

# Az atomoktól a csillagokig

Közérthető fizika, nem csak középiskolásoknak


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2020-21. tanév – 16. évad

## Fizikusként a rák ellen

Kovács István

- Új kísérleti módszerek kidolgozása (MRI)
- Terápiák fejlesztése (sugárterápia)
- Szövetek fizikai perturbálása (nanorészecskés fűtés)
- Adatelemzési módszerek kidolgozása
- Mechanizmusok feltárása matematikai modelleken keresztül
- Mi az ami nélkülözhetetlen és mit lehet elhanyagolni?
- **Általában is, bármilyen komplex rendszerben...**



*“I think the next century  
will be the century  
of complexity.”*

Stephen Hawking  
January 23, 2000`

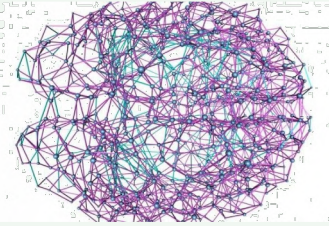
# Komplex Rendszerek

Definition from the book of Hiroki Sayama:

Complex systems are networks made of a number of components that interact with each other, typically in a nonlinear fashion. Complex systems may arise and evolve through self-organization, such that they are neither completely regular nor completely random, permitting the development of emergent behavior at macroscopic scales.

- Enigmatic example: human brain
- Several orders of magnitudes of space and time scales
- Complex structure and dynamics
- We hope to find organizing rules, guiding our understanding
- If no such rules: not “really” a “complex” system

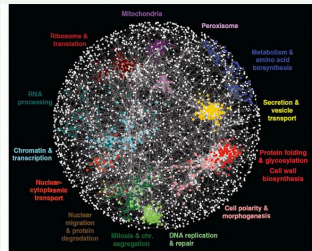
# Nagy hálózatok



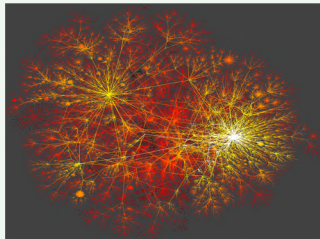
- Human brain:
  - ~86 billion neurons, >100 trillion connections



- Society:
  - ~8 billion people



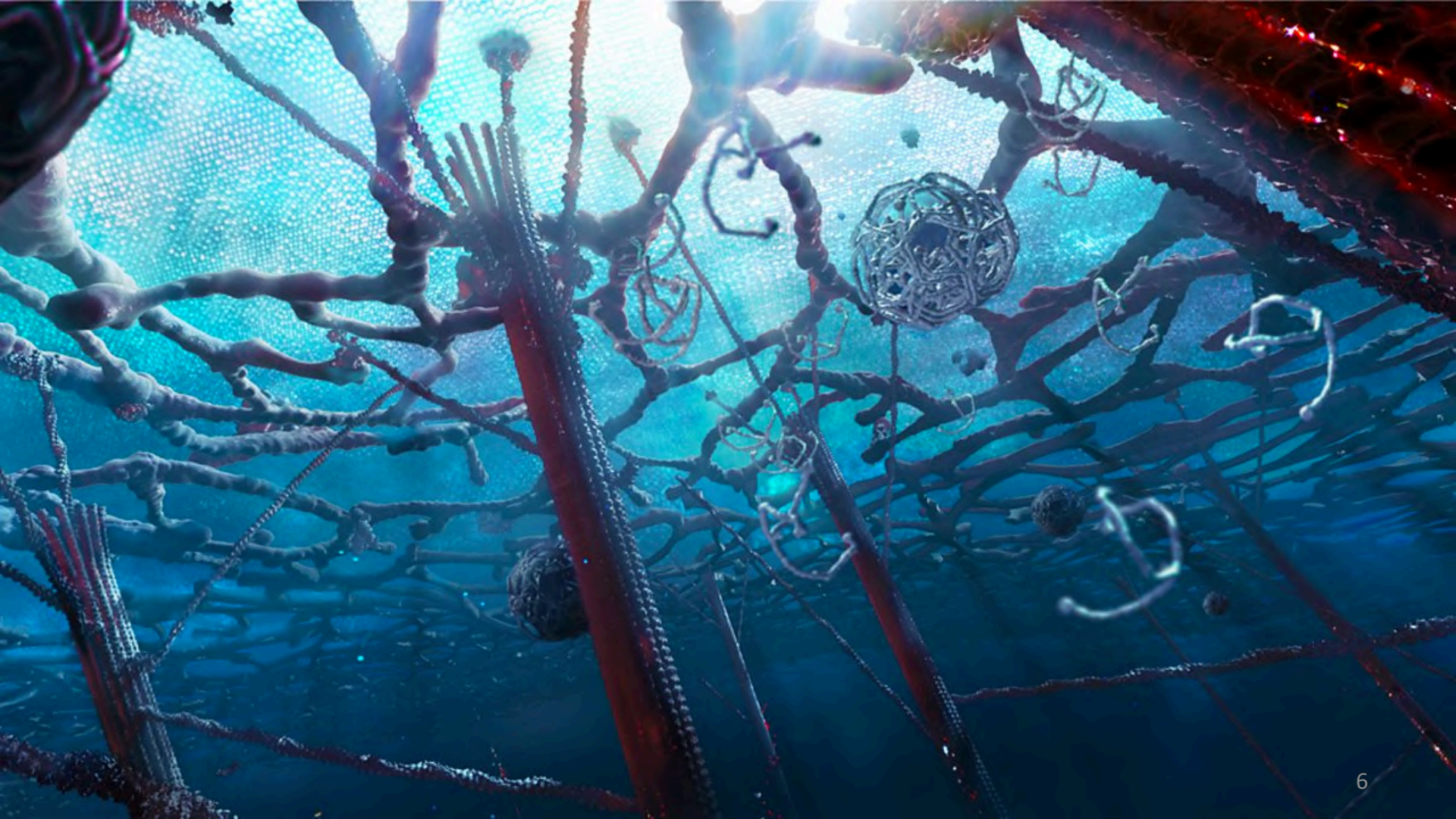
- Genetics:
  - ~3 billion base pairs



- WWW:
  - ~6 billion pages

Functional insights through:

- structural patterns
- dynamical models
- control



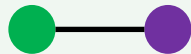
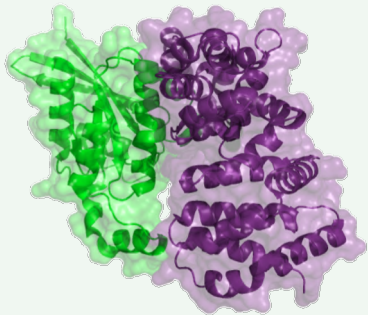
# Fehérje kölcsönhatások

Proteins and their interactions are fundamental building blocks

The basis to understand and predict:

- protein function
- complex disease mechanisms
- impact of mutations (edgotyping)
- drug effects

Huge search space of >200 million pairs

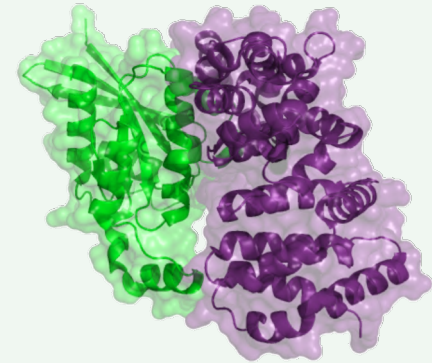


Nodes: proteins  
Links: interactions



# Fehérje kölcsönhatások mérése

Approaches	Binary interaction mapping	Protein complex mapping	
Primary screening method	Y2H	AP-MS	Co-fractionation
Space			
Screening method			
Readout	<p>+ NGS sequencing</p>		
Resulting protein pairs			
		Scoring and filtering	
Type of biophysical relationship	PPI	PPA + PPI	
Validation	MAPPIT, PCA, wNAPPA	None	SILAC-based AP-MS
Dataset	HI-II-14	BioPlex	QUBIC
Number of pairs	13 867	23 744	28 780
Number of proteins	4297	7668	5457
			CoFrac
			16 468
			3426



## Proteome-Scale Human Interactomics

Katja Luck,<sup>1,2,3,\*</sup> Gloria M. Sheynkman,<sup>1,2,3,\*</sup> Ivy Zhang,<sup>1,2,3</sup> and Marc Vidal<sup>1,2</sup>

Statistical Inference

Compromise between:

- False Positives
- False Negatives



# Hiányos információ

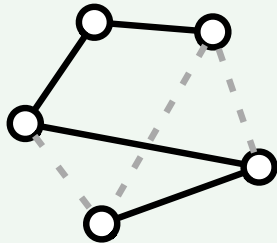


# Nagy zajos hálózatok

Incompleteness



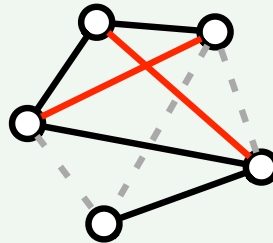
Missing links



Noise



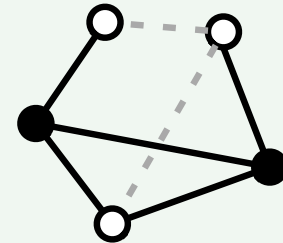
Both missing and  
**false** links



Study biases



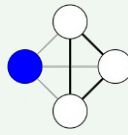
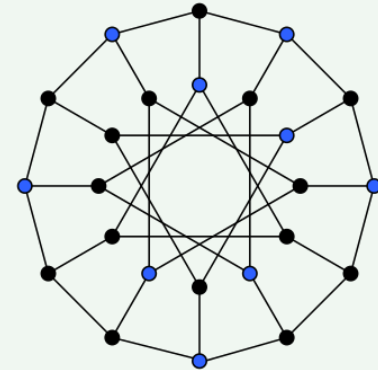
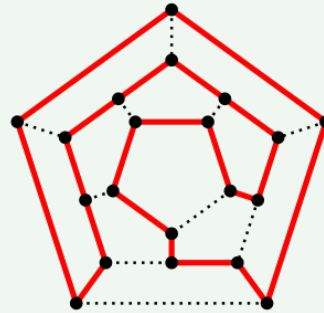
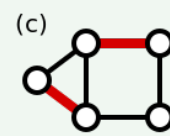
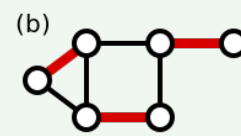
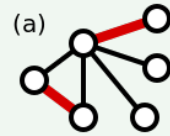
Some nodes are more  
completely mapped



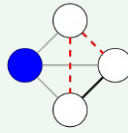
# Nagy zajos hálózatok – gráfelmélet?

- What if we know only 20% of the edges?

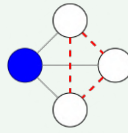
- Matching
- Independent sets
- Diameter
- Clustering
- Community structure
- Controllability
- Dynamics



$c = 1$

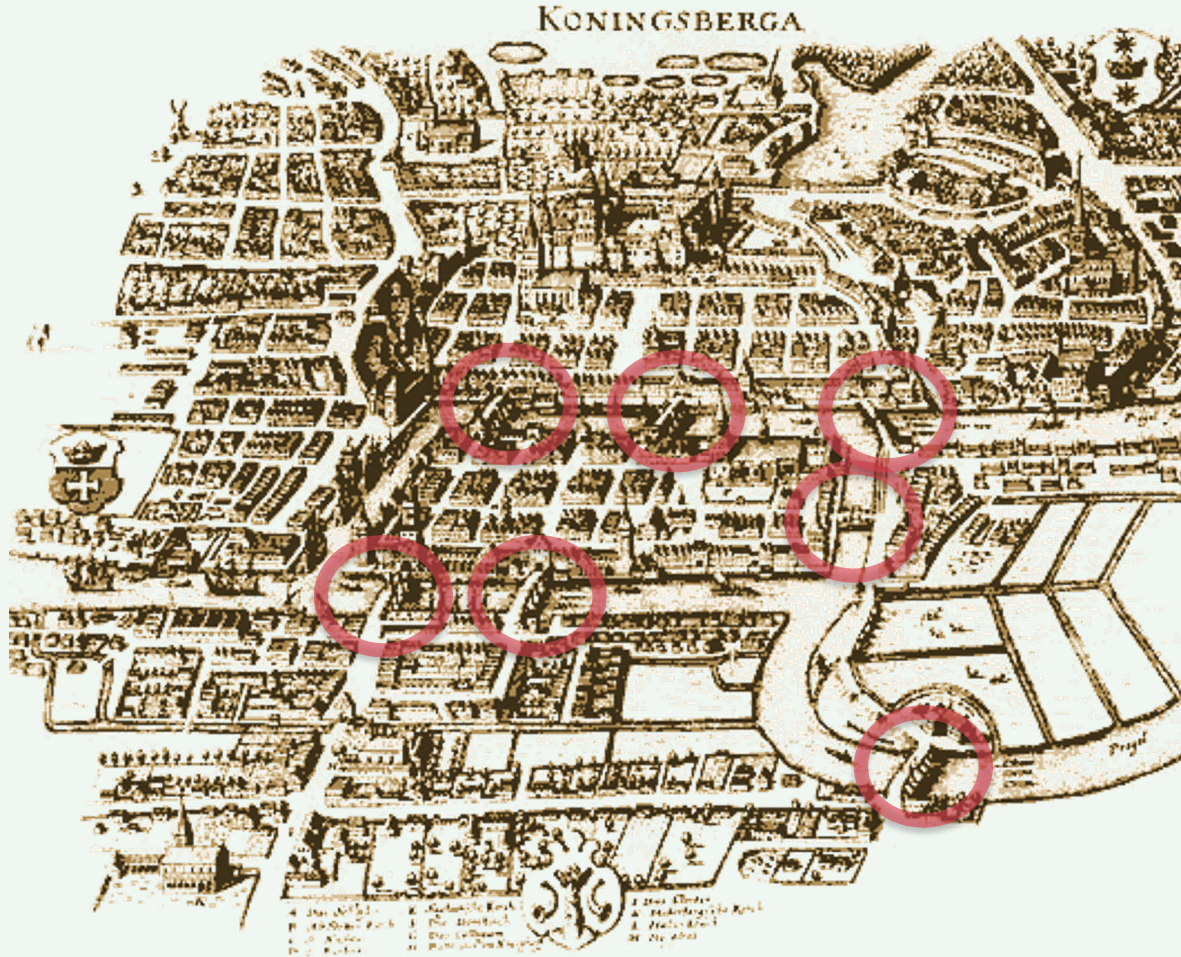


$c = 1/3$

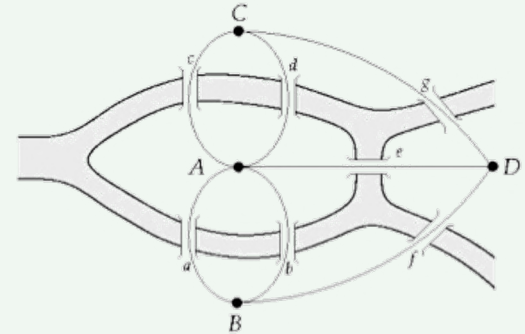


$c = 0$

# Königsbergi hidak



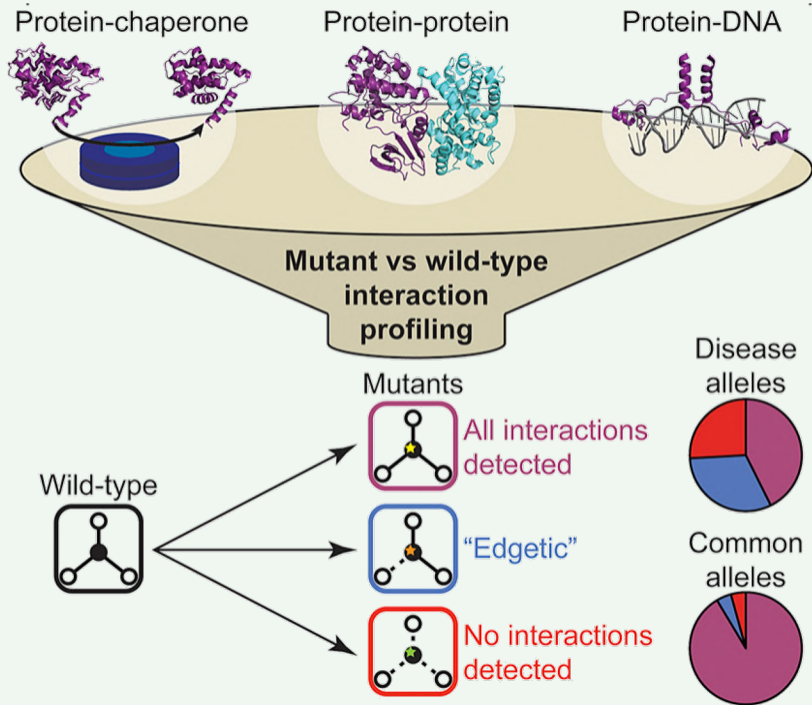
Can one walk across the seven bridges and never cross the same bridge twice?



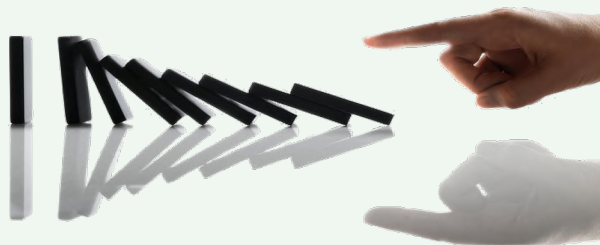
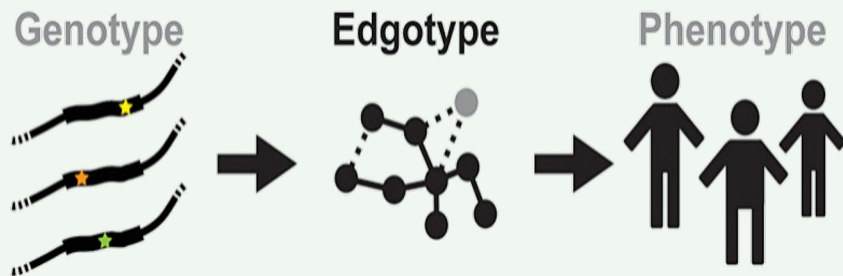
1735: Euler's theorem:

- (a) If a graph has more than two nodes of odd degree, there is no path.
- (b) If a graph is connected and has no odd degree nodes, it has at least one path.

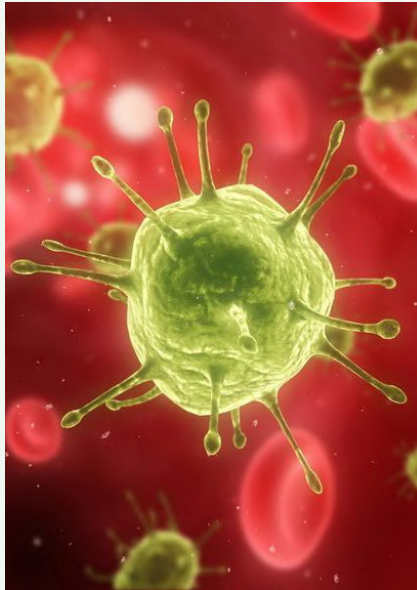
# Hálózati zavarok



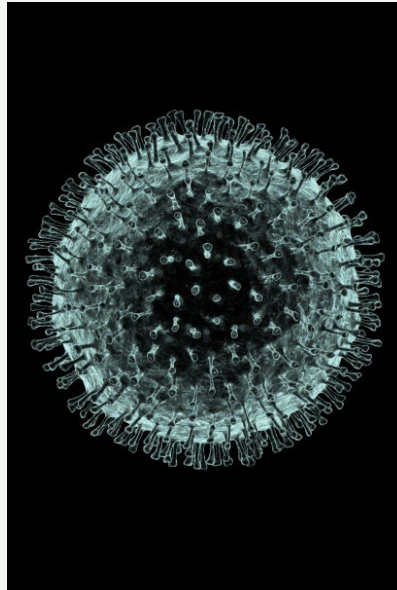
Sahni *et al.*, *Cell* 2015



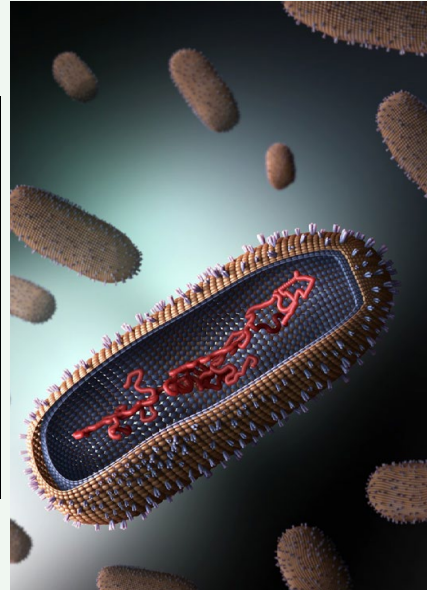
# Vírusok



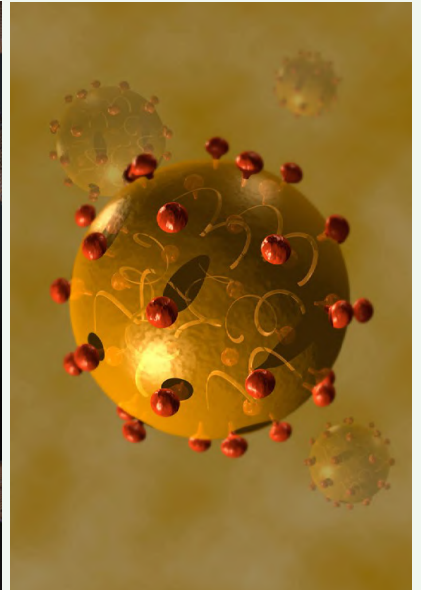
HIV



SARS

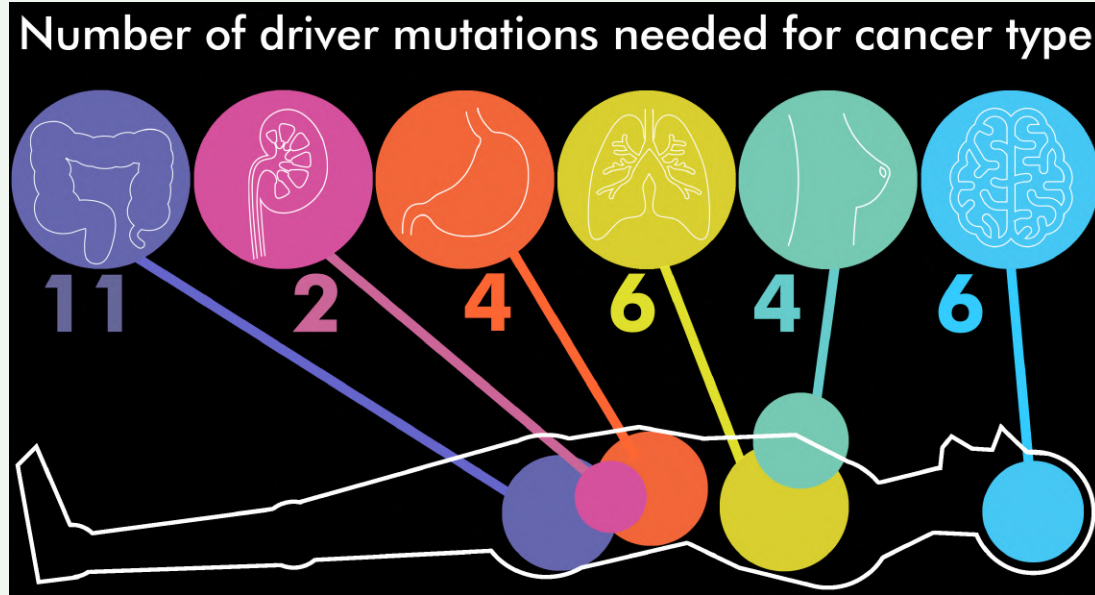


influenza



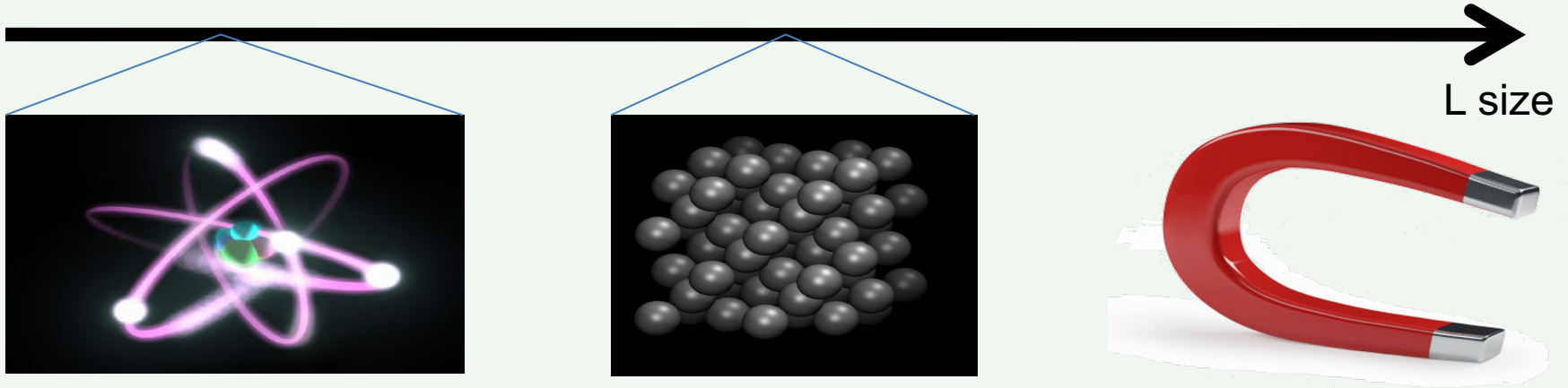
Hepatitis C

# A rák genetikai háttere



'half of these key mutations driving cancer occur in genes that are not yet identified as cancer genes'

How to infer new disease genes, and target them with drugs?

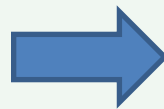
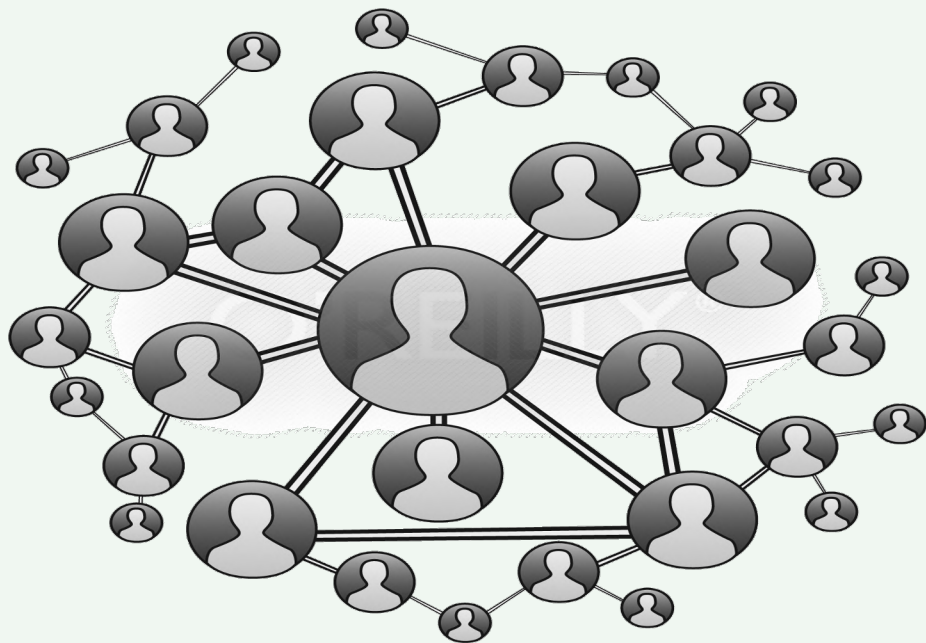


Phase transitions

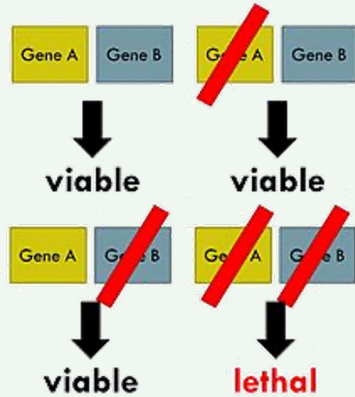
$$\mathcal{H} = - \sum_{(i,j)} J_{ij} \sigma_i^x \sigma_j^x - \sum_i h_i \sigma_i^z$$



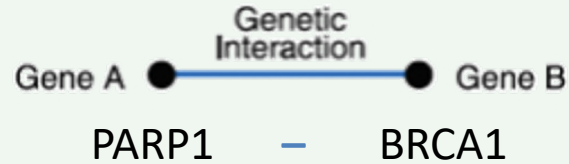
# Hasonló adatok és kérdések



Synthetic lethality:

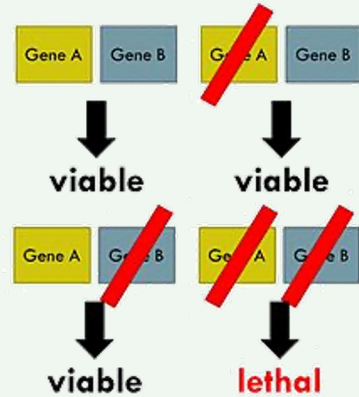


$$\epsilon_{ij} = f_{ij} - f_i f_j$$

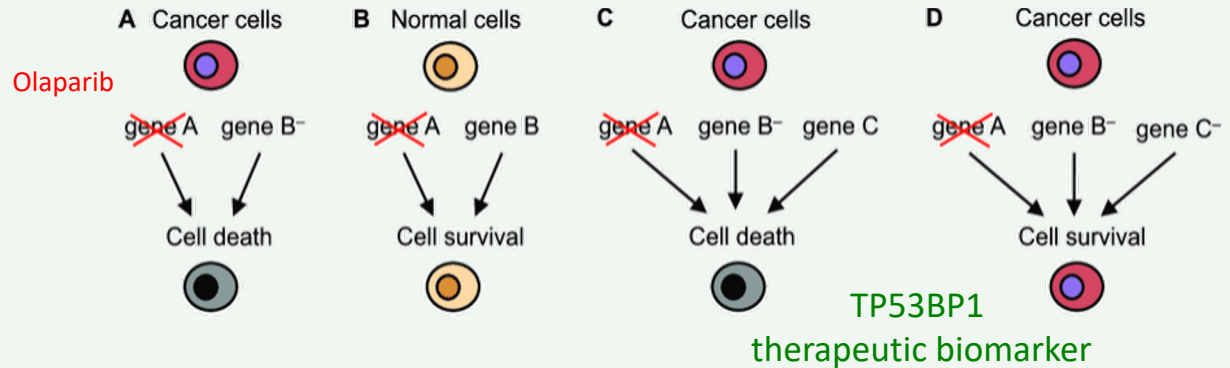
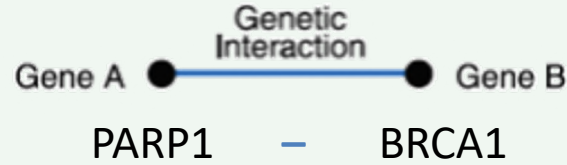


# Genetikai kölcsönhatások

Synthetic lethality:



$$\epsilon_{ij} = f_{ij} - f_i f_j$$



Goal: capture genetic interactions between 2 and more genes – spin glass problem

First: significant overlap with bio-physical interactions

# Hiányos hálózatok

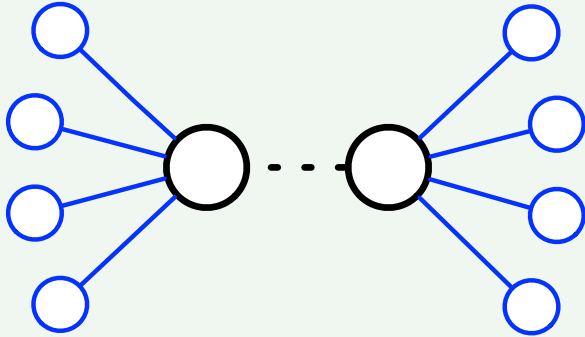


“Gentlemen, we have run out of money. It's time to start thinking.”

— **Ernest Rutherford**

# “Hasonlóság = Kölcsönhatás”

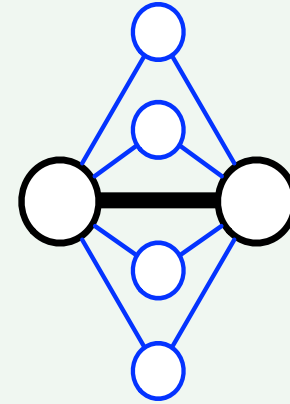
## Triadic Closure Principle



no shared neighbors  
low similarity

Jaccard index = 0

$$\frac{|N_i \cap N_j|}{|N_i \cup N_j|}$$



all neighbors shared  
high similarity

Jaccard index = 1

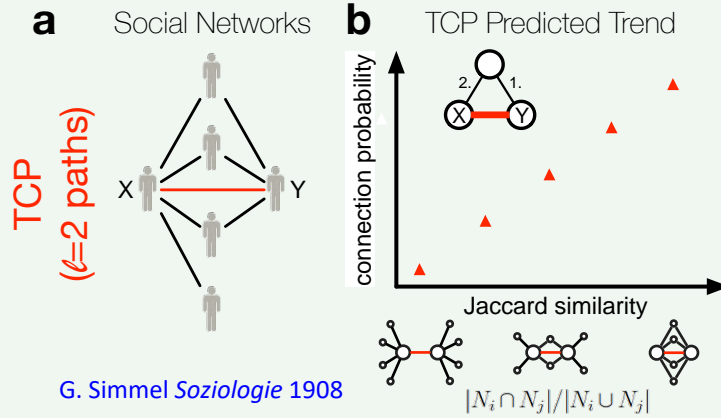
Similarity ~ Connectivity ?

# Kölcsönhatás jóslás

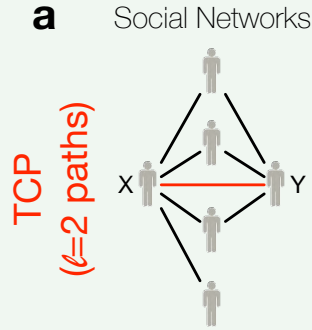
Method	Formula
CN (Common Neighbors, $A^2$ )	$CN_{ij} =  \Gamma_i \cap \Gamma_j  = [A^2]_{ij}$
JC (Jaccard index)	$JC_{ij} = \frac{CN_{ij}}{ \Gamma_i \cup \Gamma_j }$
HDI (Hub Depressed)	$HDI_{ij} = \frac{CN_{ij}}{\min(k_i, k_j)}$
HPI (Hub Promoted)	$HPI_{ij} = \frac{CN_{ij}}{\max(k_i, k_j)}$
SAL (Salton)	$SAL_{ij} = \frac{CN_{ij}}{\sqrt{k_i \times k_j}}$
SEN (Sørensen)	$SEN_{ij} = \frac{2CN_{ij}}{k_i + k_j}$
LHN (Leicht-Holme-Newman)	$LHN_{ij} = \frac{CN_{ij}}{k_i \times k_j}$
AA (Adamic-Adar)	$AA_{ij} = \sum_{z \in \Gamma_i \cap \Gamma_j} \frac{1}{\log k_z}$
RA (Resource Allocation)	$RA_{ij} = \sum_{z \in \Gamma_i \cap \Gamma_j} \frac{1}{k_z}$
LCL (Local Community Links)	$LCL_{ij} = \sum_{z \in \Gamma_i \cap \Gamma_j} \frac{ \kappa_z }{2}$
CAR	$CAR_{ij} = CN_{ij} \times LCL_{ij}$
CPA	$CPA_{ij} = e_i \times e_j + (e_i + e_j) \times CAR_{ij} + CAR_{ij}^2$
CAA	$CAA_{ij} = \sum_{z \in \Gamma_i \cap \Gamma_j} \frac{ \kappa_z }{\log_2  \Gamma_z }$
CRA	$CRA_{ij} = \sum_{z \in \Gamma_i \cap \Gamma_j} \frac{ \kappa_z }{ \Gamma_z }$
CJC	$CJC_{ij} = \frac{CAR_{ij}}{ \Gamma_i \cup \Gamma_j }$
HG (Hypergeometric)	$HG_{ij} = -\log \sum_{n=CN_{ij}}^{\min(k_i, k_j)} \frac{\binom{k_i}{n} \binom{N-k_i}{k_j-n}}{\binom{N}{k_j}}$
PA (Preferential Attachment)	$PA_{ij} = k_i \times k_j$
LP (Local Path)	$LP_{ij} = [A^2 + \beta A^3]_{ij}$
YZ (Yang-Zhang)	$YZ_{ij} = \frac{CN_{ij} + 1}{d_{ij}}$
(-1) CDD (Czekanowski-Dice Dissimilarity)	$CDD_{ij} = \frac{ \gamma_i \cup \gamma_j  -  \gamma_i \cap \gamma_j }{ \gamma_i \cup \gamma_j  +  \gamma_i \cap \gamma_j }$
(-1) ACDD (Adjusted CDD)	$ACDD_{ij} = \frac{ \gamma_i \cup \gamma_j  -  \gamma_i \cap \gamma_j  + \lambda_{ij} + \lambda_{ji}}{ \gamma_i \cup \gamma_j  +  \gamma_i \cap \gamma_j }$
FSW (Functional Similarity Weight)	$FSW_{ij} = \frac{1}{( \gamma_i - \gamma_j  + 2 \gamma_i \cap \gamma_j  + \lambda_{ij})( \gamma_j - \gamma_i  + 2 \gamma_i \cap \gamma_j  + \lambda_{ji})}$

S O I V E D

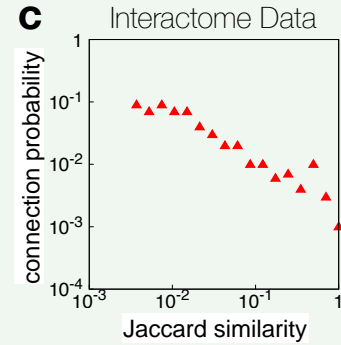
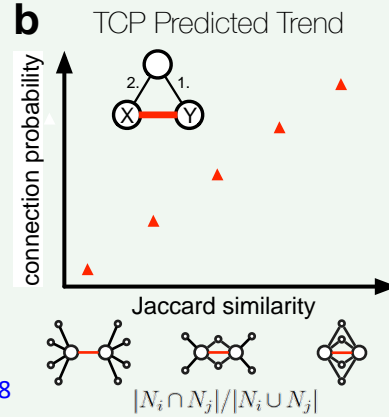
# Kölcsönhatás jóslás



# Kölcsönhatás jóslás



G. Simmel *Soziologie* 1908

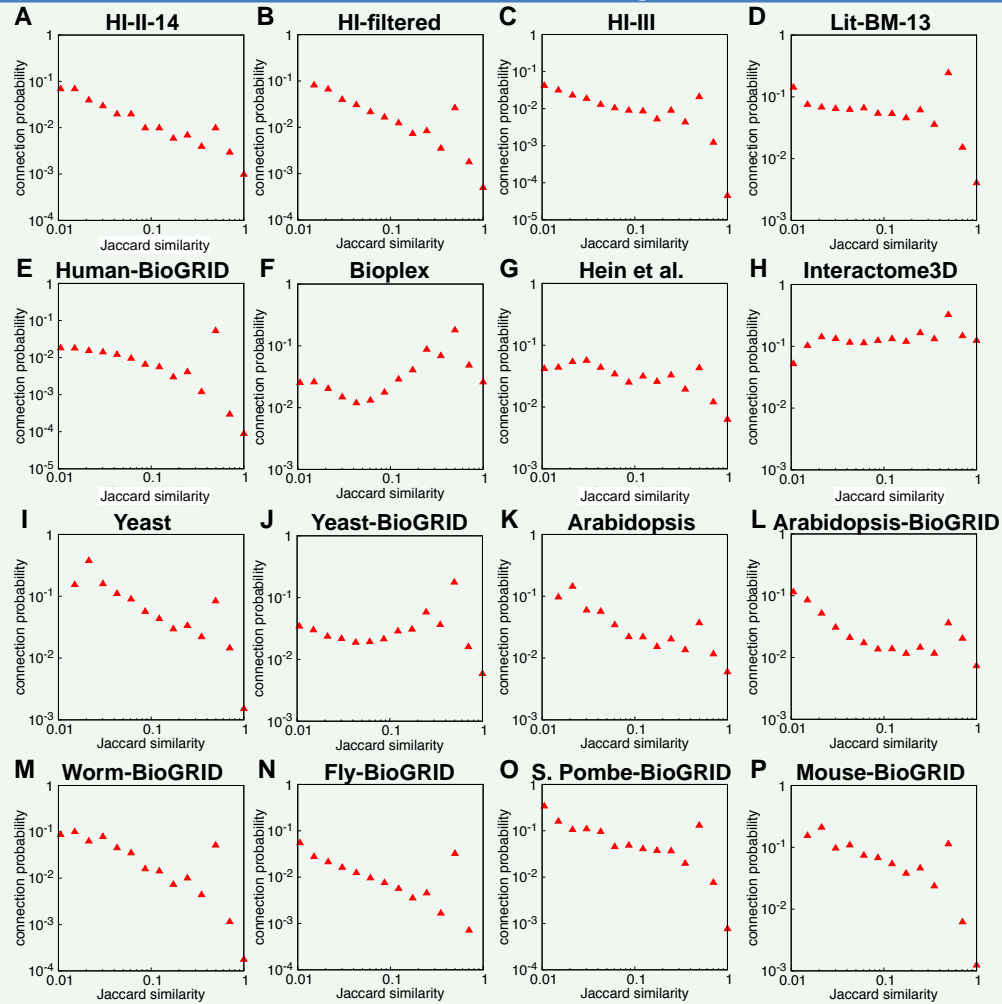


Human Data, Rolland *et al.* 2014 Cell



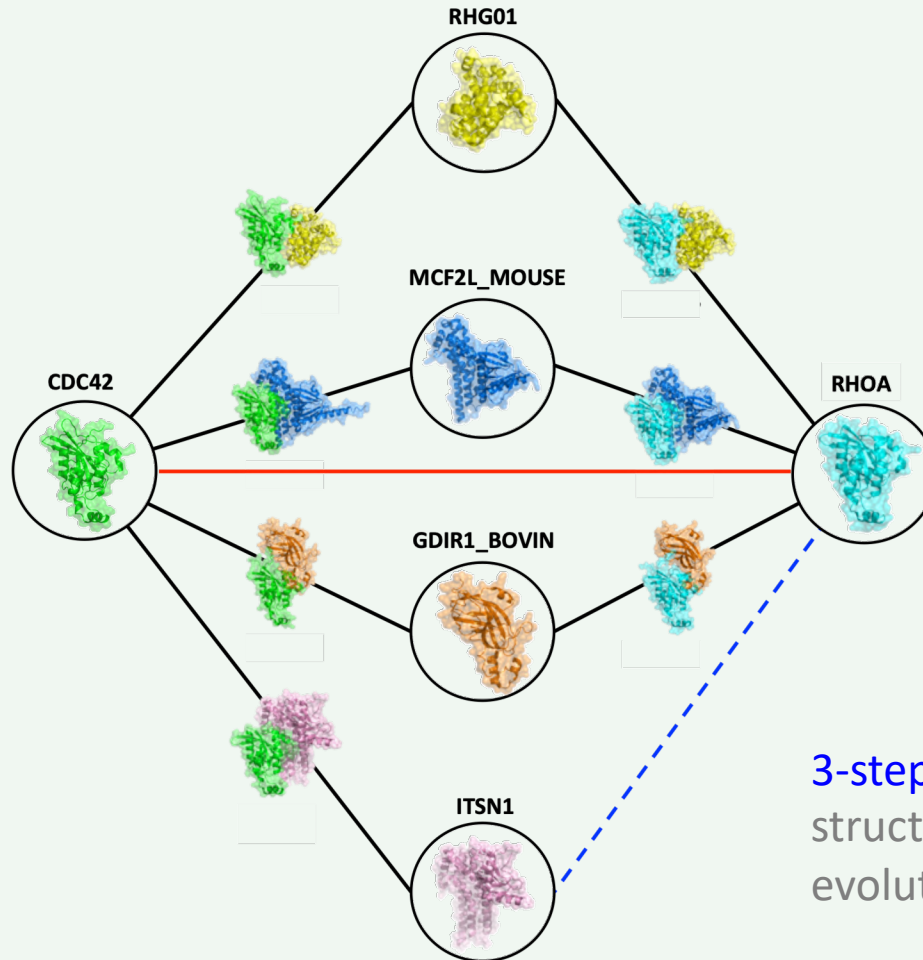


# Kölcsönhatás jóslás



Impossible to use  
for predictions!

# Egy példa



Candidate partner is:

- similar to you?

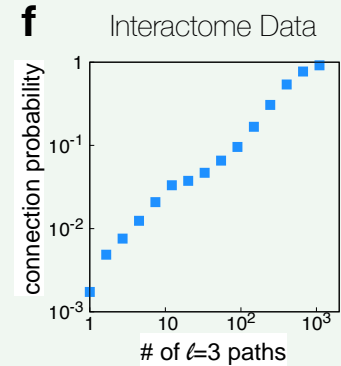
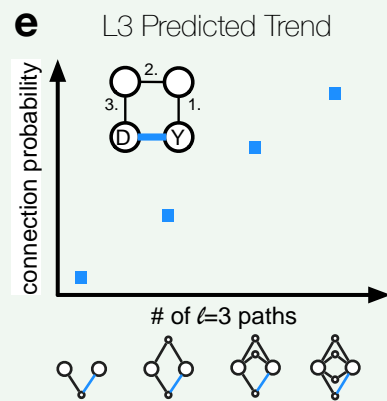
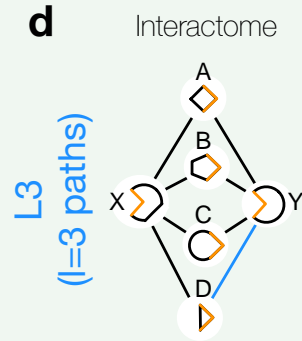
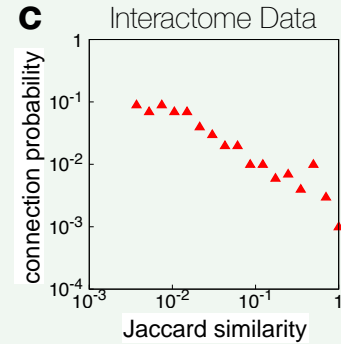
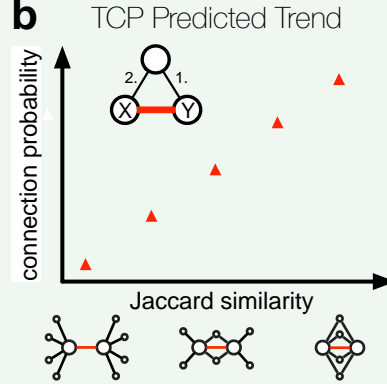
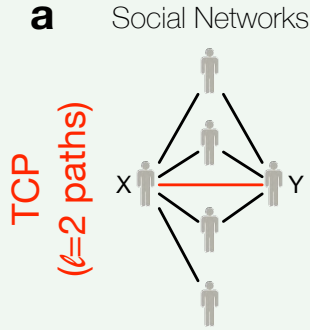
Maybe...

- similar to your partners?

Yes!

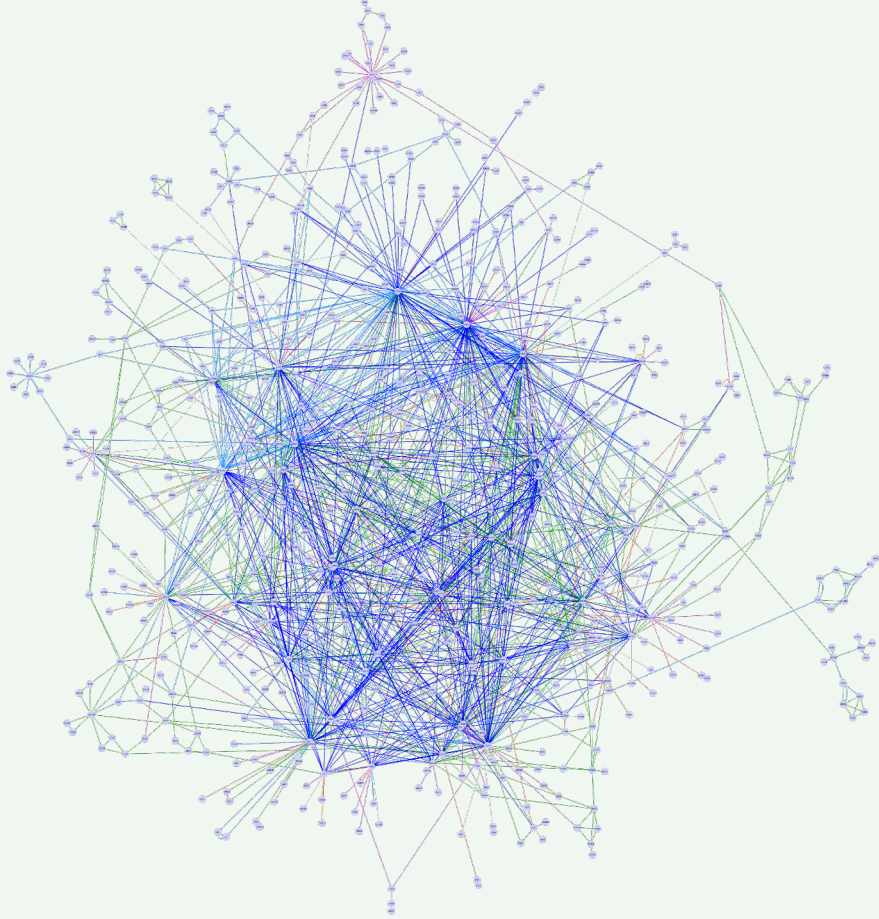
3-steps (L3):  
structural and  
evolutionary reasons

# Kölcsönhatás jóslás: 3 lépés



# Kísérleti Ellenőrzés

~3,000 tests

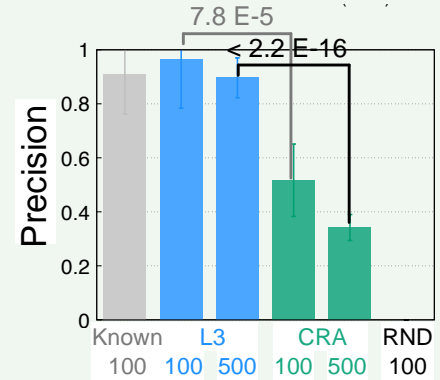


Predictive Model:

$$s_{XY} = \sum_{U,V} \frac{a_{XU}a_{UV}a_{VY}}{\sqrt{k_U k_V}}$$

~90% precision

## Experimental Validation

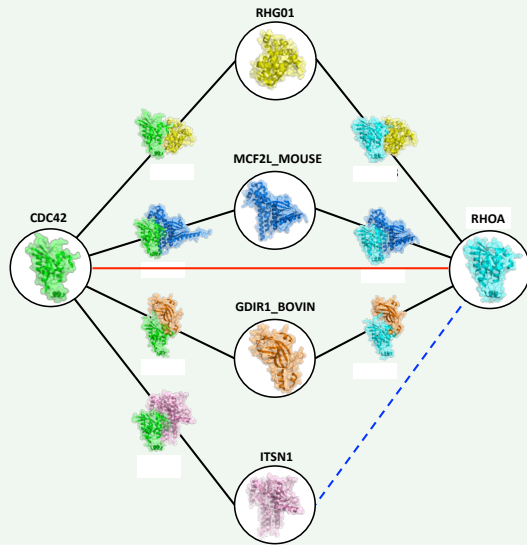


Biological methods using additional structural, domain, sequence or evolutionary information: <5%

Guide and replace costly experimental screens (fruit fly, yeast, arabidopsis)

# Gráf elméleti háttér

Maps of real networks are highly incomplete.



Link prediction

$$A = \begin{pmatrix} 1 & 1 & 0 & 1 & ? & -1 \\ 1 & ? & 1 & 0 & -1 & 0 \\ -1 & 1 & 0 & 1 & -1 & 1 \\ 0 & 0 & 1 & ? & 1 & -1 \\ -1 & -1 & 0 & -1 & 0 & ? \\ ? & 1 & -1 & 0 & -1 & -1 \end{pmatrix}$$

Matrix completion

1908: G. Simmel

Triangle Closure: the friend of my friend is my friend (3-cycles)

Link Prediction=Triangle Closure

- social networks
- recommendation systems
- cellular interactions
- food webs
- network evolution

Kovacs et al.

Biological basis of 4-cycles

Legjobb módszer: Kvantum bolyongás

# Egy online játék: Pardus

Nav Overview Messages News Diplomacy Statistics Options Forum Chat

Account | Players online: 1073  
Logout | Manual | FAQ | Rules |

### Status

Abeho [18,4] 4208

482 13

0.45 400,723

[Check Cluster & Protection](#)

### Commands

Enter starbase

Put ship in dock (10)

Fill up tank (5)

Collect nebula gas (15) x2 x5

Send distress call

### Ship

Hull: 330 / 330

Armor: 60 / 225

Shield: 270

[Check cloaking chance](#)



MSE : 1 MISSION : 8 COMBAT : 5

### Cargo

:27 :7

:8 :3 [Use]

:16 :11

:9

Drop

Cargo space left: 5t

[View Sector Building Index](#)

### Other Ships

Fermion

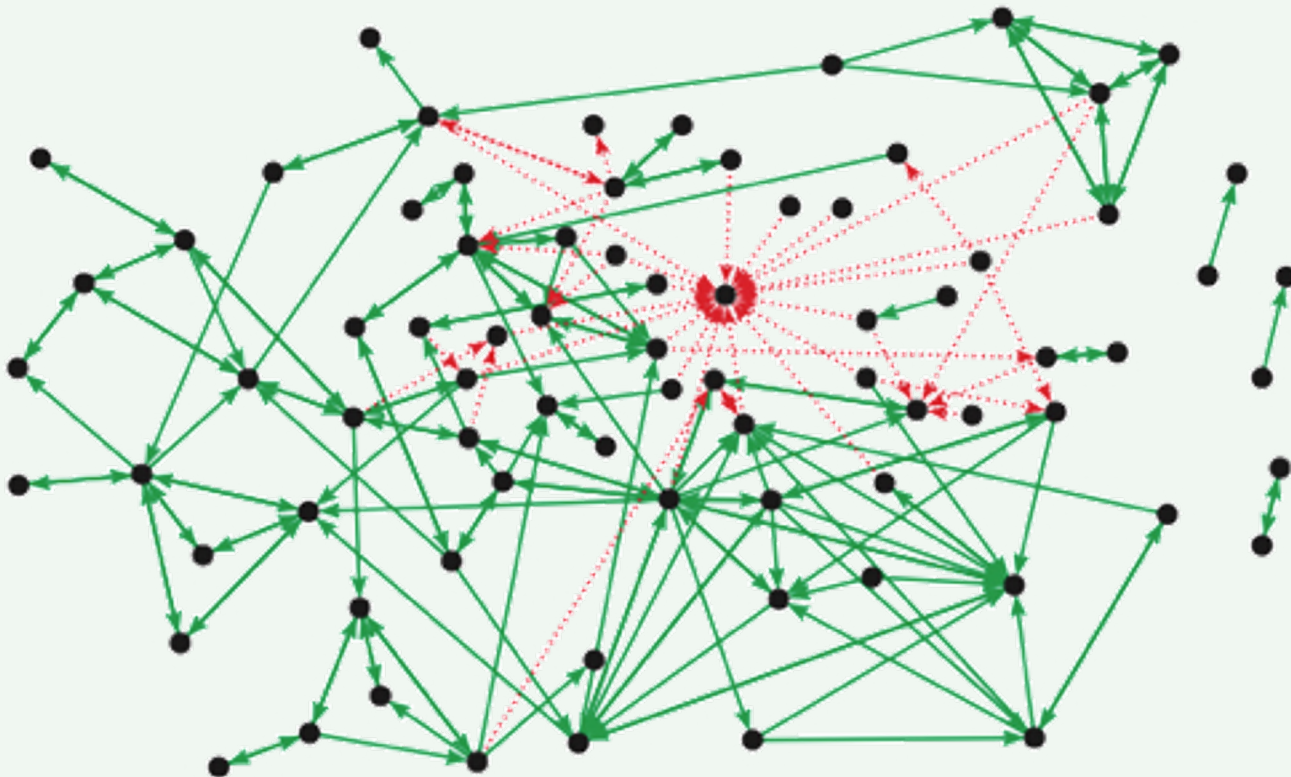
Pronto  
Red Hessians

Slider  
Atlantis Expedition

Tanis  
Atlantis Expedition

# Szociális hálózat

friends  
enemies

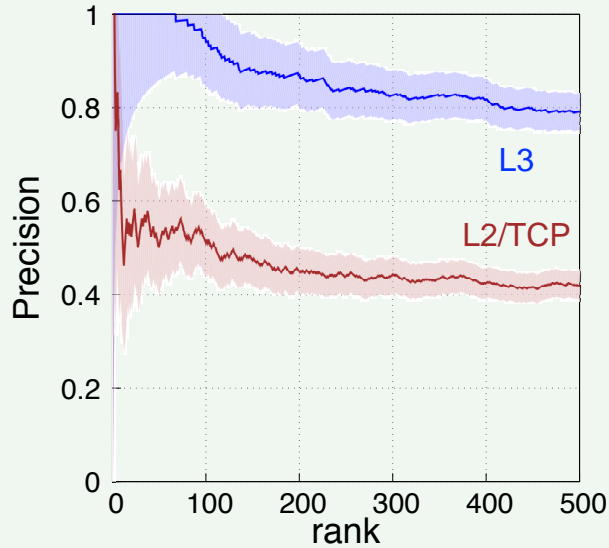


[www.pardus.at](http://www.pardus.at)

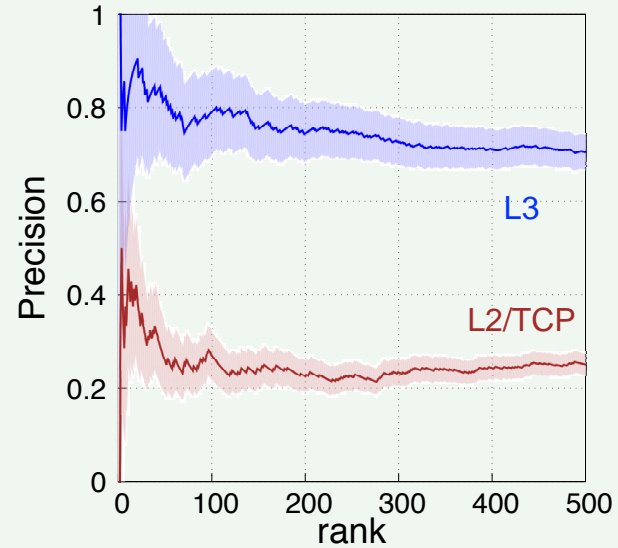
Connections between online gamers (Pardus – Michael Szell)

50% cross-validation, directed predictions

## Enemies



## Friends







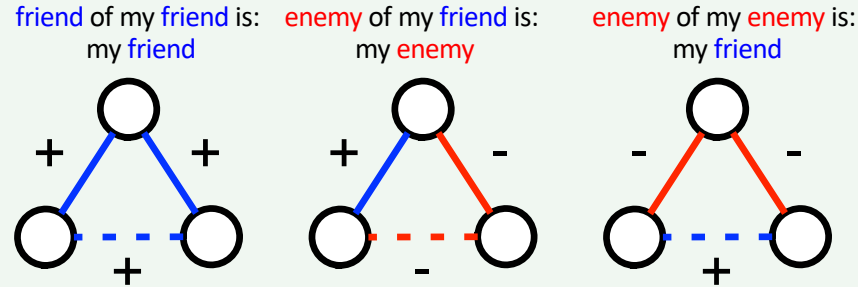
## Polypharmacy:

- 25% of people ages 65-69
- 46% of people ages 70-79 take more than 5 drugs
  
- patients frequently take >20 drugs for heart disease, depression, insomnia, etc.
- annual cost of side-effects > \$177M

Impossible to test all combinations!

# Előjeles hálózatok

## No frustration: Social Balance Theory



Real data is frustrated!

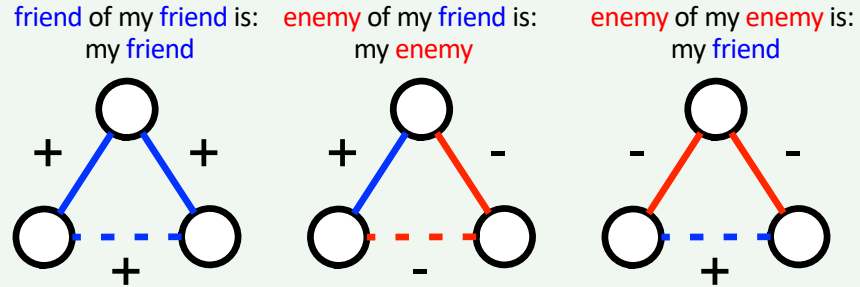
Is it more frustrated than expected by chance?

Strong balance:  
Cartwright, Harary '56  
Weak balance:  
Davis '67

**Yes!**

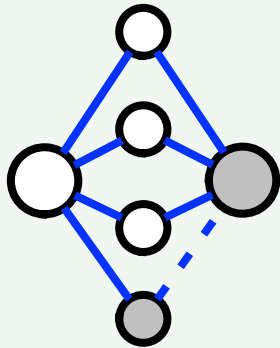
# Előjeles hálózatok

## Current Paradigm: Social Balance Theory

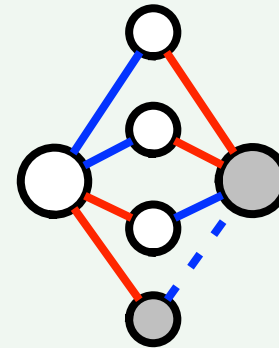
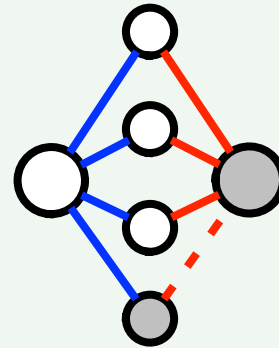
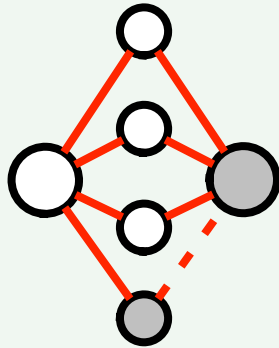


## New paradigm:

correlated



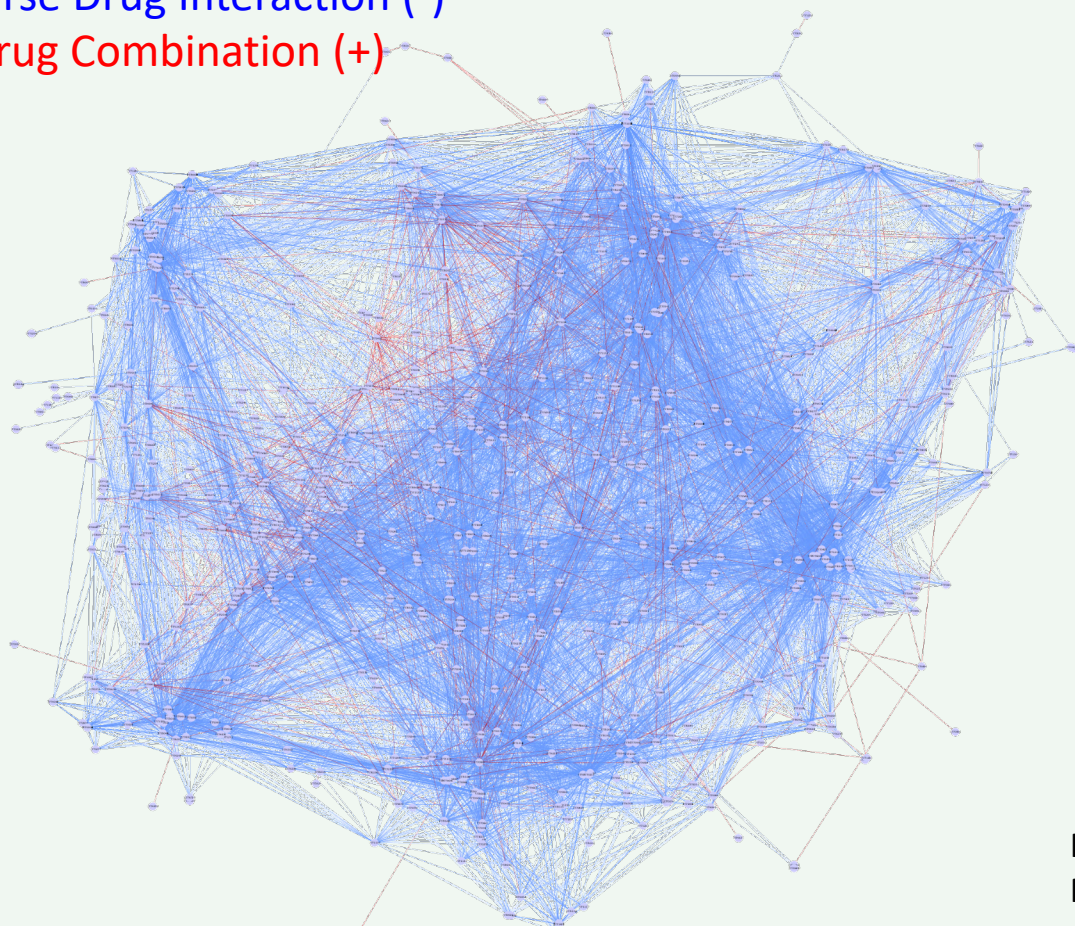
anti-correlated



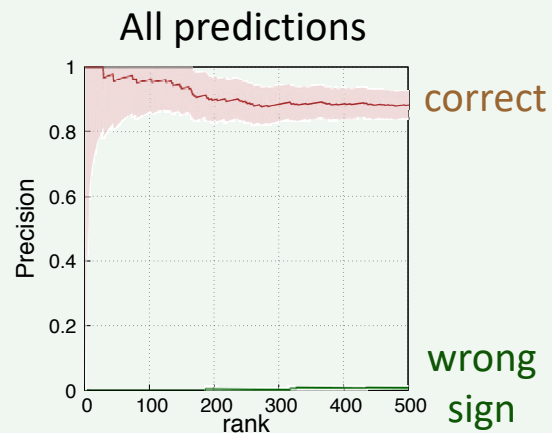
# Gyógyszer kombinációk

Adverse Drug Interaction (-)

Drug Combination (+)



~800 drugs, 17,000 interactions

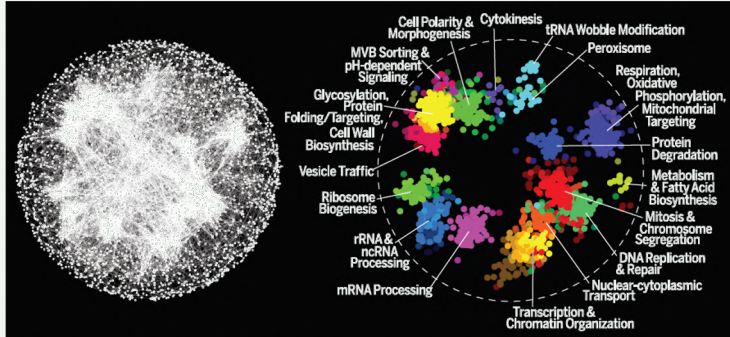


ongoing work,  
99% sign accuracy!

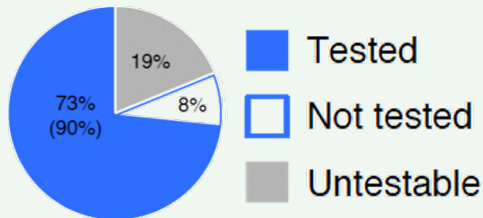
F. Cheng\*, I. A. Kovács\*, A-L. Barabási,  
Network-based prediction of drug  
combinations, *Nat. Commun.* 10, 1197 (2019)

## A global genetic interaction network maps a wiring diagram of cellular function

SCIENCE sciencemag.org 23 SEPTEMBER 2016 • VOL 353 ISSUE 6306 1381



A global network of genetic interaction profile similarities. (Left) Genes with similar genetic interaction profiles are connected in a global network, such that genes exhibiting more similar profiles are located closer to each other, whereas genes with less similar profiles are positioned farther apart. (Right) Spatial analysis of functional enrichment was used to identify and color network regions enriched for similar Gene Ontology bioprocess terms.



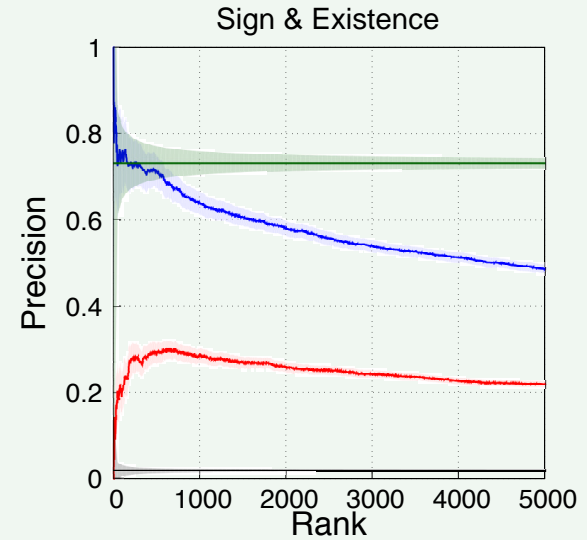
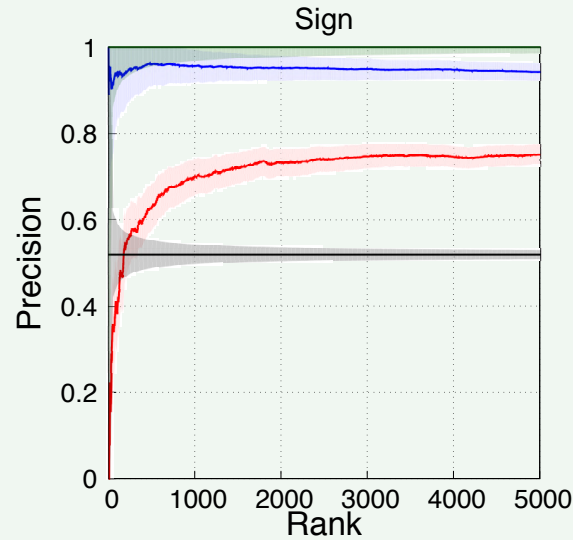
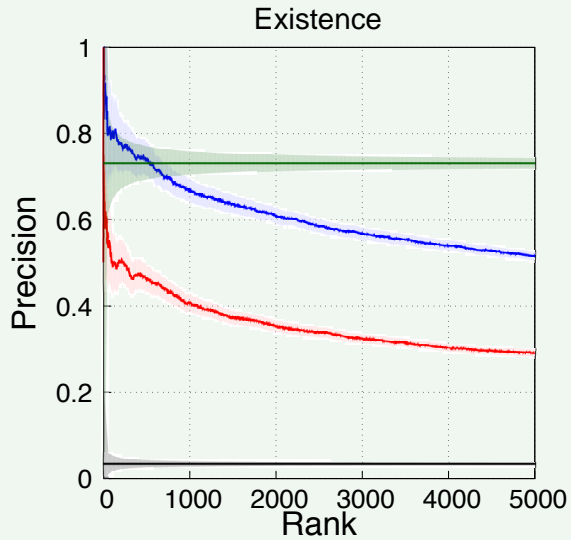
~18M pairs, 550k -, 350k +

	Essential	Nonessential	
Essential	ExE	ExN	~1,000
Nonessential	NxE	NxN	

$$\varepsilon_{ij} = f_{ij} - f_i f_j$$

connected correlation function (Ursell)

# Genetikai kölcsönhatások



Ongoing Experiments



Thuy Nguyen (Toronto)

Optimal: oracle performance (not all known)

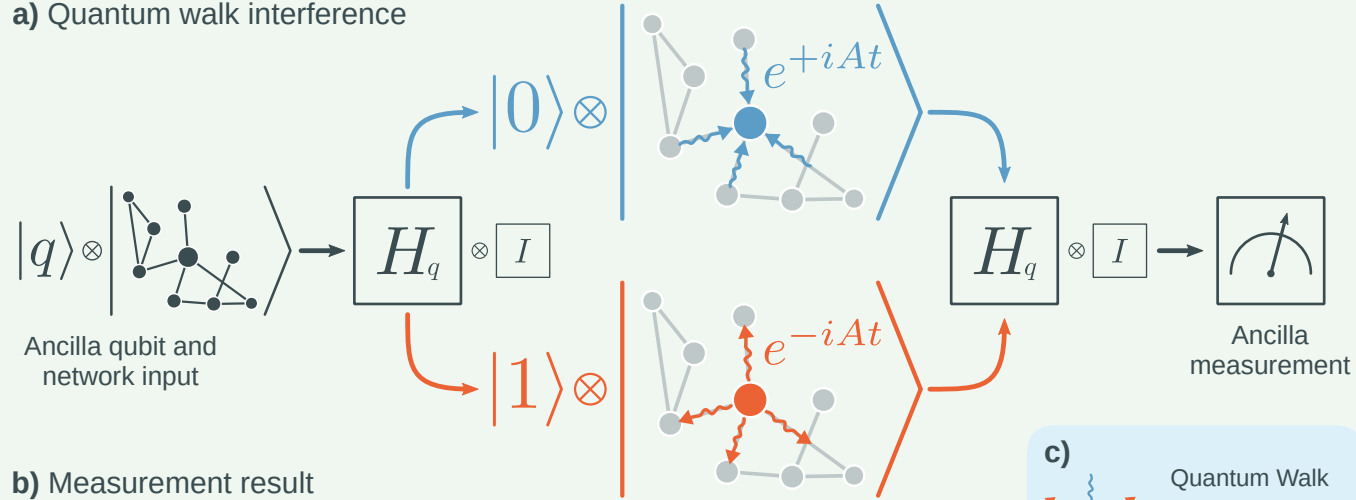
L3: paths of length  $l=3$

TCP: triadic closure principle, using paths of length  $l=2$

Random: choosing pairs randomly

# Kvantum algoritmus

a) Quantum walk interference



b) Measurement result



c)

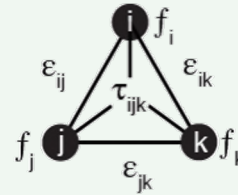
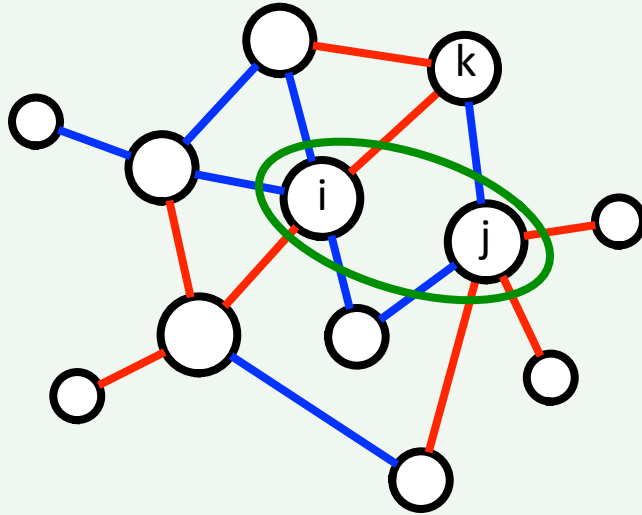
Quantum Walk  
 $U(t) = e^{-iAt}$   
 $U(t) = e^{+iAt}$

Hadamard Gate  
 $|0\rangle \rightarrow |0\rangle + |1\rangle$   
 $|1\rangle \rightarrow |0\rangle - |1\rangle$

In collaboration with the group of Yasser Omar, Lisbon

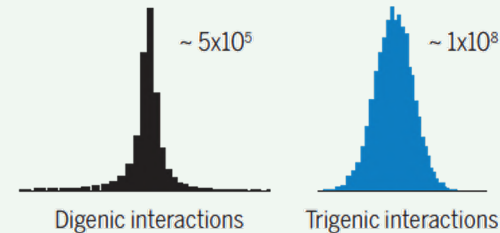
# 3-gén kölcsönhatás

Connected correlation functions:



$$\begin{aligned} \epsilon_{ij} &= f_{ij} - (f_i f_j) \\ \tau_{ijk} &= \underbrace{f_{ijk}}_{\text{observed triple mutant fitness}} - \underbrace{(f_i f_j f_k)}_{\text{expected triple mutant fitness}} - \underbrace{\epsilon_{ij} f_k - \epsilon_{ik} f_j - \epsilon_{jk} f_i}_{\text{digenic interactions}} \end{aligned}$$

~200x more trigenic:



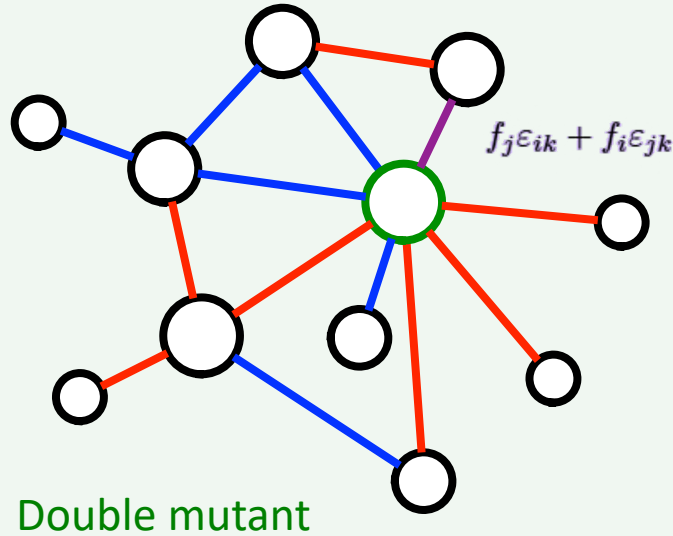
182 double mutants: 91,111 tests

...out of 36 billion triplets

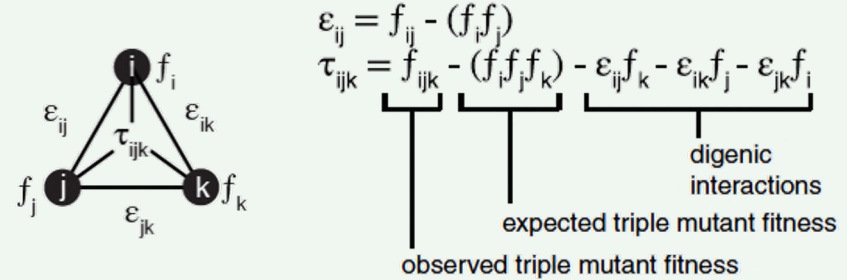


# 3-gén kölcsönhatás

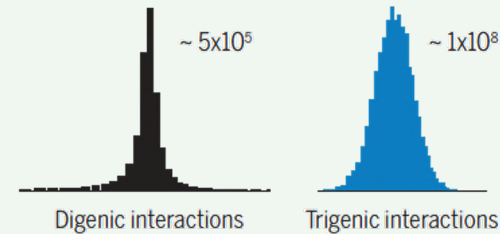
Coarse-graining (RG)



Connected correlation functions:



~200x more trigenic:

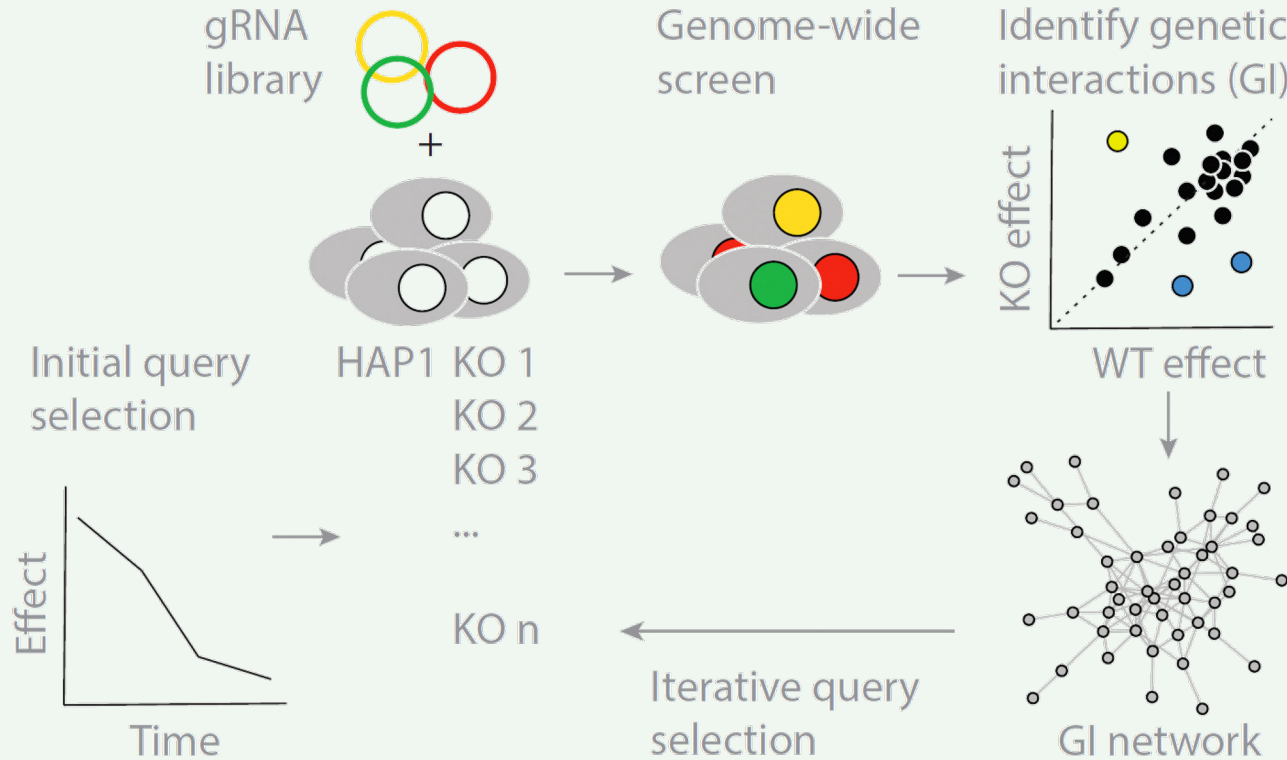


182 double mutants: 91,111 tests

Preliminary results: ~50% trigenic precision from 2-gene data!

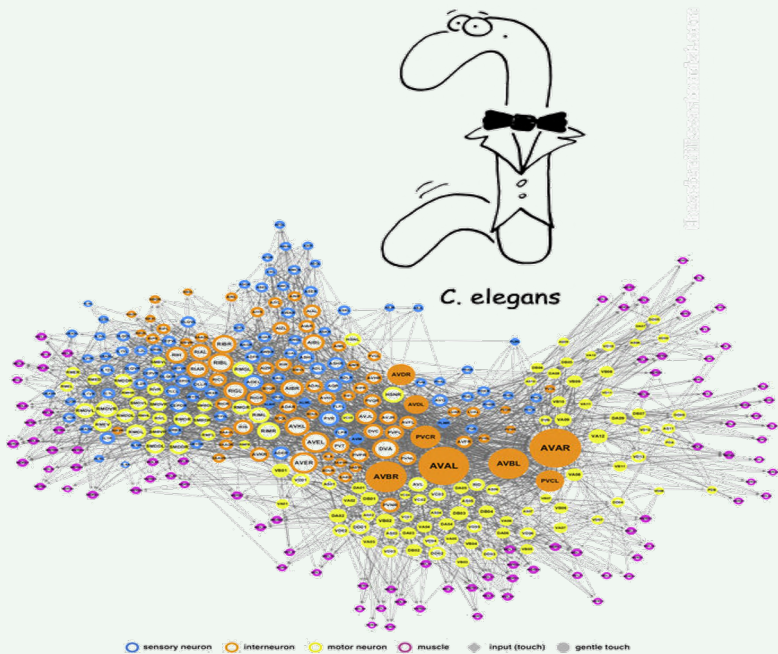
Could be extended to more genes!

# Genetikai kölcsönhatások emberben: CRISPR/Cas9



~360,000,000 combinations

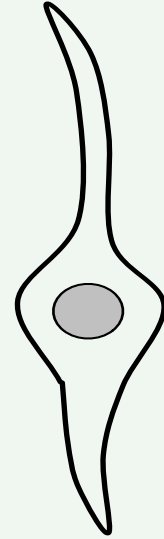
# Miért ezek a kapcsolatok?



'inx-1  
'inx-2  
**inx-3**  
'inx-5  
'inx-6  
'inx-7  
'inx-8  
'inx-9  
'che-7  
**unc-7**  
'unc-9  
'inx-10  
'inx-11  
'inx-12  
'inx-13  
'inx-17  
'inx-18  
'inx-19



'inx-1  
**inx-2**  
**inx-3**  
'inx-5  
'inx-6  
'inx-7  
'inx-8  
'inx-9  
'che-7  
'unc-7  
**unc-9**  
'inx-10  
'inx-11  
'inx-12  
'inx-13  
'inx-17  
'inx-18  
'inx-19



IAK, DL Barabasi, AL Barabasi, Uncovering the genetic blueprint of the *C. elegans* nervous system, bioRxiv

Nem-euklideszi (~Minkowski) geometria – speciális relativitás elmélet

# Köszönöm a figyelmet!

## Northeastern University:

- Albert-László Barabási

## Semmelweis University:

- Peter Csermely

## Dana-Farber Cancer Institute:

- Michael Calderwood
- David Hill
- Marc Vidal

## University of Toronto:

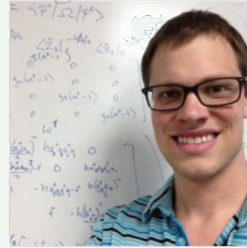
- Fritz Roth
- Charlie Boone
- Michael Costanzo
- Brenda Andrews

## University of Lisbon:

- Yasser Omar

## Pasteur Institute:

- Yves Jacob
- Anastassia Komarova



Thomas Wytock  
Postdoctoral Researcher, Tech F327



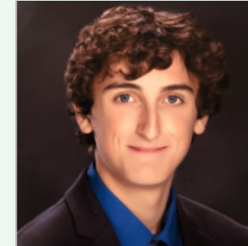
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Ravi Tyler Chou Chepuri  
Undergraduate Student, Tech F333



Sam Jacob Frank  
Undergraduate Student, Tech F333

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