Networks and stability

Part 1 – Network topology

http://linkgroup.hu
http://turbine.ai
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Péter Csermely and the Turbine team
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)
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)
1. problems of simplicity
   Leibnitz, Newton
2. disorganized complexity
   Boltzmann, Maxwell, Gibbs
3. organized complexity

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

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

Caution: Extreme data reduction!
- based on background knowledge
Emergent properties of complex systems

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

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

<table>
<thead>
<tr>
<th>Early-warning signals for critical transitions</th>
<th>Aging is an early warning signal of a critical transition: death</th>
</tr>
</thead>
<tbody>
<tr>
<td>ecosystem, market, climate</td>
<td>Prevention: elements with less predictable behaviour</td>
</tr>
<tr>
<td>• slower recovery from perturbations</td>
<td>• omnivores, top-predators</td>
</tr>
<tr>
<td>• increased self-similarity of behaviour</td>
<td>• market gurus</td>
</tr>
<tr>
<td>• increased variance of fluctuation-patterns</td>
<td>• stem cells</td>
</tr>
<tr>
<td>Nature 461:53</td>
<td>Farkas et al., Science Signaling 4:pt3</td>
</tr>
</tbody>
</table>
Creative nodes
(as possible targets of anti-aging therapies)

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

Why is such a behavior creative?

Distributor: hub, specialized to signal distribution, predictable

Problem solver: specialized to a task, predictable

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

Ron Burt, Structural holes, Harvard Univ. Press 1992

Robert: broker
James: looser

Why?

Netocracy: continuous networking → Obama
Bard-Söderquist
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)
• You may get useful hints for your jobs from distant acquaintances much better than your relatives
• Why is this surprising?
• Why is this true?

Am. J. Sociology 78:1360
Creative nodes are central and... 

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

Creative proteins
- stress proteins
- signaling switches

Creative cells
- stem cells
- our brain

Creative persons
- firms
- societies

Cyt-P450 (CYP2B4)

drug-binding

oxidation

Csermely,
Nature 454:5
TiBS 33:569
TiBS 35:539
“... To create consists in not making useless combinations. Among chosen combinations the most fertile will often be those formed of elements drawn from domains which are far apart.”

Henry Poincaré: Foundations of Science (1908)
Networks are embedded
Networks are embedded
Networks are embedded
Major classes of network topology

regular  random  small-world  scale-free

Sporns et al. Trends Cogn Sci. 8, 418
The Milgram-experiment

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

$100^6 = >100 \times$
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 \sim \text{logarithm of } N \text{ (number of elements)}]

general model
examples:
- \textit{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

\[ E = \frac{\sum_{i<j} \frac{1}{d_{i,j}}}{N(N-1)} \]

(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

Science 286, 509; 1999

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

\[ \ln P = \ln a - \alpha \ln k \]
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

music

Nature 258, 317; 1975

fractals, architecture

town size Zipf-law

rain, lightning, tic

sexual contacts

earthquakes,

Gutenberg-Richter law

science papers

Lotka-law

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
Reasons behind the generality of scale-free distributions

• preferential attachment
• cumulative success of consecutive tasks
• self-organization of matter in the Universe
Networks and stability

Part 2. – Network topology

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Péter Csermely and
the Turbine team
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

yeast protein network
–date hubs
–party hubs
Types of network centralities

- **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)

**Local**

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

- Food-chain renorm. (energy-flow)
- 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)

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

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

<table>
<thead>
<tr>
<th>child</th>
<th>adult: usual task</th>
<th>adult: rest, novel task</th>
<th>depression</th>
<th>schizophrenia</th>
<th>epilepsy</th>
</tr>
</thead>
</table>
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?

modules

- stop noise, damage and sync
- can evolve independently
- separate functions (induce diversity)
- allow sophisticated regulation by fringe areas
a.) extensively overlapping, soft modules: random routes

b.) moderately overlapping modules: converging routes

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

Csermely et al, Pharmacology & Therapeutics 183:333-408
How are modules formed?

integration
(symbiosis)

parcellation

Zachary’s charate club
administrator: circles
instructor: squares
Girvan-Newman, PNAS 99,7821
Modules and nestedness
**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

- **Periphery**
  - High variability/evolvability, fewer constraints, more plastic

- **Core**
  - Low variability/evolvability, more constraints, more rigid, cooperates efficiently

- **Periphery**
  - High variability/evolvability, fewer constraints, more plastic

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.

Rich-club, nested network, onion network

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

Masuda and Konno
Social Networks 28, 297

Radicchi
arxiv.org:1101.4028
Onion and wheel type networks

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

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

Part 3. – Network dynamics

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Péter Csermely and the Turbine team
The usefulness of networks

Csermely: Weak Links, Springer
Network tasks: dissipation of noise and response to signals

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

Noise is good: stochastic resonance

- 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

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

- continuously increasing tension
- partially restricted relaxation
  - avalanche

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

bird-migration

firefly

clapping
Nature 403, 849

yawning, laugh

menstruation
Nature 229, 244; 392, 177

syphilis
Nature 433, 417

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

Nature 431, 646
Sync conditions

- small-world $\uparrow$
- modules $\downarrow$
- scale-free $\downarrow$
- weights $\uparrow$
- weak links $\uparrow$
# 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>
Networks and stability

Part 4 – Examples for networks

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Péter Csermely and the Turbine team
Protein structure networks

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

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

Böde et al, FEBS Letters 581:2776
Protein structure networks


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

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

Where do you find key segments besides hubs?

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

Csermely, TiBS 33:569

Cyt-P450 (CYP2B4)
Modules of Met-tRNA-synthase network correspond to protein domains

Szalay-Bekő et al. Bioinformatics 28:2202
www.linkgroup.hu/modules.php
Bridges of Met-tRNA-synthase network identify signaling amino acids

Ghosh et al. PNAS 104:15711

signaling amino acids
(identified from MD cross-correlations)

other amino acids

Szalay-Bekő et al. Bioinformatics 28:2202

system dynamics
predicted from topology
Folding networks in the ‘reality’

Why is it good that it is a small world?

20 AA peptide nodes: conformations
links: transitions

JMB 342, 299
Cellular networks

membrane, organelle network

gene transcription network

nucleus

signaling networks

metabolic network

protein-protein interaction network

cytoskeletal network
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 system, bait/prey + reporter gene expression biased to nuclear proteins, false negatives due to posttranslational 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
- True negatives
- Results
- Coverage
- False positives
- New interactions + false positives
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>Organism</th>
<th>Similarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>yeast</td>
<td>4% trfactor</td>
</tr>
<tr>
<td><em>C. elegans</em></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

Why is this good?
Neural networks

- cat brain net: neurons
- human brain billion neurons
- sync
- small world
- scale-free
- modular

Trends Cogn. Sci. 8, 418
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

fungi

roots

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
cognitive 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

competent: winner
not competent: looser
Networks and stability

Part 5. – Adaptation of complex systems, a hypothesis

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Péter Csermely and the Turbine team
Topological phase transitions:
The importance of resource poor
and resource rich environments

Physica A 334, 583; PRE 69, 046117
Example 2:
Adaptation of complex systems

Plasticity-rigidity cycles form a general adaptation mechanism

Csermely arxiv.org/abs/1511.01238
Example 2:
Adaptation of complex systems
rigid and plastic properties

Gáspár & Csermely, Brief. Funct. Genom. 11:443
Csermely arxiv.org/abs/1511.01238
Example 2: Molecular mechanisms of protein structure optimization

Iterative annealing:
- Pull/release of folding protein
- Expanded peptide bonds

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

Hsp70 chaperone:
- Substrate expansion (rigid)
- Plastic: many responses
- Rigid: few responses

Literature:
- 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
Example 5: cancer stem cells

Csermely *et al.*, Seminars in Cancer Biology

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

- proliferative
- symmetric cell division
- less-invasive

- quiescent
- asymmetric cell division
- more-invasive
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

**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  \(\leftrightarrow\) selective retention

Donald T. Campbell

Dean Keith Simonton

---

**brainstorming**

**PDCA-cycle**

**OODA-loop**

Csermely arxiv.org/abs/1511.01238
Example 2: Adaptation of complex systems learning organizations

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

exploration → exploitation

in firm and product development

Csermely arxiv.org/abs/1511.01238
Network-independent mechanisms of plasticity-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

- **plastic network**
  - soft spots
    - lattice errors, where melting starts creative nodes

- **rigid network**
  - rigidity seeds
    - rigidity promoting nodes

- 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  $\rightarrow$  genetic regulatory networks more rigid  
  \(\text{via system constraint increase}\)  
  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

[choke point targeting]

specific, high centrality node
 e.g.: antibiotics

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

[central node hit causes overload: side effects & toxicity]

- multiple targets
- allonetwork 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.

2. targeting during cycle-induced attractor-change

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

   Nature 461:53

age-change: plasticity-personalized therapies
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

HYPOTHESIS

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

Lajos Rózsa¹, Péter Aperil and Viktor Müller²

When our body becomes jeopardized, our 10 billion bacteria gain more independence
Plastic behaviour (unrest) is characterized by exploration + unstability of the inner self
Alternating resource poor and resource rich periods build multi-layer complexity

- Resource rich, expansion, plastic
- Resource-poor, survival, rigid

Stability isolation

- Specialization, long-term cooperation
- New resources
- Self-organization, environment stabilization

Resource rich, expansion, plastic at a higher layer of hierarchy

Self-organization, environment stabilization

Resource-rich expansion, plastic

Self-organization, environment stabilization

New resources

Stability isolation

Specialization, long-term cooperation

Resource-poor, survival, rigid

Resource-rich expansion, plastic
Networks and stability

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

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Péter Csermely and the Turbine team
Decision-making of complex systems
key initial statements, I.

1. Learning increases the weight of edges involved

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

2. Learning develops (or deepens) attractors

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

   - John Hopfield, PNAS 79:2554
   - William A. Little, Math. Biosci 19:101
   - Jerzy Konorski, 1948
   - Alexander Bain, 1874
   - Santiago Ramon y Cajal, 1894
   - Erkki Oja, 1982
   - Donald O. Hebb, 1949
   - Carillo-Reid et al, Science 353:691

3. A few central nodes make a network core

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

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

4. Responses of complex systems form a few attractors

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

Stuart Kauffman
Nature 224:177-8

**http://turbine.ai**

attractors of T-LGL cancer cell

PLoS Comp Biol 11:1004193; arxiv.1605.08415
J Dyn Diff Eq 25:563; J Theor Biol 335:130

Réka Albert
We know a lot on complex networks.

We know a lot on their attractors.

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

This lecture tries to give a generally applicable answer to this question.
Decision-making of complex systems
fast and slow thinking of networks

Opinion leaders have consensus
usual information
fast and strong response

Opinion leaders disagree
new information
slow response requiring the contribution of the whole community (slow democracy)

Csermely arxiv.org/abs/1511.01239
Decision-making of complex systems

Example 1A: protein heat transfer

Adaptation is encoded by evolutionary selection!

PSD95 PDZ-domain protein; His76-Phe29 channel
core $\rightarrow$ fast, anisotropic heat transfer
periphery (Tyr96) $\rightarrow$ slow heat diffusion

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

Ota and Agard
JMB 350:345
Decision-making of complex systems
Example 1B: protein energy transfer

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

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

femtosecond infrared laser pulses + ultrafast time-resolved IR spectroscopy
Nature Communications 5:3100
**Decision-making of complex systems**

**Example 1C: allostery, conformational memory**

**Allostery: direct response not evolutionary selection**

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

b. ‘ballistic’ heat-transfer between albumin binding sites is enhanced by its allosteric activator  
   Nat Commun 5:3100

c. „allokairy”: higher substrate affinity after catalytic cycle completion – relaxing later  
   PNAS 112:11430/11553; Sci. Rep. 6:21696

d. conformational memory: neuronal + evolutionary memory

![Diagram of allostery and conformational memory](image-url)
Decision-making of complex systems
Example 1D: cellular networks, ecosystems

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

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

c. general and specific resilience (memory) of ecosystems shows the same core/periphery duality
Decision-making of complex systems

Example 2: brain

a. learning of *Tritonia* escape response shifts periphery neurons to the core
   Curr Biol 25:1

b. space learning of rat/mice hippocampus cells: **plastic** (periphery) **cells become rigid** (core)
   Science 351:1440; Science 354:459

c. memory retrieval activates core neurons, which were preferentially connected in the learning process
   Science 353:691; Nature 526:653
Decision-making of complex systems

Example 3: social networks

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

PNAS 110:13769

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

Science 337:337; PRE 81:057103; Phys A 343:725; Nature 461:879
Decision-making of complex systems
A more detailed mechanism

**A. Stimulus is compatible with a previously set attractor of the network core**
- Stimulus transferred fast to the rigid core
- Scenario 1: pre-set response of some core nodes is activated transferring the system to its respective attractor
- Fast system response

**B. Stimulus is incompatible with previously set attractors of the network core**
- Stimulus provokes conflicting core responses
- Scenario 2: system fluctuates between attractors + stimulus propagates to the periphery
- Slow system response

**C. Repeated stimuli set a new attractor using the contribution of the network periphery**
- Scenario 3: repeated stimuli reconfigure the network core encoding a new system attractor
- Emerging novel system response

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

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

   J Dyn Diff Eq 25:563; J Theor Biol 335:130; arxiv.1605.08415

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

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

d. Hebbian learning may form/re-shape attractors by reconfiguring
   the periphery and deepen attractors by reconfiguring the core
Decision-making of complex systems
Mechanisms 1: bridging distant network regions

a. ‘creative nodes’ bridge distant network regions

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

P. Csermely

Trends Biochem Sci 33:569

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

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

PNAS 113:2982; PNAS 113:11823
Decision-making of complex systems
Mechanisms 2: edge reversal

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

1. rigid → plastic
2. energy is concentrated in rigid regions, ‘melts’ them, making them more plastic
3. plastic → rigid

Jia et al, Nat. Comm. 4:2002
**Decision-making of complex systems**

**Mechanisms 3: core remodeling**

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

PNAS 112:4690; Nature 524:65

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

Science 337:49; Rogers: The Diffusion of Innovations

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

this may lead to the deletion of some of the old attractors (forgetting)
Decision-making of complex systems
Possible limitations

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

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

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

PNAS 113:11441; Science 351:32; Pharm. Therap. 138:333
Decision-making of complex systems

Take home messages

1. attractors of previously learned responses are encoded by the network core
2. the core gives fast and efficient/reliable responses to known situations
3. creative solutions of novel situations need the experience of the network periphery too
4. democracy is NOT only a moral stance or one decision making technique of the many but our evolutionarily encoded 'survival recipe' amidst unexpected challenges
“It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change”

- Charles Darwin
Networks and stability

Part 7. – Drug design

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Péter Csermely and the Turbine team
Drug-related networks

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

Goh et al., PNAS 104:8685

1,284 diseases & 1,777 related genes
link between two diseases: if they have a common gene

deafness
blindness
paralysis
diabetes
epilepsy + mental retardation
obesity
cancer
anemia
stroke
Alzheimer’s
high blood pressure
atherosclerosis
asthma
Parkinson’s
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
Wang et al., JCI Insight 2:e93911

Placebo effects in various diseases
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
Therapy-network

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

Nacher & Schwartz, BMC Pharmacol. 8, 5
Prediction of drug binding sites in protein structure networks

large but shallow cavity

drug binding

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

Nayal & Honig, Proteins 63:892

How would you identify here cavities?

structural holes: missing links and nodes

Csermely, TiBS 33:569
Drug target crisis

New, active drug ingredients as expenditure increased

Drugs targets

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

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

US$2.6 billion
Average pre-tax cost per approved drug, including cost of failures

FDA tightens regulation after the thalidomide scandal.

FDA begins to clear backlog of applications.

reverse Moore law
Classic and network views of drug action

Csermely et al, Pharmacol & Therap 138, 333
http://arxiv.org/abs/1210.0330
Drug design strategies I.

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
http://arxiv.org/abs/1210.0330
Drug design strategies II.
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
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
http://arxiv.org/abs/1210.0330
Allo-network drugs: atom-level interactome reveals hidden targets

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 knock-out of nodes
substituting the most needed node

partial KO 50% attenuation

\[ \begin{align*}
E. coli (1) & \quad 4.2 & \quad 5 \\
S. Cerevisiae (1) & \quad 2.8 & \quad 3 \\
\end{align*} \]

Ágoston et al., Phys. Rev. E 71:051909
Partial knock-out of links substituting the most needed node

\[ \text{distributed KO} \quad \text{distributed attn.} \]

\[ \begin{align*}
E. \text{ coli (72)} & : 15 & 38 \\
S. \text{ cerevisiae (18)} & : 6 & 10
\end{align*} \]

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
Drug development phases

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