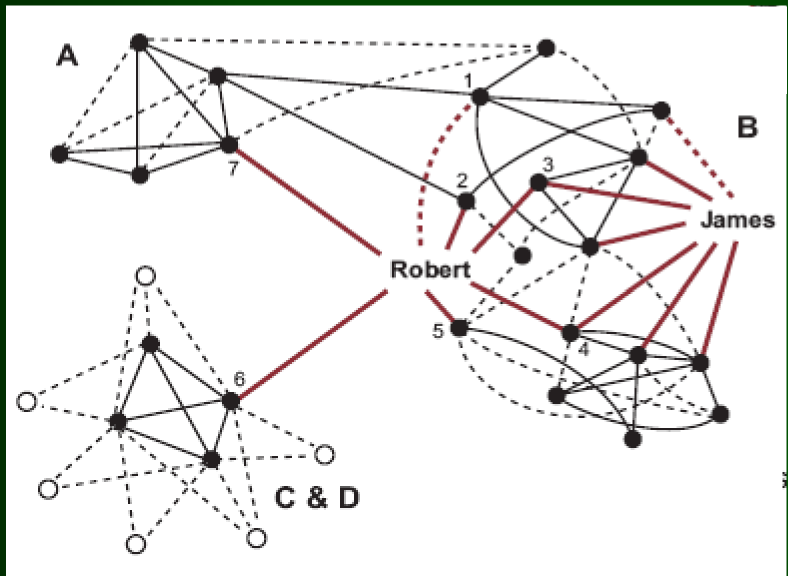


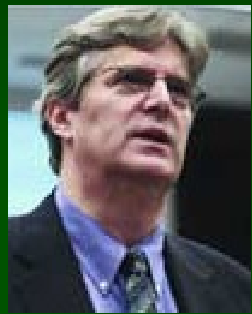
Problem solver: specialized to a task, **predictable**

change of roles

Csermely,
Nature 454:5
TiBS 33:569
TiBS 35:539

Structural holes





Ron Burt,
Structural holes,
Harvard Univ. Press 1992

Robert: broker
James: looser

Why?

Netocracy: continuous networking → Obama
Bard-Söderquist

The art of networking

Complementary networking strategies

• safety seeking (optimization)

• novelty seeking (exploration)

(seek the opinion leader,
seek the strange, seek openness,
jump to the next group)

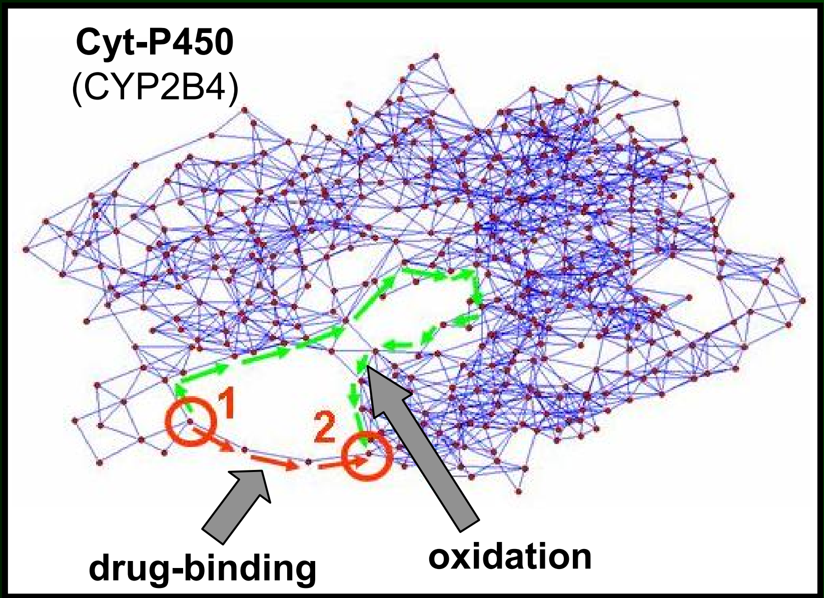
Am. J. Sociology 78:1360

Useful information comes from a long distance

Mark Granovetter (1973)

- You may get useful hints for your jobs from distant acquaintances much better than your relatives
- Why is this suprising?
- Why is this true?

Creative nodes are central and…



Creative amino acids
- centre of residue-network
- in structural holes

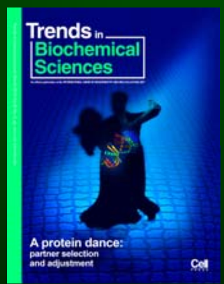
Creative proteins
- stress proteins
- signaling switches

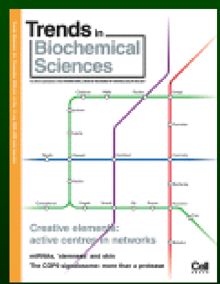
Creative cells
- stem cells
- our brain

Creative persons
- firms
- societies

mobile

Csermely,
Nature 454:5
TiBS 33:569
TiBS 35:539

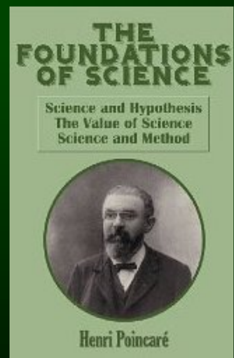




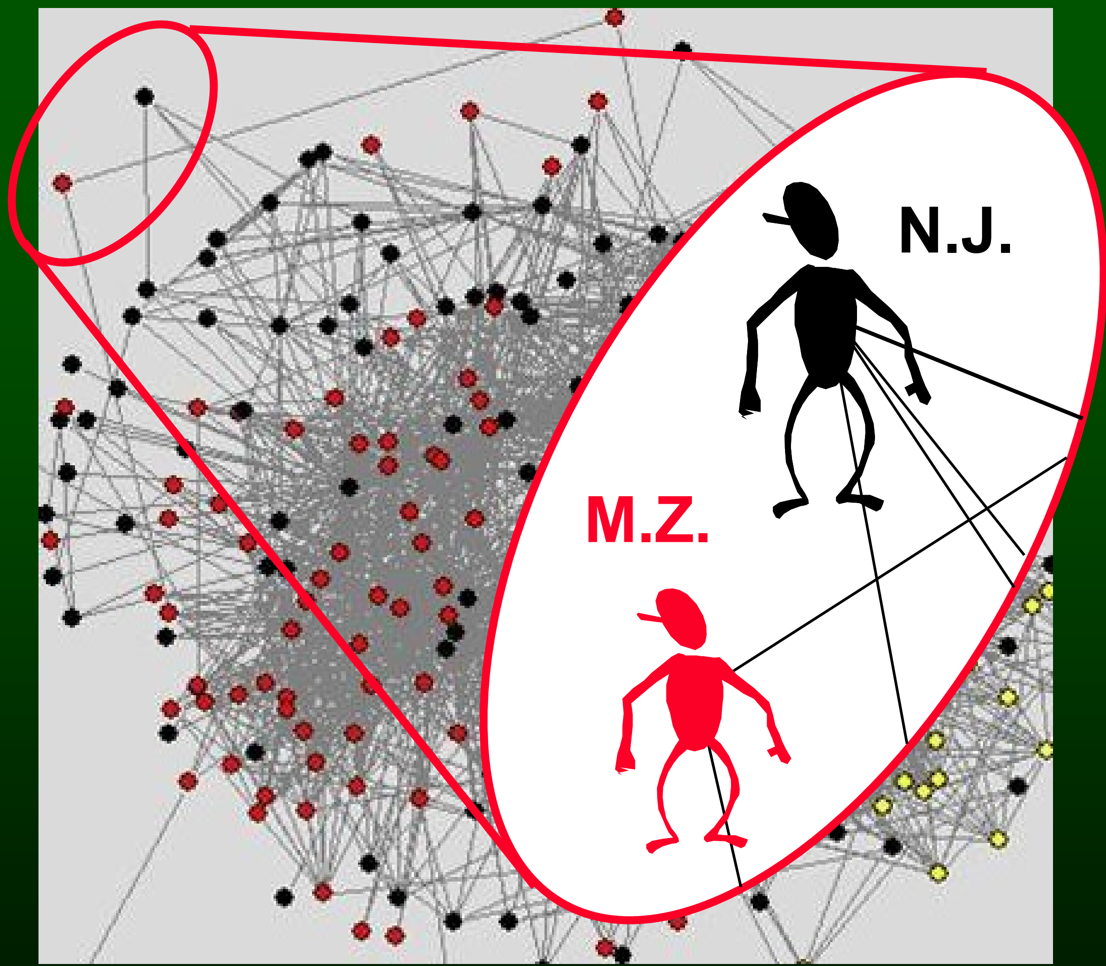
Originality:
the highest level of creativity

" ... To create consists in not making useless combinations. Among chosen combinations the most fertile will often be those formed of elements drawn from domains which are far apart."

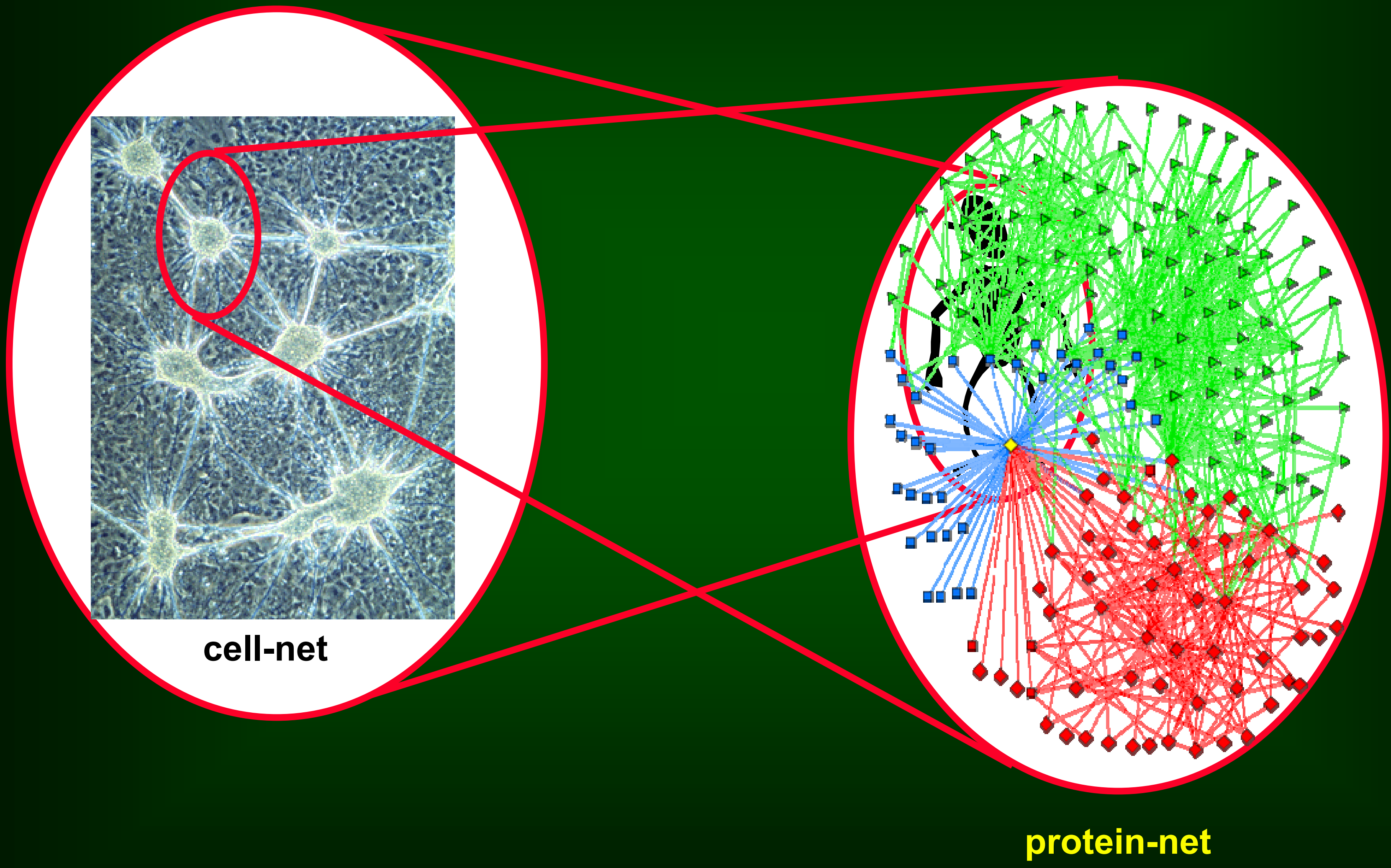
Henry Poincaré: Foundations of Science (1908)



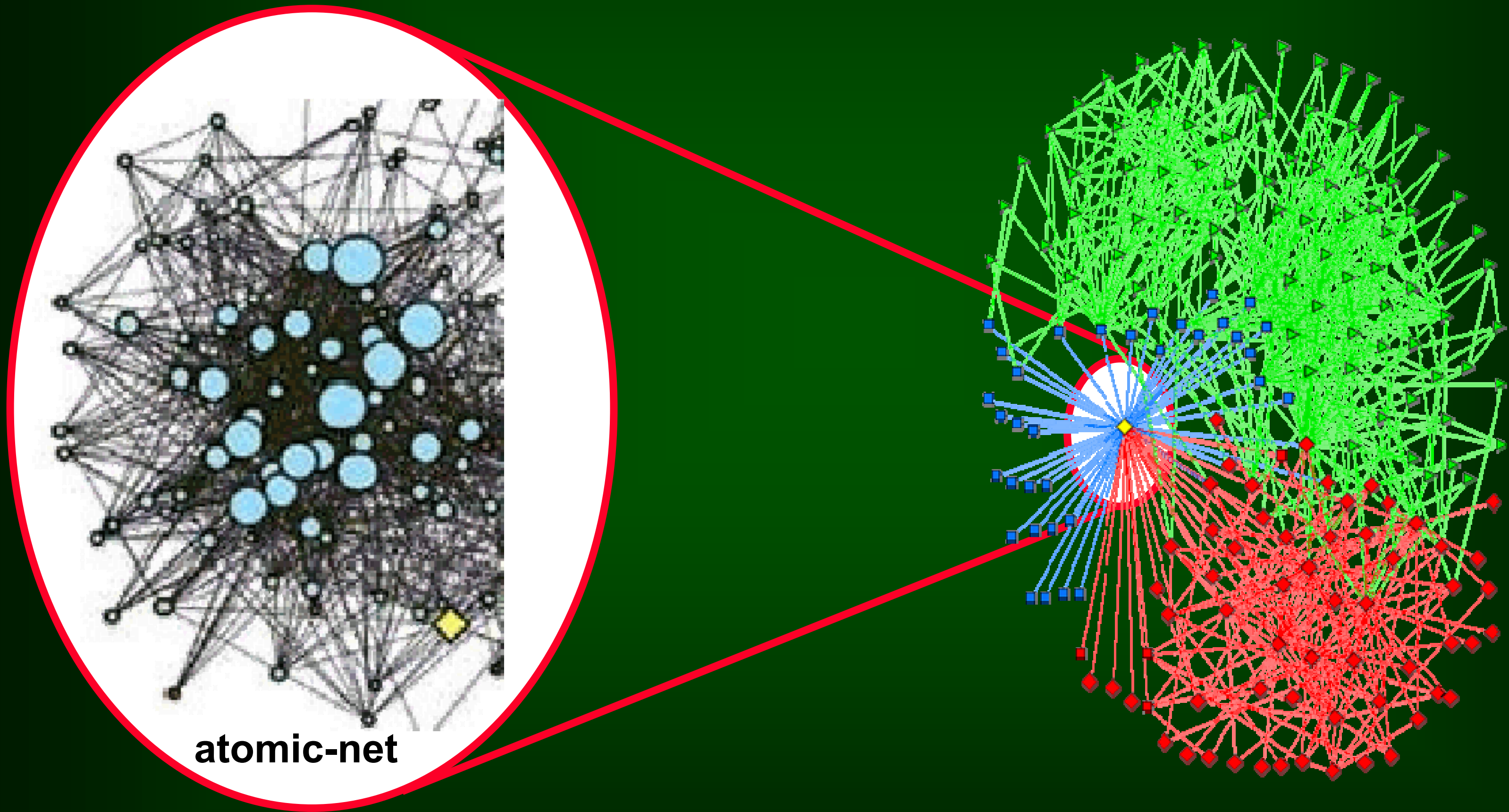
Networks are embedded



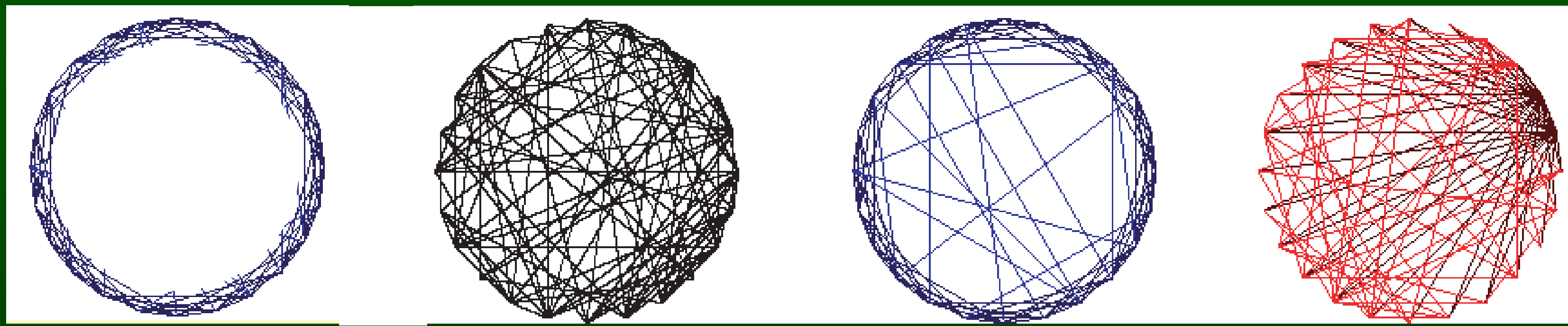
Networks are embedded



Networks are embedded



Major classes of network topology



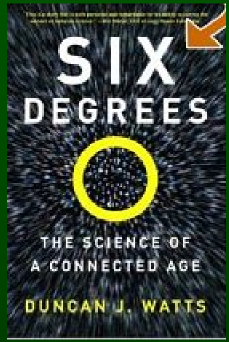
regular random **small-world** **scale-free**

Sporns et al. Trends Cogn Sci. 8, 418

The Milgram-experiment

96 participants from Nebraska,
1 target in Boston,
18 letter chains via friends
(first-name-basis)
Psych. Today 1, 62; 1967

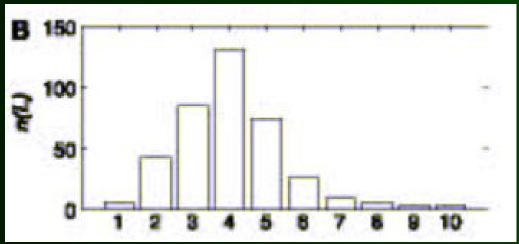
Six degrees of separation



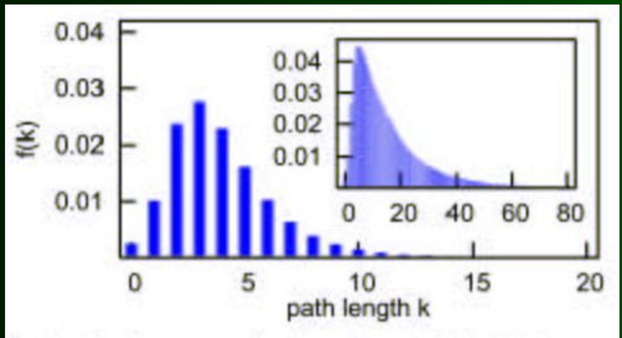
100^6 = >100 x
the total population
of the Earth

Frigyes Karinthy
(1929) Five degrees

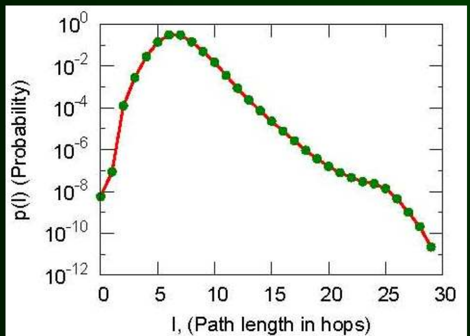
Repeated Milgram-experiments



60,000 participants,
166 countries,
18 targets,
384 email chains
4 (5-7) degrees
Science 301, 827; 2003



www.livejournal.com
500,000 US participants,
500,000 trials
PNAS 102, 11623; 2005

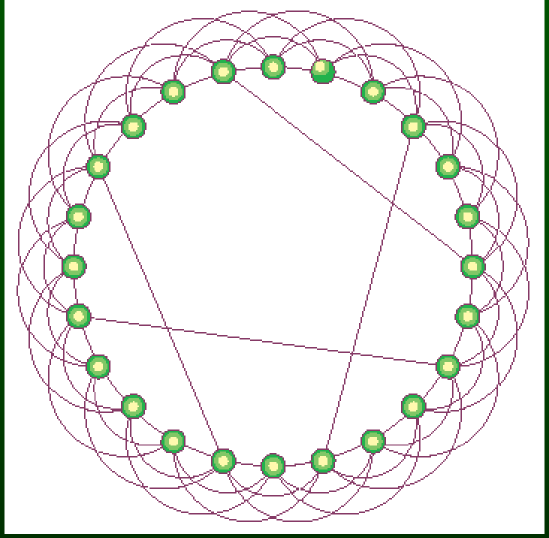


www.msn.com
18 million participants,
50 billion messages
6,6 degrees
PNAS 105, 4633; 2008

Expansion of the small-world concept

Duncan Watts

Steve Strogatz



Nature 393, 440; 1998

high clustering coefficient
AND small characteristic path length
[grows ~logarithm of N (number of elements)]

general model

examples:

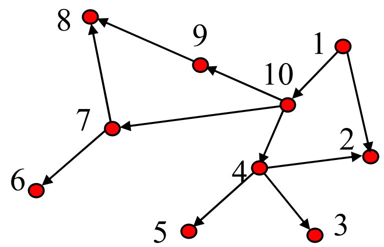
- *C. elegans* neurons
- US power grid
- film actor collaboration net

Weighted & directed small worlds

Network efficiency (cost):

a weighted world can be small even if the non-weighted is not

Efficiency $E = \dfrac{\sum_{i \neq j} \frac{1}{d_{i,j}}}{N(N-1)}$



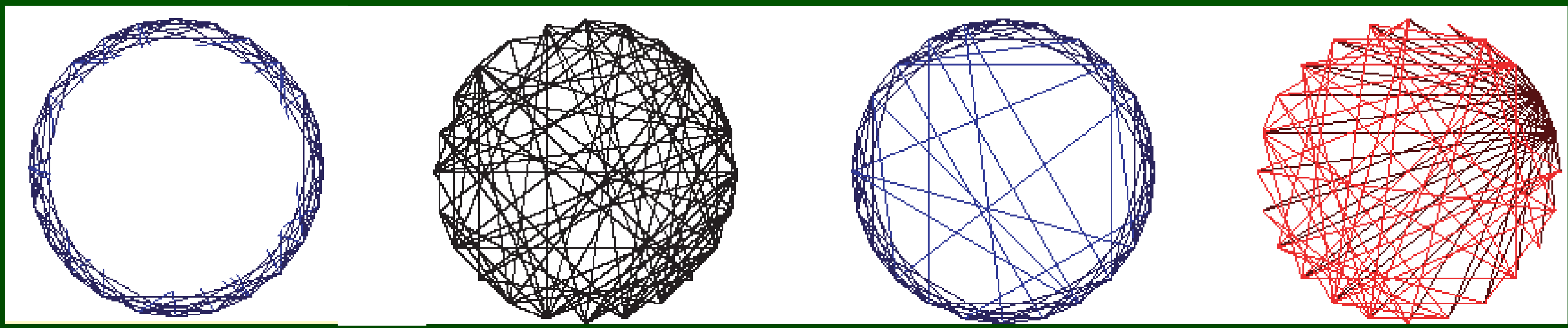
	1	2	3	4	5	6	7	8	9	10	
1	-	1	3	2	3	3	2	3	2	1	1
2	-	-	-	-	-	-	-	-	-	-	2
3	-	-	-	-	-	-	-	-	-	-	3
4	-	1	1	-	1	-	-	-	-	-	4
5	-	-	-	-	-	-	-	-	-	-	5
6	-	-	-	-	-	-	-	-	-	-	6
7	-	-	-	-	-	1	-	1	-	-	7
8	-	-	-	-	-	-	-	-	-	-	8
9	-	-	-	-	-	-	-	1	-	-	9
10	-	2	2	1	2	2	1	2	1	-	10

E = 0.181

(non-weighted, directed network)

Latora and Marchiori PRL 87, 198701

Major classes of network topology



regular random **small-world** **scale-free**

the small world network gives low cost global connections

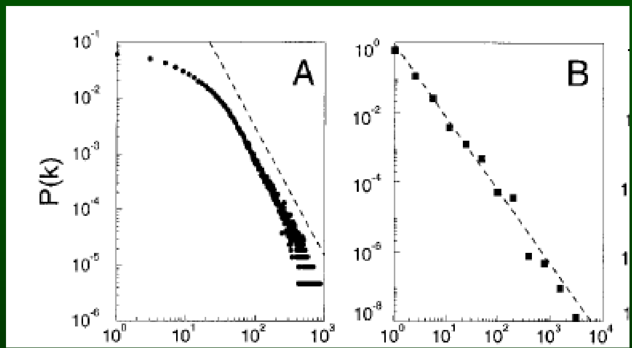
?

Sporns et al. Trends Cogn Sci. 8, 418

Scale-free degree distribution


László Barabási   Réka Albert

degree-distribution



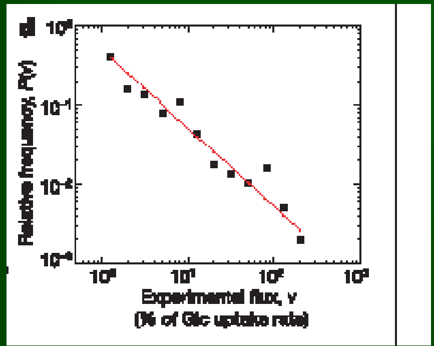
network model:
preferential attachment
(Matthew-effect, Pareto-law)
generality for actors, power grid, www
Science 286, 509; 1999

$P = a\, k^{-\alpha}$ (P probability, a constant, k degree, α exponent)

$\lg P = \lg a - \alpha \lg k$

Generality of scale-free distributions

link-strength

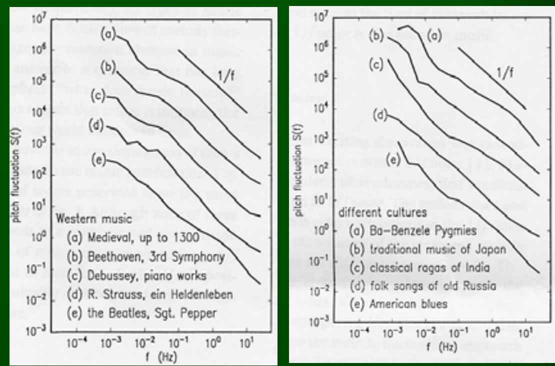


Nature 427, 839; 2004

Levy-flights

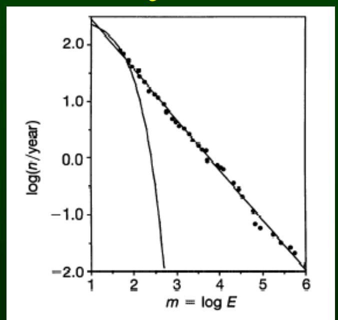
Can J. Zool. 80, 436; 2002

music



Nature 258, 317; 1975

probability, Noe-effect



PNAS 92, 6689; 1995

Kohlrausch, 1854

Leiden-jars

cumulative wins

Bernoulli, 1738

town size Zipf-law

rain, lightning, tic

sexual contacts

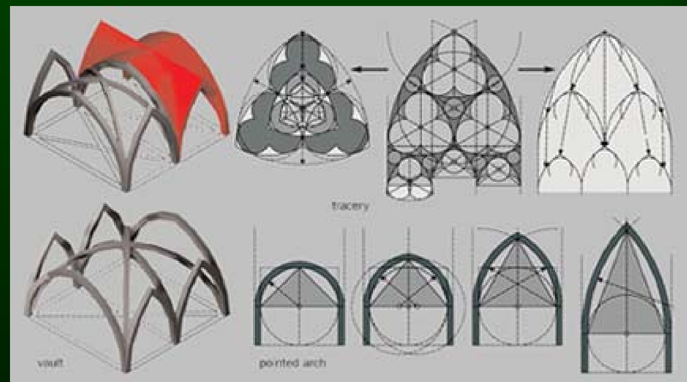
earthquakes,

Gutenberg-Richter law

science papers

Lotka-law

fractals, architecture



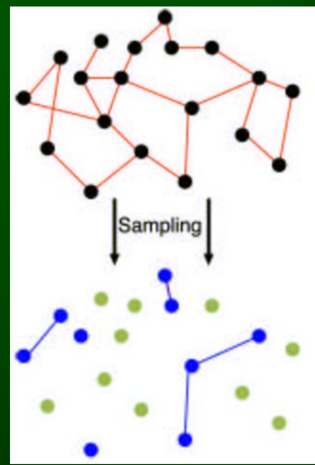
www.iemar.tuwien.ac.at/modul23/Fractals

Expansion and dangers of scale-free distributions

- must span many scales

  (network must be large enough)
- a line can be fitted to many curves…

  (log-normal, gamma, stretched exponential)
- cumulative plots are much better
- sampling bias
- unspecific data may cover real data
- distinct parts of networks are different



PNAS 102, 4221; 2005

Reasons behind the generality of scale-free distributions

- preferential attachment
- cumulative success of consecutive tasks
- self-organization of matter in the Universe

Networks and stability

Part 2. – Network topology

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Péter Csermely and
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Difficult questions of network studies

- Which are the important segments?
- How can I define groups within networks?
- How can I judge, if two networks are similar?
  How can I compare two evolving networks?
- How can I measure complexity?
- How can I influence the attractor occupancy
  of dynamic networks in their state space?

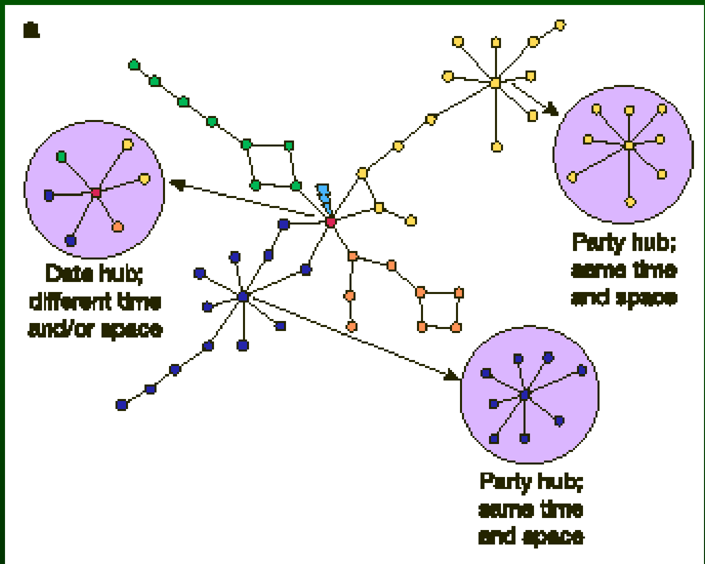
„Important" network segments

local

- hubs
- central elements
- network skeleton
- modular structure
- core/periphery structure

global

Date hubs and party hubs



Han et al. Nature 430, 88

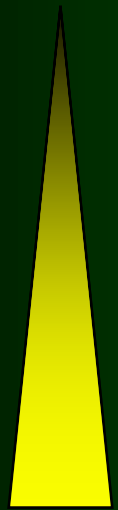
yeast protein network

–date hubs

–party hubs

Types of network centralities

local



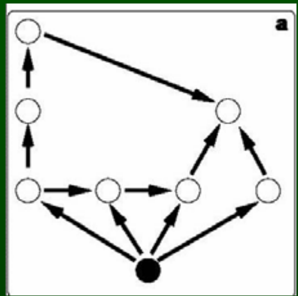
global

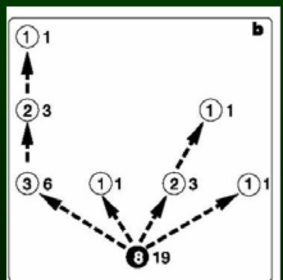
- hubs (degree)
- closeness (sum of shortests paths to other nodes)
- community centrality (influence of all other nodes)
- betweenness (number of shortests paths through the node)

> - **h-index:** node has x neighbors with degree x
> - node + neighbors adjacency matrix **eigenvector**
> - **PageRank:** damped random walk (eigenvector of the transition matrix, Google)
> - **subgraph centrality:** closed walks starting and ending on the same node
> - **information centrality:** drop of graph performance if removing the node
> - **ecosystems**

Network skeleton (local, fractal nets)

food-chain renorm.
(energy-flow)

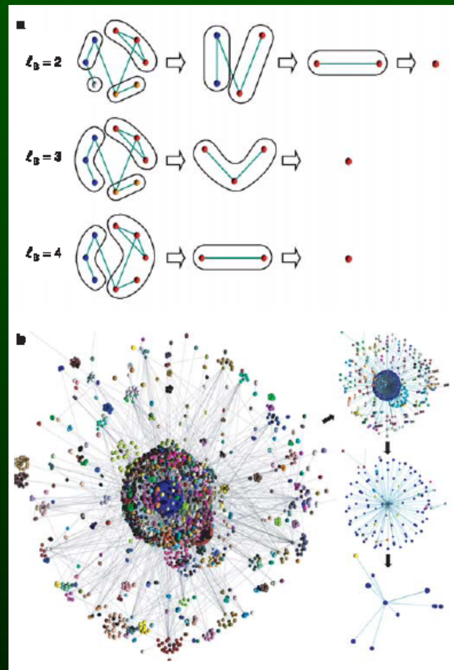




hierarchy: e.g. transcription factors

Garlaschelli et al., Nature 423,165

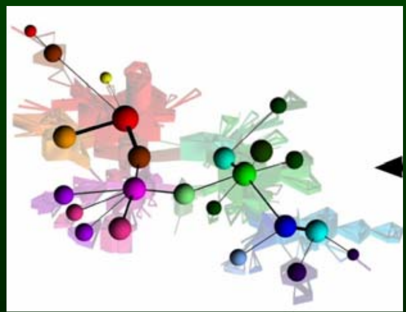
www renormalization
(unbranched ends)



Song et al., Nature 433,392

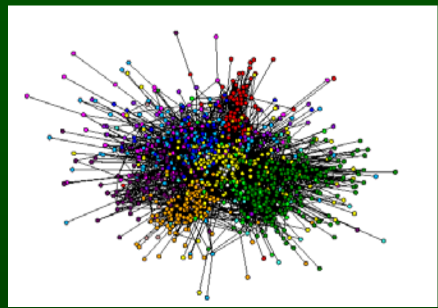
Network skeleton (mesoscopic, global)

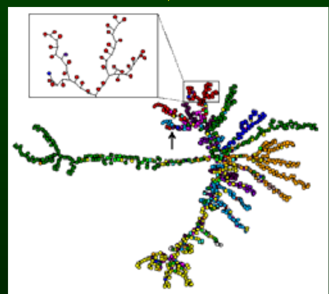
network scientists
(modules)



Kovacs et al., PLoS ONE 5, e12528
www.linkgroup.hu/modules.php

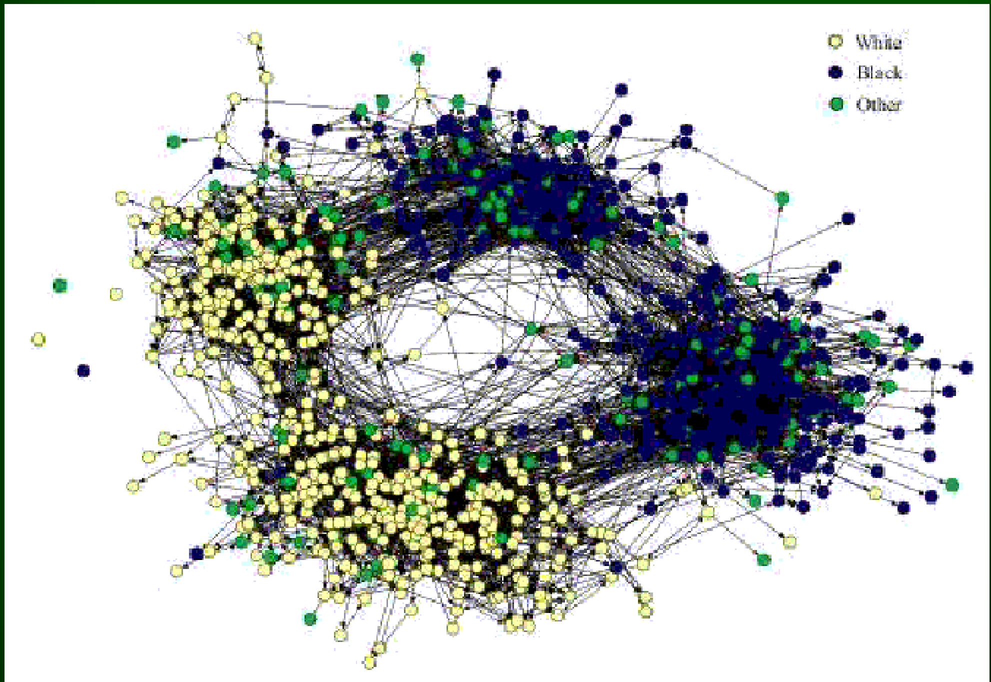
email-net renorm.
(betwenness)





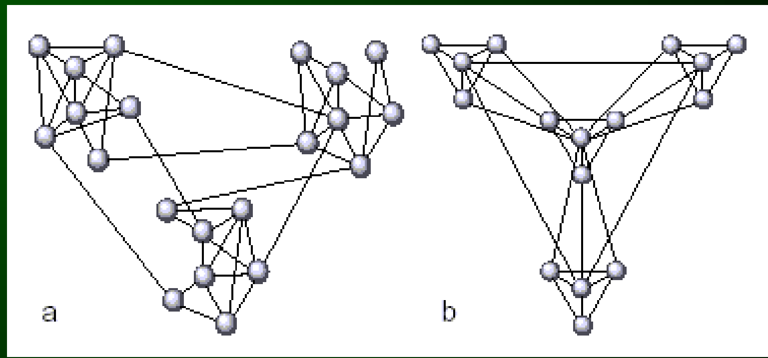
Guimera et al., PRE 68, 065103
Kim et al., PRE 70, 046126
Arenas et al, EPJ B38, 373

Modules



Newman, SIAM Rev. 45, 167

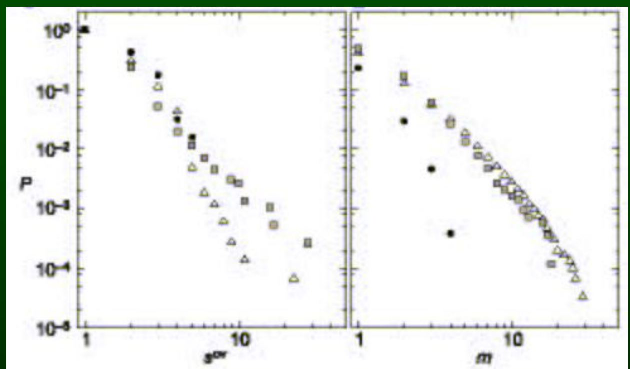
modular nets
intermodular contacts
are suppressed



hierarchical net
intermodular contacts are
preferentially suppressed

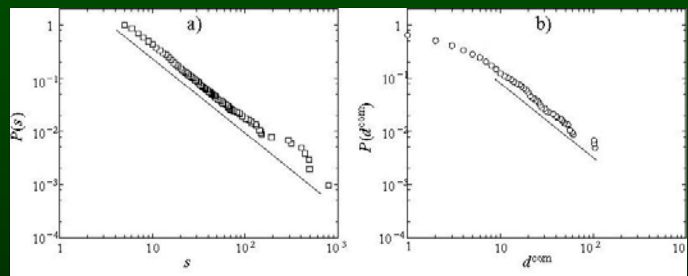
Modules have a scale-free size and degree distribution

www.arxiv.org/cond-mat
word-associations
yeast DIP protein network



Palla et al., Nature 435, 814
For size: Arenas et al.,
EPJ B38, 373

preferential attachment
model of modules

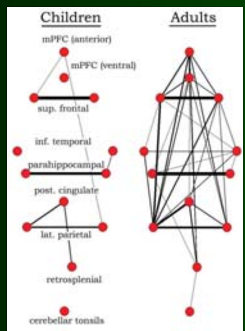


Pollner et al., Europhys. Lett 73:478

Modules need optimal overlap

(brain default-network)

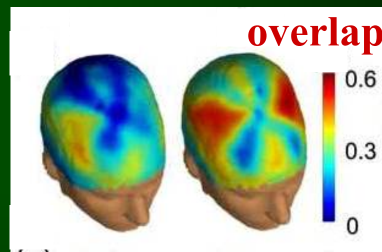
overlap of active neuronal modules



adult: usual task

adult: rest, novel task

depression



child

schizophrenia

epilepsy

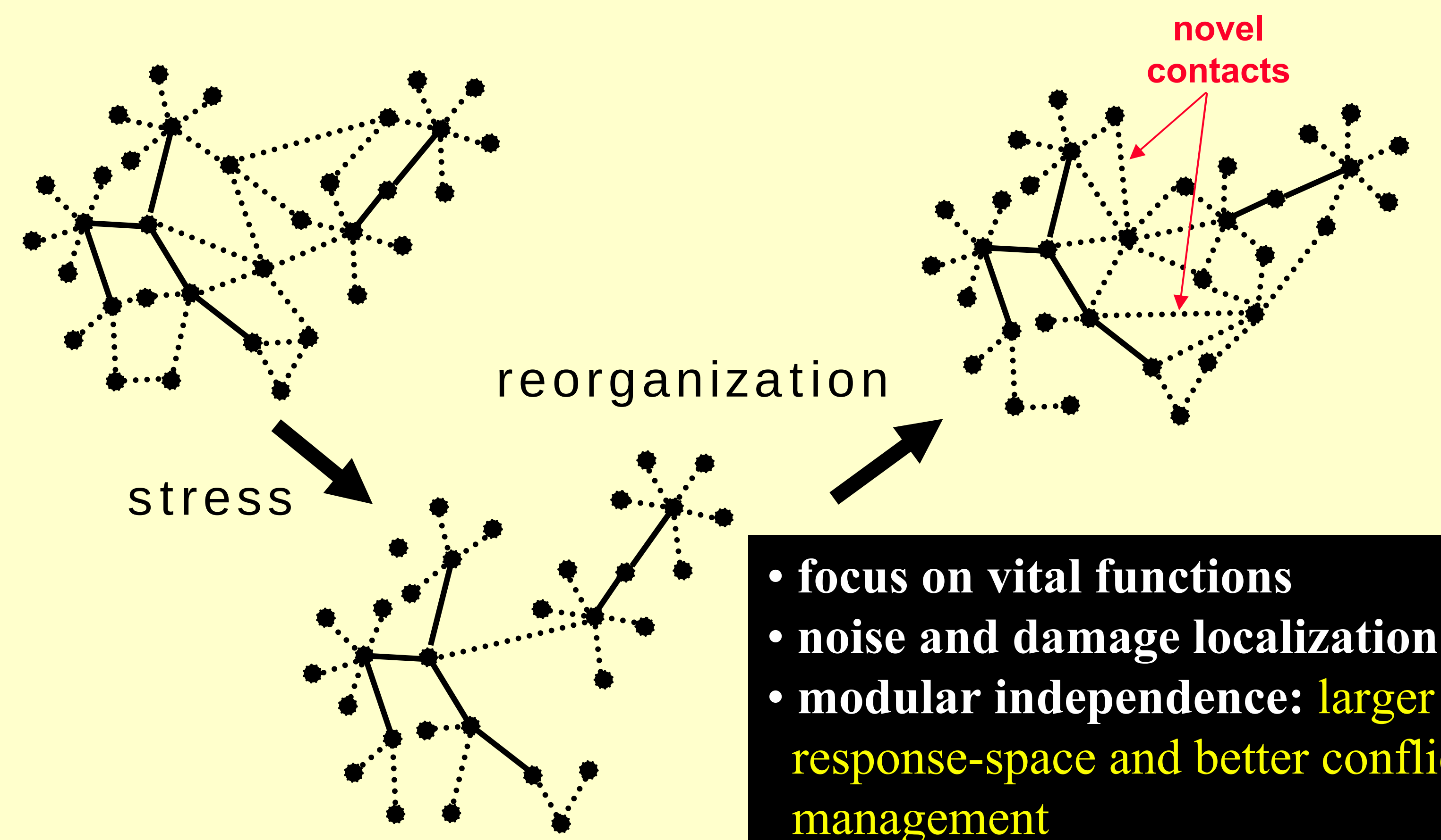
PNAS 104:13507
PNAS 105:4028

Science 315:393

PNAS 106:1279
PNAS 106:1942

PRL 104:118701

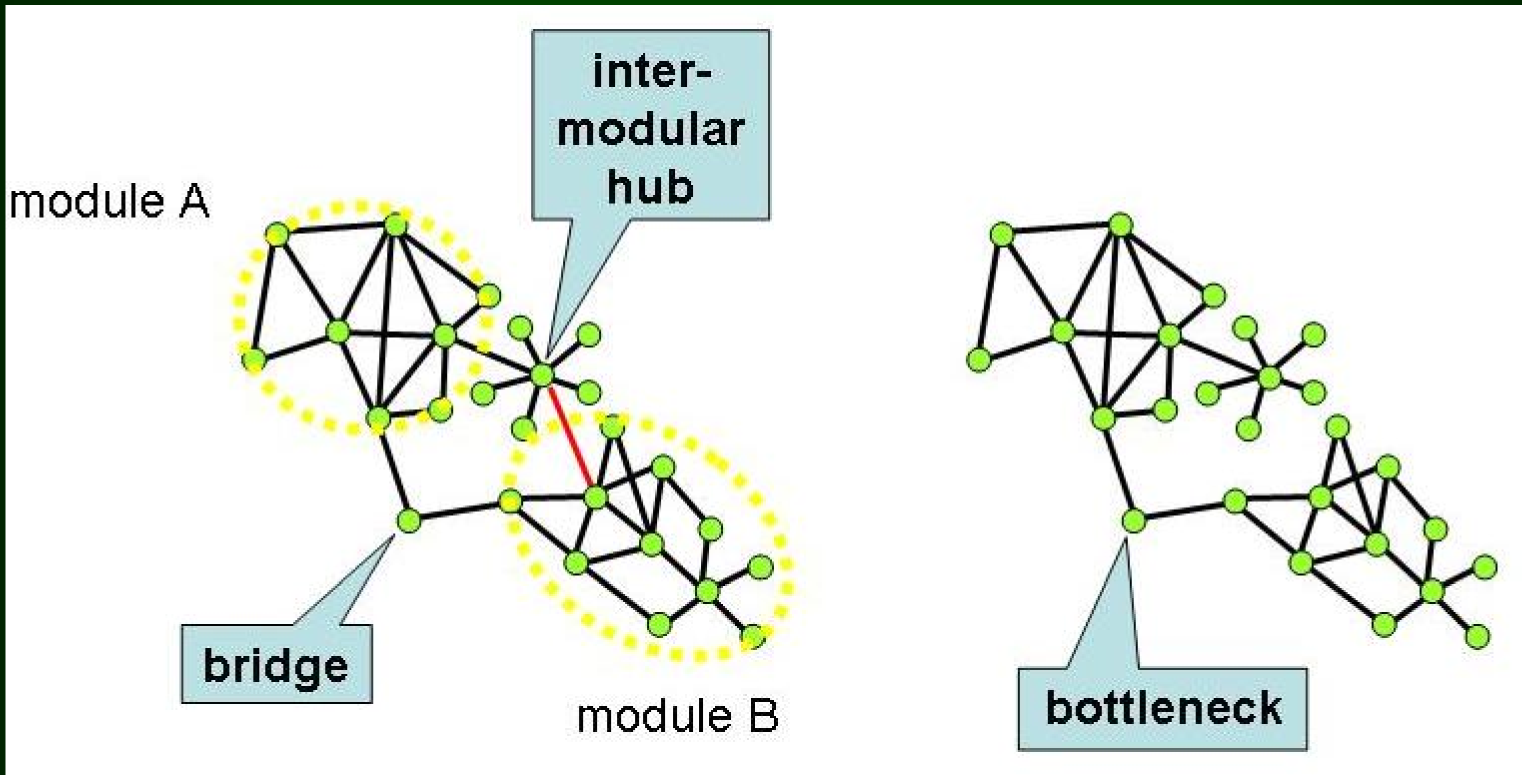
Modular overlaps as keys of adaptation processes



- **focus on vital functions**
- **noise and damage localization**
- **modular independence:** larger response-space and better conflict management

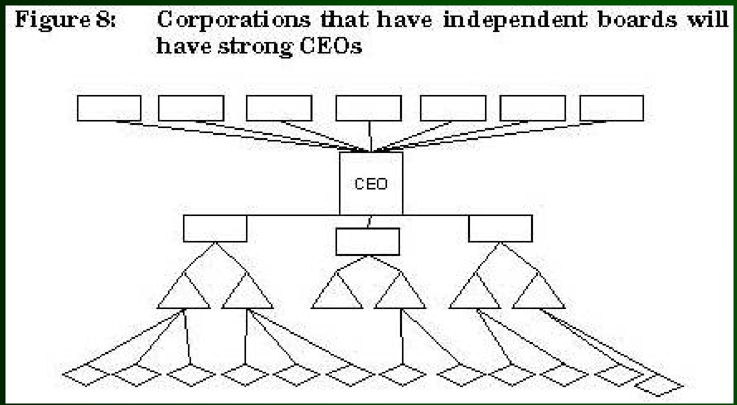
Szalay et al, FEBS Lett. 581:3675; Palotai et al, IUBMB Life 60:10; Mihalik & Csermely, PLoS Comput Biology 7:e1002187

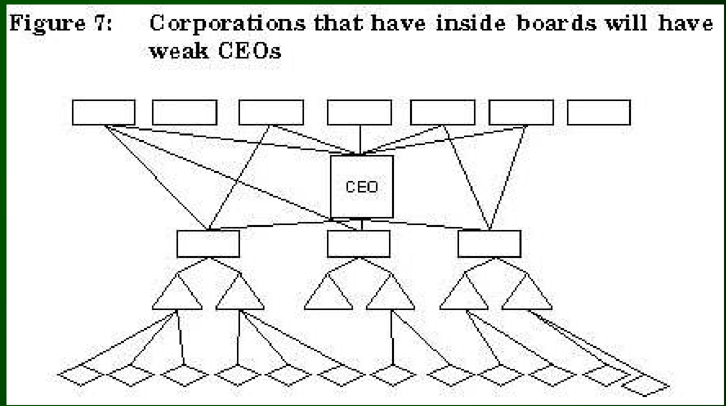
Intermodular bridges are key nodes of regulation



Csermely et al, Pharmacology & Therapeutics 183:333-408

Modular overlaps are key determinants of regulation



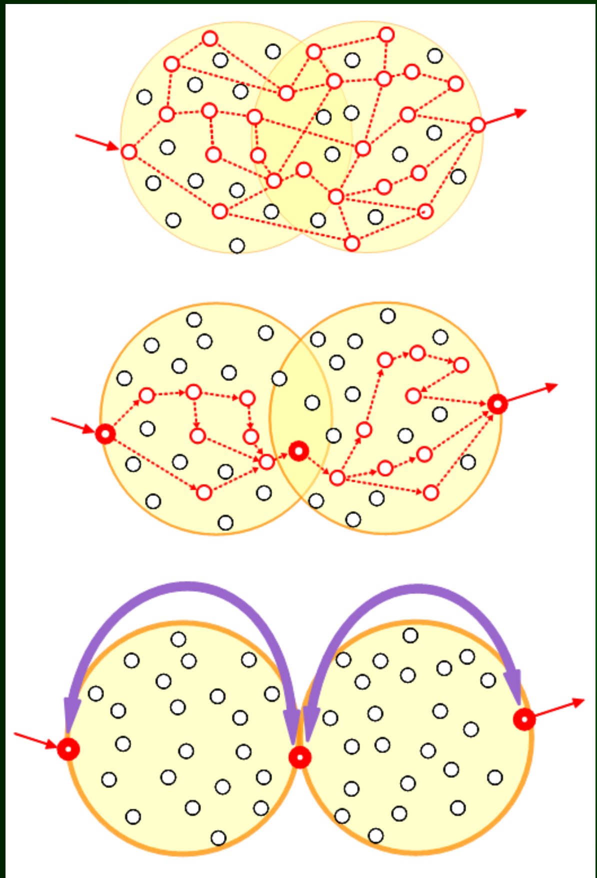


Mitchell, Brooklyn Law Rev. 70:1313

Why is it good if a network has modules?

modules

- stop noise, damage and sync
- can evolve independently
- separate functions (induce diversity)
- allow sophisticated regulation by fringe areas



a.) extensively overlapping, soft modules: random routes

b.) moderately overlapping modules: converging routes

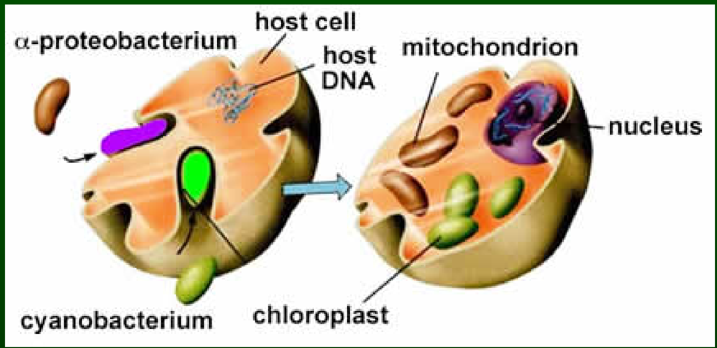
c.) non-overlapping, rigid modules: saltatoric transduction

Csermely et al, Pharmacology & Therapeutics 183:333-408

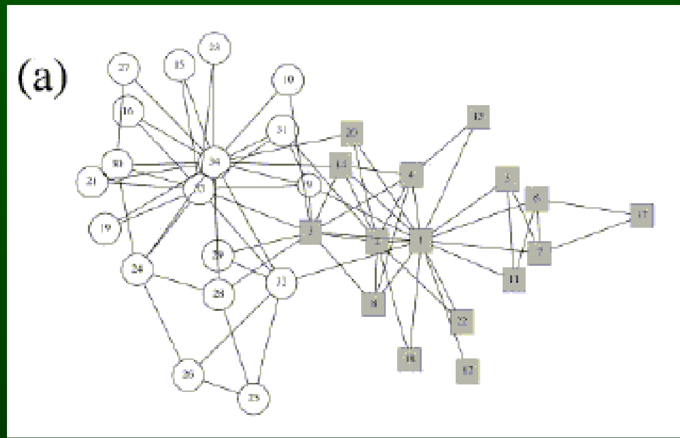
How are modules formed?

integration

(symbiosis)



parcellation



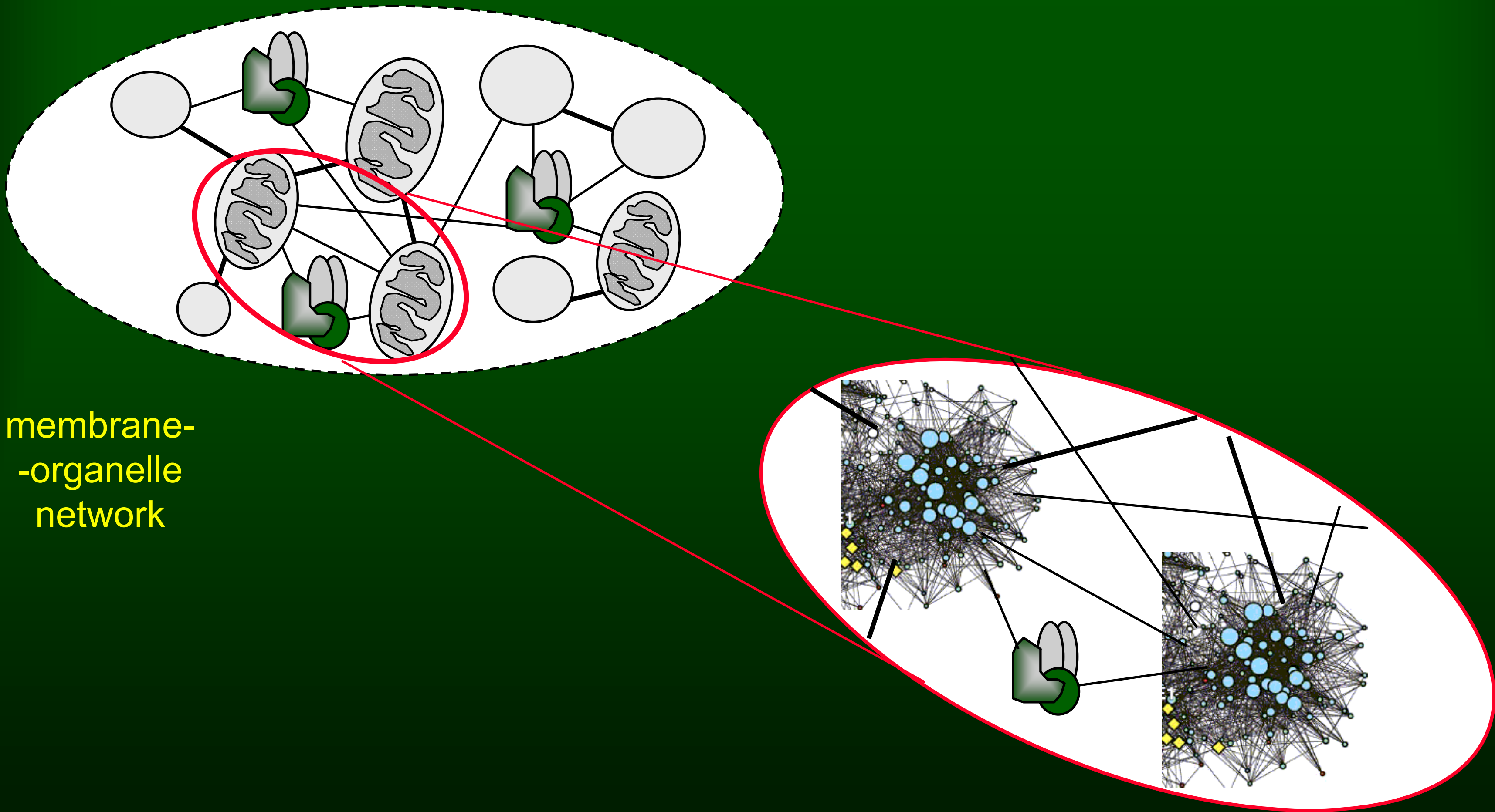
Zachary's charate club

administrator: circles

instructor: squares

Girvan-Newman, PNAS 99,7821

Modules and nestedness



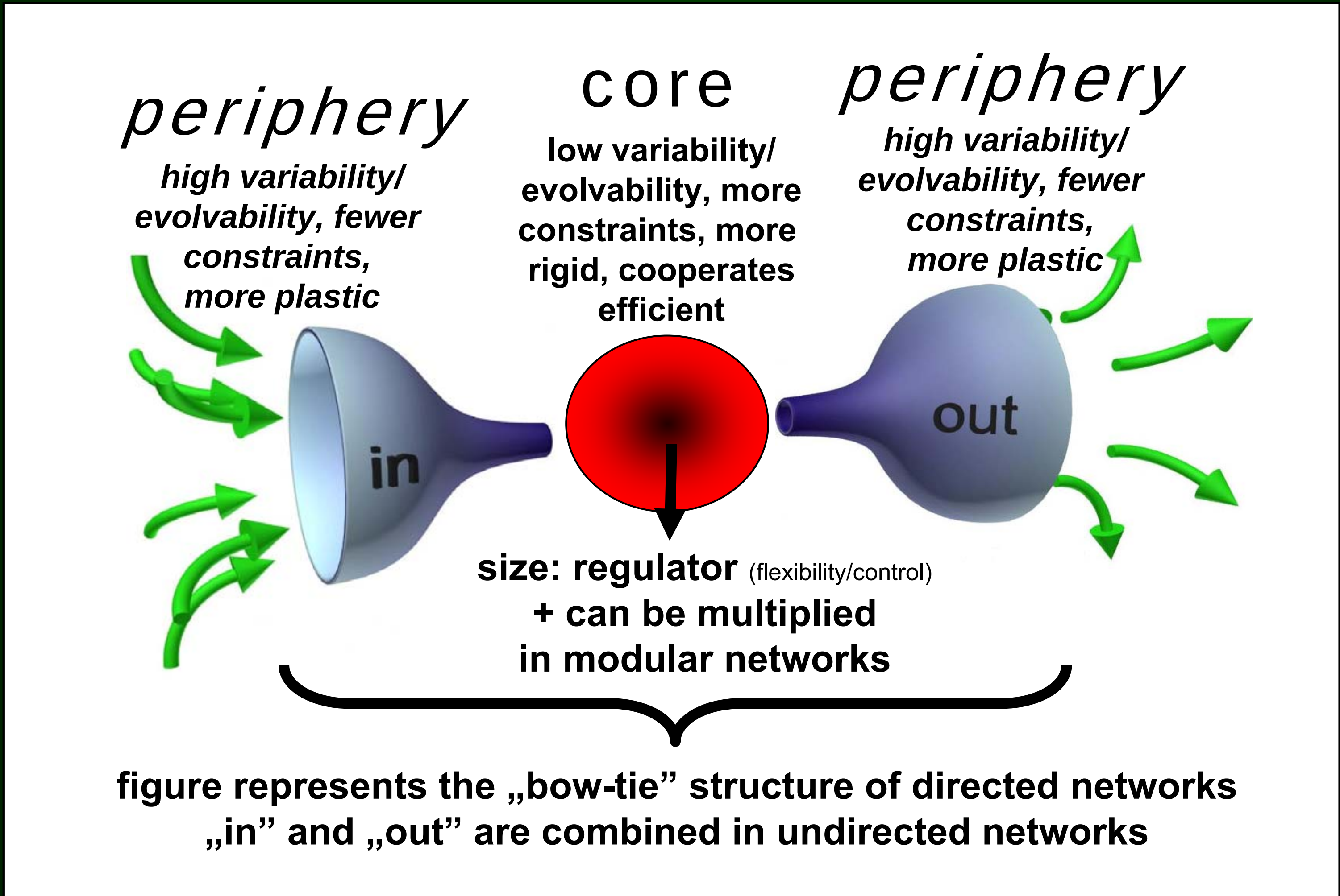
membrane-
-organelle
network

Modules *versus* bottom-networks

A module becomes a bottom-network, if

- we have many
- it is small
- it is structured
- it is separated
- it can live independently
- it has only a few constant links

Dense group in network center: core-periphery networks



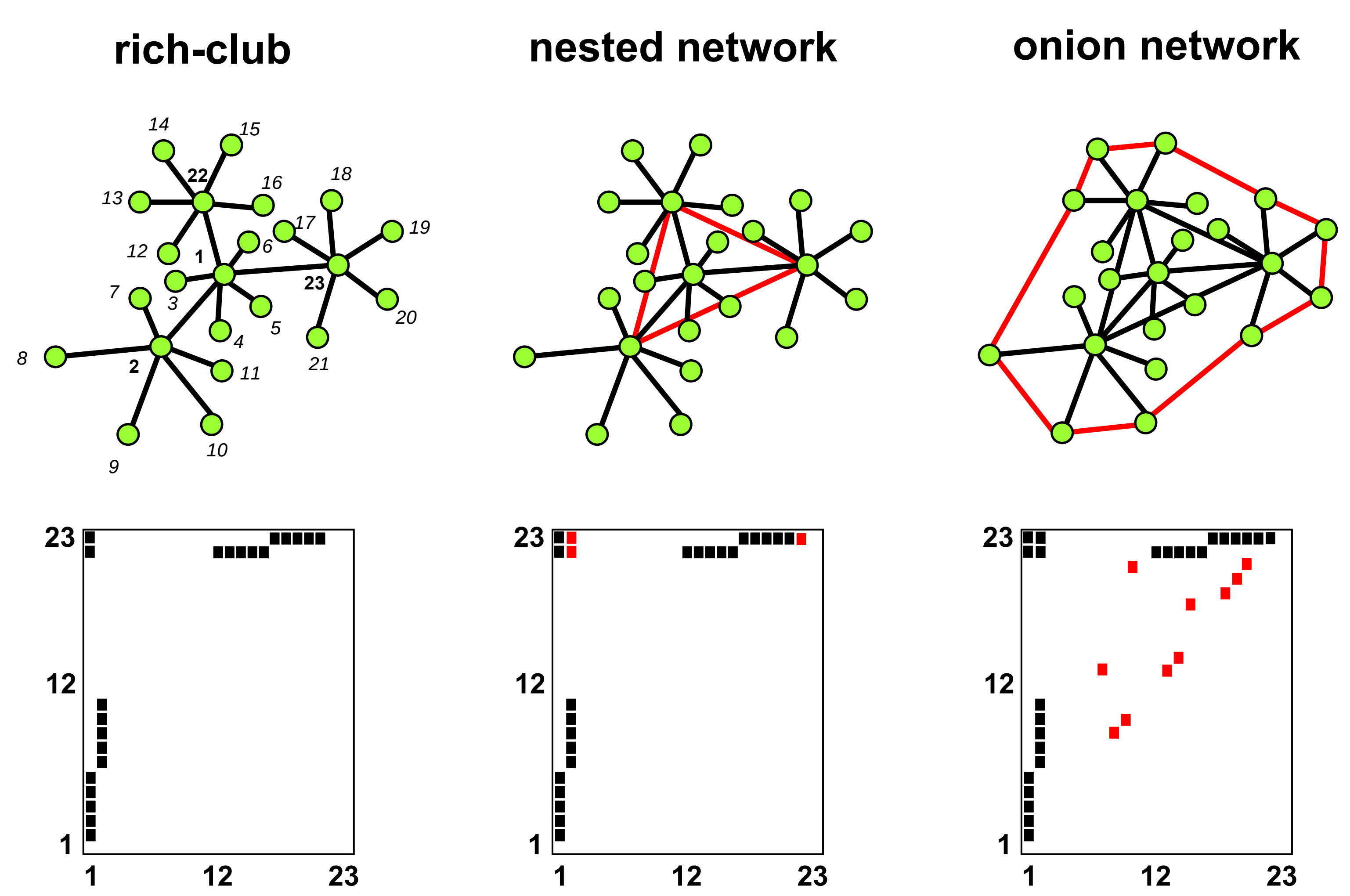
Csermely et al., J. Complex Networks 1:93-123

Major types of core-periphery networks I.

- protein structure networks
- interactomes
- metabolic, signaling, gene-regulatory networks
- immune system, brain
- ecosystems
- animal and human social networks
- World-Wide-Web, Wikipedia
- Internet, power-grids, transportation networks

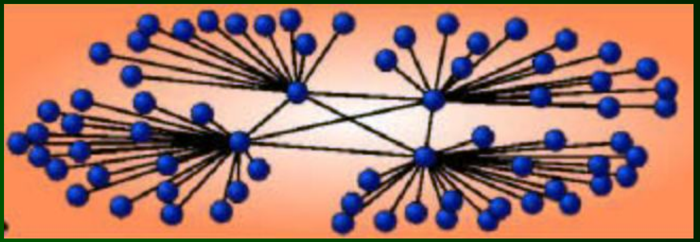
Yellow: association-type networks, less core
White: flow-type networks, more core

Major types of core-periphery networks II.



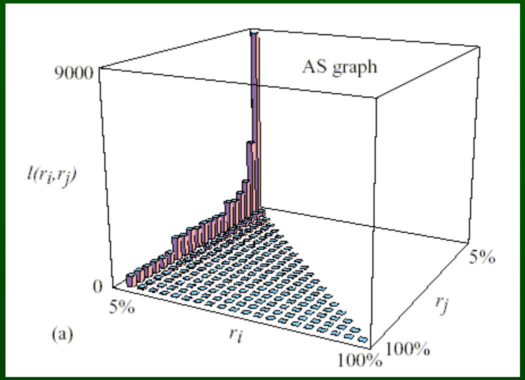
Null-models (comparison to random networks) are important!

Rich clubs

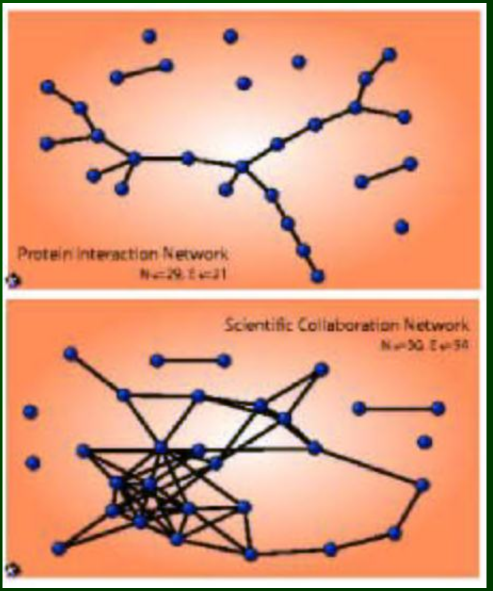


a disassortative rich club

hubs associate with hubs
(assortativity: social nets)

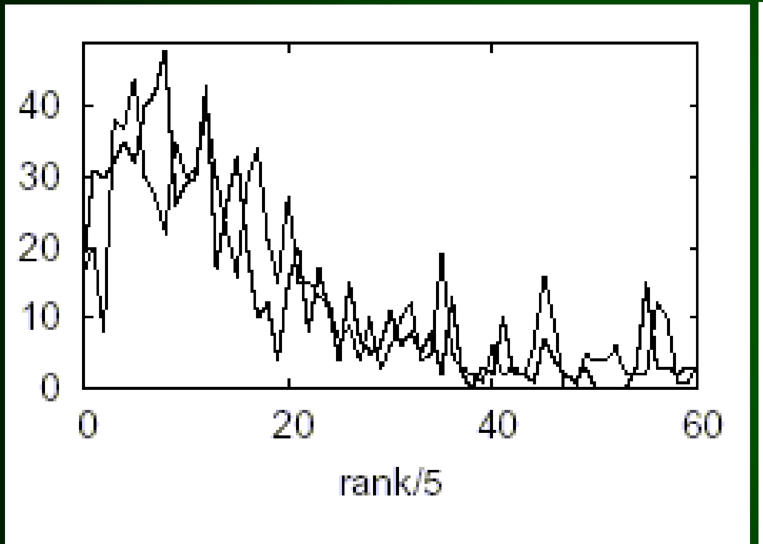


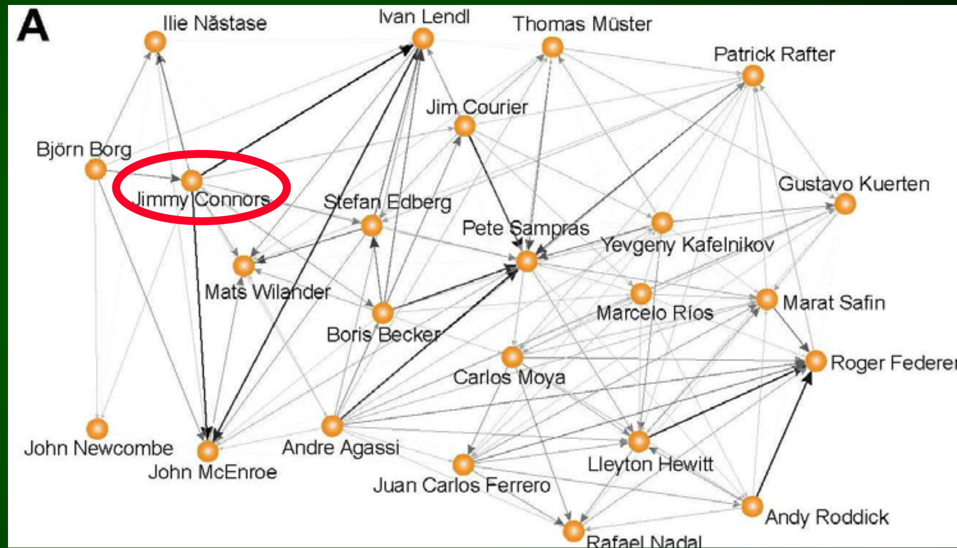
Zhou and Mondragon
IEEE Comm. Lett. 8:180



Colizza et al.
Nature Physics 2:110

Talented(VIP)**-club**
isolated top rank associates with hubs

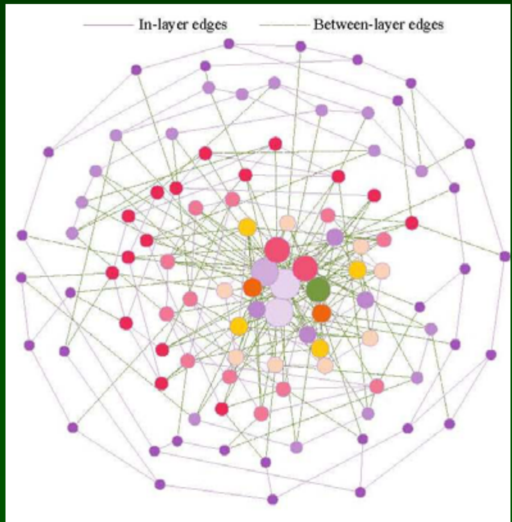




Masuda and Konno
Social Networks 28, 297

Radicchi
arxiv.org:1101.4028

Onion and wheel type networks



onion-networks:
most robust scale-free networks
against node removal

Schneider et al. PNAS 108:3838

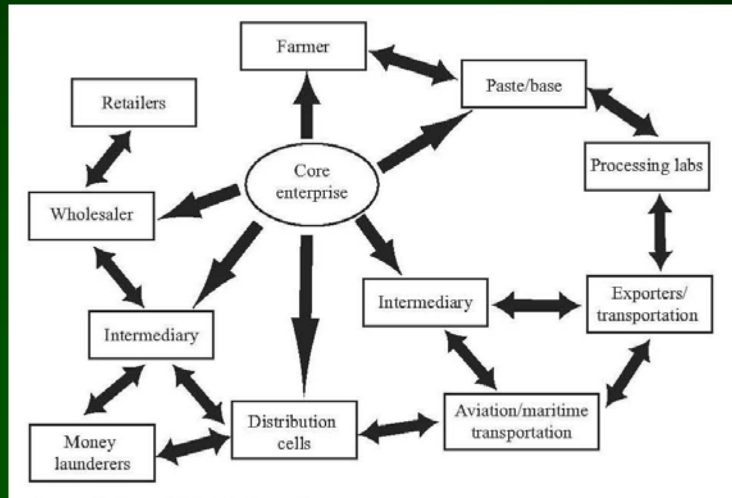


Figure 5.1. Drug trafficking "wheel" network

wheel-networks:
core + periphery
terrorist + drug traffic networks

Kenney 2008

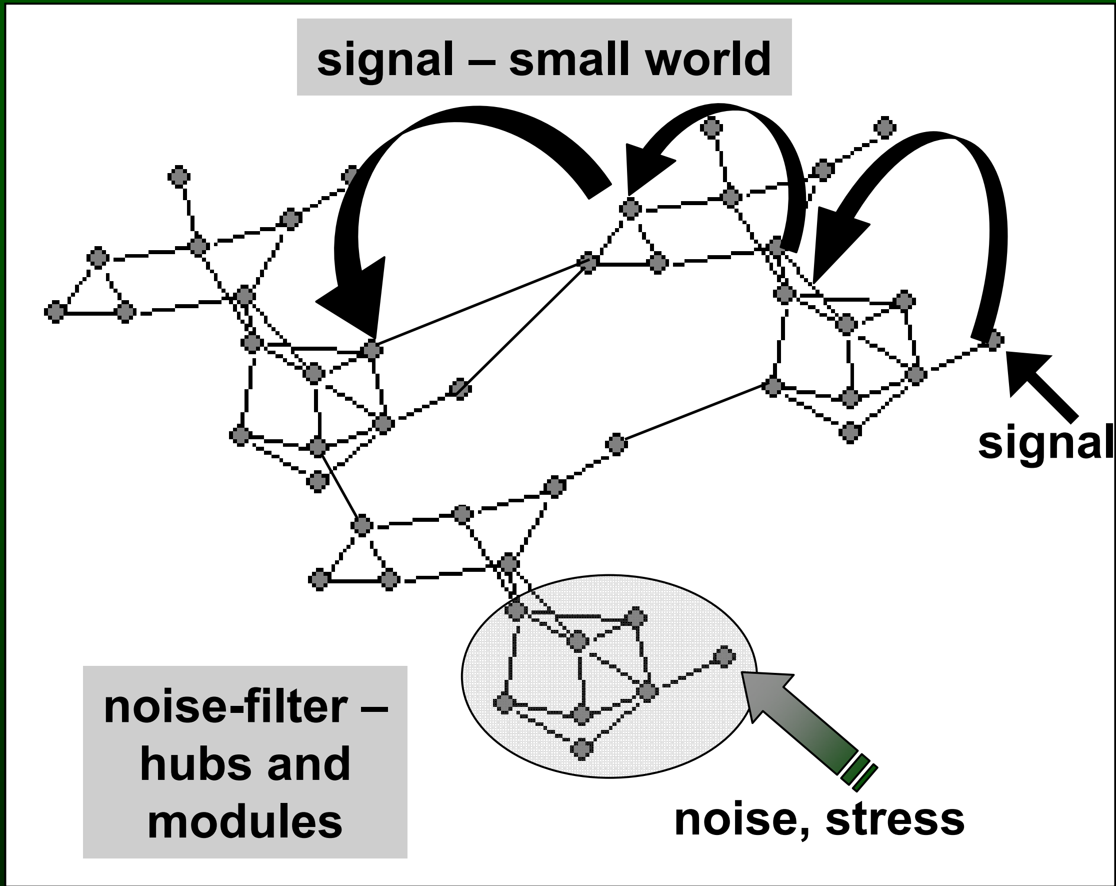
Networks and stability

Part 3. – Network dynamics

http://linkgroup.hu
http://turbine.ai
csermelynet@gmail.com

Péter Csermely and
the Turbine team

The usefulness of networks



Csermely: Weak Links, Springer

Network tasks: dissipation of noise and response to signals

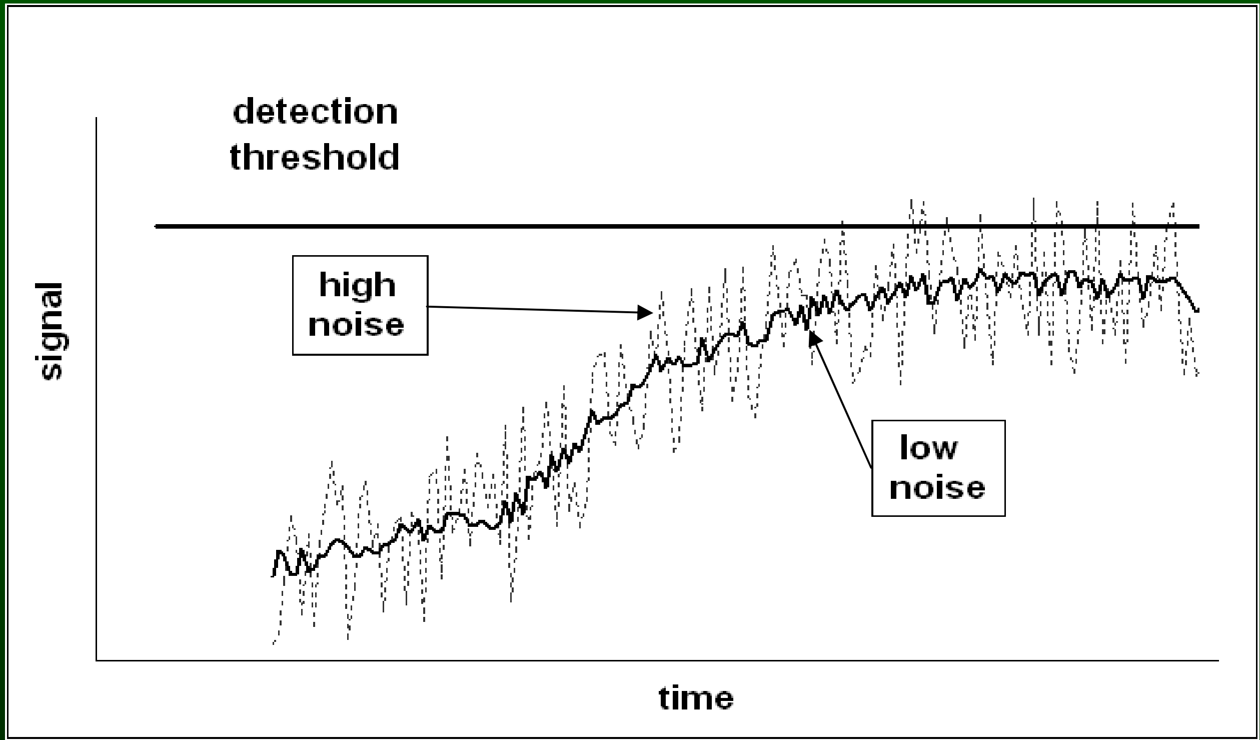
noise is bad:

- diseases, tumors (PNAS 99, 13783)
- error catastrophe (Eigen, PNAS 99. 13374)

Seminal review: Rao et al: Nature 420, 231

Noise is good: stochastic resonance

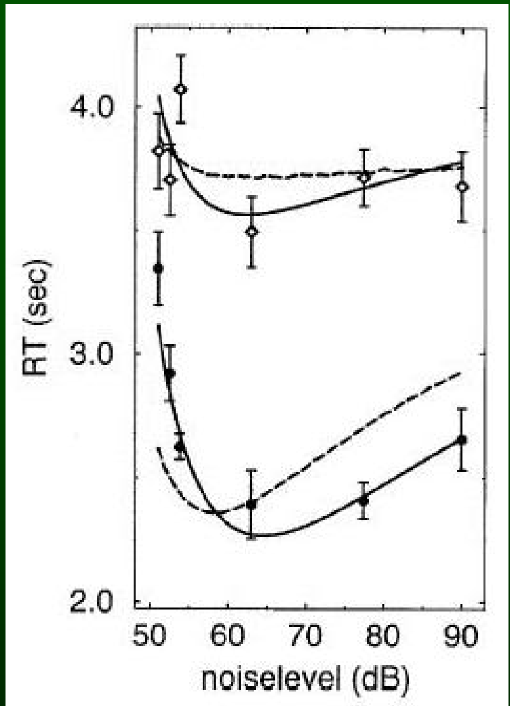
stochastic resonance: extrinsic noise
stochastic focusing: intrinsic noise



- rain calms rough seas (Reynolds, 1900)
- stochastic resonance: mechanoreceptors, hearing
- bone-growth, fish food finding is better

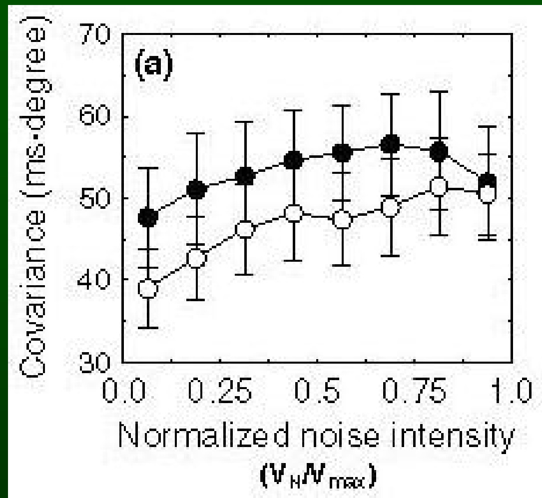
Stochastic resonance: memory retrieval, pink noise, music

response time



difficult task

easy task



1/t pink noise

white noise

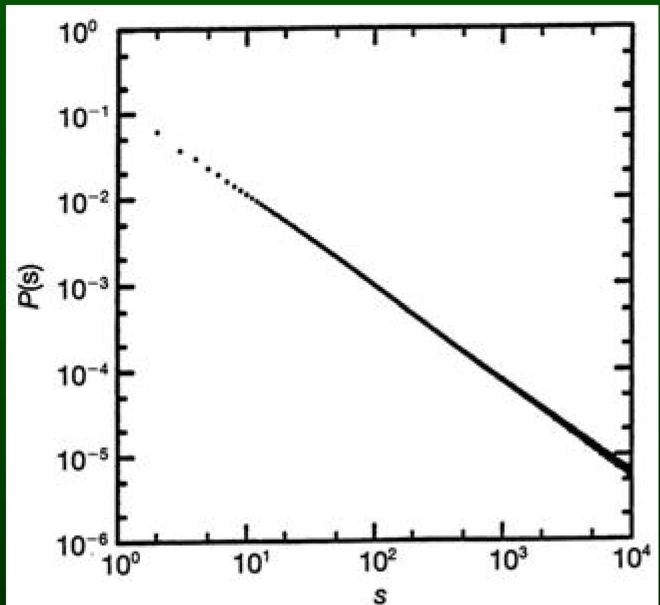
music is pink noise

Soma et al, PRL 91, 078101

Usher & Feingold, Biol. Cybern. 83, L11-L16

Self-organized criticality: our every-day avalanches

Bak-Paczuski, PNAS 92, 6689



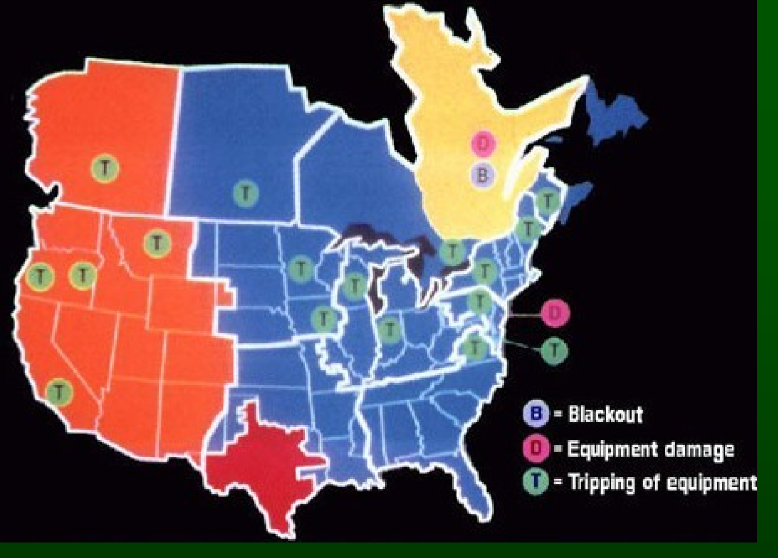
sand-pile avalanches
→ scale-free size + event distribution

- magnetization (Barkhauser-effect)
- protein quakes
- earthquakes
- vulcano-eruptions
- forest-fires
- cracks
- crackling noise
- dipping faucets
- breath
- rain
- solar flares
- quazar emissions
- cultural changes
- innovations

- continuously increasing tension
- partially restricted relaxation

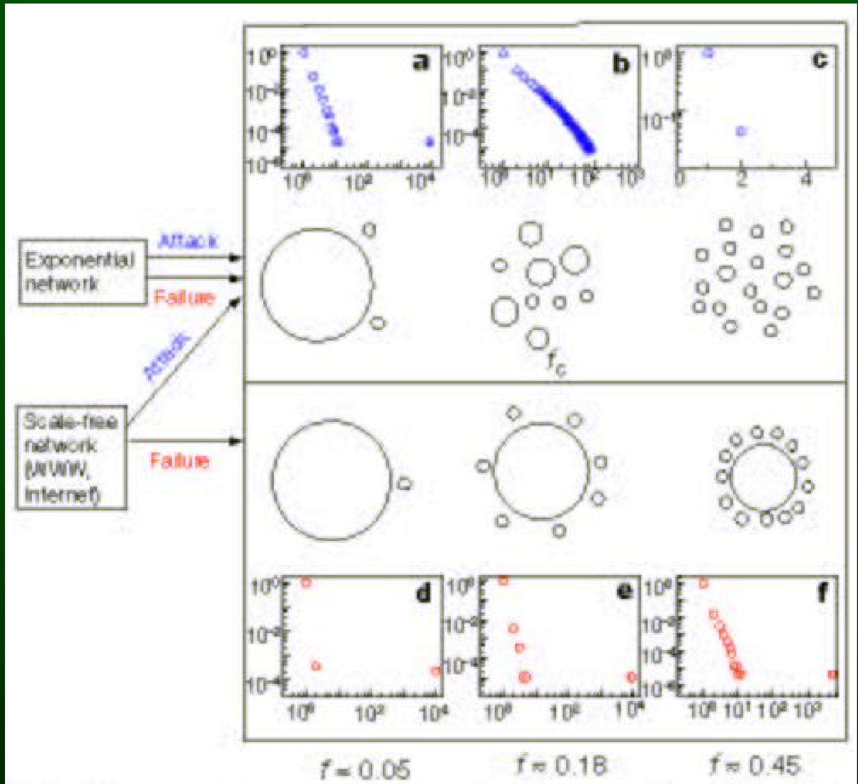
→ avalanche

Cascading failures



March 13, 1989

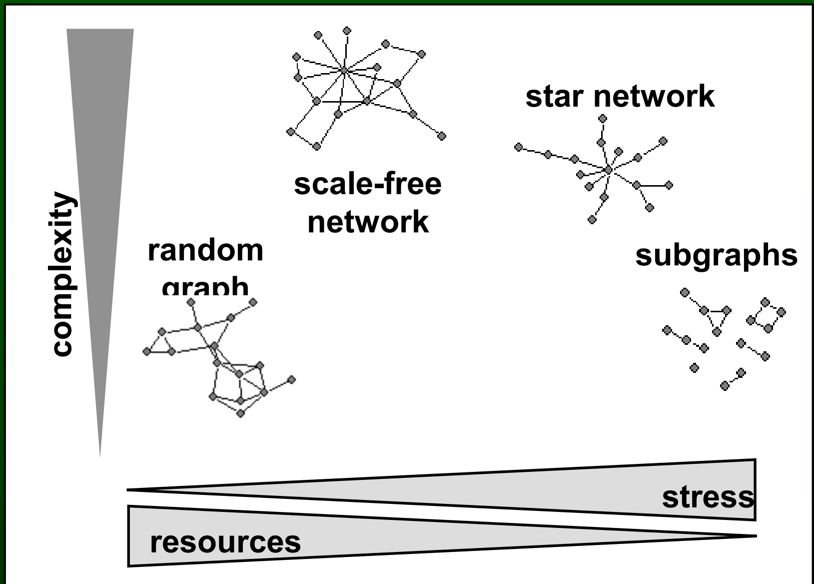
Weak points in networks

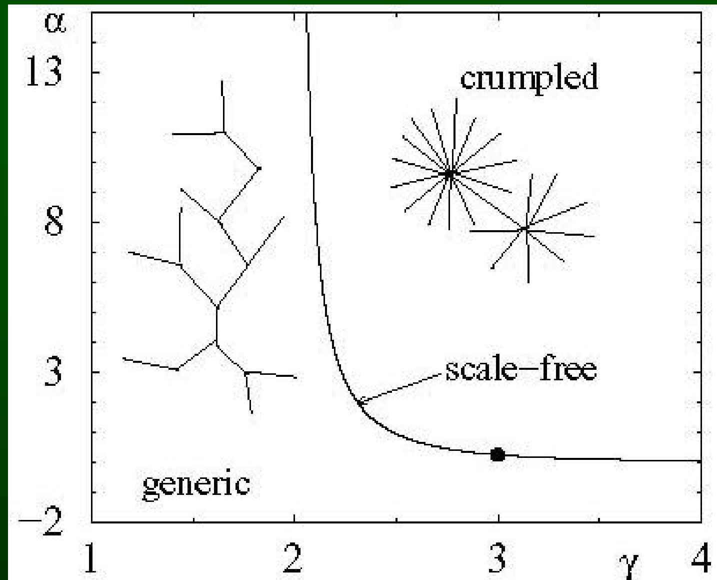


scale-free networks
are resistant against failure
but are vulnerable to attacks

Albert et al Nature 406, 378

Topological phase transitions





Physica A 334, 583; PRE 69, 046117

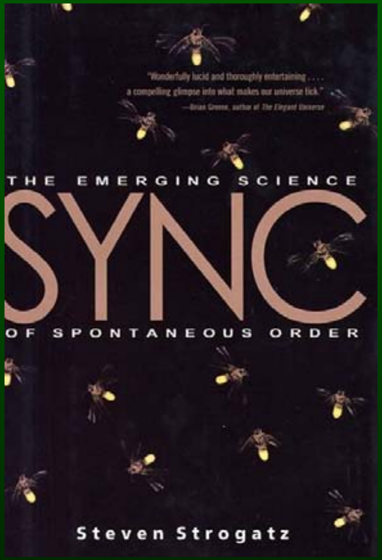
Topological phase transitions – other examples

- cells scale-free → star → apoptosis
- animals: random → scale-free [→ star]
  J. Theor. Biol. 215, 481
- firm consortia random → scale-free → star
  Santa Fe Working Papers No. 200112081
- scientific quotations random → scale-free
  J. Arch. Meth. Theor. 8, 35
- communistic equality → social classes → dictatorships → war, anarchy

Sync

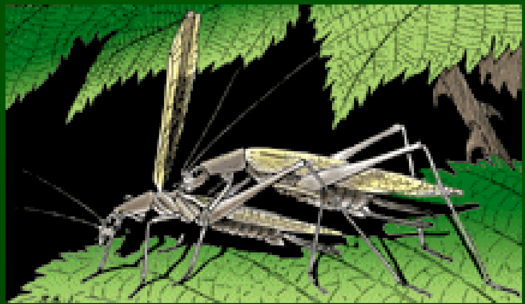
Huygens, 1665

longitude determination
pendulum clock
synchrony



Sync: other examples

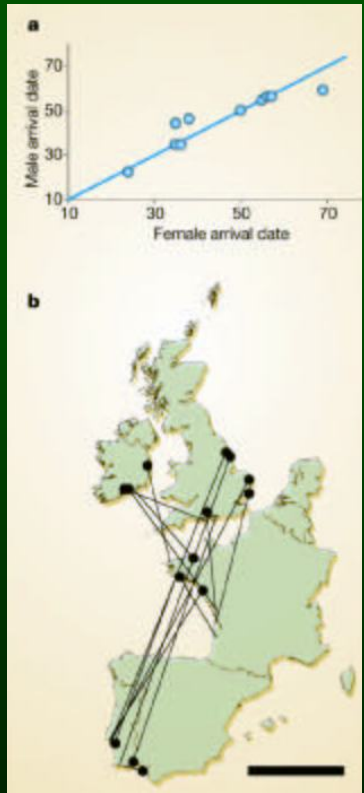
cricket



www.buzz.ifas.ufl.edu/a00samples.htm

firefly

bird-migration



Nature 431, 646

clapping

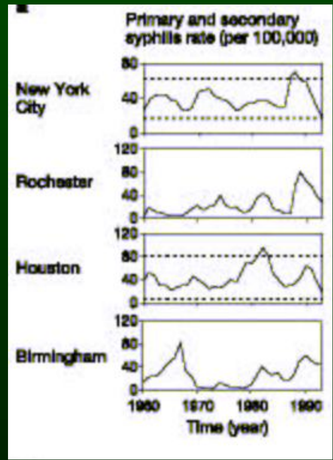
Nature 403, 849

yawning, laugh

menstruation

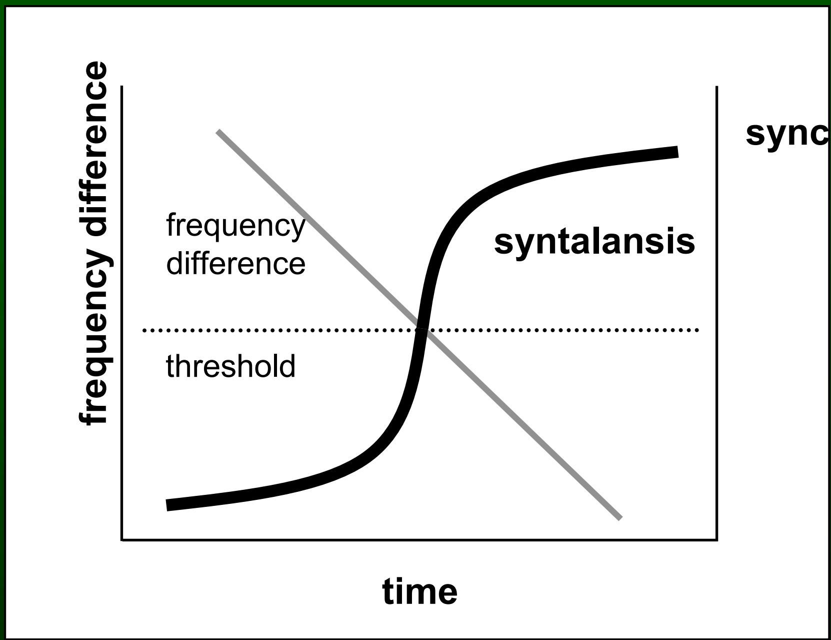
Nature 229, 244; 392, 177

syphilis



Nature 433, 417

Sync conditions



- small-world ↑
- modules ↓
- scale-free ↓
- weights ↑
- weak links ↑

Differences between engineering and evolution

Property	Engineering	Evolution
development	needs designer input	self-organization, grows
parts & whole	additive (complicated)	non-additive (complex)
optimization	one-time, parts piece by piece	continuous the whole only
optimized parameters	few	many
intermediates	many times virtual	need to be stable
designability	low	high (many configurations)
elements	isolated (?), have low complexity	not isolated, but many times independent, complex
degeneracy	low, „thrifty”	high, „overspending”
unexpected changes	low survival	high survival

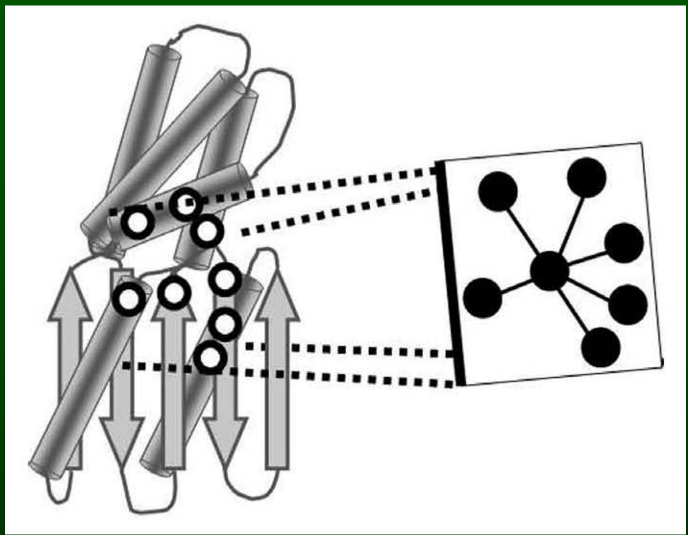
Networks and stability

Part 4 – Examples for networks

http://linkgroup.hu
http://turbine.ai
csermelynet@gmail.com

Péter Csermely and
the Turbine team

Protein structure networks

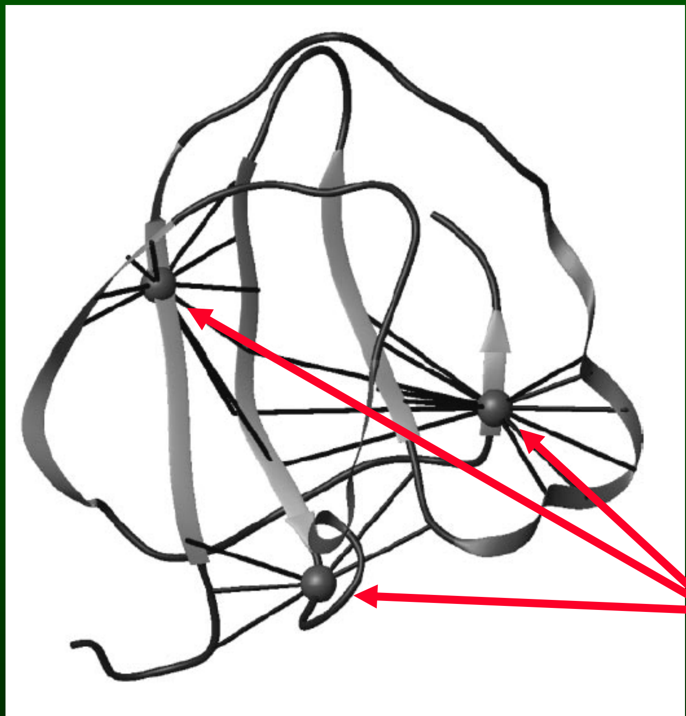


Böde et al, FEBS Letters 581:2776

- protein structure networks
- residue interaction network
- amino acid networks

How do we construct a network from a 3D image?

Protein structure networks

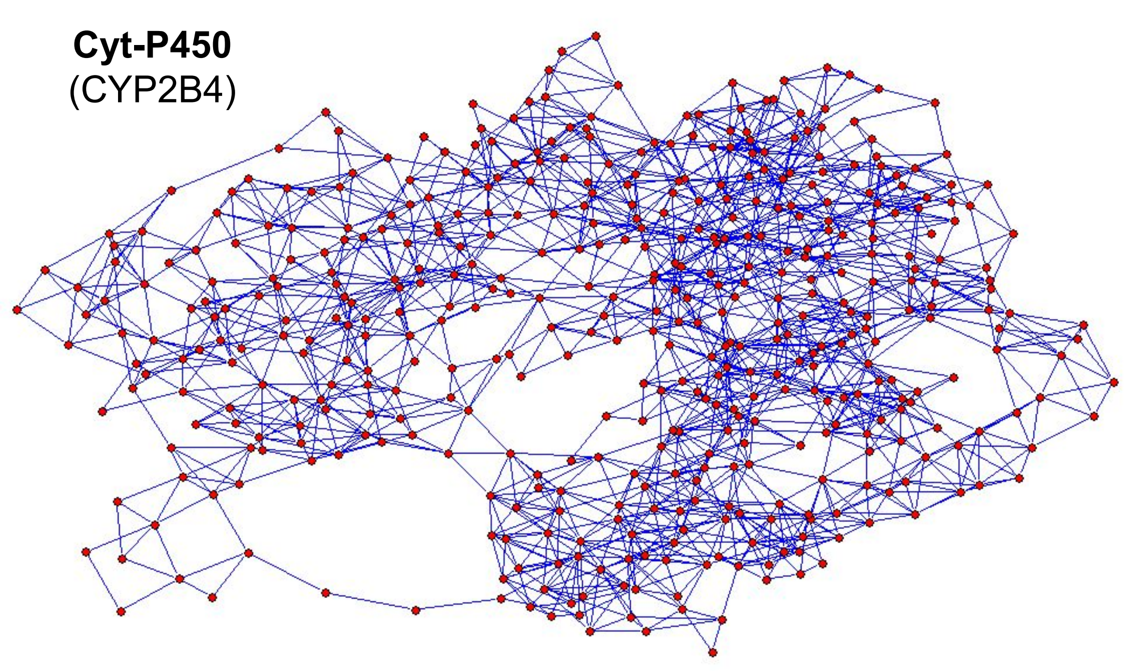


It is a small world
but not scale-free.
Why?

hot spots, key residues
for protein folding:
hubs of transition state

Vendruscolo et al:
Phys. Rev. E. 65:061910

Key segments of protein structures

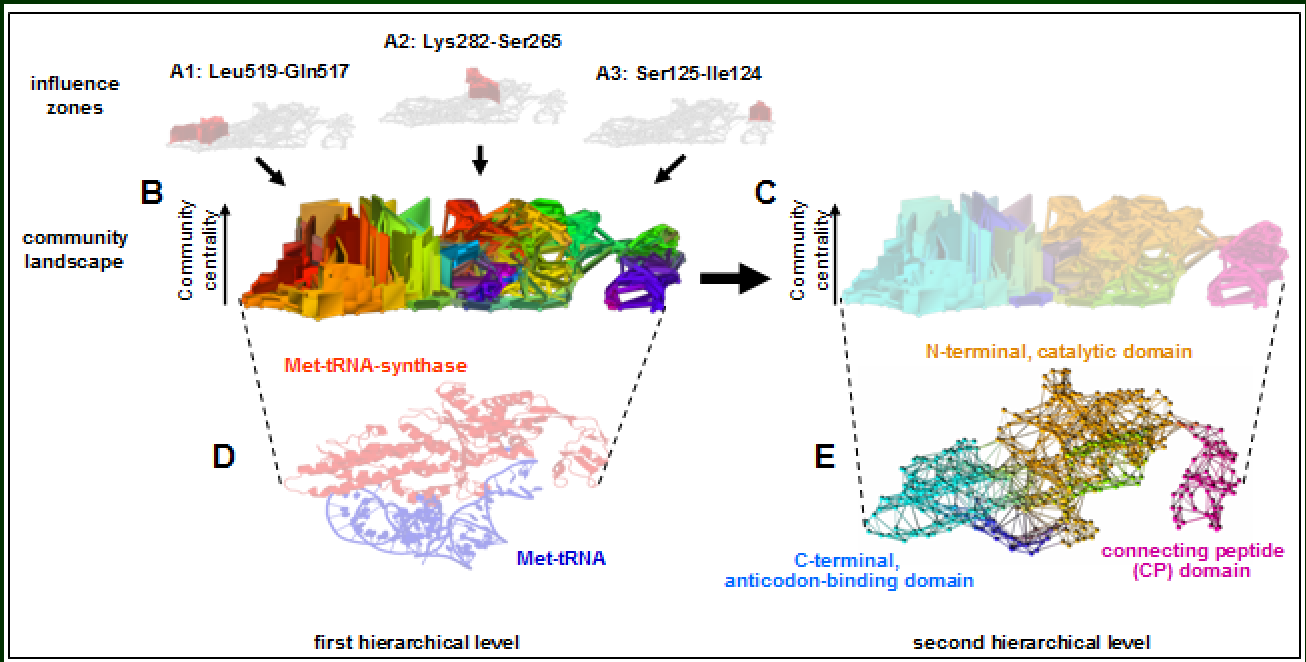


Where do you find key segments besides hubs?

Csermely, TiBS 33:569

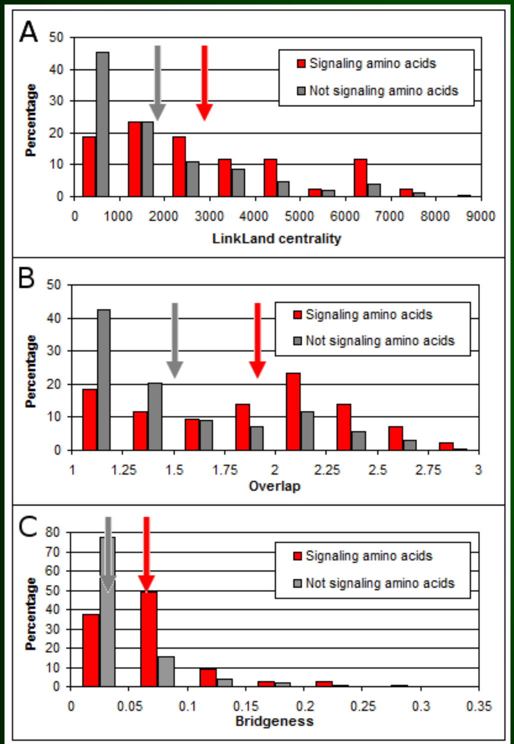
- anchor and latch residues
- bridges, central residues, hinges, discrete-breathers: independent dynamic regions

Modules of Met-tRNA-synthase network correspond to protein domains

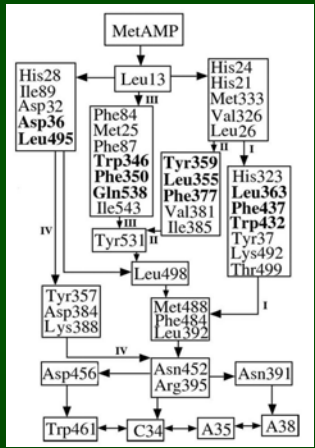


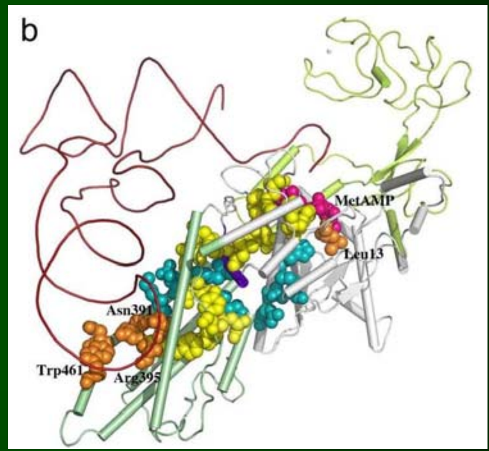
Szalay-Bekő *et* al. Bioinformatics 28:2202
www.linkgroup.hu/modules.php

Bridges of Met-tRNA-synthase network identify signaling amino acids



Ghosh *et al*. PNAS 104:15711





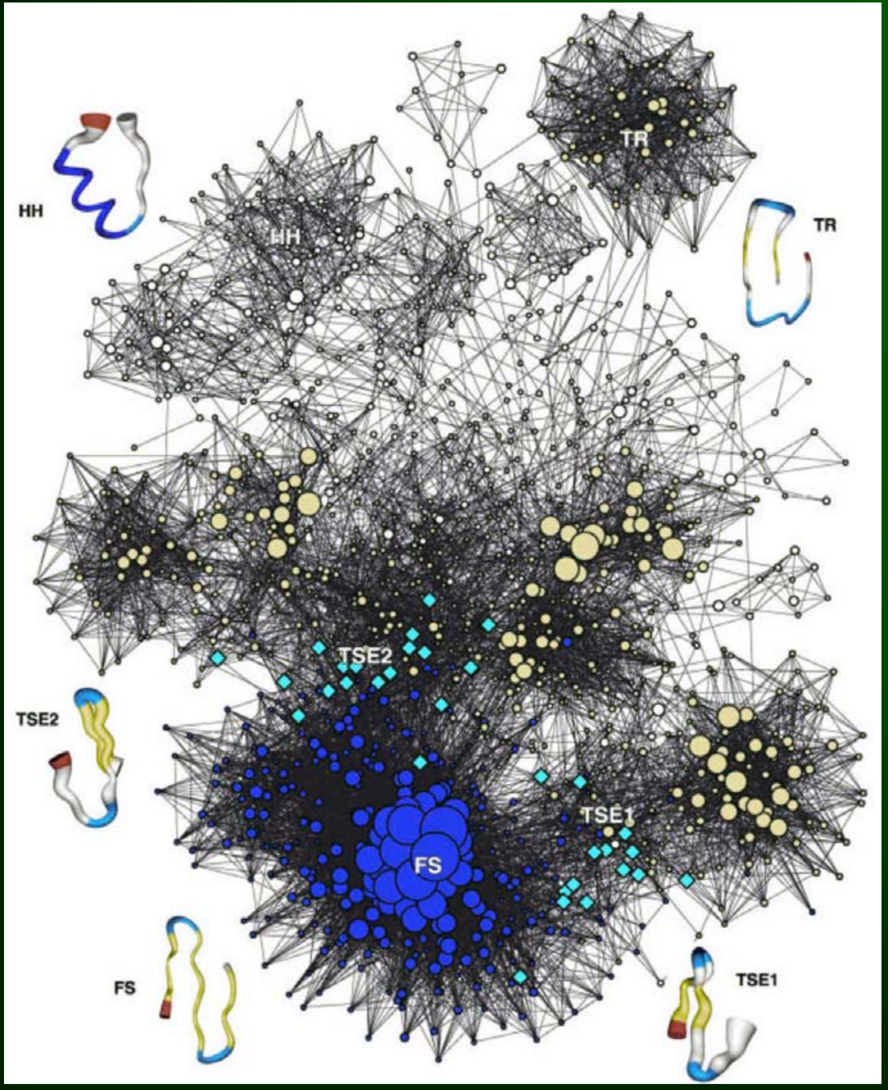
signaling amino acids

(identified from MD cross-correlations)

other amino acids

system dynamics
predicted from topology

Szalay-Bekő *et* al. Bioinformatics 28:2202



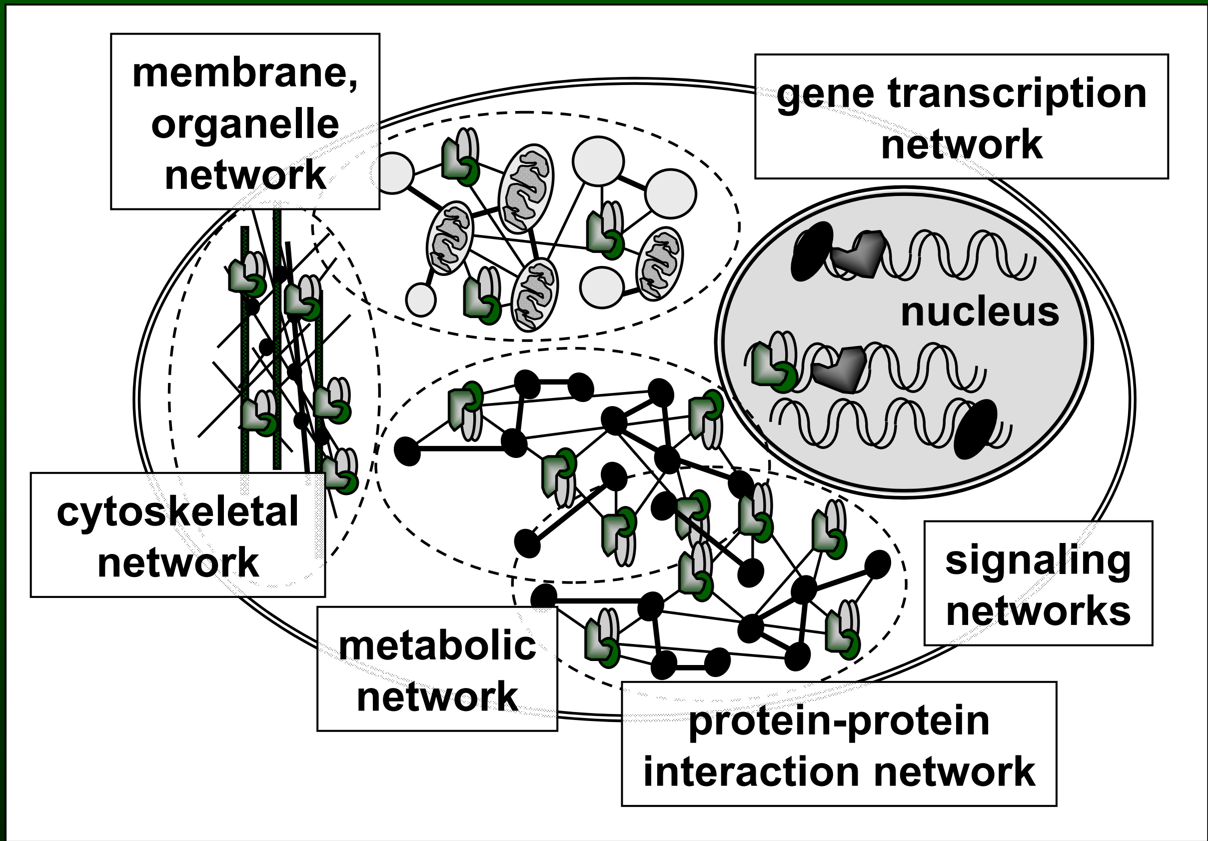
Folding networks in the 'reality'

Why is it good
that it is a small world?

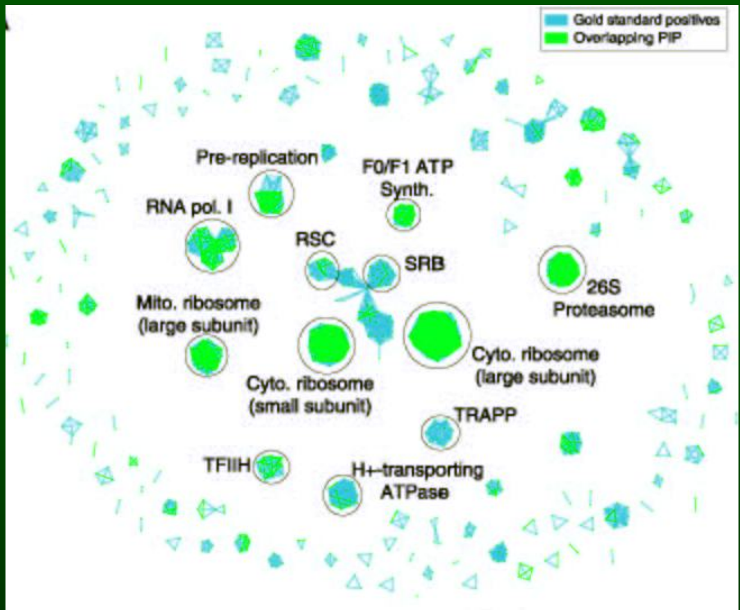
20 AA peptide
nodes: conformations
links: transitions

JMB 342, 299

Cellular networks



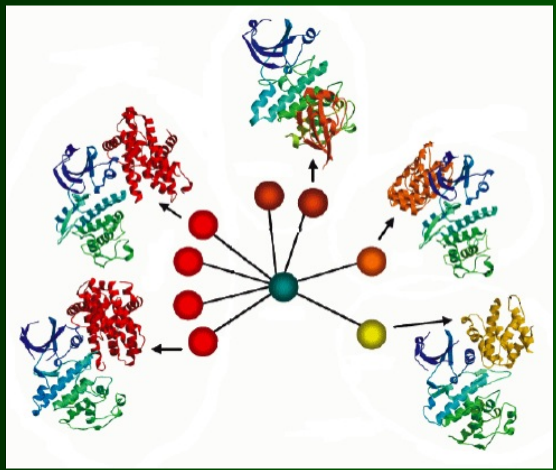
Protein interaction networks



Science 302, 449

yeast
C. elegans
Drosophila
human

• small-world, scale-free (sampling, core)
• lethality: hubs, high betweenness
• modules, herpes, etc.



Definition of protein-protein interaction networks

- nodes: proteins
- edges: physical interactions
- probability networks

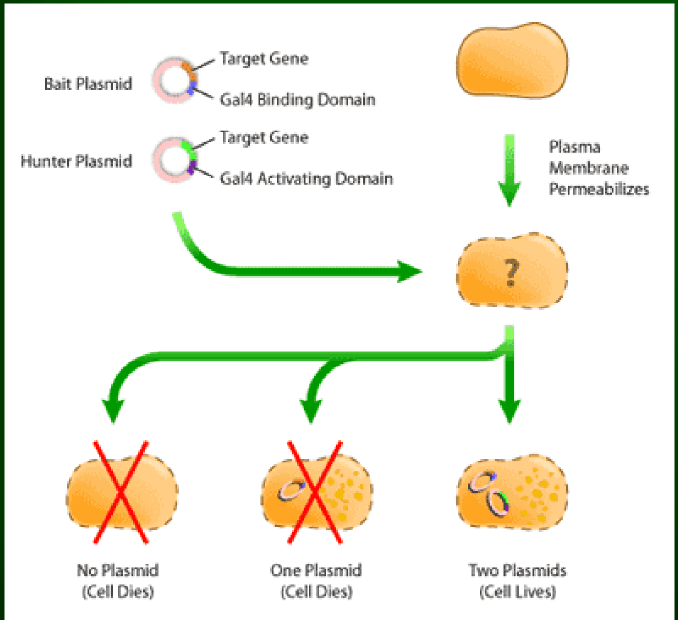
Main databases of protein-protein interaction networks

best data are from yeast, *C. elegans*, *Drosophila* (see Science cover photo) and humans

http://string-db.org/ genetic, high-throughput, coexpression and text-mining data: v9, 5,214,234 proteins from 1133 organisms

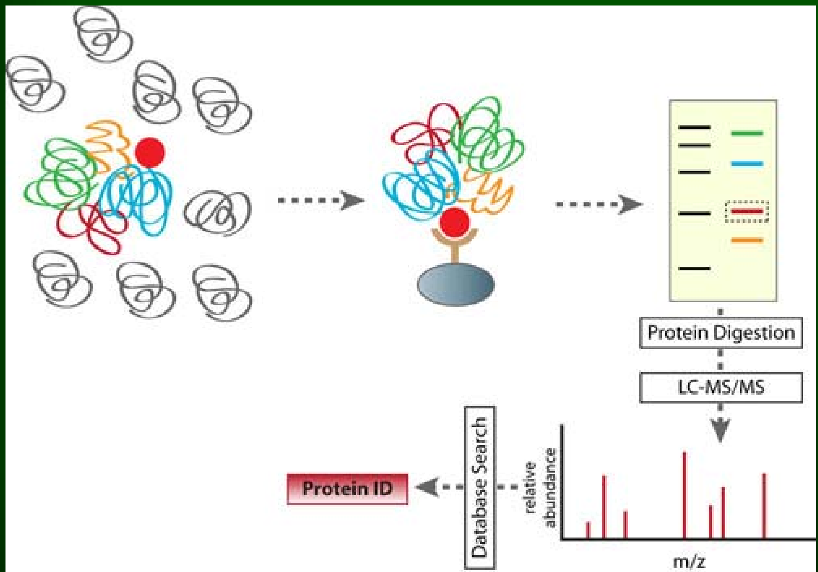
http://thebiogrid.org/ curated data from literature: v3.1.82, 288,588 edges

Main methods to identify protein-protein interactions I.



binary methods (e.g. yeast 2-hybrid sytem, bait/prey + reporter gene expression biased to nuclear proteins, false negatives due to posttransl.modifications, etc.)

Main methods to identify protein-protein interactions II.

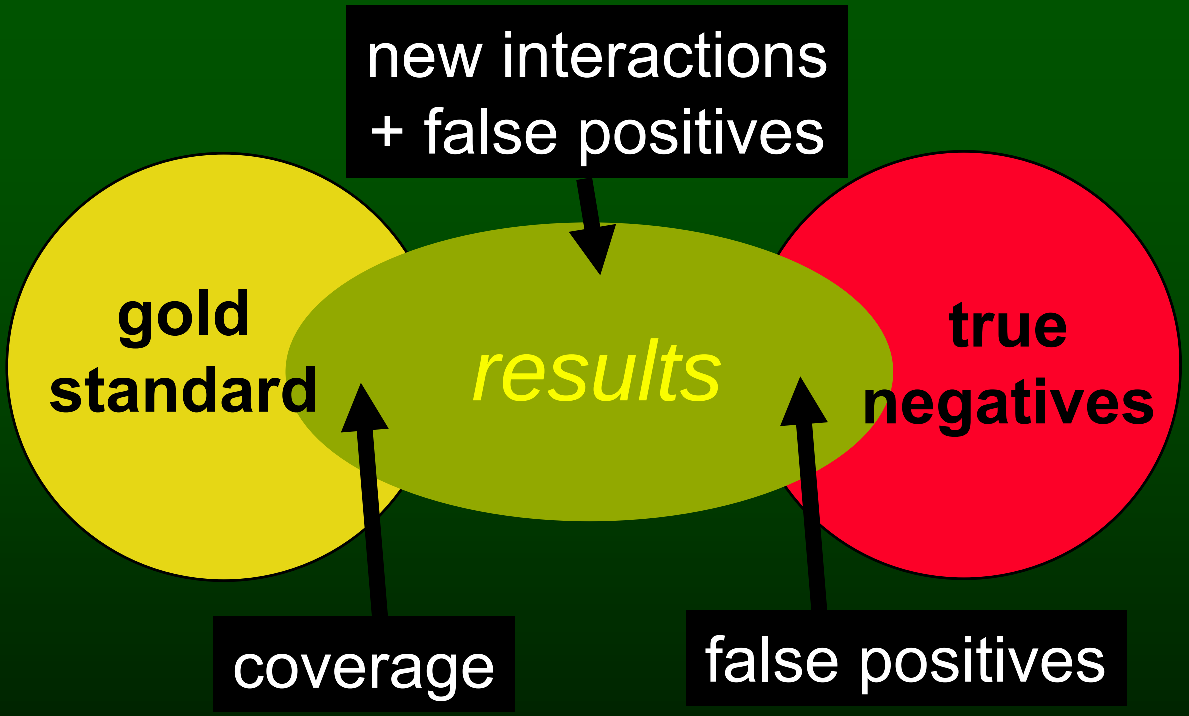


co-complex methods
(e.g. affinity purification + mass spectrometry, other associating proteins/washes, lost weakly binding preys/cross-links, etc.)

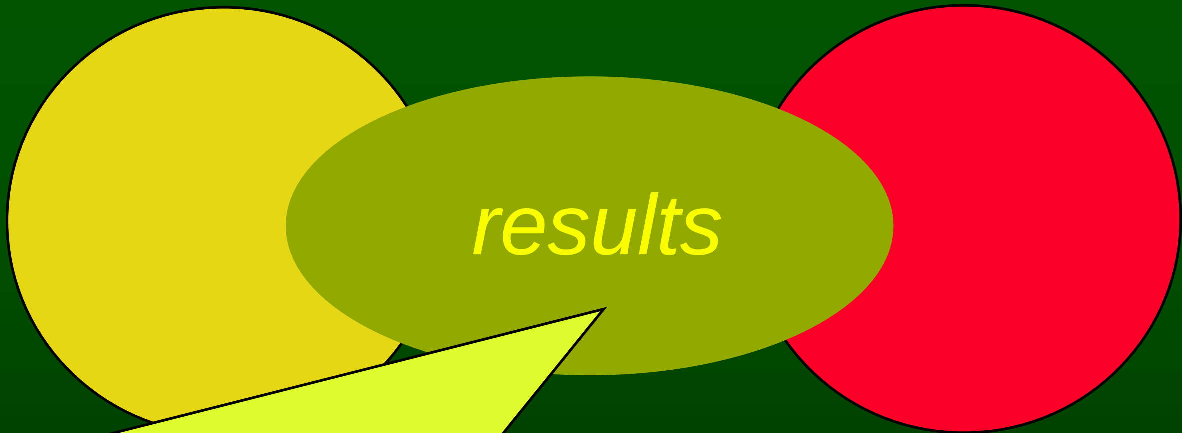
Main methods to identify protein-protein interactions III.

• genetic interactions (may be indirect)
• co-expression data (may be indirect)
• text-mining (if well-curated, can be very accurate)

Assessment of protein-protein interaction data

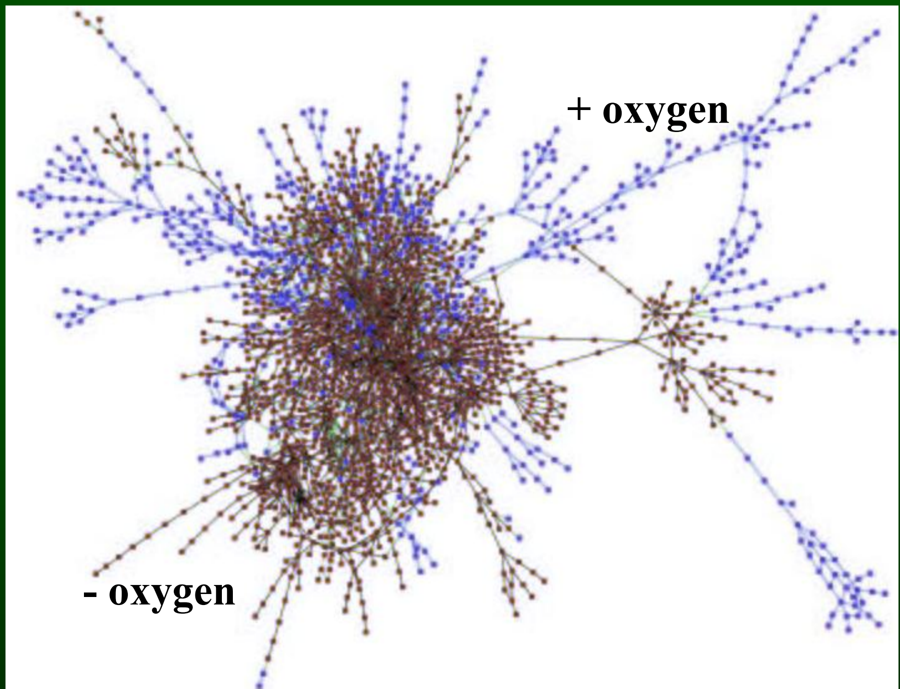


The low confidence *versus* low affinity problem



Those results which are not confirmed by many experiments, are not all low confidence, false positives but may be true, but low affinity interactions

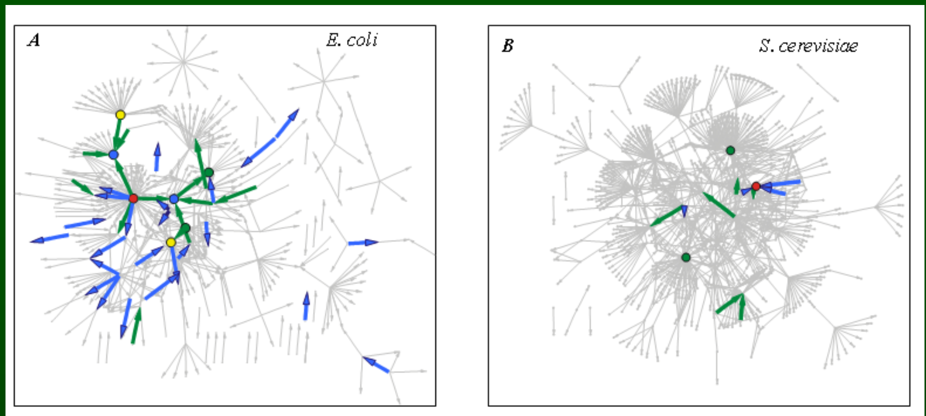
Metabolic networks



Science 311, 1764

- metabolites (nodes)
  + enzymes (links)
- small-world (?), scale-free (?)
- lethality: depends on reaction, high betweenness
- symbionts

Gene transcription networks

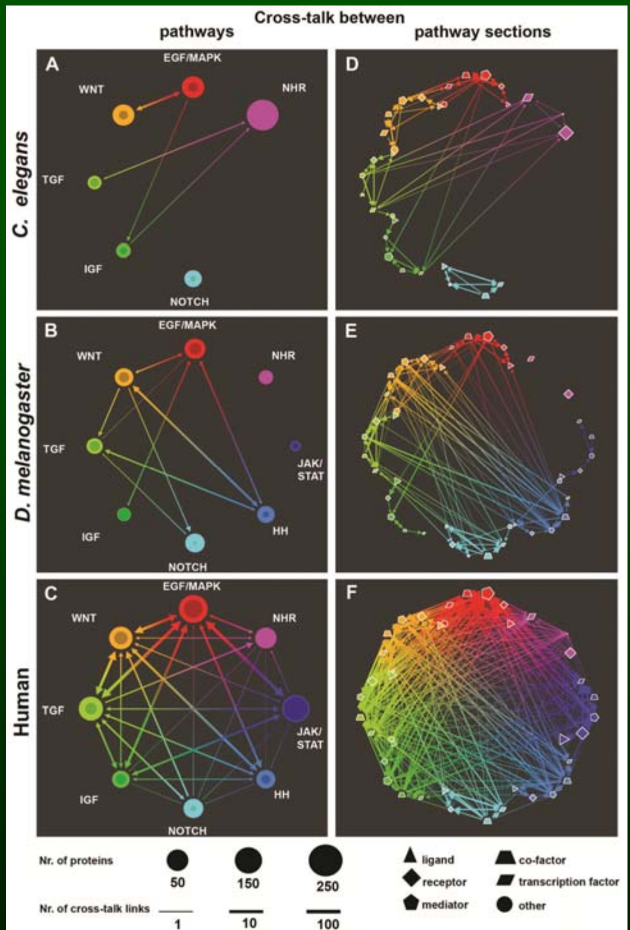


- genes (nodes)
  + transcription factors (links)
- derived from expression profile sets
- similar expression profile: interacting proteins

E. coli and *S. cerevisiae* networks
Agoston et al. Phys Rev. E 71, 051909

yeast	4% trfactor
C. elegans	5
human	8

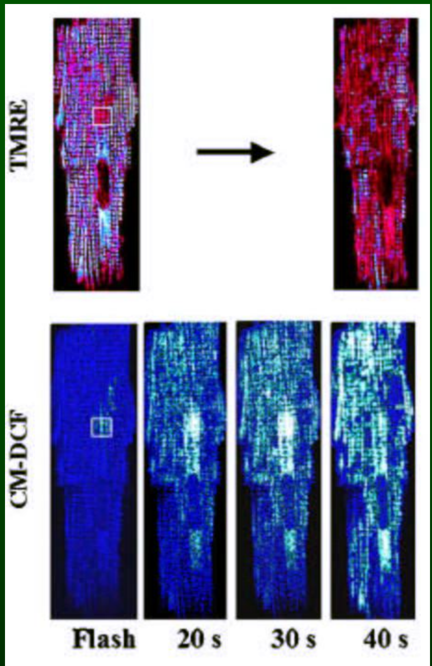
Signal transduction networks



- signaling proteins (nodes)
  + regulation (links)
- partial maps: kinome (kinases)

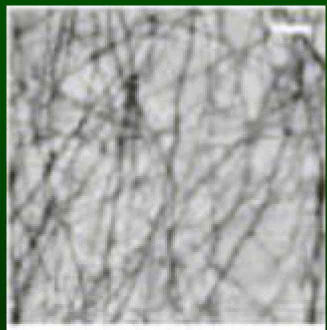
Bioinformatics 26:2042
BMC Syst. Biol. 7:7
www.SignaLink.org

Cell organelle networks



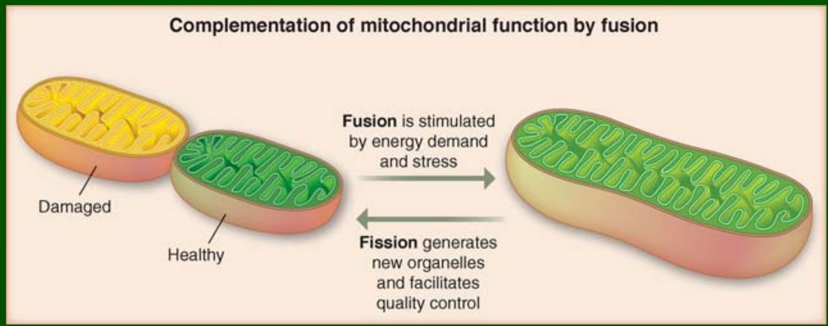
- mitochondrial net (cardiomyocyte)
- chaperone-coupling (decoupling in stress)

BBA 1762, 232



Actin-net, PNAS 101, 9636

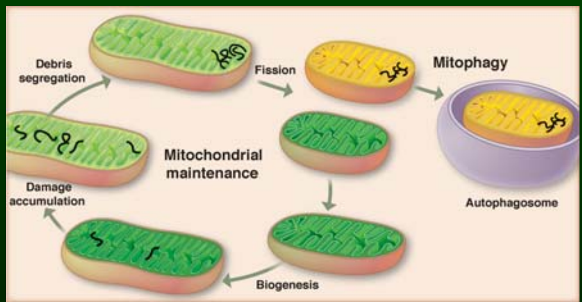
Cell organelle networks in stress

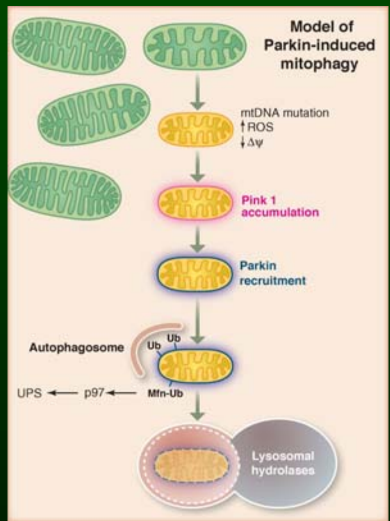


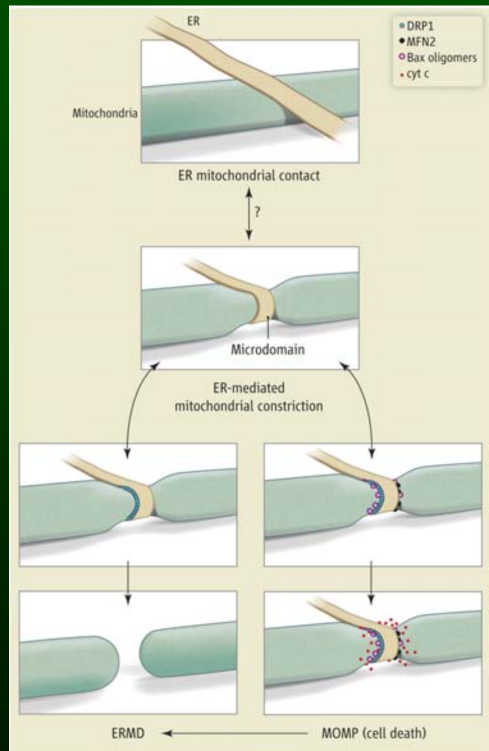
Science 337, 1052 & 1062

Why is this good?

stress

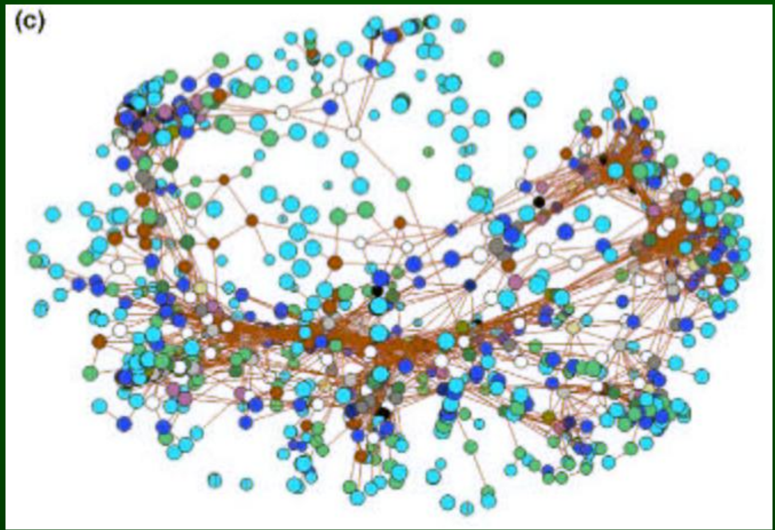


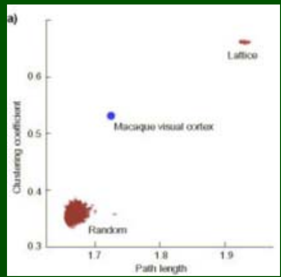




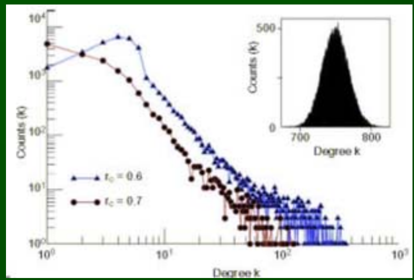
stress

Neural networks



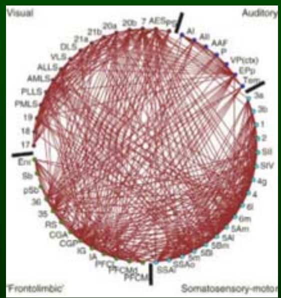


small world



scale-free

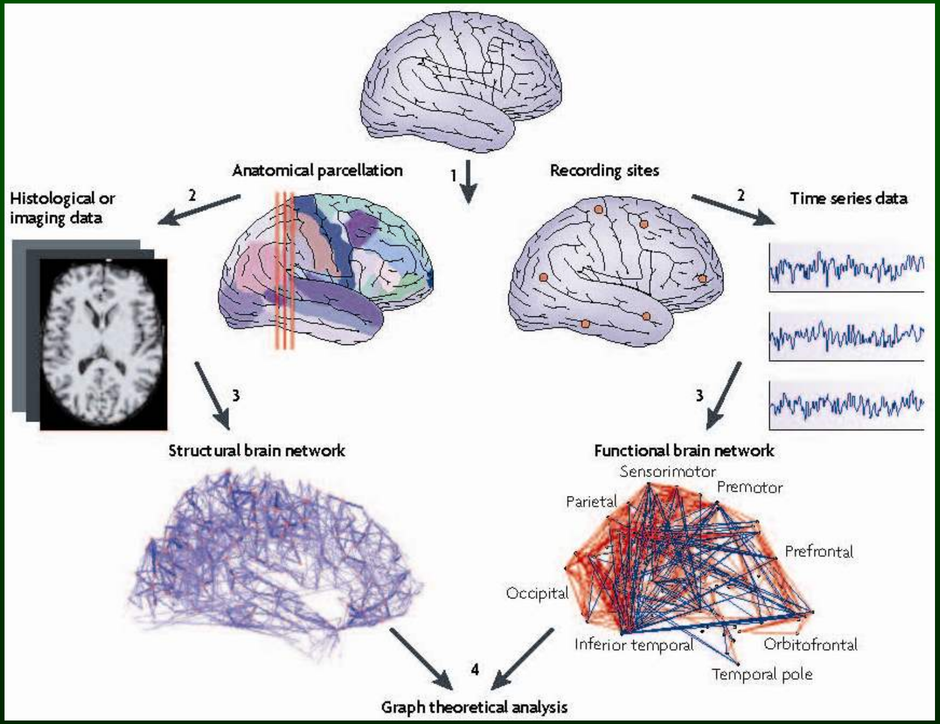
Trends Cogn. Sci. 8, 418



modular

- cat brain net: neurons
- human brain billion neurons
- sync

Networks of human neurons: methods of network construction



Nature Neuroscience 10:186

How many nodes &
links are in the human brain?

10 billion neurons with
50-100 thousand contacts each

Reverse engineering:

figuring out the parts
from the whole

Memory-net:
Effect of context to the accuracy of memory

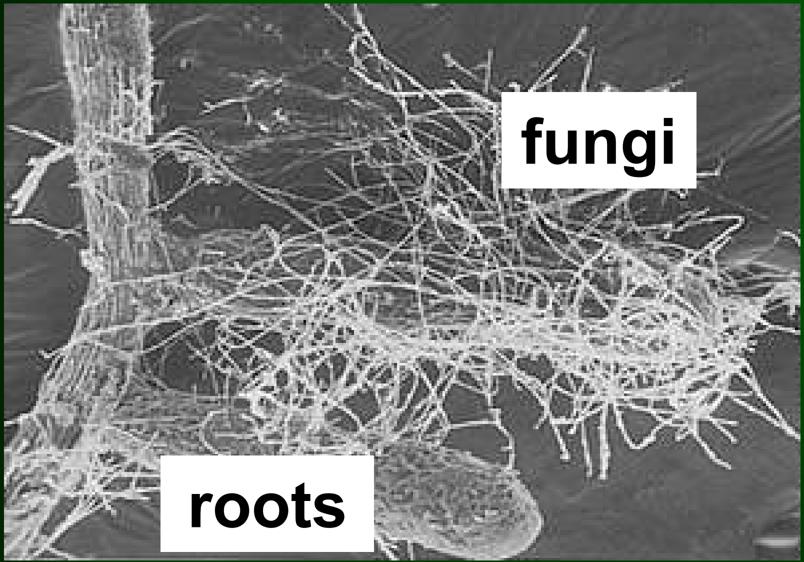
- if you learn detoxicated, you should drink before the exam
- alcoholics remember to hidden liquor or money only when detoxicated again (Science, 163, 1358 –1969 –)
- divers, medical students etc.

Greater self-complexity buffers stress

More social dimensions +
high stress result in
- less flu, backaches, headaches, menstrual cramps
- less depression, mood-swings

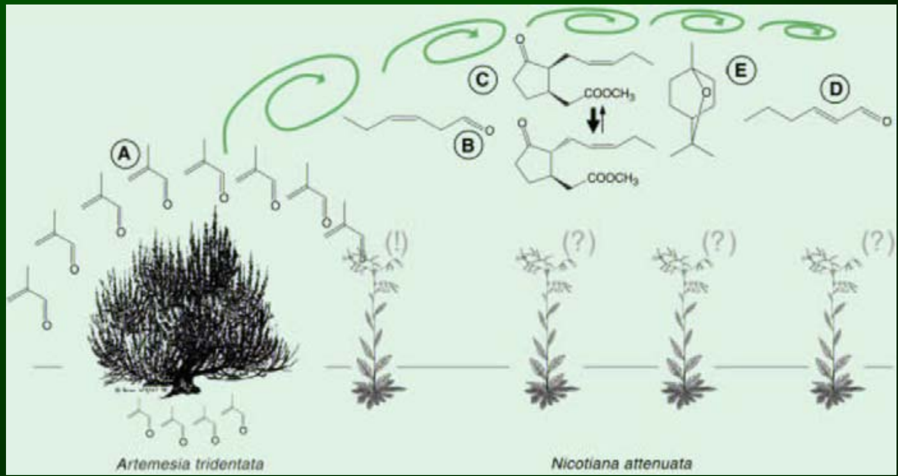
Linville, J. Pers. Soc. Psych. 52, 663

Wood-wide web



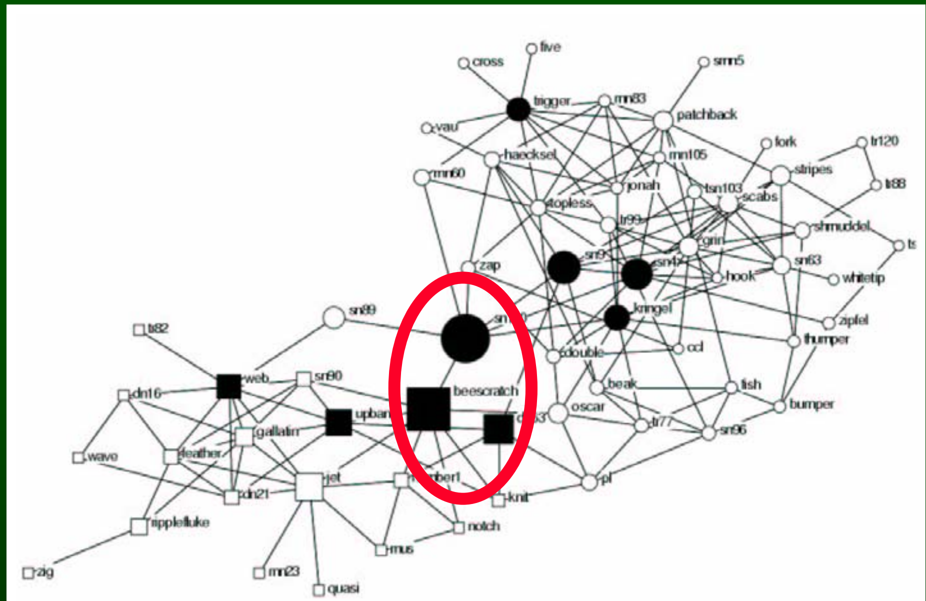
mycorrhiza
100 m/g soil

danger signals elicit
stress conditioning



Science 311, 812

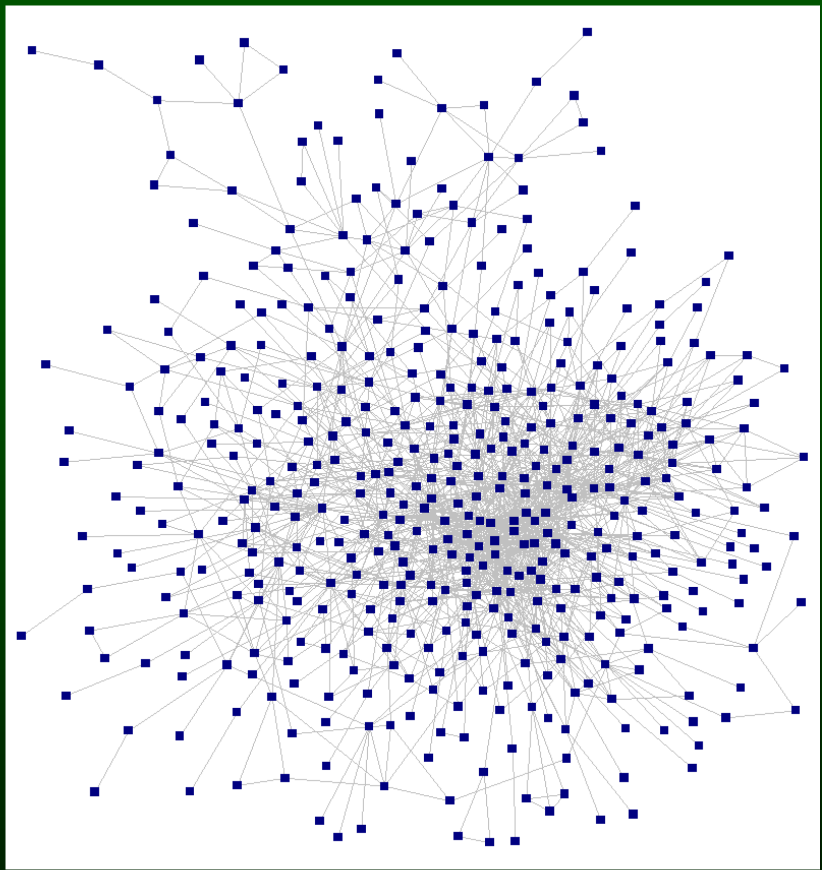
Dolphin networks



Lusseau & Newman Proc. Roy. Soc 271:S477 -04-

small worlds, bridges, VIP-s

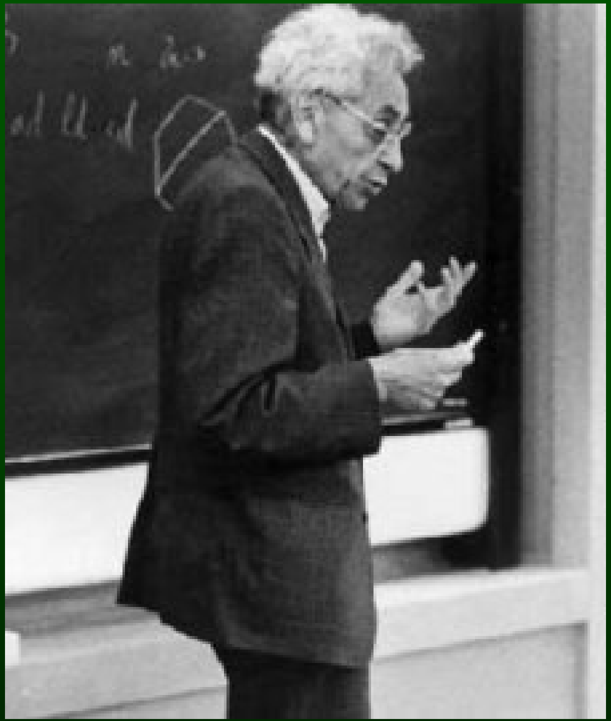
The Erdős-net



509 co-authors of Pál Erdős
(having an Erdős number of 1)
(Erdős number 2: >6984 persons)

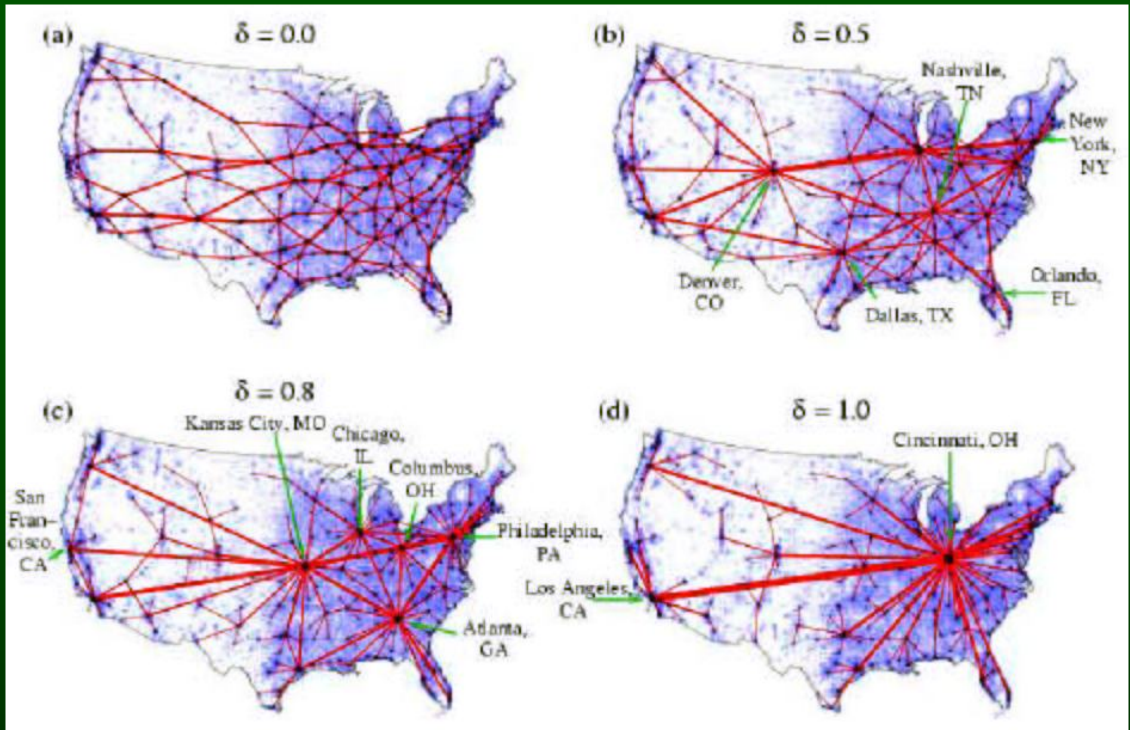
Where is Erdős?

Erdős is already in another dimension...



Pál Erdős
1913-1996

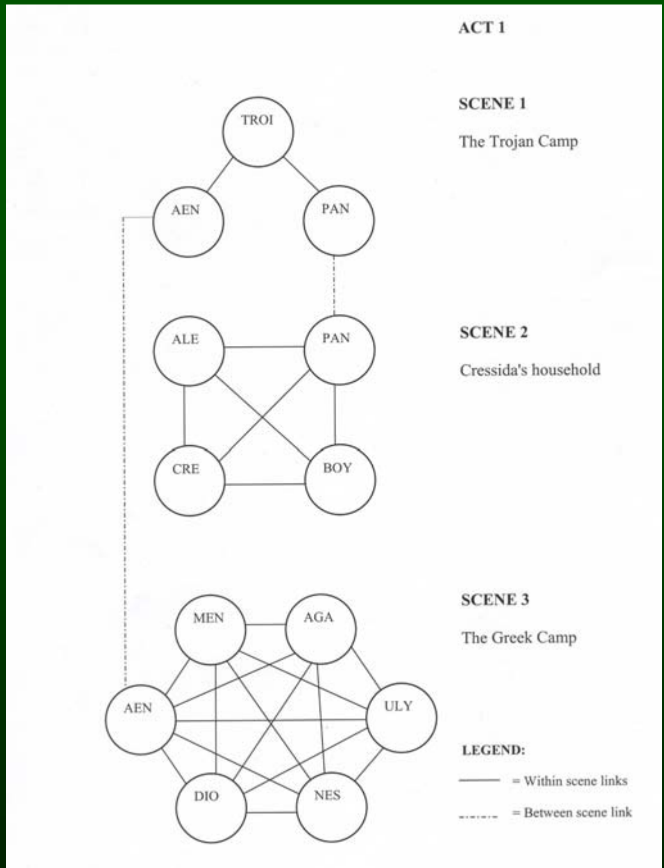
Traffic networks



PRE 74:016117

optimal US-traffic net with
increasing costs of flight changes

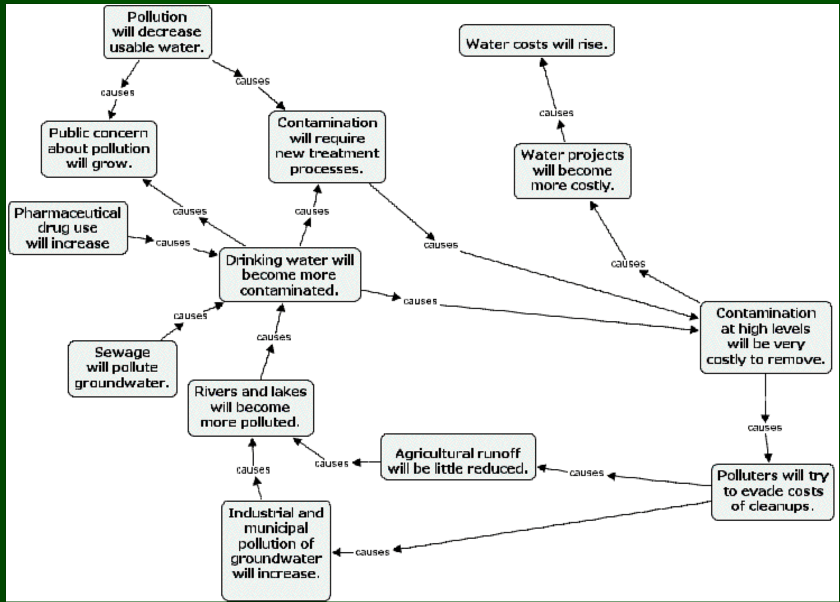
Drama-scenes
Shakespeare: Troilus and Cressida



weak links connect and stabilize the scenes

Stiller and Hudson,
J. Cult. Evol. Psychol. 3, 57

social dimensions
social circles
catharsis – relaxation
congitive dimensions – masterpieces

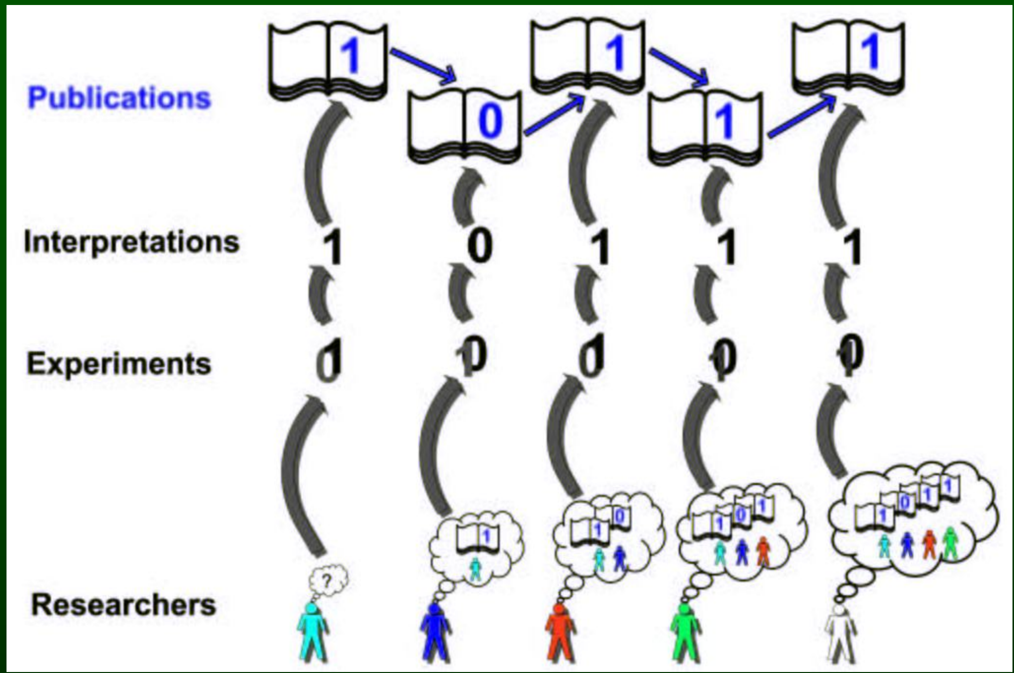


Important predictions are hubs

Raymond L. Johnson
Futures 36, 1095

„Some predictions are more interesting than others.”
„...not because they differ boldly from a consensus view but because they relate to a number of other predictions to form a web of interlinked expectations.”

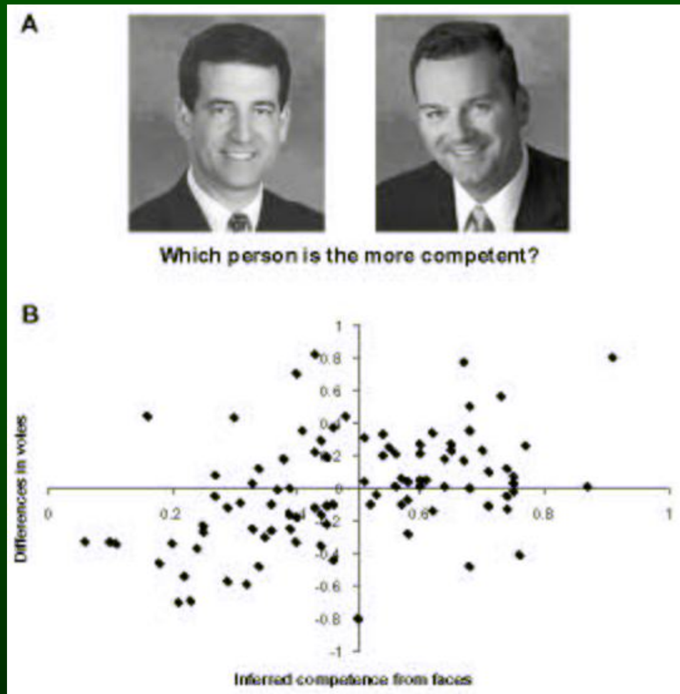
Scientific judgements are not independent



PNAS 103, 4940

optimistic universe: <5% false results
pessimistic universe: >90% false results

The power of judgements: US elections



competent: winner

not competent: looser

70% of cases
Science 308, 1623

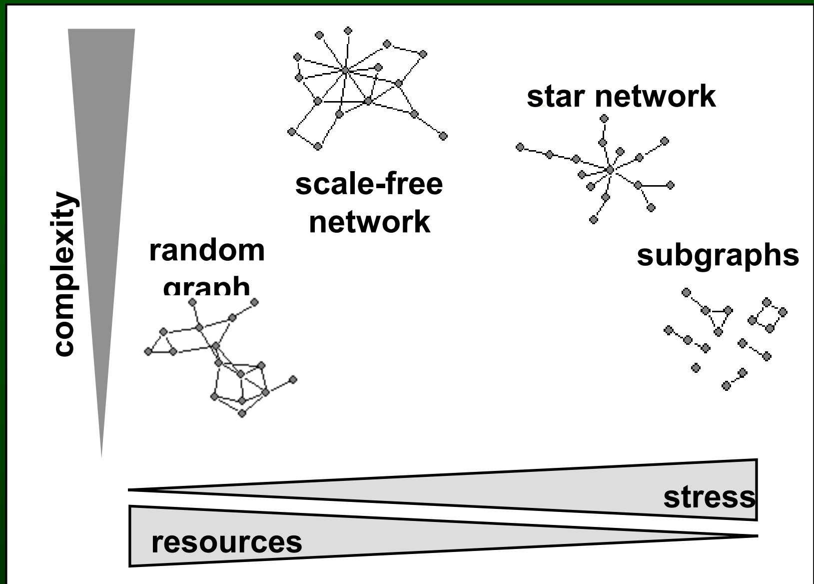
Networks and stability

Part 5. – Adaptation of complex systems, a hypothesis

http://linkgroup.hu
http://turbine.ai
csermelynet@gmail.com

Péter Csermely and
the Turbine team

Topological phase transitions: The importance of resource poor and resource rich environments

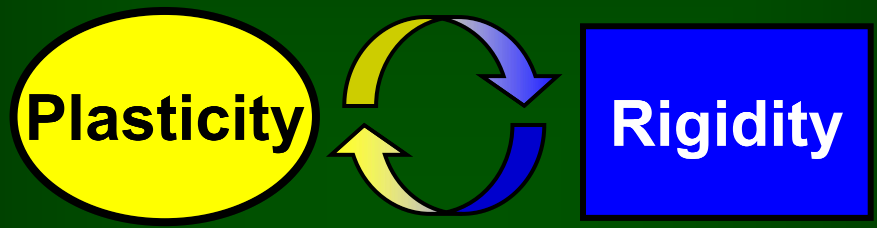


Physica A 334, 583; PRE 69, 046117

Example 2:

Adaptation of complex systems

resource rich



resource poor

Plasticity-rigidity cycles form a general adaptation mechanism

Csermely arxiv.org/abs/1511.01238

Example 2:

Adaptation of complex systems

rigid and plastic properties

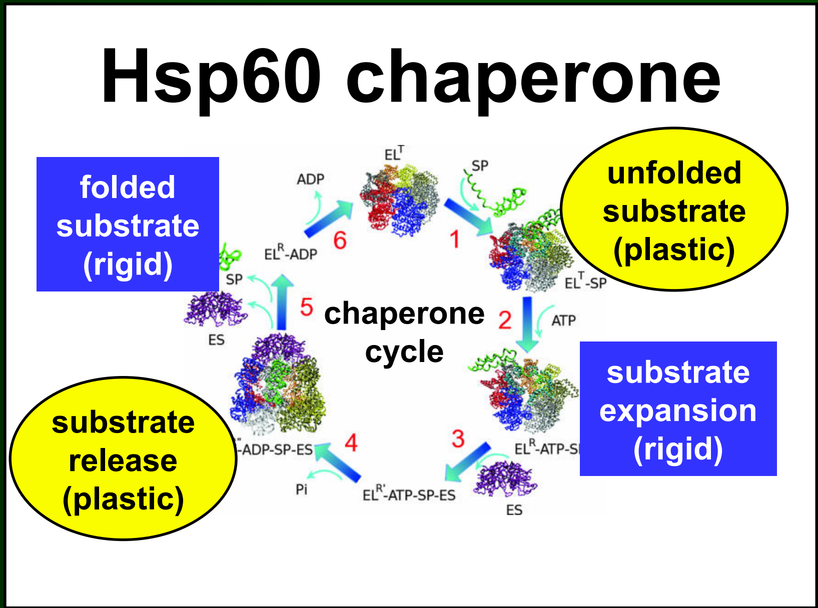
–	+	+	possibility of adaptation
+	+	–	effect of adaptation

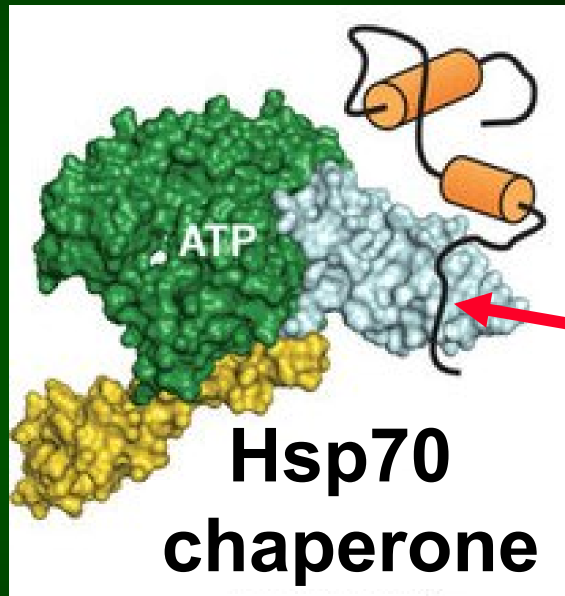
Gáspár & Csermely, Brief. Funct. Genom. 11:443
Gyurkó et al. Curr. Prot. Pept. Sci. 15:171
Csermely arxiv.org/abs/1511.01238

learning competent *(exploration)* →

← **memory competent** *(optimization)*

Example 2: **Molecular mechanisms of protein structure optimization**





extended peptide bonds

iterative annealing:
pull/release of folding protein

Todd et al, PNAS 93:4030
Csermely BioEssays 21:959
Lin & Rye, Mol. Cell 16:23

push/release of extended pepti

plastic: many responses

Bukau & Horwich
Cell 92:351

rigid: few responses

Example 3:
cell differentiation

progenitor cells

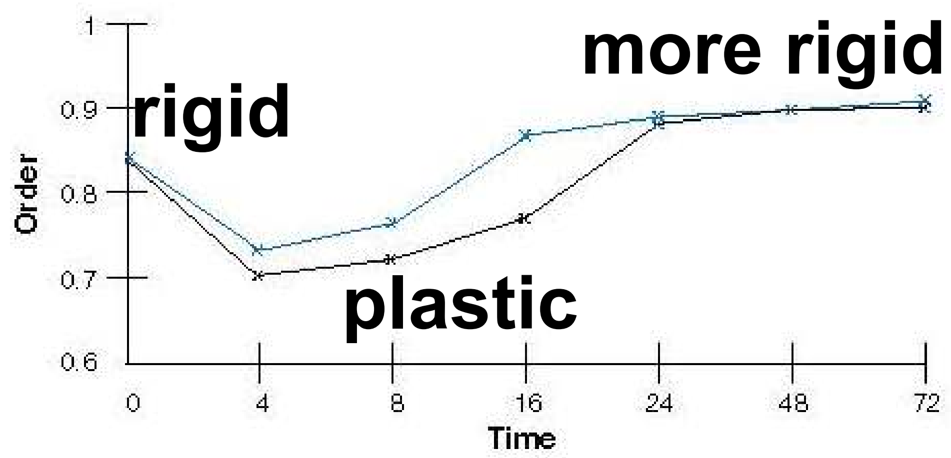


Fig. 3. Dynamics of order during cell specialization. When a progenitor commits to either the erythroid (black) or the neutrophil lineage (blue), there is a concomitant increase in order, eventually stabilizing at a level greater than that of the original multipotent progenitor (7).

differentiated cells

Rajapakse *et al.*, PNAS 108:17257

plastic: many responses

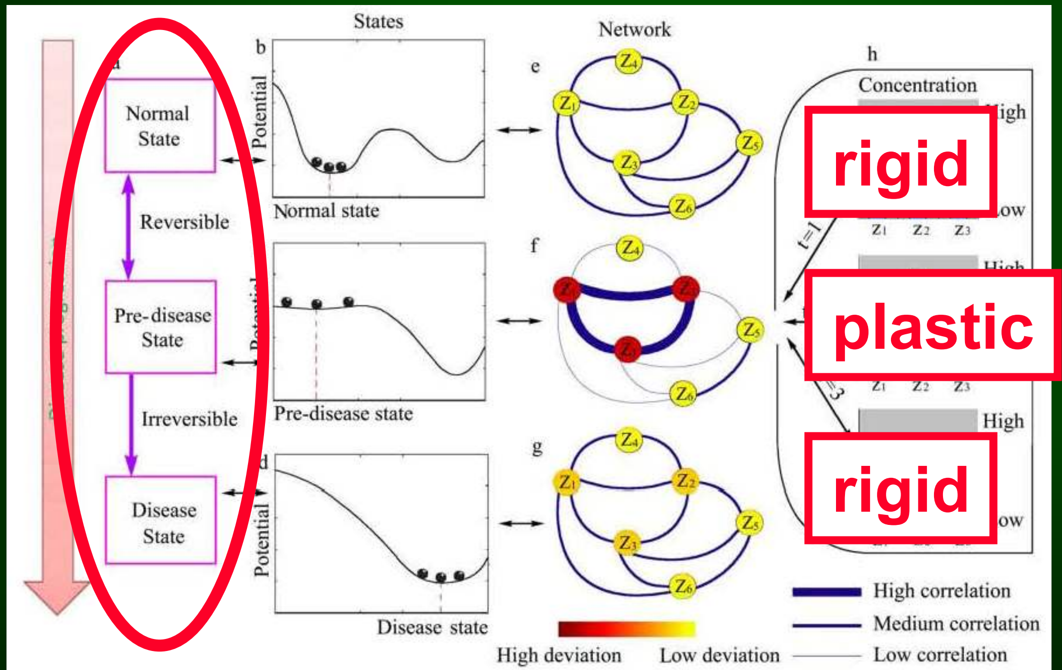
rigid: few responses

Example 4:
disease progression

Detecting early-warning signals for sudden deterioration of complex diseases by dynamical network biomarkers

Luonan Chen[1,2], Rui Liu[2], Zhi-Ping Liu[1], Meiyi Li[1] & Kazuyuki Aihara[2]

Scientific Reports 2:342; 813

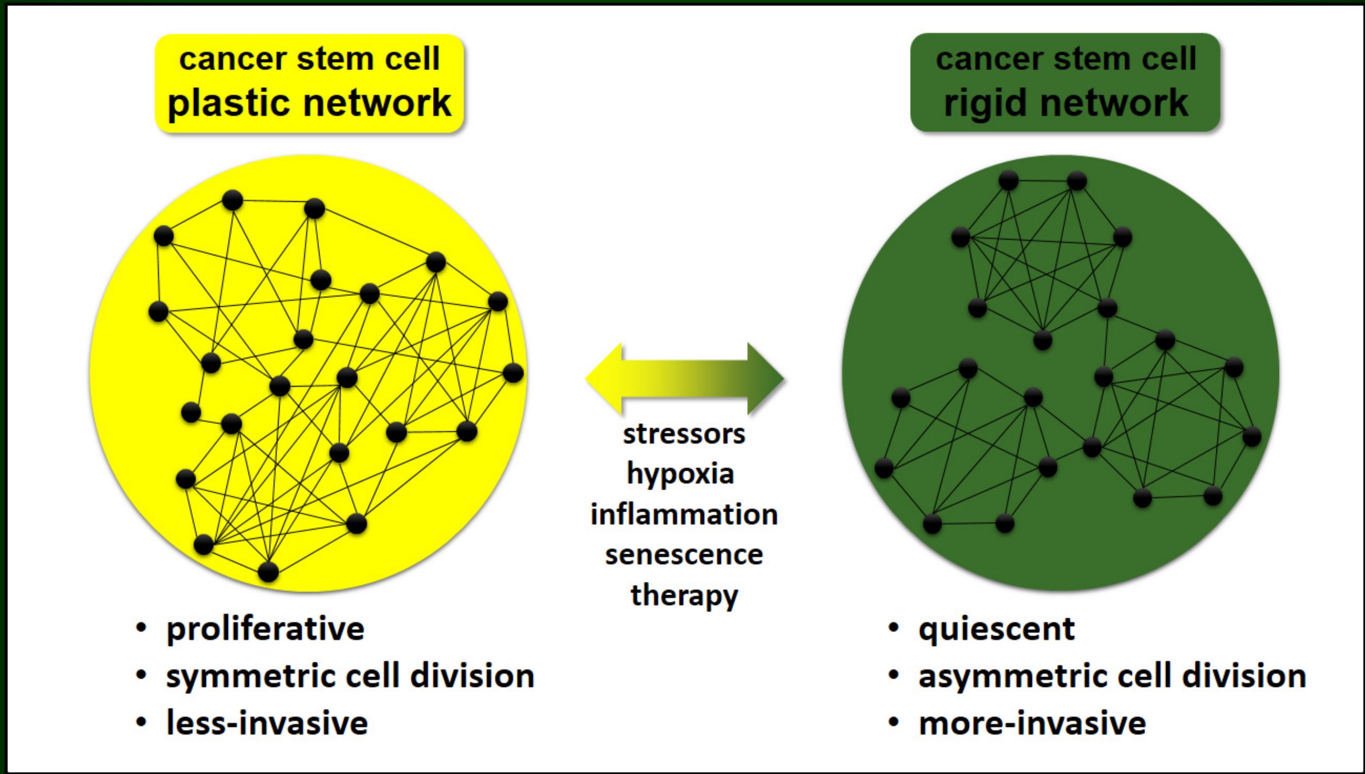


phosgene inhalation-induced lung injury, chronic hepatitis B/C, liver cancer

plastic: many responses

rigid: few responses

Example 5:
cancer stem cells



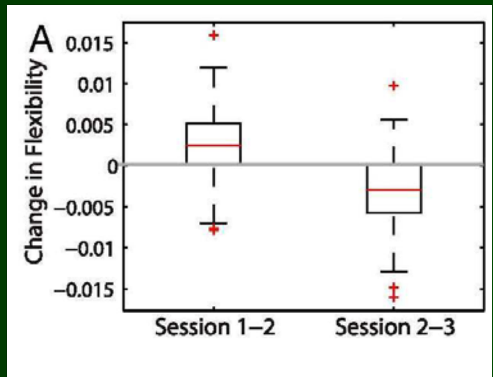
Csermely *et al.*, Seminars in Cancer Biology
doi: 10.1016/j.semcancer.2013.12.004

plastic: many responses

rigid: few responses

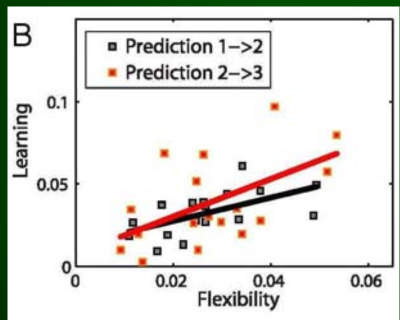
Example 6:

Animal and human learning



modular position of nodes in brain neuronal network becomes more plastic than more rigid during learning

Bassett et al. PNAS 108:7641



plasticity in previous learning session predicts the success of later learning session

plastic: many responses

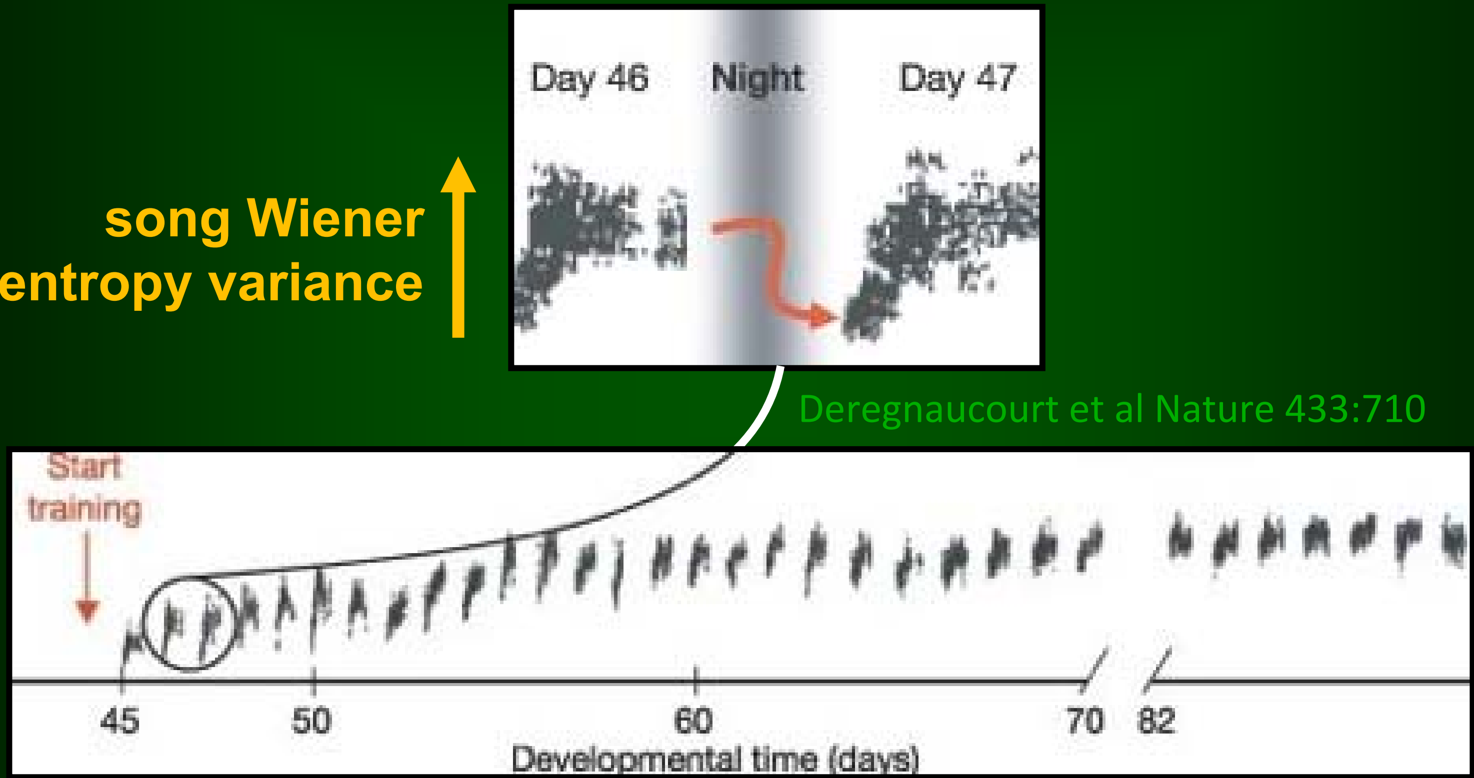
rigid: few responses

Example 2:

Adaptation of complex systems

learning processes

song Wiener
entropy variance



Deregnaucourt et al Nature 433:710

Male bird synaptic plasticity alternates

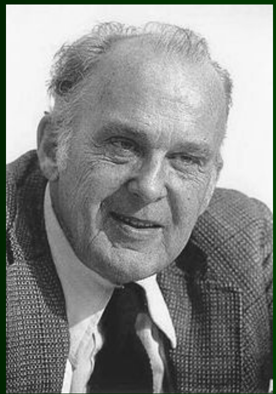
(same kinetics of infant word learning)

Lipkind et al Nature 498:104
Day et al Dev. Neurobiol. 69:796

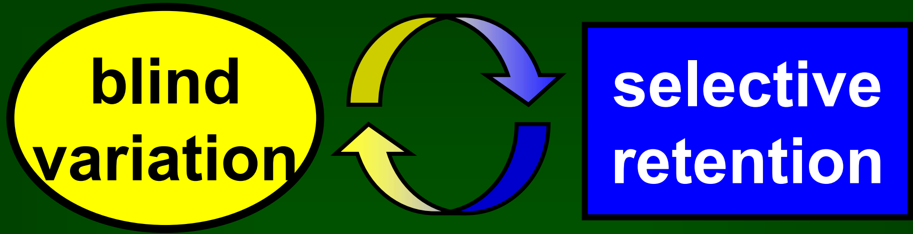
Csermely arxiv.org/abs/1511.01238

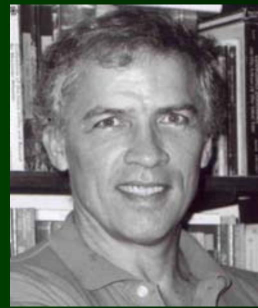
Example 2: Adaptation of complex systems

creativity

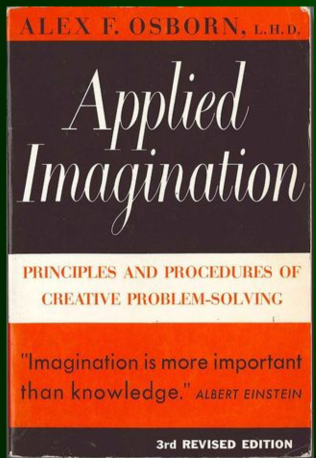


Donald T. Campbell

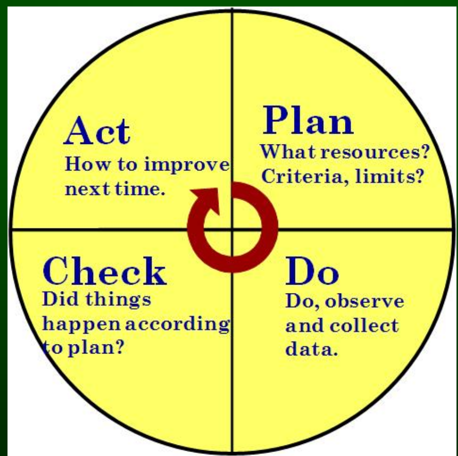




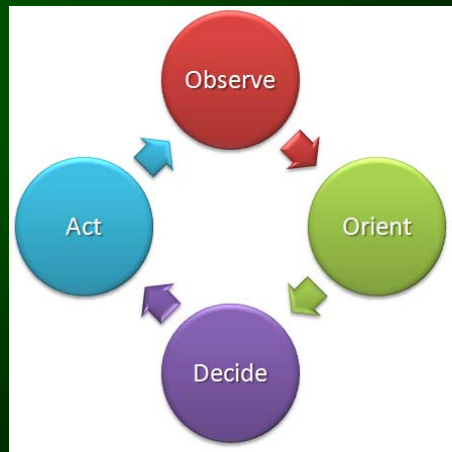
Dean Keith Simonton



brainstorming



PDCA-cycle



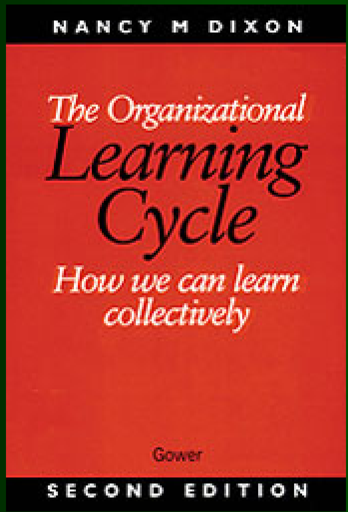
OODA-loop

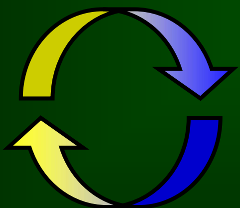
Csermely arxiv.org/abs/1511.01238

Example 2:

Adaptation of complex systems

learning organizations

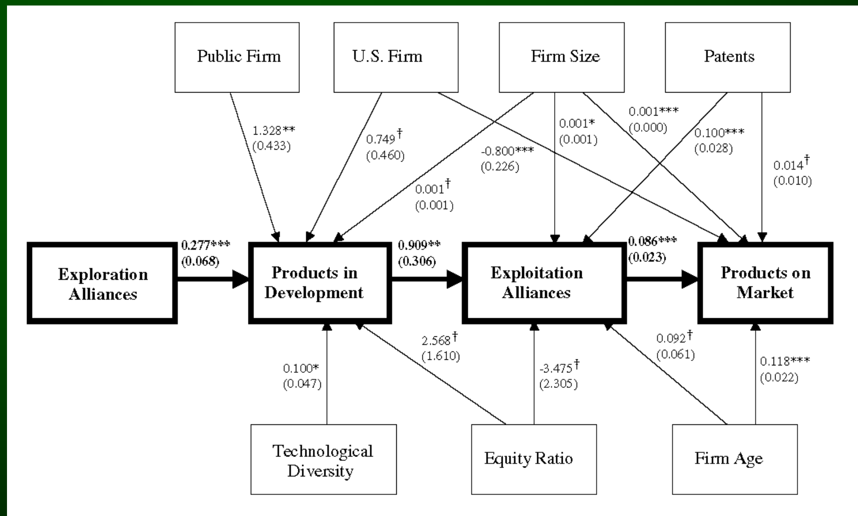




Rothaermel & Deeds, Strat. Mgmt. J. 25:201

exploration → **exploitation**

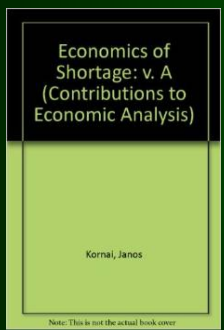
in firm and product development

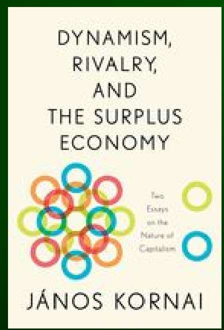


Csermely arxiv.org/abs/1511.01238

Network-independent mechanisms of plasticity-rigidy cycles

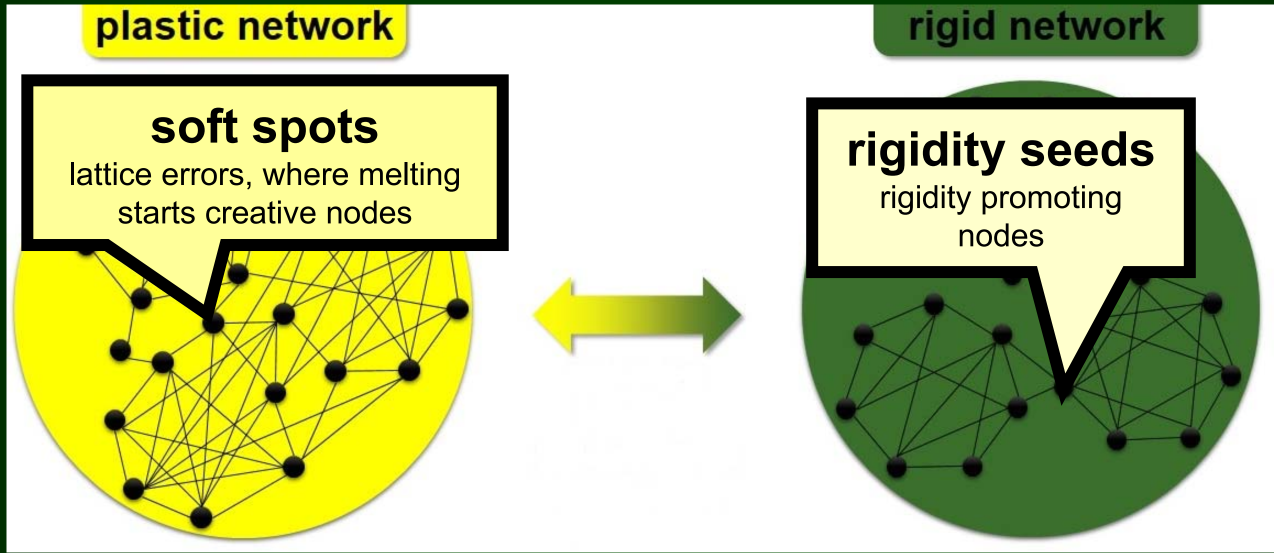
1. noise: reaching hidden attractors
   coloured noise, node-plasticity
2. medium-effects: water, chaperones
   membrane-fluidity, volume transmission
   as neuromodulation, money





Socialism: shortage economy → rigid
Capitalism: surplus economy → plastic

Example 4:
System resources determine network structure
properties of plastic/rigid networks



- extended, fuzzy core
- fuzzy modules
- no hierarchy
- **source-dominated**

- small, dense core
- disjunct, dense modules
- strong hierarchy
- **sink-dominated**

Ruths & Ruths, Science 343:1373; Csermely *et al.,* Seminars in Cancer Biology 30:42; Csermely, arxiv.org/abs/1511.01238

Applications 1: **Aging as a rigidity-shift**

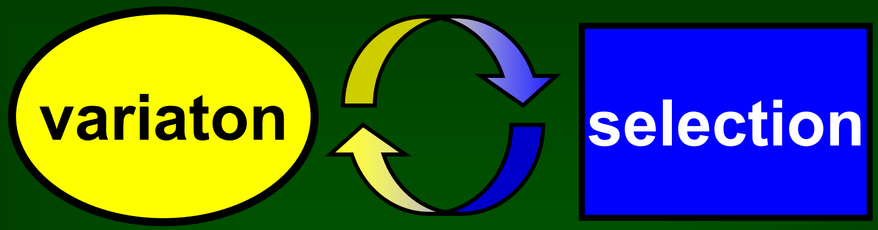
- cognitive functions become more rigid Psychol. Aging 4:136
- fluid intelligence decreases Intelligence 30:485
- practiced performance increases Handb. Phys. Aging 3:310
- personality rigidity increases Gen. Soc. Gen. Psych. Monogr. 128:165

- epigenetic modifications → genetic regulatory networks more rigid *(via system constraint increase)* Sui Huang's group arxiv.org/abs/1407.6117
- age of human cells is 99% predictable by their DNA methylation Horvath, Genome. Biol. 14:R115

age-induced cognitive decline is associated with epigenetic decrease in synaptic plasticity

Mendelsohn & Larrick, Rejuv. Res. 15:98

Applications 2: **Evolution**

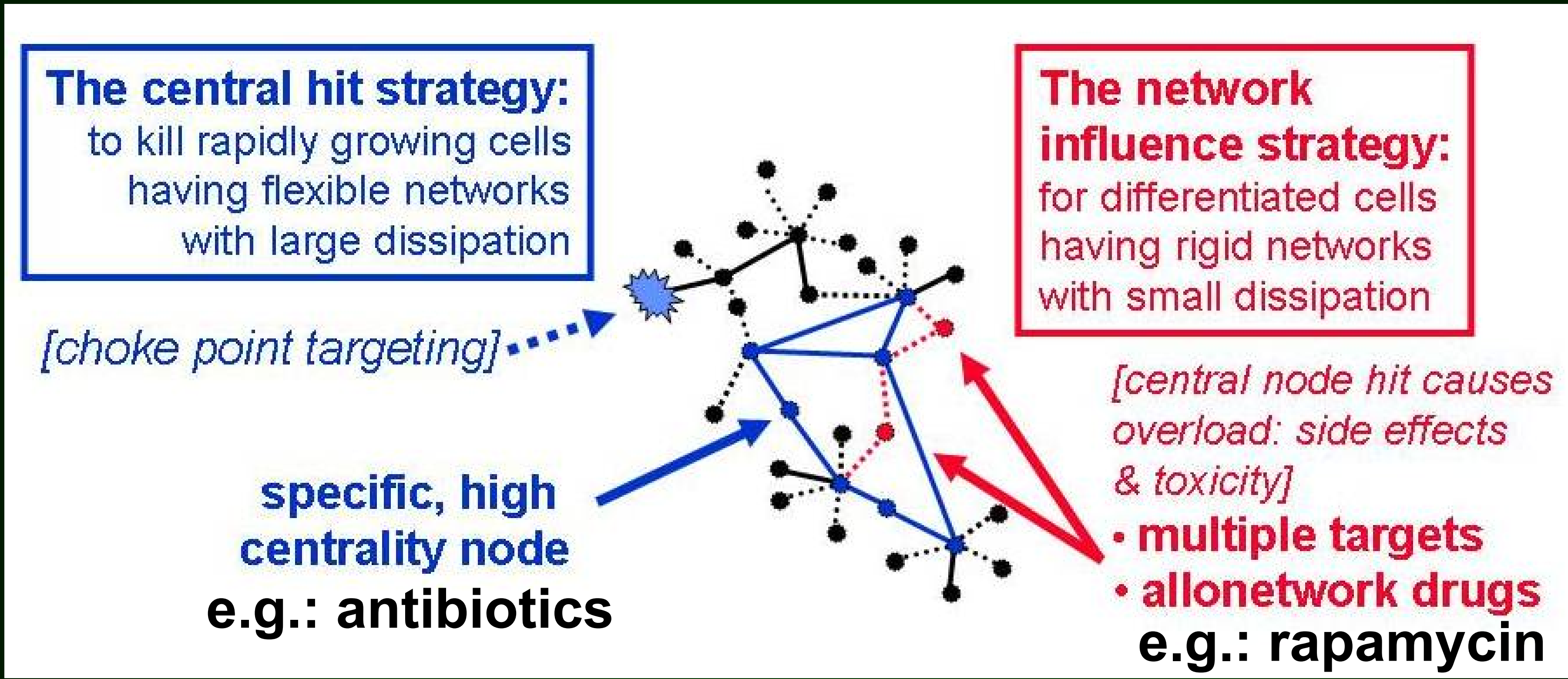


"evolutionary adaptation proceeds by **cycles of exploration** of a neutral network, **and** dramatic **diversity reduction** as beneficial mutations discover new phenotypes residing on new neutral networks"

Wagner, Nature Rev. Genet. 9:965

- *in vitro* tRNA evolution Science 280:1451
- 3000 *E. coli* generations Science 272:1802
- in vivo evolution of HIV-1 and H3N2 influenza viruses
  J. Virol. 73:10489; Science 305:371; Science 314:1898

Applications 3: Drug design strategies for plastic and rigid cells



Csermely *et al*, Pharmacol & Therap 138: 333-408

Applications 3: **Intervention design**

1. plasticity-rigidity cycle boosting or freezing

Science 344:1392

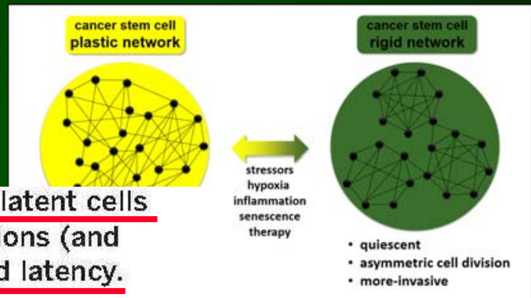
HIV LATENCY

Screening for noise in gene expression identifies drug synergies

Roy D. Dar,[1] Nina N. Hosmane,[2] Michelle R. Arkin,[3,4*] Robert F. Siliciano,[2,5*] Leor S. Weinberger[1,6,7†]

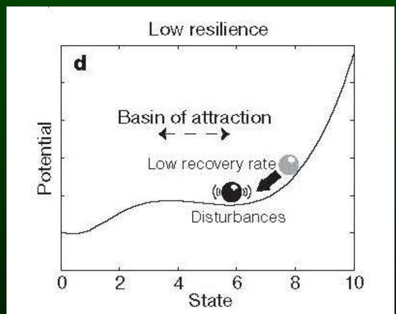
Stochastic fluctuations are inherent to gene expression and can drive cell-fate specification.

Noise enhancers reactivated latent cells significantly better than existing best-in-class reactivation drug combinations (and with reduced off-target cytotoxicity), whereas noise suppressors stabilized latency.



age-change: plasticity-personalized therapies

2. targeting during cycle-induced attractor-change



‘windows of opportunity’
for successful intervention
close to bifurcation points

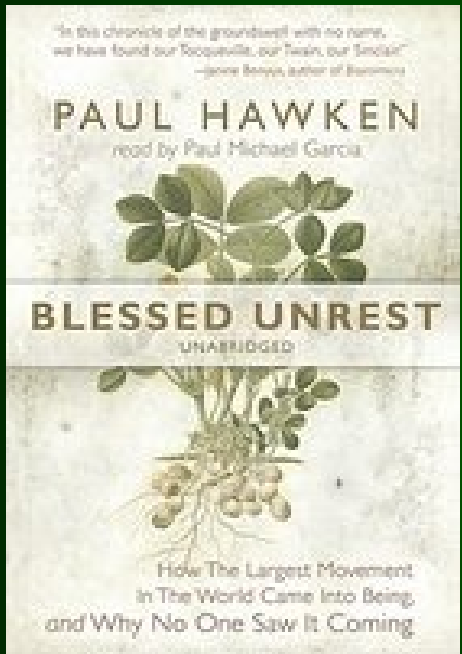
Nature 461:53

Adaptation to gross changes of environment need a transient, plastic phase triggering the emergence of unpredictable nodes

Gross emergence of
independent, unpredictable,
creative nodes: unrest

Csermely arxiv.org/abs/1511.01238

Gross changes of environment trigger the emergence of unpredictable nodes



When a system becomes jeopardized, its nodes (actors) gain more 'independence'

Gross changes of environment
trigger the emergence of unpredictable nodes

Rózsa *et al. Biology Direct*
DOI 10.1186/s13062-014-0034-5

Biology Direct

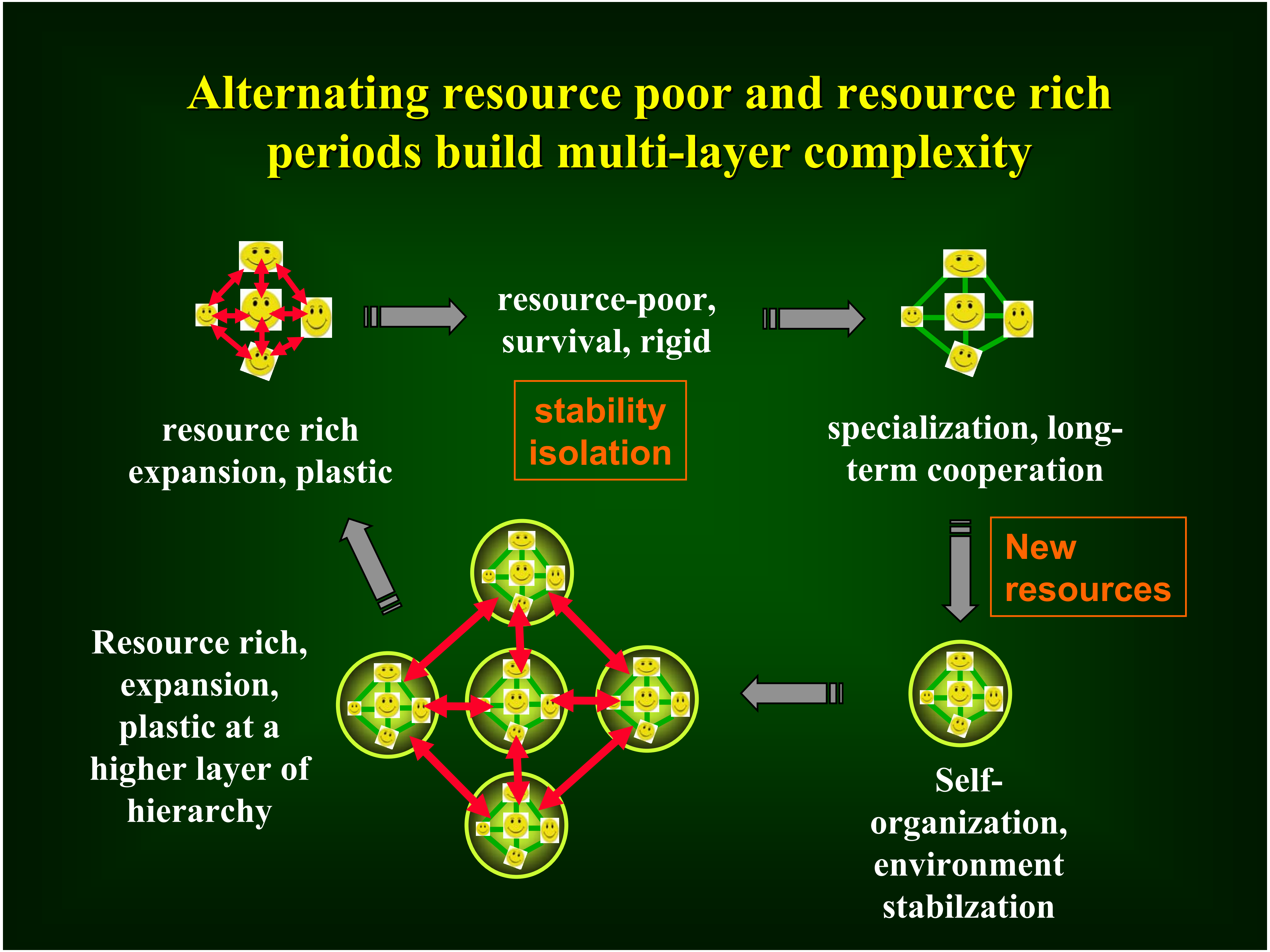
HYPOTHESIS Open Access

The microbiome mutiny hypothesis: can our microbiome turn against us when we are old or seriously ill?

Lajos Rózsa[1,2], Péter Apari[3,4] and Viktor Müller[4,5*]

When our body becomes jeopardized,
our 10 billion bacteria gain more independence

Plastic behaviour (unrest) is characterized by exploration + unstability of the inner self


Alternating resource poor and resource rich periods build multi-layer complexity
resource-poor, survival, rigid
stability isolation
resource rich expansion, plastic
specialization, long-term cooperation
New resources
Resource rich, expansion, plastic at a higher layer of hierarchy
Self-organization, environment stabilzation

Networks and stability

Part 6. – Learning and decision making of complex systems, a hypothesis

http://linkgroup.hu
http://turbine.ai
csermelynet@gmail.com

Péter Csermely and the Turbine team

Decision-making of complex systems

key initial statements, I.

1. Learning increases the weight of edges involved

Alexander Bain, 1874

Santiago Ramon y Cajal, 1894

Jerzy Konorski, 1948

Donald O. Hebb,1949

Erkki Oja, 1982

Carillo-Reid et al, Science 353:691

Hebb/Oja-rule (co-firing and weight increase + normalization; conformational memory of unstructured proteins + signaling hysteresis)

2. Learning develops (or deepens) attractors

Willam A. Little Math. Biosci 19:101

John Hopfield PNAS 79:2554

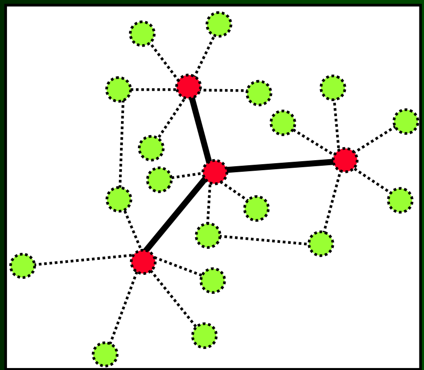
- attractors of state space are developed by a Hebbian process
- Hopfield-like attractor networks are used as artificial intelligence – this needs backpropagation to avoid flat attractors

Toulouse G et al PNAS 83:1695; Amit, D. J. (1989) Modeling brain function: The world of attractor neural networks. New York, NY: Cambridge University Press

Decision-making of complex systems

key initial statements, II.

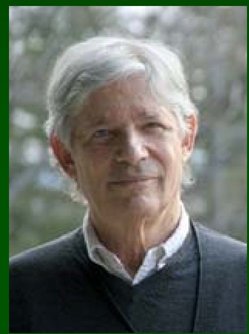
3. A few central nodes make a network core



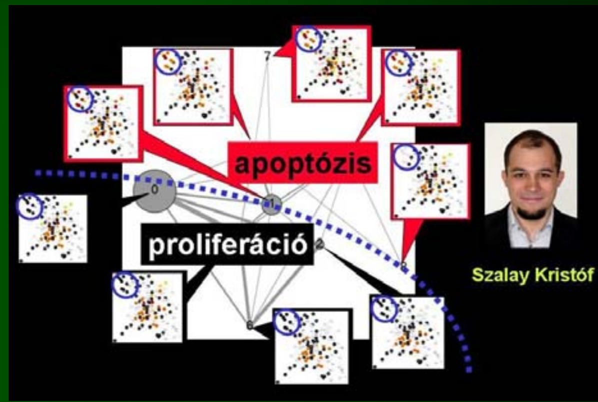
- most of nodes form the network **periphery**
- core is evolutionary conserved and shielded from the environment

Csermely et al
J. Compl. Networks 1:93-123

4. Responses of complex systems form a few attractors



Stuart Kauffman
Nature 224:177-8



attractors of T-LGL cancer cell
http://turbine.ai

- attractors of state space represent the most important responses of complex systems
- attractors are determined by nodes of the strongly connected component (core)

SIAM J Appl Dyn Syst 12:1997
PLoS Comp Biol 11:1004193; arxiv.1605.08415
J Dyn Diff Eq 25:563; J Theor Biol 335:130

Réka Albert

Decision-making of complex systems

THE open question

We know a lot on complex networks.

We know a lot on their attractors.

We know surprisingly little, how a complex system develops + encodes a new attractor, when it needs a new response in a new situation.

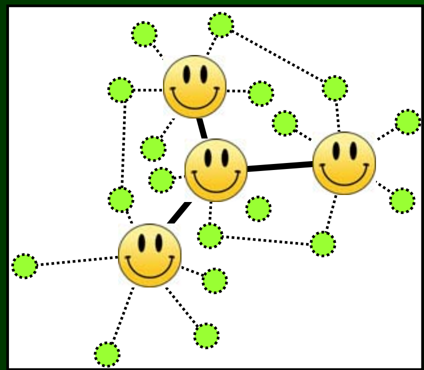
This lecture tries to give a generally applicable answer to this question.

Decision-making of complex systems

fast and slow thinking of networks

usual information

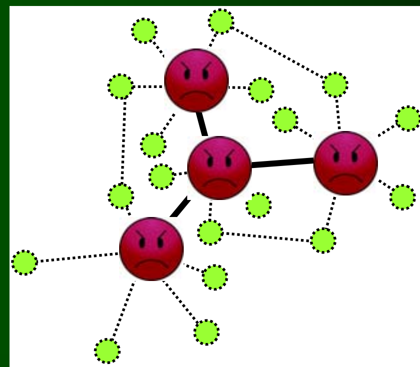
Opinion leaders have consensus

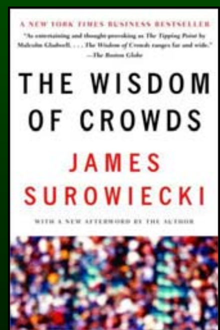


fast and strong response

new information

Opinion leaders disagree



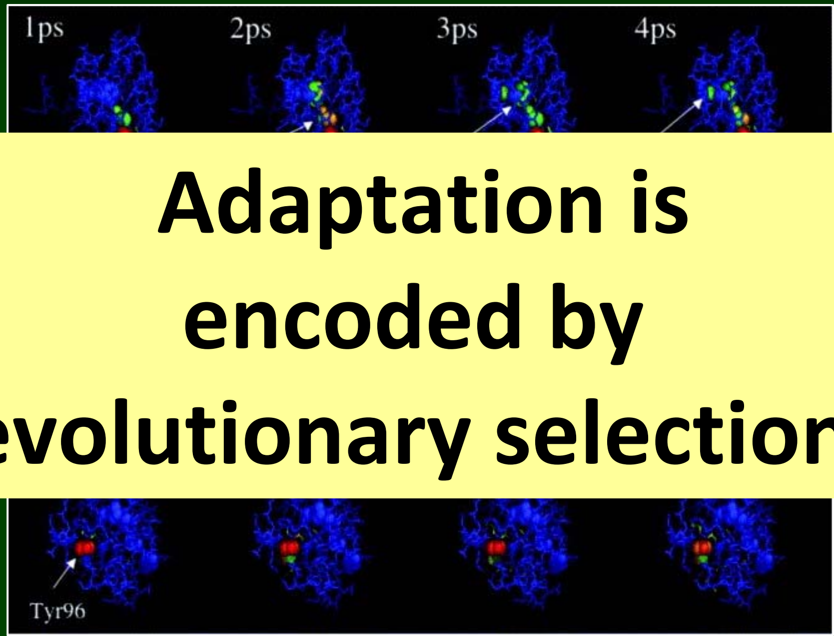


slow response requiring the contribution of the whole community *(slow democracy)*

Csermely arxiv.org/abs/1511.01239

Decision-making of complex systems

Example 1A: protein heat transfer



Adaptation is encoded by evolutionary selection!

Ota and Agard JMB 350:345

PSD95 PDZ-domain protein; His76-Phe29 channel

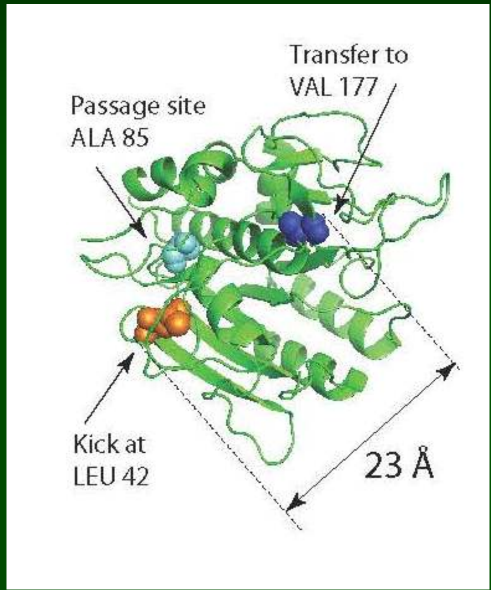
core → fast, anisotropic heat transfer

periphery (Tyr96) **→ slow heat diffusion**

- **other methods**: anisotropic thermal diffusion; pump-probe molecular dynamics (Proteins 65:347); evolutionary conserved sequences (Science 286:295)
- **agrees well with experimental proofs**
- **valid in other proteins too** (sequence analysis, NMR, molecular dynamics)

Decision-making of complex systems

Example 1B: protein energy transfer



Piazza and Sanejouand
nonlinear elastic network model
EPL 88, 68001

a. Stiffest parts of subtilyzin have
'discrete breathers', which transfer energy between them

b. 'ballistic' heat transfer between albumin binding sites without heating connecting amino acids

femtosecond infrared laser pulses + ultrafast time-resolved IR spectroscopy
Nature Communications 5:3100

Decision-making of complex systems

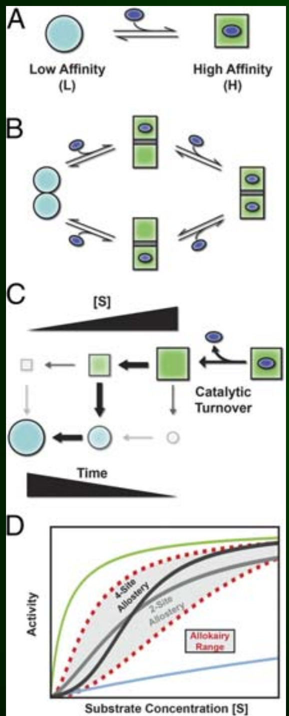
Example 1C: allostery, conformational memory

Allostery: direct response not evolutionary selection

a. allosteric activator of Pin1 increased microdomain connectedness Biophys J 108:2771

b. 'ballistic' heat-transfer between albumin binding sites is enhanced by its allosteric activator

Nat Commun 5:3100



c. „allokairy": higher substrate affinity after catalytic cycle completion – relaxing later

PNAS 112:11430/11553; Sci. Rep. 6:21696

d. conformational memory: neuronal + evolutionary memory

Neuroscience Vol. 86, No. 4, pp. 1037–1043, 1998
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amon PII: S0306-4522(98)00148-1

COMMENTARY

PRION PROTEINS AS MEMORY MOLECULES: AN HYPOTHESIS

P. TOMPA* and P. FRIEDRICH

Cell 157:163
Cell 167:369

Decision-making of complex systems

Example 1D: cellular networks, ecosystems

a. metabolic networks can be divided to core-metabolism + environment-dependent periphery

OPEN ACCESS Freely available online — PLoS COMPUTATIONAL BIOLOGY

The Activity Reaction Core and Plasticity of Metabolic Networks

Eivind Almaas[1,2], Zoltán N. Oltvai[3*], Albert-László Barabási[2,4]

nature

LETTERS

Chance and necessity in the evolution of minimal metabolic networks

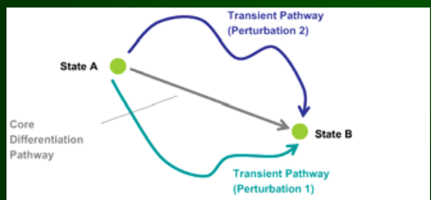
Csaba Pál[1,2*], Balázs Papp[3*], Martin J. Lercher[1,4], Péter Csermely[5], Stephen G. Oliver[3] & Laurence D. Hurst[1]

OPEN ACCESS Freely available online — PLOS ONE

Attractor Metabolic Networks

Ildefonso M. De la Fuente[1,2,3*], Jesus M. Cortes[1,4], David A. Pelta[5], Juan Veguillas[1]

b. cell differentiation can be described by attractor change + numerous environment-dependent trajectories



Mar & Quackenbush
PLoS Comp. Biol. 5:e1000626

c. general and specific resilience (memory) of ecosystems shows the same core/periphery duality

Nykvist, B., and J. von Heland. 2014. Social-ecological memory as a source of general and specified resilience. *Ecology and Society* 19 (2): 47. http://dx.doi.org/10.5751/ES-06167-190247

Journal of Ecology 1992, **80**, 217–230

Seasonal succession of phytoplankton in a large shallow lake (Balaton, Hungary) — a dynamic approach to ecological memory, its possible role and mechanisms

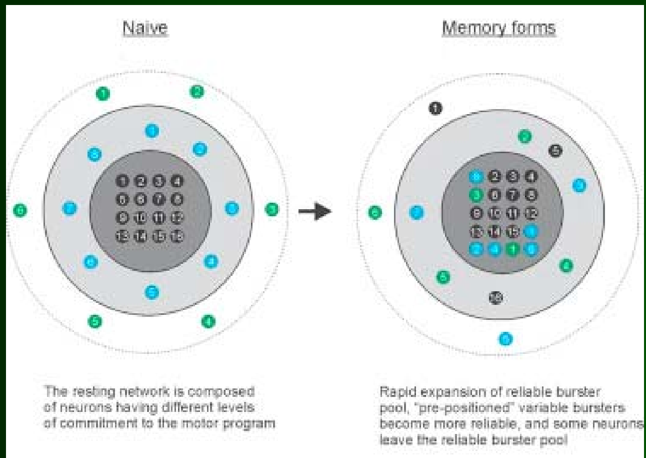
JUDIT PADISÁK*

Social-ecological memory as a source of general and specified resilience

Björn Nykvist[1,2] and Jacob von Heland[1]

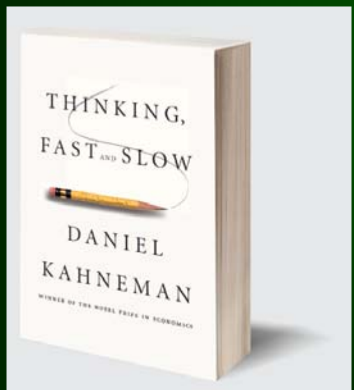
Decision-making of complex systems

Example 2: brain



a. learning of *Tritonia* escape response **shifts periphery neurons to the core**

Curr Biol 25:1



b. space learning of rat/mice hippocampus cells: **plastic** (periphery) **cells become rigid** (core)

Science 351:1440; Science 354:459

c. **memory retrieval activates core neurons**, which were **preferentially connected in the learning process**

Science 353:691; Nature 526:653

Decision-making of complex systems

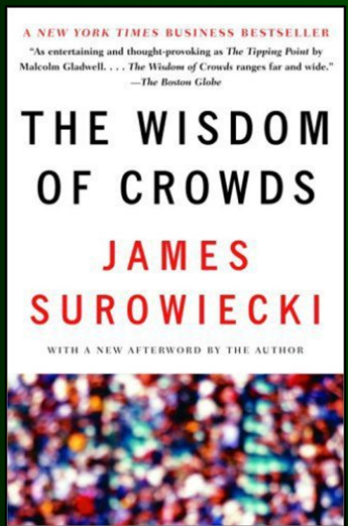
Example 3: social networks

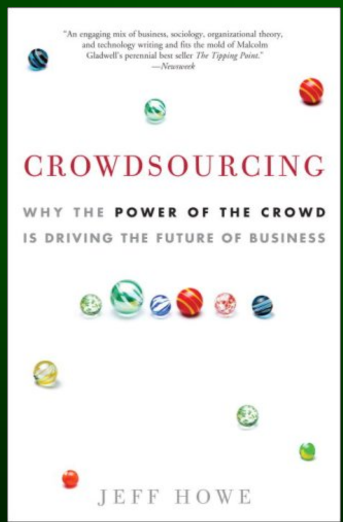
a. whole ant colonies solve complex tasks better than individuals
however, individuals solve simple tasks better than the colony

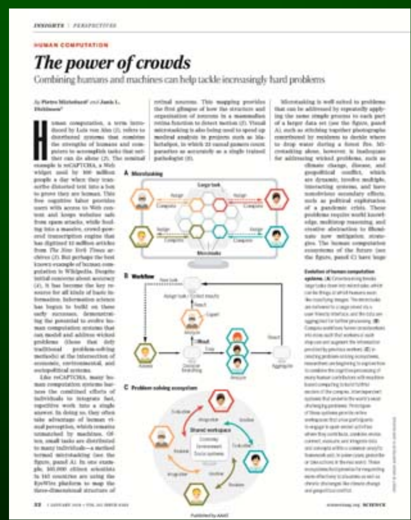
PNAS 110:13769

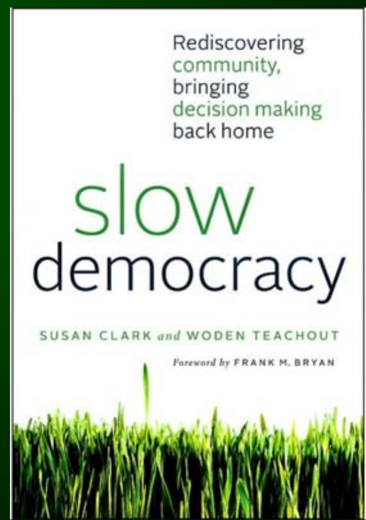
b. the elite of social networks forms a tightly connected, rigid core whose mistakes are repaired by the social periphery providing novel, creative solutions

Science 337:337; PRE 81:057103; Phys A 343:725; Nature 461:879



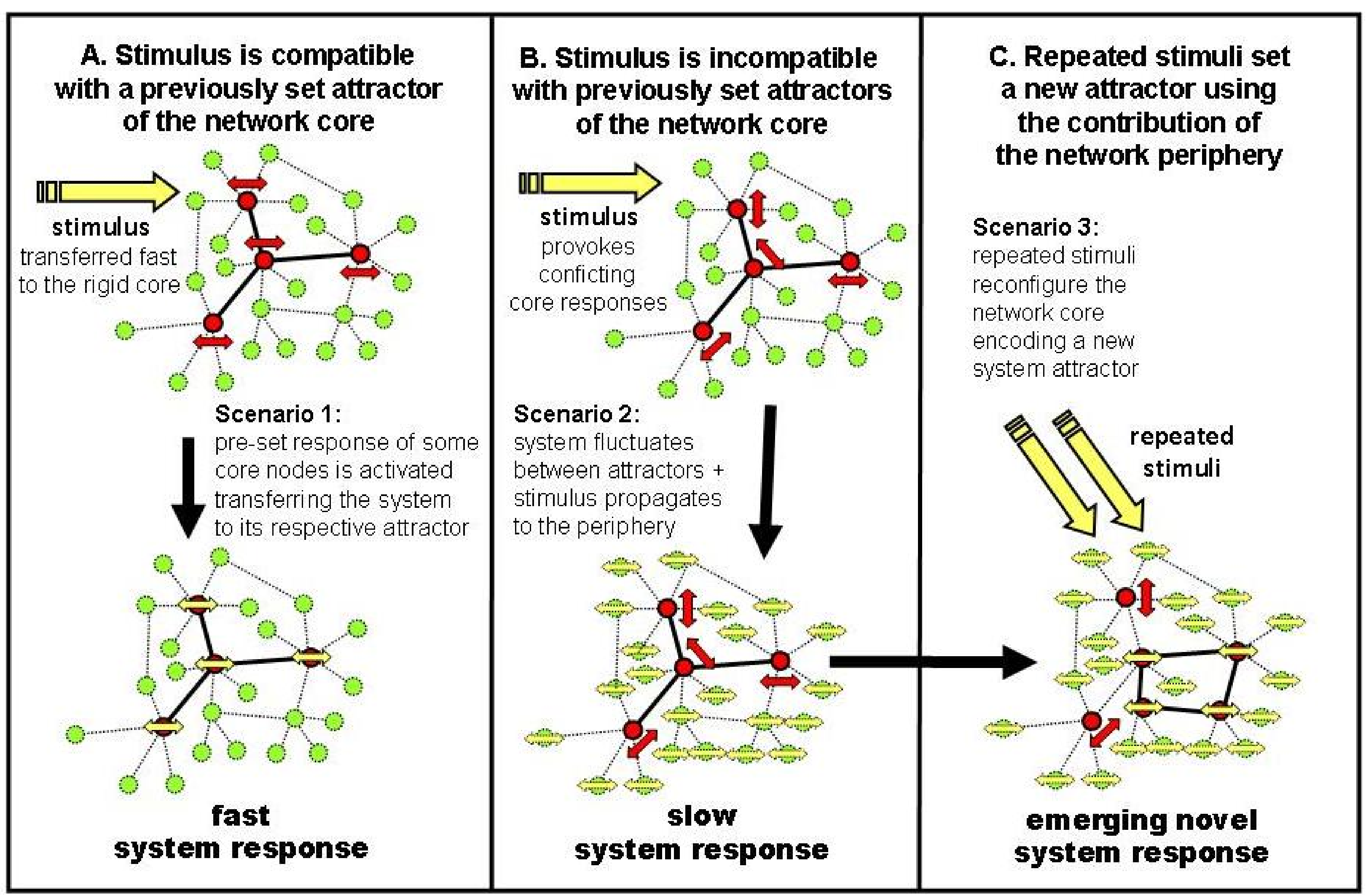






Decision-making of complex systems

A more detailed mechanism



Decision-making of complex systems
hypothetical links to the initial comments

a. nodes defining major attractors are part of the network core (attractor-preserving network reduction deletes peripheral nodes; system controlling stable motifs and „minimal feedback vertex sets" are parts of the strongly connected component)

SIAM J Appl Dyn Syst 12:1997; PLoS Comp Biol 11:1004193
J Dyn Diff Eq 25:563; J Theor Biol 335:130; arxiv.1605.08415

b. attractors are defined by different and overlapping core node sets not all core nodes participate in the definition of attractors (e.g. mediating nodes may not define attractors)

c. peripheral nodes define the size and shape of attractor basins, but not their number and occupancy

d. Hebbian learning may form/re-shape attractors by reconfiguring the periphery and deepen attractors by reconfiguring the core

Decision-making of complex systems

Mechanisms 1: bridging distant network regions

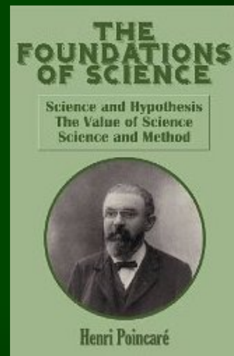
a. ‘creative nodes’ birdge distant network regions

Creative elements: network-based predictions of active centres in proteins and cellular and social networks

Peter Csermely

Trends Biochem Sci 33:569

b. ” ... To create consists in not making useless combinations. Among chosen combinations **the most fertile will often be those formed of elements drawn from domains which are far apart** *(Poincare, 1908)”*



c. re-connection of social groups leads to more creative solutions
+ combination of topics mentioned seldom together brings more attention

PNAS 113:2982; PNAS 113:11823

Decision-making of complex systems

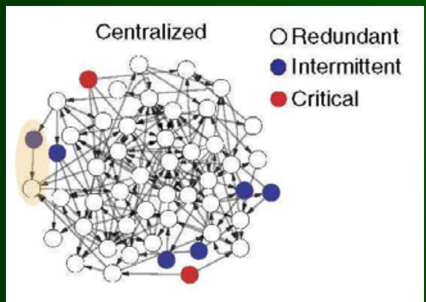
Mechanisms 2: edge reversal

Changing the direction of only one edge may be enough to change the controllability of networks from centralized to distributed control (source → sink, positive → negative, energy giving → energy vampire)

1

rigid

plastic

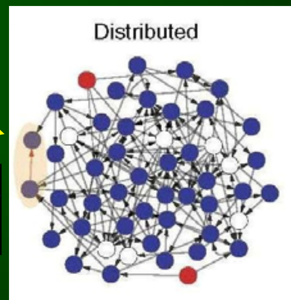


Jia et al, Nat. Comm. 4:2002

3

plastic

rigid



2

energy is concentrated in rigid regions, 'melts' them, making them more plastic

Decision-making of complex systems

Mechanisms 3: core remodeling

a. conflicts of network core are mediated by inter-hub bridges in Twitter, telephone networks and fish schools

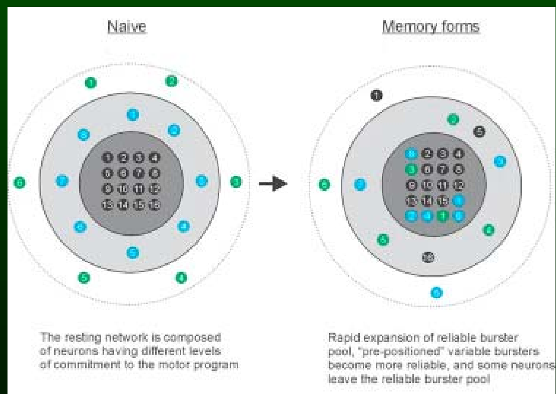
PNAS 112:4690; Nature 524:65

b. innovators are often the bridges connecting ‘early adopter’ hubs (bridges are not bound by social norms + hubs are afraid to change the status quo losing their priviledges → no innovation)

Science 337:49; Rogers: The Diffusion of Innovations

c. the new response is encoded by a new segment of the core, which encodes a new system attractor

this may lead to the deletion of some of the old attractors (forgetting)



Decision-making of complex systems

Possible limitations

a. [*optimal response of simple systems (e.g. proteins) may be encoded by evolution*]
b. [*nodes of core and periphery may overlap*]
c. **the initial fast core response is often refined by the better/slow periphery**
d. **many complex systems may not find the best response to a new situation**
(may become extinct and give way to successful members of the population)
e. **the ‘wisdom of crowds’ may become the ‘madness of crowds’, this is diminished by creative nodes**
f. **the core may be super-rigid and super-slow → bureaucracies**
g. **the core may consist of multiple parts** (modular-cores)
h. **learning and response-encoding may require multiple cycles**

Decision-making of complex systems
Possible proofs + applications

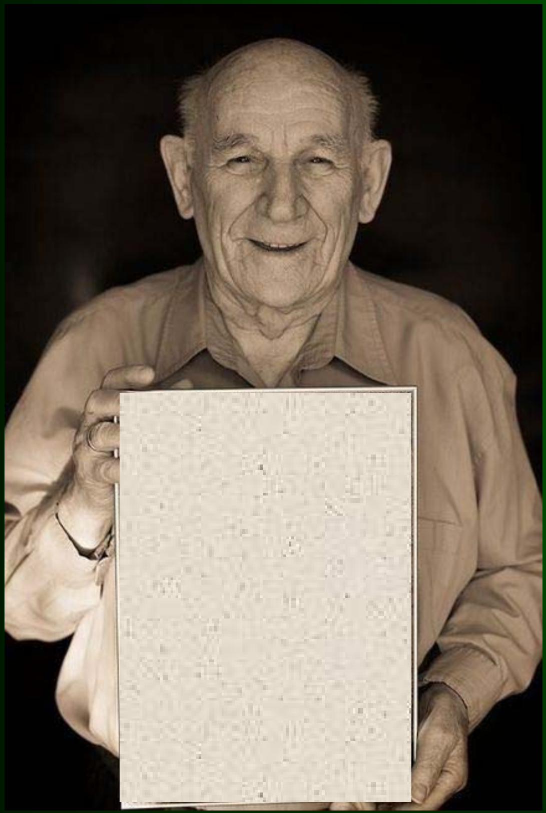
Potential possible proofs
a. core and periphery of signaling networks is not clear yet
b. we do not have enough data on the periphery of neuronal nets
c. reconfiguration mechanisms of social network cores are not known

Possible applications
a. **artificial intelligence**, neural networks, deep-learning (neuromorphic computing, layer-specific learning rates, etc.)
b. **Internet** (adaptable core, flexible periphery)
c. **drug design** (central hit/network influence methods)

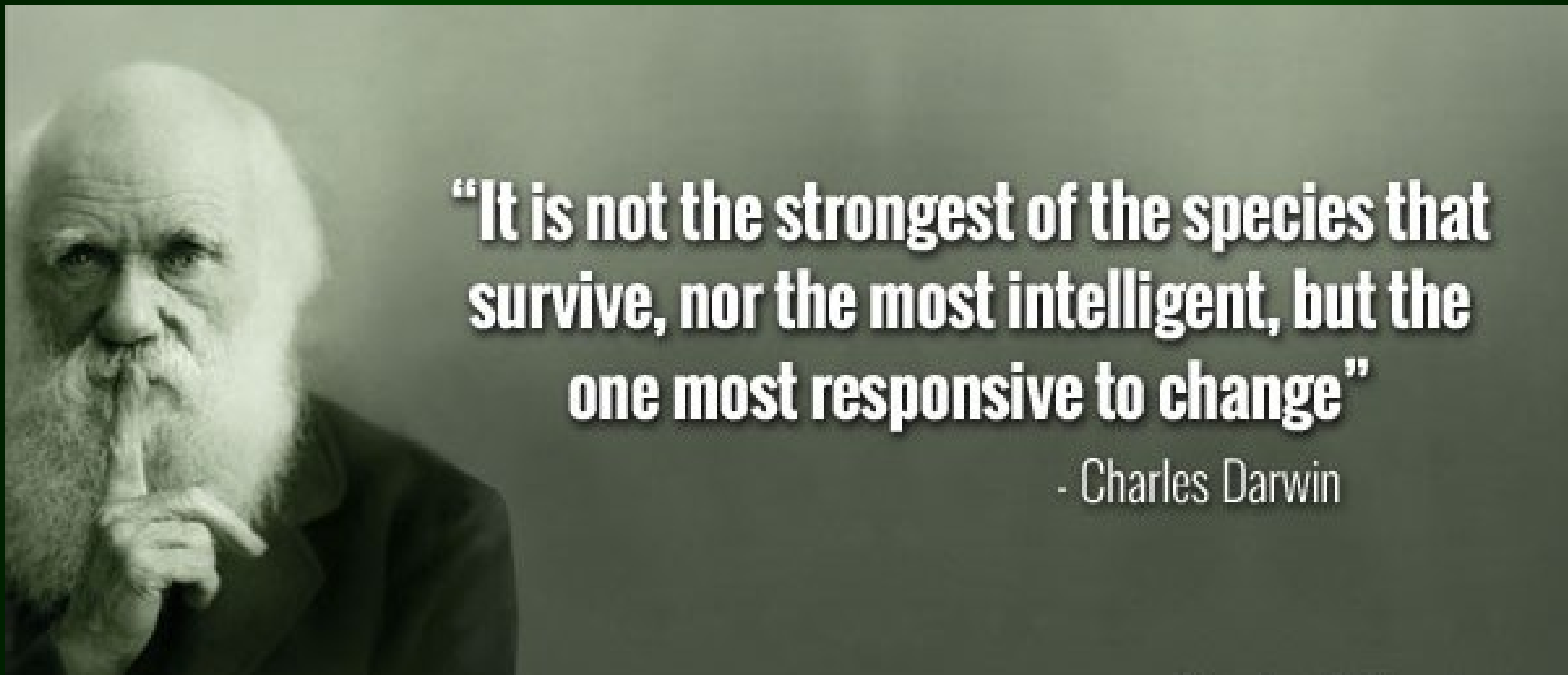
PNAS 113:11441; Science 351:32; Pharm. Therap. 138:333

Decision-making of complex systems

Take home messages



1. attractors of previously learned responses are encoded by the network core
2. the core gives fast and efficient/reliable responses to known situations
3. creative solutions of novel situations need the experience of the network periphery too
4. **democracy is NOT only a moral stance or one decision making technique of the many but our evolutionarily encoded 'survival recipe' amidst unexpected challenges**


"It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change"
- Charles Darwin

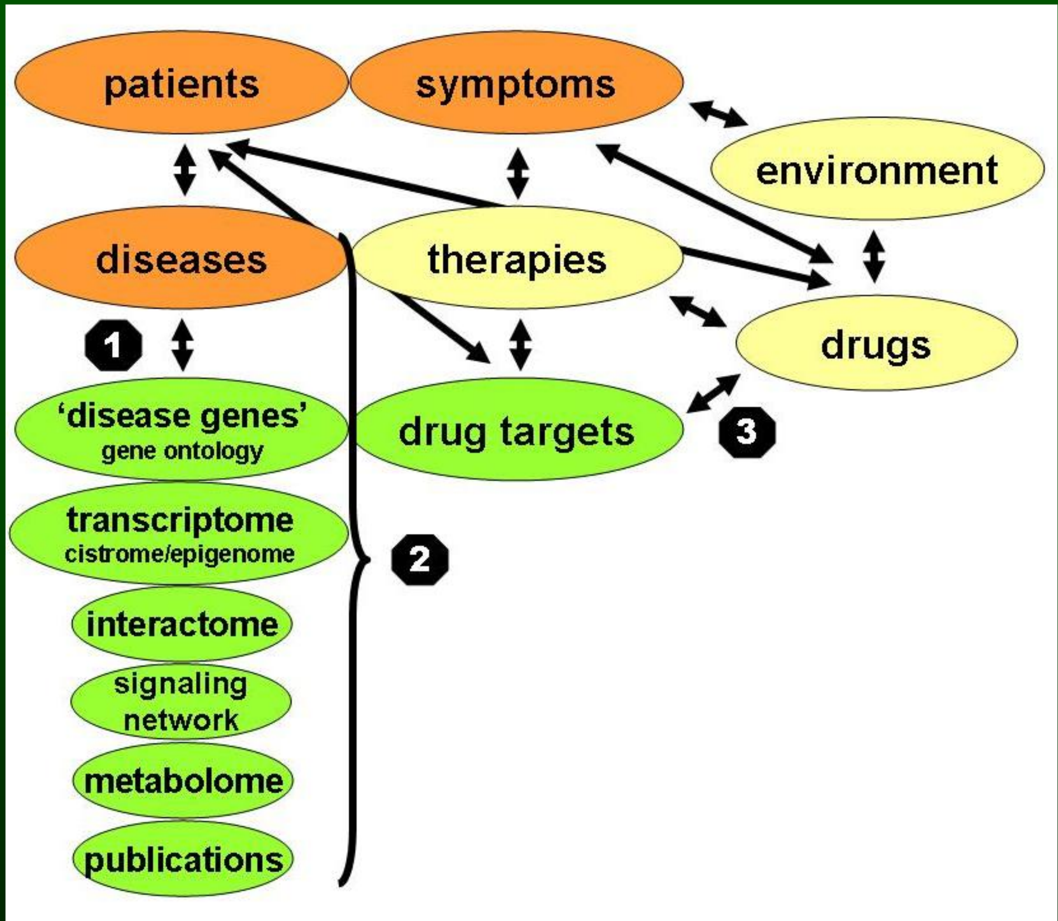
Networks and stability

Part 7. – Drug design

http://linkgroup.hu
http://turbine.ai
csermelynet@gmail.com

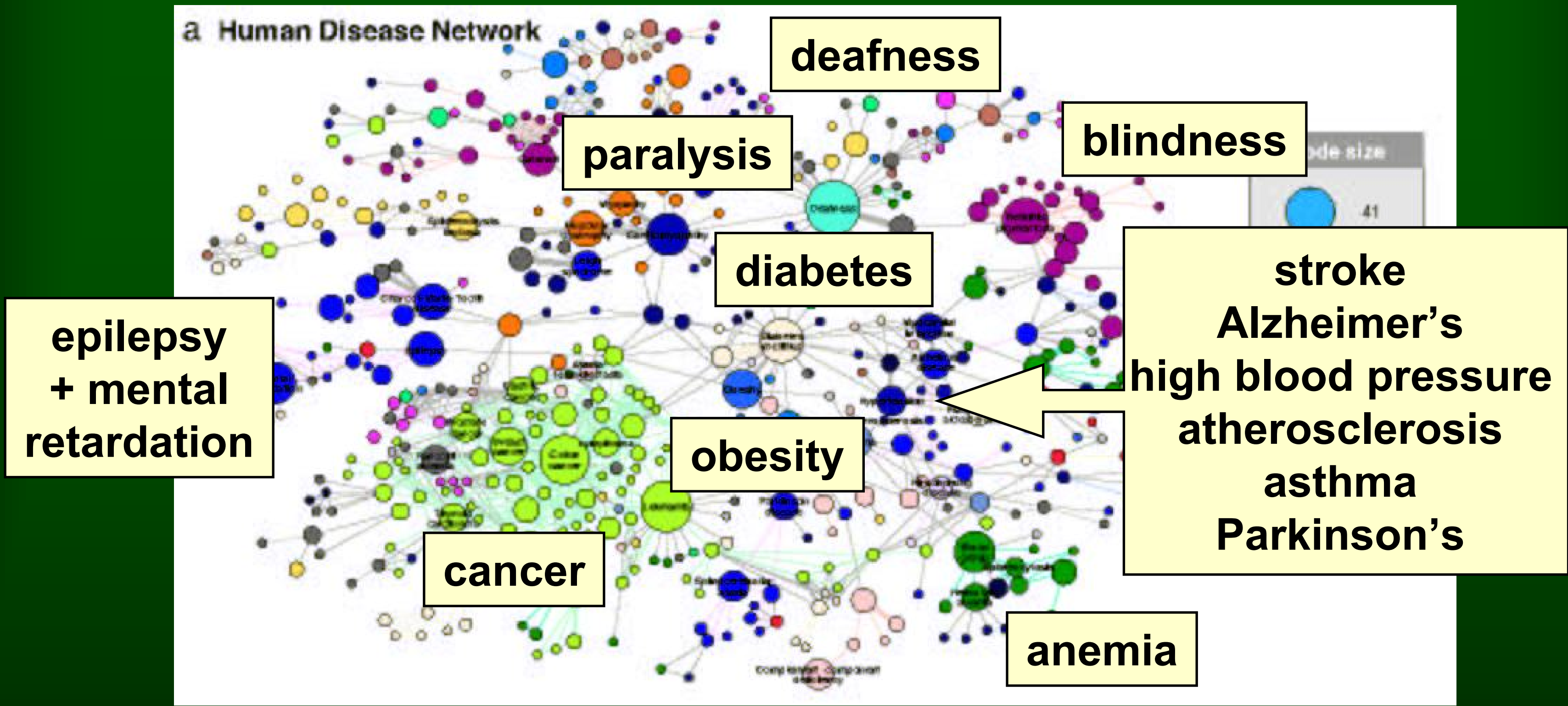
Péter Csermely and
the Turbine team

Drug-related networks



Csermely *et al*, Pharmacol & Therap 138, 333
http://arxiv.org/abs/1210.0330

Disease network

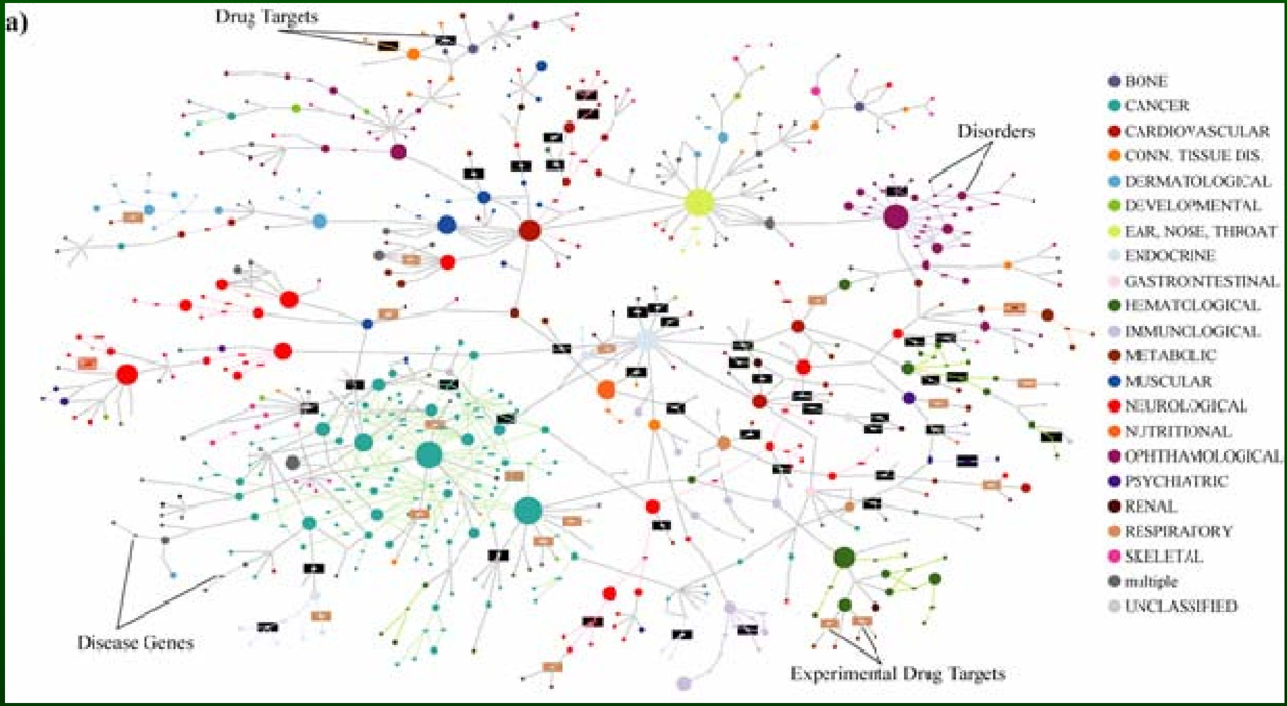


Goh et al., PNAS 104:8685

1,284 diseases & 1,777 related genes

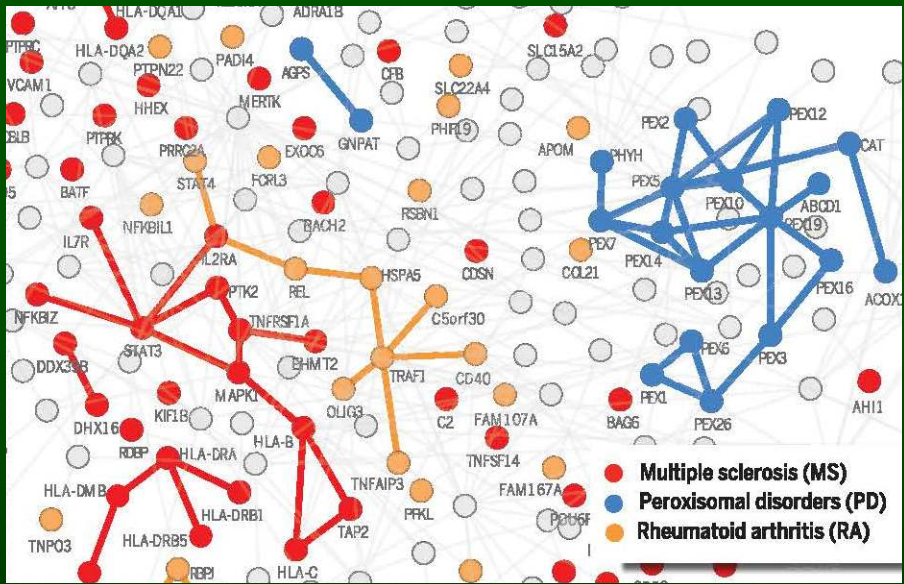
link between two diseases: if they have a common gene

Drug targets on the disease network



Yildirim et al., Nat. Biotech. 25:1119

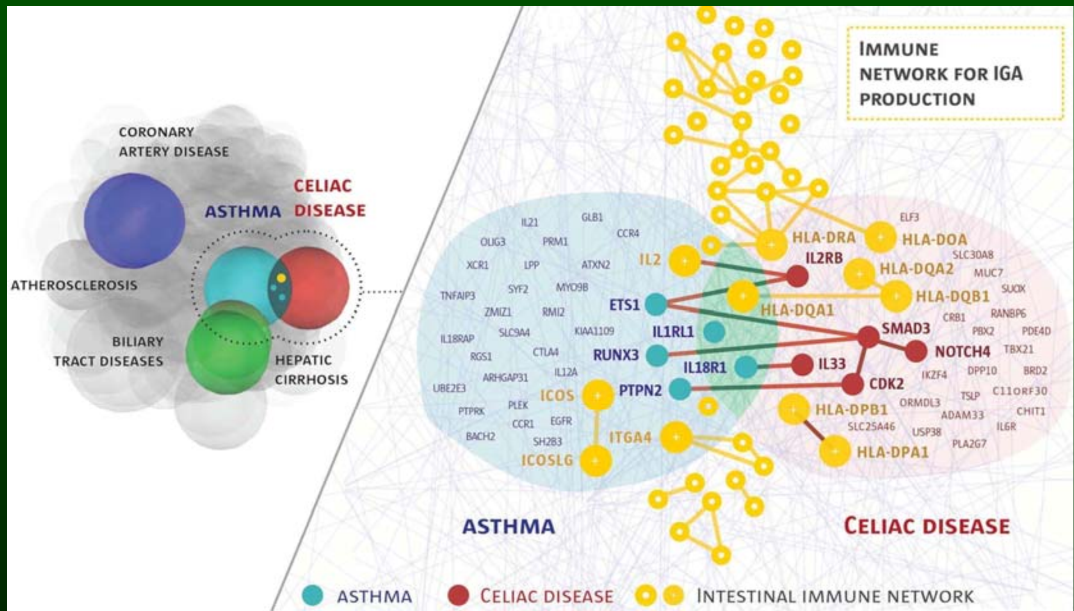
Diseasome network 1.



Menche et al., Science 347:841

disease-related proteins form overlapping modules in the human interactome

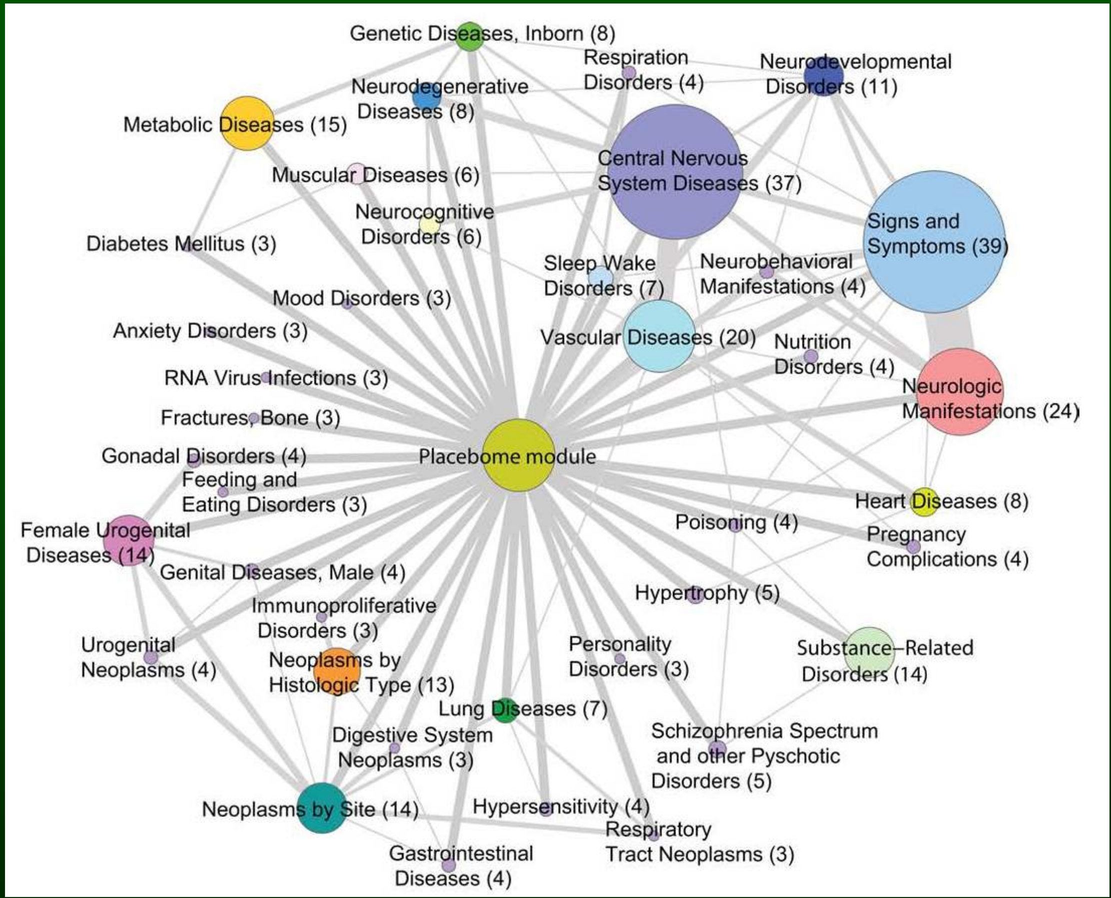
Diseasome network 2.



Menche et al., Science 347:841

disease-related proteins form overlapping modules in the human interactome

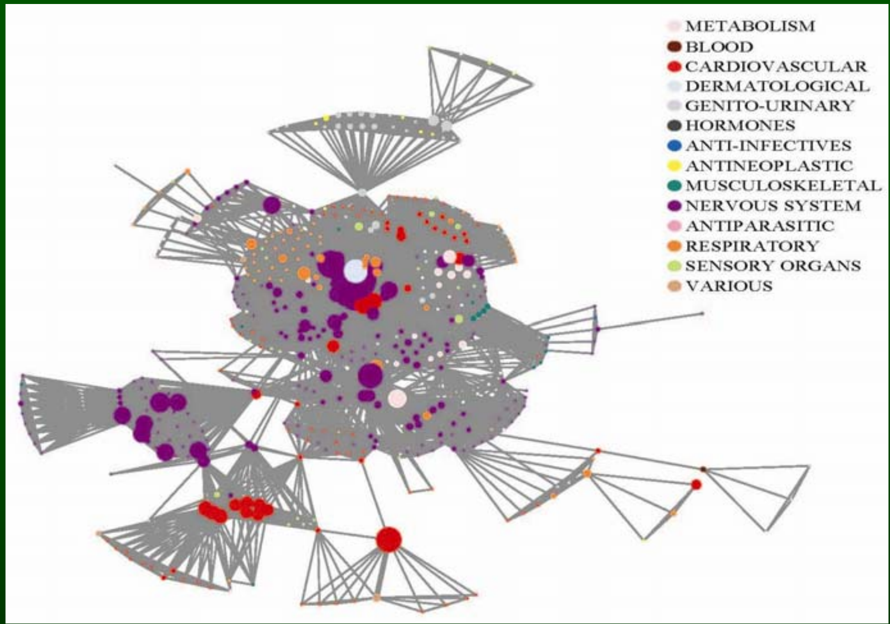
Placebome



Wang et al., JCI Insight 2:e93911

Placebo effects in various diseases

Drug network

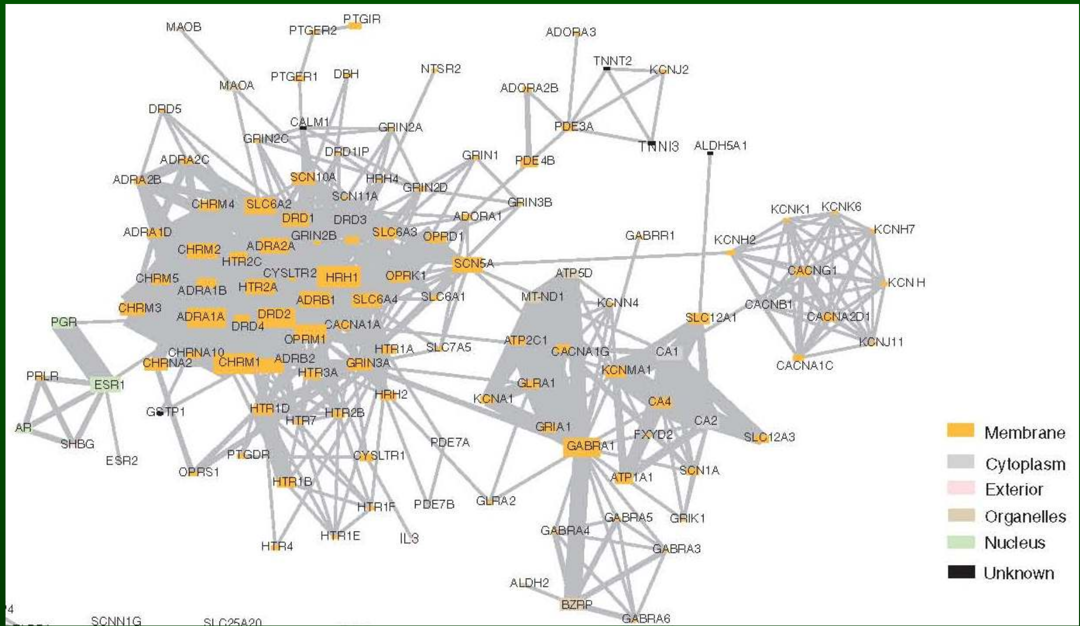


Yildirim et al., Nat. Biotech. 25:1119

Small giant component:
follow-on drugs
(experimental drugs:
bigger giant. comp.
→ diversity)

1,178 drugs and 394 target-proteins
link between two drugs:
if they have a common target

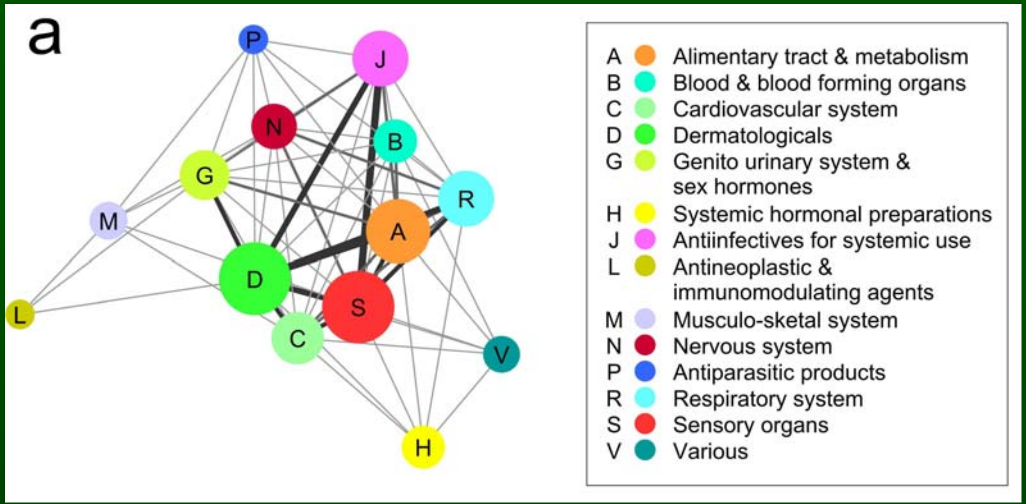
The reverse: drug target network



Yildirim et al., Nat. Biotech. 25:1119

1,178 drugs and 394 target-proteins
Link between two target proteins:
if they have a common drug

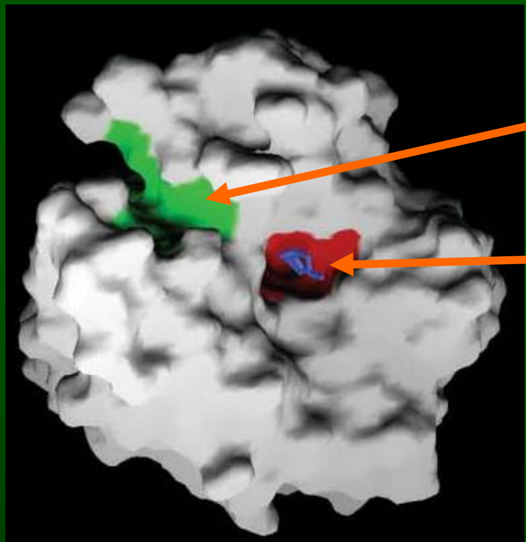
Therapy-network



Nacher & Schwartz, BMC Pharmacol. 8, 5

5 levels: 3rd level: 106 therapies & their 338 drugs
if a drug is used in 2 therapies (21%): the 2 therapies are linked
The top level is shown, circle size – number of therapies
Link-weight – number of common drugs

Prediction of drug binding sites in protein structure networks

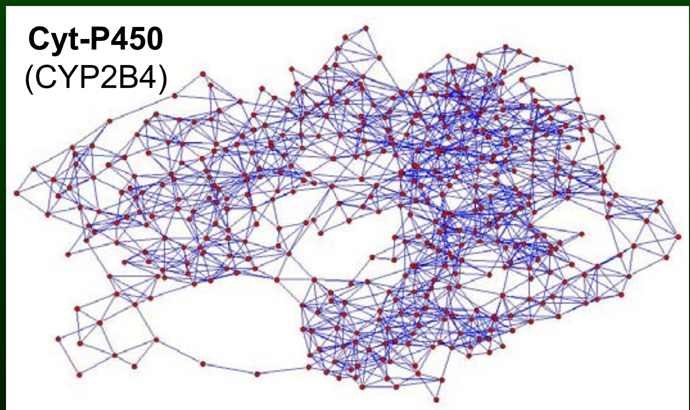


large but shallow cavity

drug binding

18 cavity size & shape attributes:
machine learning (neural network)

Nayal & Honig, Proteins 63:892



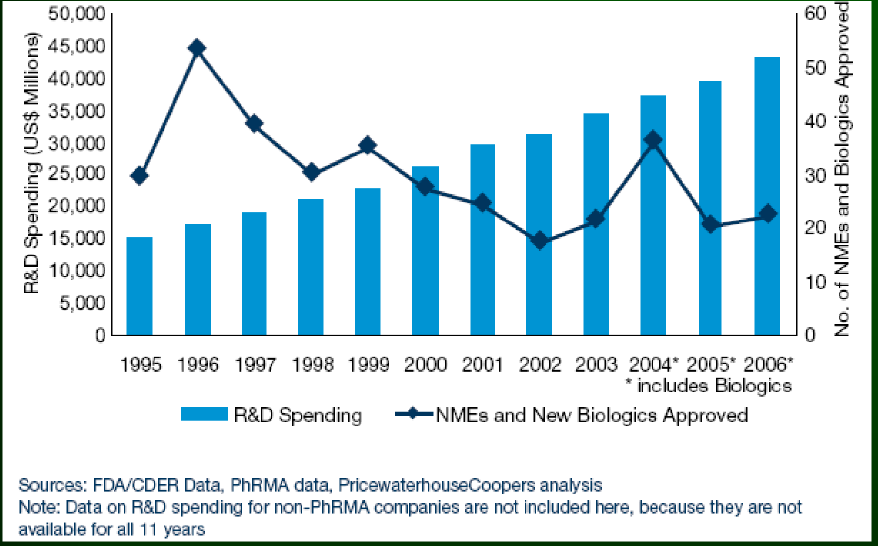
How would you identify here cavities?

structural holes:
missing links and nodes

Csermely, TiBS 33:569

Drug target crisis

New, active drug ingredients as expenditure increased



Drug targets

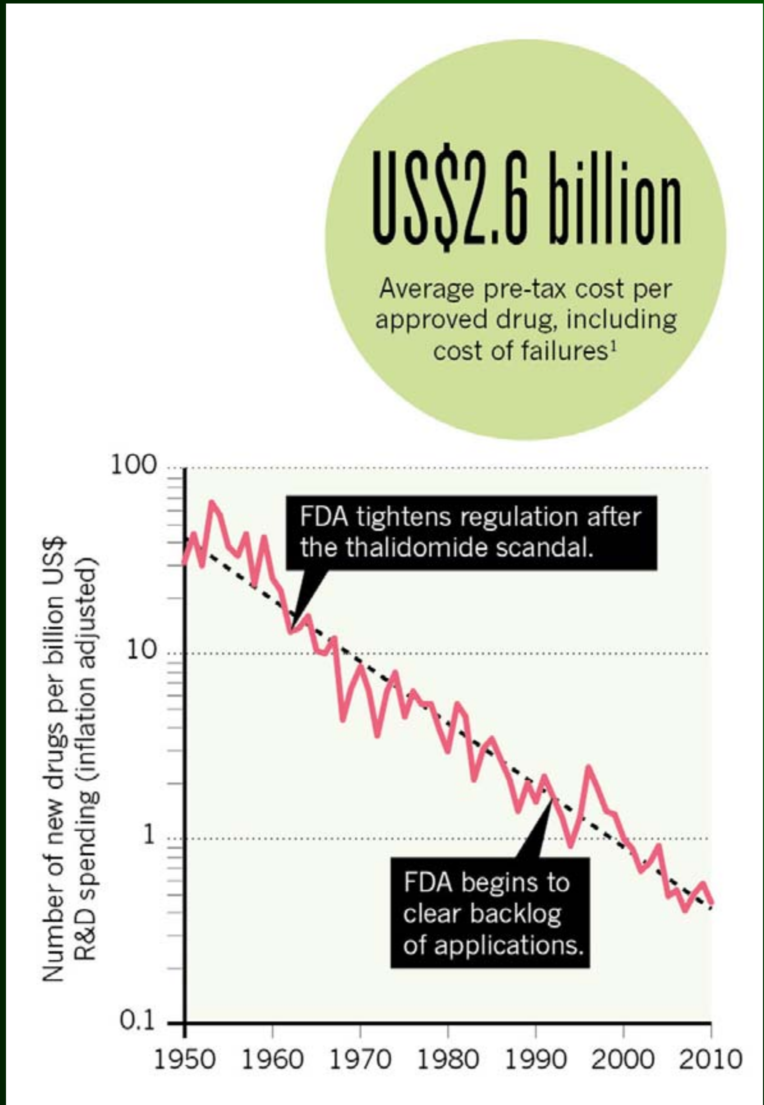
Human genome: ~30,000 genes
~100,000 proteins

Modifying ligands: 836 proteins

From this drug-like: 529

Approved: 394

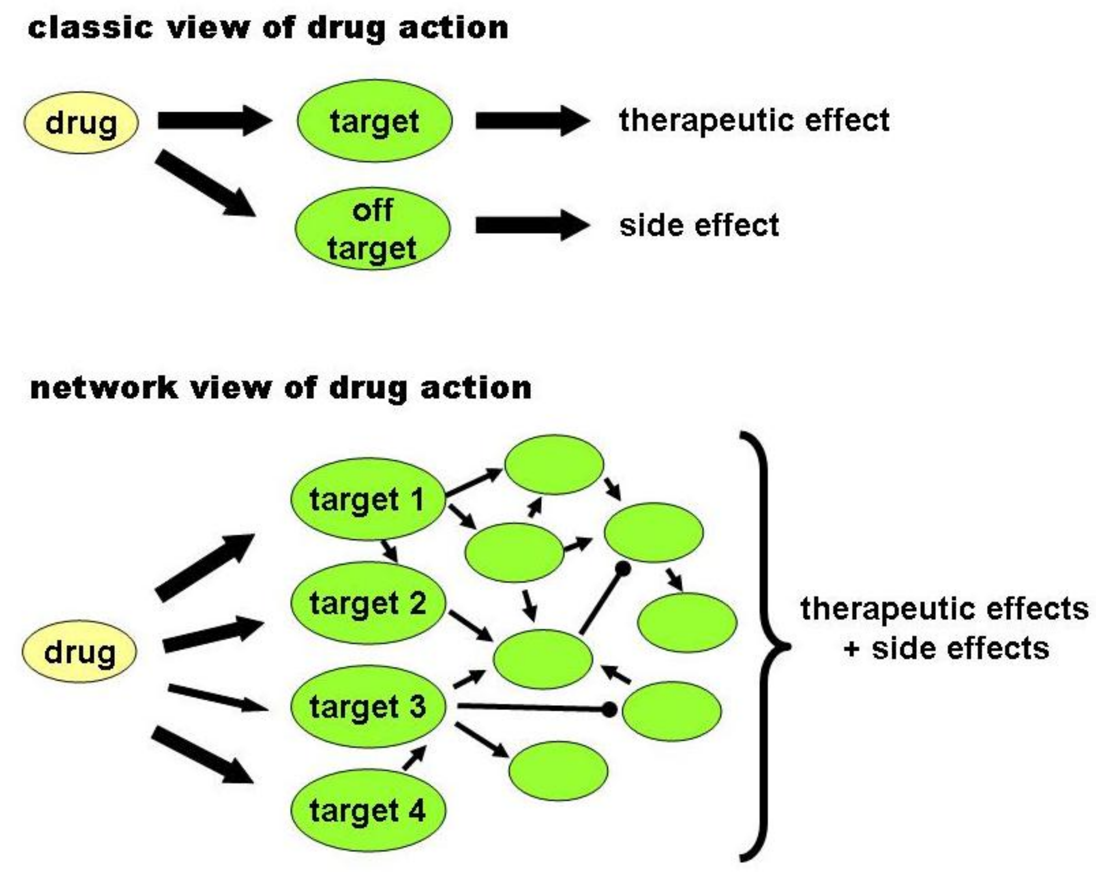
Csermely *et al*, Pharmacol & Therap 138, 333
http://arxiv.org/abs/1210.0330



Drug target crisis

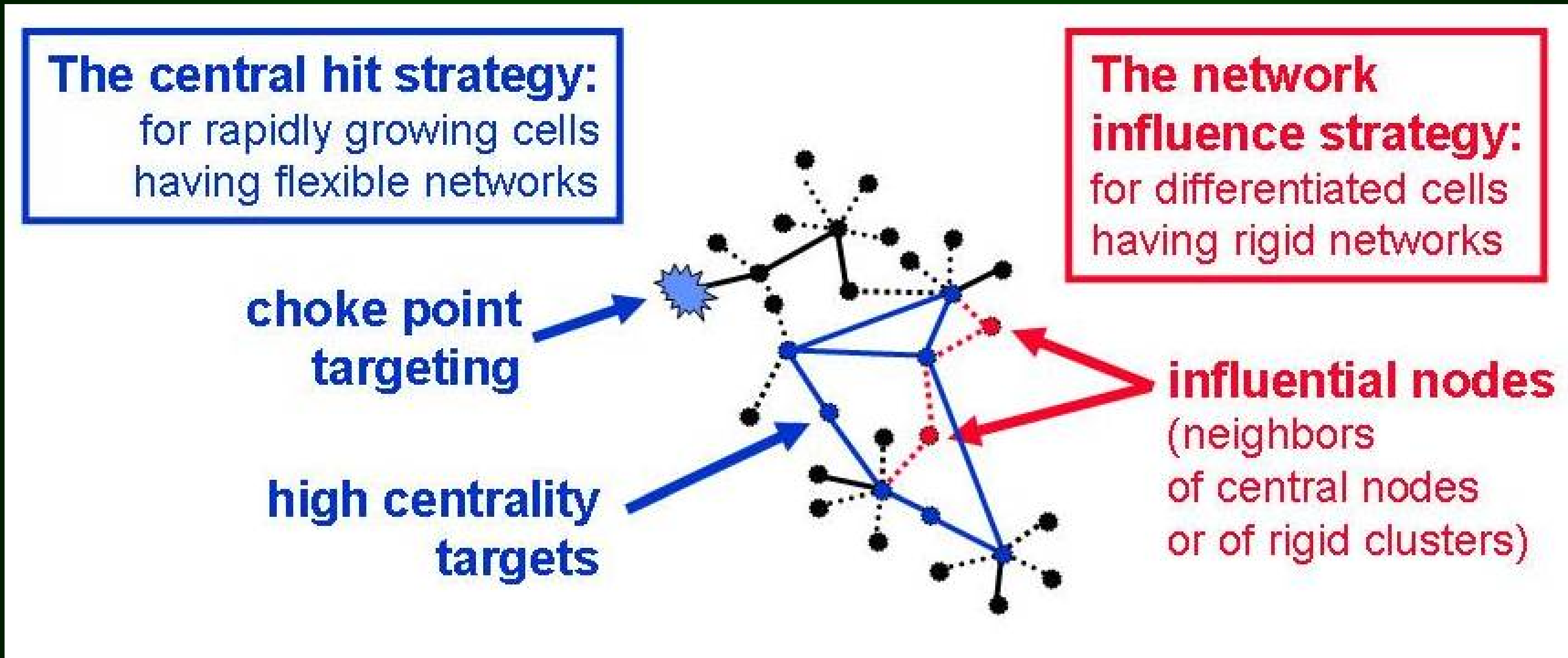
reverse Moore law

Classic and network views of drug action



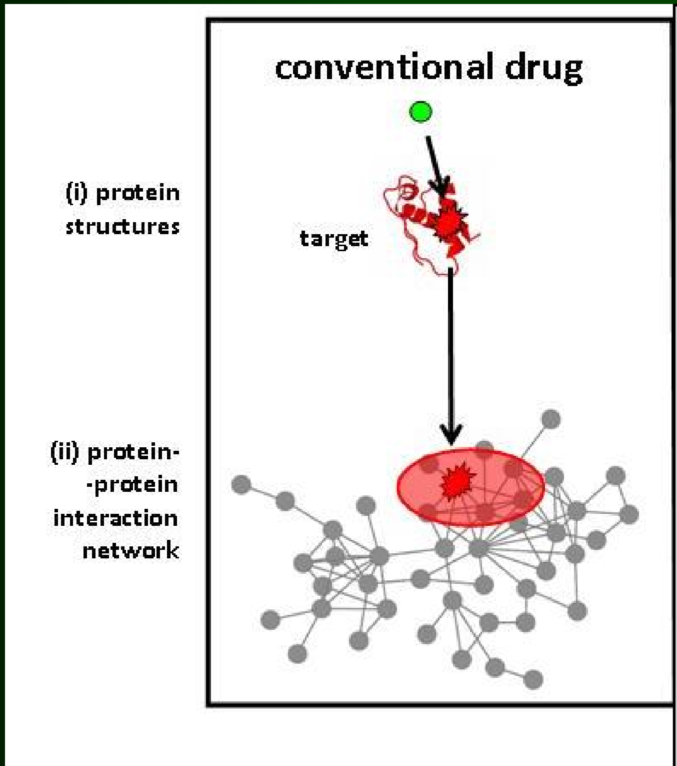
Csermely *et al*, Pharmacol & Therap 138, 333
http://arxiv.org/abs/1210.0330

Drug design strategies I.

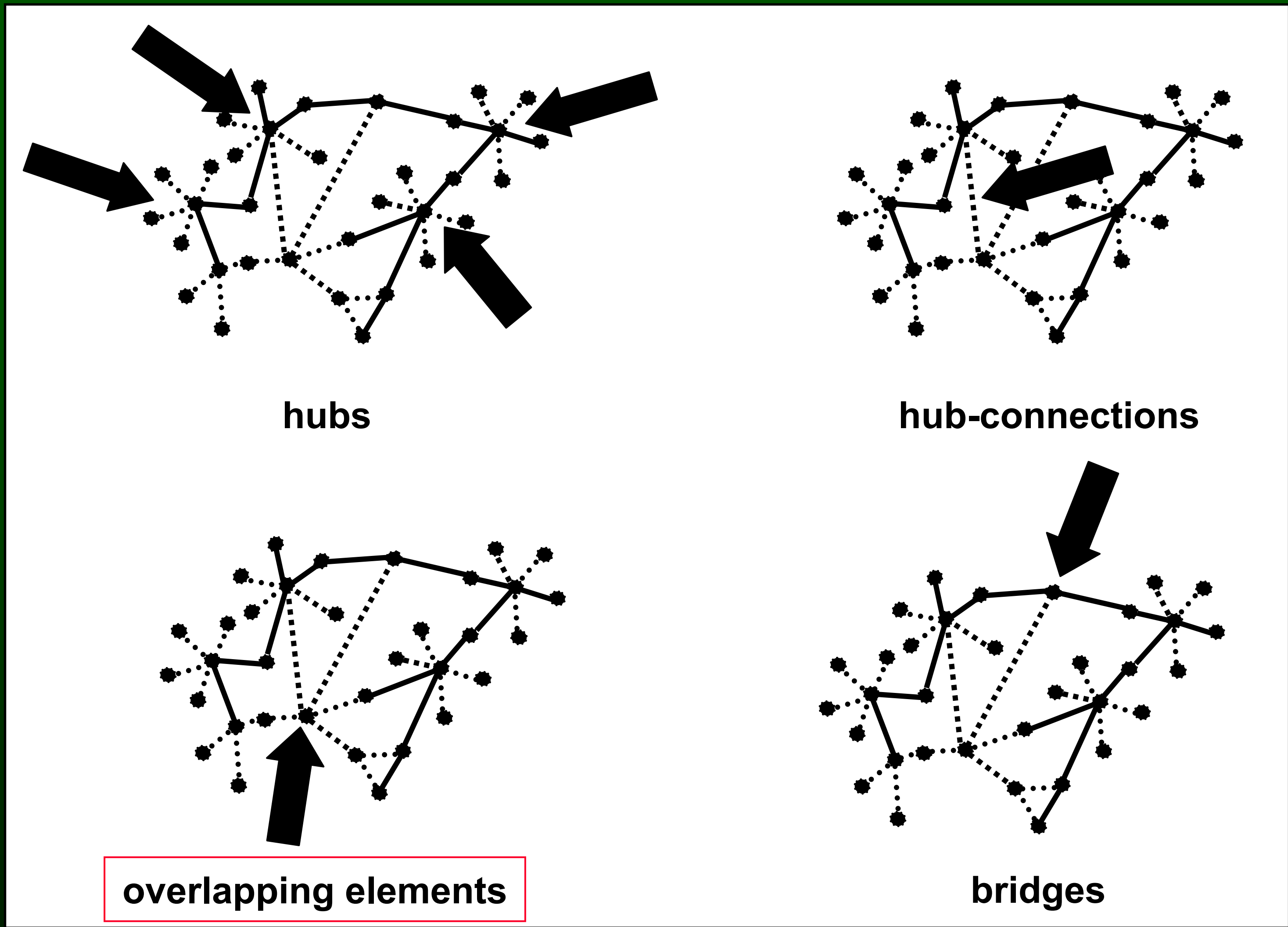


Csermely *et al*, Pharmacol & Therap 138, 333
http://arxiv.org/abs/1210.0330

Drug design strategies II.

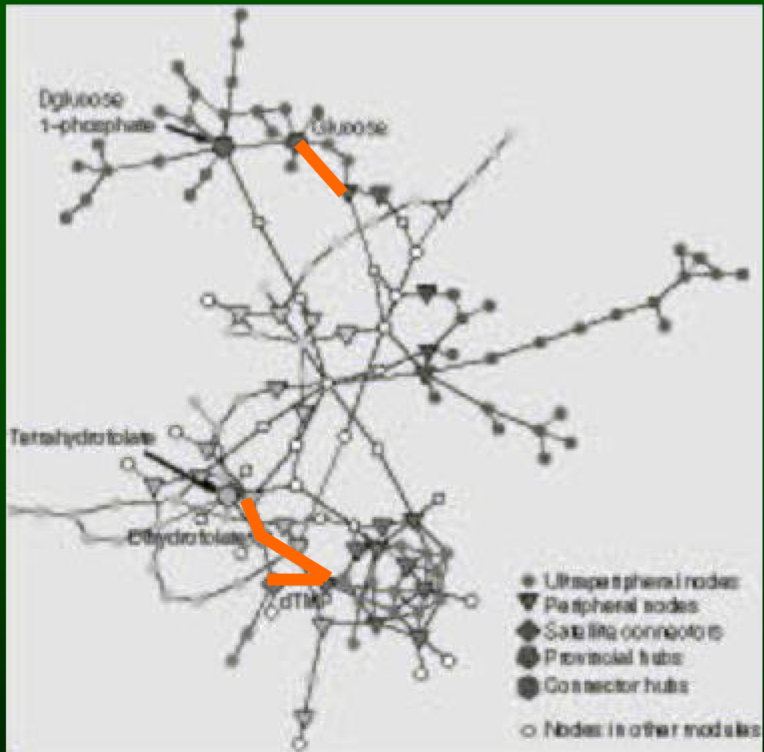


Network-based drug target options



Korcsmáros et al., Exp. Op. Drug Discov. 2:799

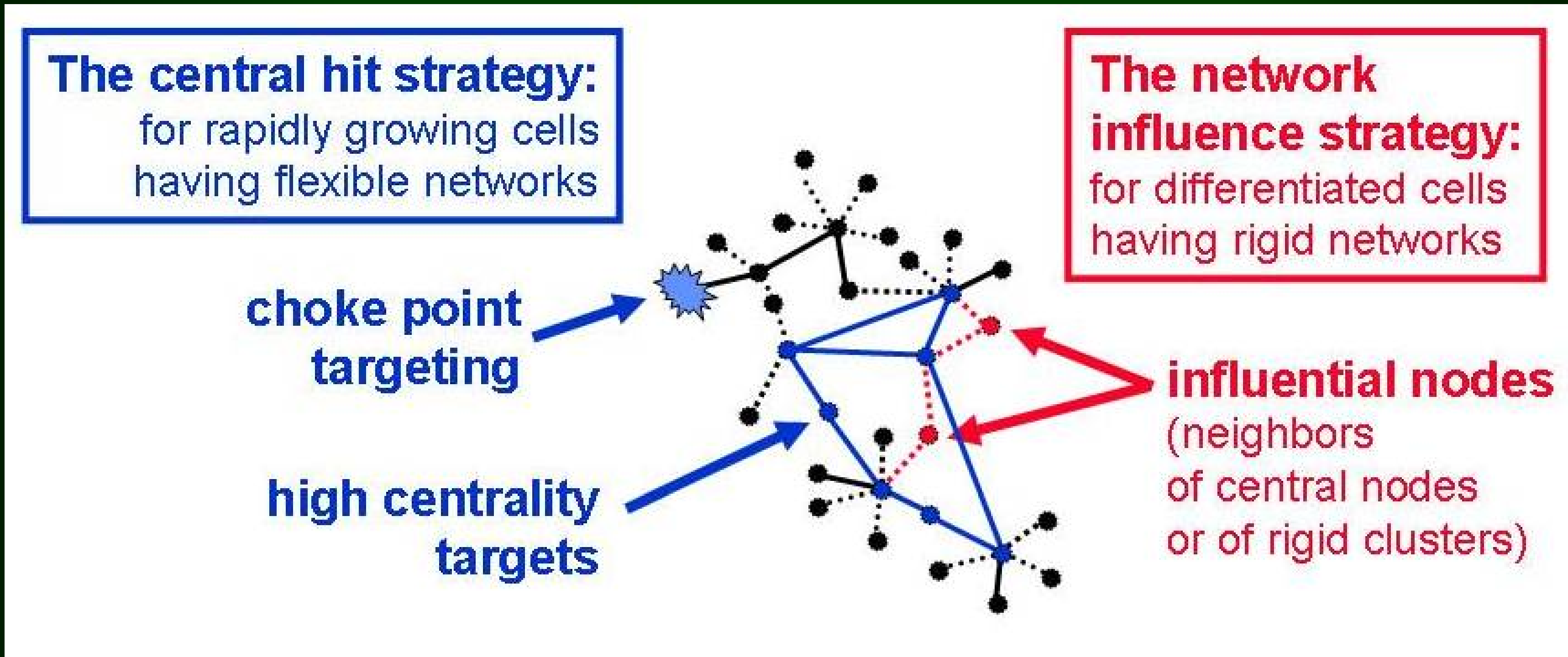
Overlapping nodes as drug targets



Guimera et al., Bioinformatics 23:1616

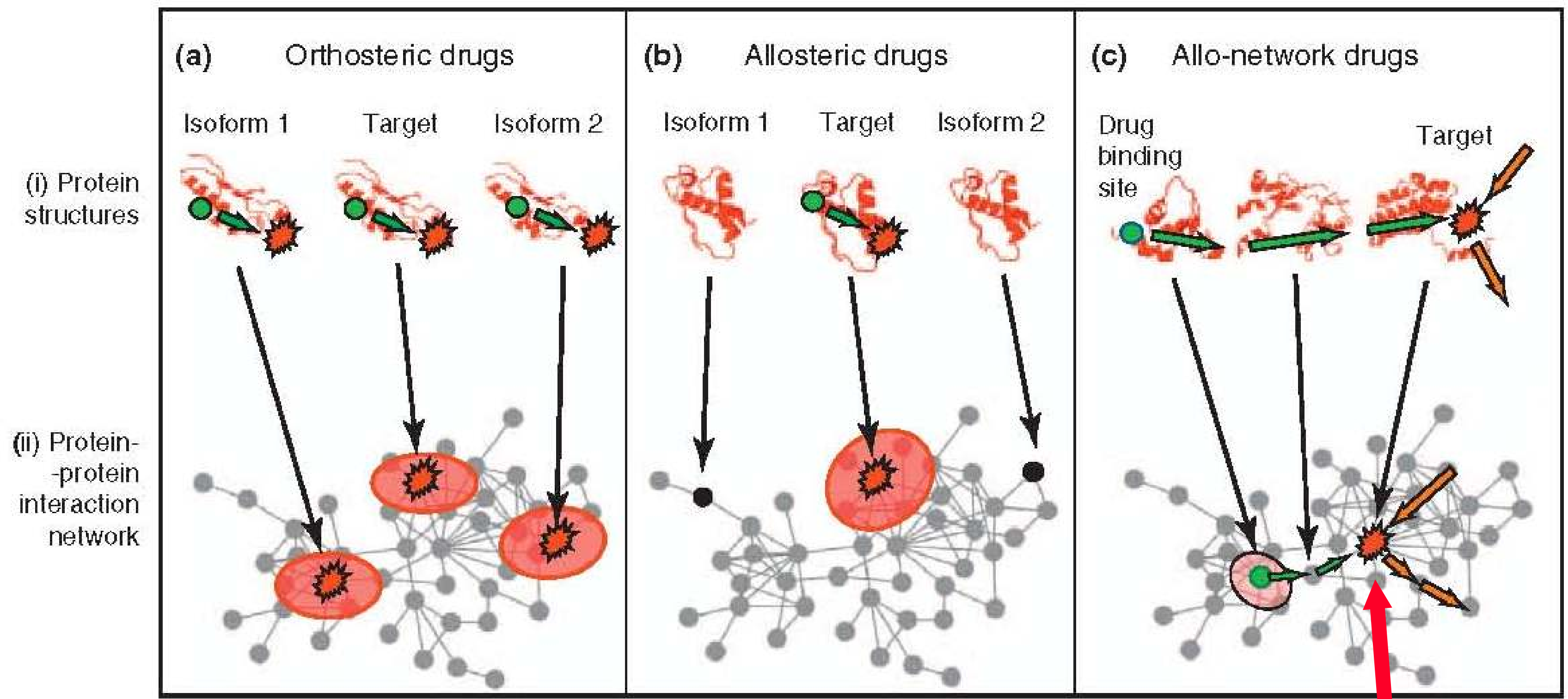
E. coli metabolic network
(links: enzymes)
known drug targets:
- *glmS* (cell wall synthesis)
- *pfs* (quorum sensing blocker)
- *ptsI* (sugar uptake-metabolism)

Drug design strategies I.



Csermely *et al*, Pharmacol & Therap 138, 333
http://arxiv.org/abs/1210.0330

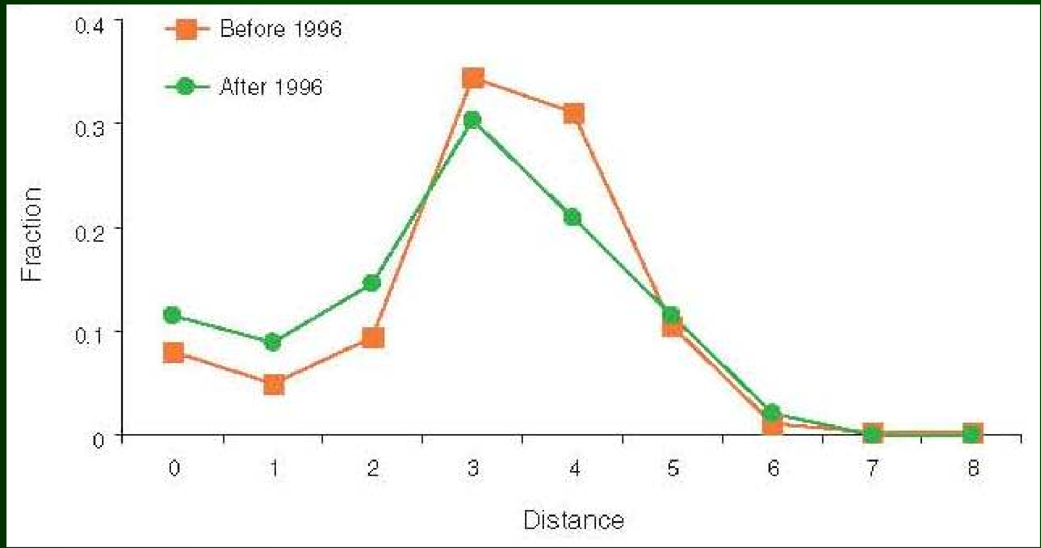
Allo-network drugs: atom-level interactome reveals hidden targets



Nussinov *et al*, Trends Pharmacol Sci 32:686

+ hit of intra-cellular paths

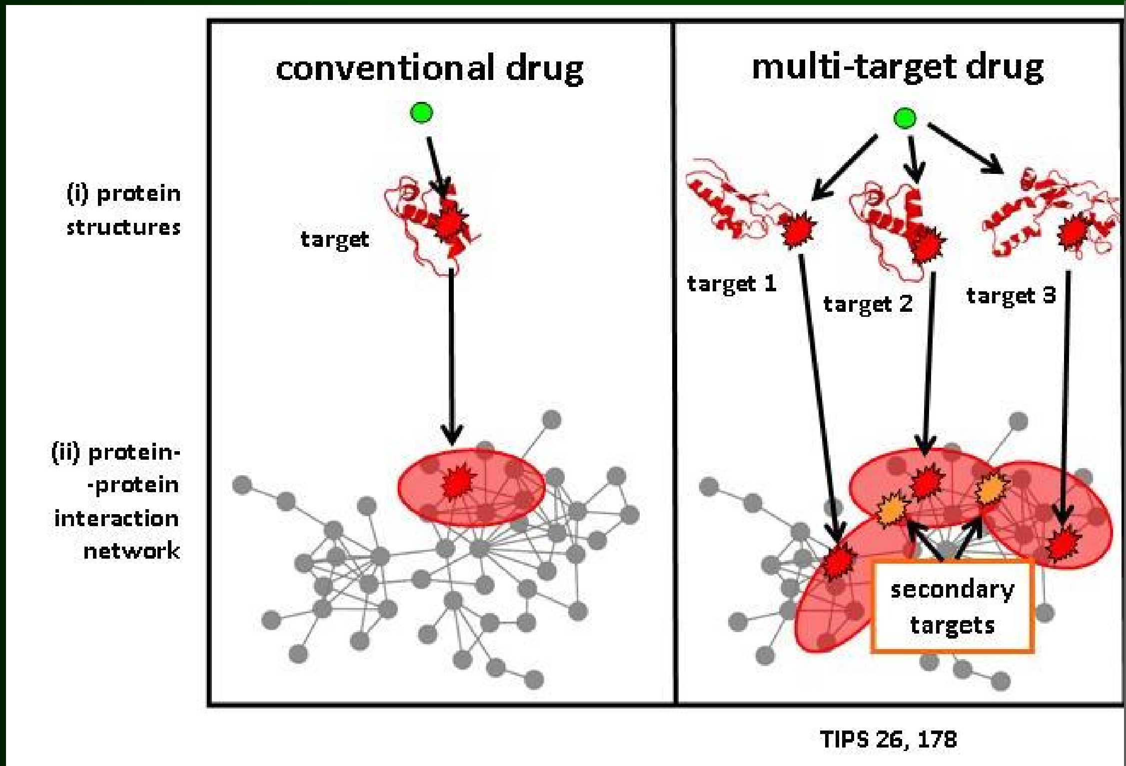
Distance of human disease genes and drug targets



Yildirim *et al*, Nature Biotechnol. 25:1119

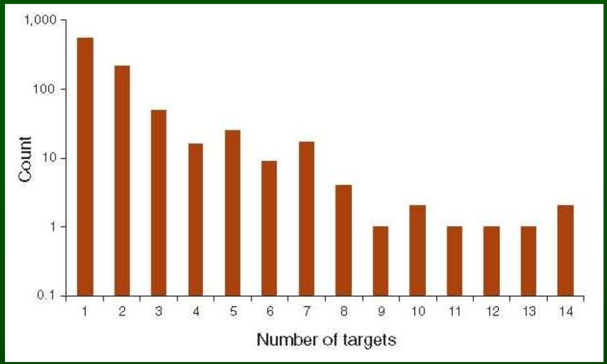
most drugs act *via* network-perturbation

Multi-target drugs

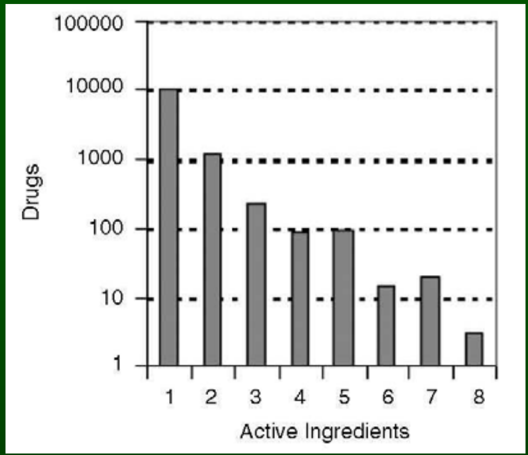


Csermely *et al*, Trends Pharmacol Sci 26:178

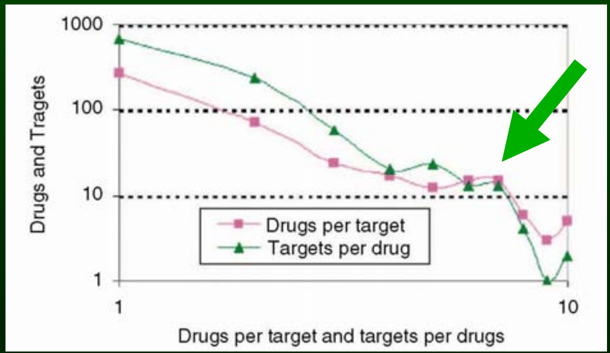
Multitarget drugs: a non-negligible segment



Yildirim et al., Nat. Biotech. 25:1119



Ma’ayan et al.,
Mt. Sinai J. Med. 74:27

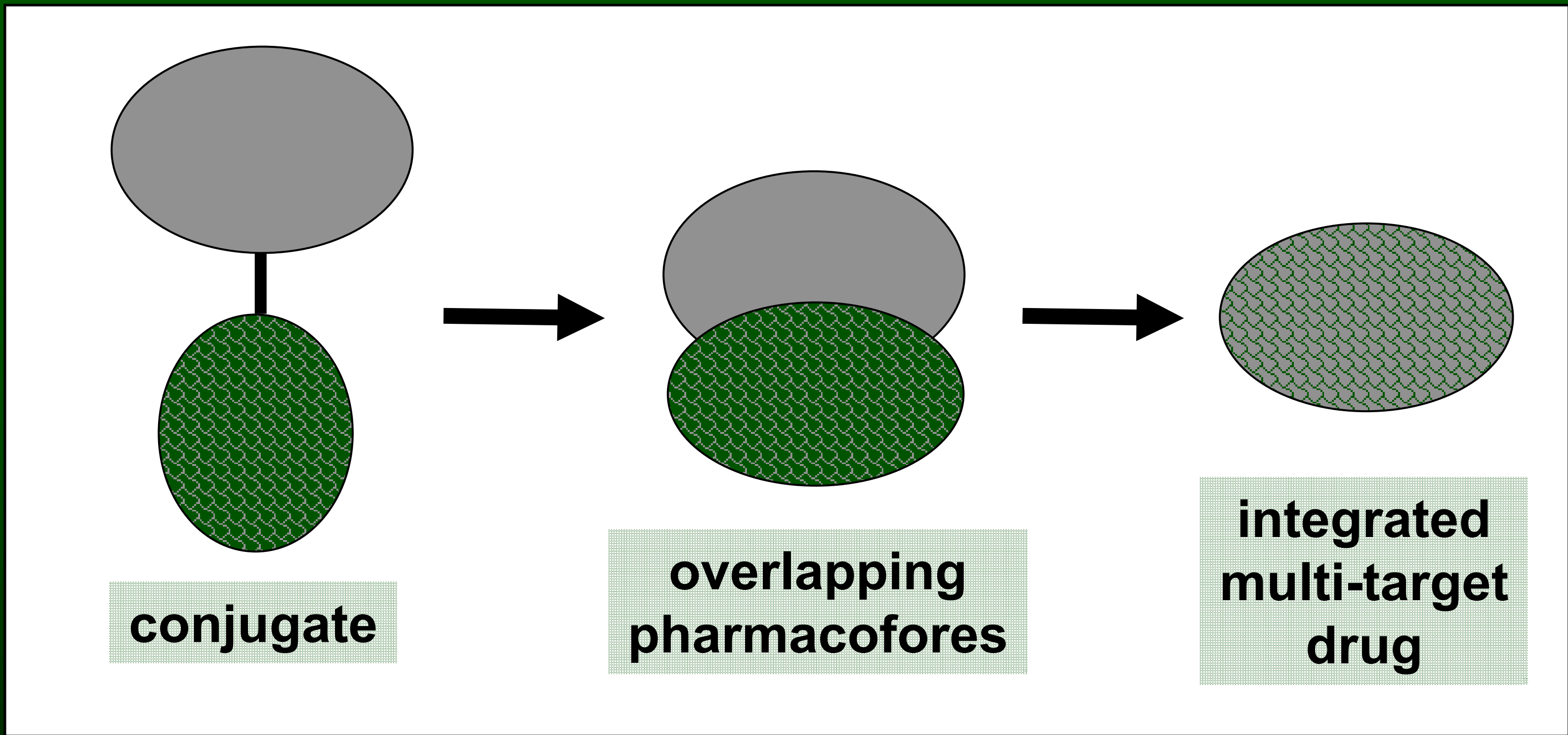


Multitarget drugs: more prevalent than thought

- single target drugs: back-ups, robustness
- most drugs are multi-target drugs
- combinational therapies
- venoms, natural medicines: mixtures

Csermely et al., Trends in Pharmacol. Sci. 26:178

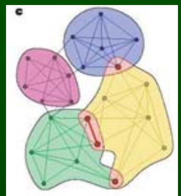
Multitarget drug-types



Korcsmáros et al., Exp. Op. Drug Discov. 2:799

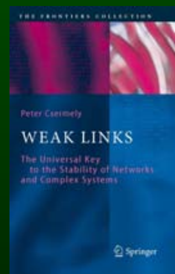
Multitarget drugs: low affinity drugs

- smaller dose and toxicity
- smaller blockade of alternative pathways



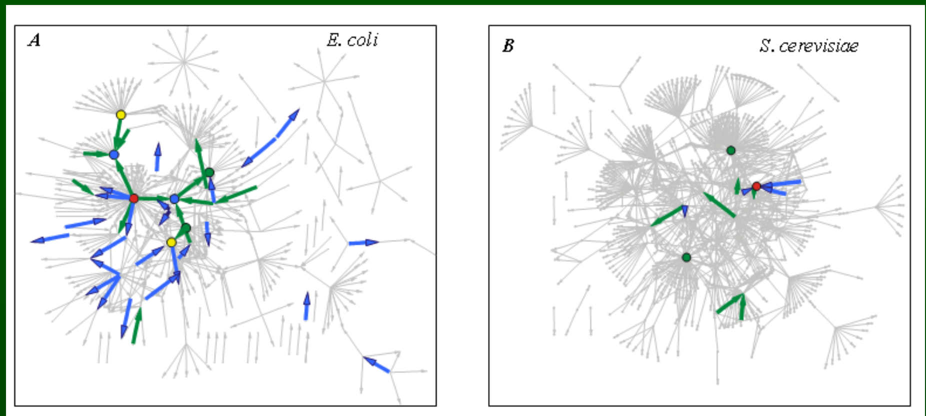
- proteins → in overlapping modules with different functions
- single protein inhibition → blocks multiple functions
- partial inhibition of many proteins → blocks module/function

- [more weak links: more stable cell]



Csermely et al., Trends in Pharmacol. Sci. 26:178
Csermely, Weak Links, Springer 2009

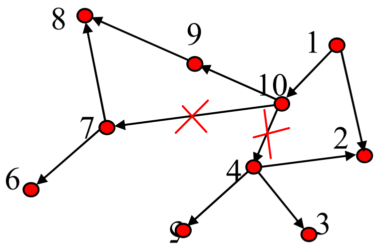
How many partial attacks can substitute a single full attack?



Model: *E. coli* and *S. cerevisiae* gene transcription networks

Ágoston et al.,
Phys. Rev. E 71:051909

Efficiency $E = \dfrac{\sum_{i \neq j} \frac{1}{d_{i,j}}}{N(N-1)}$

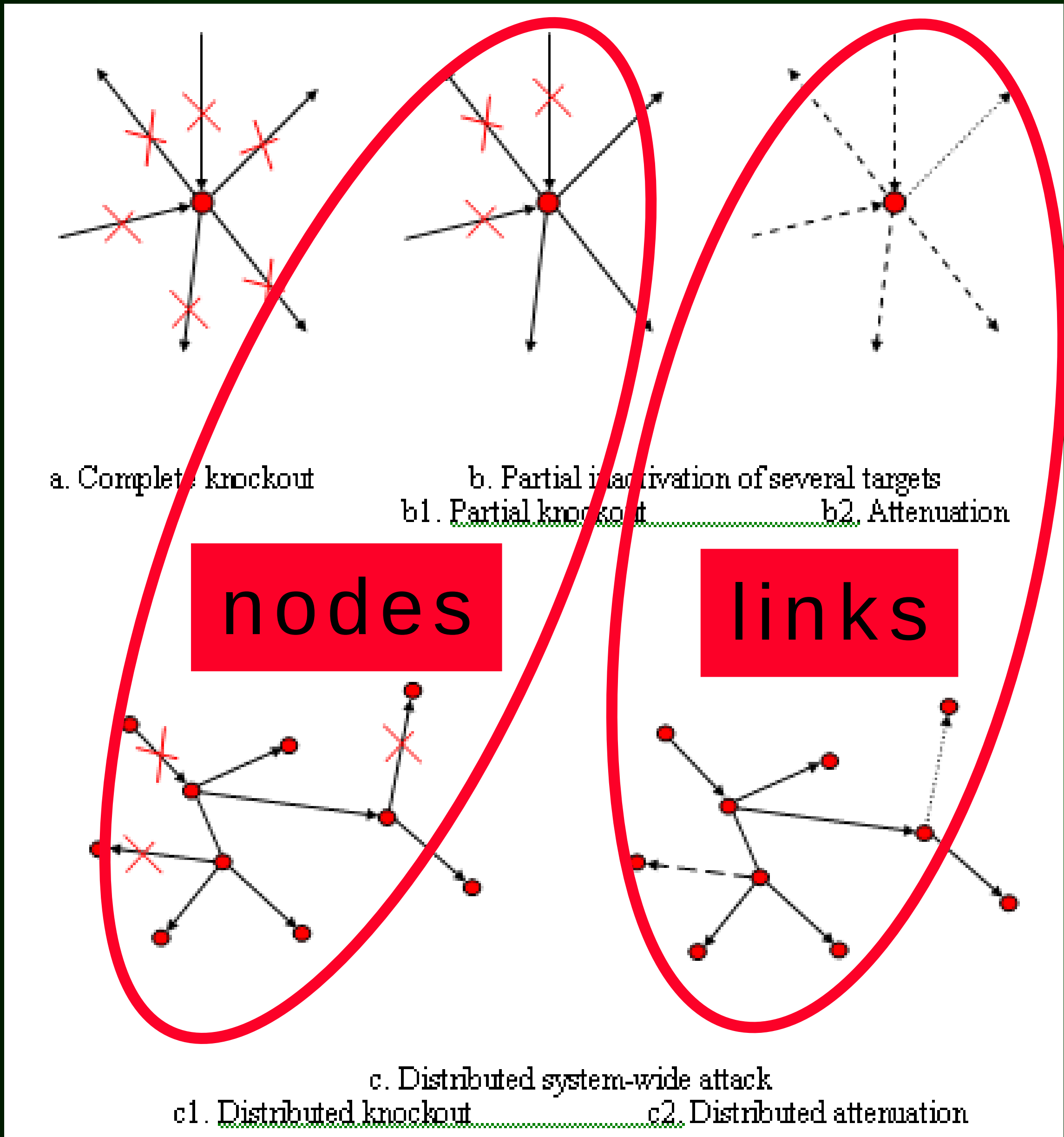


	1	2	3	4	5	6	7	8	9	10	
1	-	1	3	2	3	3	2	3	2	1	1
2	-	-	-	-	-	-	-	-	-	-	2
3	-	-	-	-	-	-	-	-	-	-	3
4	-	1	1	-	1	-	-	-	-	-	4
5	-	-	-	-	-	-	-	-	-	-	5
6	-	-	-	-	-	-	-	-	-	-	6
7	-	-	-	-	-	1	-	1	-	-	7
8	-	-	-	-	-	-	-	-	-	-	8
9	-	-	-	-	-	-	-	1	-	-	9
10	-	2	2	1	2	2	1	2	1	-	10

E = 0,181
E_{xx} = 0,104
(57,5%)

Attack measure:
network efficiency

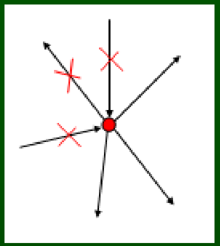
Latora and Marchiori
Phys. Rev. Lett. 87:198701

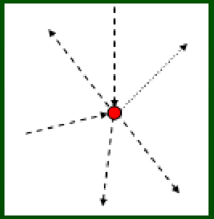


Partial attack types

Ágoston et al.,
Phys. Rev. E 71:051909

Partial knock-out of nodes substituting the most needed node

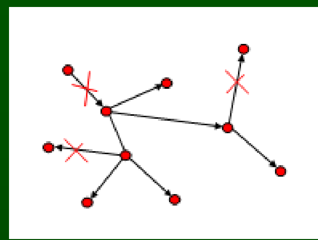


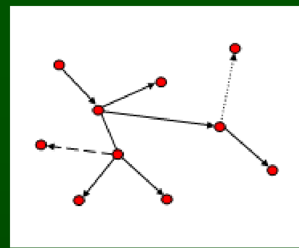


	partial KO	50% attenuation
E. coli (1)	4.2	5
S. Cerevisiae (1)	2.8	3

Ágoston et al., Phys. Rev. E 71:051909

Partial knock-out of links substituting the most needed node

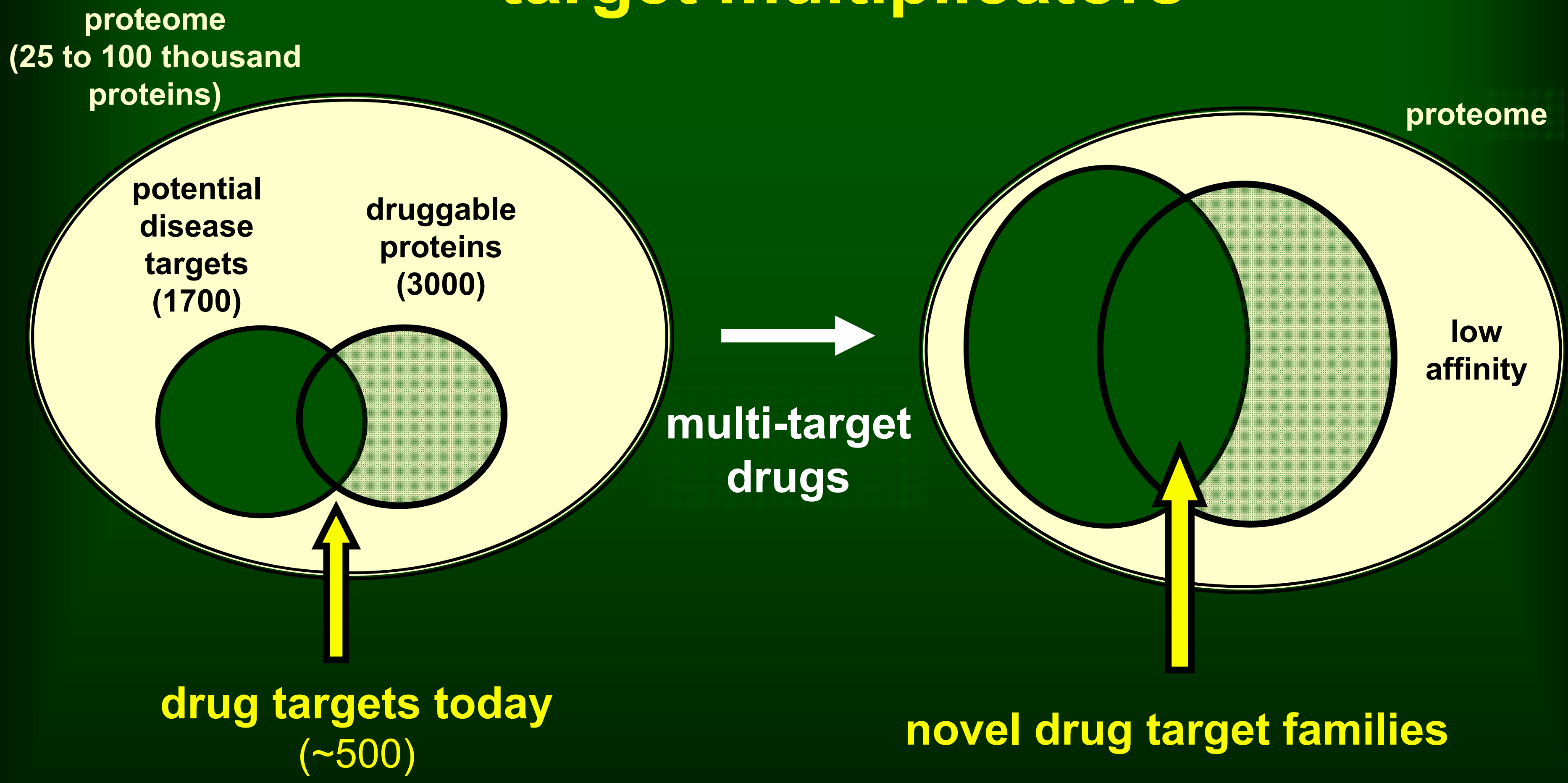




	distributed KO	distributed attn.
E. coli (72)	15	38
S. cerevisiae (18)	6	10

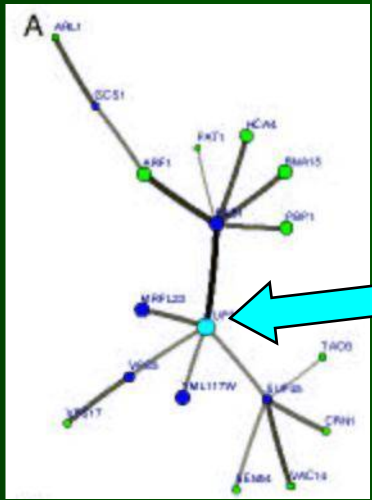
Ágoston et al., Phys. Rev. E 71:051909

Multitarget drugs =
= target multiplicators



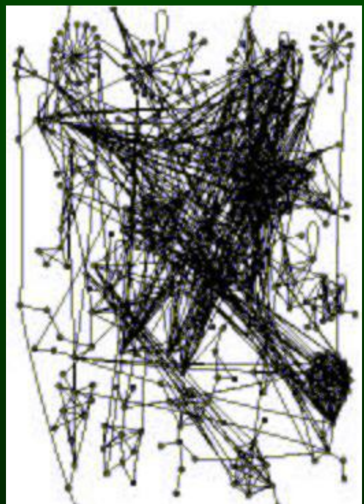
Korcsmáros et al, Exp. Op. Drug Discov. 2:799

Effects are specific

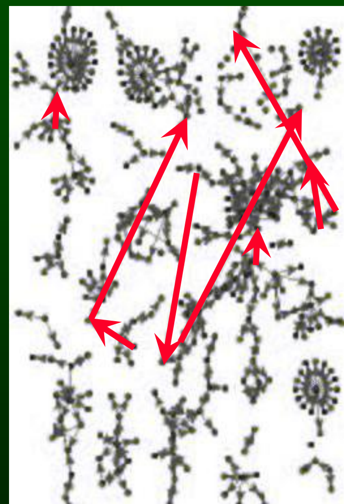


two-fold increase
(blue neighbors: decrease
green 2nd neighbors: increase)

PNAS 104:13655



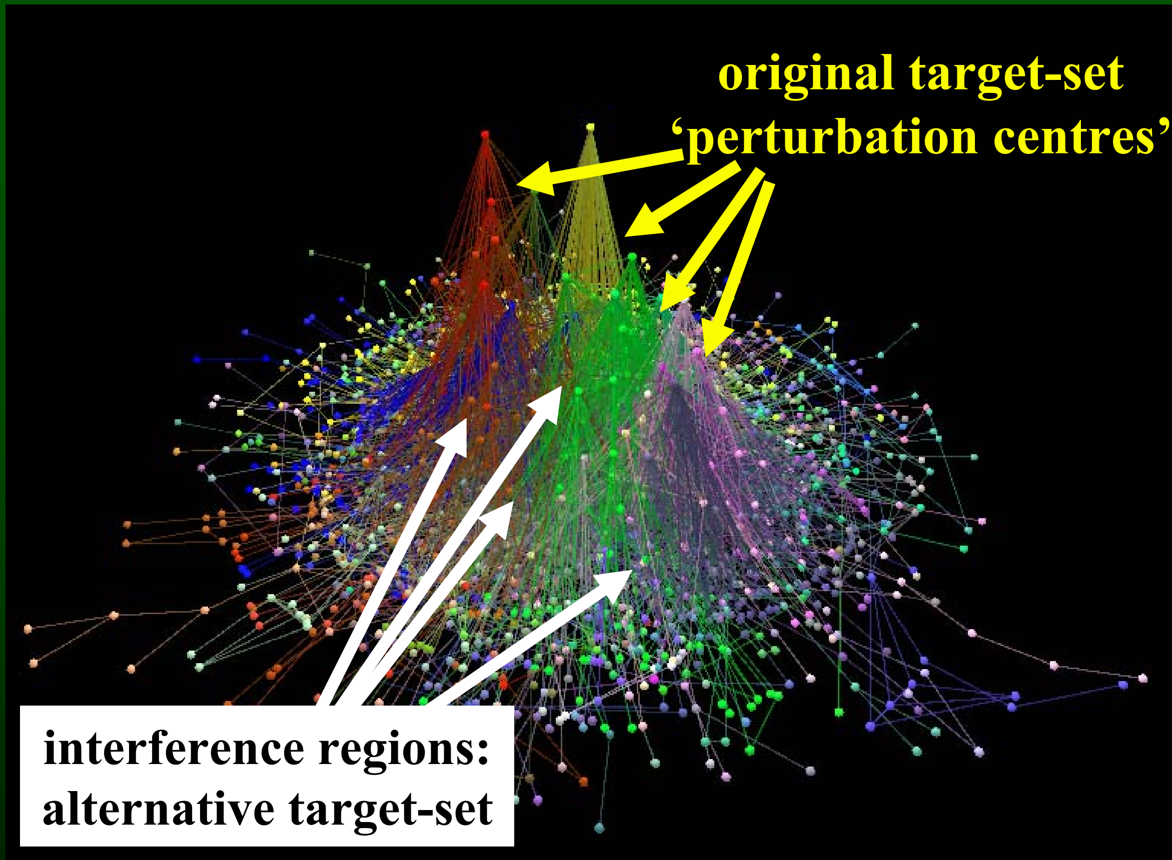
yeast interactome



long-range effects

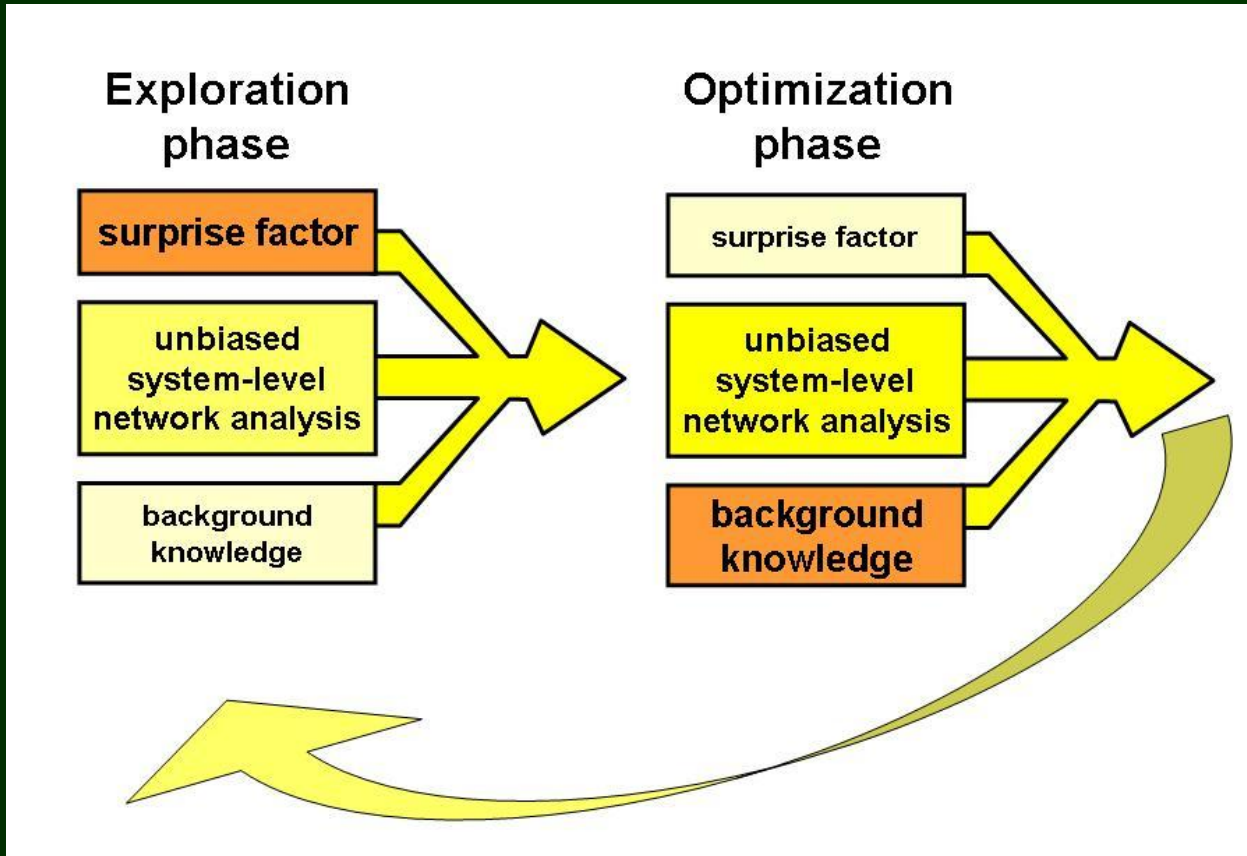
yeast interactome:
at least 20% changes

Multitarget drug search by modular analysis and multi-perturbation



www.linkgroup.hu/modules.php
Antal et al, Curr. Pept. Prot. Sci. 10:161

Drug development phases



Csermely *et al*, Pharmacol & Therap 138, 333
http://arxiv.org/abs/1210.0330