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 csermelynnet@gmail.com
Networks and stability

Part 1 – Network topology

Peter Csermely

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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

- visual image
- right hemisphere
- emotions
- subconsciousness
New synthesis: networks

✓ both visual and
✓ logical

Newest synthesis: subconscious + emotions...
Traditional view

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

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

Generality of network properties offers
- judgment of importance
- innovation-transfer across different layers of complexity

Karinthy, 1929
Watts/Strogatz, 1998
Albert & Barabasi, 1999
Csermely, 2004
Crisis-prevention in different systems: example to break conceptual barriers

Early-warning signals for critical transitions

- 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

\[100^6 = >100 \times\]

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

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

Nature 393, 440; 1998
Weighted & directed small worlds

Network efficiency (cost):
a weighted world can be small
even if the non-weighted is not

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

(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

network model: preferential attachment (Matthew-effect, Pareto-law) generality for actors, power grid, www

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

\log P = \log a - \alpha \log k

Science 286, 509; 1999

László Barabási  Réka Albert
Generality of scale-free distributions

link-strength

Nature 427, 839; 2004

probability, Noe-effect

PNAS 92, 6689; 1995

Kohlrusch, 1854

Leiden-jars

cumulative wins

Bernoulli, 1738

Levy-flights

Can J. Zool. 80, 436; 2002

town size Zipf-law

ear, lightning, tic

sexual contacts

earthquakes,

Gutenberg-Richter law

science papers

Lotka-law

music

Nature 258, 317; 1975

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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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

- hubs
- central elements
- network skeleton
- modular structure
- core/periphery structure
Date hubs and party hubs

Han et al. Nature 430, 88
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**
  - hubs (degree)
  - closeness (sum of shortest paths to other nodes)
  - community centrality (influence of all other nodes)
  - betweenness (number of shortest paths through the node)

- **Global**
  - 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**

change of roles
Csermely,
Nature 454:5
TiBS 33:569
TiBS 35:539

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

Robert: broker
James: looser

Netocracy: continuous networking → Obama
Bard-Söderquist

Ron Burt,
Structural holes,
Harvard Univ. Press 1992
Complementary networking strategies
- safety seeking (optimization)
- novelty seeking (exploration)
  (seek the opinion leader,
  seek the strange, seek openness,
  jump to the next group)
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 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

Cyt-P450 (CYP2B4)

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

Creative elements are central and...
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)

WWW renormalization (unbranched ends)

Hierarchy: e.g. transcription factors

Garlaschelli et al., Nature 423, 165

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. (betweenness)

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

modular nets
intermodular contacts are suppressed

Newman, SIAM Rev. 45, 167

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

preferential attachment
model of modules

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

Pollner et al., Europhys. Lett 73:478
Modules need optimal overlap (brain default-network)

overlap of active neuronal modules

- **child**
  - usual task: PNAS 104:13507, PNAS 105:4028
  - novel task: Science 315:393

- **adult**
  - rest: PNAS 106:1279
  - novel task: PNAS 106:1942

- depression: PNAS 106:1279
- schizophrenia: PNAS 106:1942
- epilepsy: 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

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?

- 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

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
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
- 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

Colizza et al.
Nature Physics 2:110

a disassortative rich club
Nested networks

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.
Onion and wheel type networks

onion-networks: most robust scale-free networks against node removal
Schneider et al. PNAS 108:3838

wheel-networks: core + periphery
terrorist + drug traffic networks
Kenney 2008
Networks and stability

Part 3. – Network dynamics

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The usefulness of networks
Network tasks: dissipation of noise and response to signals

Noise is bad:
• diseases, tumors (PNAS 99, 13783)
• error catastrophe (Eigen, PNAS 99, 13374)

Noise is good: stochastic resonance

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

stochastic resonance: extrinsic noise
stochastic focusing: intrinsic noise
Stochastic resonance:
memory retrieval, pink noise, music

response time

difficult task
1/t pink noise

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

longitude determination
pendulum clock
synchrony

Huygens, 1665
Sync: other examples

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

- firefly

- bird-migration
  - Nature 431, 646

- clapping
  - Nature 403, 849

- yawning, laugh
  - Nature 229, 244; 392, 177

- menstruation
  - Nature 433, 417

- syphilis
Sync conditions

- small-world ↑
- modules ↓
- scale-free ↓
- weights ↑
- weak links ↑
## Differences between engineering and evolution

<table>
<thead>
<tr>
<th>Property</th>
<th>Engineering</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>development</td>
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<td></td>
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<tr>
<td>parts &amp; whole</td>
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<tr>
<td>optimization</td>
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<tr>
<td>optimized parameters</td>
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<td>intermediates</td>
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<td>elements</td>
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<tr>
<td>degeneracy</td>
<td></td>
<td></td>
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<tr>
<td>unexpected changes</td>
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</tbody>
</table>
Networks and stability

Part 4 – Examples for networks

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Peter Csermely
## Differences between engineering and evolution

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

- Membrane, organelle network
- Cytoskeletal network
- Metabolic network
- Signalng networks
- Protein-protein interaction network
- Gene transcription network
- Nucleus
Protein interaction networks

- yeast
- C. elegans
- Drosophila
- human

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

Science 302, 449
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

- Gold standard
- Coverage
- New interactions + false positives
- False positives
- True negatives

results
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

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

Science 311, 1764
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

<table>
<thead>
<tr>
<th>Species</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>yeast</td>
<td>4% trfactor</td>
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<tr>
<td>C. elegans</td>
<td>5</td>
</tr>
<tr>
<td>human</td>
<td>8</td>
</tr>
</tbody>
</table>
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?
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

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

Nature Neuroscience 10:186
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

danger signals elicit stress conditioning

mycorrhiza 100 m/g soil

Science 311, 812
Dolphin networks

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

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

“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.”

Raymond L. Johnson
Futures 36, 1095
Scientific judgements are not independent

optimistic universe: <5% false results
pessimistic universe: >90% false results
The power of judgements: US elections

70% of cases
Science 308, 1623
Networks and stability

Part 5. – Networks and drug design

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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
disease-related proteins form overlapping modules in the human interactome

Menche et al., Science 347:841
Drug network

Small giant component: follow-on drugs (experimental drugs: bigger giant. comp. $\rightarrow$ diversity)

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

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
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

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
Classic and network views of drug action

Csermely et al, Pharmacol & Therap 138, 333
Drug design strategies I.

The central hit strategy: for rapidly growing cells having flexible networks

choke point targeting

high centrality targets

The network influence strategy: for differentiated cells having rigid networks

influential nodes (neighbors of central nodes or of rigid clusters)

Csermely et al, Pharmacol & Therap 138, 333
Drug design strategies II.

- (i) Protein structures
- (ii) Protein-protein interaction network
Network-based drug target options

Overlapping nodes as drug targets

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

Guimera et al., Bioinformatics 23:1616
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.

- **The central hit strategy:** for rapidly growing cells having flexible networks
  - choke point targeting
  - high centrality targets

- **The network influence strategy:** for differentiated cells having rigid networks
  - influential nodes (neighbors of central nodes or of rigid clusters)

Csermely et al, Pharmacol & Therap 138, 333
Allo-network drugs: atom-level interactome reveals hidden targets


+ hit of intracellular 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

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

Multitarget drugs: low affinity drugs

- smaller dose and toxicity
- smaller blockade of alternative pathways
  - proteins \(\rightarrow\) in overlapping modules with different functions
  - single protein inhibition \(\rightarrow\) blocks multiple functions
  - partial inhibition of many proteins \(\rightarrow\) 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

Attack measure: network efficiency

Latora and Marchiori
Phys. Rev. Lett. 87:198701
Partial attack types

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

- Partial attack types:
  - a. Complete knockout
  - b. Partial inactivation of several targets
    - b1. Partial knockout
    - b2. Attenuation
  - c. Distributed system-wide attack
    - c1. Distributed knockout
    - c2. Distributed attenuation
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

proteome
(25 to 100 thousand proteins)

potential disease targets
(1700)

druggable proteins
(3000)

drug targets today
(~500)

multi-target drugs

novel drug target families

Effects are specific

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

PNAS 104:13655

long-range effects

yeast interactome

yeast interactome:
at least 20% changes
Multitarget drug search by modular analysis and multi-perturbation

www.linkgroup.hu/modules.php
Turbine: general network dynamics tool

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

www.Turbine.linkgroup.hu

Szalay & Csermely, Science Signaling 4:pt3
PLoS ONE 8:e78059
The Turbine network dynamics toolkit

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**

<table>
<thead>
<tr>
<th>Node</th>
<th>Size</th>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC28</td>
<td>100000</td>
<td>5</td>
</tr>
<tr>
<td>GSY2</td>
<td>50000</td>
<td>3</td>
</tr>
<tr>
<td>SLT2</td>
<td>8000</td>
<td>1</td>
</tr>
</tbody>
</table>

**Perturbation generated by Turbine::Designer**

<table>
<thead>
<tr>
<th>Node</th>
<th>Size</th>
<th>Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC28</td>
<td>99945</td>
<td>5</td>
</tr>
<tr>
<td>GSY2</td>
<td>49805</td>
<td>5</td>
</tr>
<tr>
<td>SLT2</td>
<td>7512</td>
<td>3</td>
</tr>
</tbody>
</table>

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)

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

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.

Mutations shifting back cancer cells from apoptosis to proliferation

<table>
<thead>
<tr>
<th>Set 1</th>
<th>Set 2</th>
<th>Set 3</th>
<th>Set 4</th>
<th>Set 5</th>
<th>Set 6</th>
<th>Set 7</th>
<th>Set 8</th>
<th>Set 9</th>
<th>Set 10</th>
<th>Set 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHK X</td>
<td>P53 X</td>
<td>P53 X</td>
<td>PIP3 +</td>
<td>IKK +</td>
<td>EEF2 +</td>
<td>P53 X</td>
<td>BCL-2 +</td>
<td>BCL-2 +</td>
<td>PIP3 +</td>
<td>APC +</td>
</tr>
<tr>
<td>IKK +</td>
<td>PIP3 +</td>
<td>GSK-3 X</td>
<td>IKK +</td>
<td>MYC X</td>
<td>MYC X</td>
<td>MYC X</td>
<td>RB X</td>
<td>RHEB +</td>
<td>P14 +</td>
<td></td>
</tr>
<tr>
<td>ERK X</td>
<td>ATM X</td>
<td>ATM X</td>
<td>ATM X</td>
<td>ATM X</td>
<td>ATM X</td>
<td>ATM X</td>
<td>ATM X</td>
<td>ATM X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSH X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCL-XL +</td>
</tr>
</tbody>
</table>

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

Interventions reversing proliferation of mutated cancer cells to apoptosis

(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:

<table>
<thead>
<tr>
<th>Set 1</th>
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<th>Set 8</th>
<th>Set 9</th>
<th>Set 10</th>
<th>Set 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTK -</td>
<td>RAF -</td>
<td>PDK1 -</td>
<td>P53+</td>
<td>P53+</td>
<td>P53+</td>
<td>RTK -</td>
<td>RAS - and</td>
<td>BAX +</td>
<td>BCL-2 -</td>
<td>PDK-1 -</td>
</tr>
<tr>
<td>PDK1 -</td>
<td>JNK +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BAX +</td>
<td>TGF-B + or BAX +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JNK +</td>
<td>BAD +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug development phases

Csermely et al, Pharmacol & Therap 138, 333
Networks and stability

Part 6. – A hypothesis

Peter Csermely

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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

<table>
<thead>
<tr>
<th>rigid</th>
<th>balanced</th>
<th>plastic</th>
<th>possibility of adaptation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td></td>
<td></td>
<td>effect of adaptation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gáspár & Csermely, Brief. Funct. Genom. 11:443
Csermely arxiv.org/abs/1511.01238

learning competent (exploration)

memory competent (optimization)
Example 2: Molecular mechanisms of protein structure optimization

**Hsp60 chaperone**
- Folded substrate (rigid)
- Unfolded substrate (plastic)
- Substrate release (plastic)
- Substrate expansion (rigid)

**Hsp70 chaperone**
- ATP
- Extended peptide bonds

Iterative annealing:
- Pull/release of folding protein

*plastic: many responses*
*rigid: few responses*

**References**
- Todd et al, PNAS 93:4030
- Csermely BioEssays 21:959
- Bukau & Horwich Cell 92:351
Example 3: cell differentiation

Rajapakse et al., PNAS 108:17257

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).
Example 4: disease progression

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

Scientific Reports 2:342; 813

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

rigid: few responses
plastic: many responses
Example 5: cancer stem cells

Csermely et al., Seminars in Cancer Biology
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
Example 2:
Adaptation of complex systems learning processes

Male bird synaptic plasticity alternates
(same kinetics of infant word learning)
Csermely arxiv.org/abs/1511.01238

Deregnaucourt et al Nature 433:710

Lipkind et al Nature 498:104
Day et al Dev. Neurobiol. 69:796
Example 2: Adaptation of complex systems creativity

blind variation → selective retention

Donald T. Campbell

Adaptation of complex systems creativity

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

Adaptation of complex systems learning organizations

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

Opinion leaders have consensus

Opinion leaders disagree

fast and strong response

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

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 \(\rightarrow\) sink, positive \(\rightarrow\) negative, energy giving \(\rightarrow\) energy vampire)

1. rigid \(\rightarrow\) plastic
2. energy is concentrated in rigid regions, ‘melts’ them, making them more plastic
3. plastic \(\rightarrow\) rigid

Jia et al, Nat. Comm. 4:2002
Network-independent mechanisms of plasticity-rigidity 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  

- 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*
"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

- The central hit strategy: to kill rapidly growing cells having flexible networks with large dissipation.

- The network influence strategy: for differentiated cells having rigid networks with small dissipation.

Specific, high centrality node, e.g.: antibiotics

[choke point targeting]

[central node hit causes overload: side effects & toxicity]
- multiple targets
- allo network drugs, e.g.: rapamycin

Csermely et al, Pharmacol & Therap 138: 333-408
Applications 3: Intervention design

1. plasticity-rigidity cycle boosting or freezing

Science 344:1392

Screening for noise in gene expression identifies drug synergies

- 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.

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