Project works in the LINK-Group

- overlapping network modules (http://modules.linkgroup.hu)
- cooperation of networks (http://NetworGame.linkgroup.hu)
- best information spreaders (http://turbine.linkgroup.hu)
- determination of the attractor-network of complex systems
  + determination of their intervention points (http://turbine.hu)
- analysis of network entropy/plasticity-rigidity changes
in biological and social networks and their stress & adaptation

If interested to join our seminars on
each 2nd Thursday at 16.30, write to
csermelynet@gmail.com

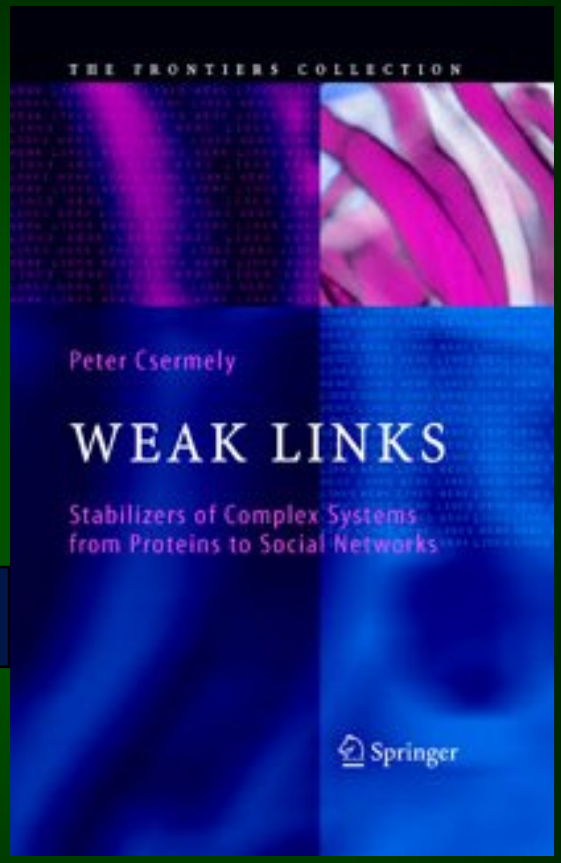
Networks and stability

Part 1 – Network topology

Peter Csermely

www.linkgroup.hu
csermelynet@gmail.com

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

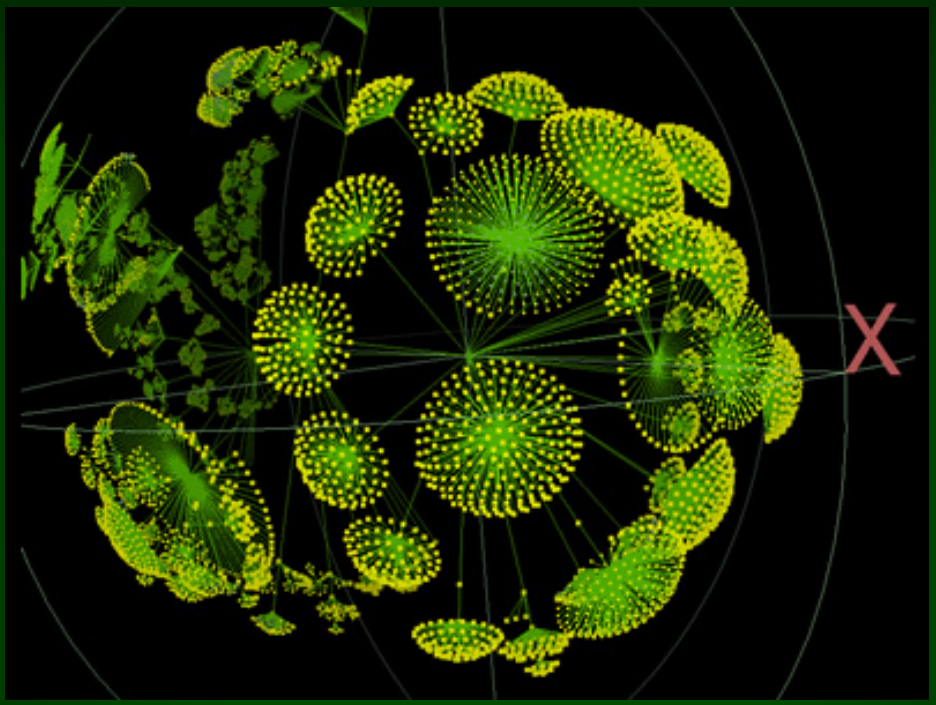
„we are drowning in a sea of data and starving for knowledge"

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

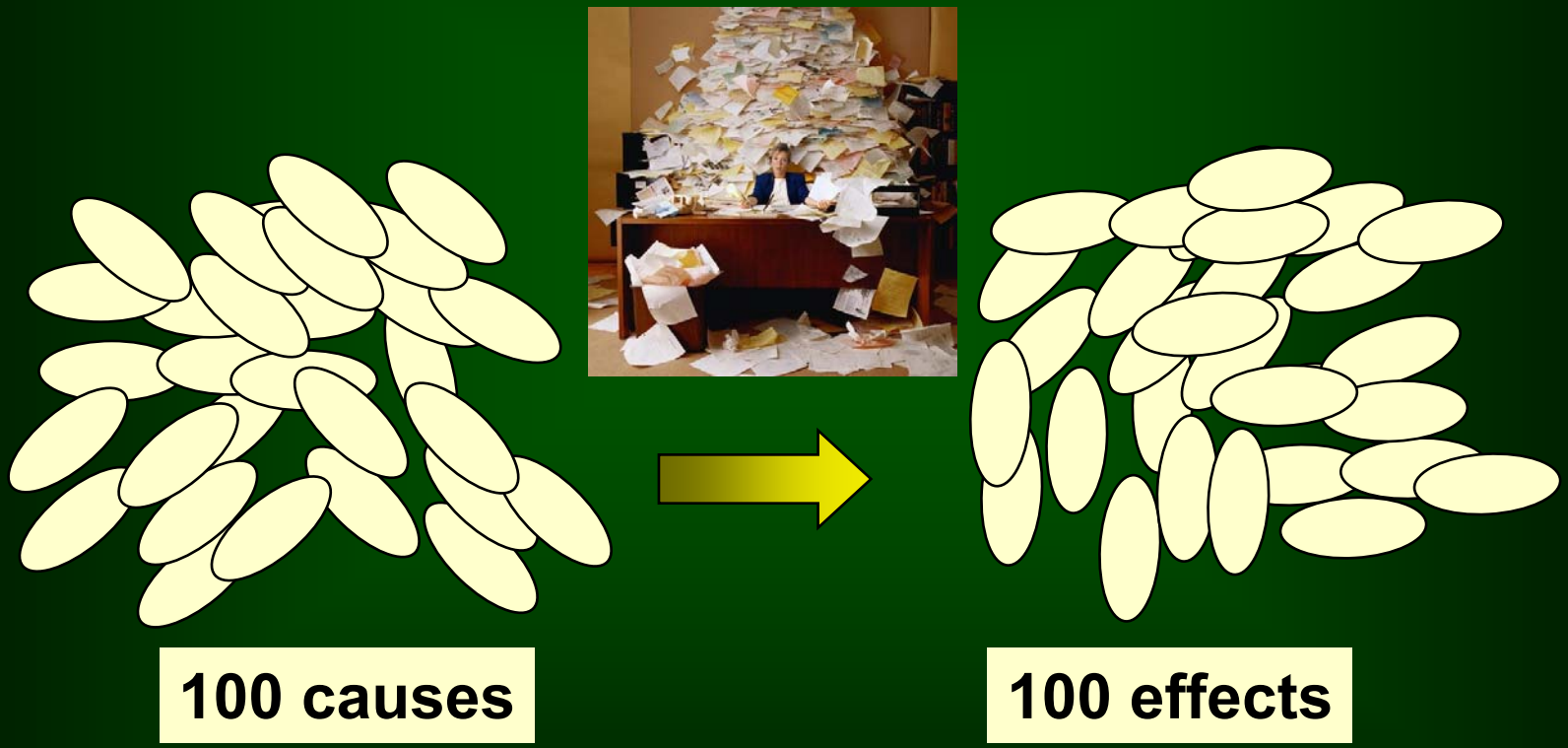
Newest synthesis: subconscious + emotions…

Traditional view

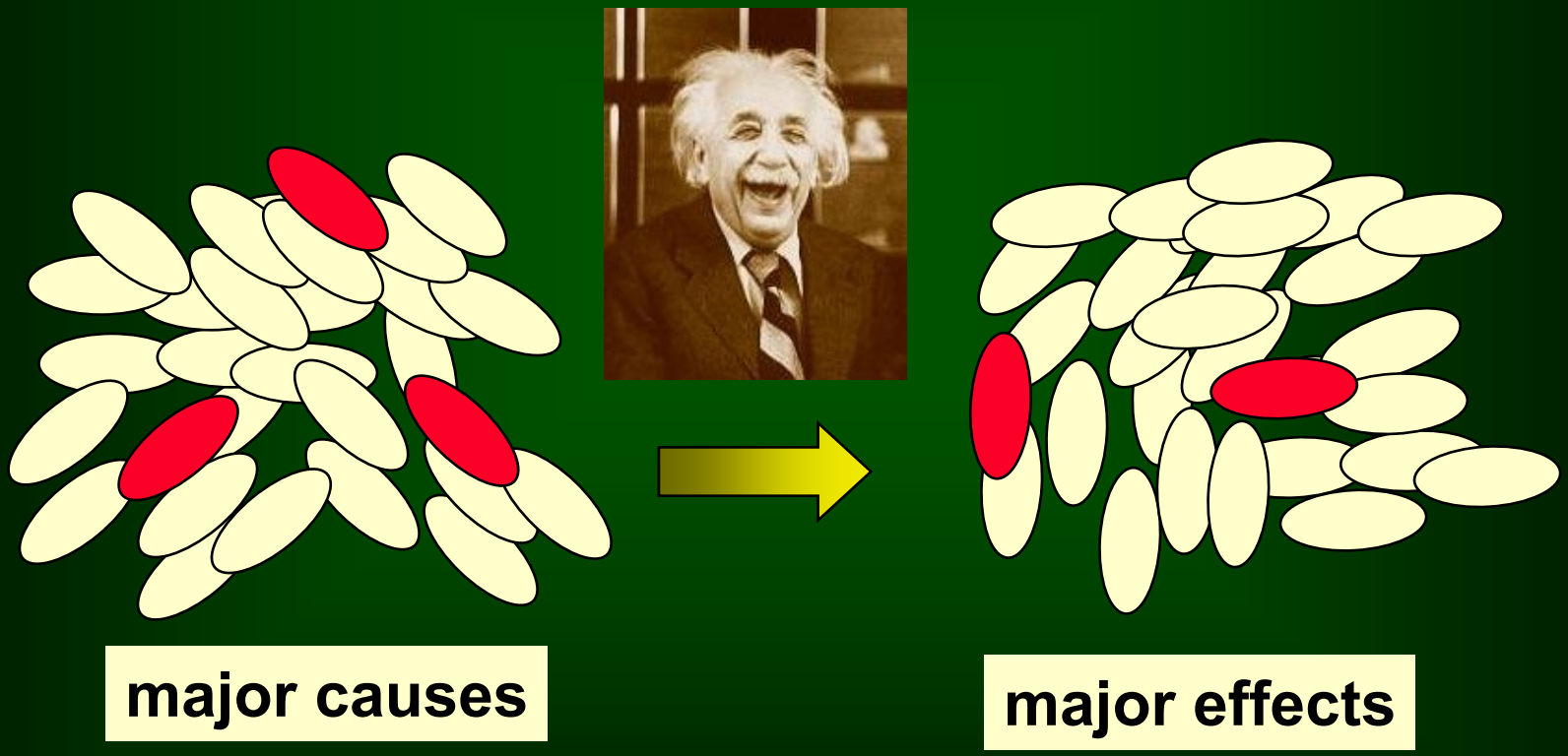
cause → **effect**

(Paul Ehrlich's magic bullet)

Recently changed view



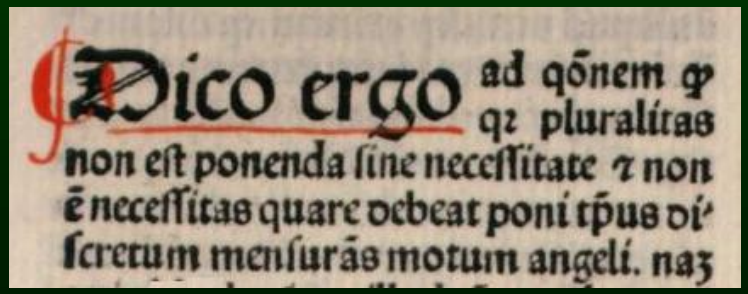
Networks may help!



Occam's razor

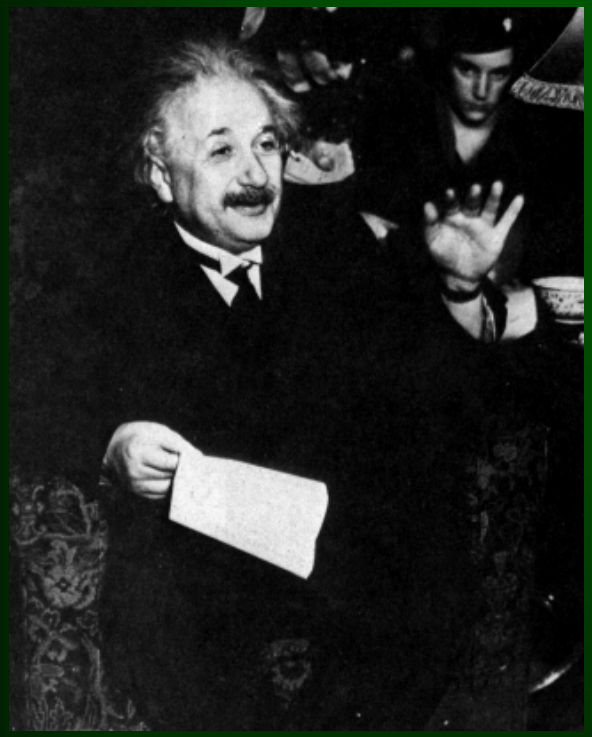
" ... plurality is not to be posited without necessity…"

William of Occam (1285-1349)



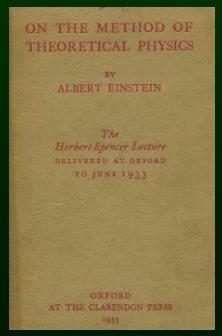
Dico ergo ad qõnem ꝙ
qz pluralitas
non eſt ponenda ſine neceſſitate ⁊ non
ē neceſſitas quare debeat poni tp̄us di-
ſcretum menſurās motum angeli. naz

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

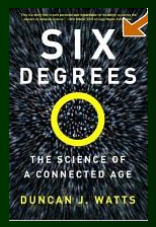
natural sciences	physician	social sciences
point, node, exact	⟷	identity, context, fuzzy

Networks can break conceptual barriers

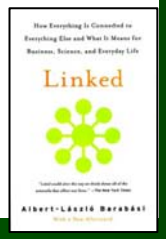
Networks have general properties

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

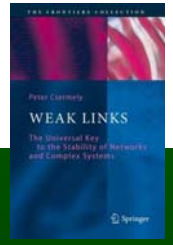
Karinthy
1929



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

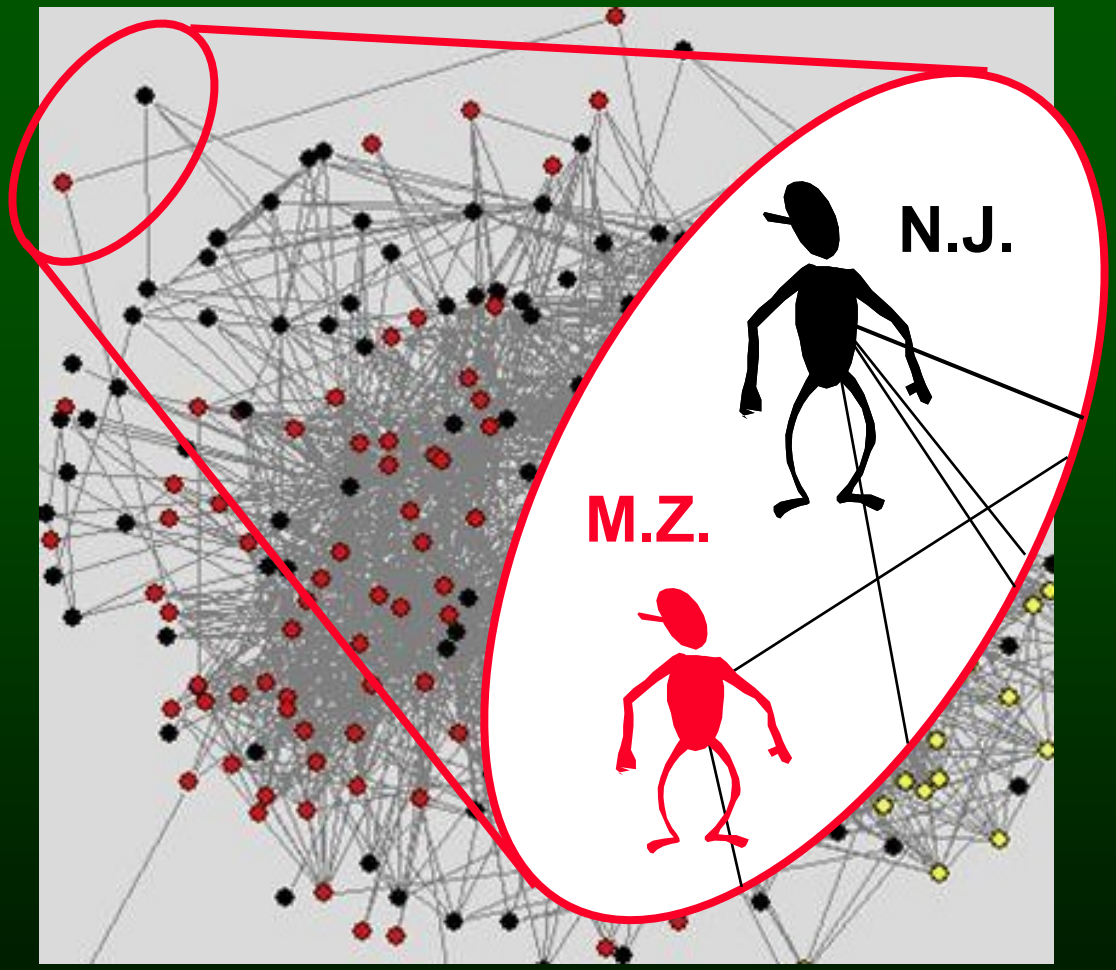
Nature 461:53

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

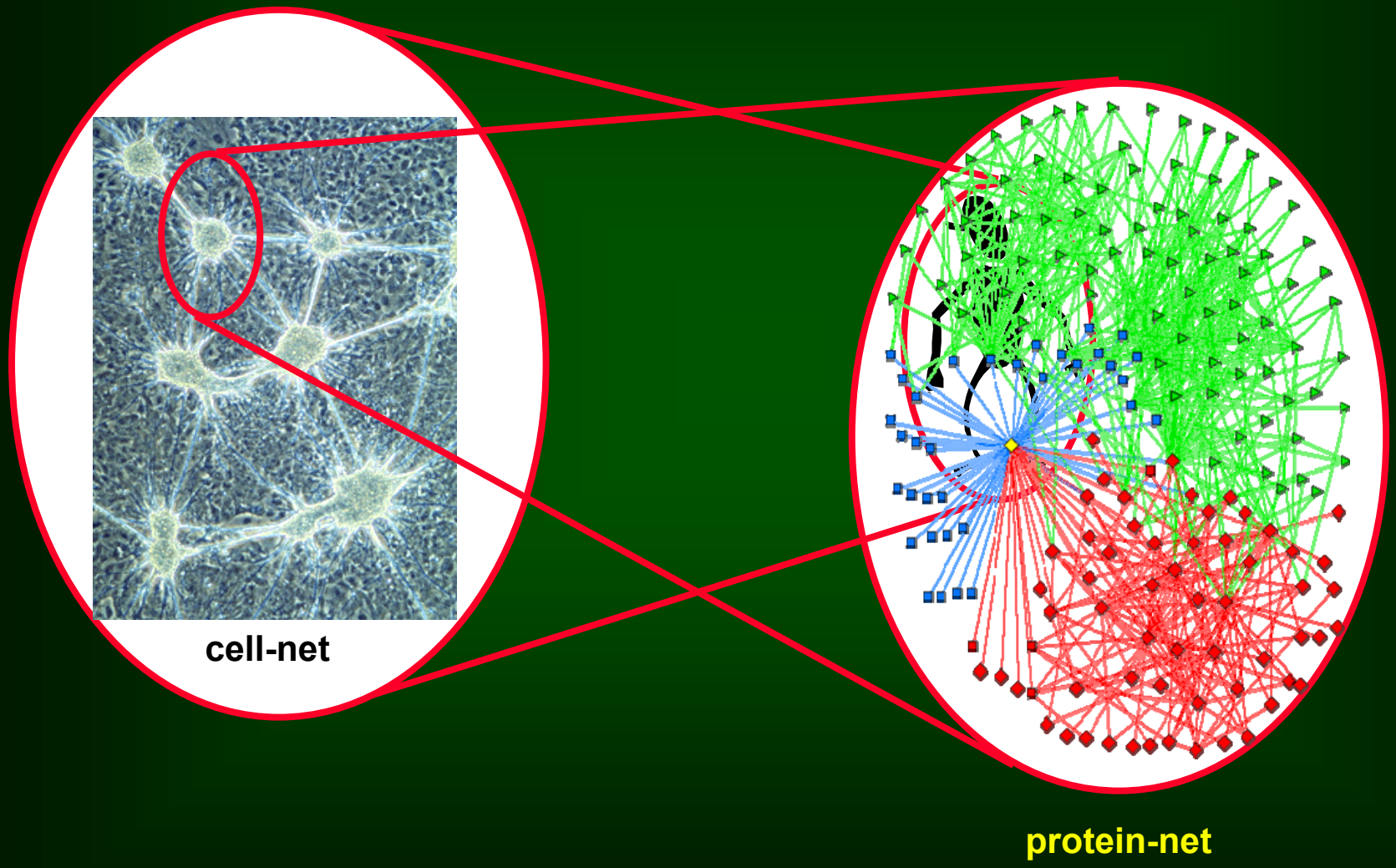
Prevention: elements with less predictable behaviour
- omnivores, top-predators
- market gurus
- stem cells

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

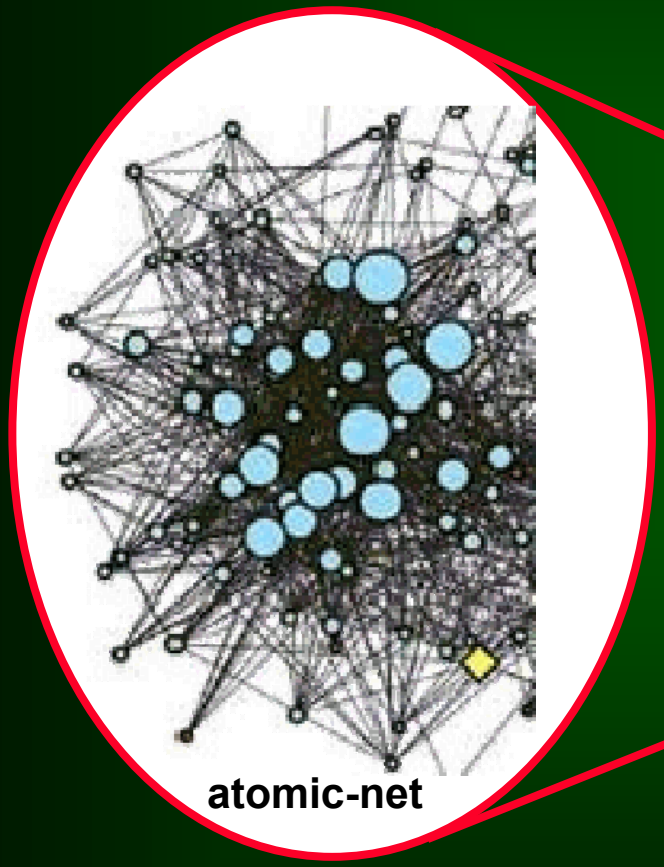
Networks are embedded

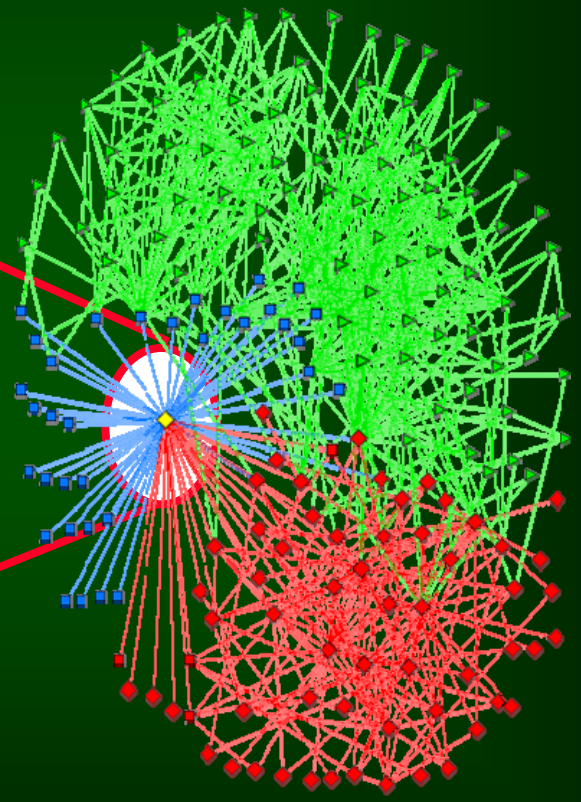


Networks are embedded

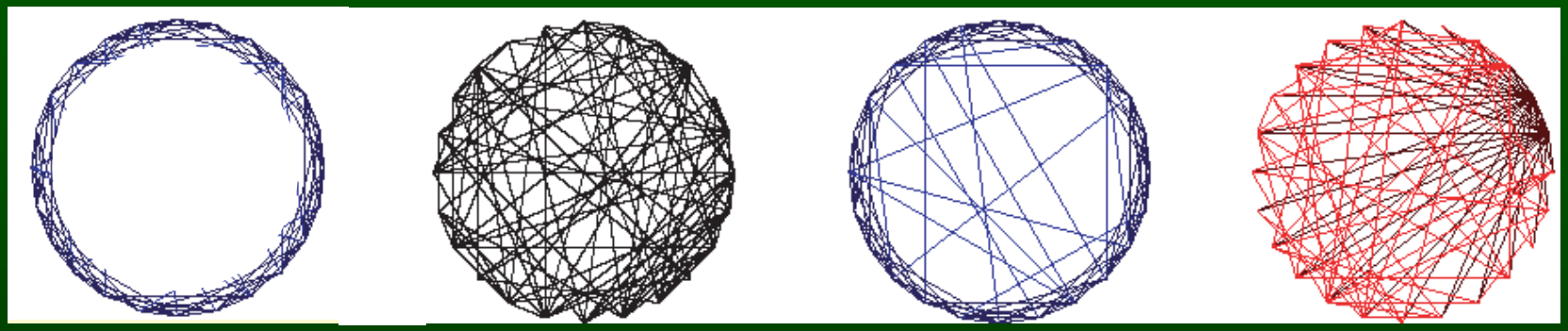


Networks are embedded





Major classes of network topology



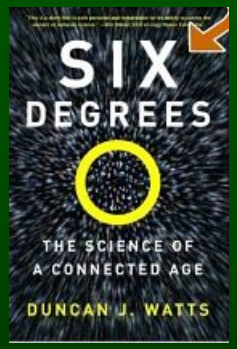
regular	random	**small-world**	**scale-free**

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

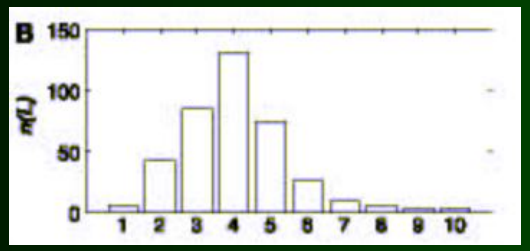
Six degrees of separation



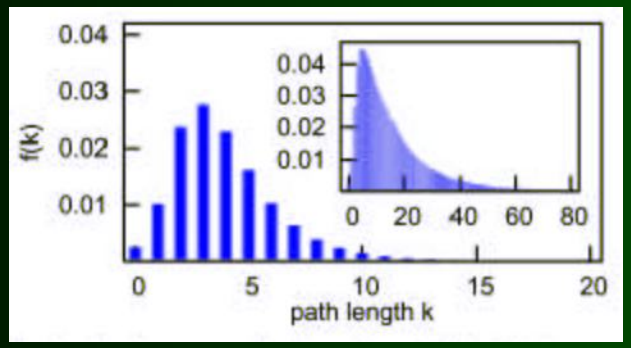
100^6 = >100 x
the total population
of the Earth

Frigyes Karinthy
(1929) Five degrees

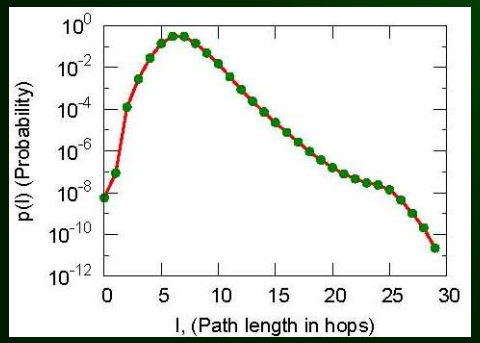
Repeated Milgram-experiments



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

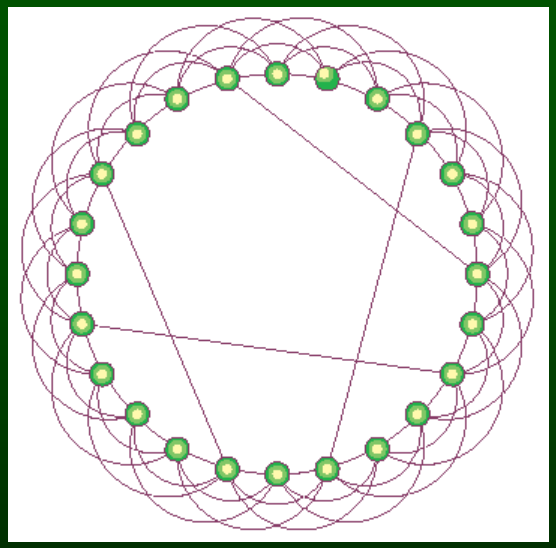


www.msn.com
18 million participants,
50 billion messages
6,6 degrees
PNAS 105, 4633; 2008

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)]

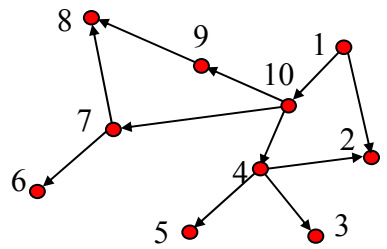
general model
examples:

- *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

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

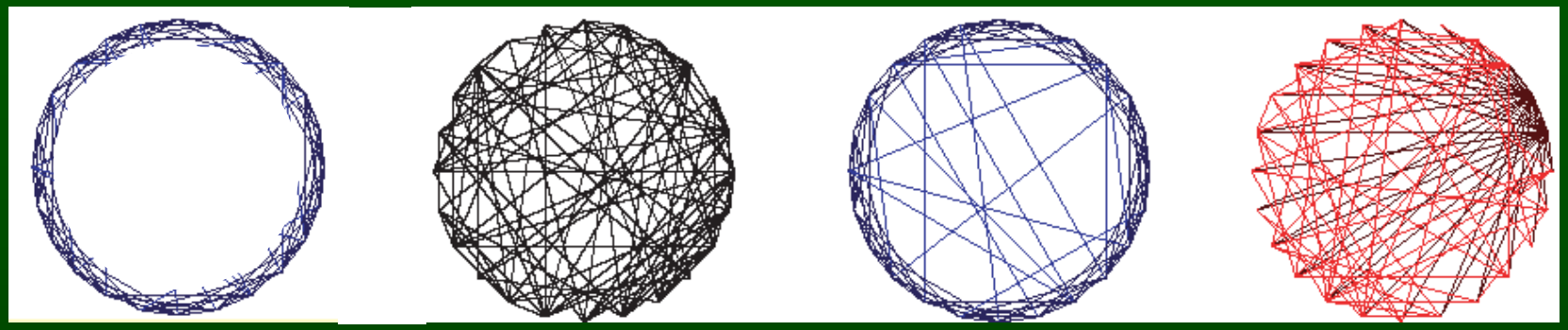


	1	2	3	4	5	6	7	8	9	10	
1	-	1	3	2	3	3	2	3	2	1	1
2	-	-	-	-	-	-	-	-	-	-	2
3	-	-	-	-	-	-	-	-	-	-	3
4	-	1	1	-	1	-	-	-	-	-	4
5	-	-	-	-	-	-	-	-	-	-	5
6	-	-	-	-	-	-	-	-	-	-	6
7	-	-	-	-	-	1	-	1	-	-	7
8	-	-	-	-	-	-	-	-	-	-	8
9	-	-	-	-	-	-	-	1	-	-	9
10	-	2	2	1	2	2	1	2	1	-	10

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

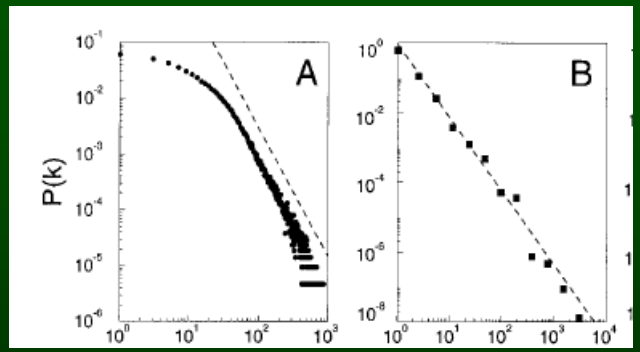
?

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

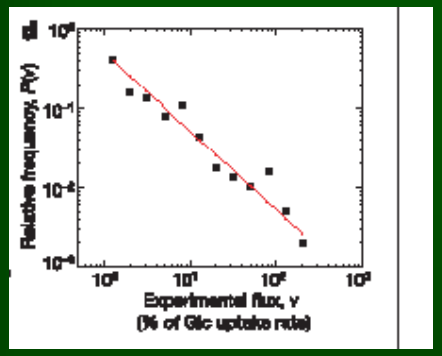
Science 286, 509; 1999

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

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

Generality of scale-free distributions

link-strength

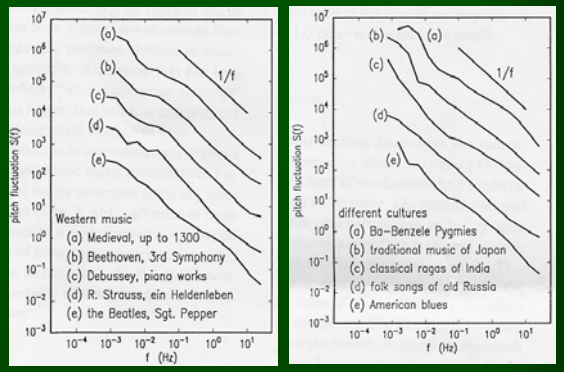


Nature 427, 839; 2004

Levy-flights

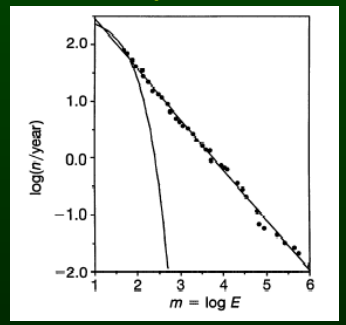
Can J. Zool. 80, 436; 2002

music



Nature 258, 317; 1975

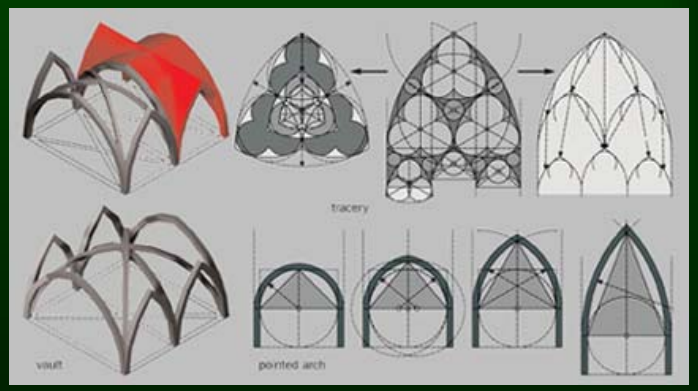
probability, Noe-effect



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



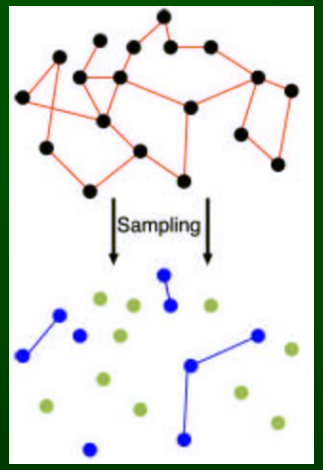
www.iemar.tuwien.ac.at/modul23/Fractals

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

Peter Csermely

www.linkgroup.hu
csermelynet@gmail.com

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?

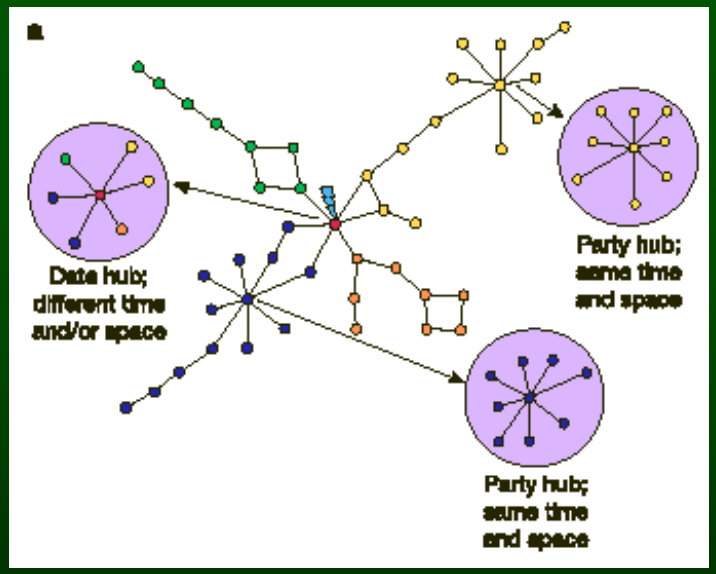
„Important” network segments

local

global

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

Date hubs and party hubs



Han et al. Nature 430, 88

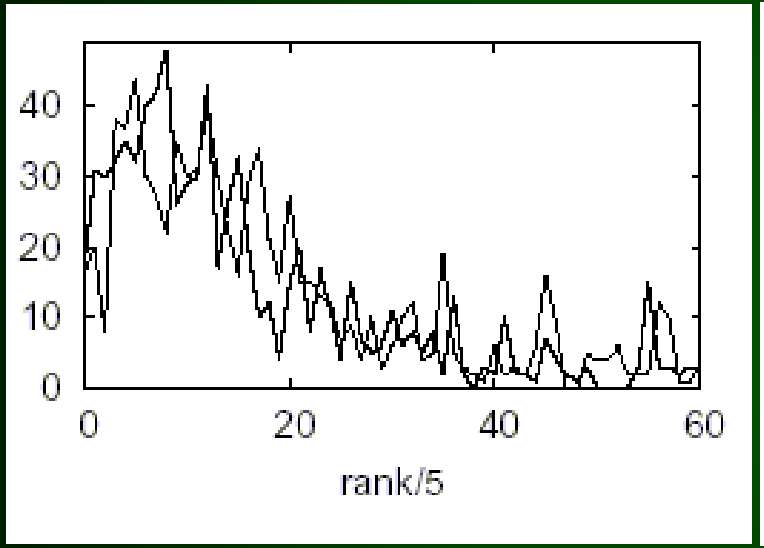
yeast protein network

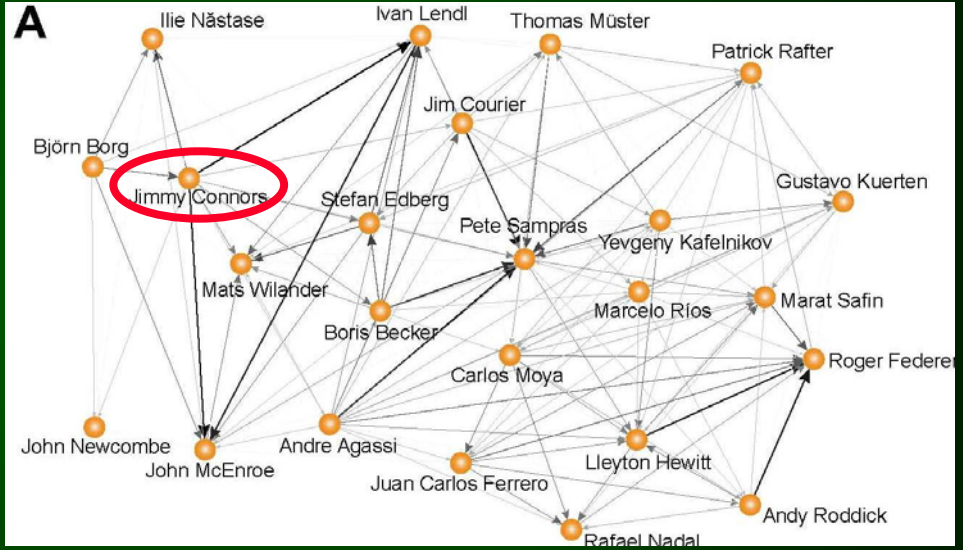
–date hubs

–party hubs

Talented(VIP)**-club**

isolated top rank associates with hubs





Masuda and Konno
Social Networks 28, 297

Radicchi
arxiv.org:1101.4028

Types of network centralities

local

global

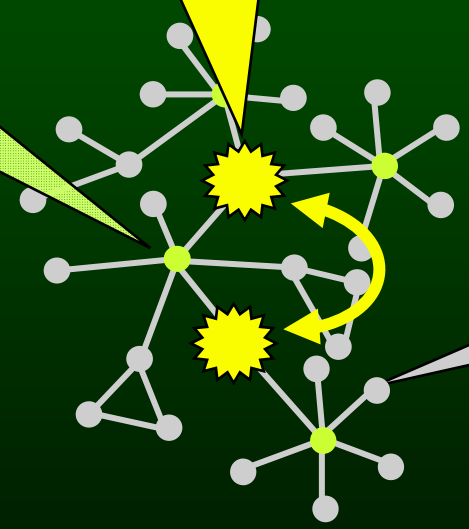
- hubs (degree)
- closeness (sum of shortests paths to other nodes)
- community centrality (influence of all other nodes)
- betweenness (number of shortests paths through the node)

- **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**

Creative nodes

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

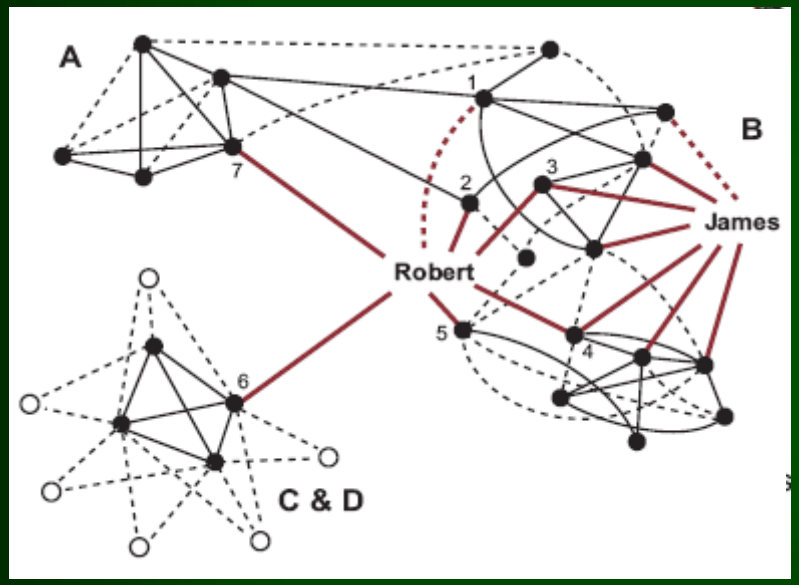
Distributor: hub, specialized to signal distribution, **predictable**



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

Netocracy: continuous networking → Obama
Bard-Söderquist

The art of networking

Complementary networking strategies

- safety seeking (optimization)
- novelty seeking (exploration)

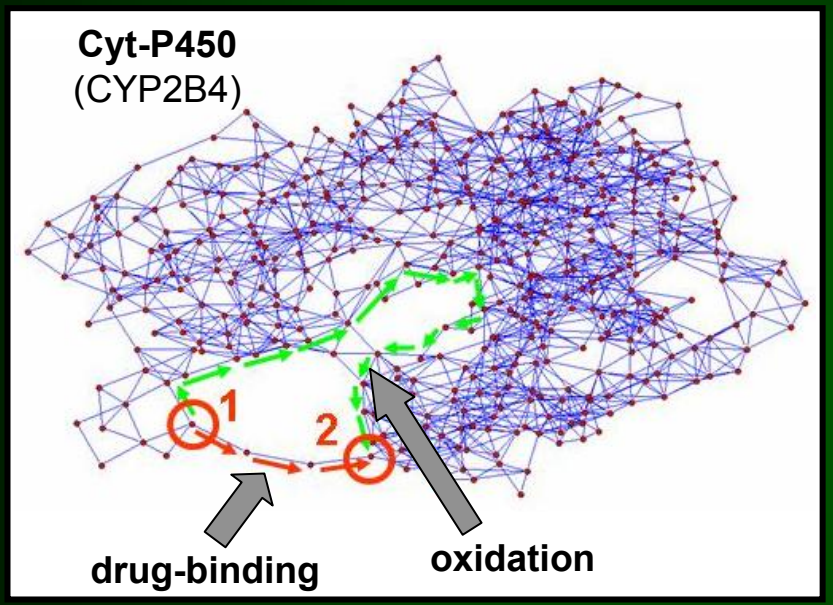
(seek the opinion leader,
seek the strange, seek openness,
jump to the next group)

Am. J. Sociology 78, 1360

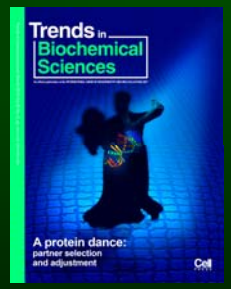
Useful information comes from a long distance

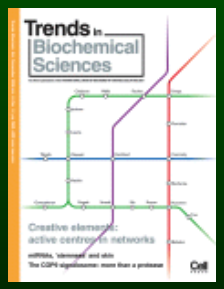
- Mark Granovetter (1973)
- transmodular links are weak
- these links stabilize the society
- unusual ideas, innovation (trust)
- cognitive flexibility
  (understanding completely different ideas)

Creative elements are central and…



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





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

Creative proteins
- stress proteins
- signaling switches

Creative cells
- stem cells
- our brain

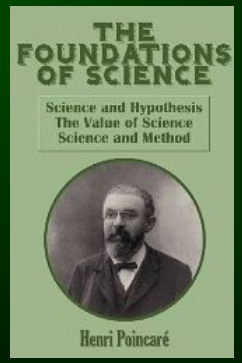
Creative persons
- firms
- societies

mobile

Originality:
the highest level of creativity

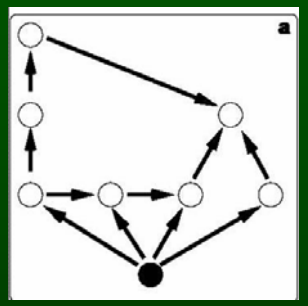
" ... To create consists in not making useless combinations. Among chosen combinations the most fertile will often be those formed of elements drawn from domains which are far apart."

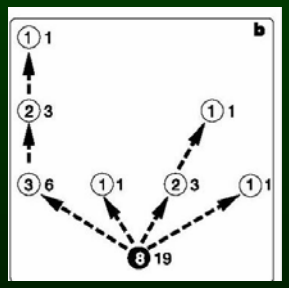
Henry Poincaré: Foundations of Science (1908)



Network skeleton (local, fractal nets)

food-chain renorm.
(energy-flow)

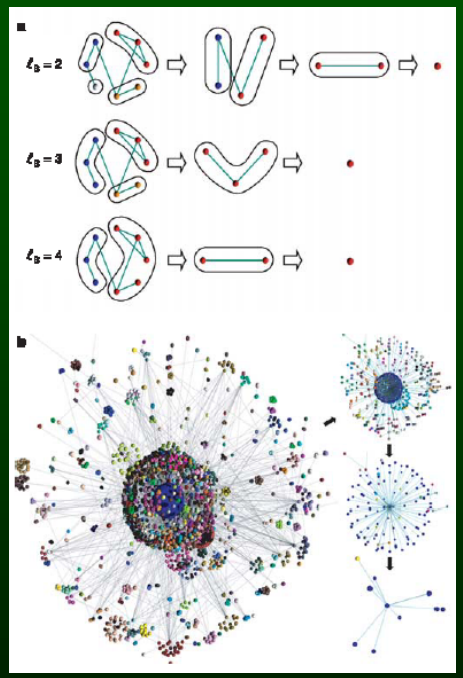




hierarchy: e.g. transcription factors

Garlaschelli et al., Nature 423,165

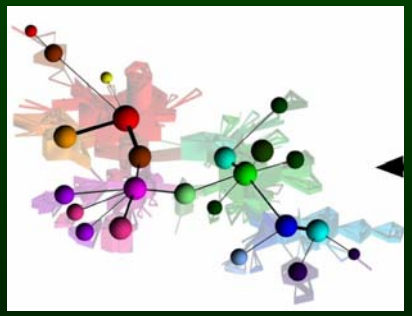
www renormalization
(unbranched ends)



Song et al., Nature 433,392

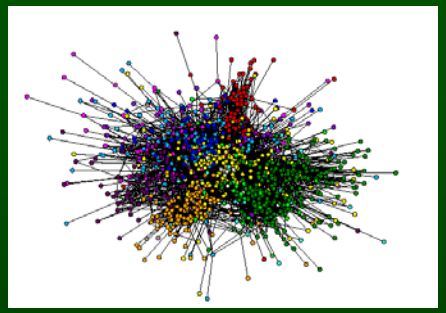
Network skeleton (mesoscopic, global)

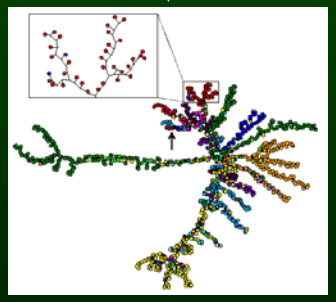
network scientists
(modules)



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

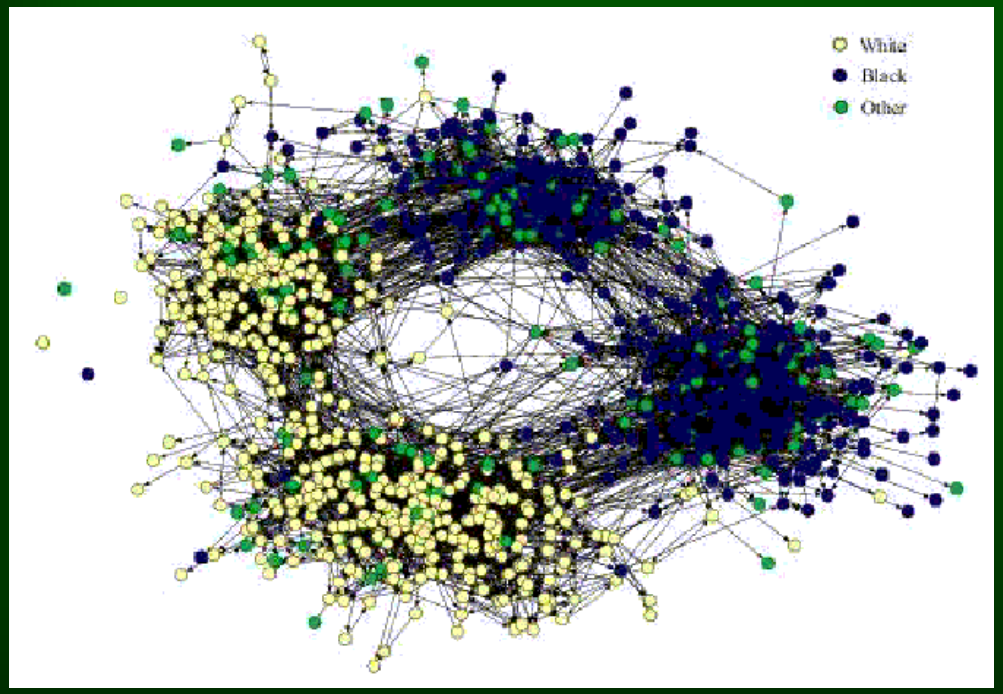
email-net renorm.
(betwenness)





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

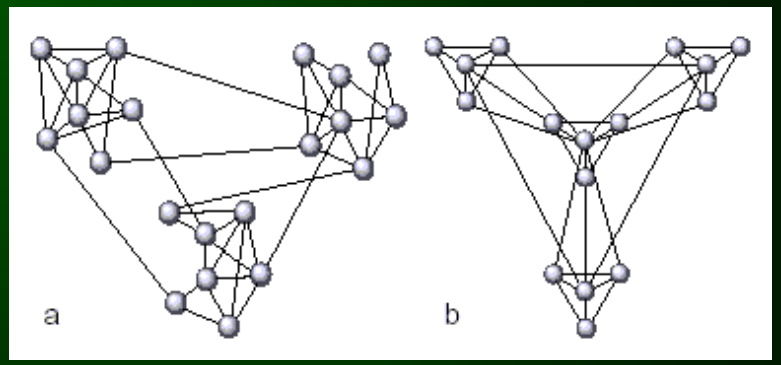
Modules



Newman, SIAM Rev. 45, 167

modular nets

intermodular contacts are suppressed

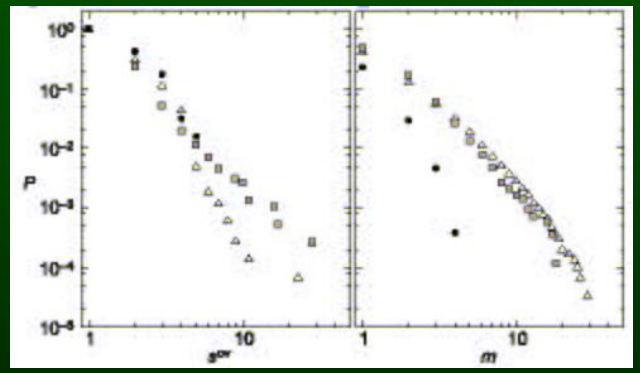


hierarchical net

intermodular contacts are preferentially suppressed

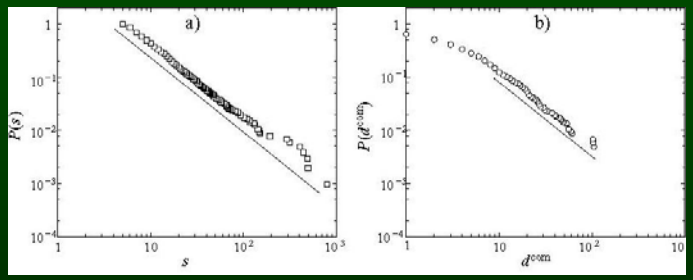
Modules have a scale-free size and degree distribution

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

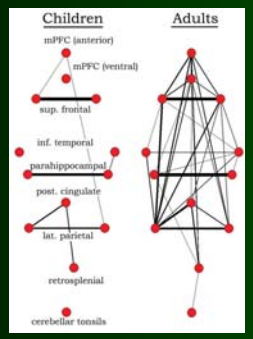


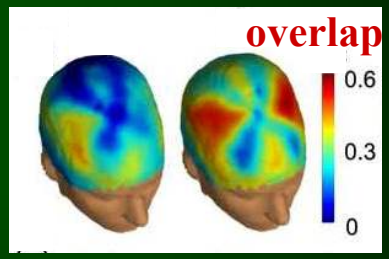
Pollner et al., Europhys. Lett 73:478

Modules need optimal overlap

(brain default-network)

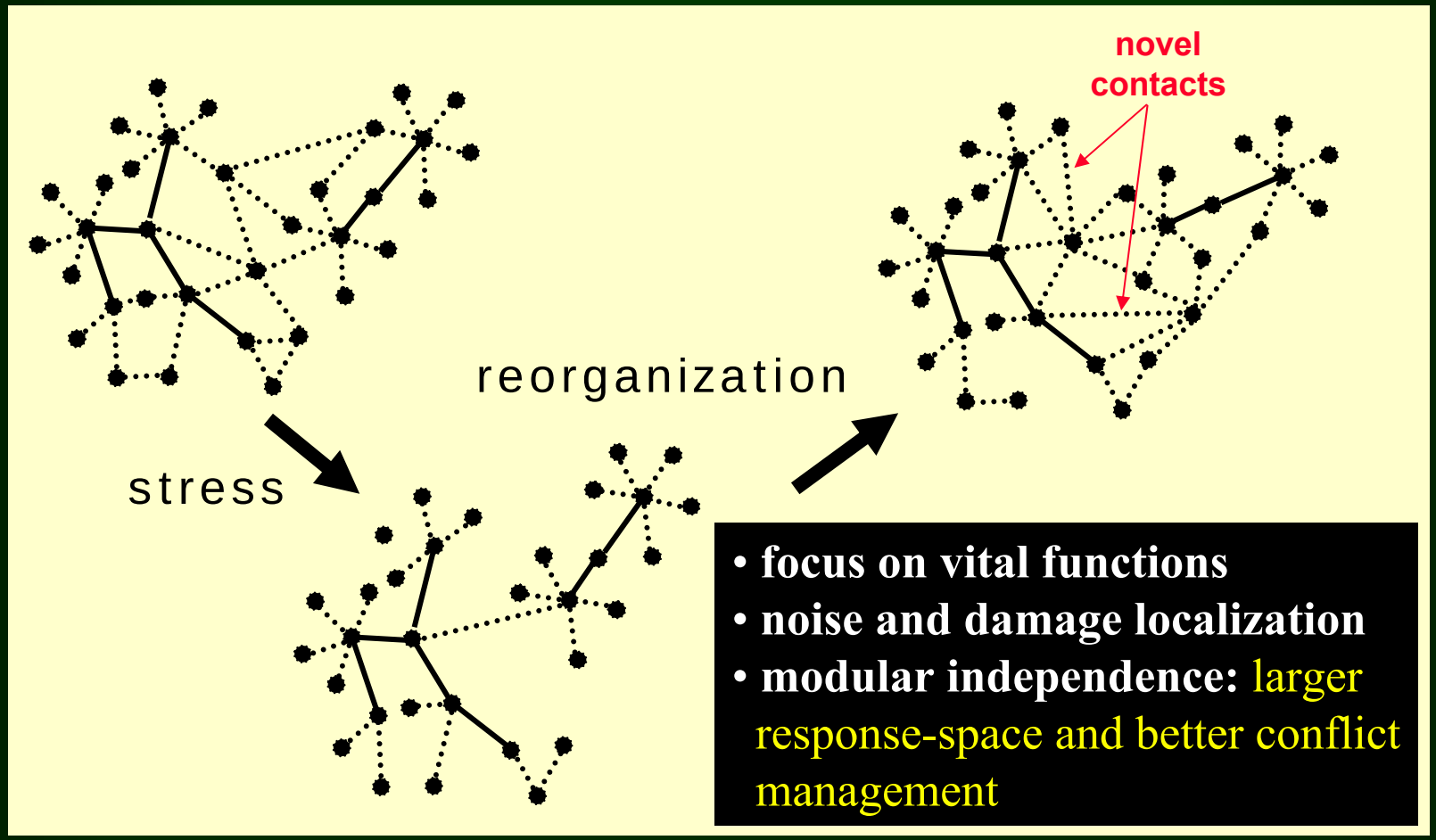
overlap of active neuronal modules





child	adult: usual task	adult: rest, novel task	depression	schizophrenia	epilepsy
PNAS 104:13507 PNAS 105:4028	Science 315:393		PNAS 106:1279 PNAS 106:1942		PRL 104:118701

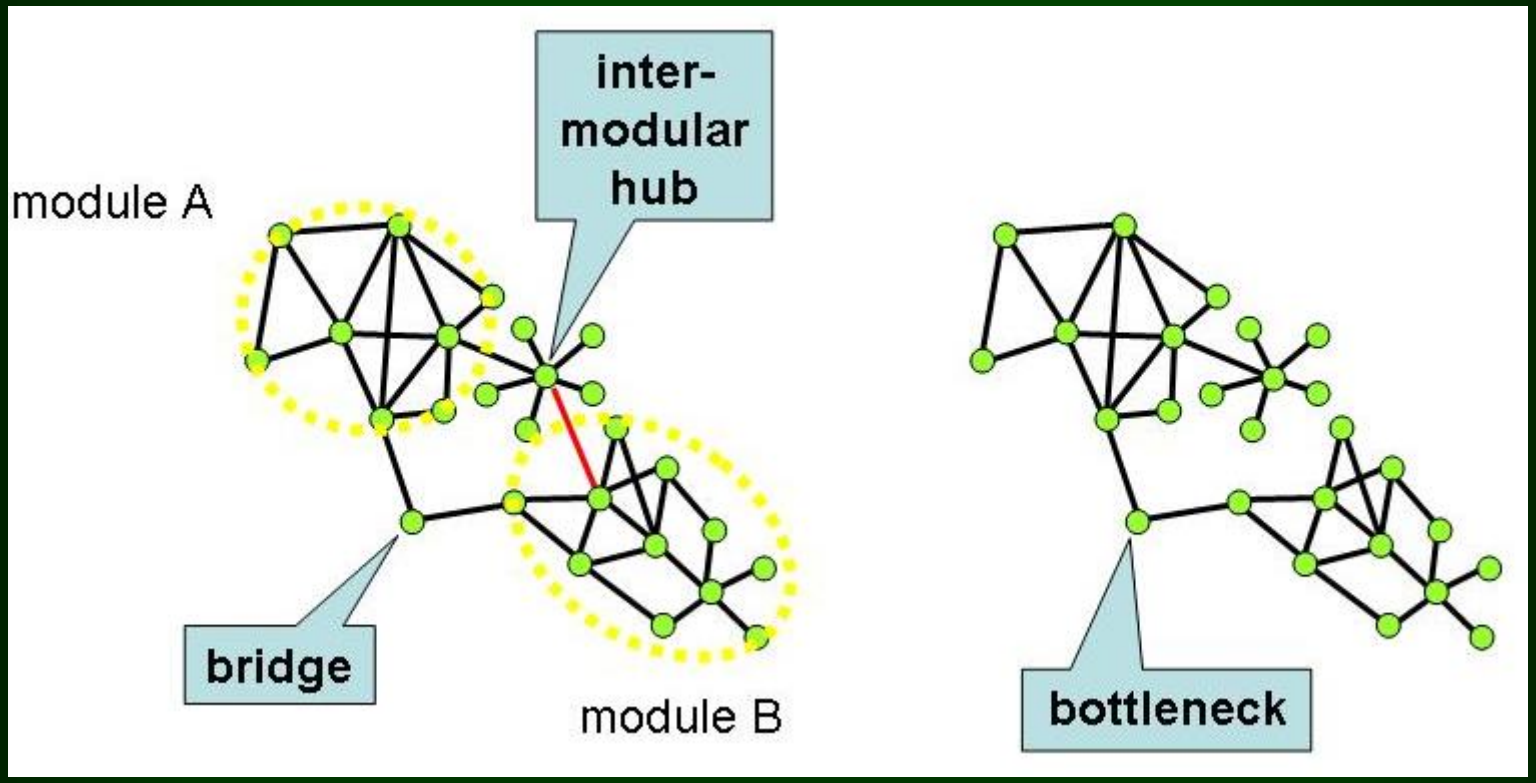
Modular overlaps as keys of adaptation processes



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

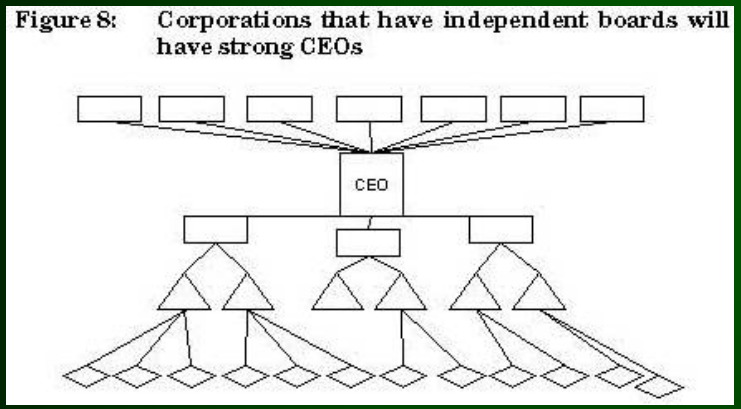
Szalay et al, FEBS Lett. 581:3675; Palotai et al, IUBMB Life 60:10; Mihalik & Csermely, PLoS Comput Biology 7:e1002187

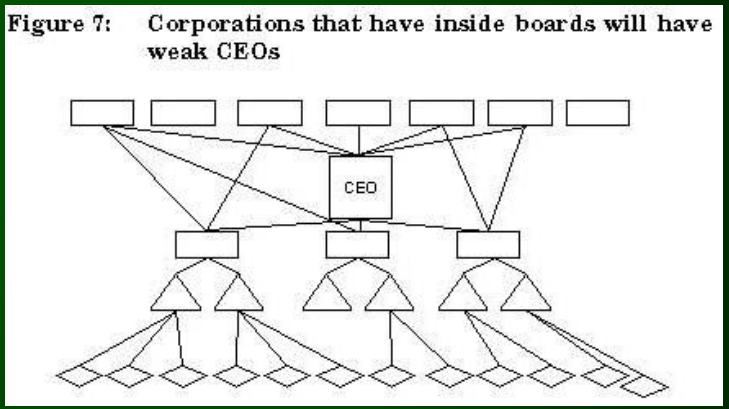
Intermodular bridges are key nodes of regulation



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

Modular overlaps are key determinants of regulation



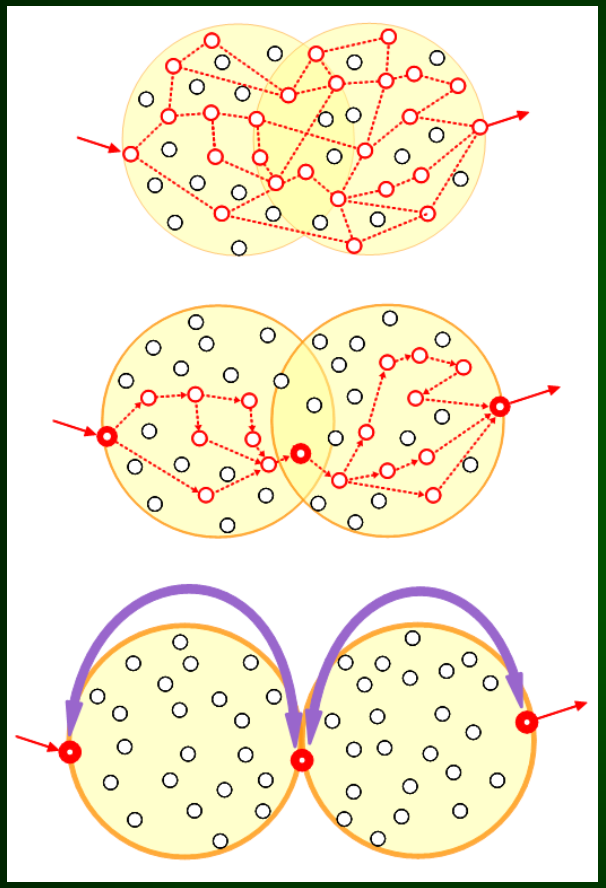


Mitchell, Brooklyn Law Rev. 70:1313

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



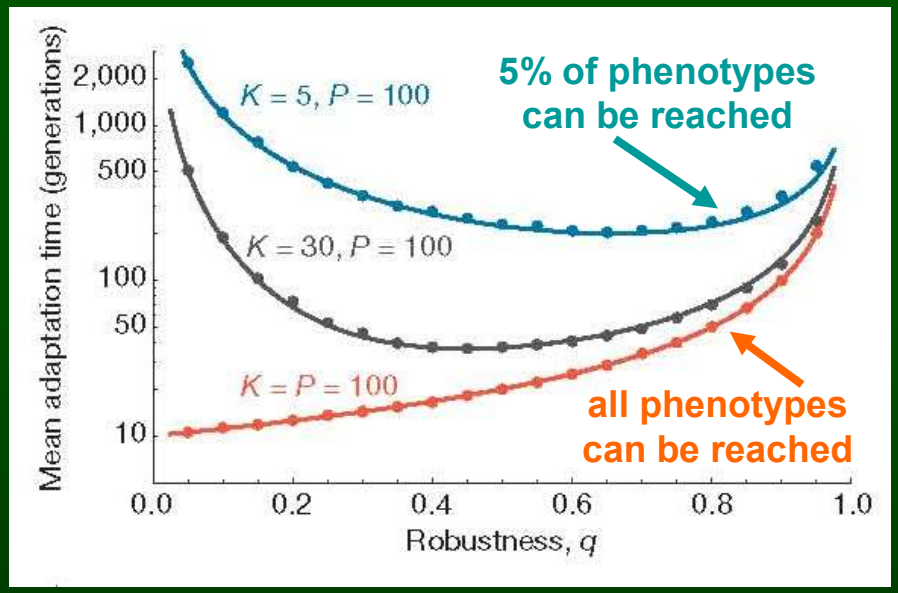
a.) extensively overlapping, soft modules: random routes

b.) moderately overlapping modules: converging routes

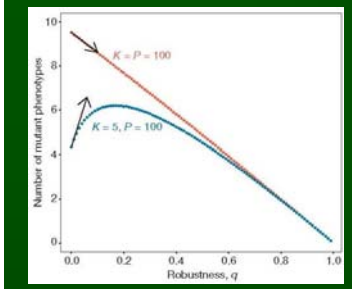
c.) non-overlapping, rigid modules: saltatoric transduction

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

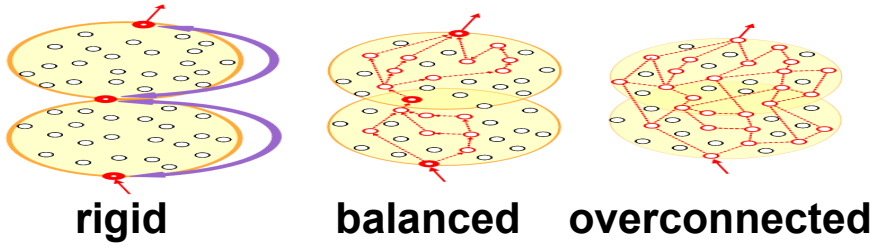
Intermediate form of robustness is optimal for adaptation



diversity



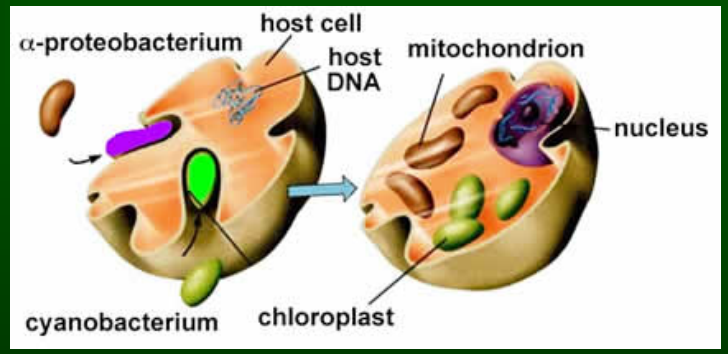
Wagner-Plotkin, Nature 463, 353



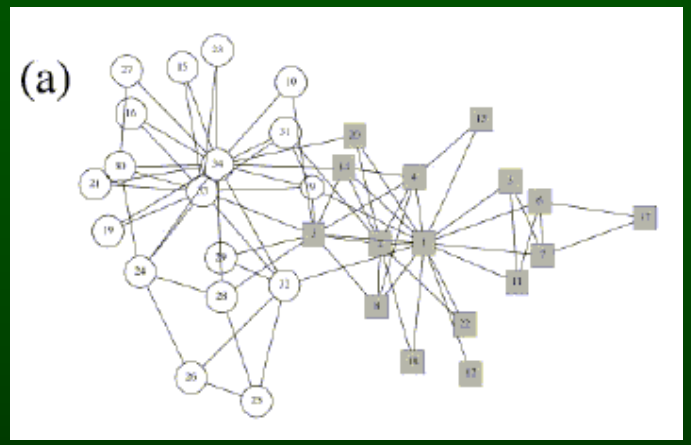
- **rigid:** efficient but over-specialized, not evolvable
- **overconnected:** neither efficient, nor evolvable

How are modules formed?

integration
(symbiosis)

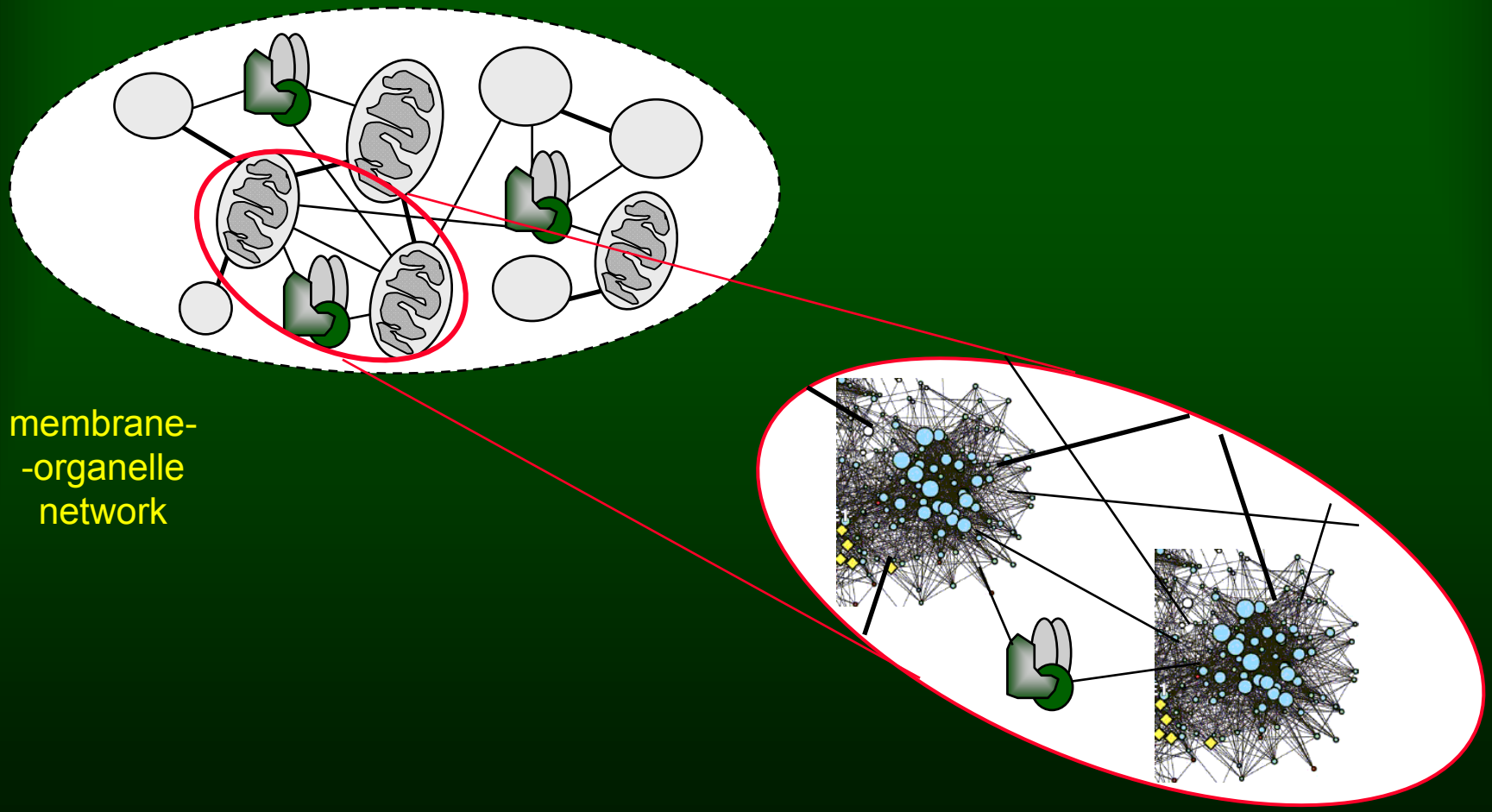


parcellation



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

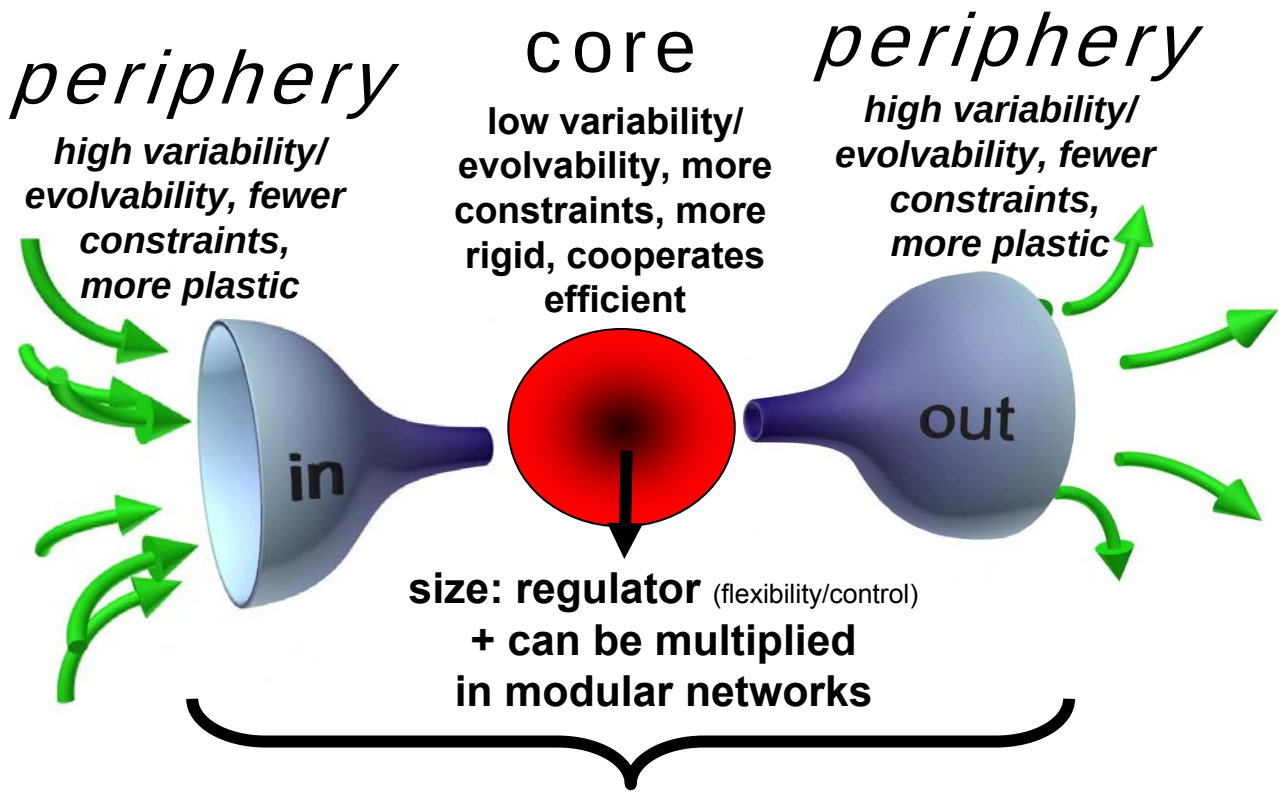


figure represents the „bow-tie" structure of directed networks
„in" and „out" are combined in undirected networks

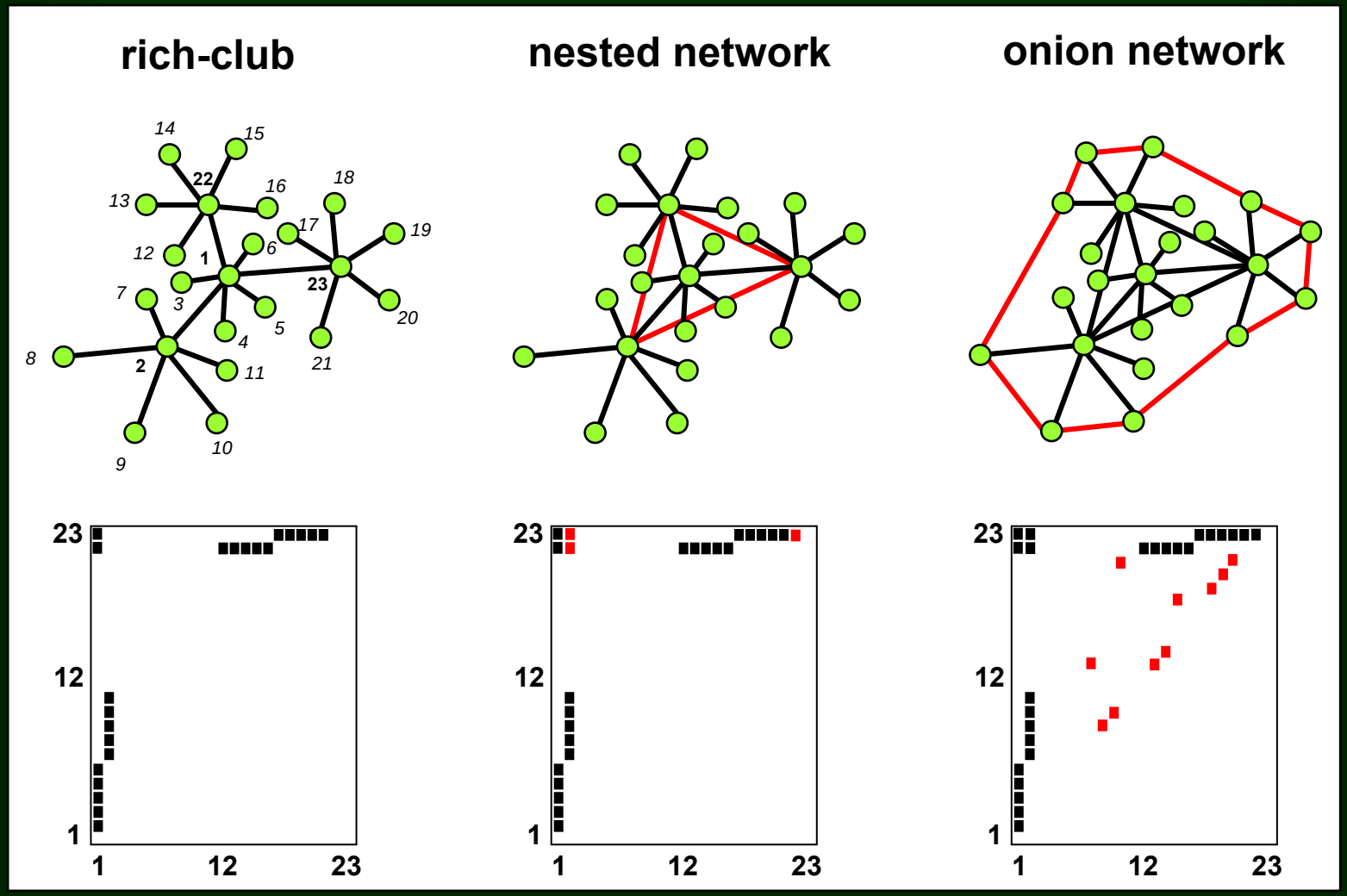
Csermely et al., J. Complex Networks 1:93-123

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

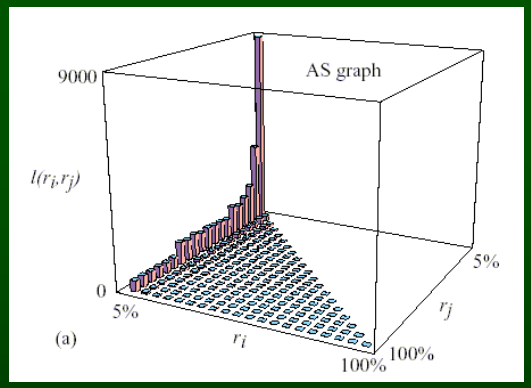
Major types of core-periphery networks II.



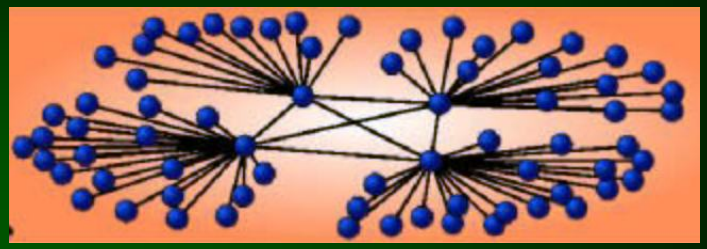
Null-models (comparison to random networks) are important!

Rich clubs

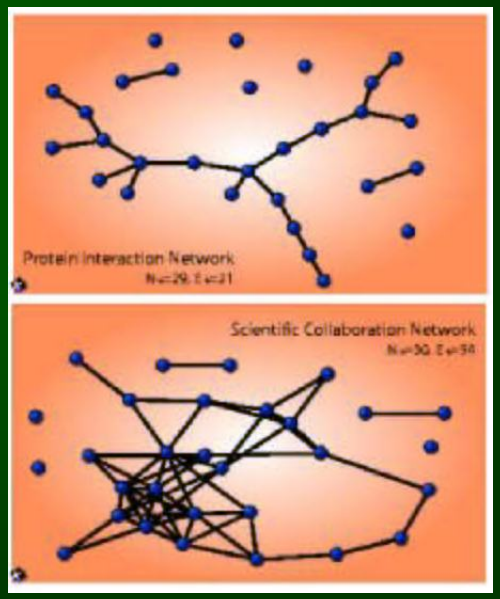
hubs associate with hubs
(assortativity: social nets)



Zhou and Mondragon
IEEE Comm. Lett. 8:180



a disassortative rich club



Colizza et al.
Nature Physics 2:110

Nested networks

generalists

specialists

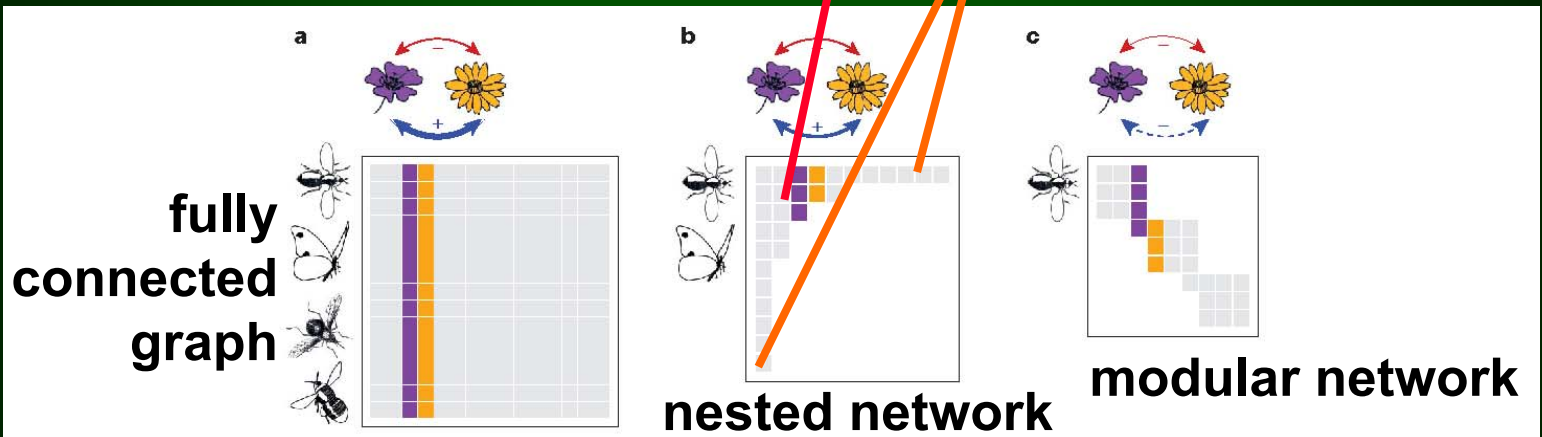
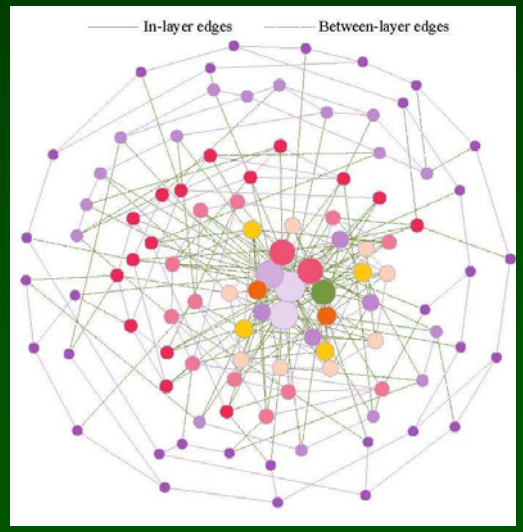


Figure 1 | The structure of mutualistic networks determines the number of coexisting species. Each panel represents a plant–animal network with different structures: **a**, fully connected; **b**, nested; **c**, compartmentalized. Two plants and their respective interactions are highlighted. They compete for resources such as nutrients (red arrow), but also have indirect interactions mediated by their common pollinators (blue arrow), which may change in sign and magnitude (indicated by arrow line style). As the number of shared pollinators is higher, positive effects outweigh negative ones, and the theory predicts a higher number of coexisting species as indicated by the size of the matrices.

Bastolla et al. Nature 458:1018

Onion and wheel type networks



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

Schneider et al. PNAS 108:3838

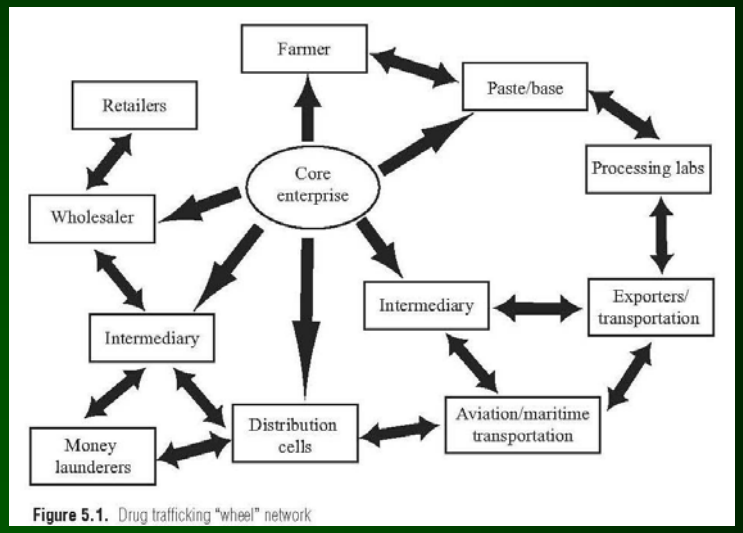


Figure 5.1. Drug trafficking "wheel" network

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

Kenney 2008

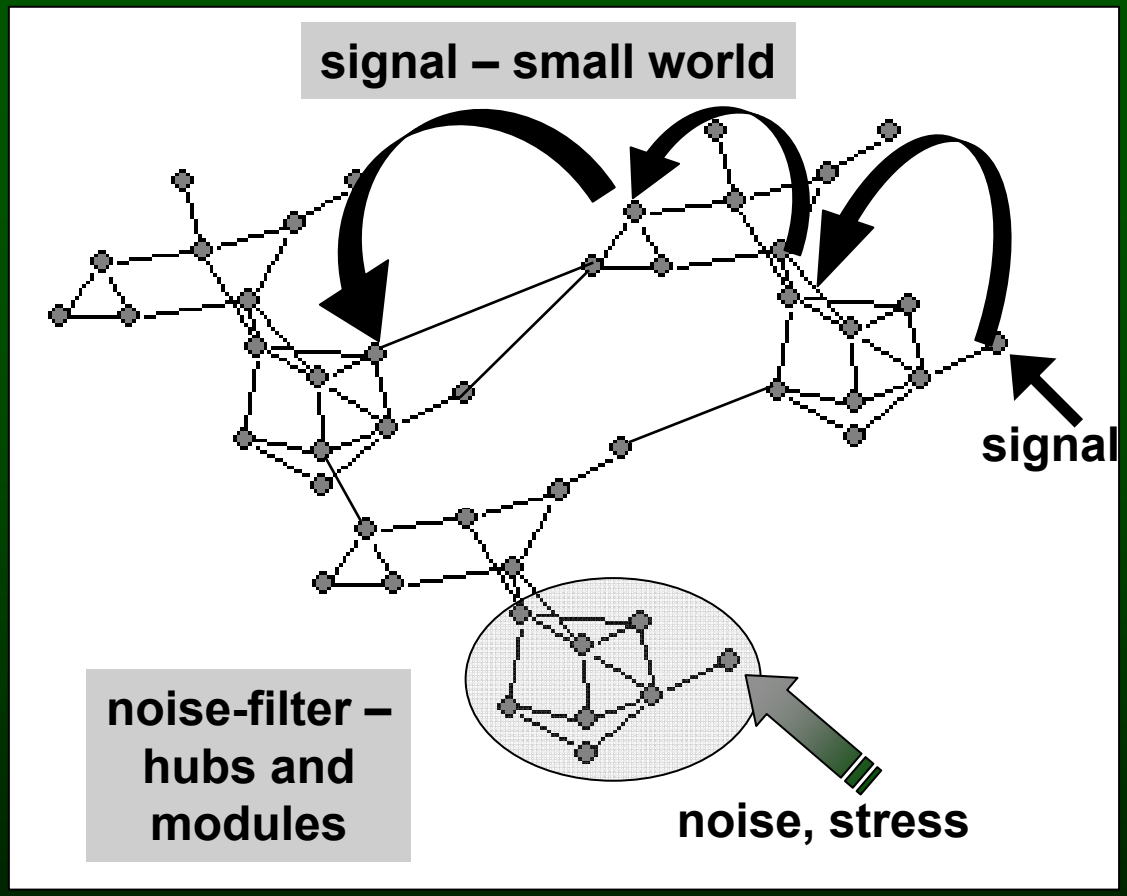
Networks and stability

Part 3. – Network dynamics

Peter Csermely

www.linkgroup.hu
csermelynet@gmail.com

The usefulness of networks



Csermely: Weak Links, Springer

Network tasks: dissipation of noise and response to signals

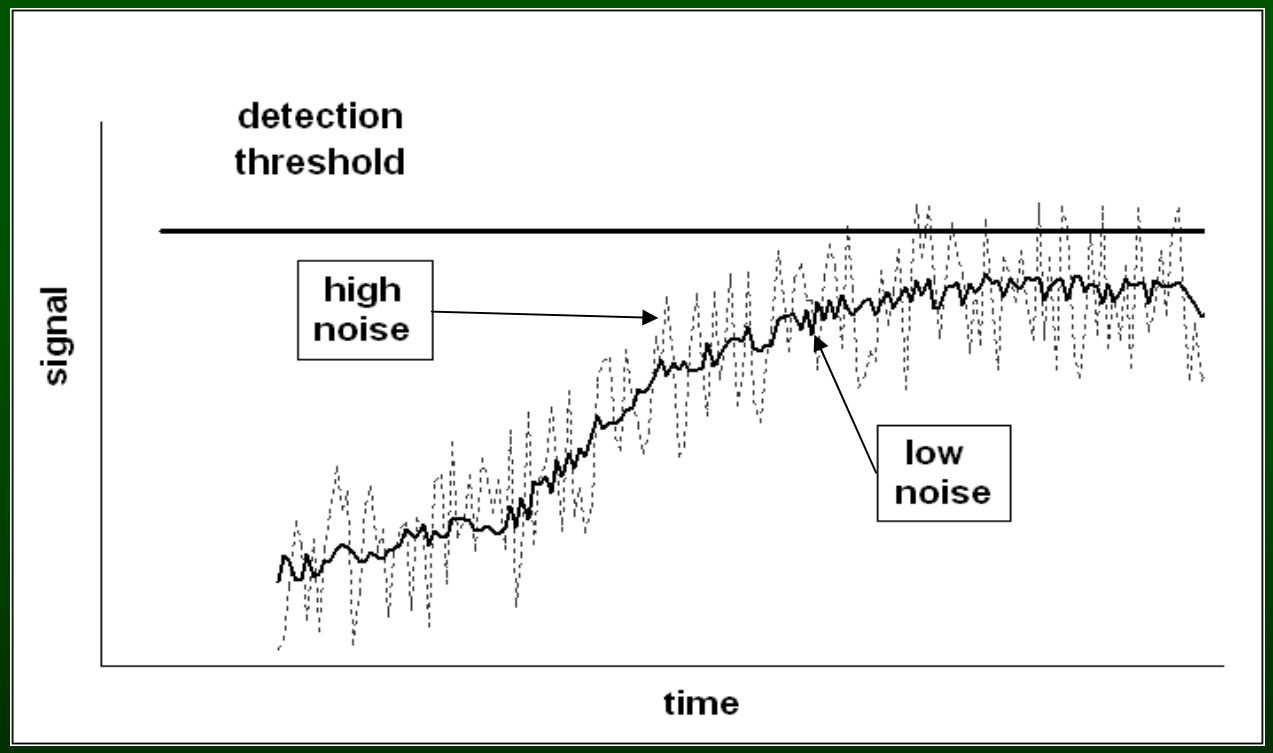
noise is bad:

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

Seminal review: Rao et al: Nature 420, 231

Noise is good: stochastic resonance

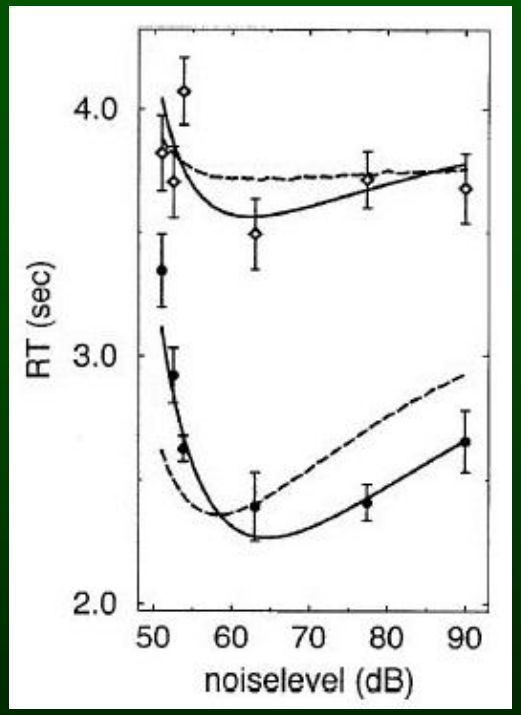
stochastic resonance: extrinsic noise
stochastic focusing: intrinsic noise



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

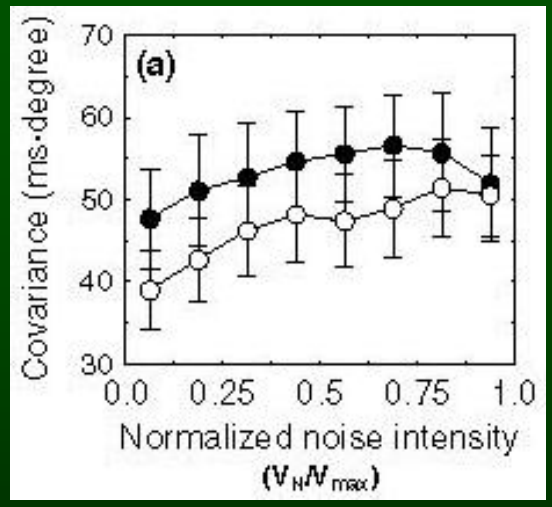
Stochastic resonance: memory retrieval, pink noise, music

response time



difficult task

easy task



1/t pink noise

white noise

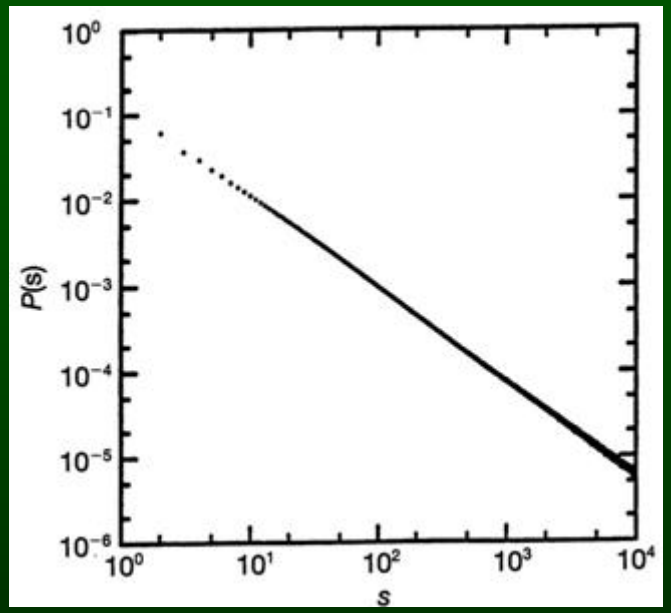
music is pink noise

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



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

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

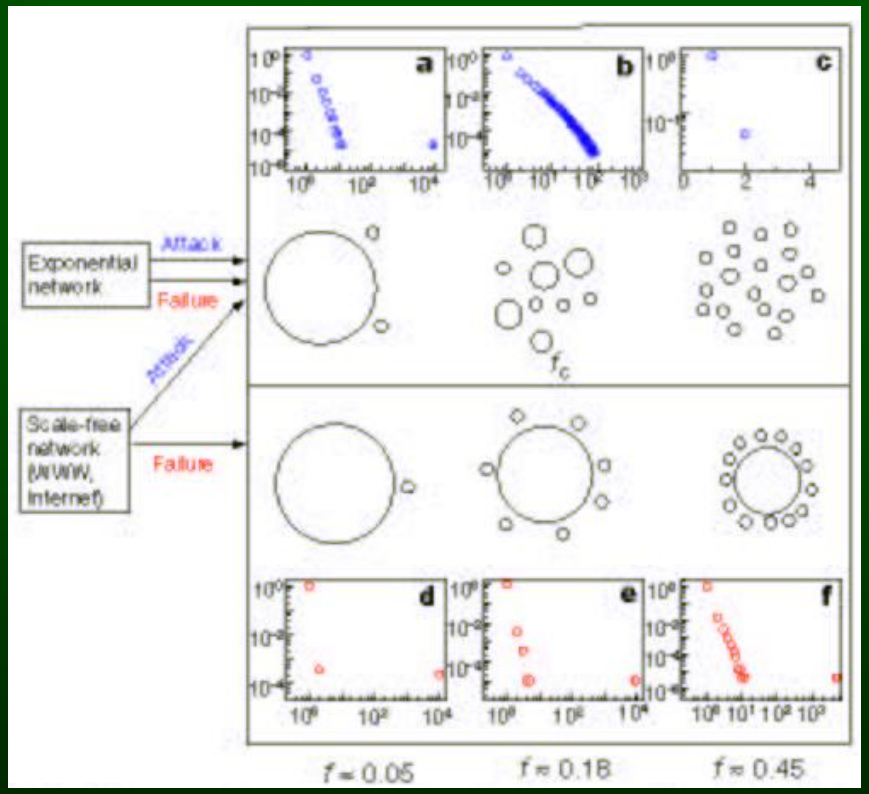
- continuously increasing tension
- partially restricted relaxation

→ avalanche

Cascading failures

March 13, 1989

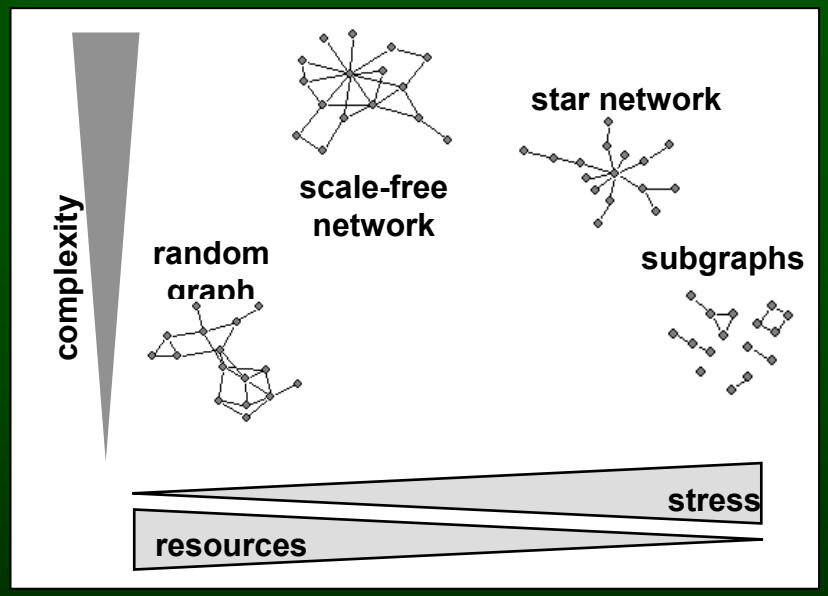
Weak points in networks

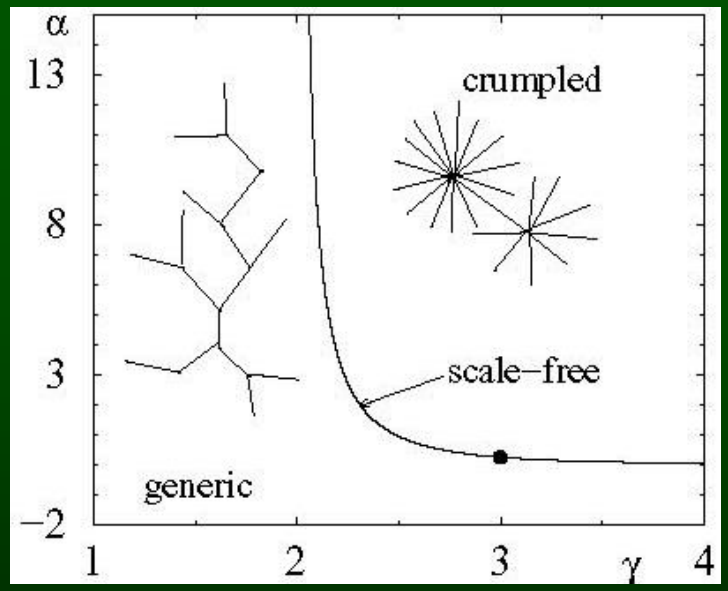


scale-free networks
are resistant against failure
but are vulnerable to attacks

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

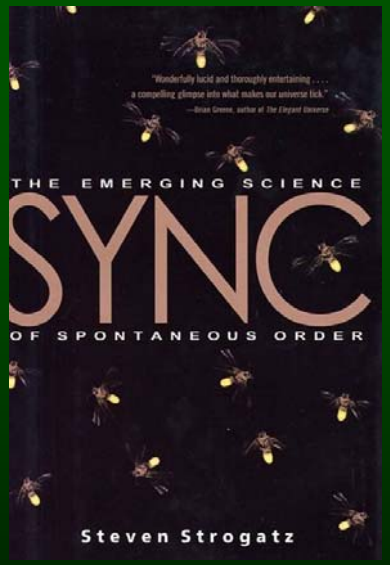
  Santa Fe Working Papers No. 200112081
- scientific quotations random → scale-free

  J. Arch. Meth. Theor. 8, 35
- communistic equality → social classes → dictatorships → war, anarchy

Sync

Huygens, 1665

longitude determination
pendulum clock
synchrony

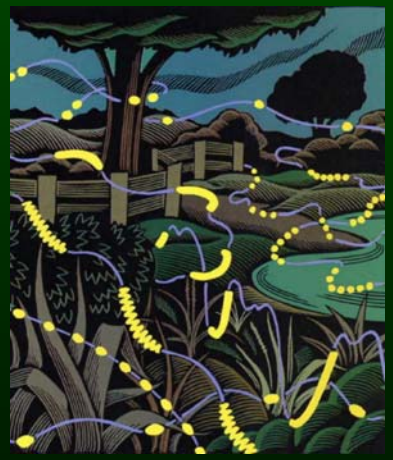


Sync: other examples

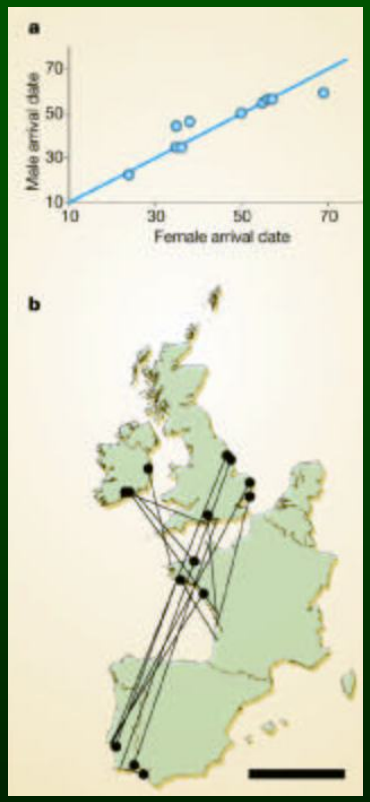
cricket

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

firefly



bird-migration



Nature 431, 646

clapping

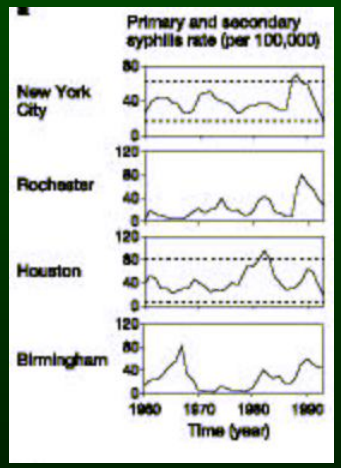
Nature 403, 849

yawning, laugh

menstruation

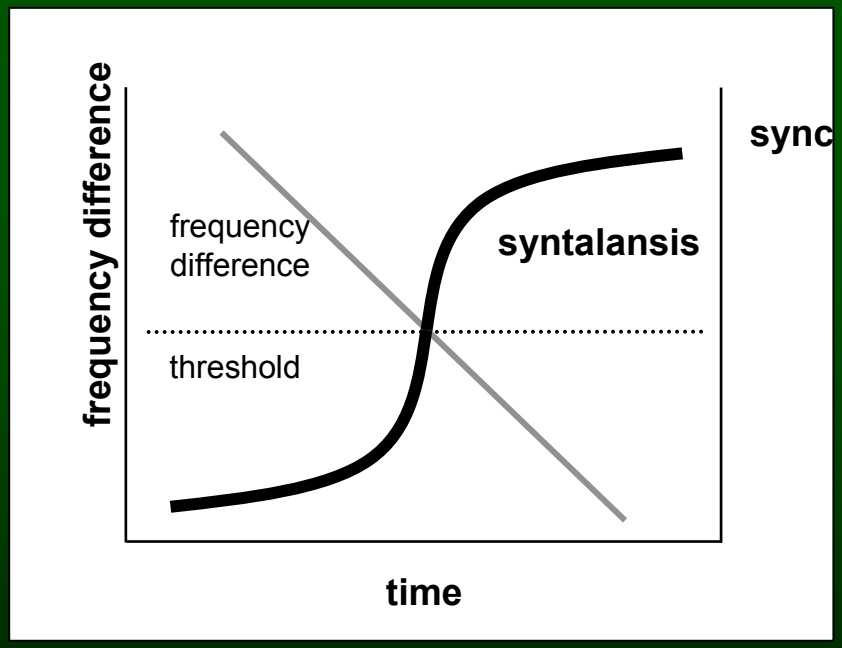
Nature 229, 244; 392, 177

syphilis



Nature 433, 417

Sync conditions



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

Differences between engineering and evolution

Property	Engineering	Evolution
development		
parts & whole		
optimization		
optimized parameters		
intermediates		
elements		
degeneracy		
unexpected changes		

Networks and stability

Part 4 – Examples for networks

Peter Csermely

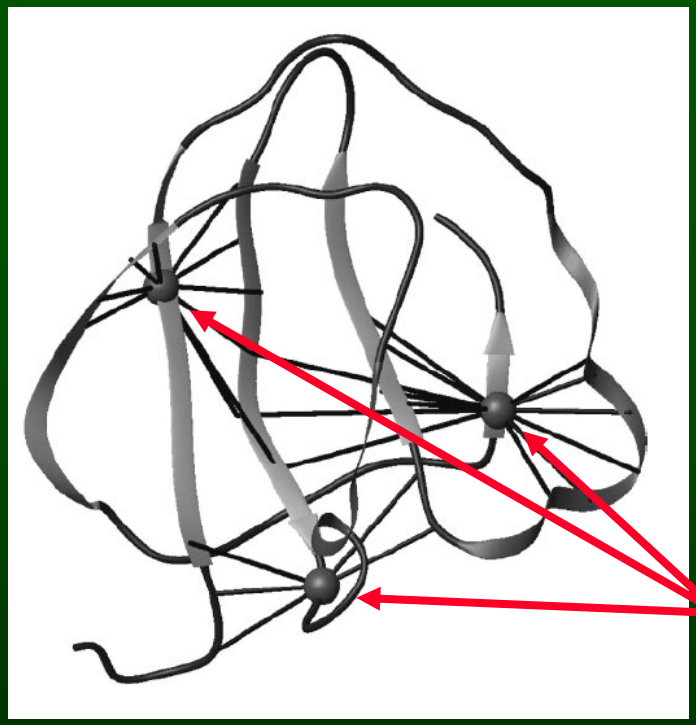
www.linkgroup.hu
csermelynet@gmail.com

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

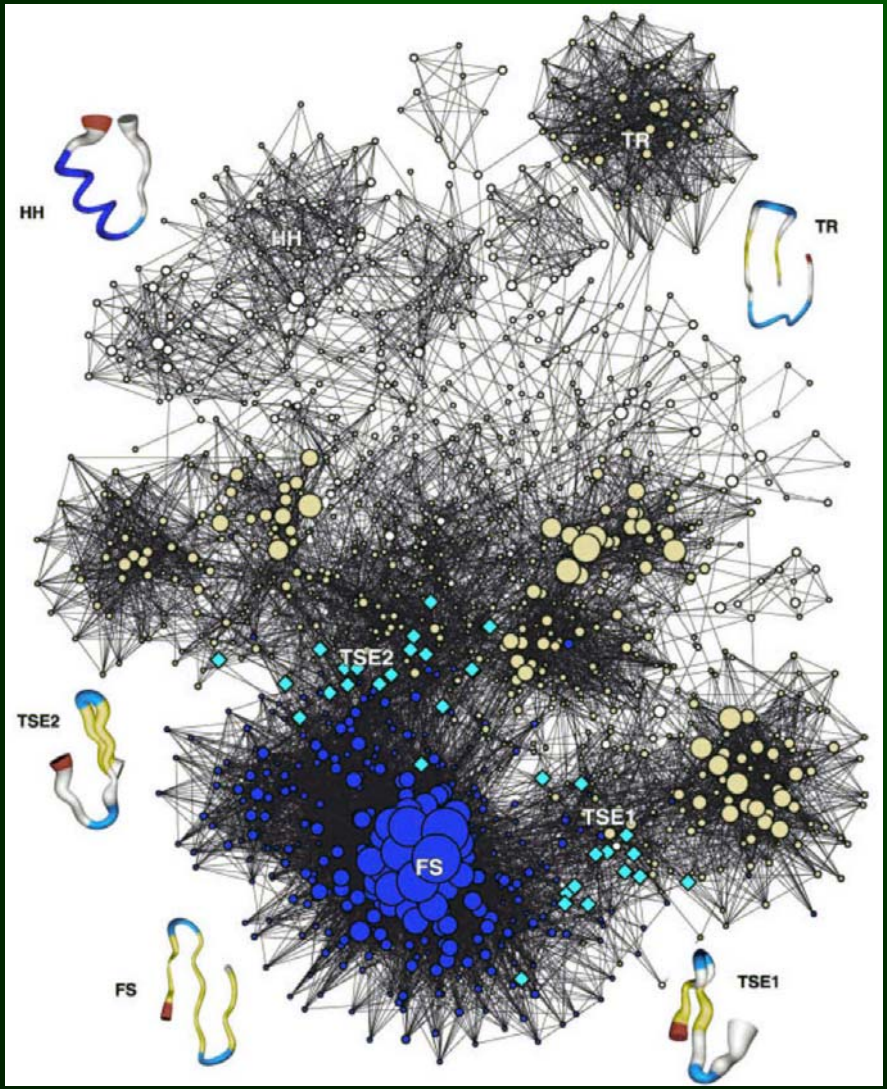
Atomic-networks

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



key atomic residues
for protein folding

key atomic residues correspond to
central elements of the residue network
in transition state

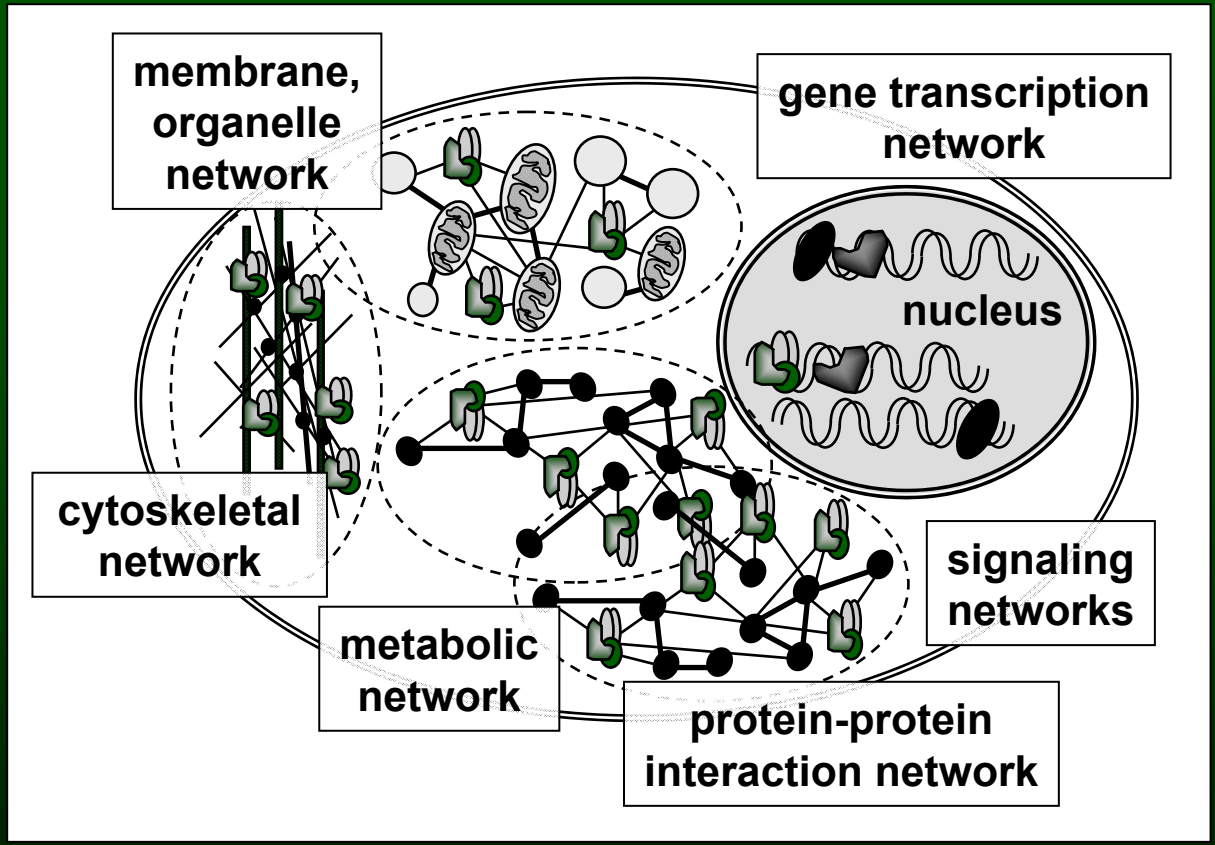


Folding networks

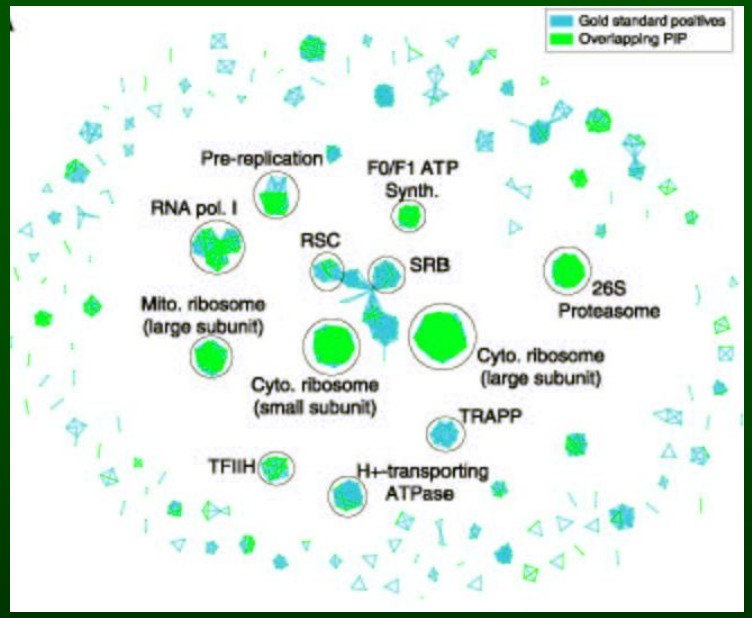
20 AA peptide
nodes: conformations
links: transitions

JMB 342, 299

Cellular networks



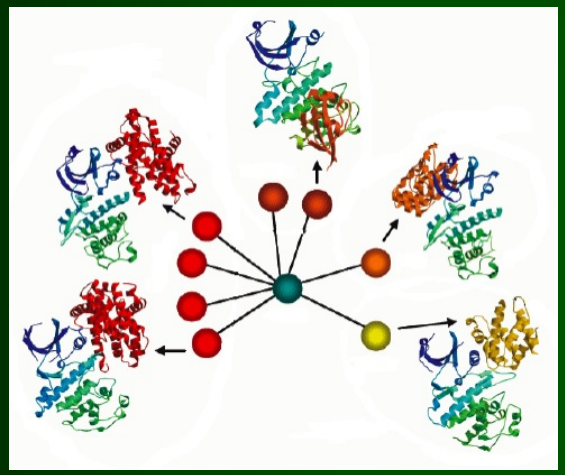
Protein interaction networks



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

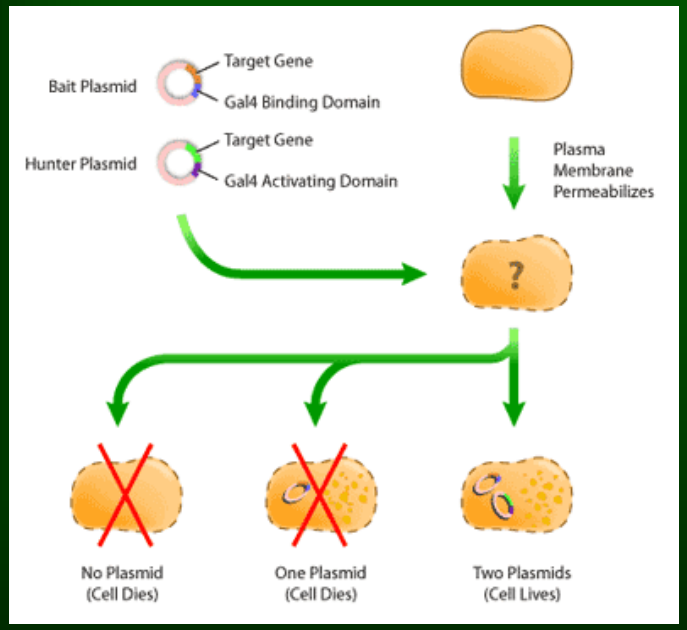
Main databases of protein-protein interaction networks

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

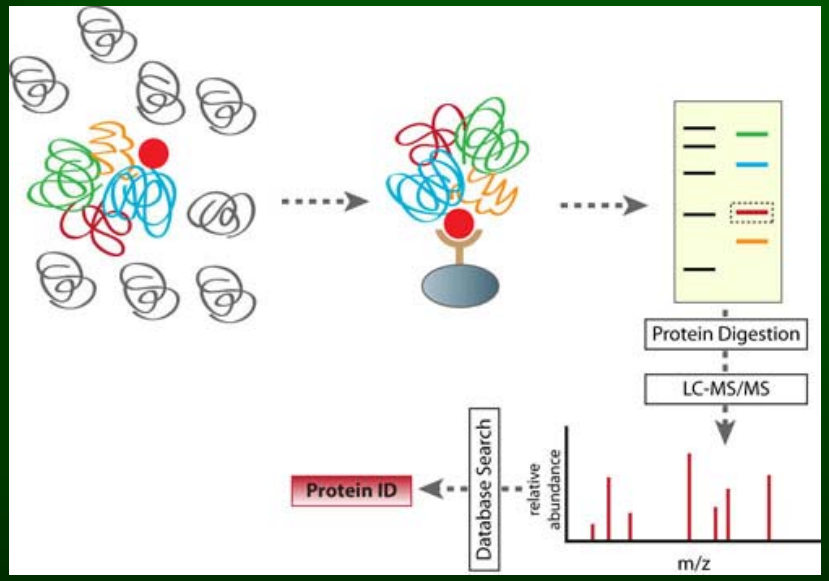
http://thebiogrid.org/ curated data from literature: v3.1.82, 288,588 edges

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.

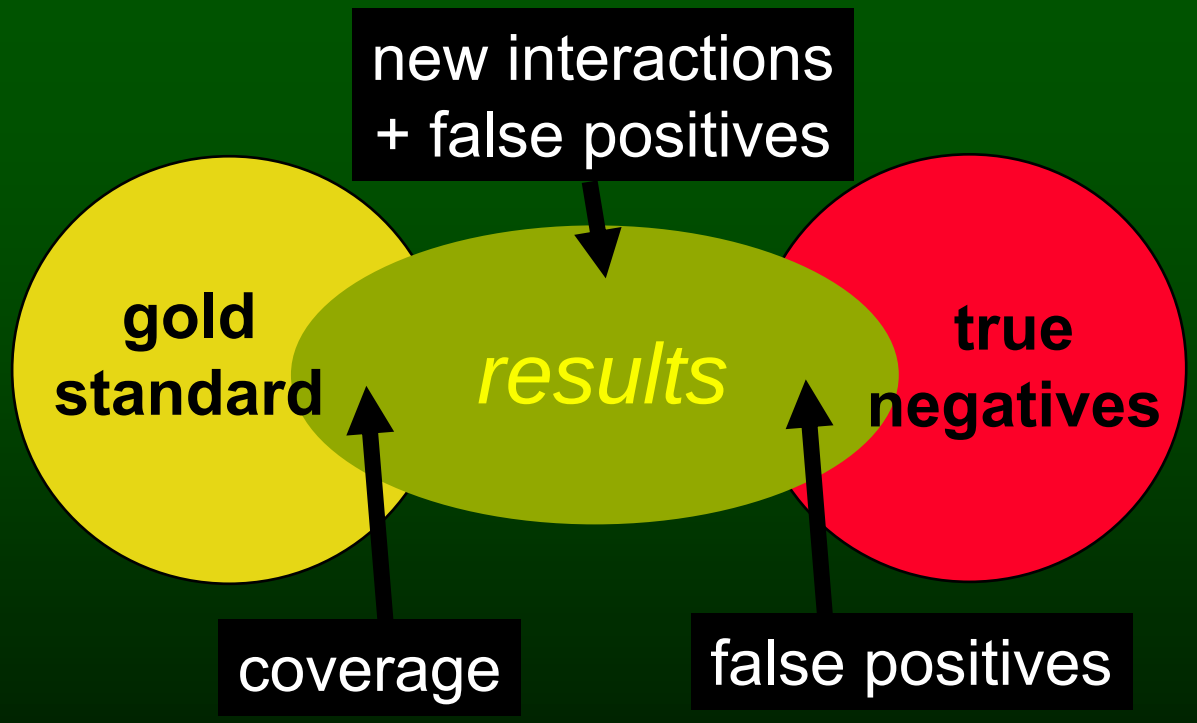


co-complex methods (e.g. affinity purification + mass spectrometry, other associating proteins/washes, lost weakly binding preys/cross-links, etc.)

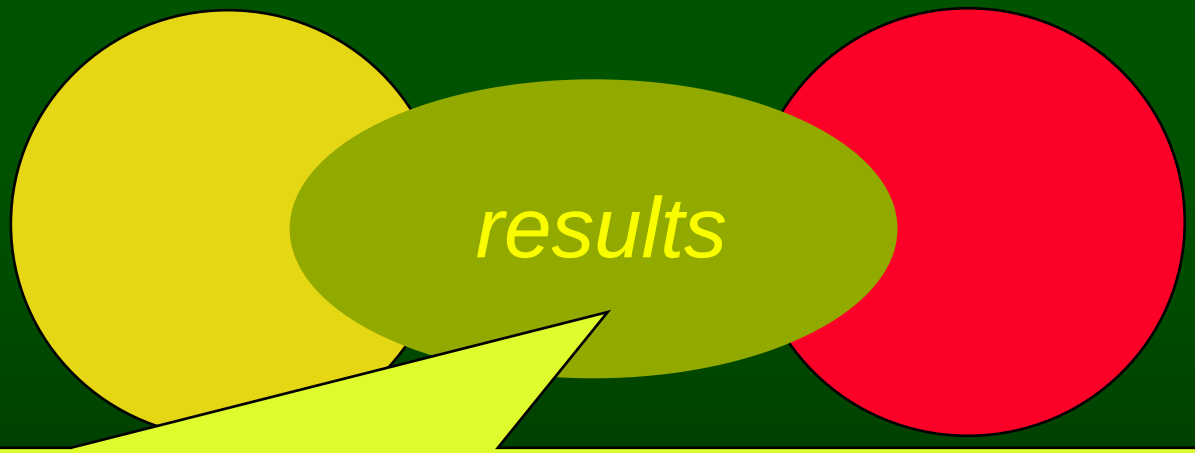
Main methods to identify protein-protein interactions III.

- 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

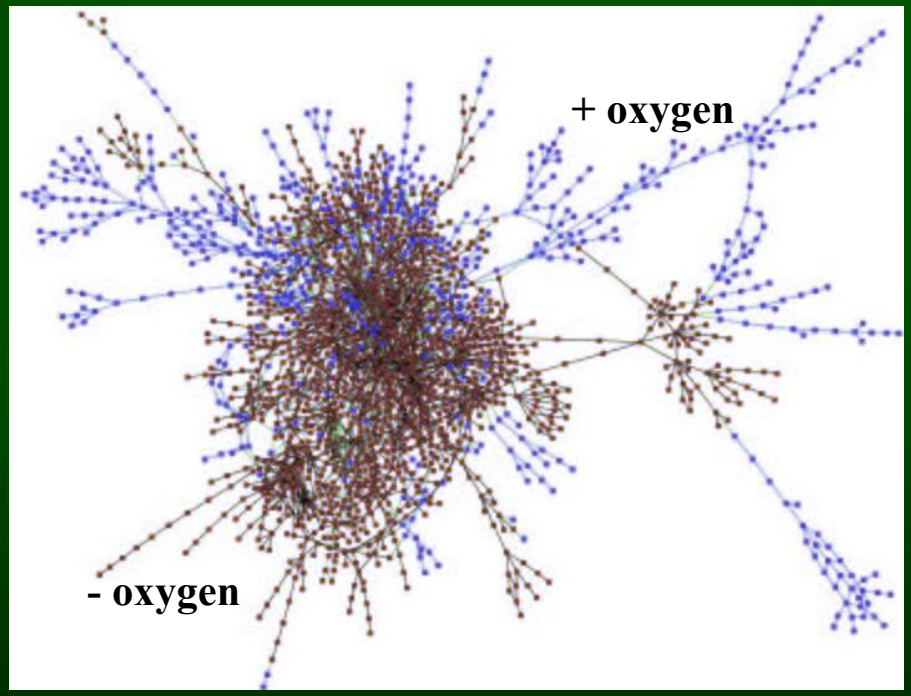


The low confidence *versus* low affinity problem



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

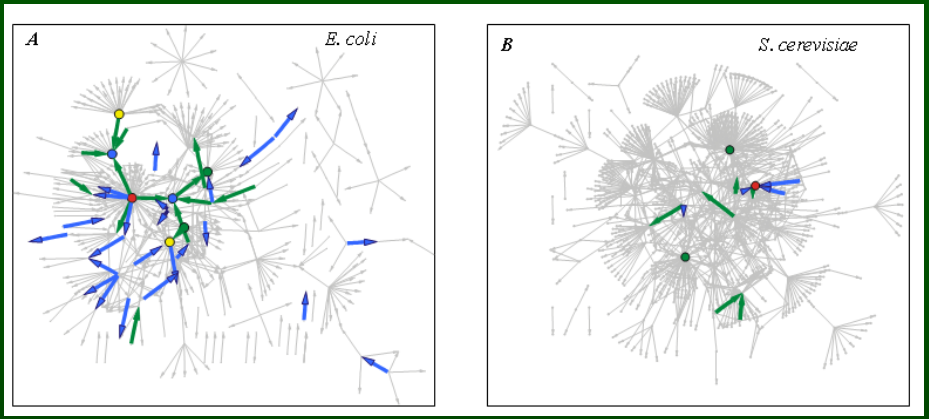
Metabolic networks



Science 311, 1764

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

Gene transcription networks

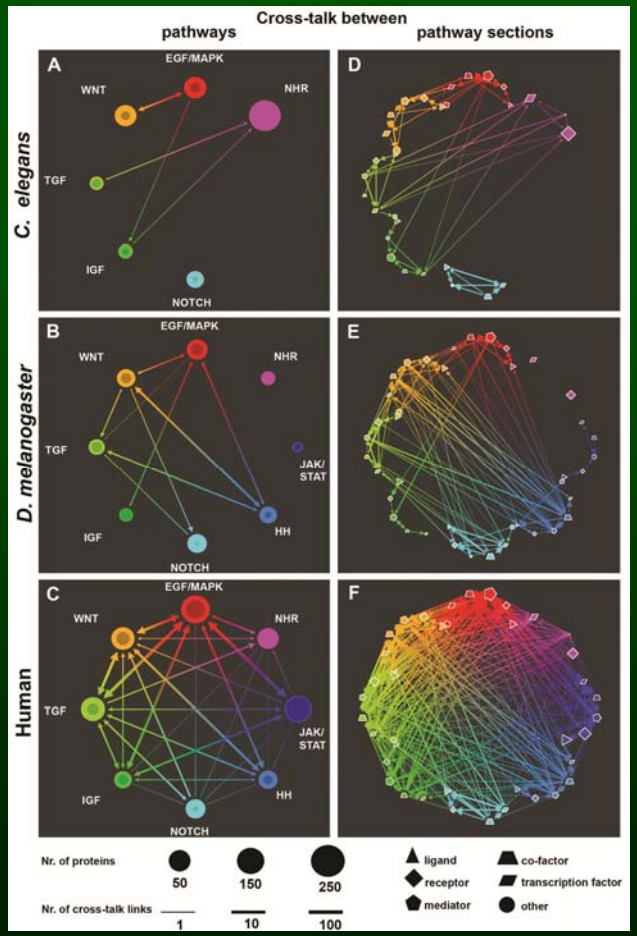


- genes (nodes)
  + transcription factors (links)
- derived from expression profile sets
- similar expression profile: interacting proteins

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

yeast	4% trfactor
C. elegans	5
human	8

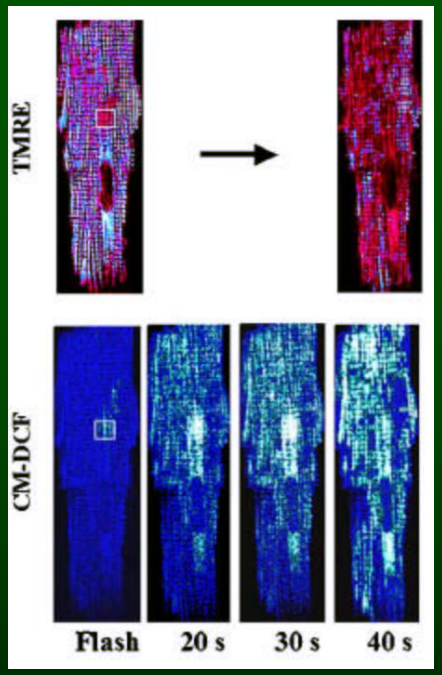
Signal transduction networks



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

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

Cell organelle networks

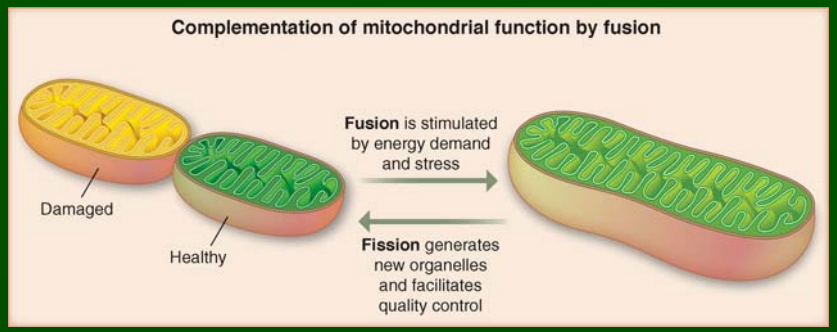


- mitochondrial net (cardiomyocyte)
- chaperone-coupling (decoupling in stress)

BBA 1762, 232

Actin-net, PNAS 101, 9636

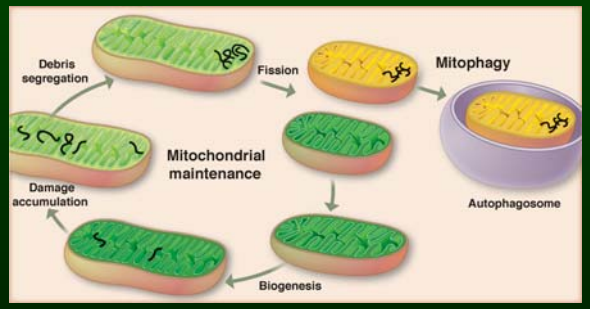
Cell organelle networks in stress

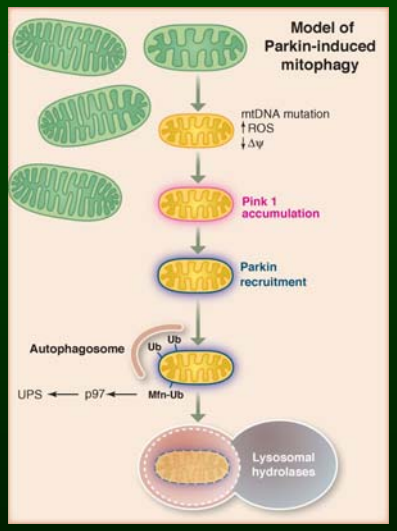


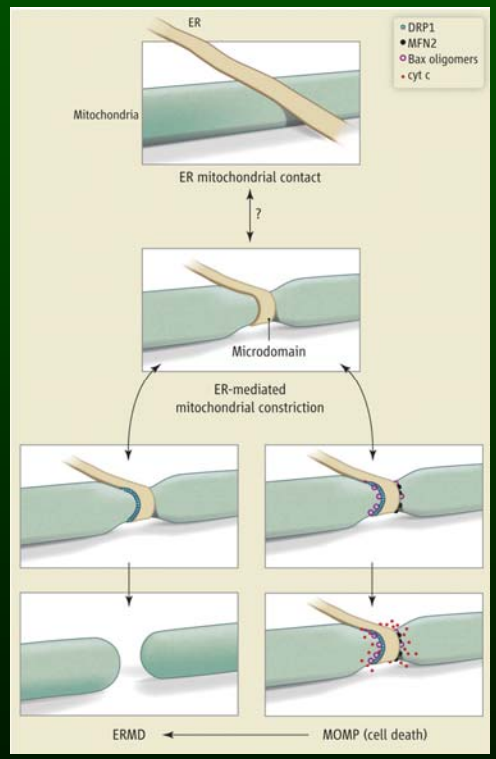
Science 337, 1052 & 1062

Why is this good?

stress

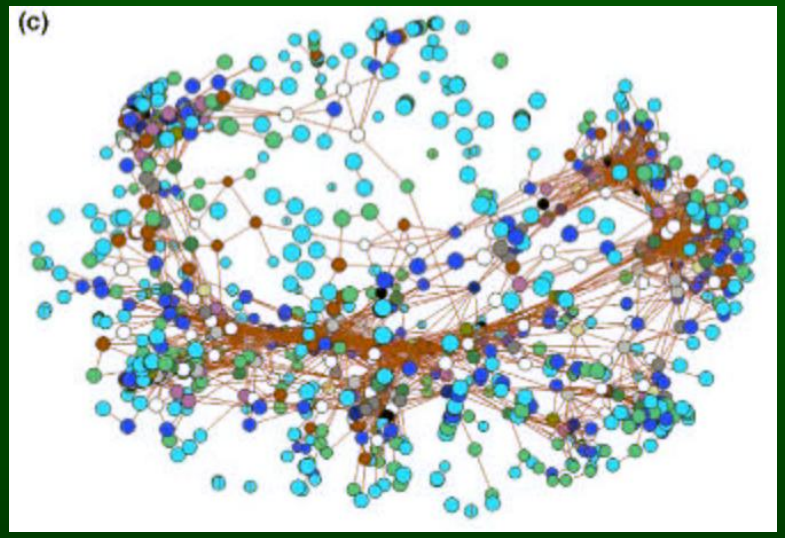






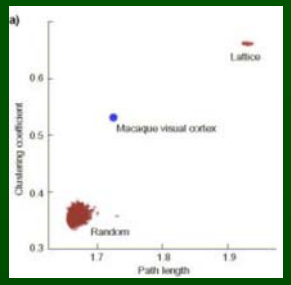
stress

Neural networks

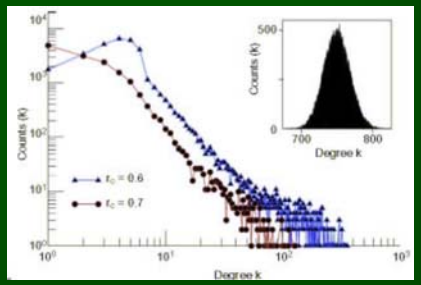


Trends Cogn. Sci. 8, 418

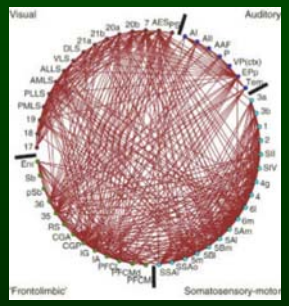
- cat brain net: neurons
- human brain billion neurons
- sync



small world

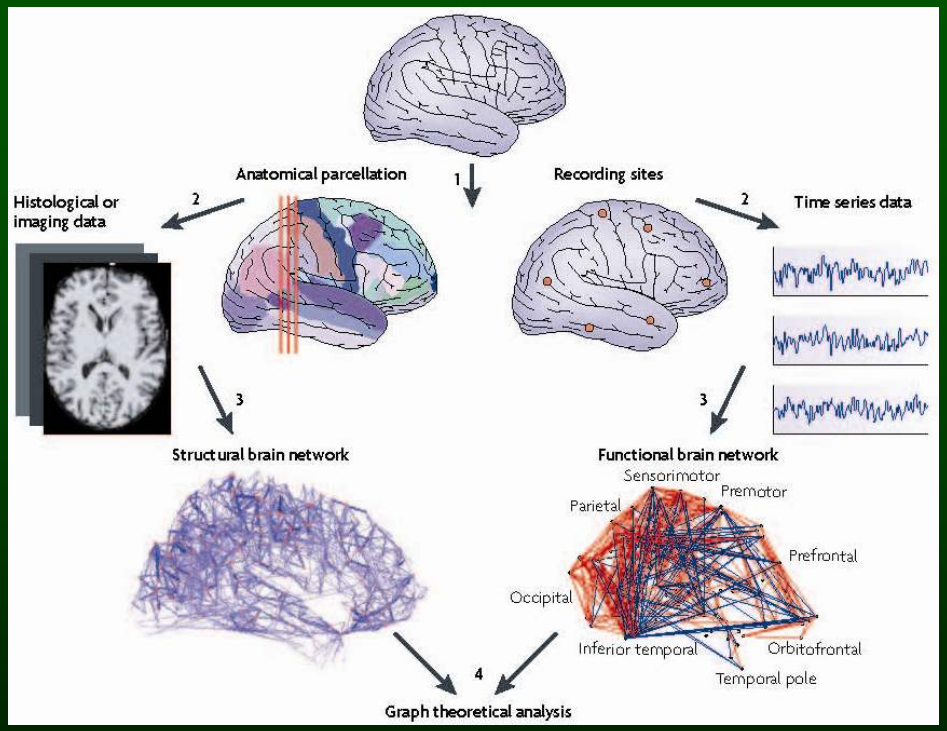


scale-free



modular

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

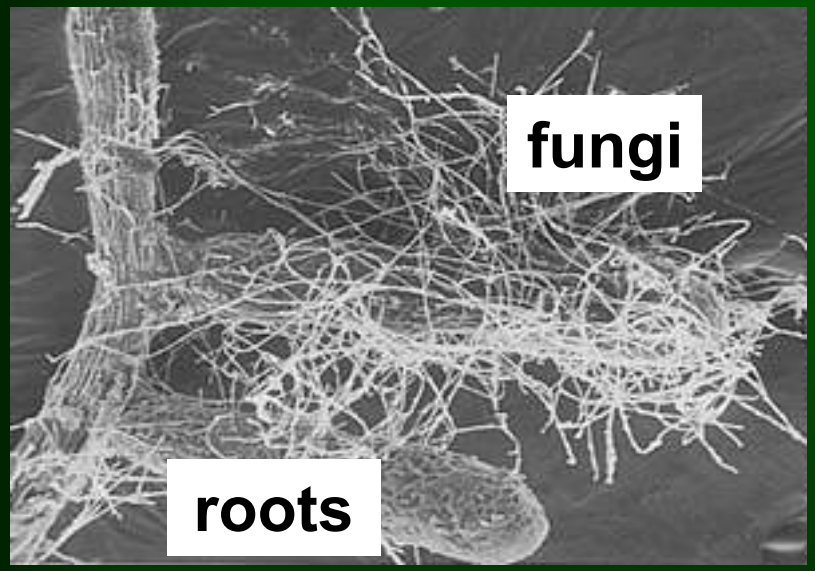
- if you learn detoxicated, you should drink before the exam
- alcoholics remember to hidden liquor or money only when detoxicated again
  (Science, 163, 1358 –1969 –)
- divers, medical students etc.

Greater self-complexity buffers stress

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

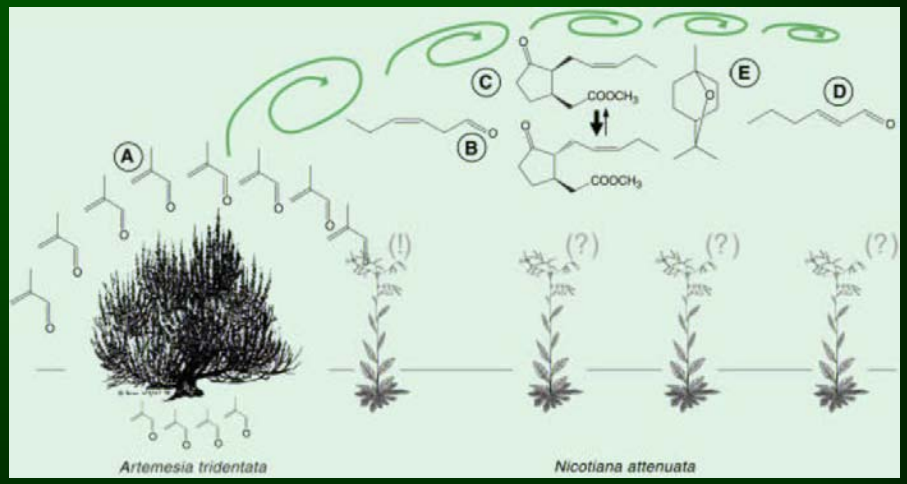
Linville, J. Pers. Soc. Psych. 52, 663

Wood-wide web



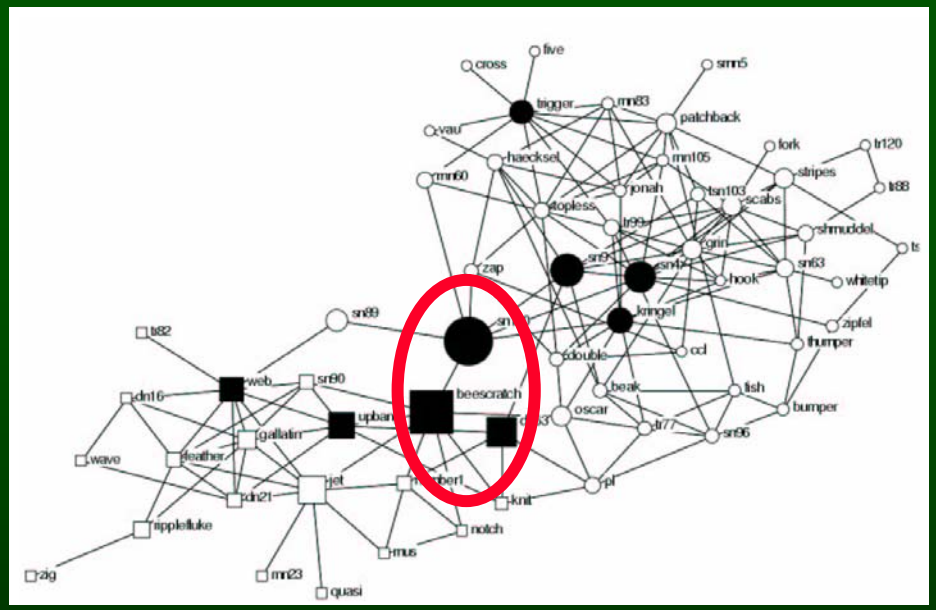
mycorrhiza
100 m/g soil

danger signals elicit
stress conditioning



Science 311, 812

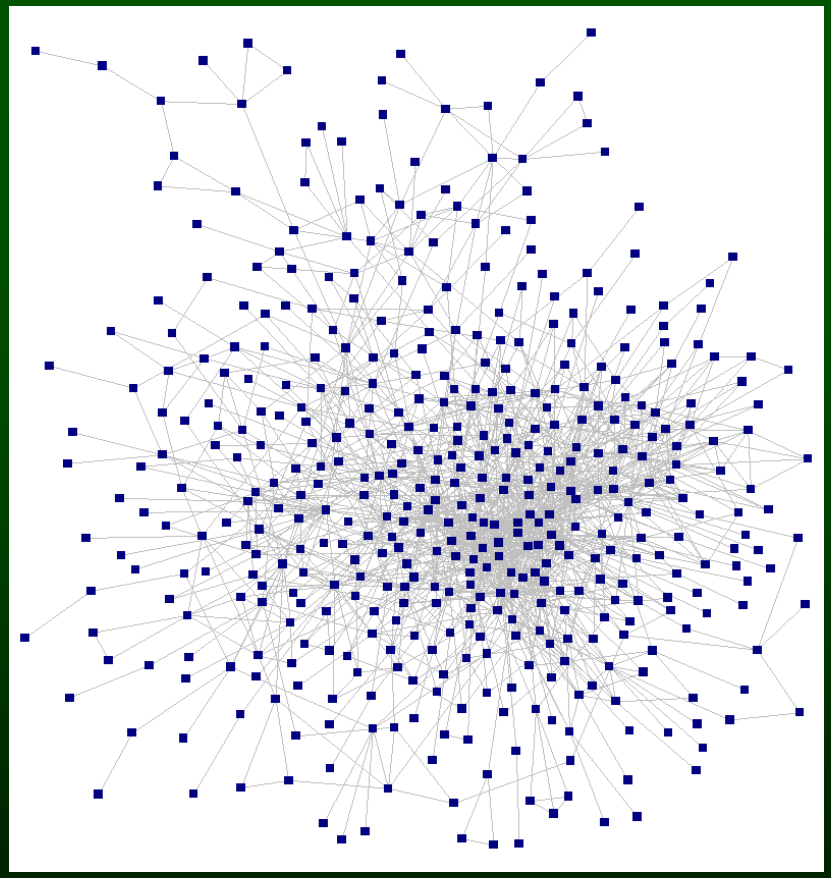
Dolphin networks



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

small worlds, bridges, VIP-s

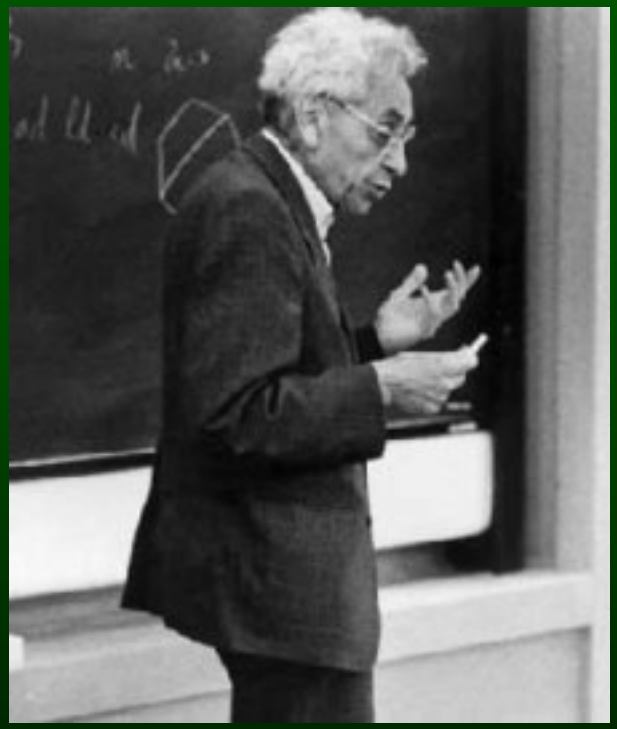
The Erdős-net



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

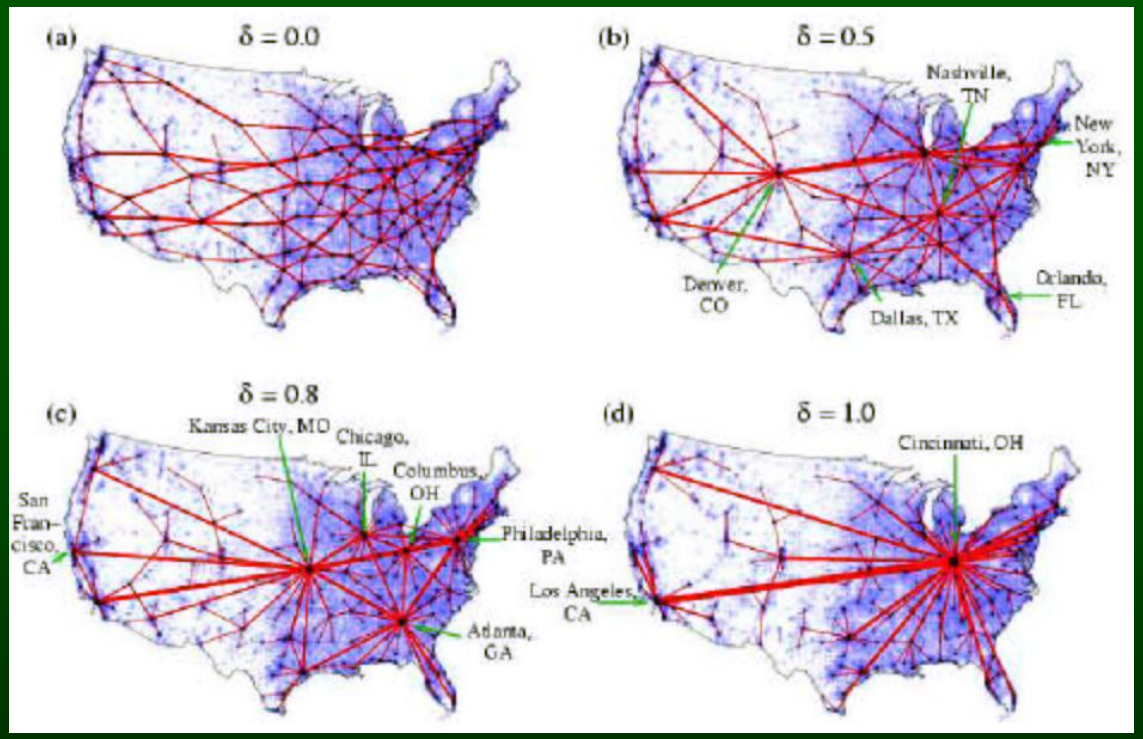
Where is Erdős?

Erdős is already in another dimension...



Pál Erdős
1913-1996

Traffic networks

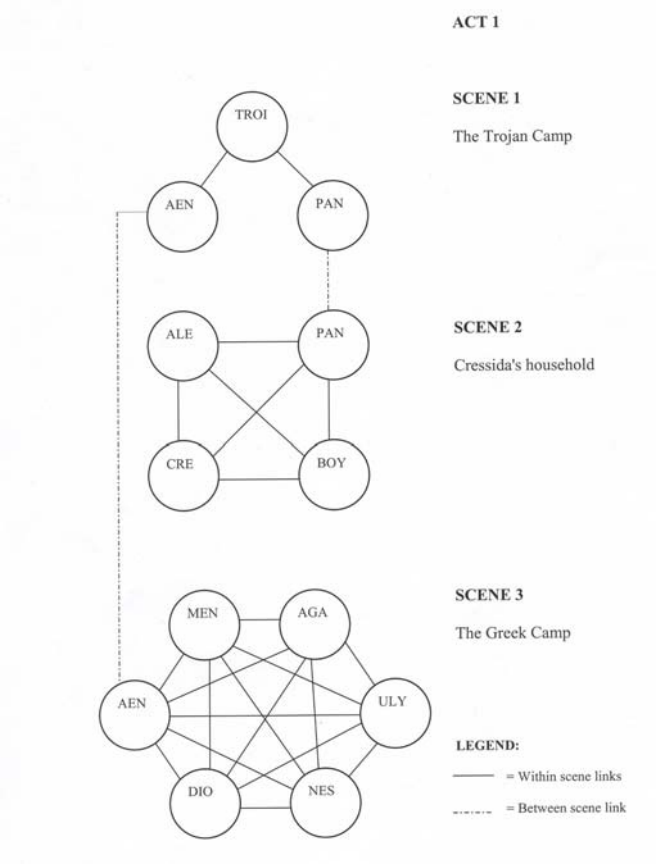


PRE 74:016117

optimal US-traffic net with increasing costs of flight changes

Drama-scenes

Shakespeare: Troilus and Cressida

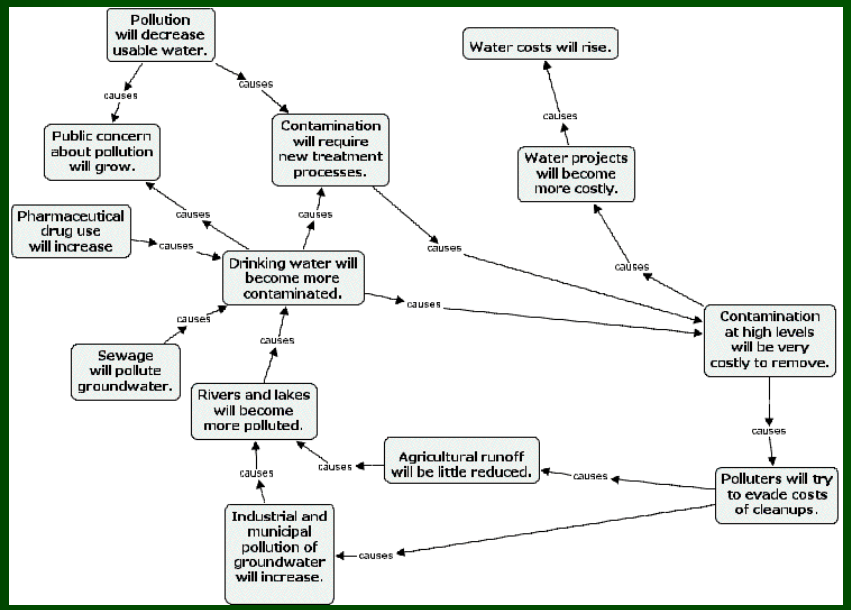


weak links connect and stabilize the scenes

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

social dimensions
social circles
catharsis – relaxation
congitive dimensions – masterpieces

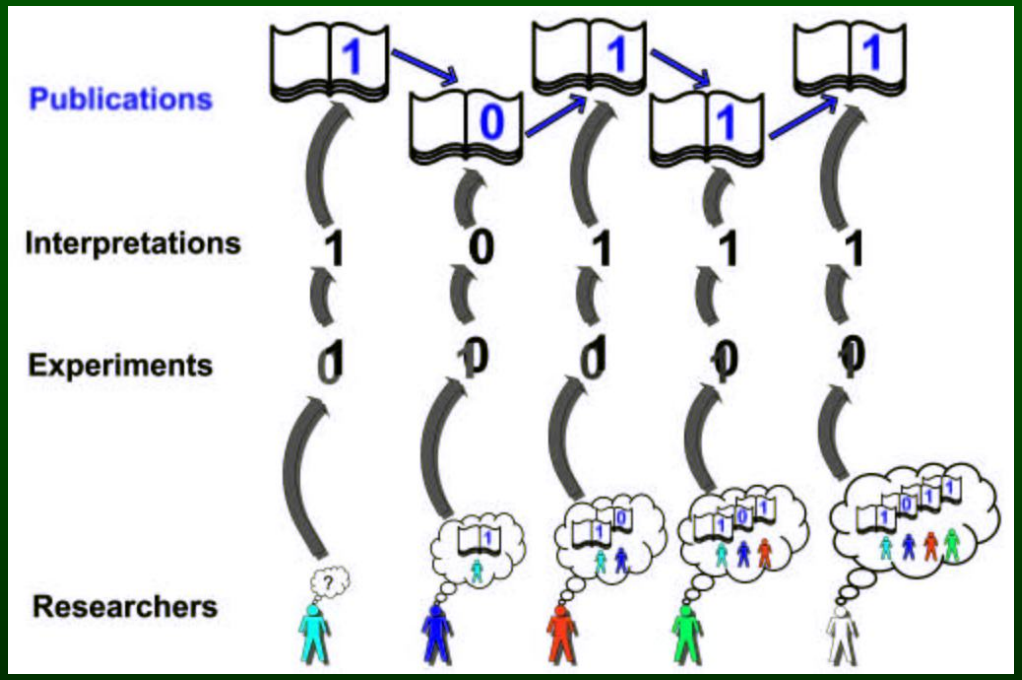
Important predictions are hubs



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

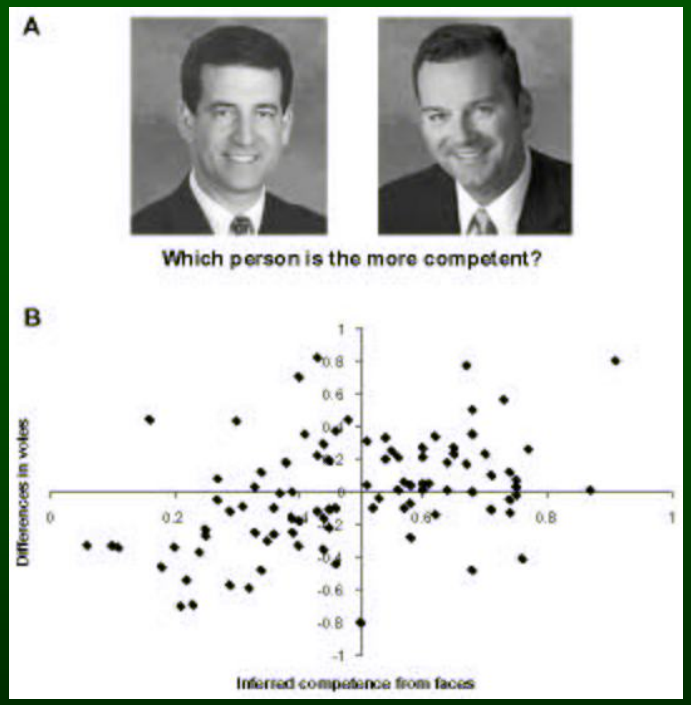


PNAS 103, 4940

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

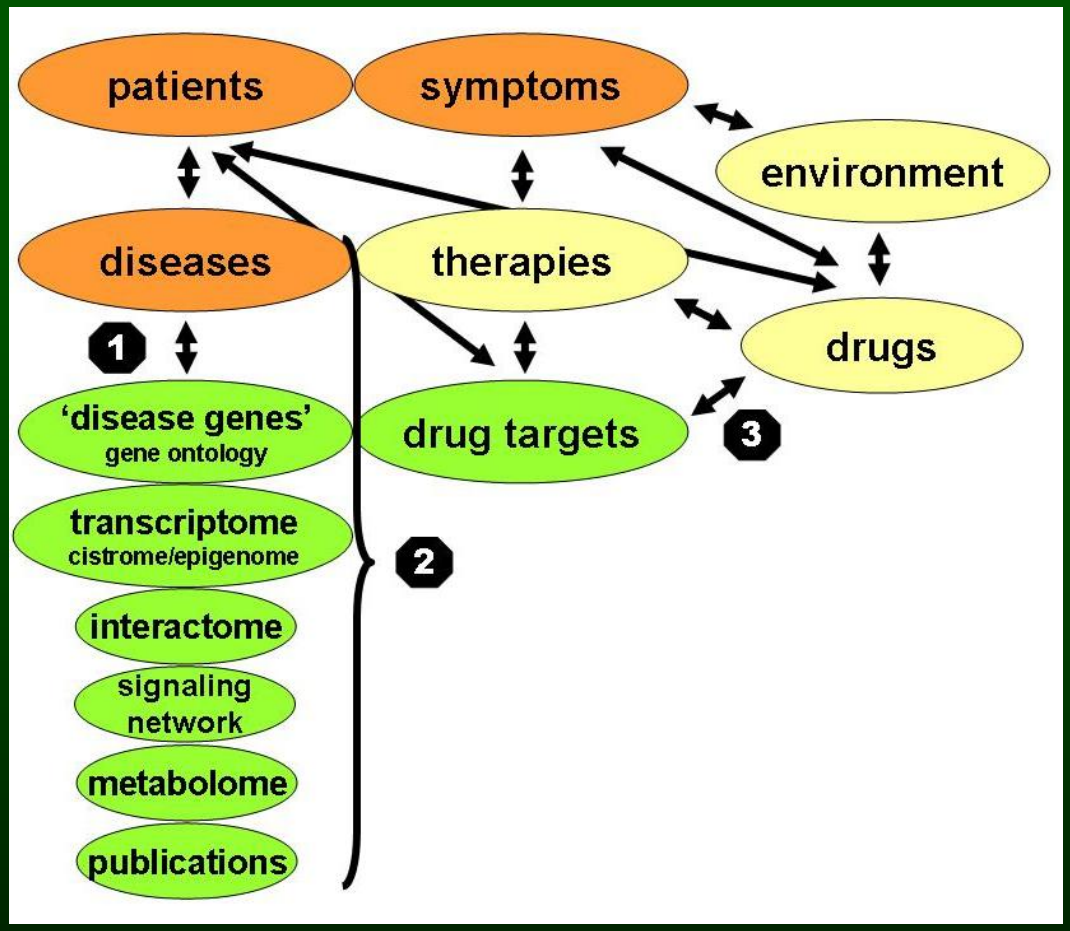
Networks and stability

Part 5. – Networks and drug design

Peter Csermely

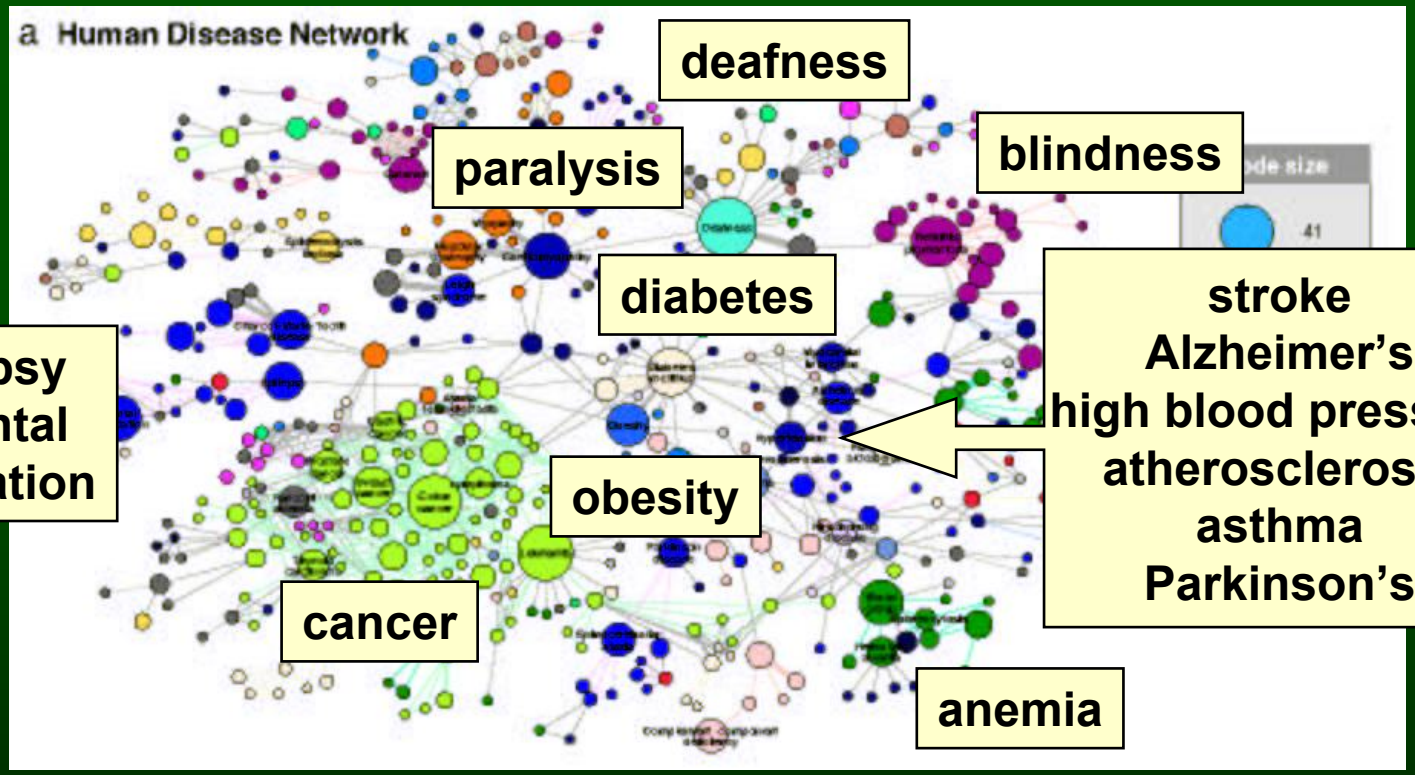
www.linkgroup.hu
csermelynet@gmail.com

Drug-related networks



Csermely *et al*, Pharmacol & Therap 138, 333

Disease network

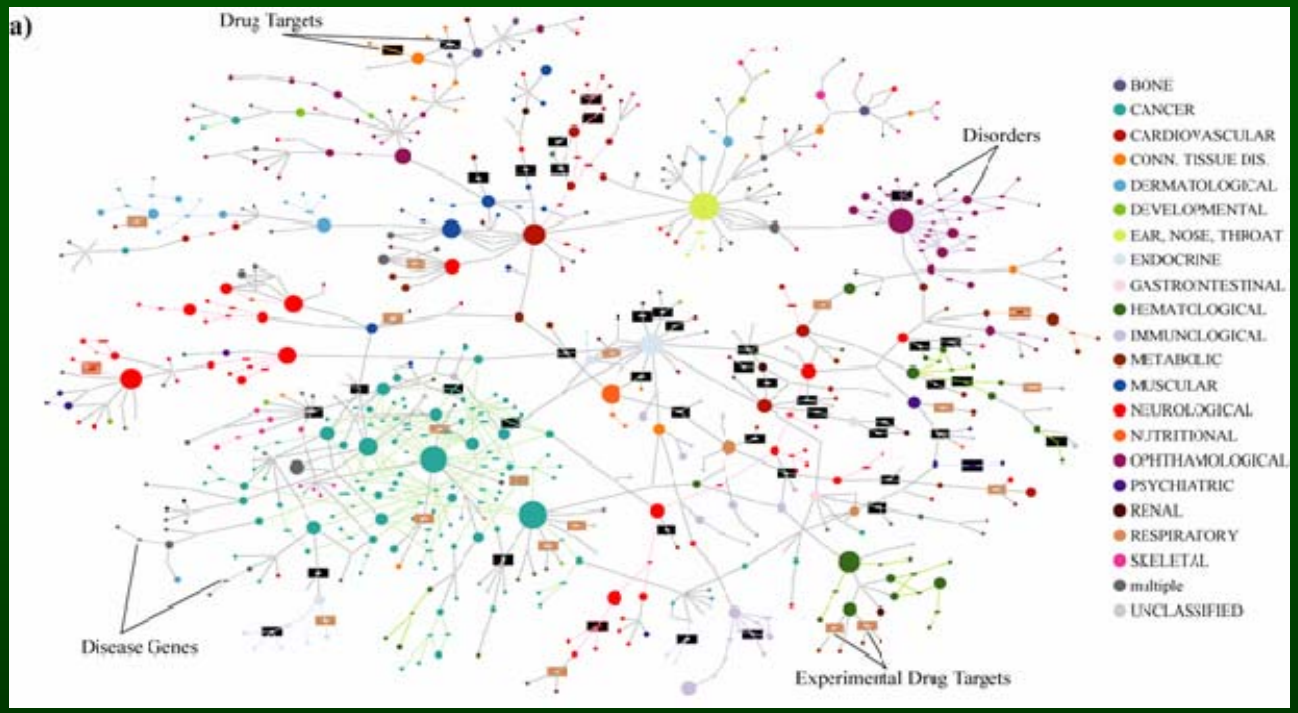


Goh et al., PNAS 104:8685

1,284 diseases & 1,777 related genes

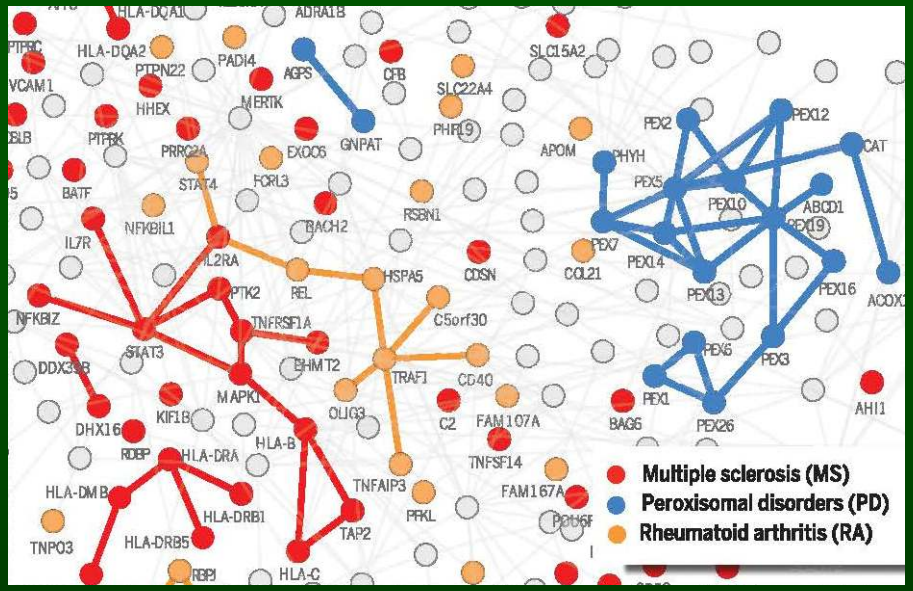
link between two diseases: if they have a common gene

Drug targets on the disease network



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

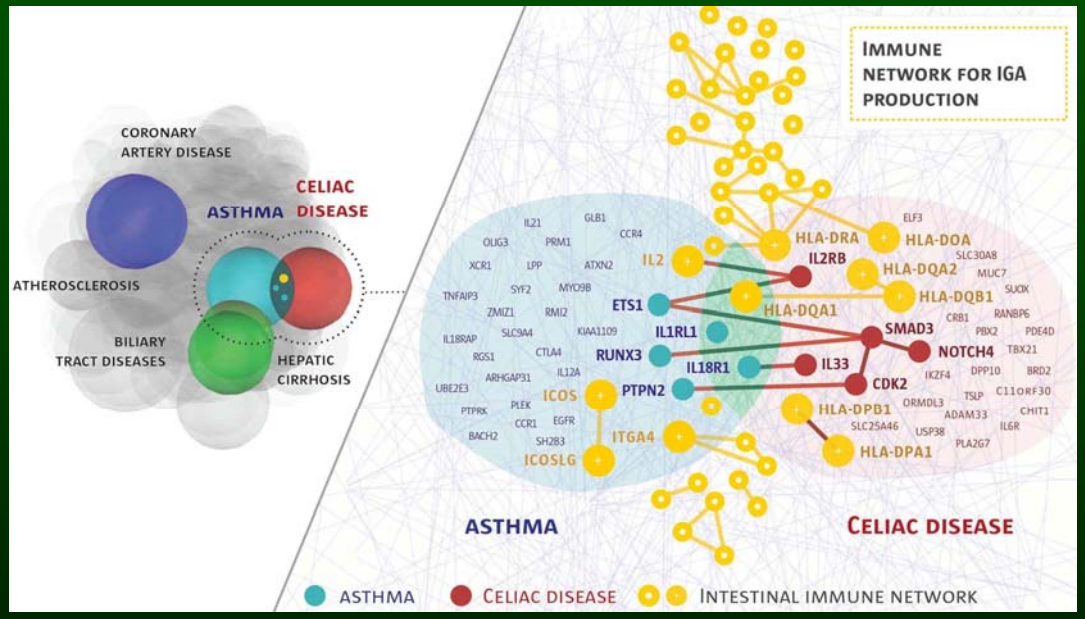
Diseasome network 1.



Menche et al., Science 347:841

disease-related proteins form overlapping modules in the human interactome

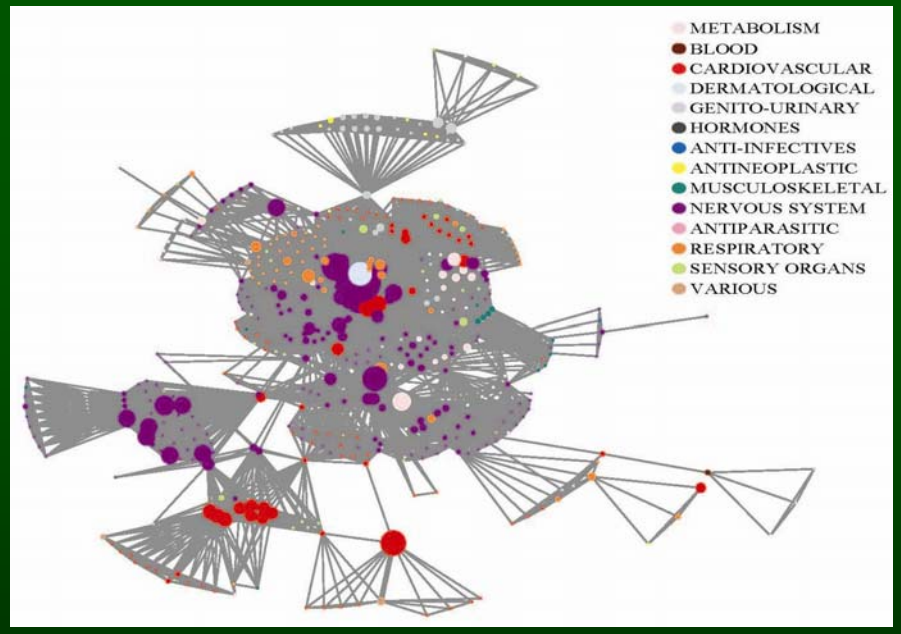
Diseasome network 2.



Menche et al., Science 347:841

disease-related proteins form overlapping modules in the human interactome

Drug network

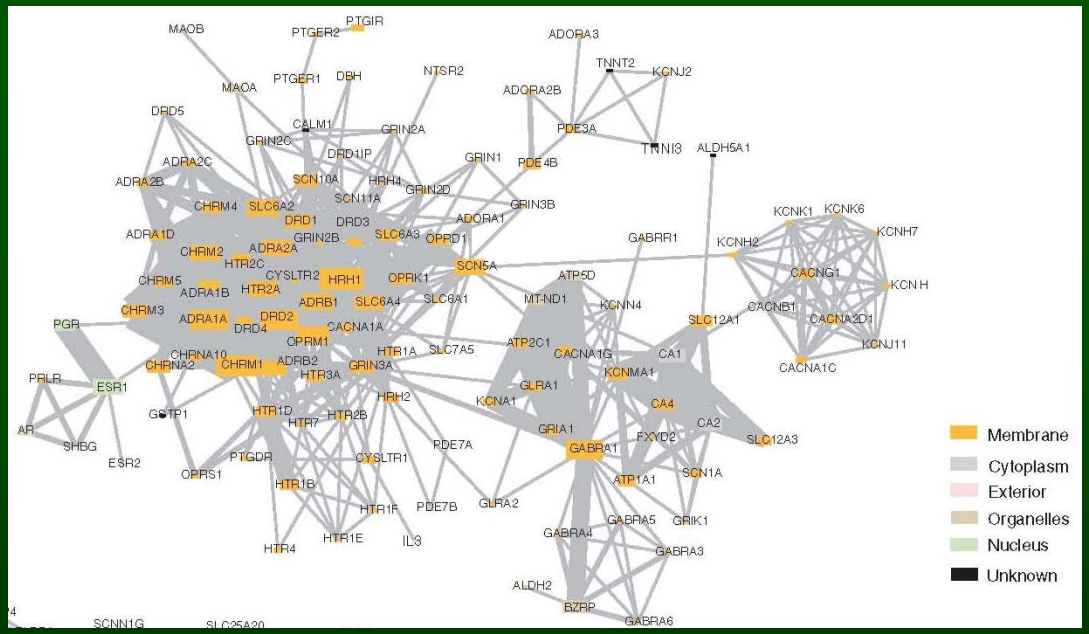


Yildirim et al., Nat. Biotech. 25:1119

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

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

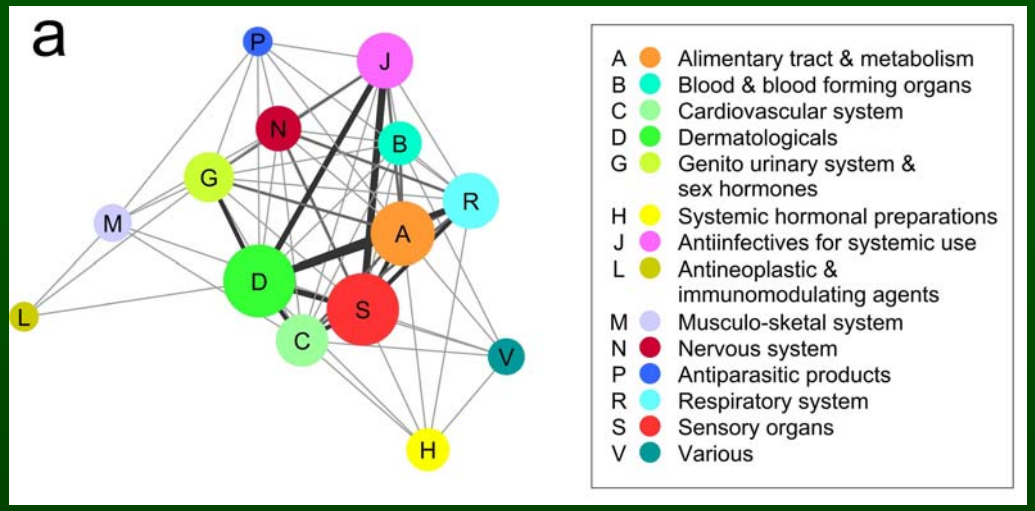
The reverse: drug target network



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

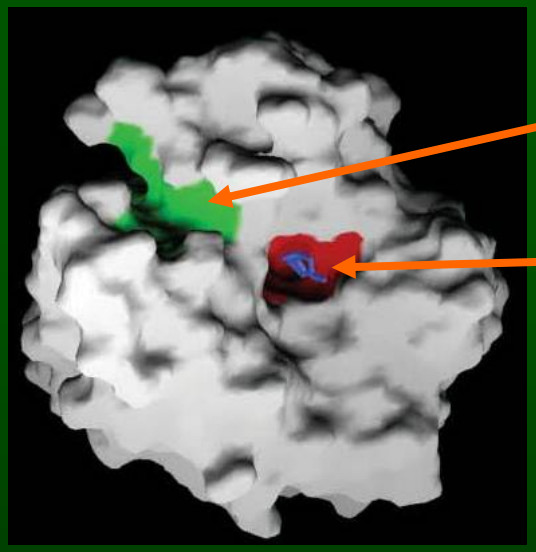
Therapy-network



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

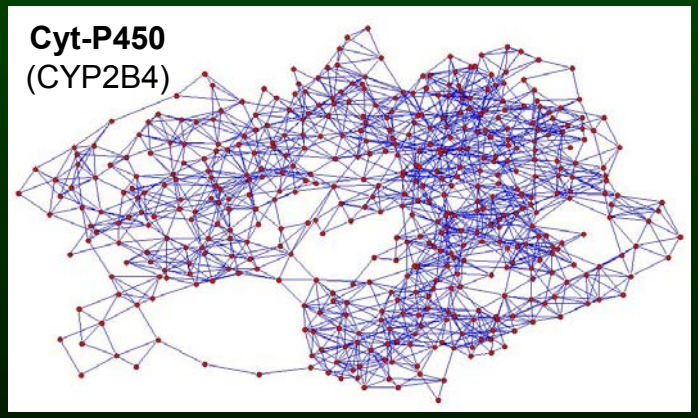


large but
shallow cavity

drug binding

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

Nayal & Honig, Proteins 63:892



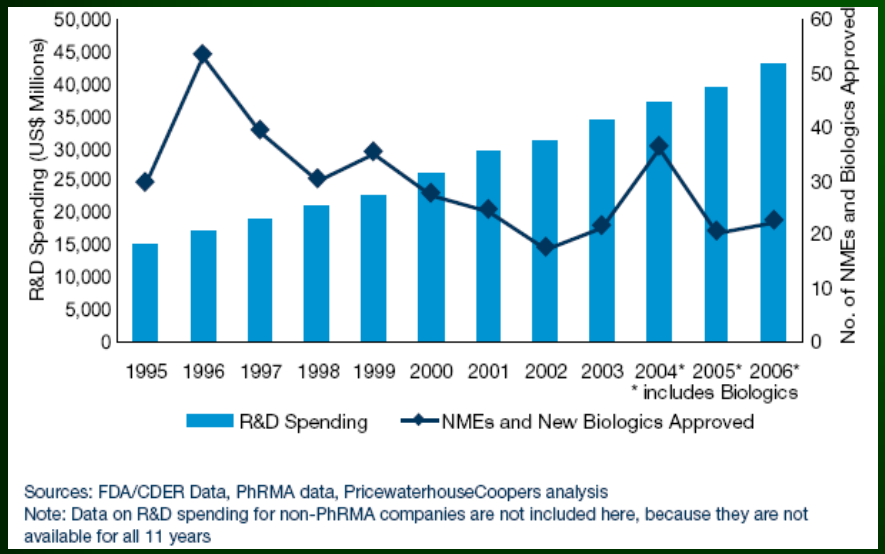
Csermely, TiBS 33:569

How would you identify here cavities?

structural holes:
missing links and nodes

Drug target crisis

New, active drug ingredients as expenditure increased

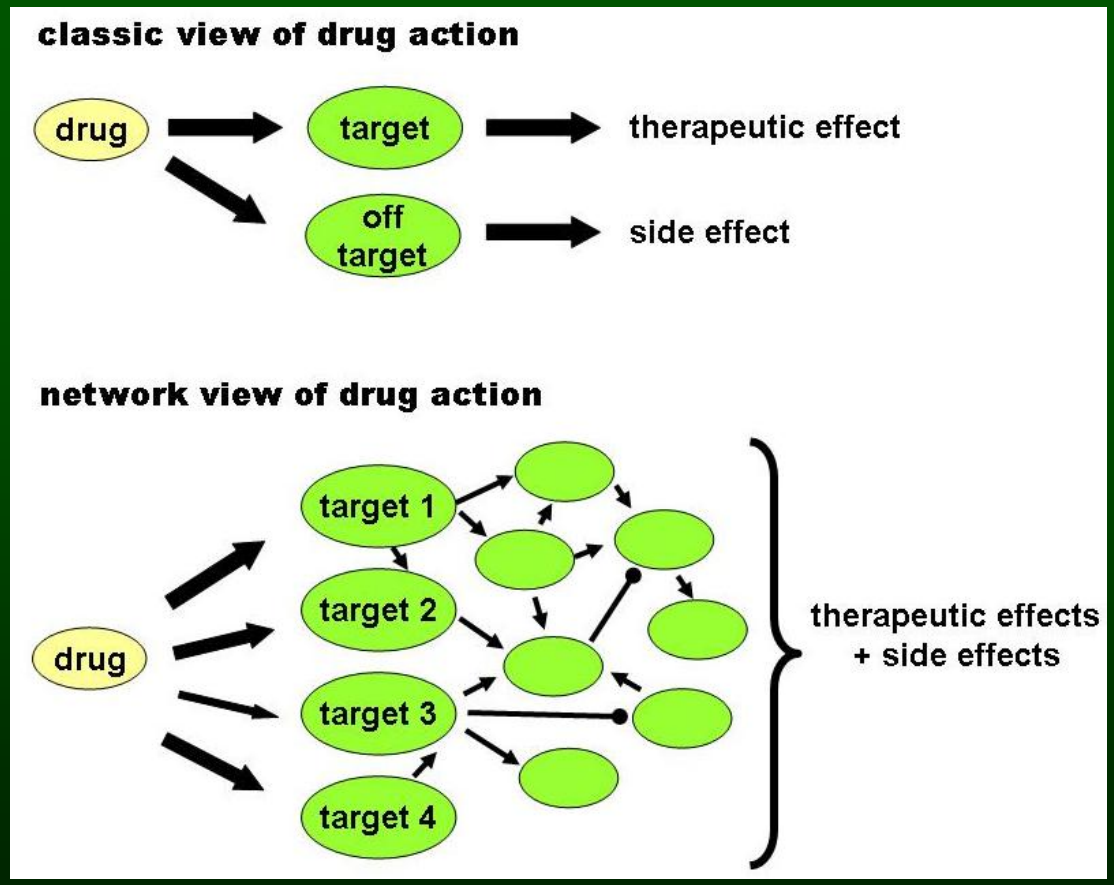


Csermely *et al*, Pharmacol & Therap 138, 333

Drug targets

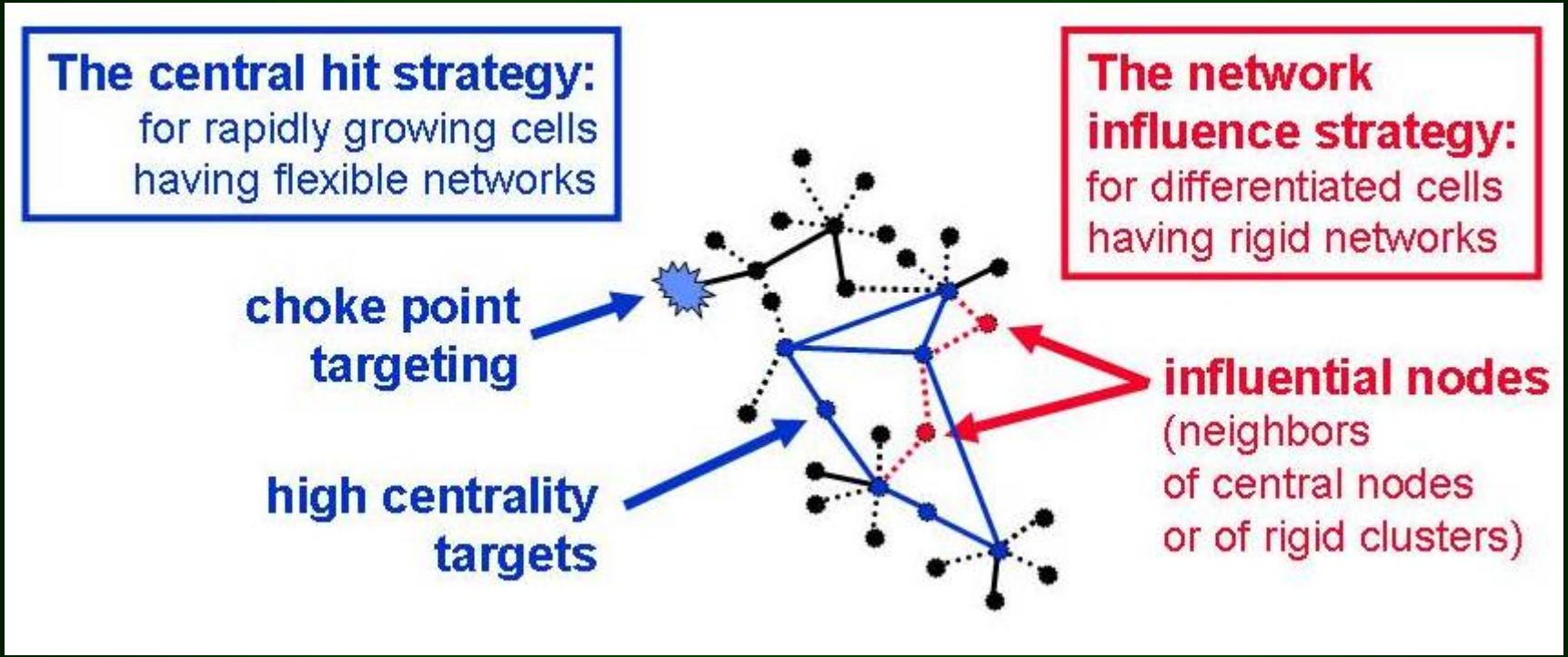
Human genome: ~30,000 genes
~100,000 proteins
Modifying ligands: 836 proteins
From this drug-like: 529
Approved: 394

Classic and network views of drug action



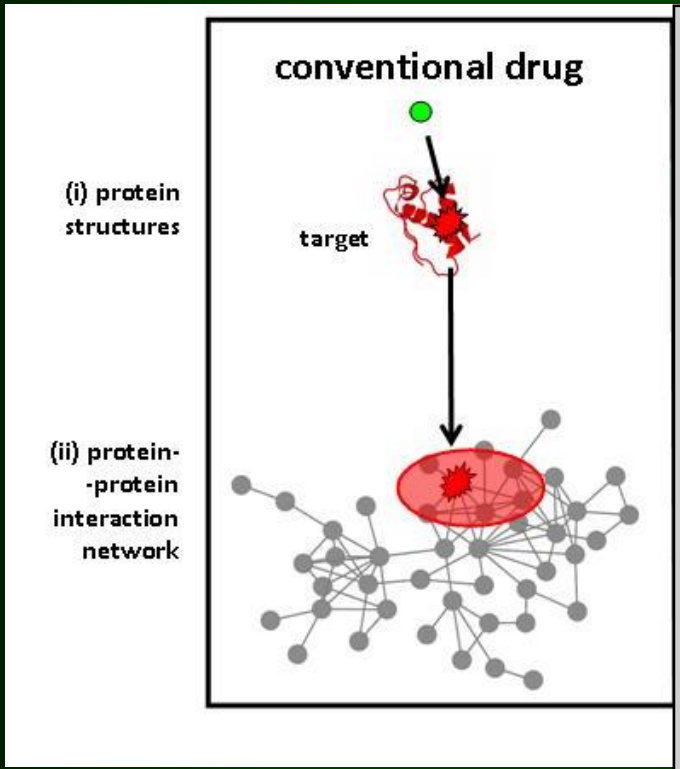
Csermely *et al*, Pharmacol & Therap 138, 333

Drug design strategies I.

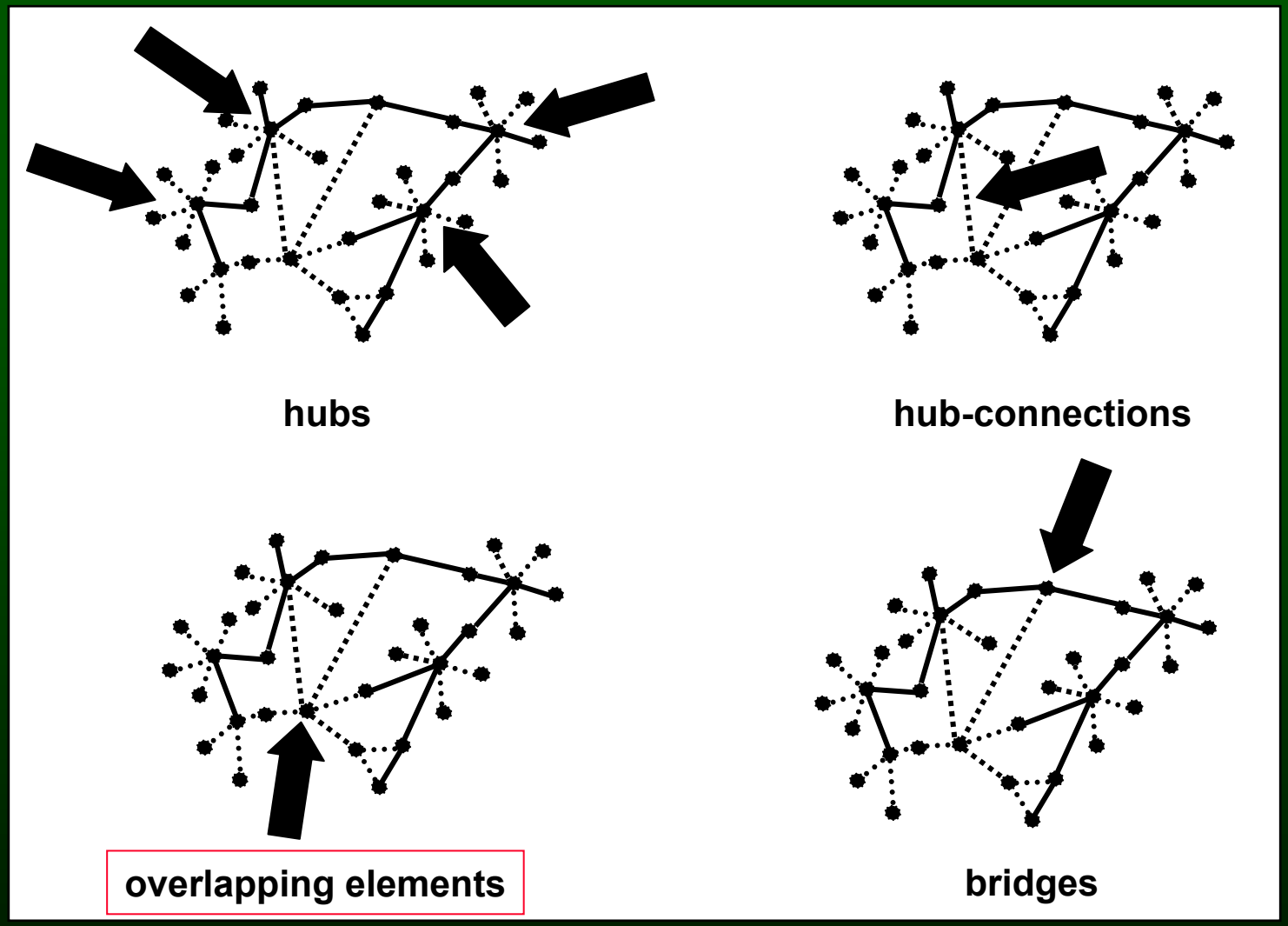


Csermely *et al*, Pharmacol & Therap 138, 333

Drug design strategies II.

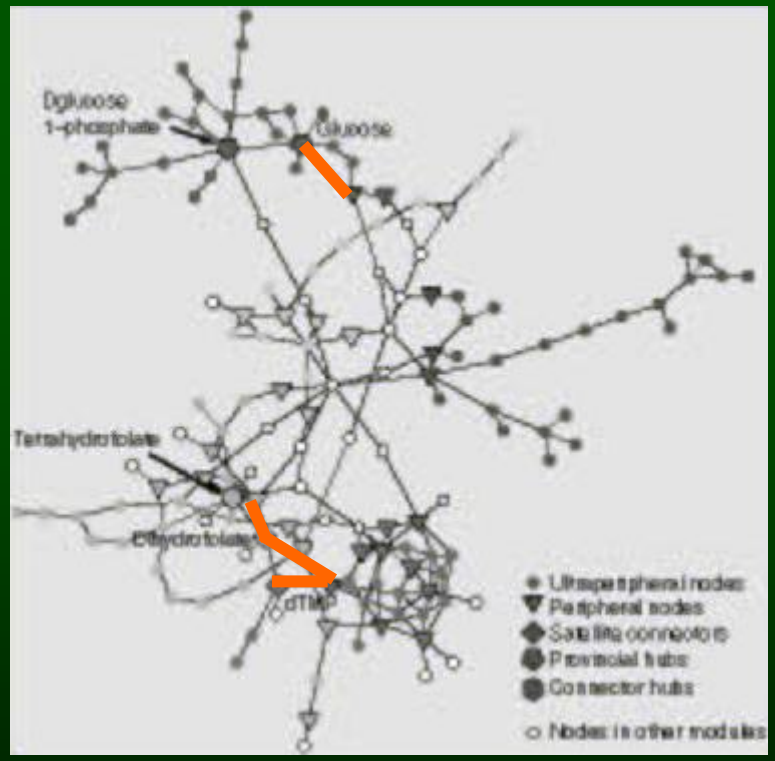


Network-based drug target options



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

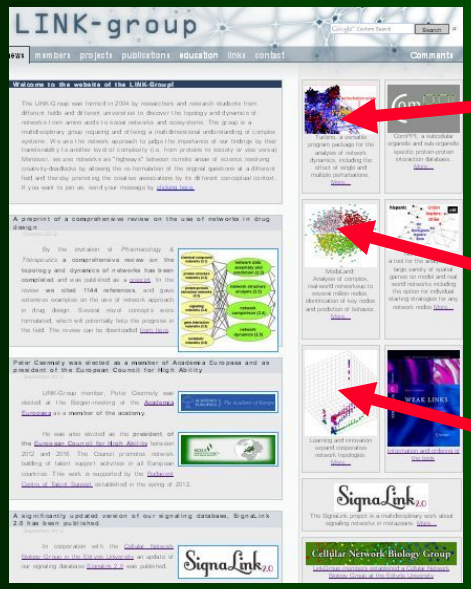
Overlapping nodes as drug targets



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)

3 novel network centralities reveal influential nodes



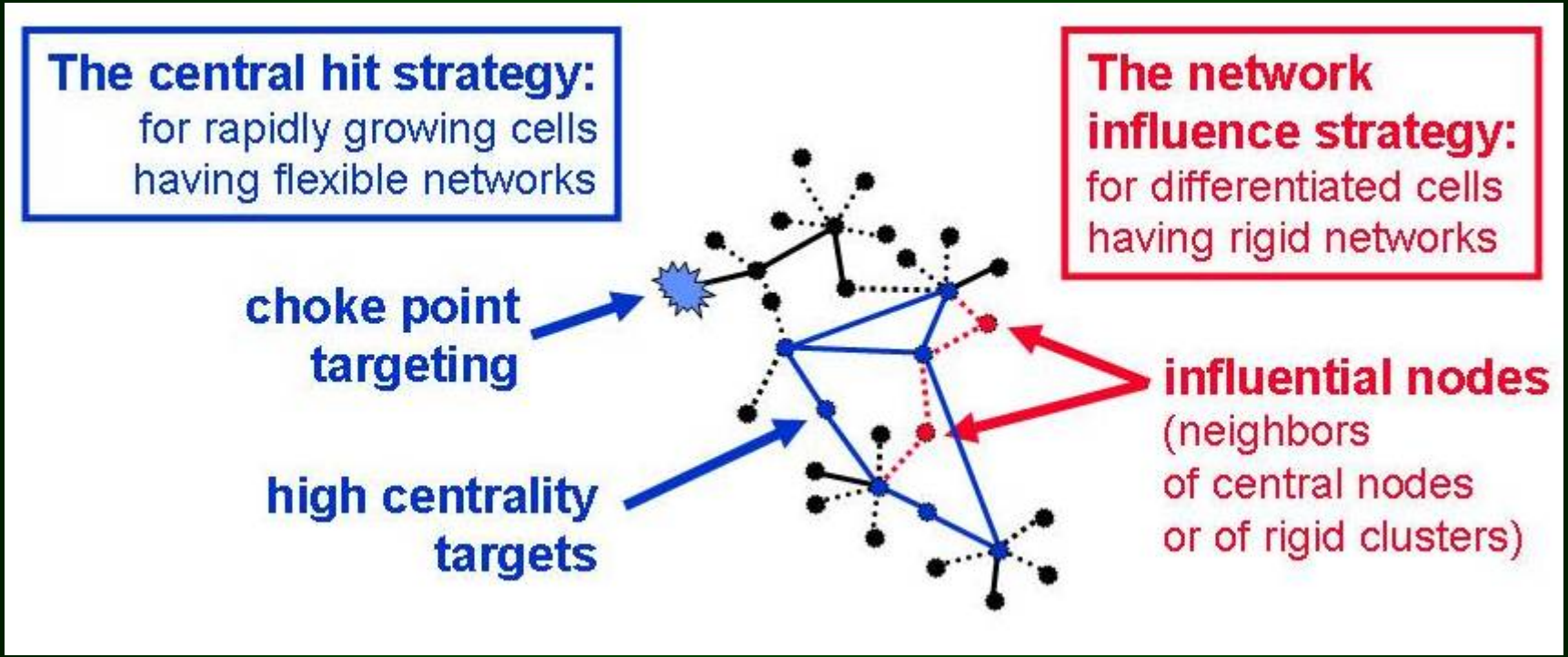
perturbation centrality
(www.Turbine.linkgroup.hu)

community centrality
(www.modules.linkgroup.hu)

game centrality
(www.NetworGame.linkgroup.hu)

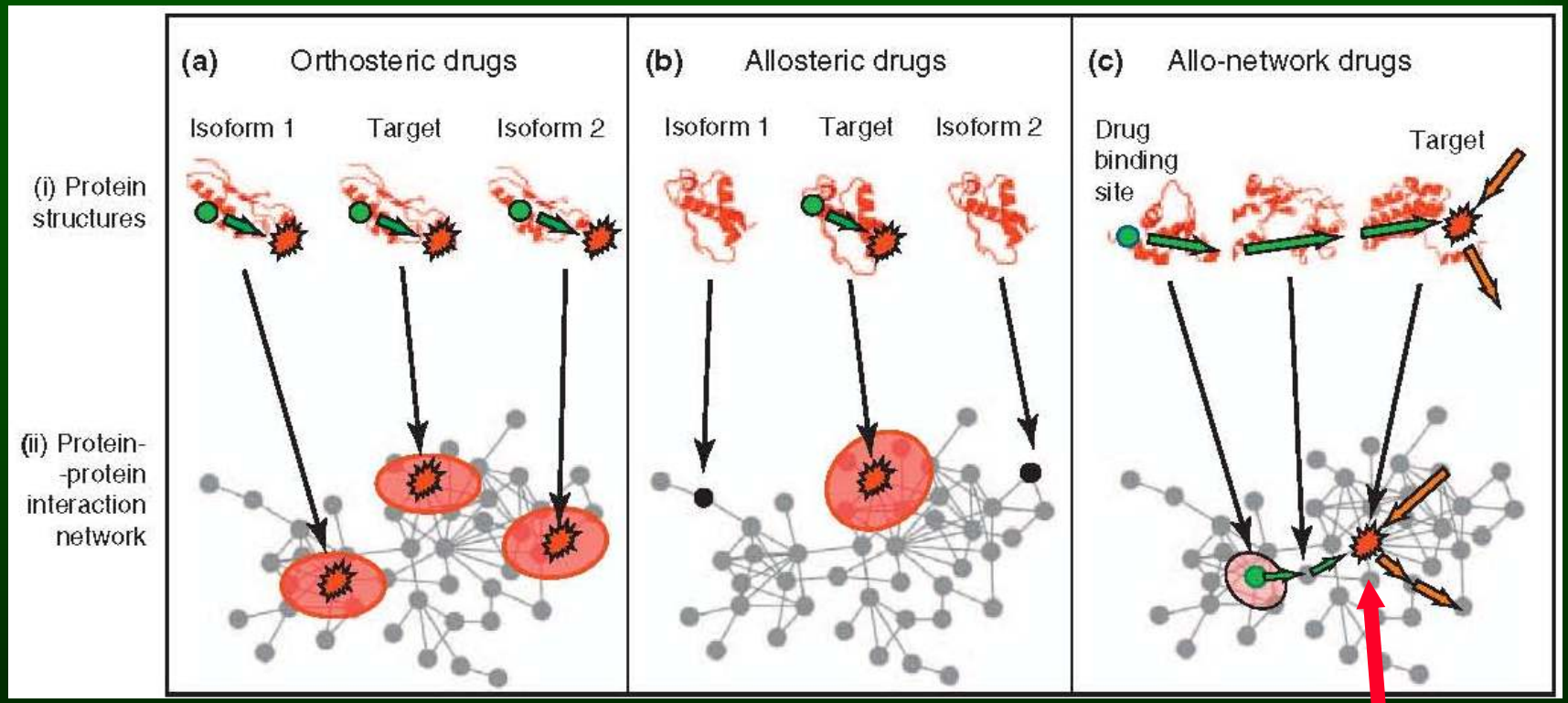
PLoS ONE 5:e12528
Bioinformatics 28:2202
Science Signaling 4:pt3
PLoS ONE 8:e67159
PLoS ONE 8:e78059

Drug design strategies I.



Csermely *et al*, Pharmacol & Therap 138, 333

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



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

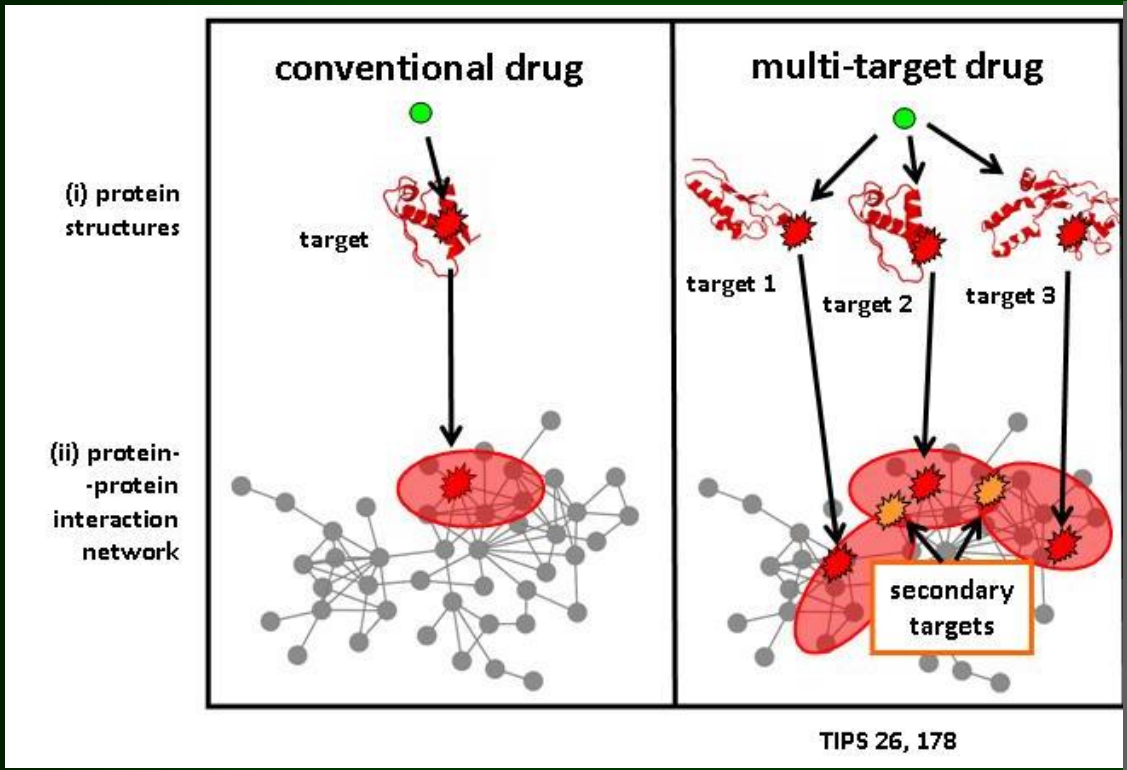
+ hit of intra-cellular paths

Distance of human disease genes and drug targets

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

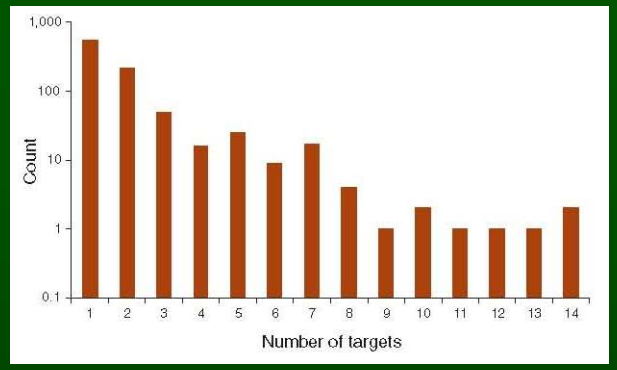
most drugs act *via* network-perturbation

Multi-target drugs

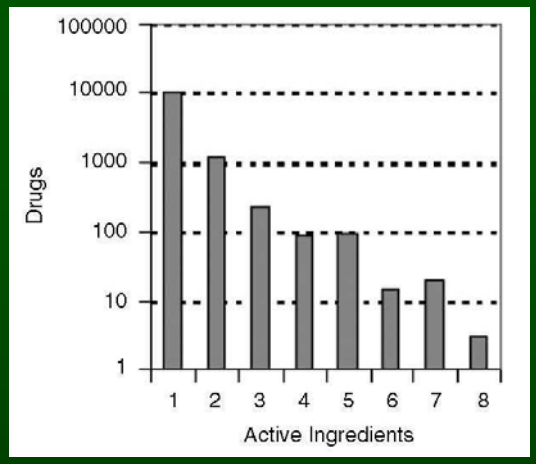


Csermely *et al*, Trends Pharmacol Sci 26:178

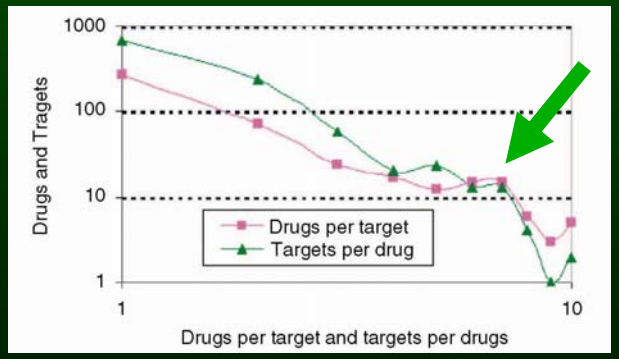
Multitarget drugs: a non-negligible segment



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



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

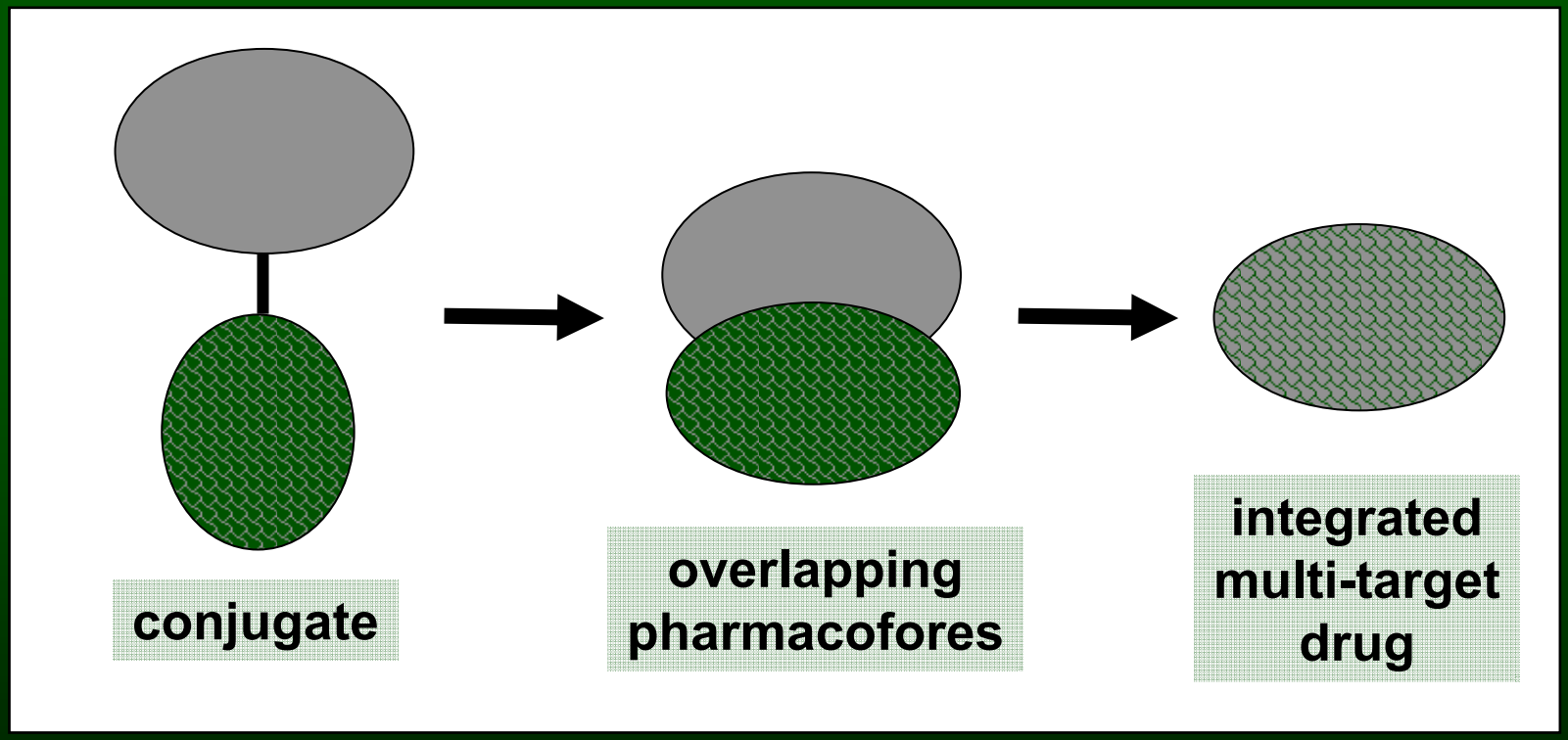


Multitarget drugs:
more prevalent than thought

- 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

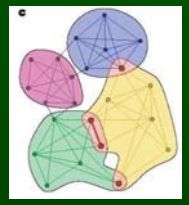
Multitarget drug-types



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

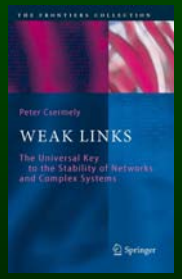
Multitarget drugs: low affinity drugs

- smaller dose and toxicity
- smaller blockade of alternative pathways



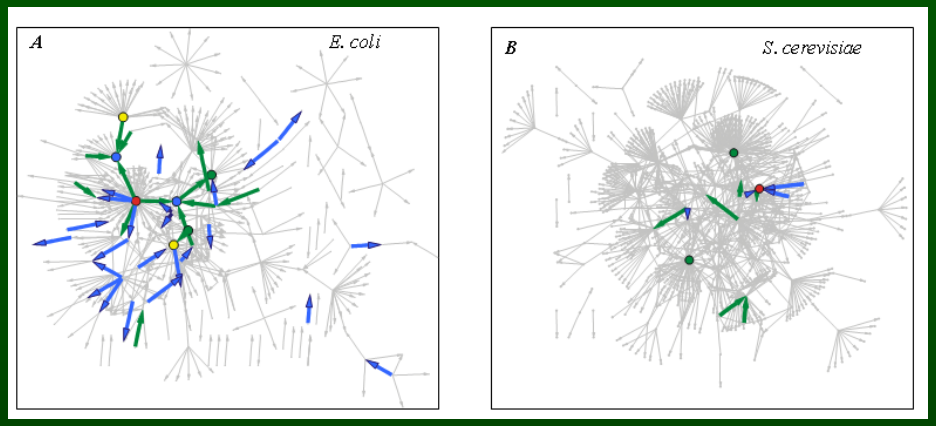
- proteins → in overlapping modules with different functions
- single protein inhibition → blocks multiple functions
- partial inhibition of many proteins → blocks module/function

- [more weak links: more stable cell]



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

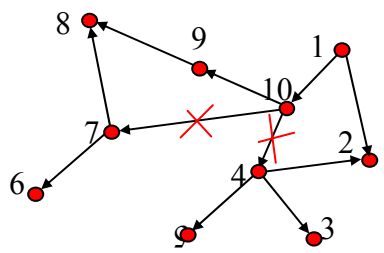
How many partial attacks can substitute a single full attack?



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

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

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

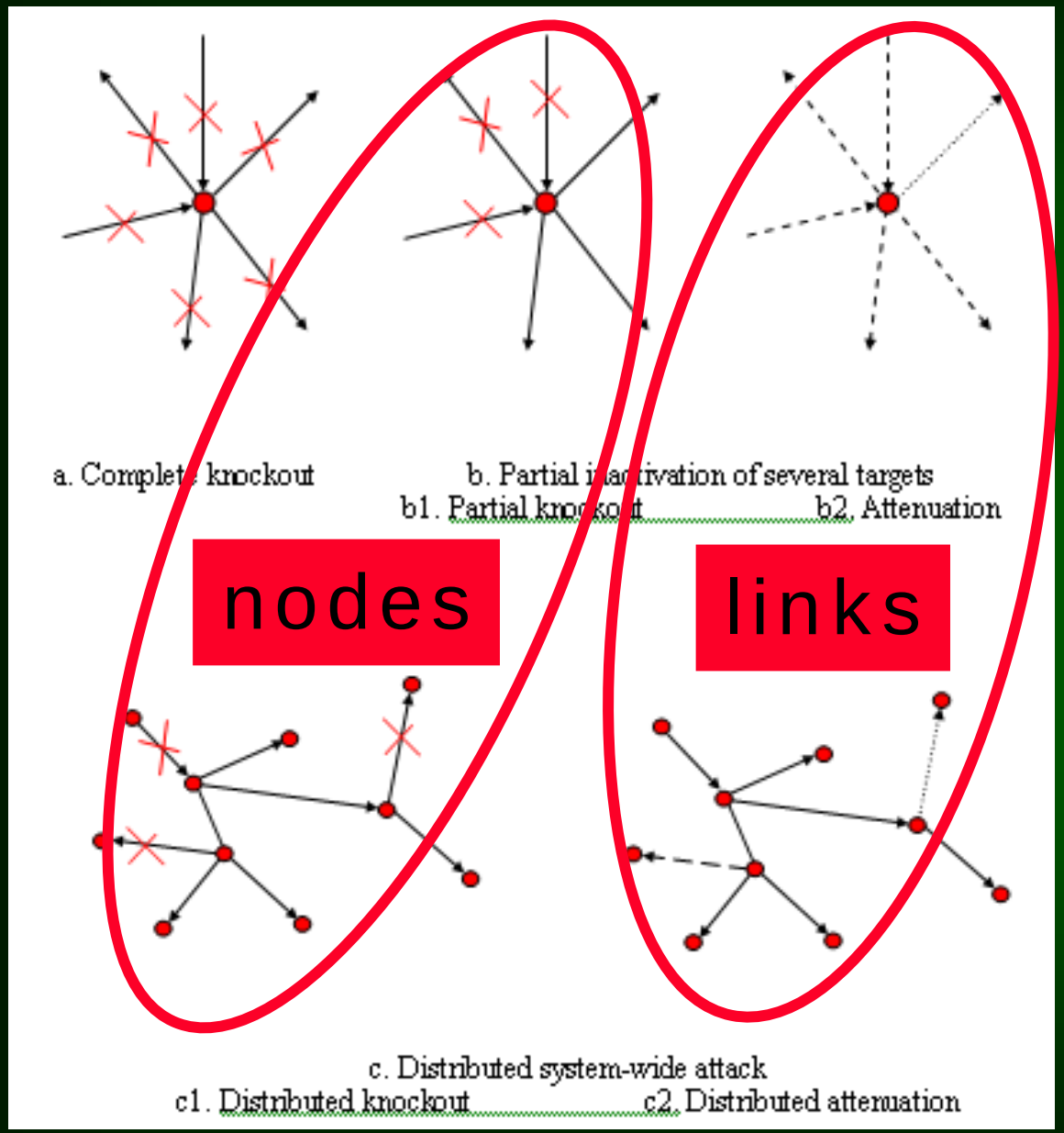


	1	2	3	4	5	6	7	8	9	10	
1	-	1	3	2	3	3	2	3	2	1	1
2	-	-	-	-	-	-	-	-	-	-	2
3	-	-	-	-	-	-	-	-	-	-	3
4	-	1	1	-	1	-	-	-	-	-	4
5	-	-	-	-	-	-	-	-	-	-	5
6	-	-	-	-	-	-	-	-	-	-	6
7	-	-	-	-	-	1	-	1	-	-	7
8	-	-	-	-	-	-	-	-	-	-	8
9	-	-	-	-	-	-	-	1	-	-	9
10	-	2	2	1	2	2	1	2	1	-	10

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

Attack measure: network efficiency

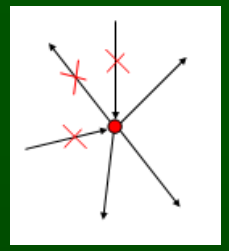
Latora and Marchiori
Phys. Rev. Lett. 87:198701

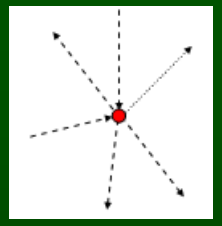


Partial attack types

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

Partial knock-out of nodes substituting the most needed node

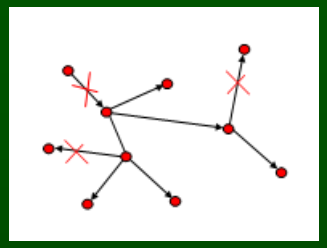


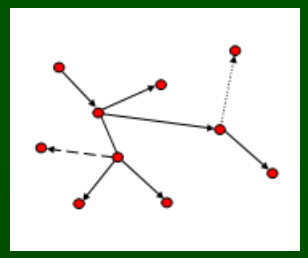


	partial KO	50% attenuation
E. coli (1)	4.2	5
S. Cerevisiae (1)	2.8	3

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

Partial knock-out of links substituting the most needed node

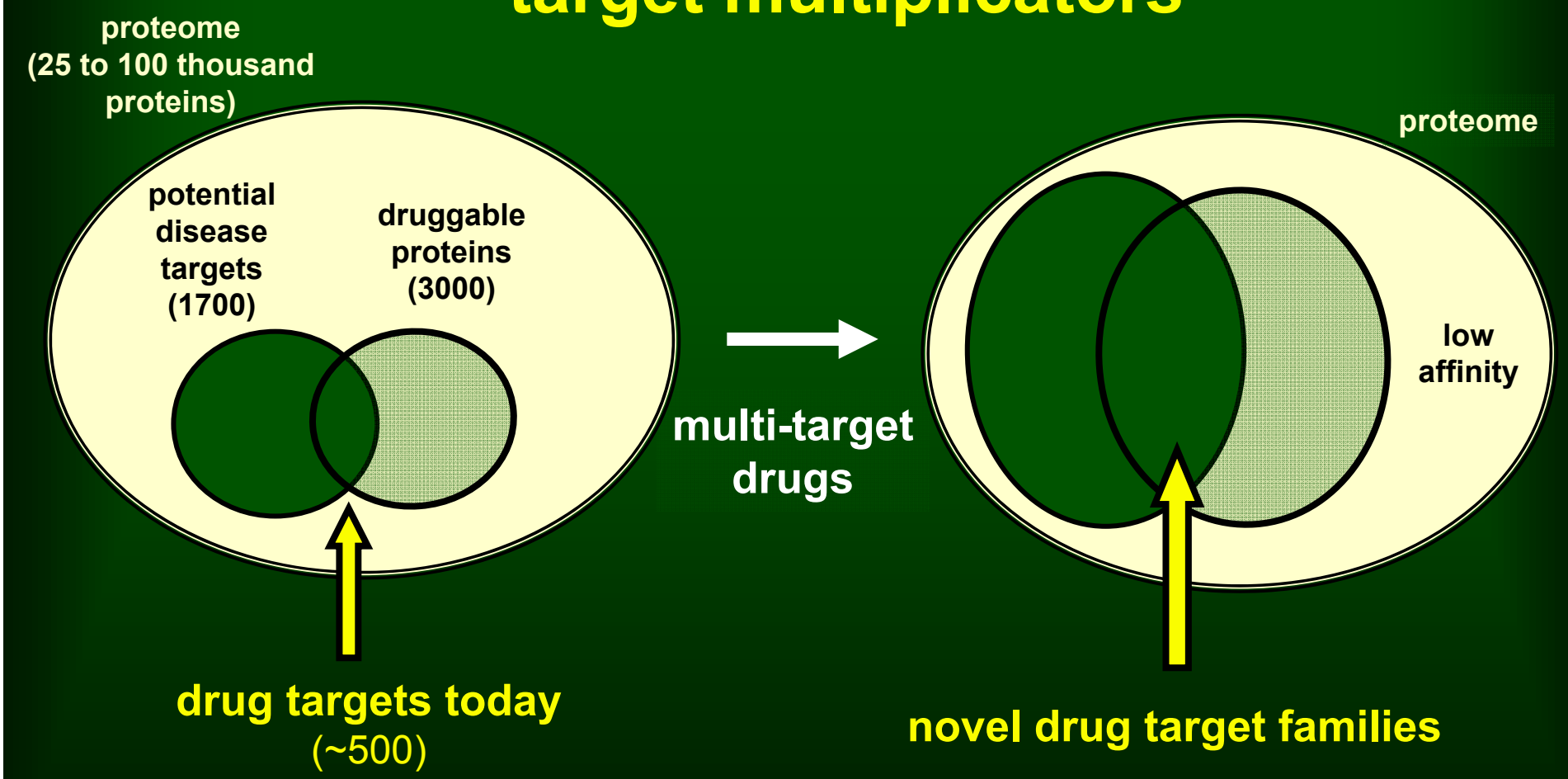




	distributed KO	distributed attn.
E. coli (72)	15	38
S. cerevisiae (18)	6	10

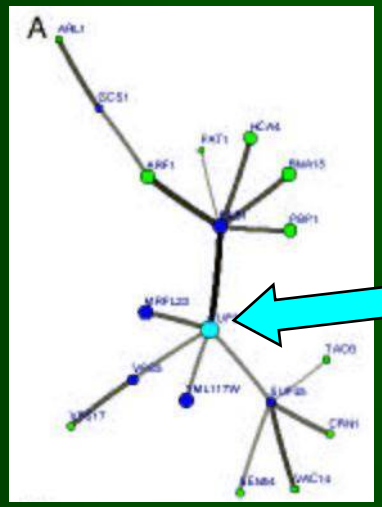
Ágoston et al., Phys. Rev. E 71:051909

Multitarget drugs =
= target multiplicators



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

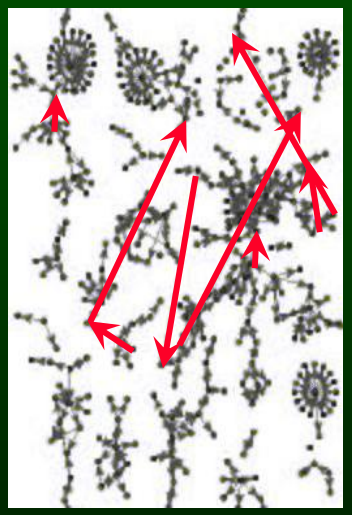
Effects are specific



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

PNAS 104:13655

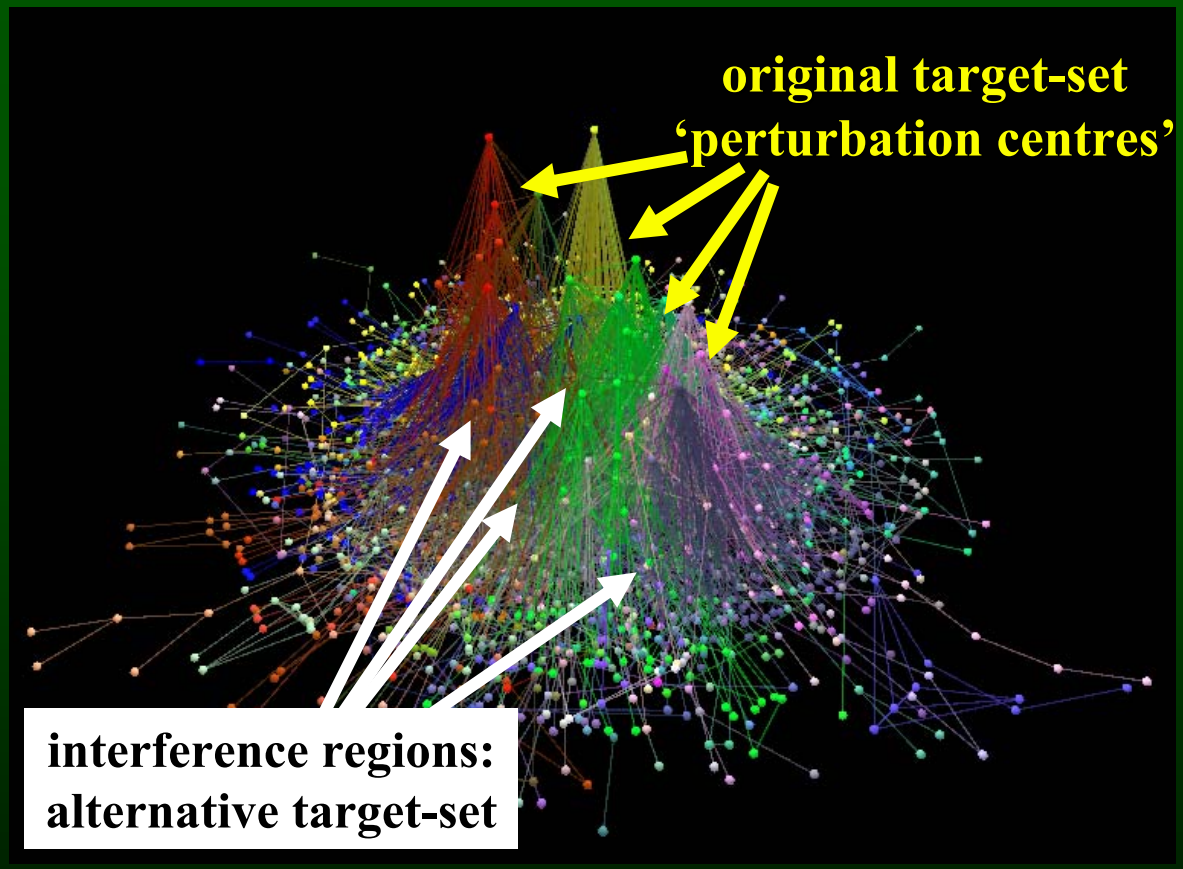
yeast interactome



long-range
effects

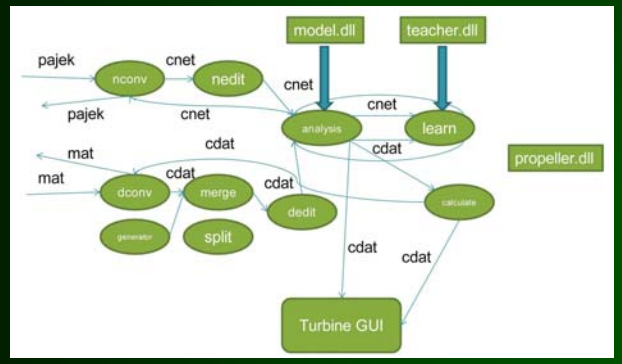
yeast interactome:
at least 20% changes

Multitarget drug search by modular analysis and multi-perturbation



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

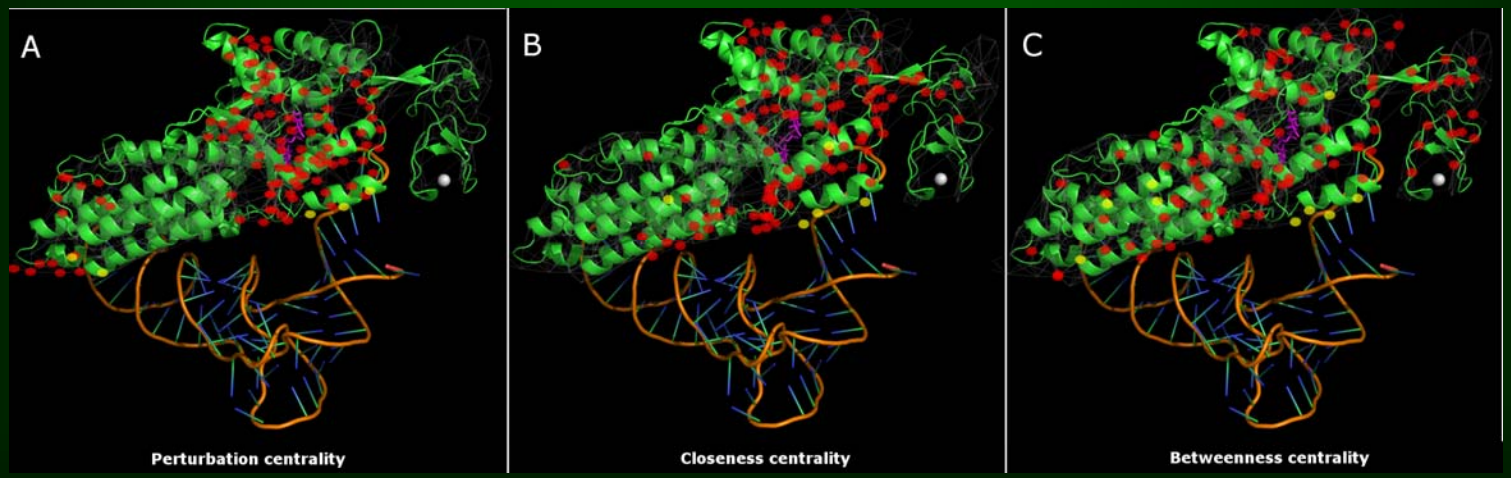
Turbine: general network dynamics tool



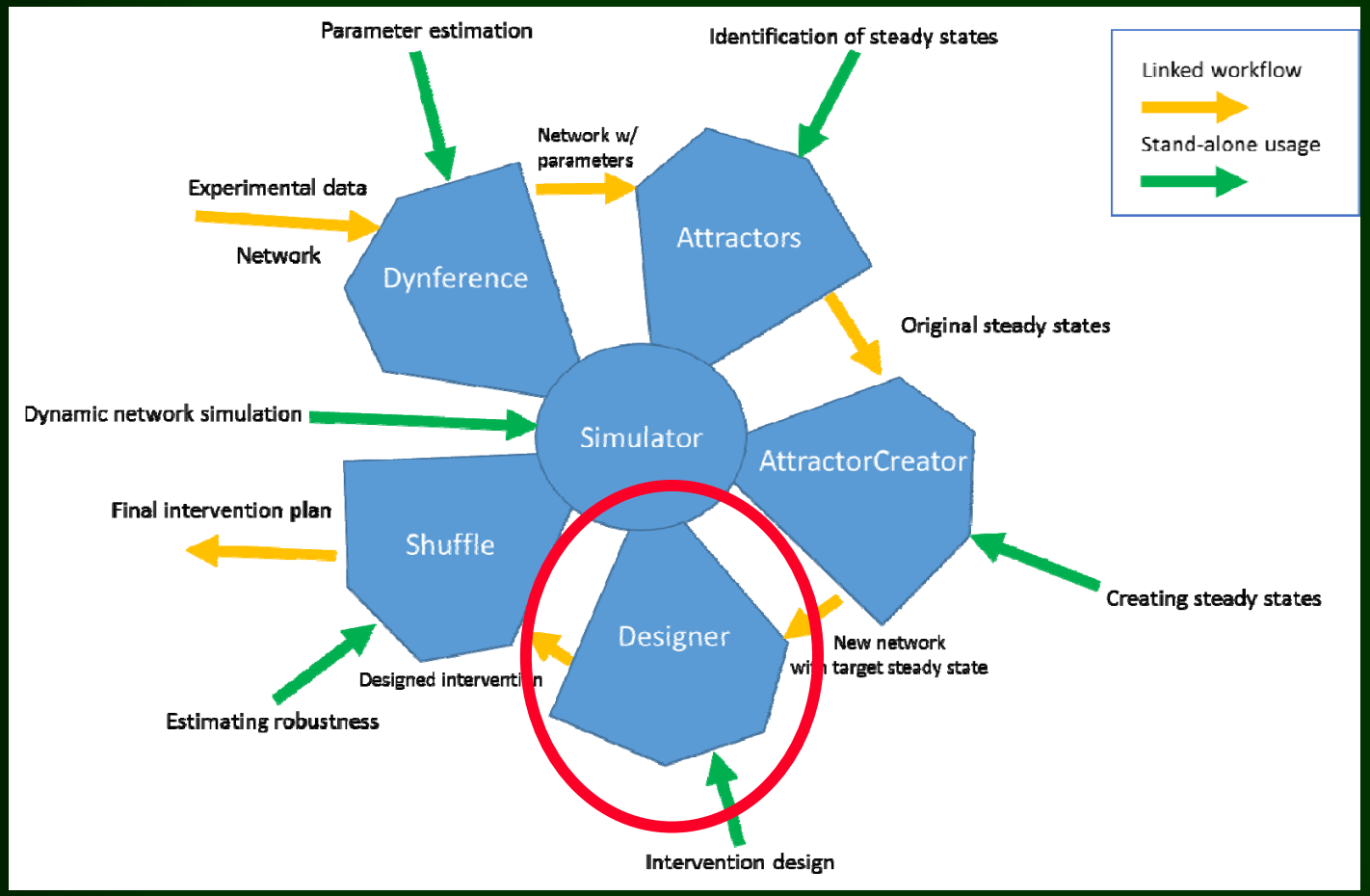
www.Turbine.linkgroup.hu

any real networks can be added, modified
normalizes the input network
any perturbation types (communicating vessel model, multiple, repeated, etc.)
any models of dissipation, teaching and aging
Matlab compatible

Szalay & Csermely, Science Signaling 4:pt3
PLoS ONE 8:e78059



The Turbine network dynamics toolkit



Kristóf Szalay

Peter Csermely

Simulator is available here: www.linkgroup.hu/Turbine.php; the rest is proprietary

Szalay & Csermely, Science Signaling 4:pt3 +
PLoS ONE 8:e78059 + patent application HU1300737

Accuracy of Turbine::Designer

Original perturbations

Node	Size	Step
CDC28	100000	5
GSY2	50000	3
SLT2	8000	1

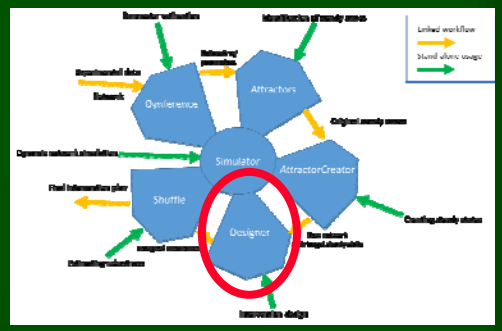
Perturbation generated by Turbine::Designer

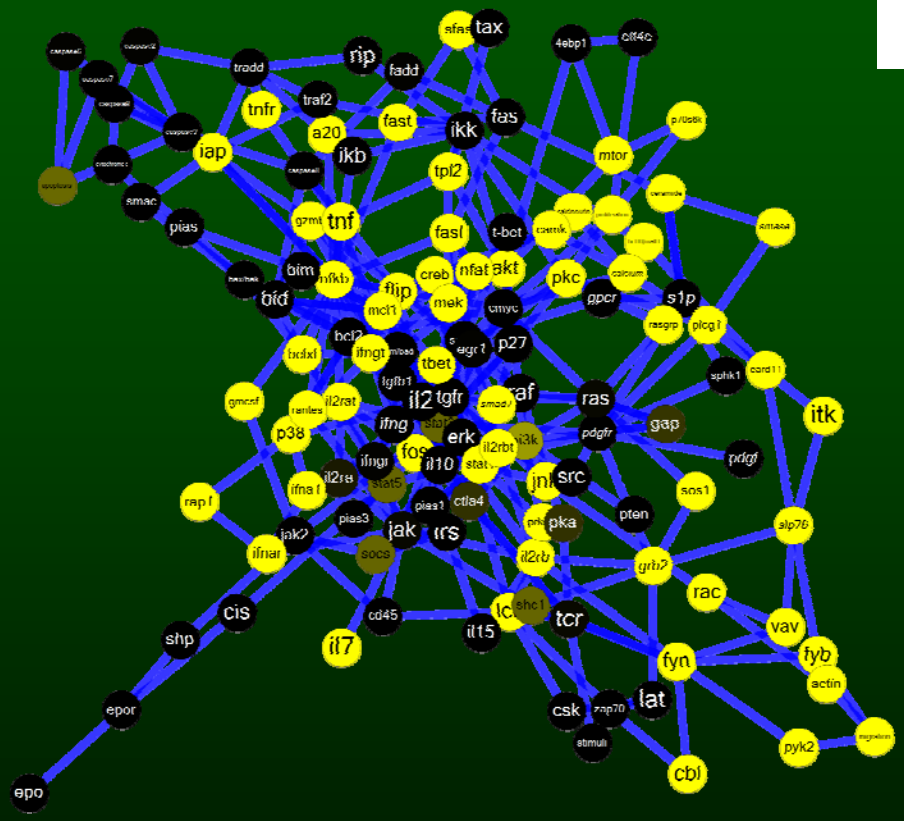
Node	Size	Step
CDC28	99945	5
GSY2	49805	5
SLT2	7512	3

2444 node, 6271 link DP2 yeast interactome
Communicating vessels model
Target state: 15th step of simulation with artificial perturbation
Shape: Dirac-delta

Multi-drug design with Turbine::Designer

T-LGL survival signaling network: leukemia specific edges
Starting state: pattern after activating IL7
Target state: quiescent network (all black)





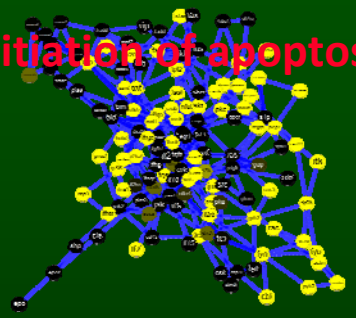
Inactive protein

Activated protein

Network: Zhang R, Shah MV, Yang J, Nyland SB, Liu X, Yun JK, Albert R, Loughran TP Jr. (2008) Network model of survival signaling in large granular lymphocyte leukemia. PNAS 105: 16308–13.

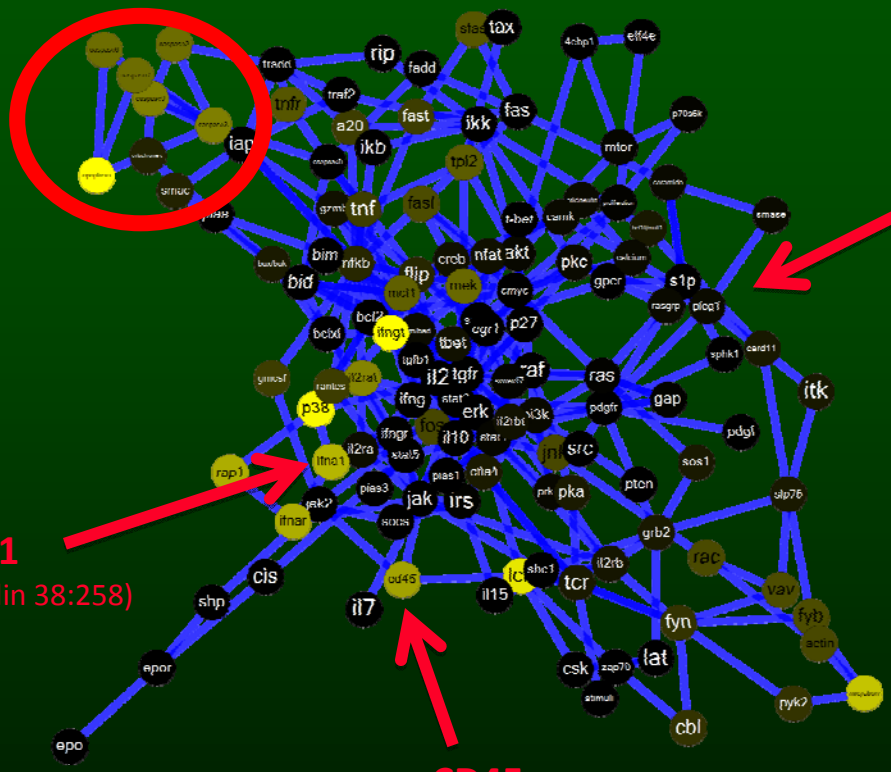
Multi-drug design with Turbine::Designer

T-LGL survival signaling network: leukemia specific edges
Starting state: IL7-activation; target-state: all black
Turbine::Designer solution to reach target state



initiation of apoptosis

starting state



Phospholipase CΥ1
(inhibition; Cancer Res. 68:10187)

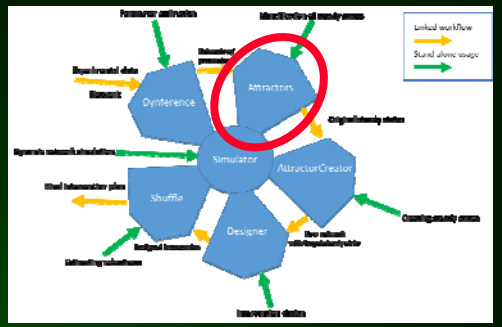
Interferon α1
(activation; CA Cancer J Clin 38:258)

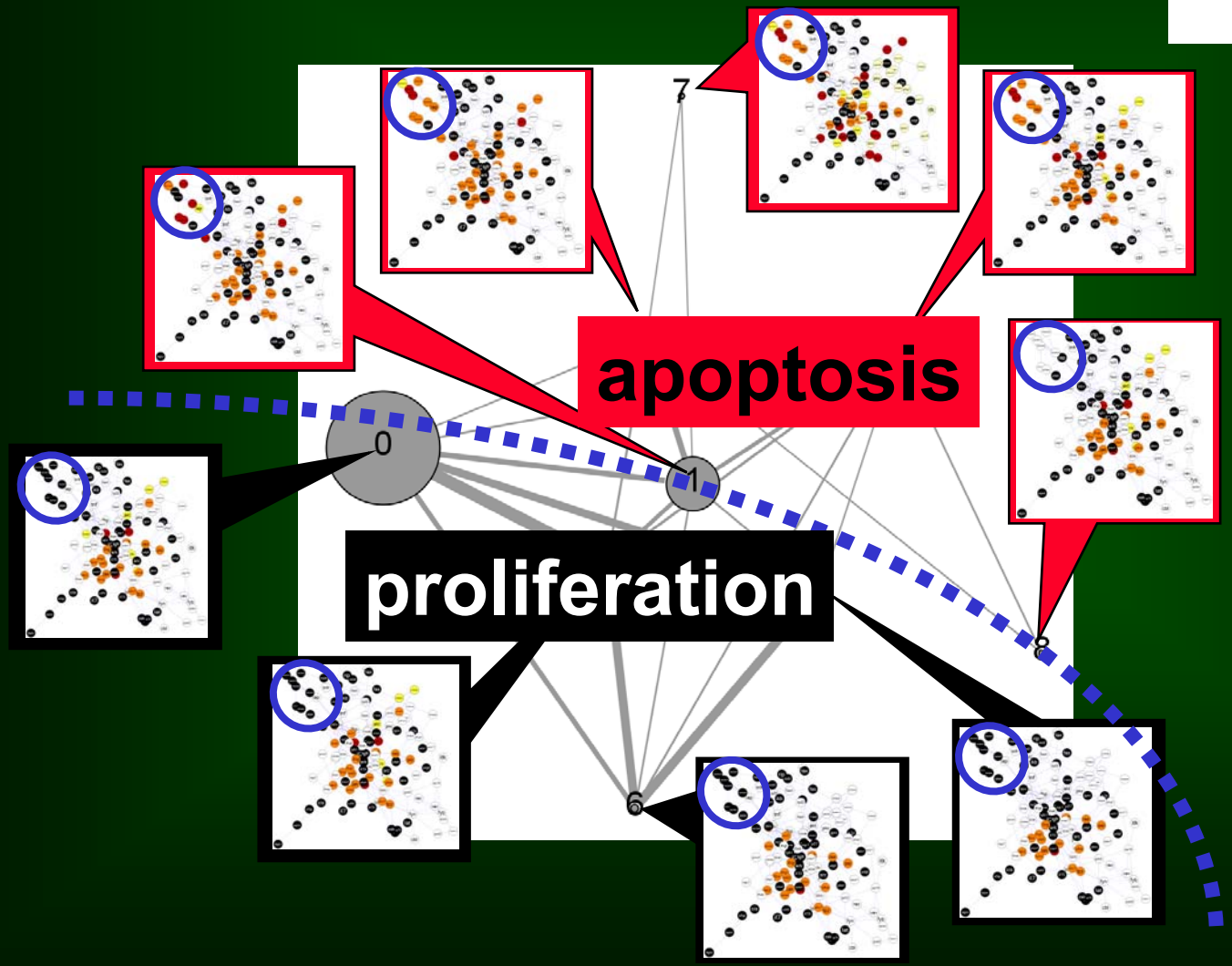
CD45
(activation; Blood 119:4446)

● Inactive protein
● Activated protein

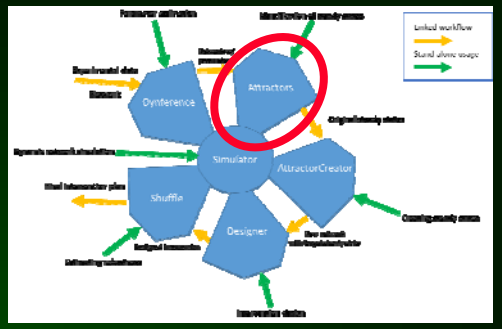
Network: Zhang R, Shah MV, Yang J, Nyland SB, Liu X, Yun JK, Albert R, Loughran TP Jr. (2008) Network model of survival signaling in large granular lymphocyte leukemia. PNAS 105: 16308–13.

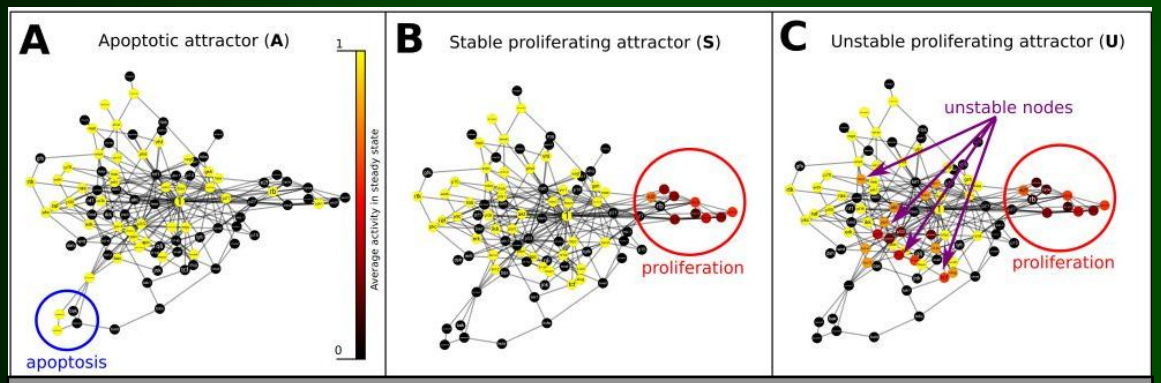
Attractors of T-LGL network using Turbine::Attractor





Effect of noise on attractors of a cancer related network



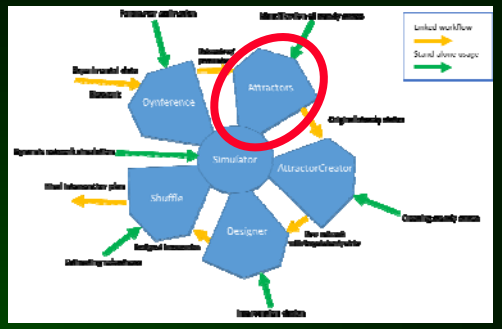


Three major attractors of cancer-related network

Natural noise stabilizes the apoptotic attractor, which is the „healthy state" under the genotoxic conditions selected

Network: Fumia HF, Martins ML (2013) Boolean network model for cancer pathways: predicting carcinogenesis and targeted therapy outcomes. PLoS ONE 8: e69008, 96 nodes, 249 edges

Mutations shifting back cancer cells from apoptosis to proliferation



Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9	Set 10	Set 11
CHK X	P53 X	P53 X	PIP3 +	IKK +	EEF2 +	P53 X	BCL-2 +	BCL-2 +	PIP3 +	APC +
IKK +	PIP3 +	GSK-3 X	IKK +	MYC X	MYC X	MYC X		RB X	RHEB +	P14 +
	ERK X		ATM X	ATM X	ATM X			RAS X	NF-KB +	ATM X
	DSH X									BCL-XL +

+ = constantly „ON” mutations
X = constantly „OFF” mutations

Network: Fumia HF, Martins ML (2013) Boolean network model for cancer pathways: predicting carcinogenesis and targeted therapy outcomes. PLoS ONE 8: e69008, 96 nodes, 249 edges

Interventions reversing proliferation of mutated cancer cells to apoptosis

Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9	Set 10	Set 11
RTK -	RAF -	PDK1 -	P53+	P53+	P53+	RTK -	RAS - and	BAX +	BCL-2 -	PDK-1 -
	PDK1 -	JNK +				BAX +	TGF-B + or BAX +			
	JNK +	BAD +								

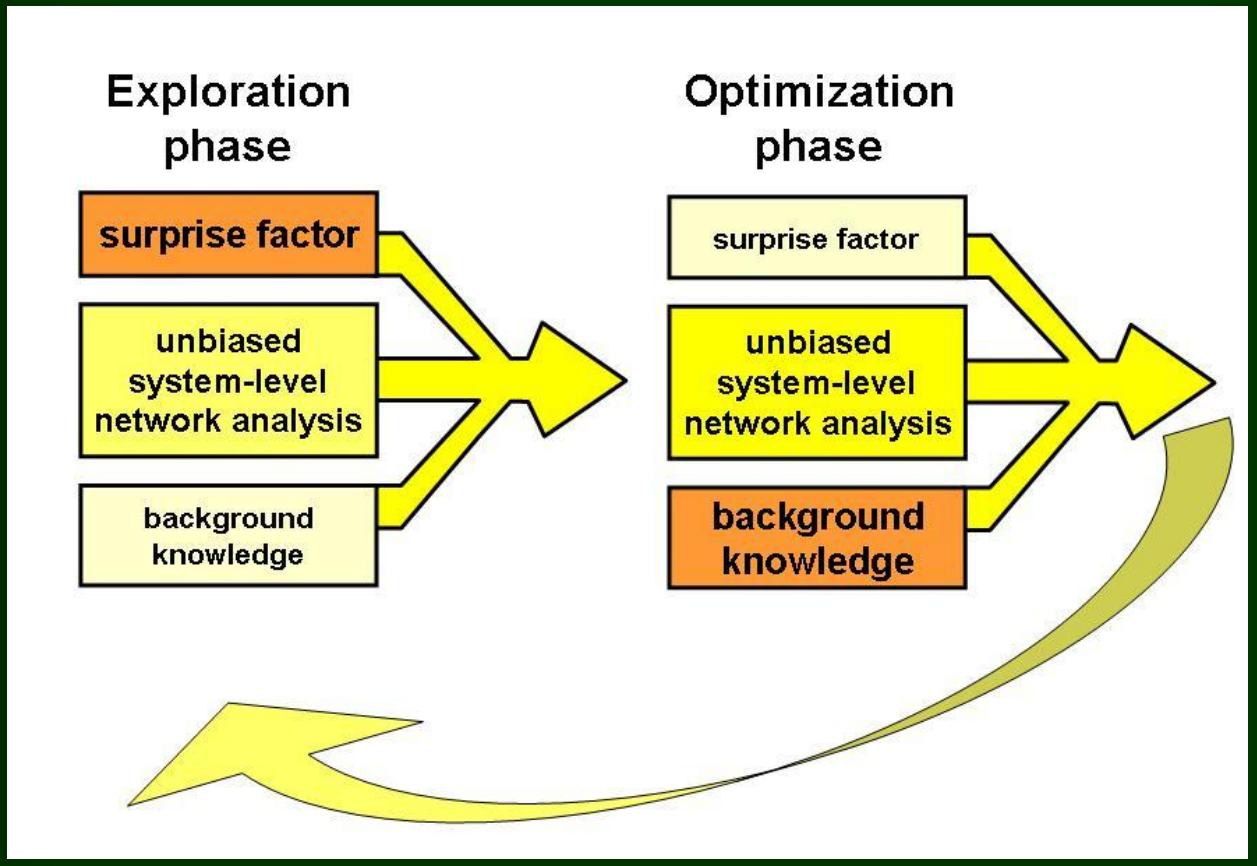
(activation of trivial apoptosis-inducing targets + mutations were not allowed to be selected)
+: activation, -: inhibition, red: predicted to be toxic to healthy (non-mutated) cells

apoptosis of healthy (non-mutated) cells was excluded; alternative/larger target-sets:

Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9	Set 10	Set 11
Non-toxic	*N/A*	RTK -	BCL-2 -	RTK -	RAS -	JNK +	AKT -	JNK + and	*Non-toxic*	*Non-toxic*
		VHL -	VHL -	VHL -	VHL -	RTK -	BAX + and	E2F+ or GSK-3 -		
		P90 -	FOXO -			APC -	PKC + or PIP3 +			
			MYC -							

Network: Fumia HF, Martins ML (2013) Boolean network model for cancer pathways: predicting carcinogenesis and targeted therapy outcomes. PLoS ONE 8: e69008, 96 nodes, 249 edges

Drug development phases



Csermely *et al*, Pharmacol & Therap 138, 333

Networks and stability

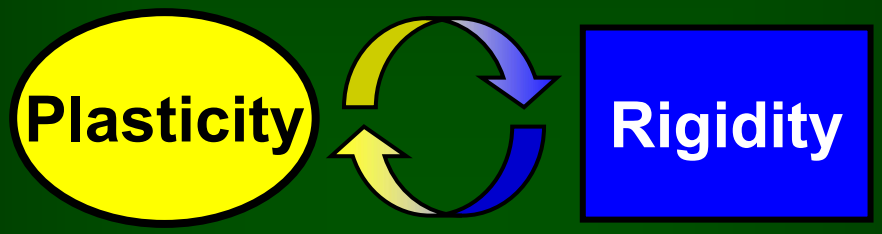
Part 6. – A hypothesis

Peter Csermely

www.linkgroup.hu
csermelynet@gmail.com

Example 2:

Adaptation of complex systems



Plasticity-rigidity cycles form a general adaptation mechanism

Csermely arxiv.org/abs/1511.01238

Example 2:
Adaptation of complex systems
rigid and plastic properties

rigid balanced plastic

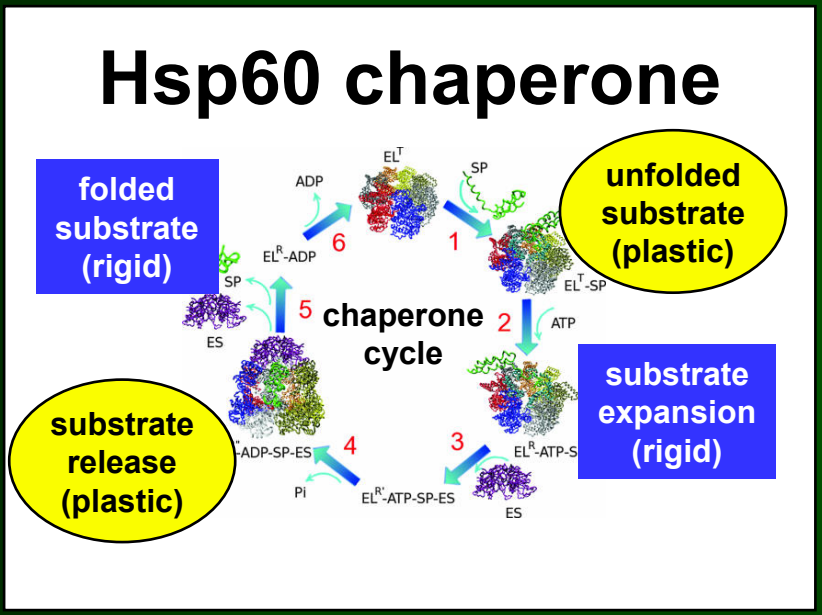
−	+	+	possibility of adaptation
+	+	−	effect of adaptation

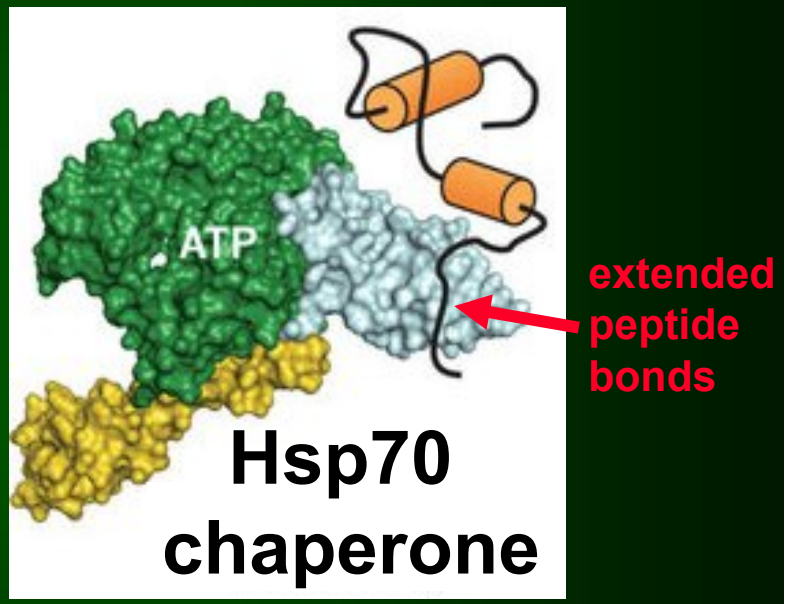
Gáspár & Csermely, Brief. Funct. Genom. 11:443
Gyurkó et al. Curr. Prot. Pept. Sci. 15:171
Csermely arxiv.org/abs/1511.01238

learning competent *(exploration)* →

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

Example 2: Molecular mechanisms of protein structure optimization





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 o
extended pepti

plastic: many responses

Bukau & Horwich
Cell 92:351

rigid: few responses

Example 3:
cell differentiation

progenitor cells

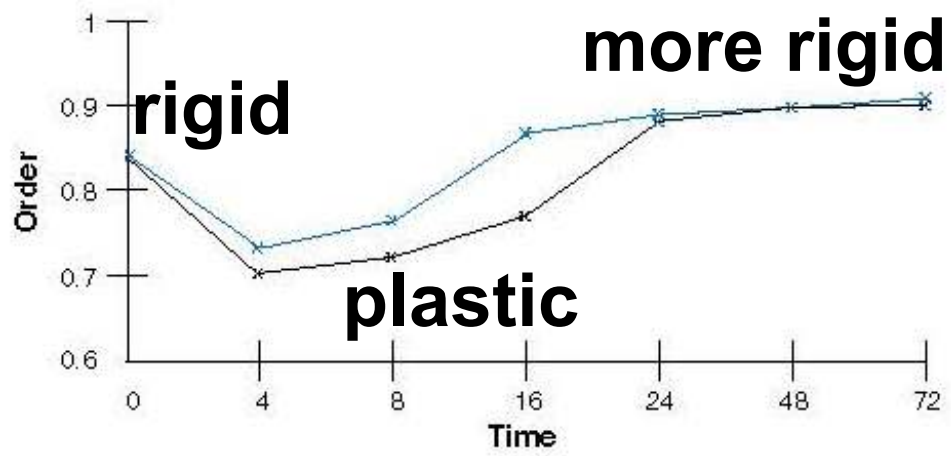


Fig. 3. Dynamics of order during cell specialization. When a progenitor commits to either the erythroid (black) or the neutrophil lineage (blue), there is a concomitant increase in order, eventually stabilizing at a level greater than that of the original multipotent progenitor (7).

differentiated cells

Rajapakse *et al.*, PNAS 108:17257

plastic: many responses

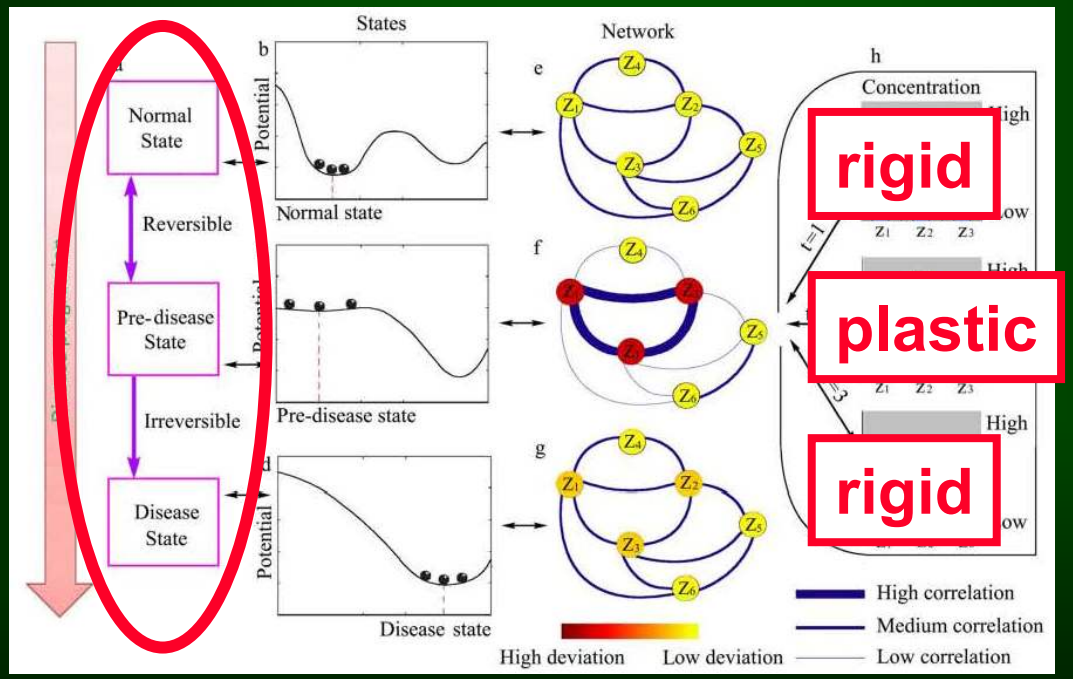
rigid: few responses

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

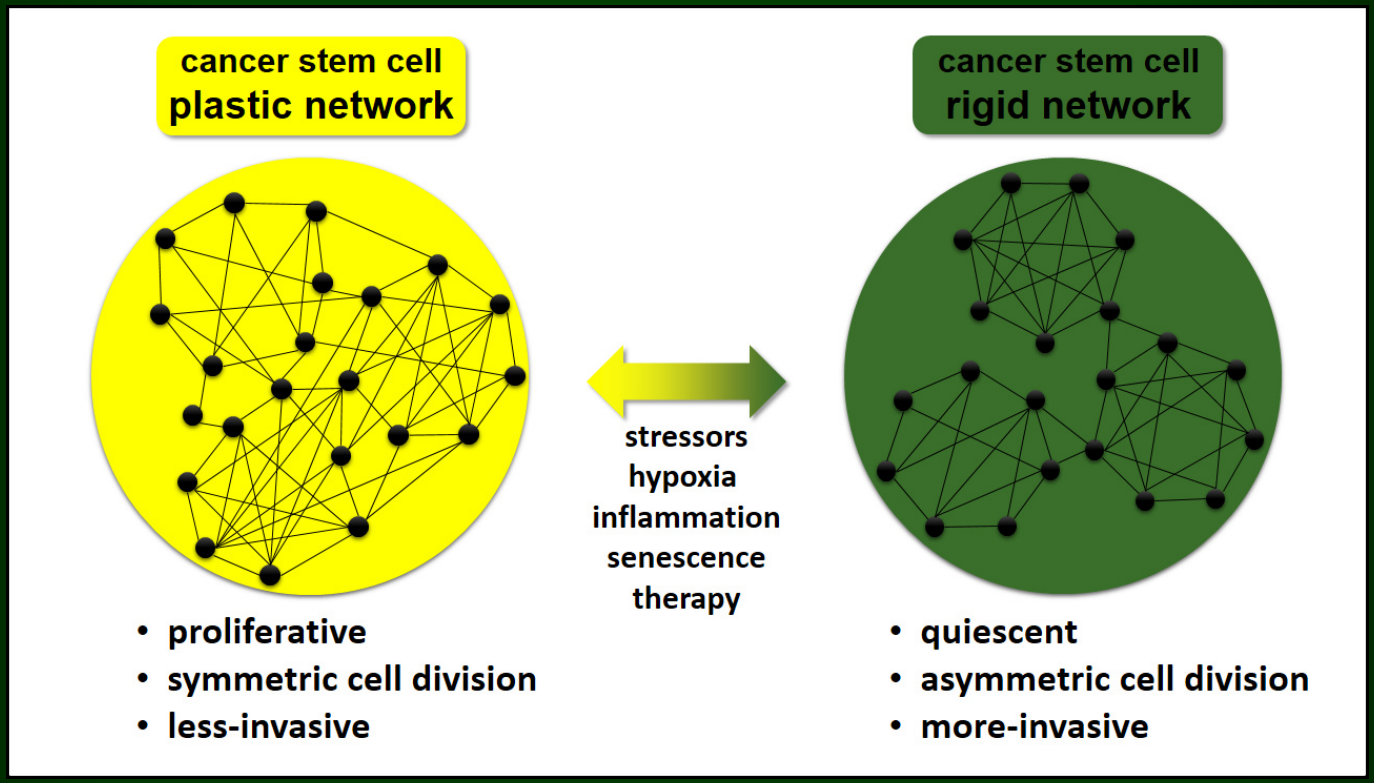


phosgene inhalation-induced lung injury, chronic hepatitis B/C, liver cancer

plastic: many responses

rigid: few responses

Example 5:
cancer stem cells



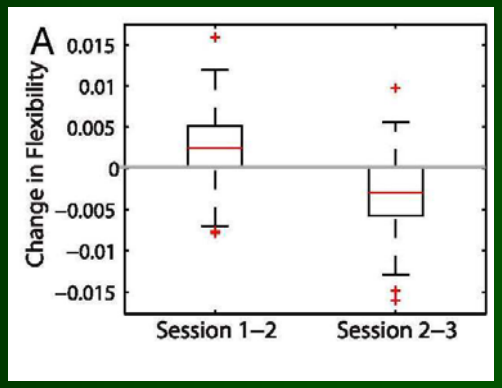
Csermely *et al.*, Seminars in Cancer Biology
doi: 10.1016/j.semcancer.2013.12.004

plastic: many responses

rigid: few responses

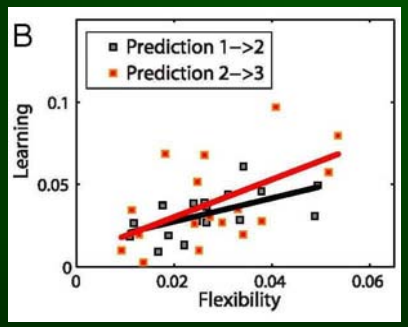
Example 6:

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



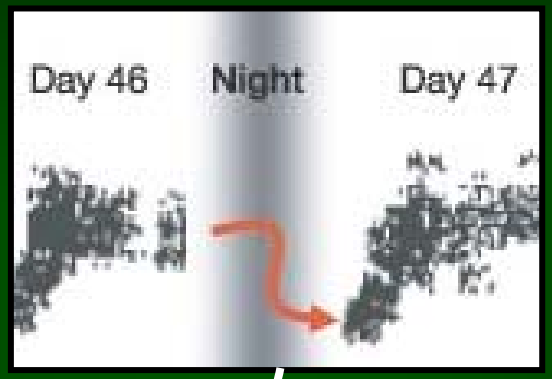
plasticity in previous learning session predicts the success of later learning session

plastic: many responses

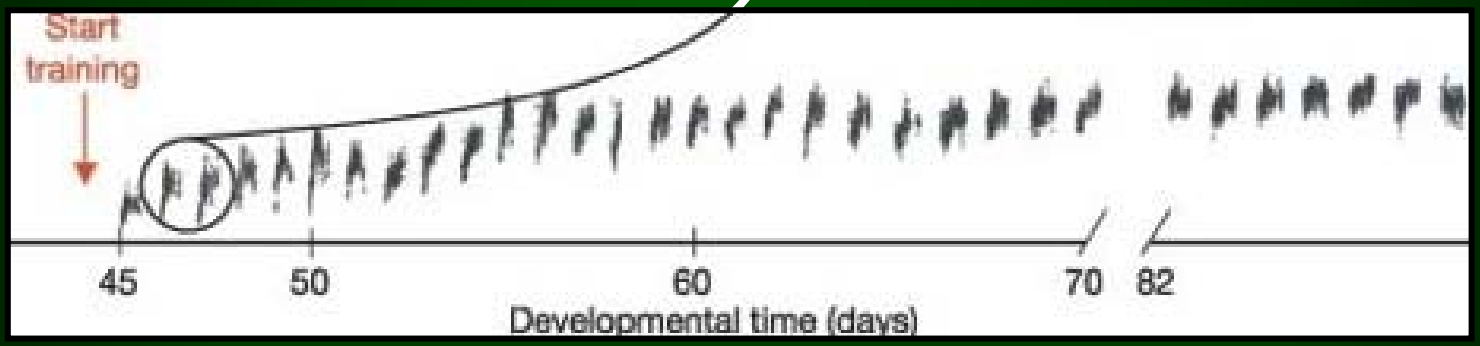
rigid: few responses

Example 2:
Adaptation of complex systems
learning processes

song Wiener entropy variance



Deregnaucourt et al Nature 433:710



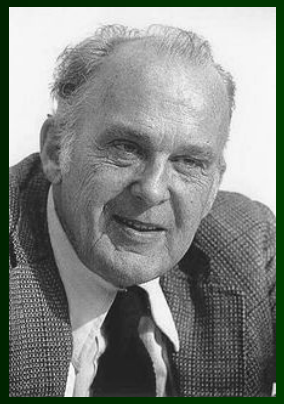
Male bird synaptic plasticity alternates
(same kinetics of infant word learning)

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

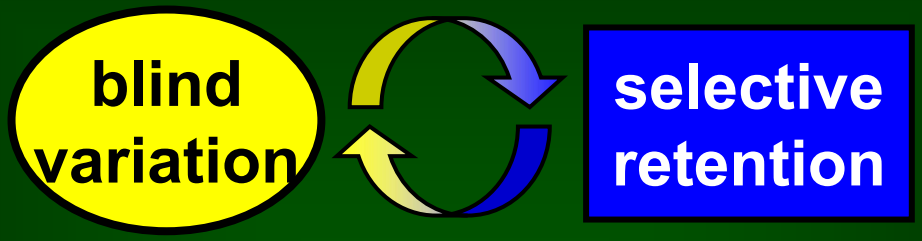
Csermely arxiv.org/abs/1511.01238

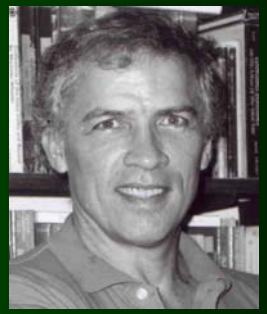
Example 2:
Adaptation of complex systems

creativity

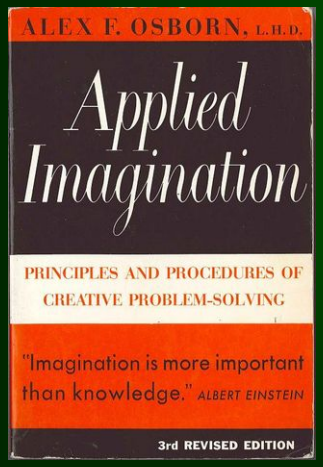


Donald T. Campbell

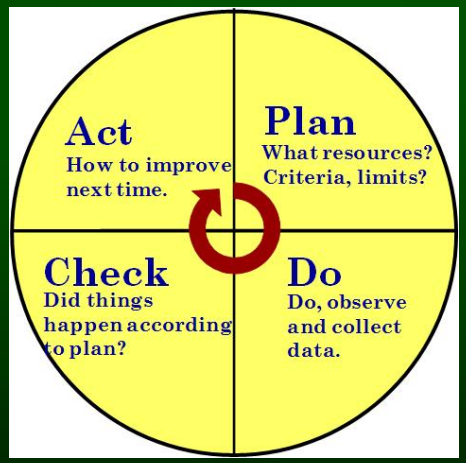




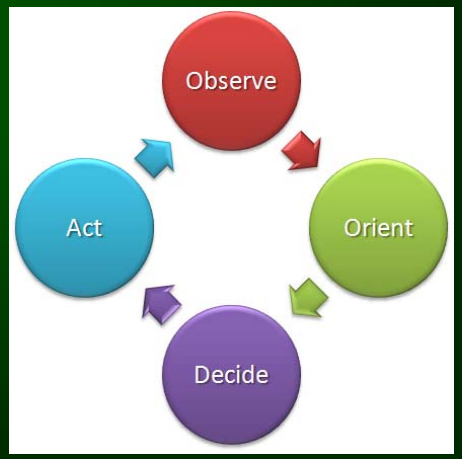
Dean Keith Simonton



brainstorming



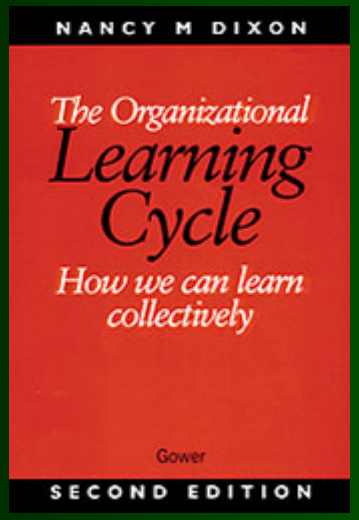
PDCA-cycle

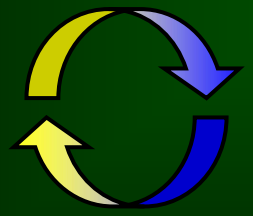


OODA-loop

Csermely arxiv.org/abs/1511.01238

Example 2:
Adaptation of complex systems
learning organizations

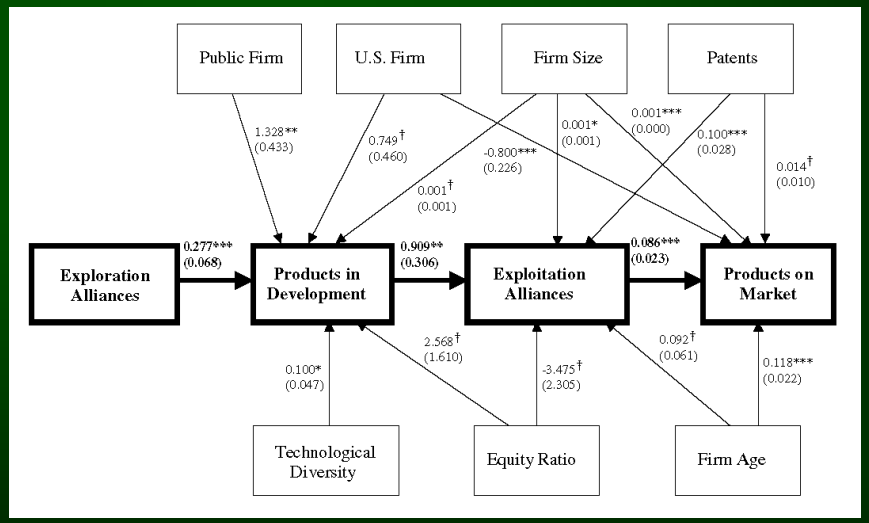




Rothaermel & Deeds, Strat. Mgmt. J. 25:201

exploration → **exploitation**

in firm and product development

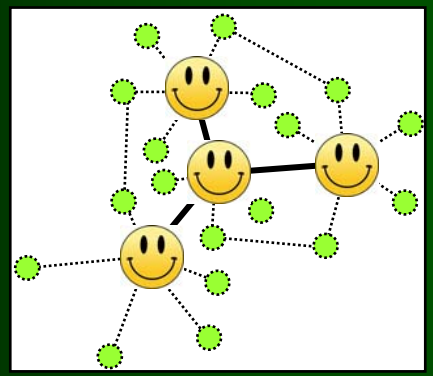


Csermely arxiv.org/abs/1511.01238

Example 3:
Decision-making of complex systems
fast and slow thinking of networks

usual information

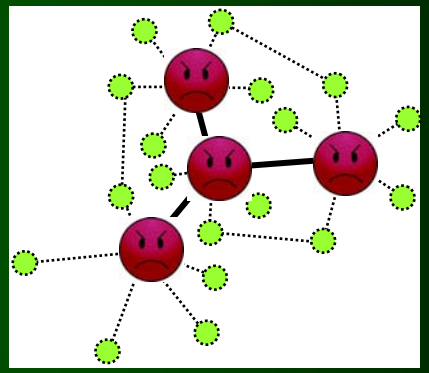
Opinion leaders have consensus

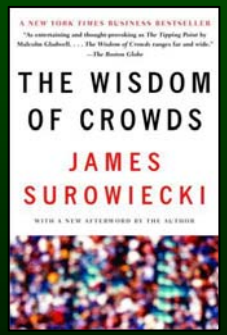


fast and strong response

new information

Opinion leaders disagree

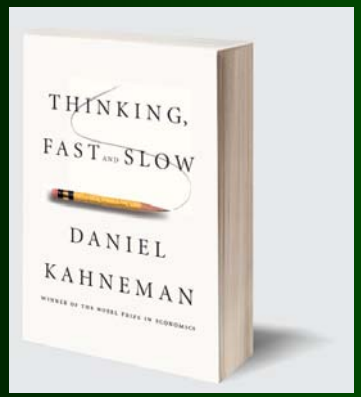


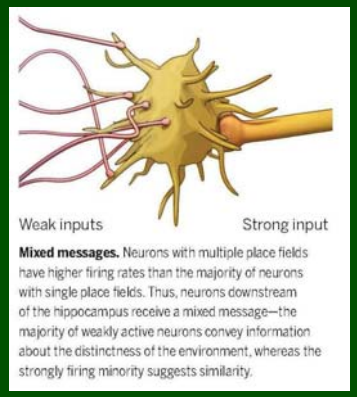


slow response requiring the contribution of the whole community *(slow democracy)*

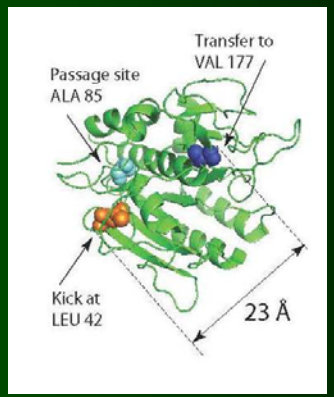
Csermely arxiv.org/abs/1511.01239

Example 3:
Decision-making of complex systems
fast and slow thinking of networks





Science 347:612



EPL 88, 68001

How do we decide?
a.) known situation
'reflex-type' decision
b.) unknown situation
'wisdom of the crowd'

Where we are?
a.) known place
'boss neurons' decide
b.) unknown place
'wisdom of the crowd'

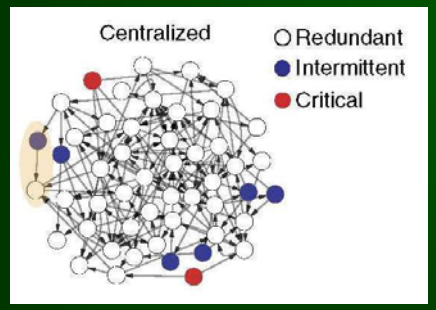
Protein movements
a.) known effect
'boss atoms' decide
b.) unknown effect
'wisdom of the crowd'

Csermely arxiv.org/abs/1511.01239

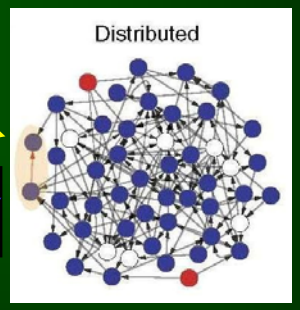
Example 3:
Decision-making of complex systems
possible mechanism of rigid-plastic transition

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 →



3 plastic → rigid →

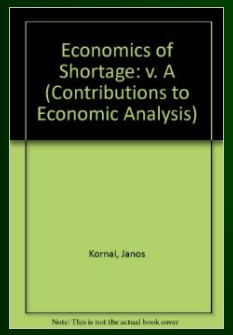


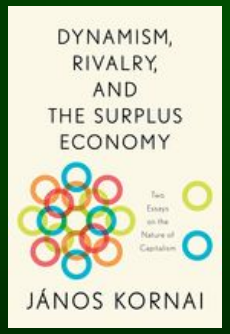
Jia et al, Nat. Comm. 4:2002

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

Network-independent mechanisms of plasticity-rigidy cycles

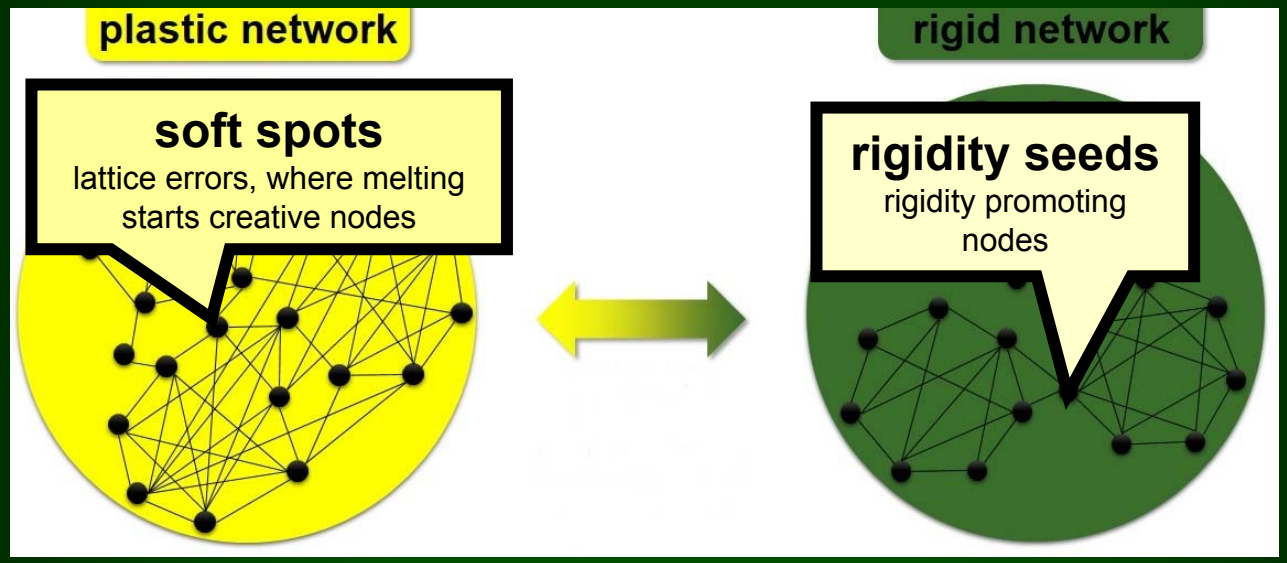
1. noise: reaching hidden attractors
   coloured noise, node-plasticity
2. medium-effects: water, chaperones
   membrane-fluidity, volume transmission
   as neuromodulation, money





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

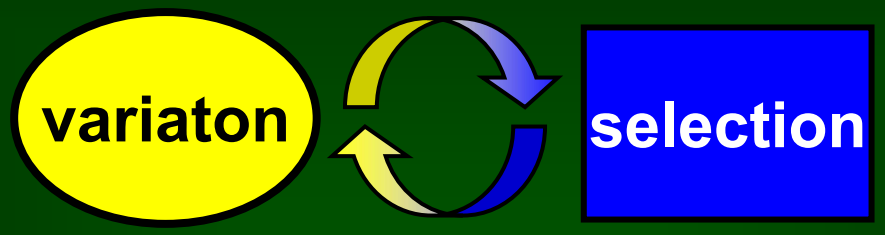
- cognitive functions become more rigid Psychol. Aging 4:136
- fluid intelligence decreases Intelligence 30:485
- practiced performance increases Handb. Phys. Aging 3:310
- personality rigidity increases Gen. Soc. Gen. Psych. Monogr. 128:165

- 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**

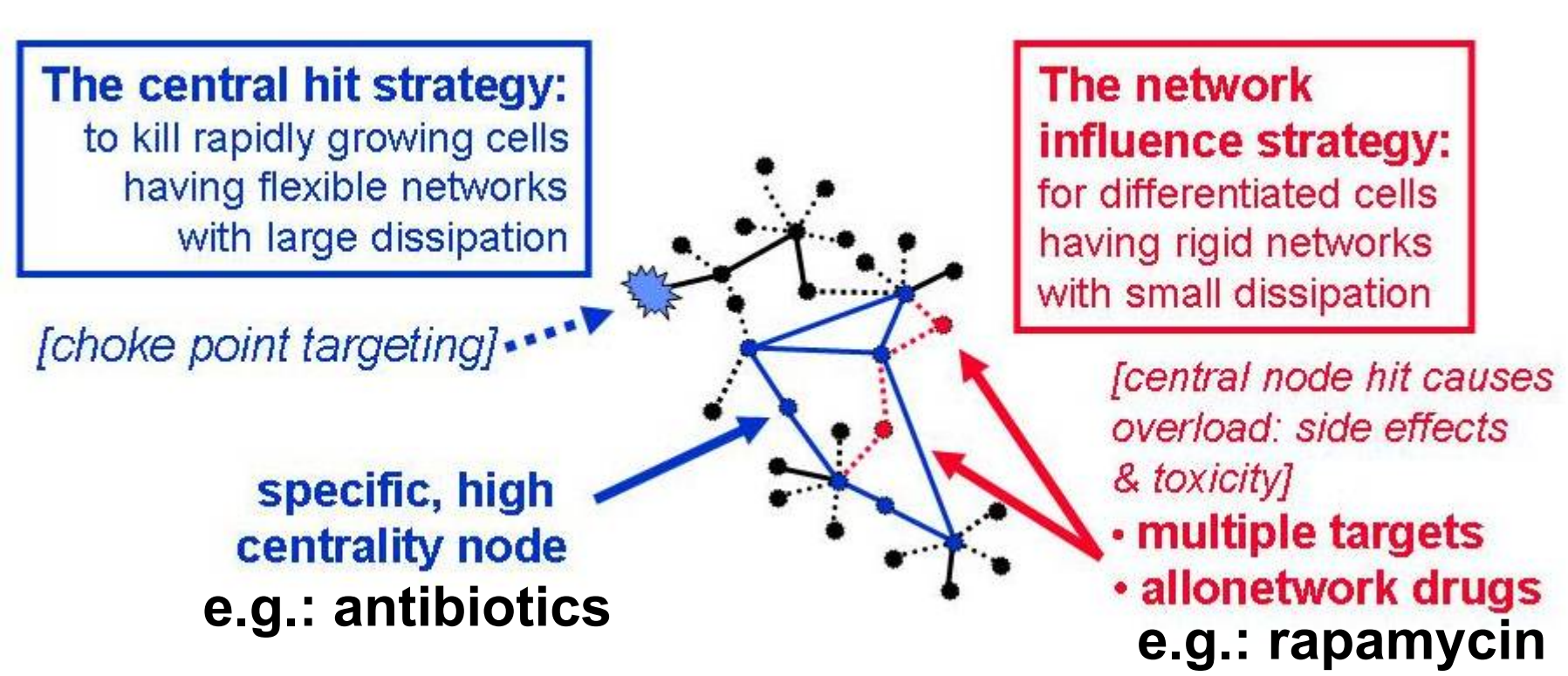


"evolutionary adaptation proceeds by **cycles of exploration** of a neutral network, **and** dramatic **diversity reduction** as beneficial mutations discover new phenotypes residing on new neutral networks"

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

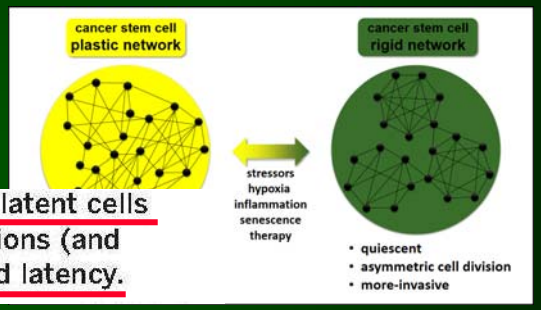
HIV LATENCY

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†]

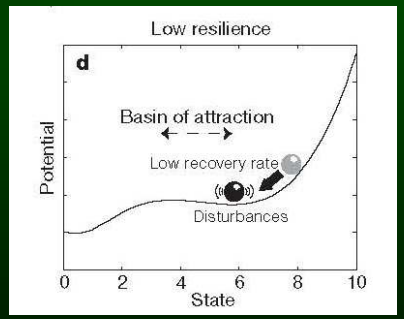
Stochastic fluctuations are inherent to gene expression and can drive cell-fate specification.

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

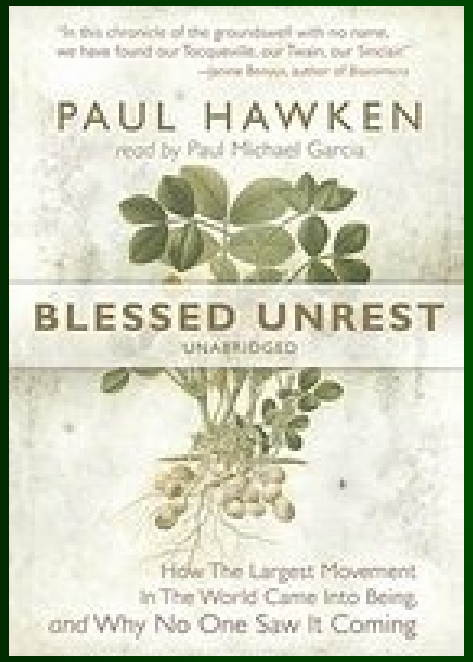
Nature 461:53

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

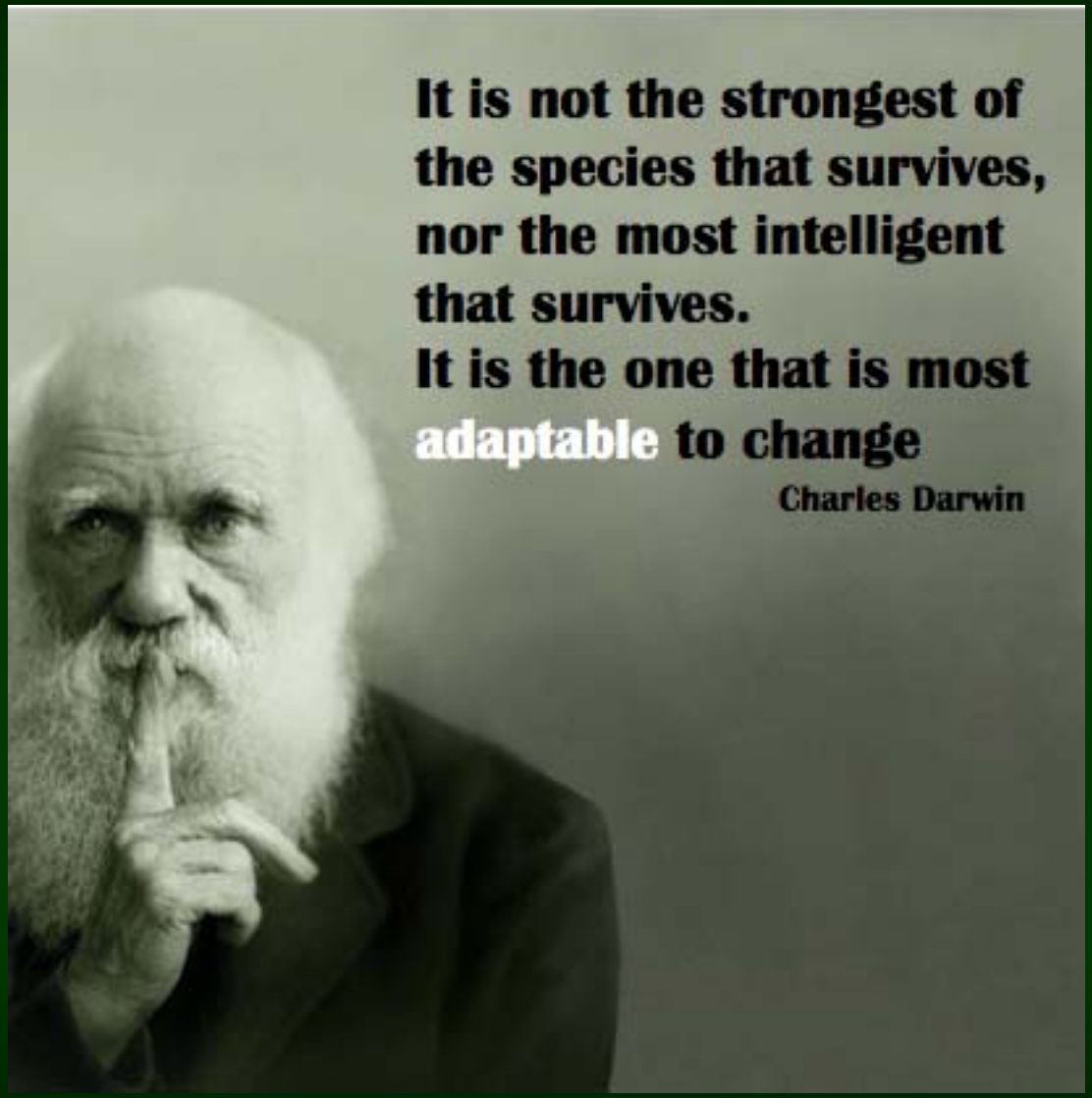
HYPOTHESIS Open Access

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


It is not the strongest of
the species that survives,
nor the most intelligent
that survives.
It is the one that is most
adaptable to change
Charles Darwin