IRKUTSK NATIONAL RESEARCH TECHNICAL UNIVERSITY

Shahid Beheshti University

Higher-order genetic interactions and their contribution to cancerous cells

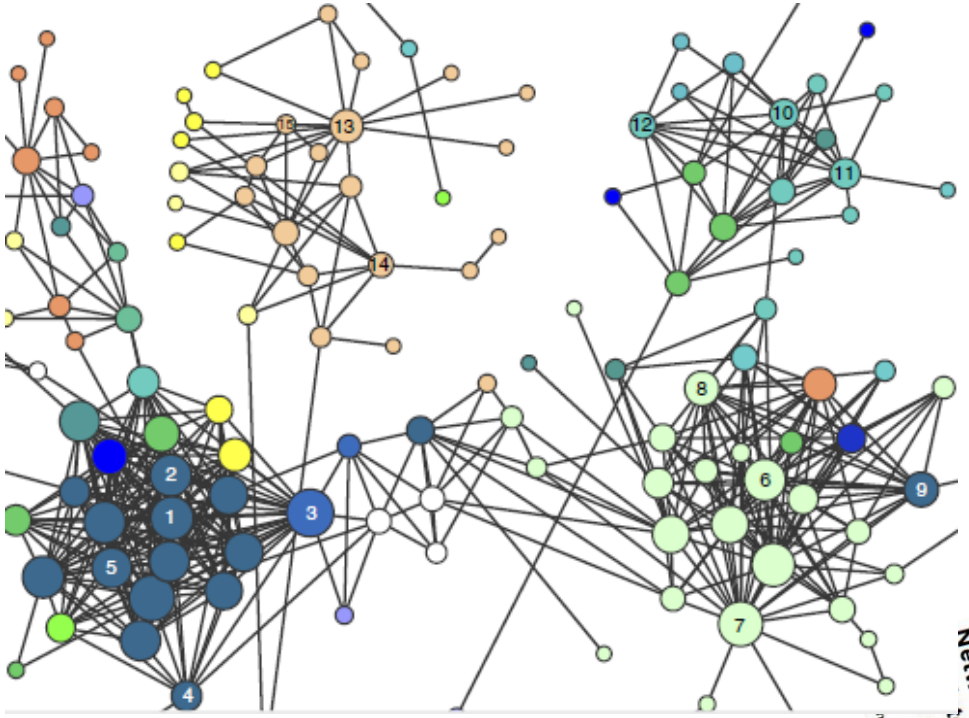
Reza Jafari

Evolution of Complexity from the Statistical Physics Perspective

June 29 - July 2, 2022

Yerevan Physics Institute, Yerevan - Armenia

Cancer & Social science



nature COMMUNICATIONS

ARTICLE

Received 7 Nov 2013 | Accepted 27 May 2014 | Published 26 Jun 2014

DOI: 10.1038/ncomms5212

Human symptoms–disease network

XueZhong Zhou[1,2,3,*], Jörg Menche[2,3,4,*], Albert-László Barabási[2,3,4,5,6] & Amitabh Sharma

PNAS

The human disease network, Kwang Goh, Michael E. Cusick, David Valle, Barton Childs, Marc Vidal, and Albert-Laszlo´ Barabasi, PNAS **May 22, 2007** vol. 104 no. 21 **8685–8690**

Nature is more complex than we previously thought

NAUTILUS

ISSUES TOPICS BLOG NEWSLETTER STORE PRIME

BIOLOGY | GENETICS

Aging Is a Communication Breakdown

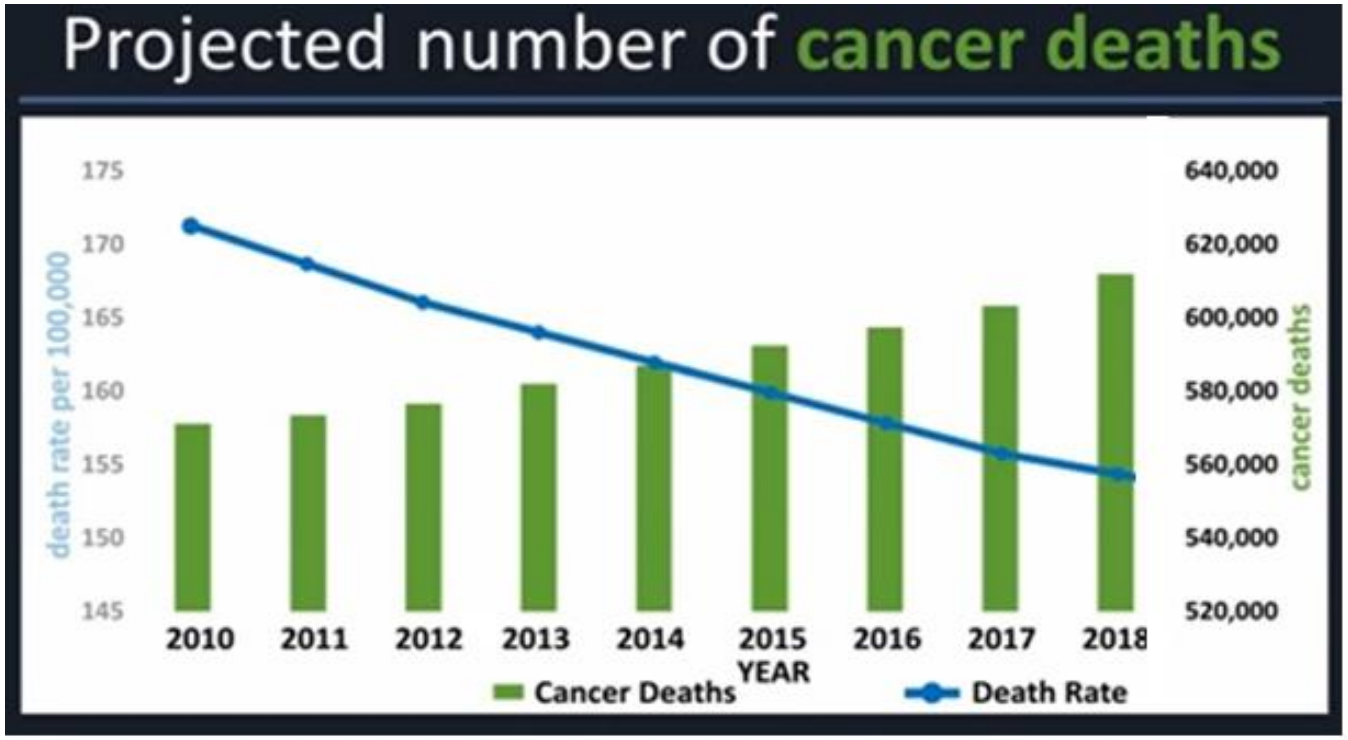
Genes that can't express themselves may be hallmarks of cancer.

BY JIM KOZUBEK

MARCH 21, 2019

Cancer

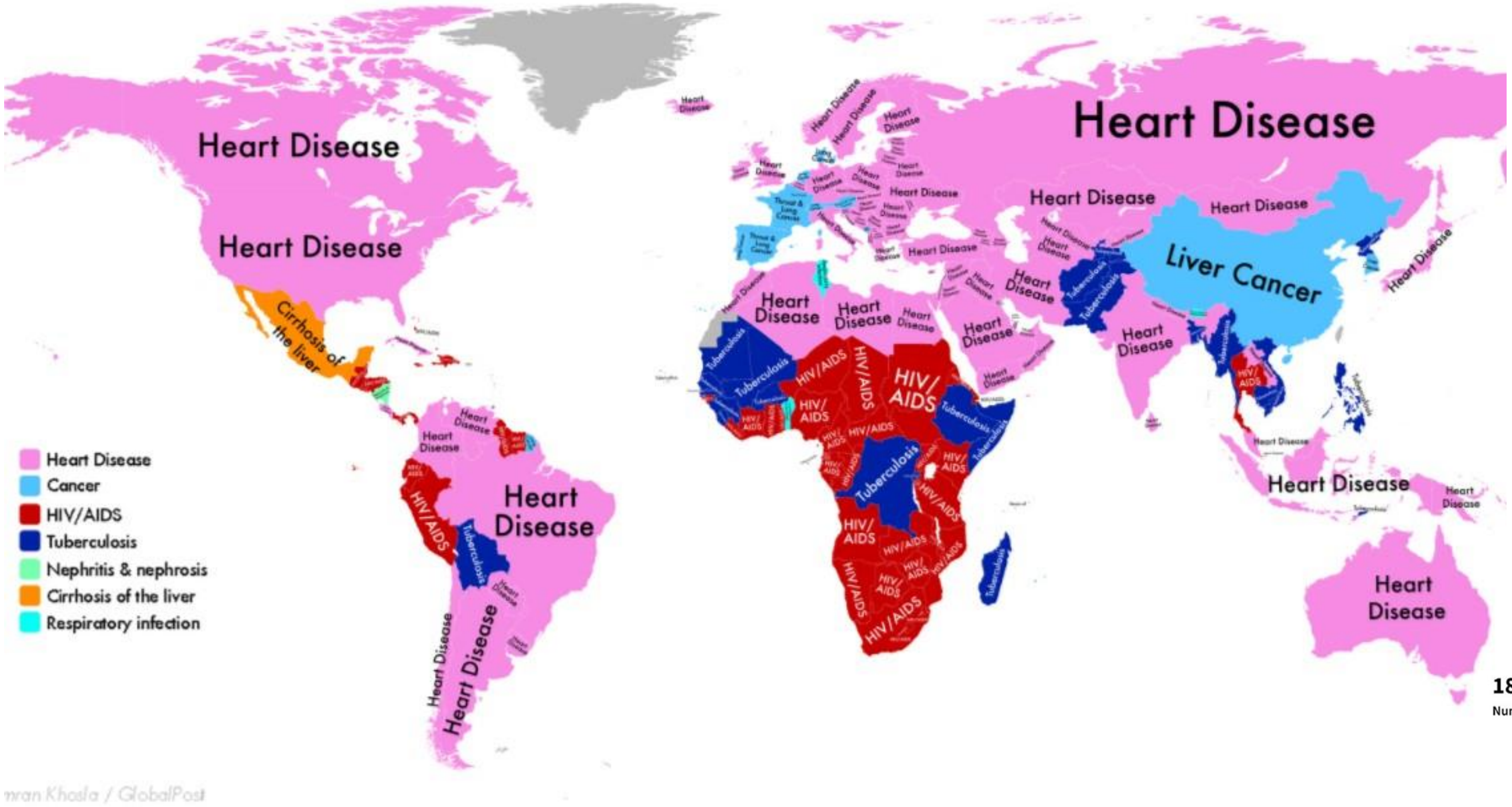
- Cancer is a name that refers to a set of diseases that occurs as a result of uncontrolled cell proliferation.
- Contrary to the many researches in medicine over the past years, we are still faced with many challenges in controlling and treating cancer.



Weir HK, Thompson TD, Soman A, Møller B, Leadbetter S. The past, present, and future of cancer incidence in the United States: 1975 through 2020.External, *Cancer* 2015;121(11):1827–1837.

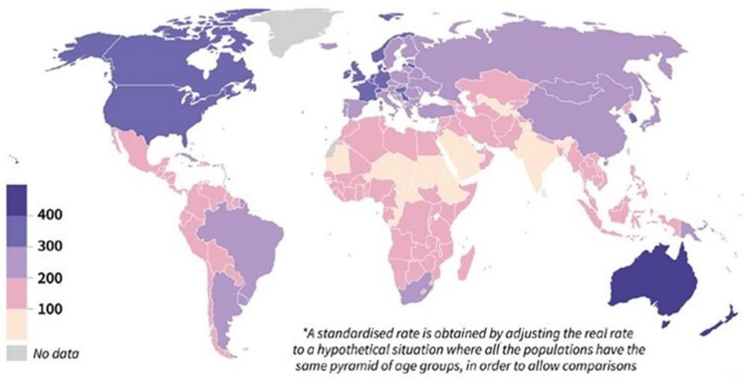
https://www.cdc.gov/cancer/dcpc/research/articles/cancer_2020.htm

Cancer is the second leading cause of death among diseases

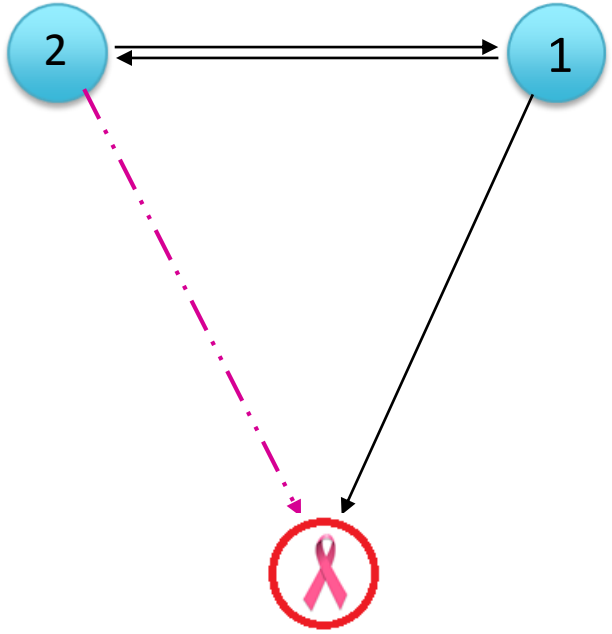


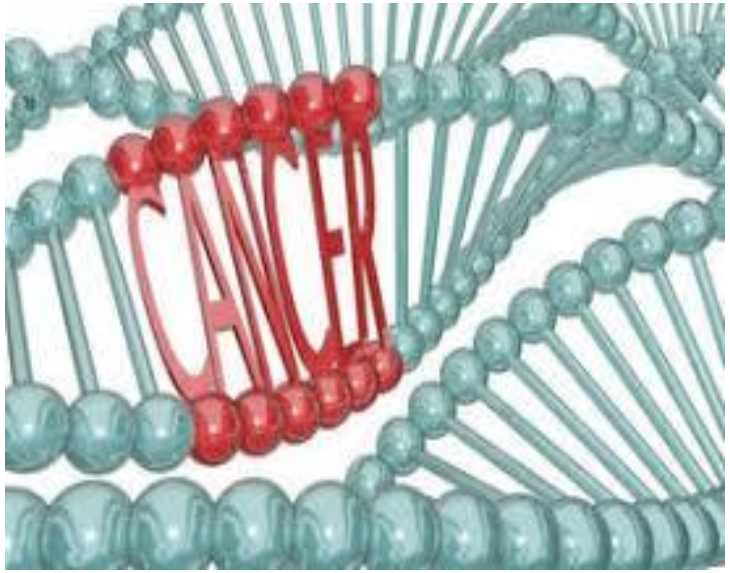
18.1 million new cancer cases predicted for 2018

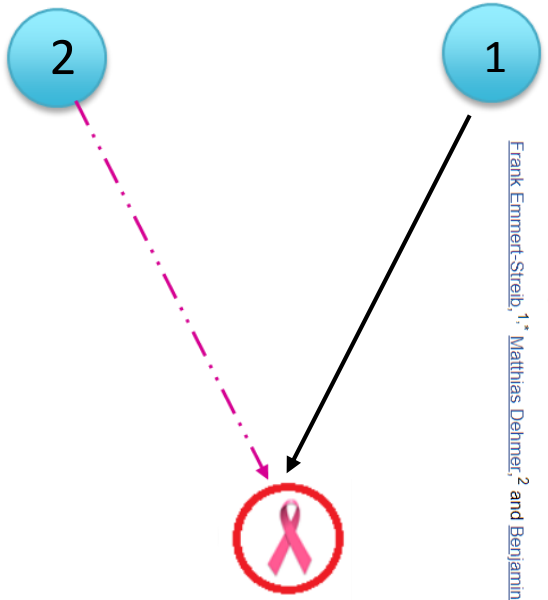
Number of estimated cases per 100,000 people, rate standardised* for age

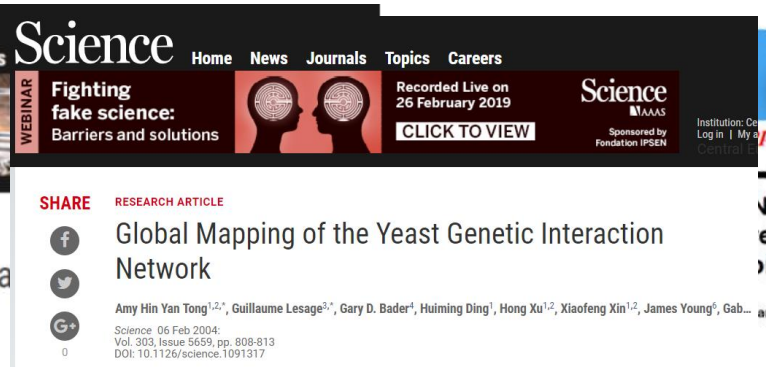


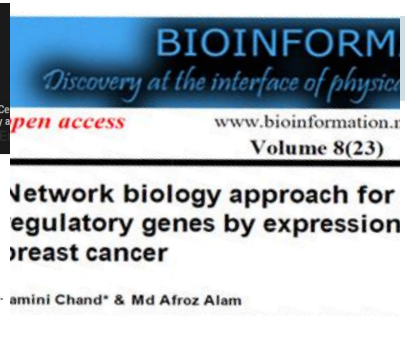
Cancer is known as a Gene disease

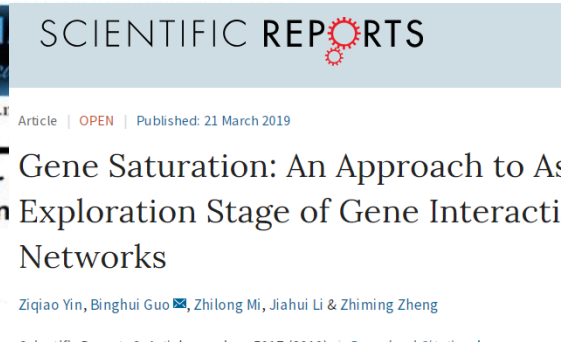












Gene regulatory networks and their applications: understanding biological and medical problems in terms of networks

Frank Emmert-Streib,[1,*] Matthias Dehmer,[2] and Benjamin Haibe-Kains[3,*]

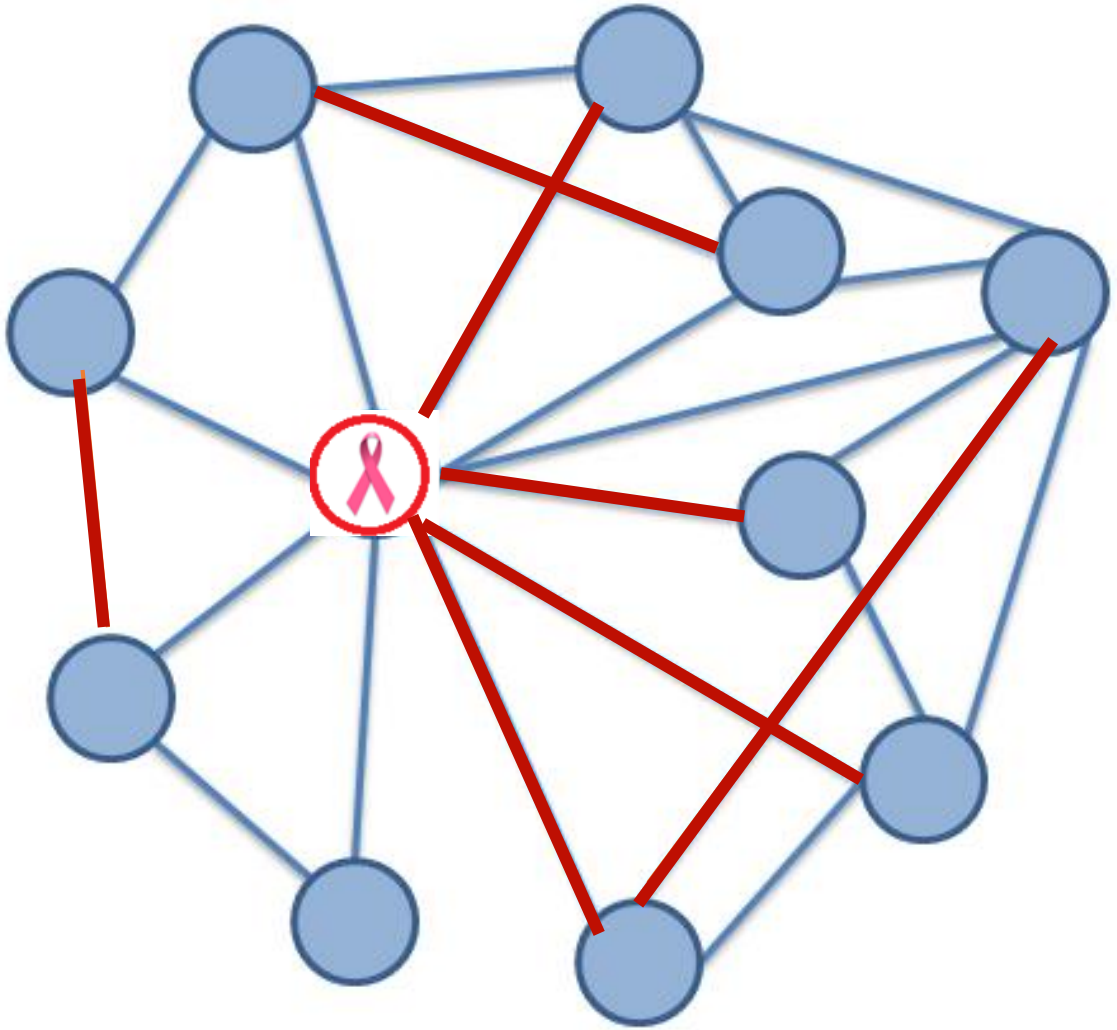
Front Cell Dev Biol. 2014; 2: 38.
Published online 2014 Aug 19. doi: 10.3389/fcell.2014.00038
PMCID: PMC4207011
PMID: 25364745

frontiers in Cell and Developmental Biology

PNAS

The human disease network, Kwang Goh, Michael E. Cusick, David Valle, Barton Childs, Marc Vidal, and Albert-Laszlo´ Barabasi, PNAS **May 22, 2007** vol. 104 no. 21 **8685–8690**

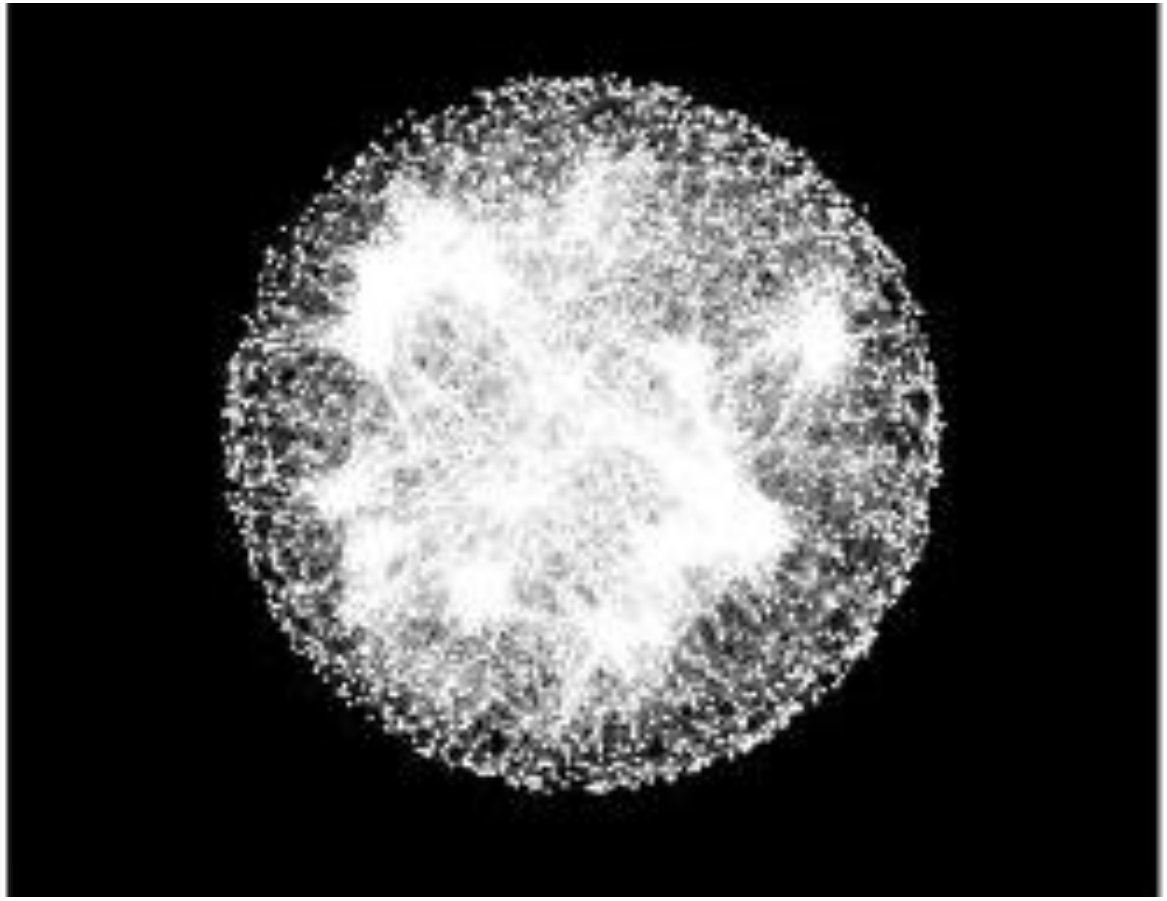
Gene – Gene Interactions

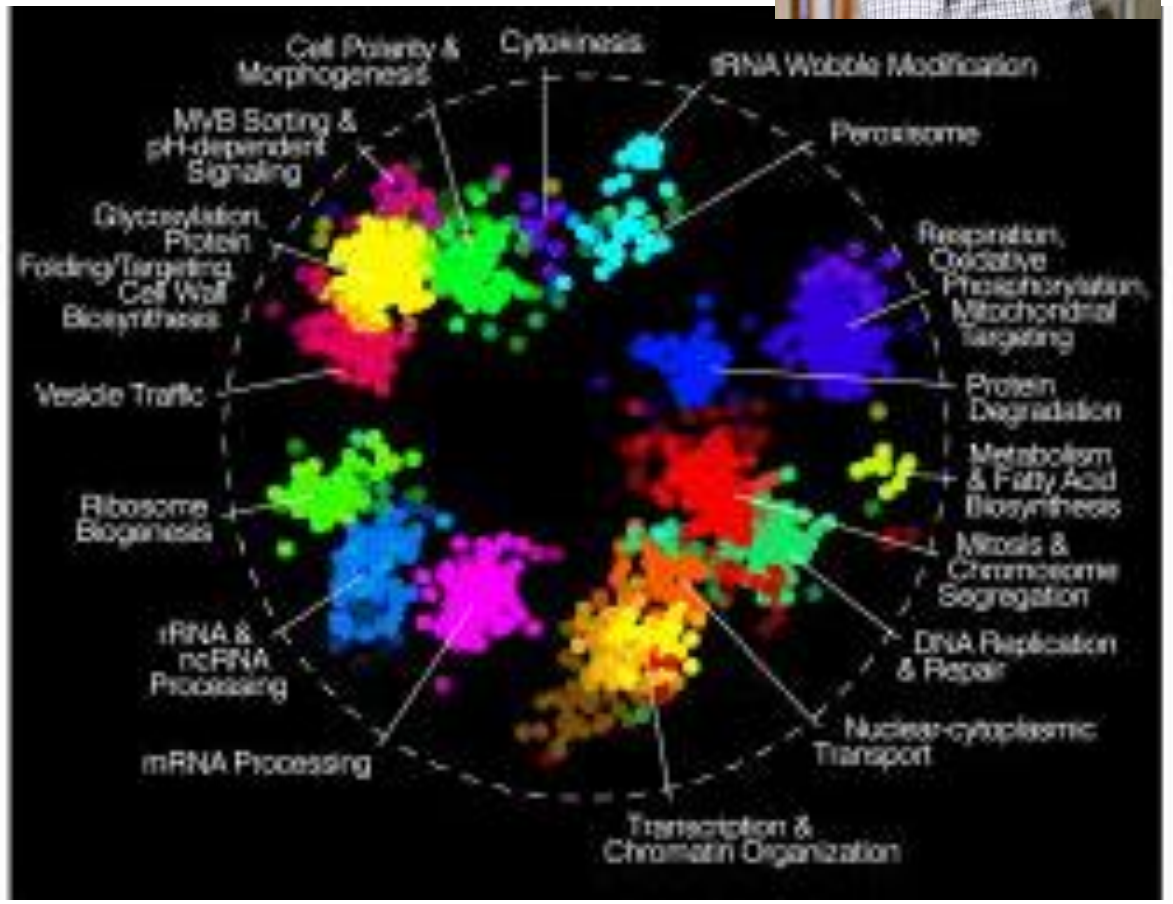


Michael Costanzo
University of Toronto

Gene – Gene interaction networks (Saccharomyces is a genus of fungi)

Saccharomyces 6000 genes, identifying about one million interactions, which 550,000 are negative, and 350,000 positives.





M. Costanzo and et. al, SCIENCE 353, 6306 (2016).

An idea from Social and Psychology sciences

The relationships between two persons is not depends on them.

frontiers in Physiology

ORIGINAL RESEARCH
published: 20 January 2021
doi: 10.3389/fphys.2020.573732

Stability of Imbalanced Triangles in Gene Regulatory Networks of Cancerous and Normal Cells

PLOS ONE

The structure balance of gene-gene networks beyond pairwise interactions

Frustration
Cognitive Balance Theories

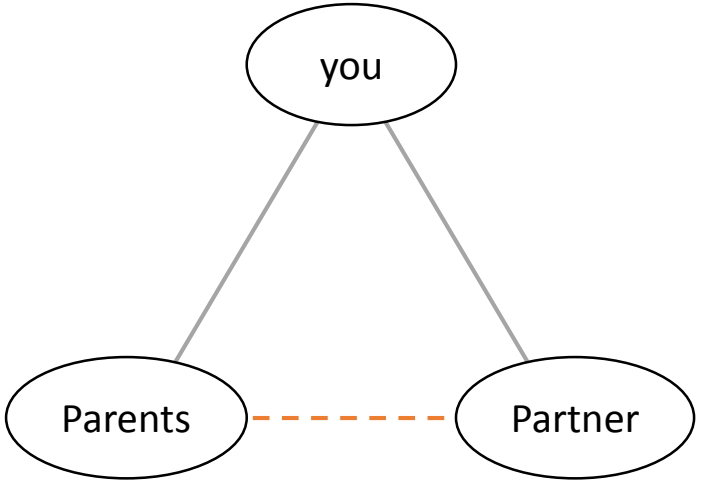
(Fritz Heider 1946)

We adjust our relationship based on reducing the psychological stresses

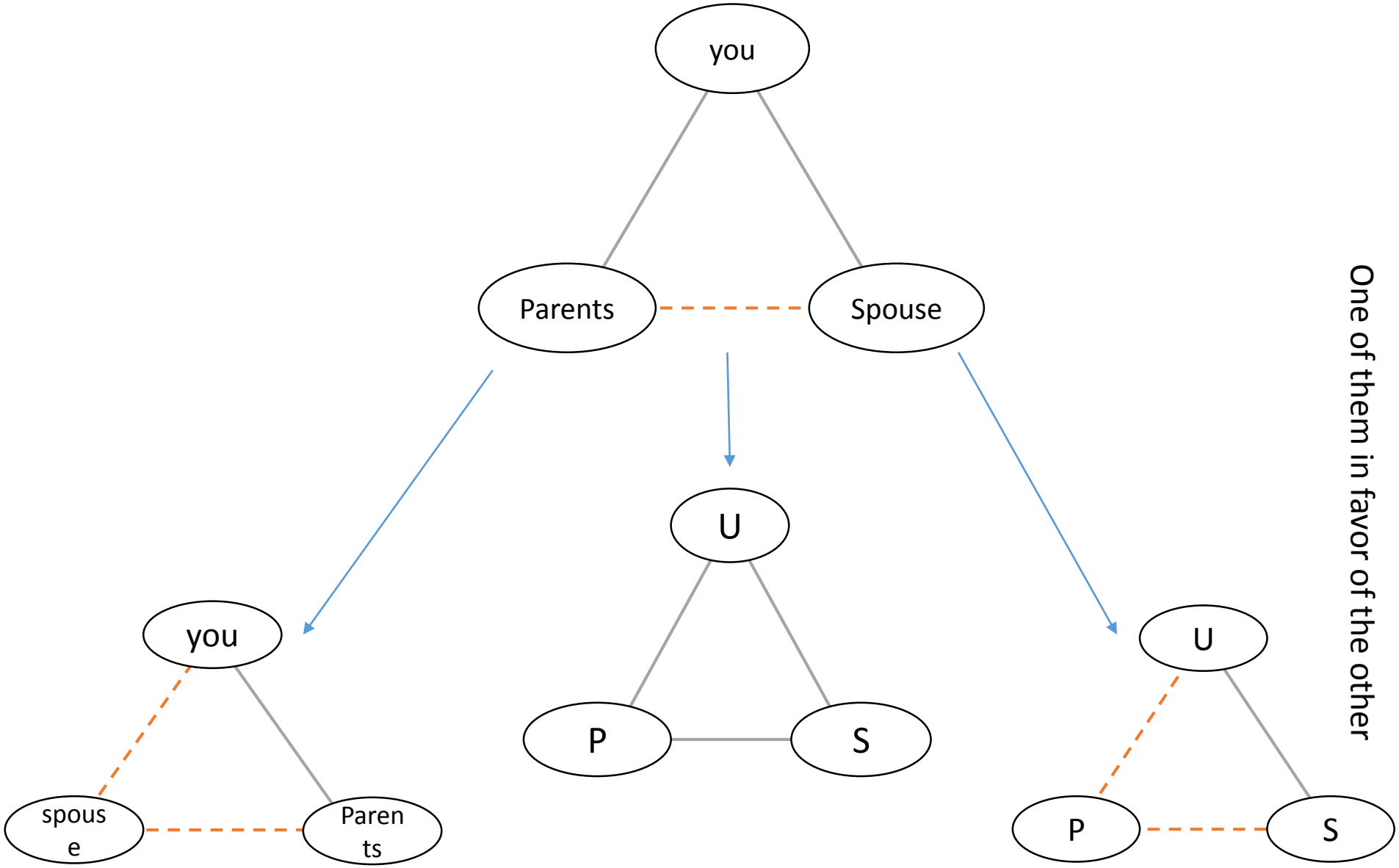
If a person's beliefs are unbalanced, psychological stresses will generate internal pressures to change either some of the sentiments (liking, disliking) or some relationships (proximity, membership) into a more congruent pattern.

The hard situation

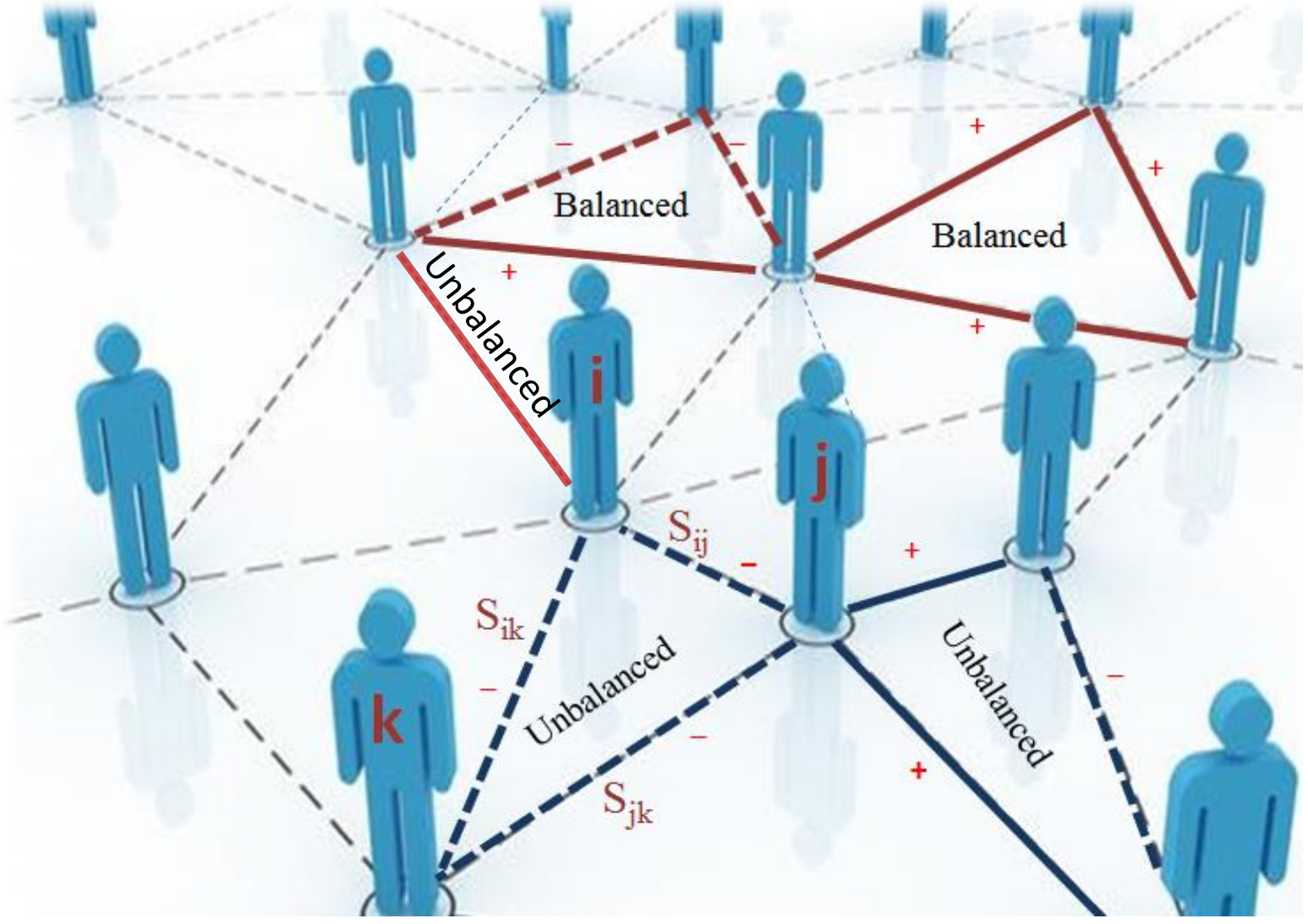
Cartwright and Harary (1950)



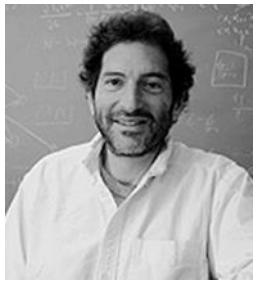
Reducing the stress

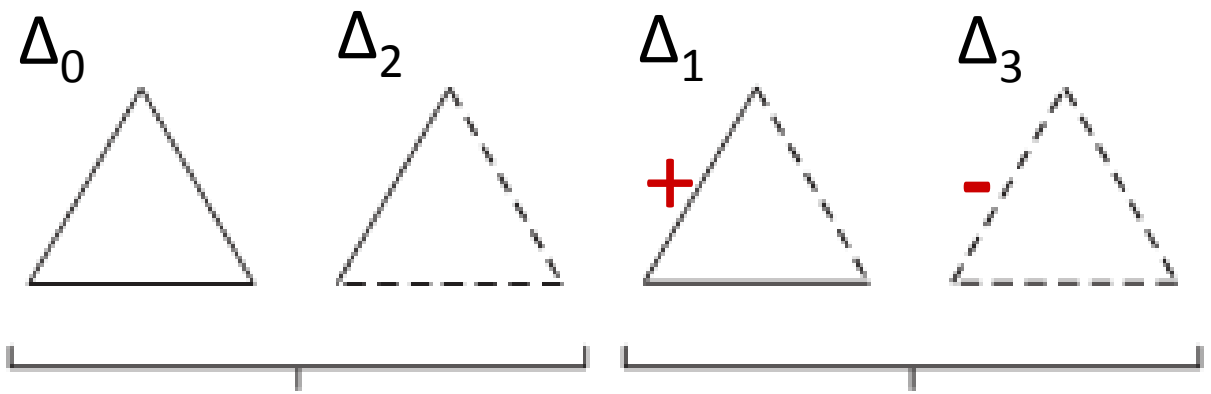


The influence of relationship



Mathematical model





$S_{ij}\, S_{jk}\, S_{ki}=1$

$S_{ij}\, S_{jk}\, S_{ki}=-1$

Even number of dashed edges

Odd number of dashed edges

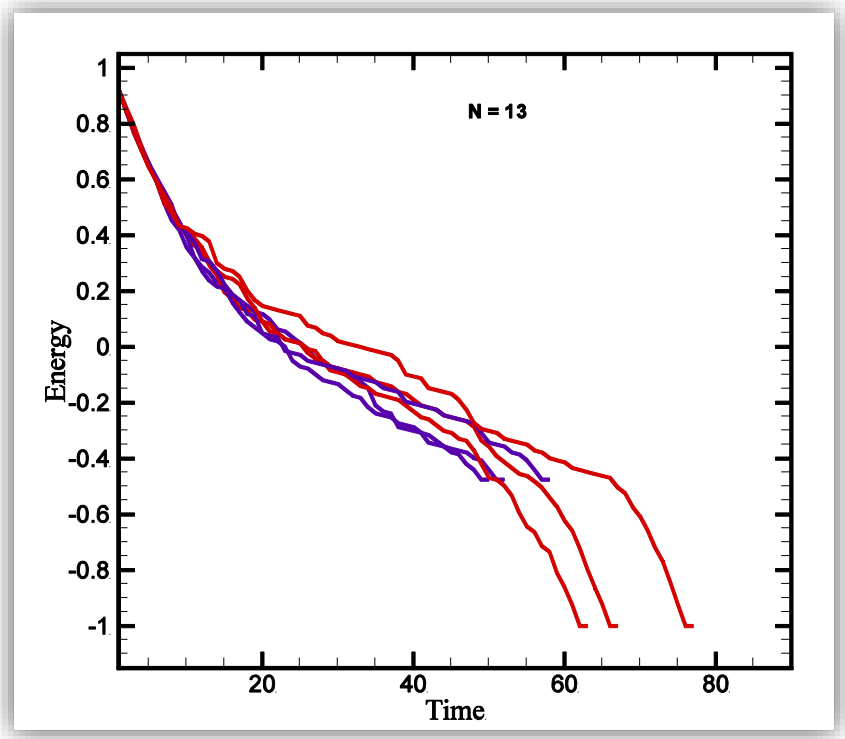
$$H = -\frac{1}{\binom{n}{3}} \sum s_{ij} s_{jk} s_{ik}$$

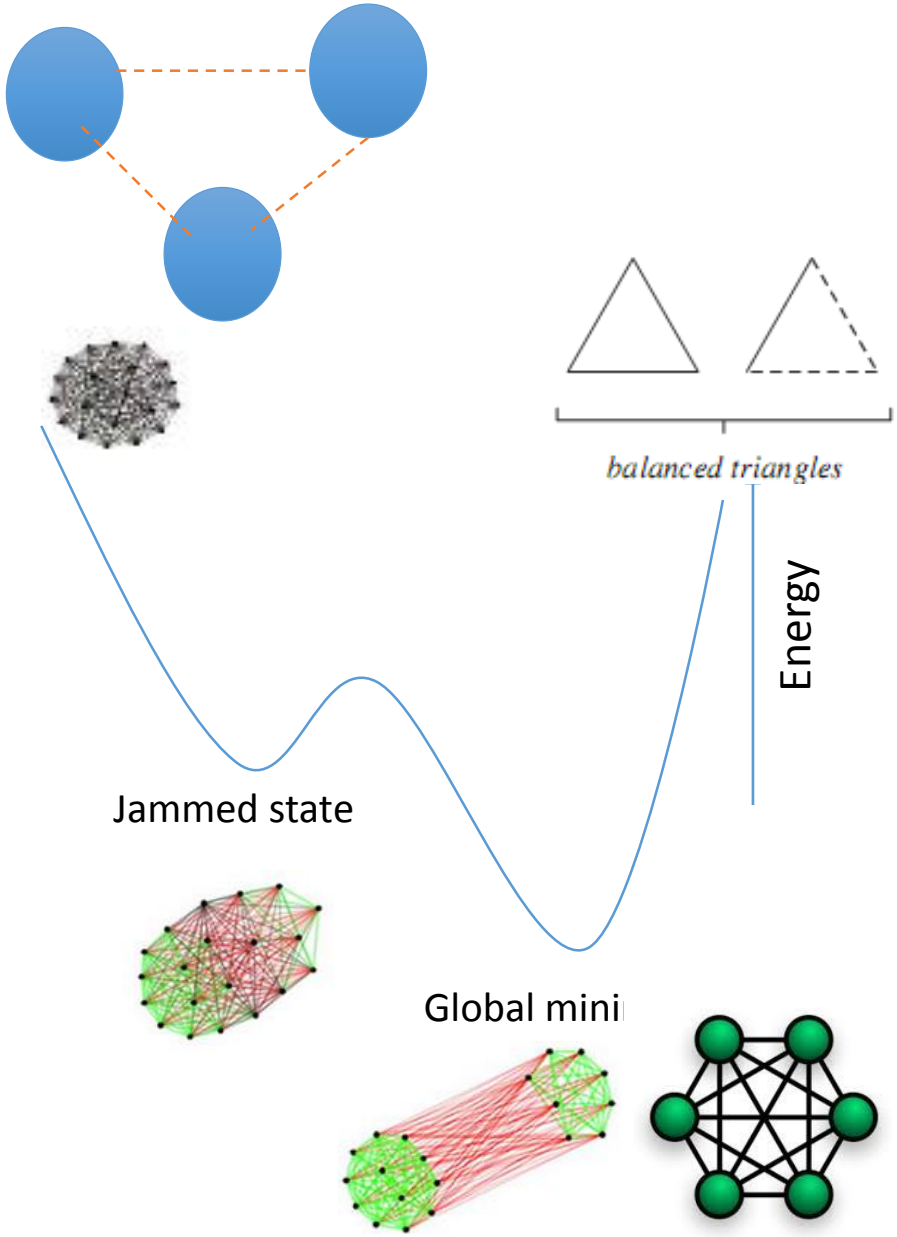
$$\frac{dx_{ki}}{dt} = \sum_{l=1} X_{kl}(t') X_{li}(t')$$

T. Antal, P. L. Krapivsky, and S. Redner, Phy. Rev. E 72. 036121 (2005)

Jammed states

$$H = -\frac{1}{\binom{n}{3}} \sum s_{ij} s_{jk} s_{ik}$$

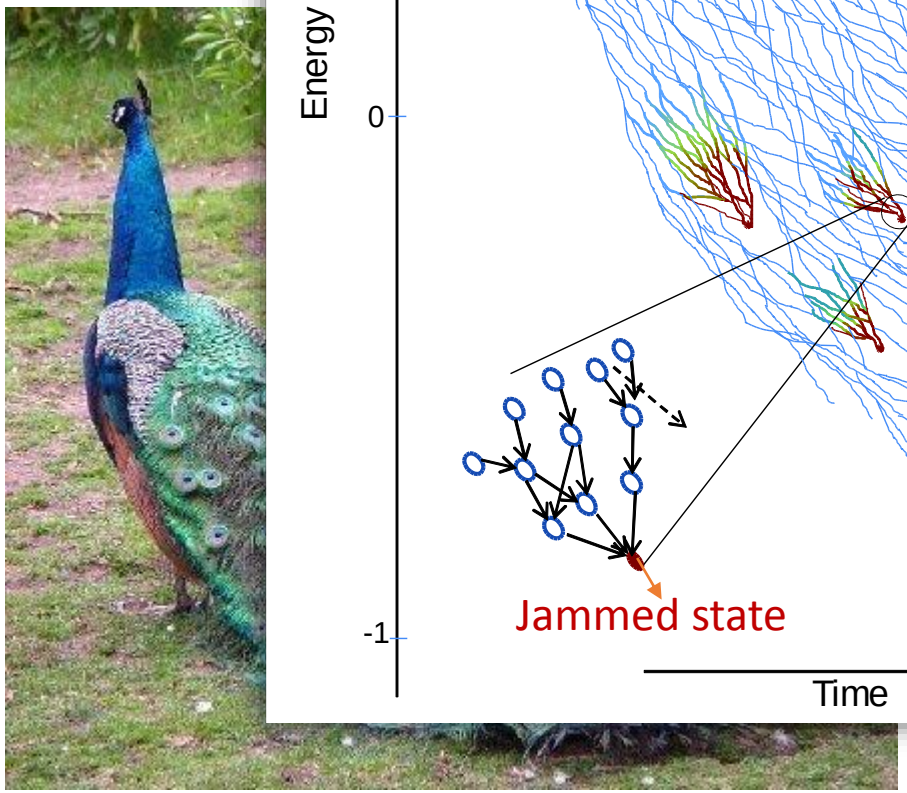




Jammed states are possible if and only if the network size is **N = 9 or N ≥ 11**

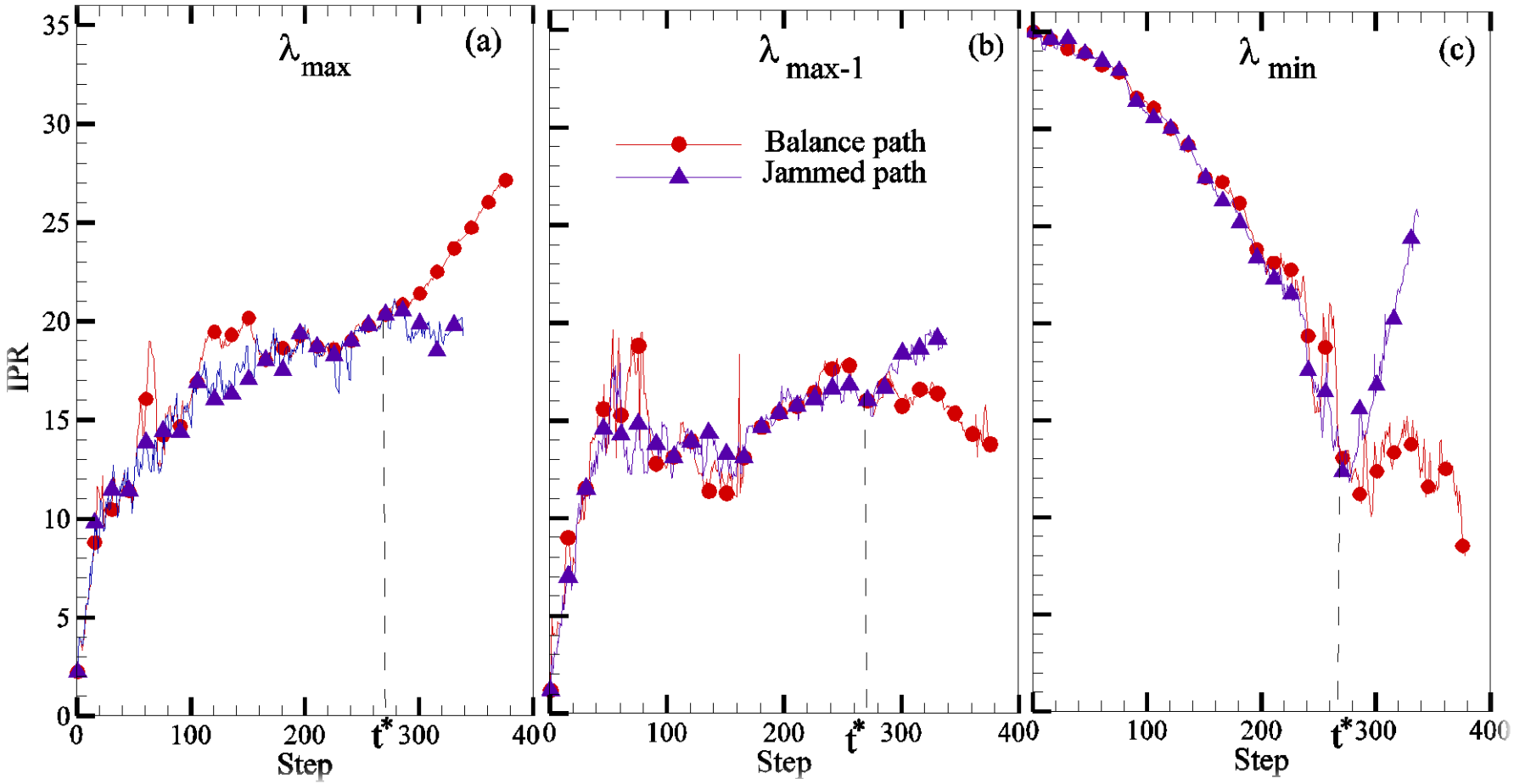
S. A. Marvel, S. H. Strogatz, and J. M. Kleinberg, Phys. Rev. Lett. 103, 198701 (2009)

Pseudo Paths



Pseudo paths towards minimum energy states in network dynamics, L. Hedayatifar, F. Hassanibesheli, A.H. Shirazi, S.V. Farahani, G.R. Jafari, Physica A, 483, 109-116 (2017)

Inverse participation ratio (IPR)



$$|\psi>=\begin{pmatrix}\psi_1\\ \psi_2\\ \psi_3\end{pmatrix}$$

$$\mathrm{IPR}=\frac{1}{\sum_i |\psi_n(i)|^4}$$

$$1 \le \mathrm{IPR} \le N$$

Pseudo paths towards minimum energy states in network dynamics, L. Hedayatifar, F. Hassanibesheli, A.H. Shirazi, S.V. Farahani, G.R. Jafari, Physica A, 483, 109-116 (2017)

The data: 20532 genes in the case of Breast Cancer

(BRCA: Breast invasive carcinoma)

It has been downloaded from data bank:

The Cancer Genome Atlas (*TCGA*) project.

The expression levels have done with the technique of RNA sequencing.

	Normal	Cancerous samples
#Samples	114	764

nature genetics

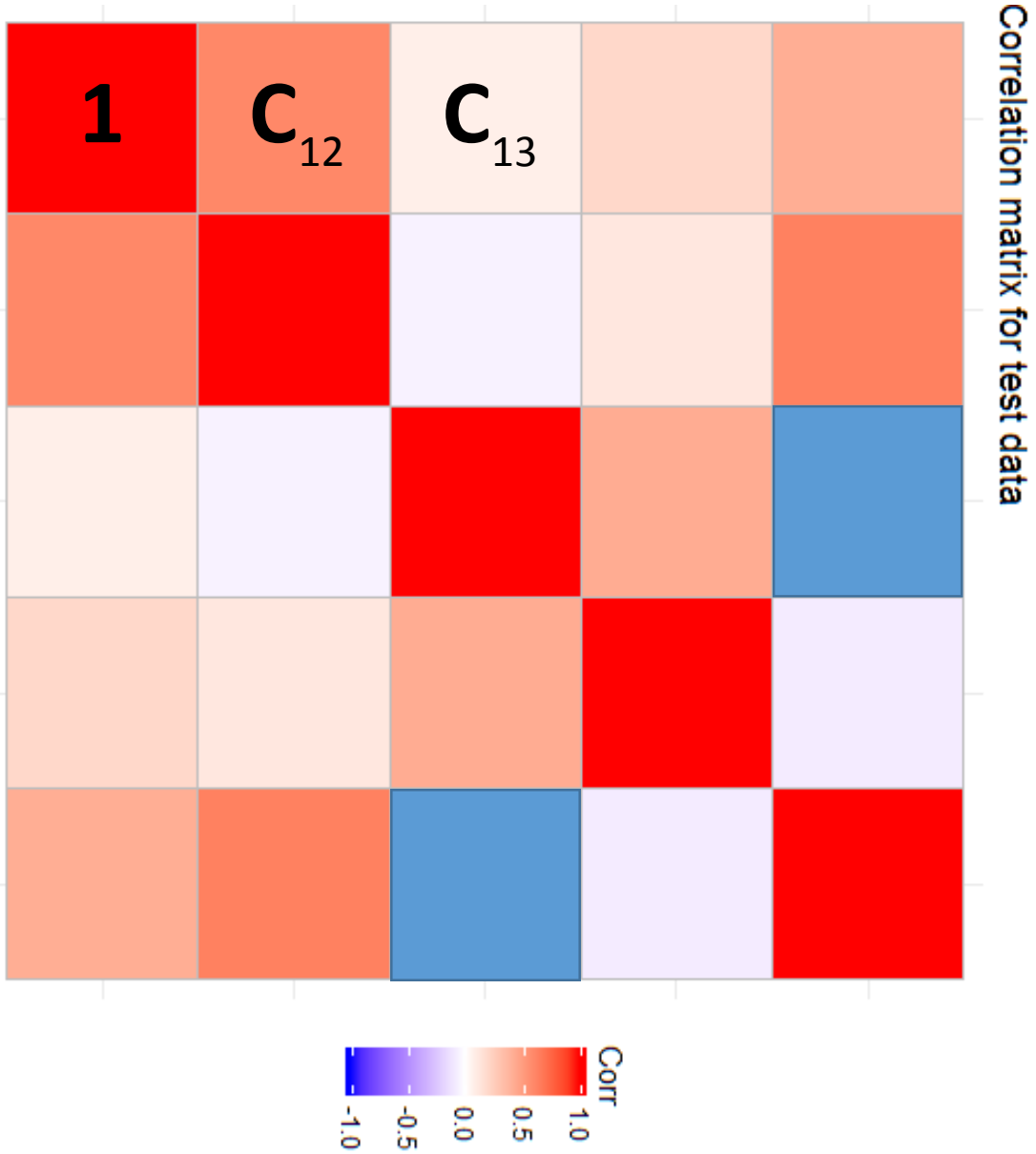
Commentary | OPEN | Published: 26 September 2013

The Cancer Genome Atlas Pan-Cancer analysis project

The Cancer Genome Atlas Research Network, John N Weinstein, Eric A Collisson, Gordon B Mills, Kenna R Mills Shaw, Brad A Ozenberger, Kyle Ellrott, Ilya Shmulevich, Chris Sander & Joshua M Stuart

Nature Genetics **45**, 1113–1120 (2013) | Download Citation

Correlation Matrix

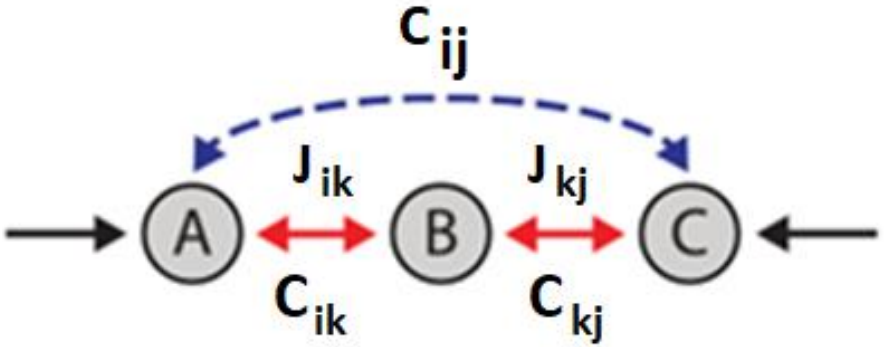


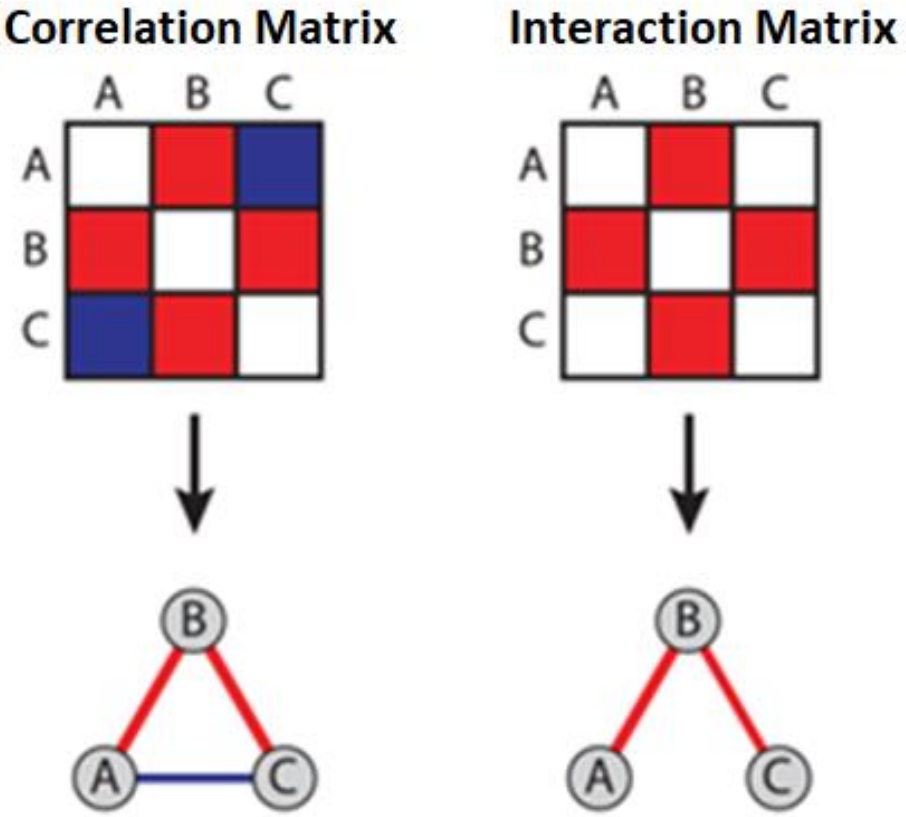
$$C_{ij} = \frac{\sum_{l=1}^{n}(X_l - < X >)(Y_l - < Y >)}{\sqrt{\sum_{l=1}^{n}(X_l - < X >)^2}\sqrt{\sum_{l=1}^{n}(Y_l - < Y >)^2}}$$

We had to reduce the number of genes because it is a difficult task to handle a 20532 in 20532 matrix computationally.

- Fortunately, most of the correlation matrix is zero
- There are many Genes that their expressions are the same in normal and cancerous cells. So for better comparison, we removed from our data sets. Now, we have only 450 genes to study.

Partial Correlation

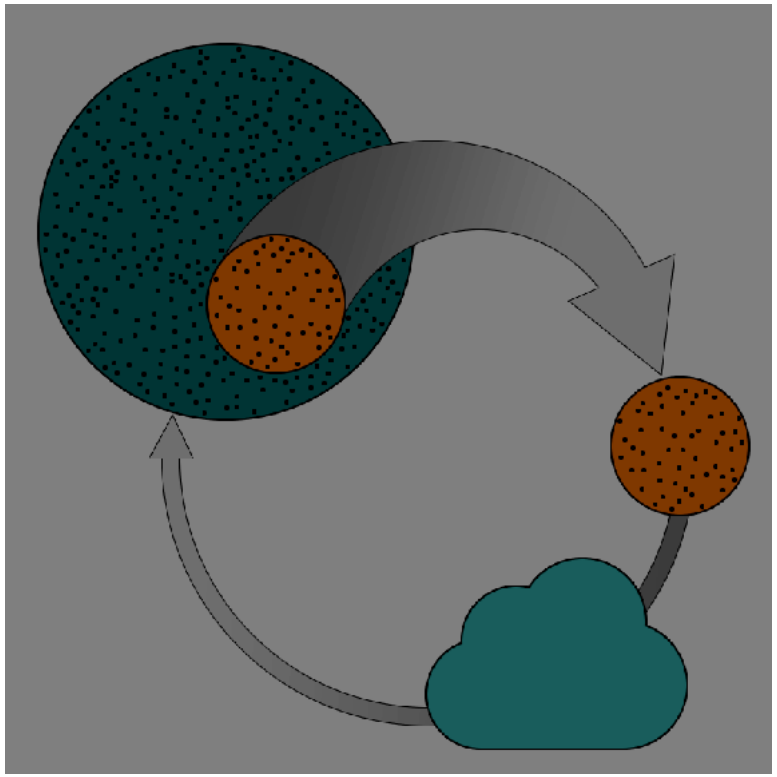




Inverse Spin Glass and Related Maximum Entropy Problems,
Michele Castellana, and William Bialek, 2013 PRL 113(11)

Lezon TR, Banavar JR, Cieplak M, Maritan A, Fedoroff NV, PNAS, 12;103(50):19033-8 (2006)

Invers problem



$$H = -\sum_{ij}^{N} J_{ij} s_i s_j - \sum_{i}^{N} h_i s_i$$

$$\int_x P(x)dx = 1$$

$$\langle x_i \rangle = \int_x P(x) x_i dx = \frac{1}{M} \sum_{m=1}^{M} x_i^m = \overline{x_i}$$

$$\langle x_i x_j \rangle = \int_x P(x) x_i x_j dx = \frac{1}{M} \sum_{m=1}^{M} x_i^m x_j^m = \overline{x_i x_j}$$

Max Entropy

With some Conjunctions

$$maximize S = -\int_x P(x)\ln P(x)dx$$

$$L = L(P(x);\alpha,\beta,\gamma)$$

$$\frac{\delta L}{\delta P(x)} = 0$$

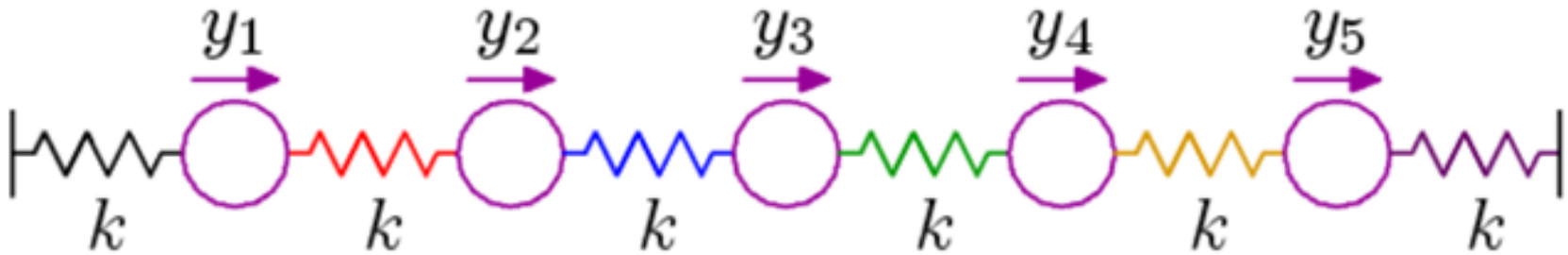
$$P(x,\beta,\gamma) = \exp(-1+\alpha+\sum_i^L \beta_i x_i + \sum_{i,j}^L \gamma_{ij}x_i x_j) = \frac{1}{Z}e^{-H(x,\beta,\gamma)}$$

$$P(x;<x>,C) = (2\pi)^{\frac{-L}{2}} det(C)^{\frac{-1}{2}} \exp(-\frac{1}{2}(x-<x>)^T C^{-1}(x-<x>))$$

$$J = -\frac{1}{2}C^{-1}$$

Lezon TR, Banavar JR, Cieplak M, Maritan A, Fedoroff NV, PNAS, 12;103(50):19033-8 (2006)

Inverse-covariance matrix

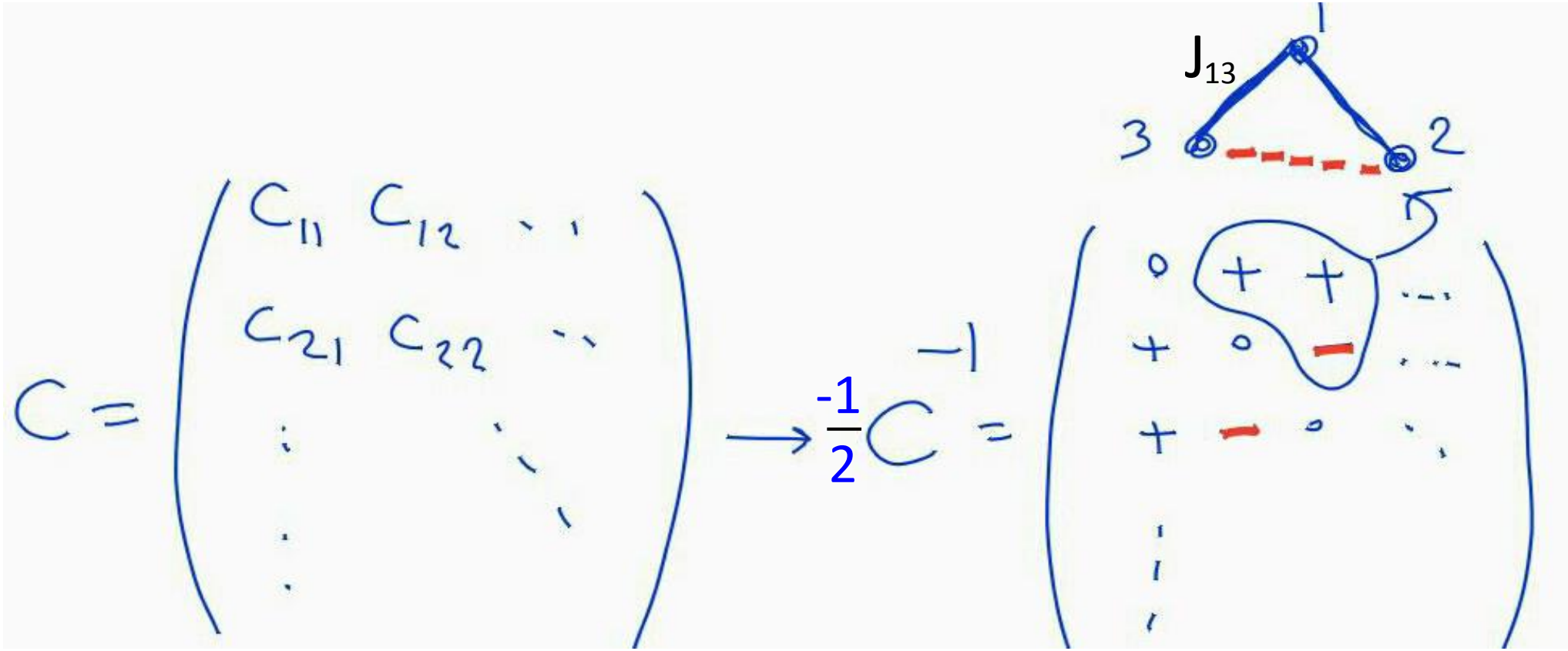


inverse-covariance matrix or covariance matrix?

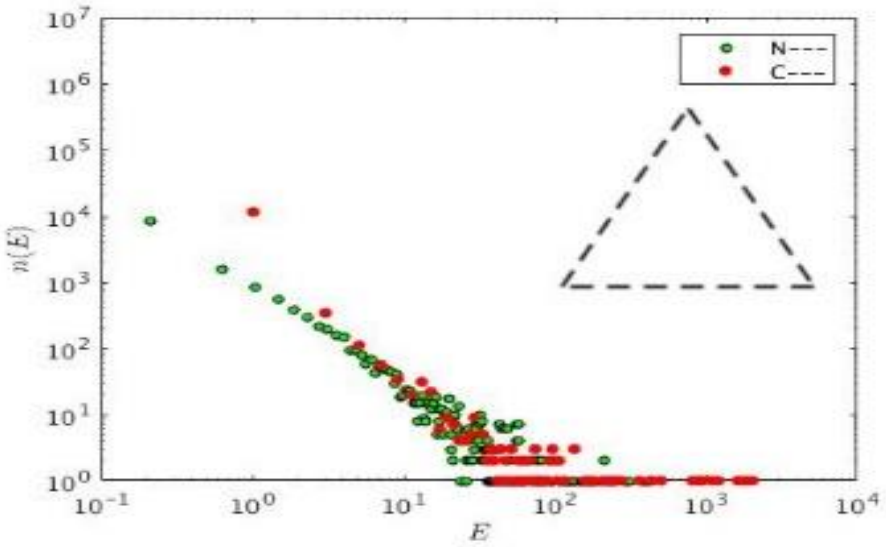
$$\mathbf{K}^{-1} = \frac{k}{T}\begin{bmatrix} 2 & -1 & 0 & 0 & 0 \\ -1 & 2 & -1 & 0 & 0 \\ 0 & -1 & 2 & -1 & 0 \\ 0 & 0 & -1 & 2 & -1 \\ 0 & 0 & 0 & -1 & 2 \end{bmatrix} \qquad \mathbf{K} = \frac{T}{k}\begin{bmatrix} 1.00 & 0.67 & 0.50 & 0.33 & 0.17 \\ 0.67 & 1.00 & 1.00 & 0.67 & 0.33 \\ 0.50 & 1.00 & 1.00 & 1.00 & 0.50 \\ 0.33 & 0.67 & 1.00 & 1.00 & 0.67 \\ 0.17 & 0.33 & 0.50 & 0.67 & 1.00 \end{bmatrix}$$

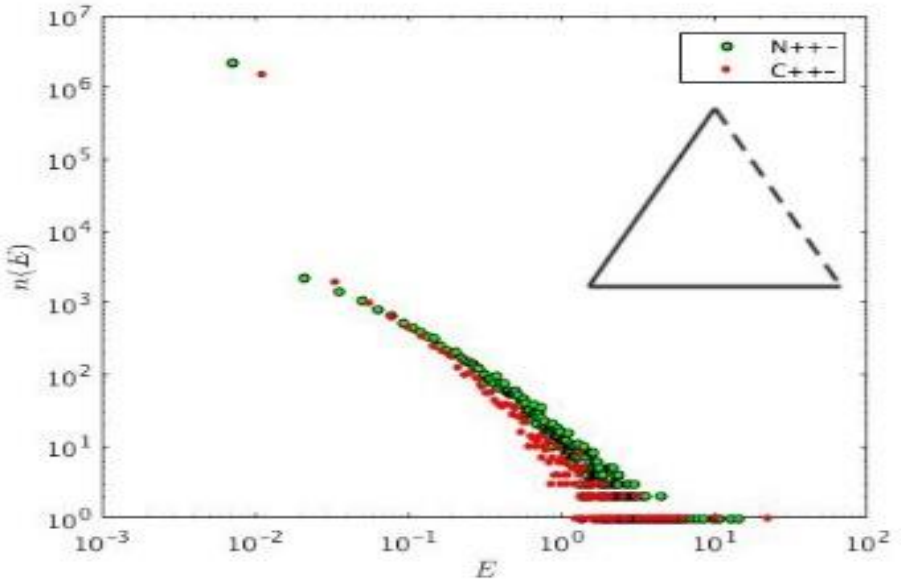
Correlation matrix to Interaction matrix

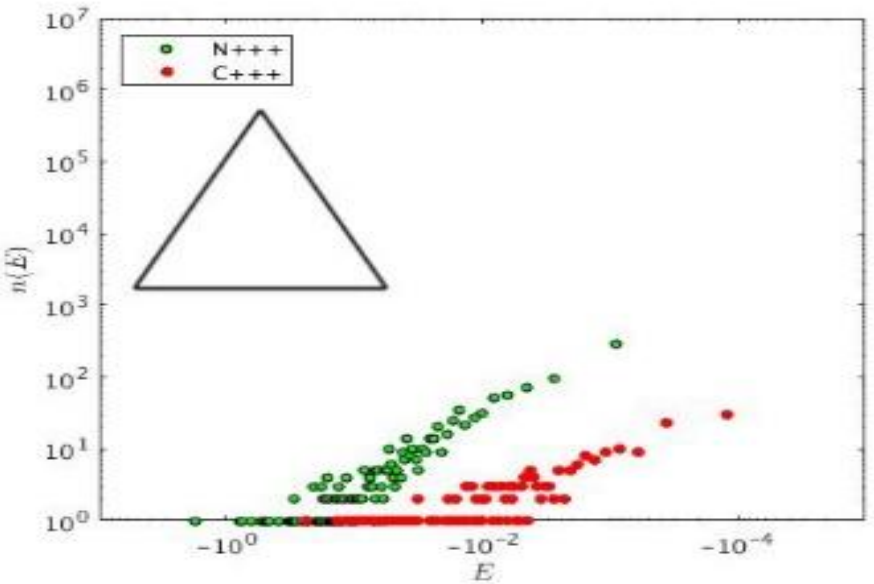
$E = -J_{12} J_{13} J_{23}$

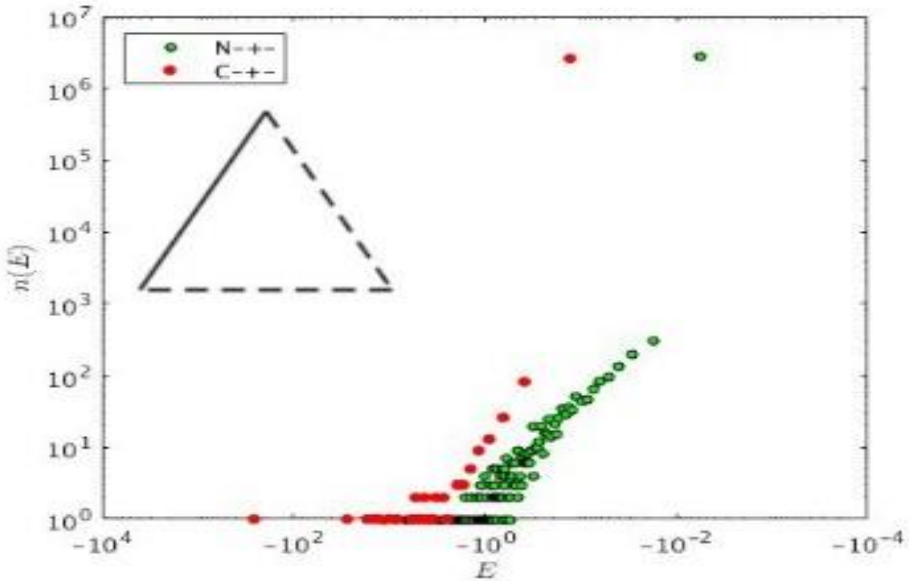


Energy distribution

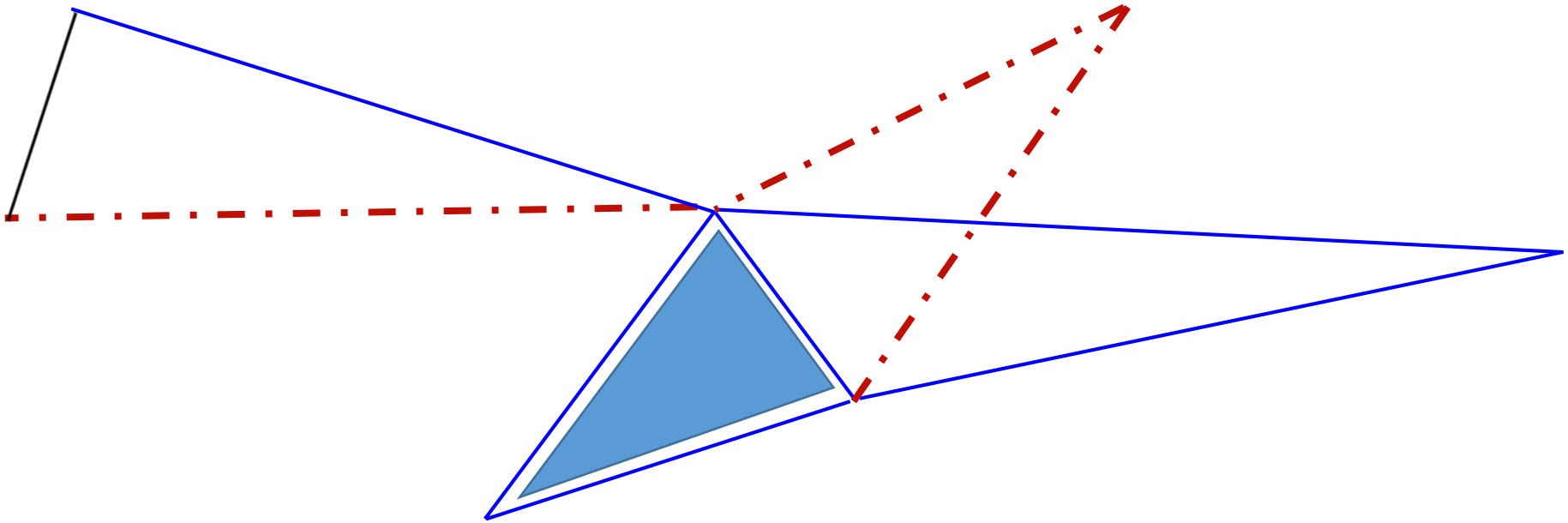


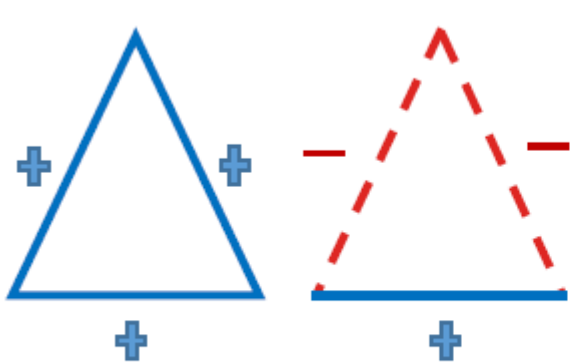




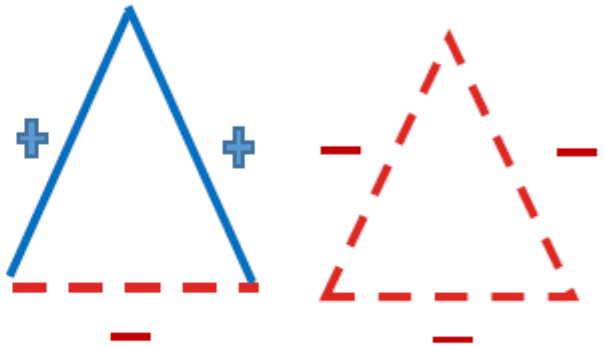


Energy-Energy Correlation





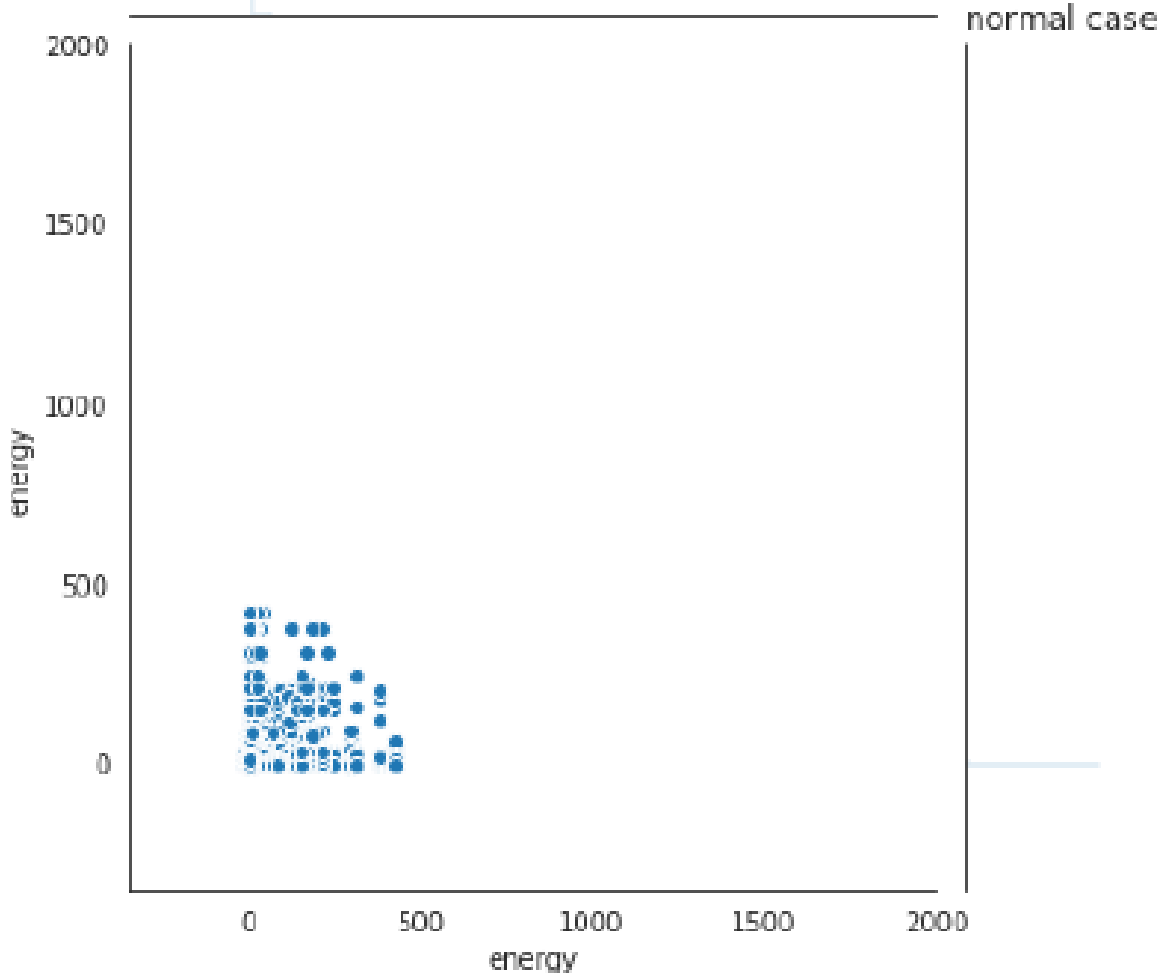
(a) Balanced



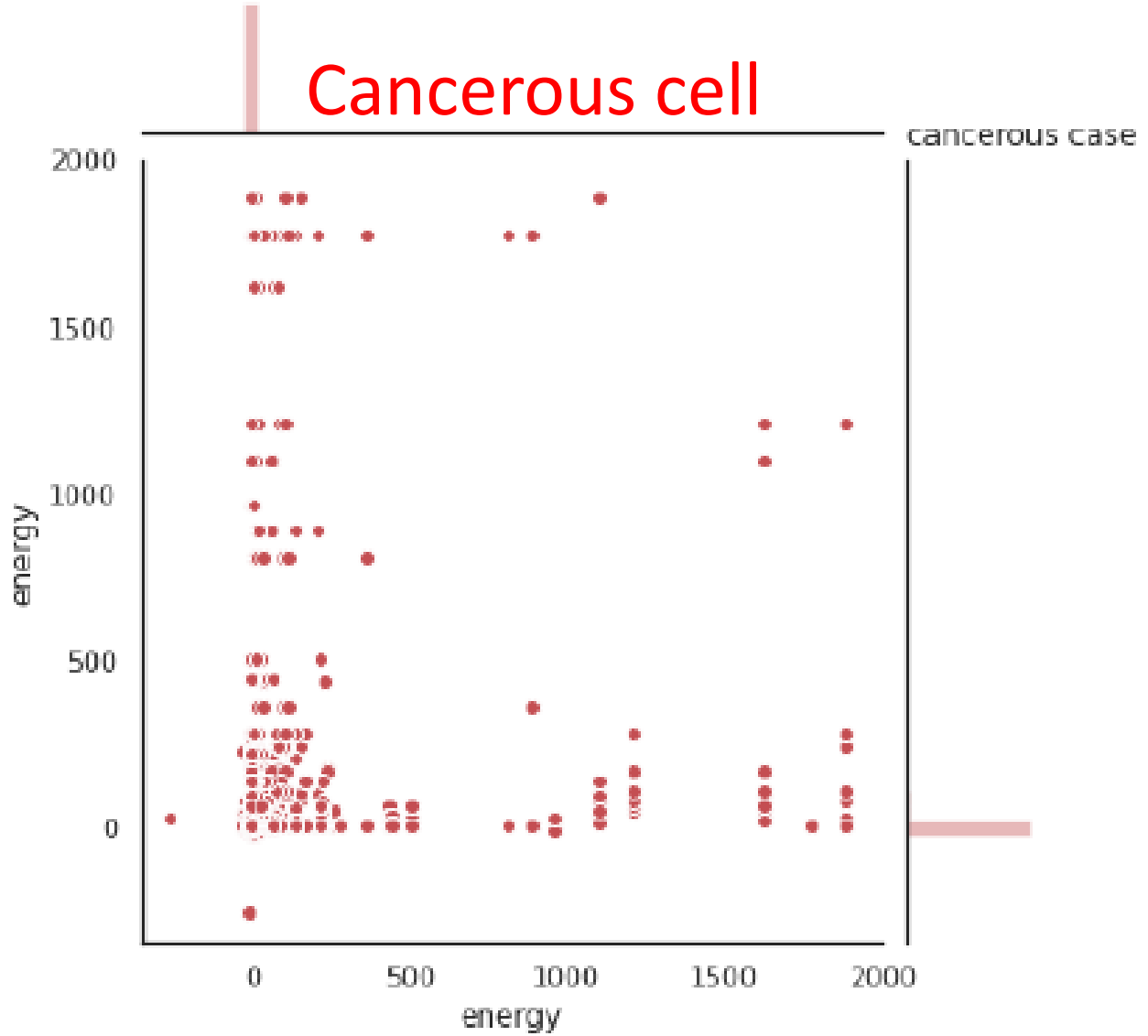
(b) Imbalanced

How triads with different energies are connected to each other?

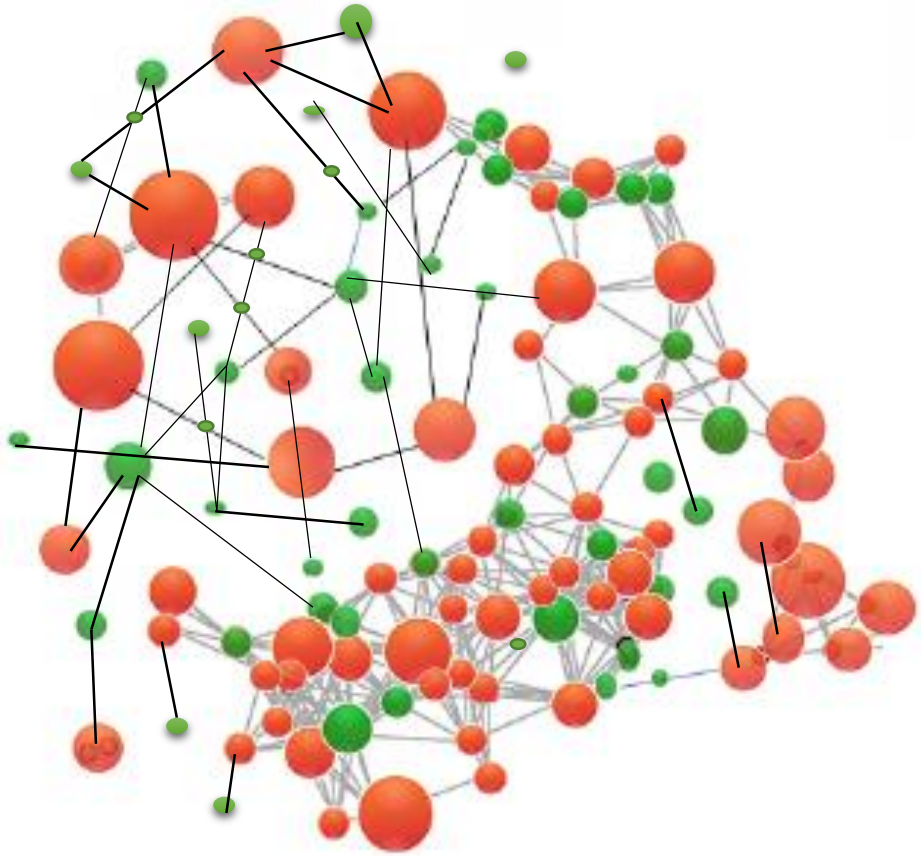
Normal Cells



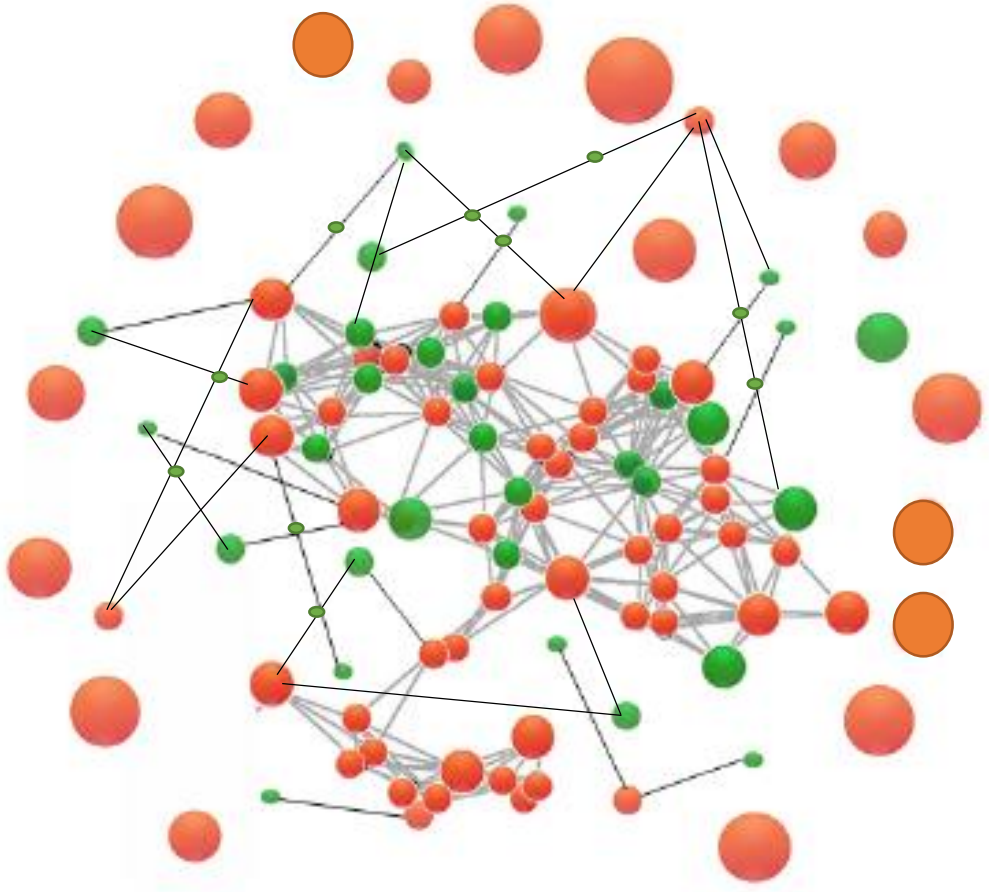
Cancerous cell



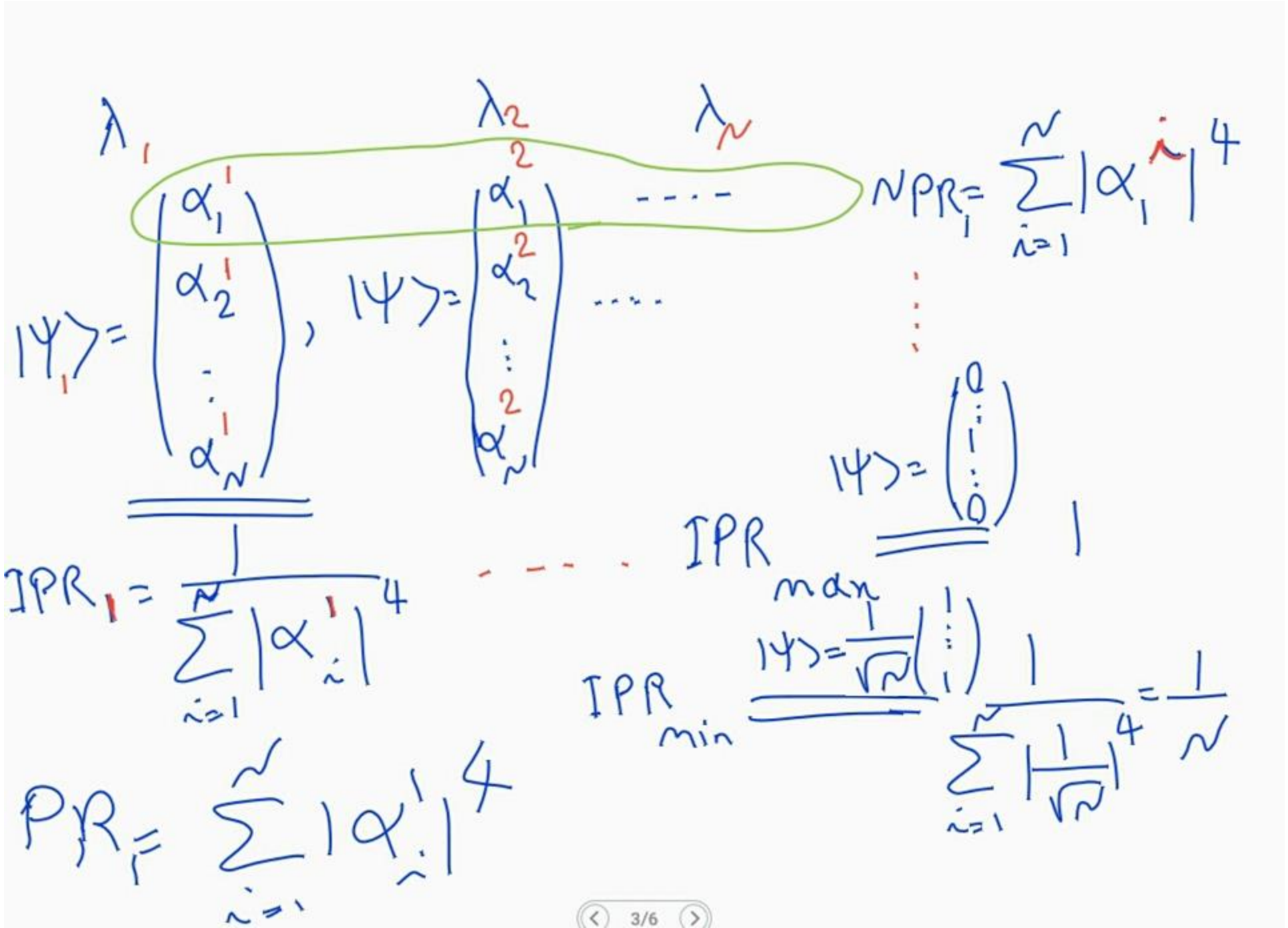
Network of balance and imbalance triangles

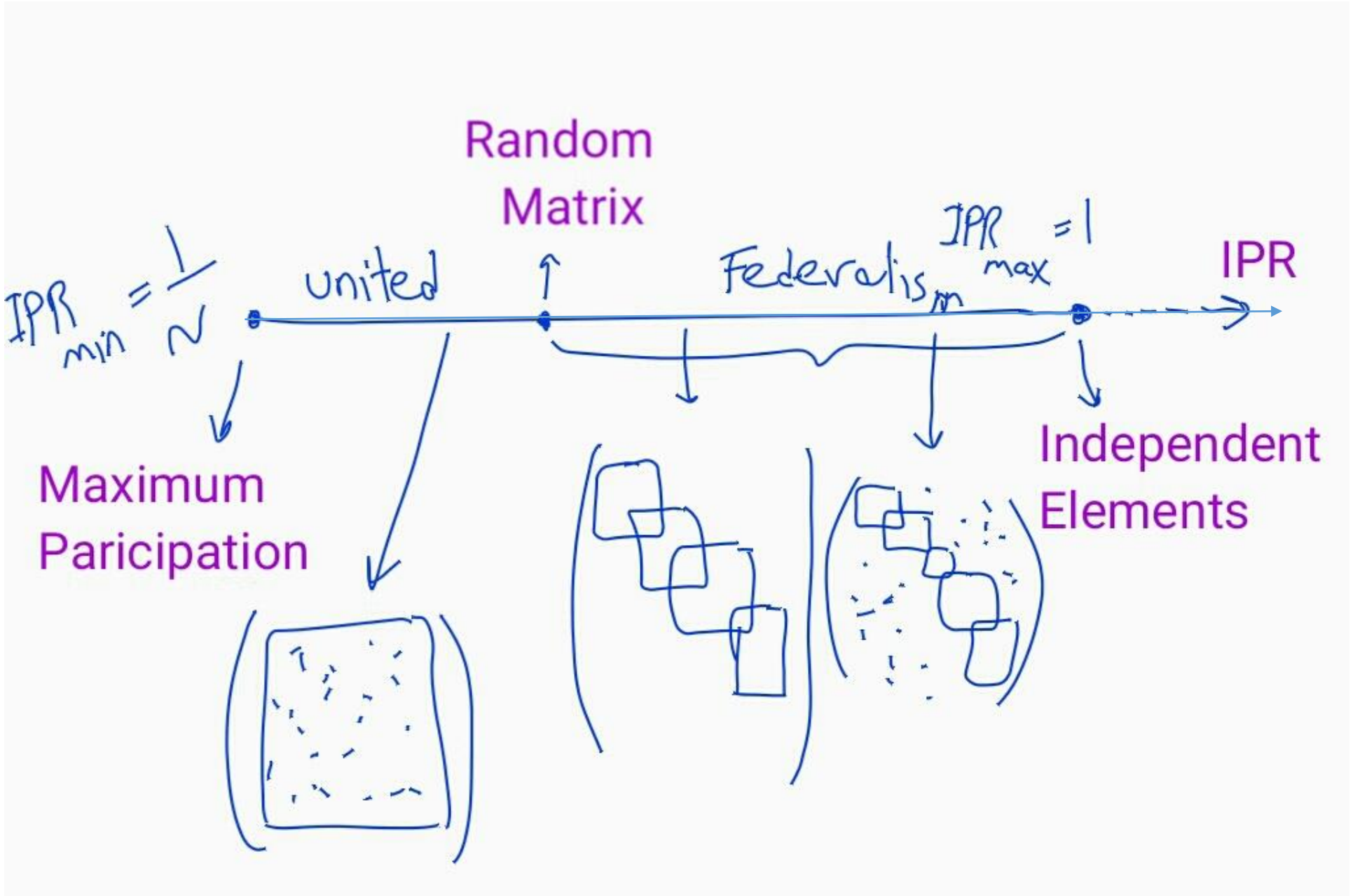


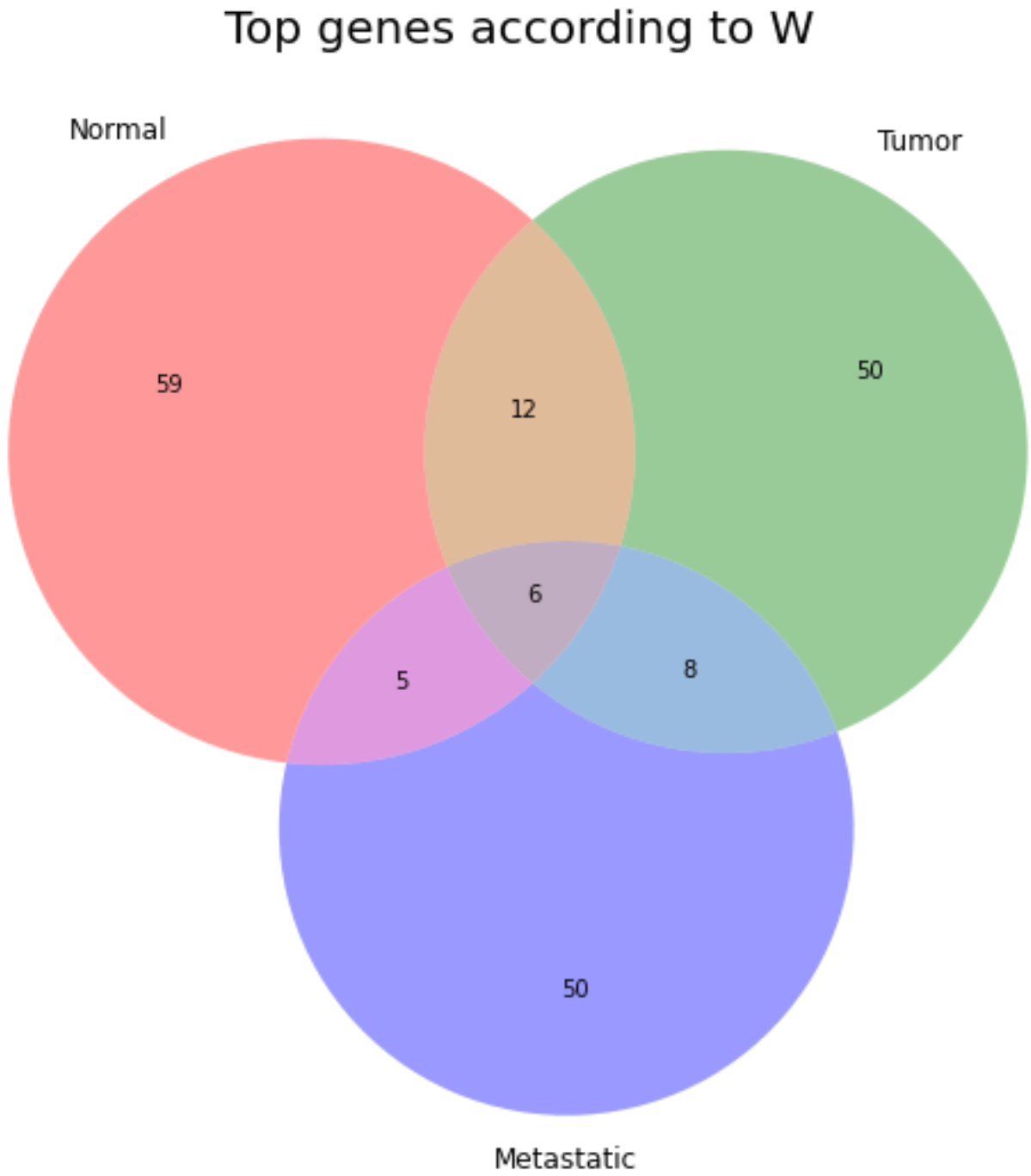
Cancerous cell



Normal Cells


λ1
λ2
λN
|ψ1⟩ = (α1^1, α2^1, ..., αN^1)
|ψ⟩ = (α1^2, α2^2, ..., αN^2)
NPR1 = Σ_{i=1}^{N} |αi^1|^4
|ψ⟩ = (0, ..., 1, ..., 0)
IPR1 = 1 / Σ_{i=1}^{N} |αi^1|^4
IPR 1
IPR max |ψ⟩ = (1/√N)(1, ..., 1)
IPR min = 1 / Σ_{i=1}^{N} |1/√N|^4 = 1/N
PR1 = Σ_{i=1}^{N} |αi^1|^4

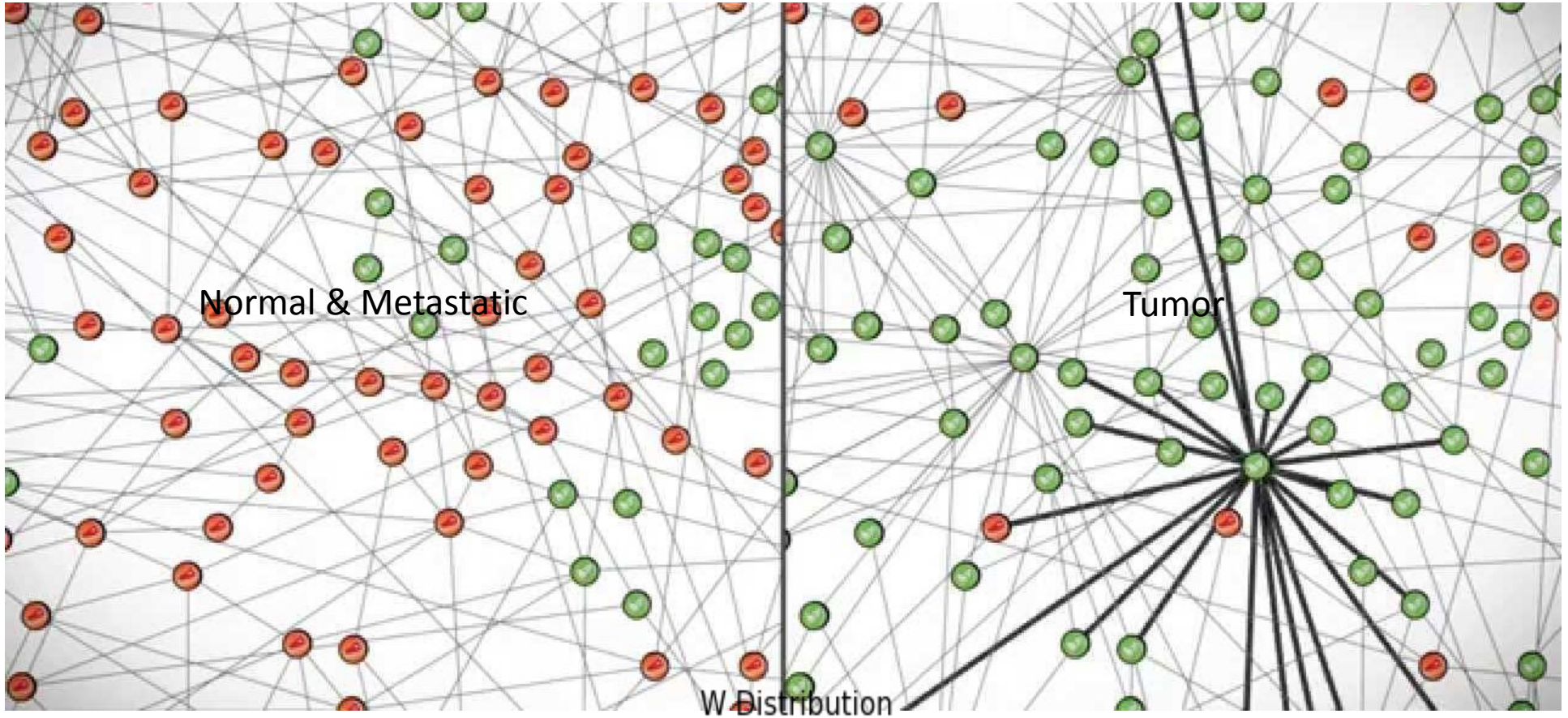

Random
Matrix
IPR min = 1/N
united
Federalism
IPR max = 1
IPR
Maximum
Paricipation
Independent
Elements

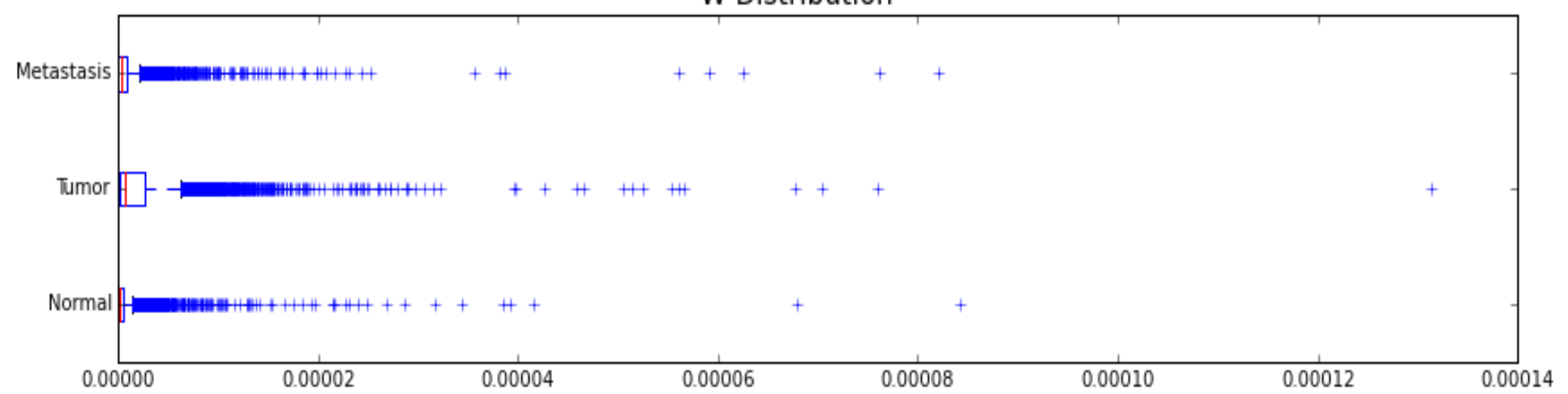

Top genes according to W
Normal
Tumor
Metastatic
59
12
50
6
5
8
50

Top driver genes in metastatic cells

ALB	M64936	CSTA	IGL@	APOA1	DST	LOC100126583	D26561	ESM1	NF1
PCK1	RBP4	MUC1	FN1	KLK3	CYP3A7	HPR	ACTG2	PDE5A	ALDOB
CRP	IGL@	CHI3L1	FN1	FABP4	ALB	KLK2	IRS1	MAPK8	TGM4
MYH11	IGHV4-31	MCF2	UGT2B15	PSPH	FGG	HPGD	APOB	HPGD	STAC
KLK3	GATM	SULT1C2	PRKG2	MAGEB1	PRG4	SSX2B	KLK3	FGB	SLC25A13
FGA	KLK2	FABP1	DDC	C5	MHY11	CPB1	PLAT	IL2	PF4V1
IGK@	SLC25A24	MSMB	AF070543	ORM2	IGH@	KNG1	PCK1	SERPINA1	

Cancer related
Immune system related
Growth related
Adhesion and migration related
Proliferation and differentiation

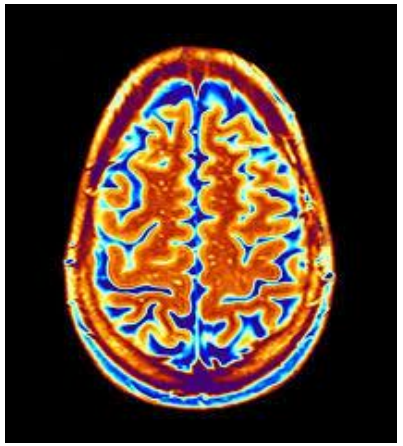

Normal & Metastatic
Tumor


W Distribution
Metastasis
Tumor
Normal
0.00000
0.00002
0.00004
0.00006
0.00008
0.00010
0.00012
0.00014

ABIDE

Autism Brain Imaging Data Exchange

Summary of data:



- The data used to build the brain networks is borrowed from the **Autism Brain Imaging Data Exchange (ABIDE II)** which is available in:

  http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html

- We chose **the longitudinal collections** in ABIDE II, which are from the university of California Los Angeles and the university of Pittsburgh.

- We had **23** and **15** participants in the Autism Spectrum Disorder and the control groups, respectively. Each participant underwent **two resting-state fMRI sessions**, collected one to three years apart.

NYU Langone Medical Center

Hyperactive

Summary of data:

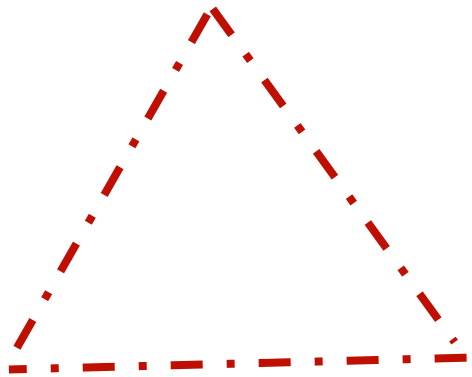
- The data used to build the following brain networks is from the **ADHD-200** dataset and is available in:

  http://fcon_1000.projects.nitrc.org/indi/adhd200/

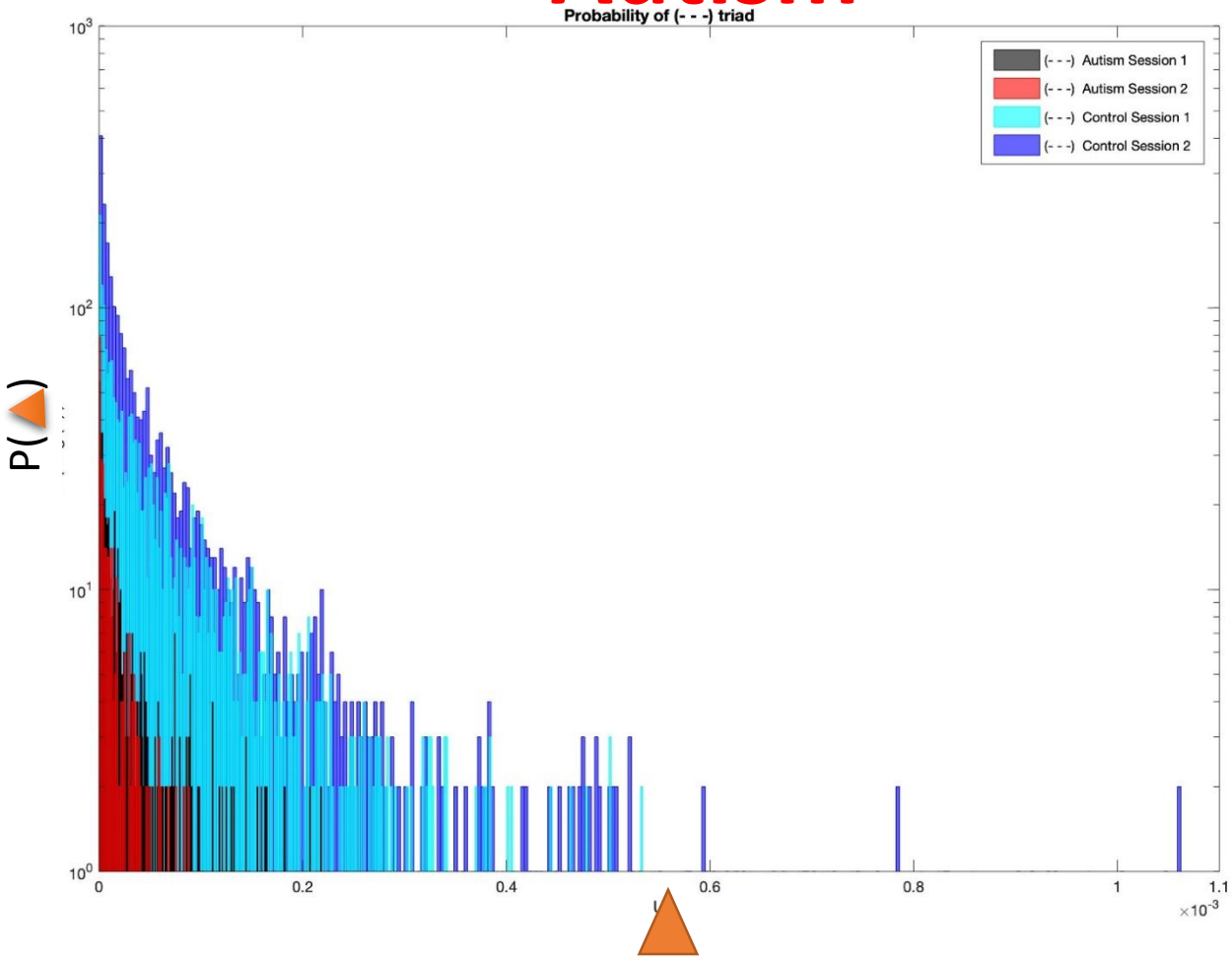
- We chose the **New York University Child Study Center** site, from the ADHD-200.

- After the preprocessing steps, the sample size was:
  - **98** individuals in the **Control group**
  - **115** individuals in the **ADHD (Attention Deficit Hyperactivity Disorder)**

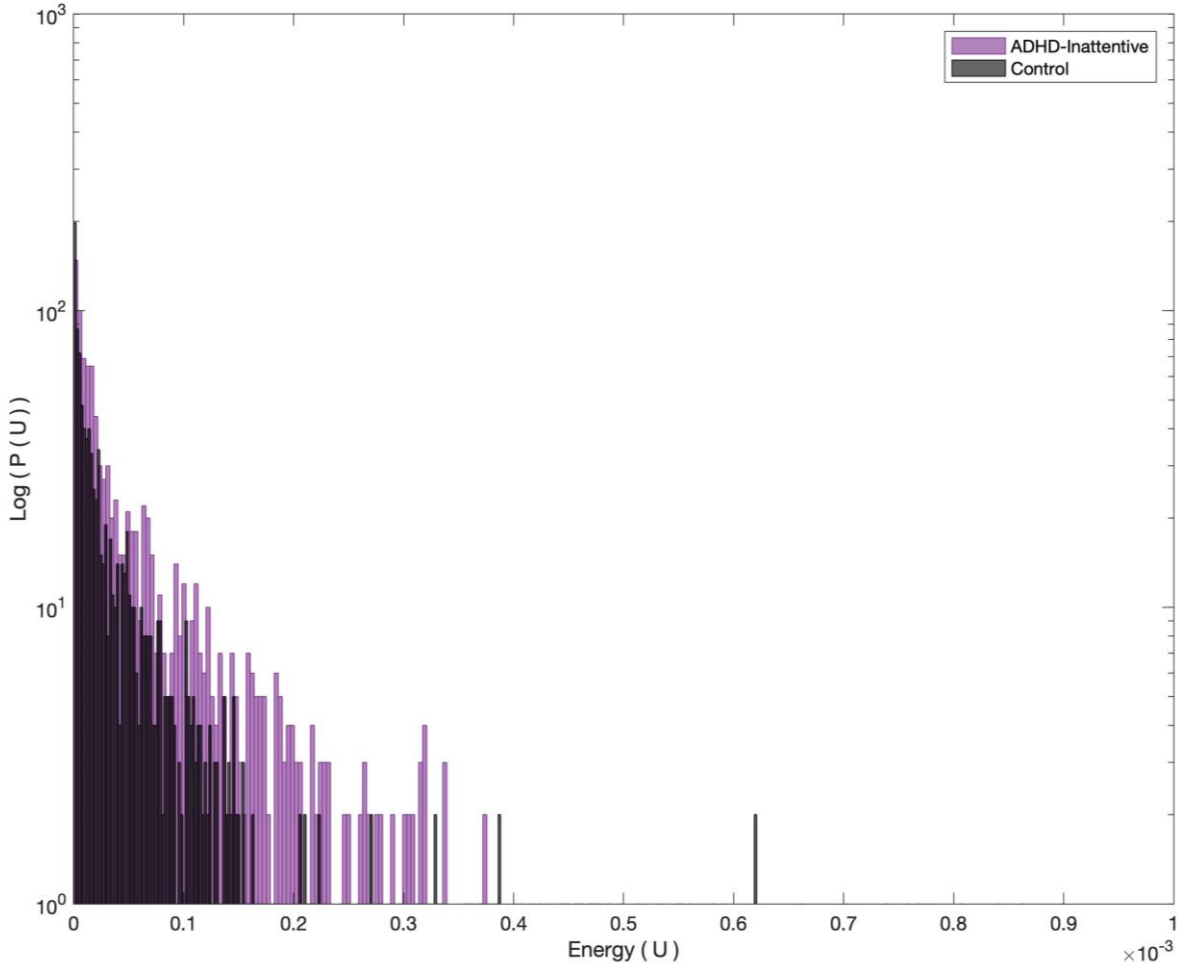
PDF of

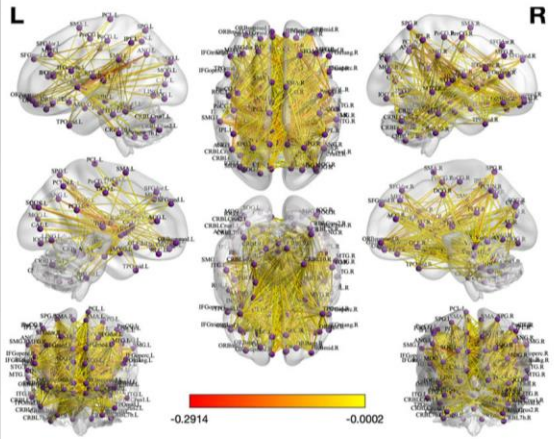
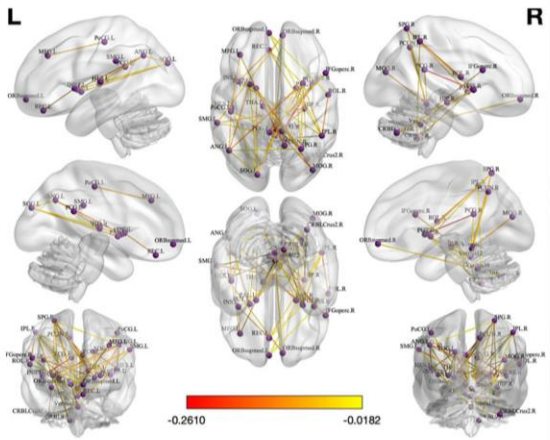
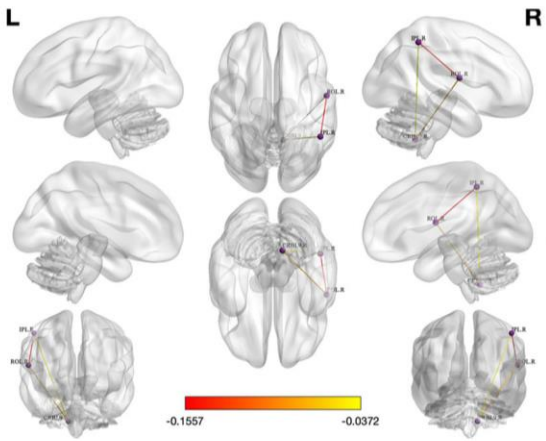
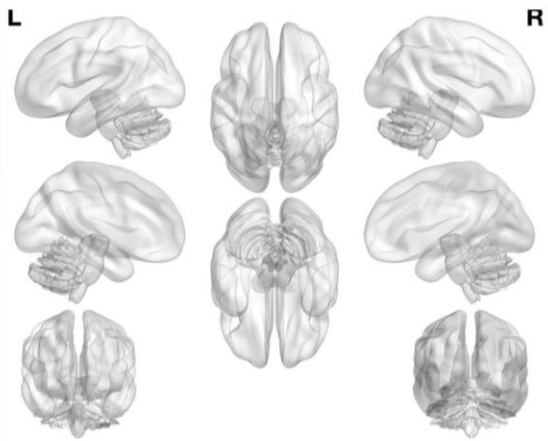
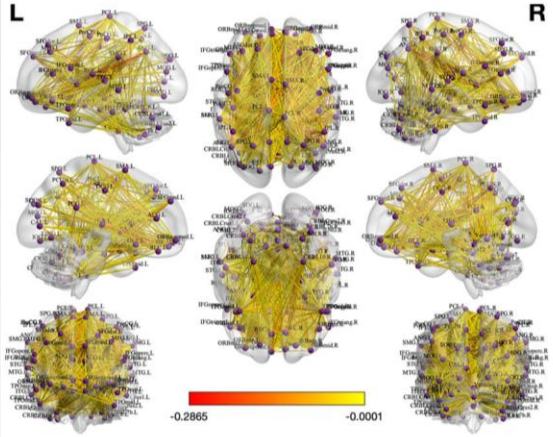
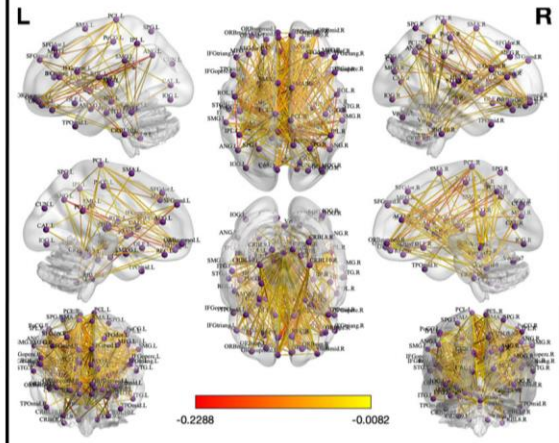
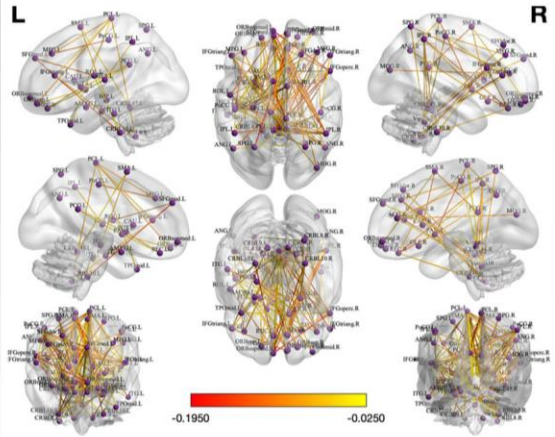
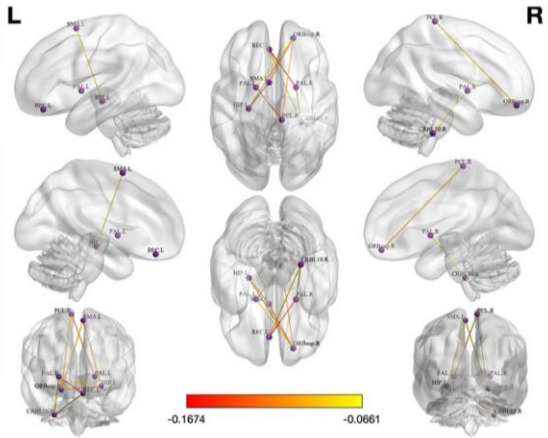


Autism



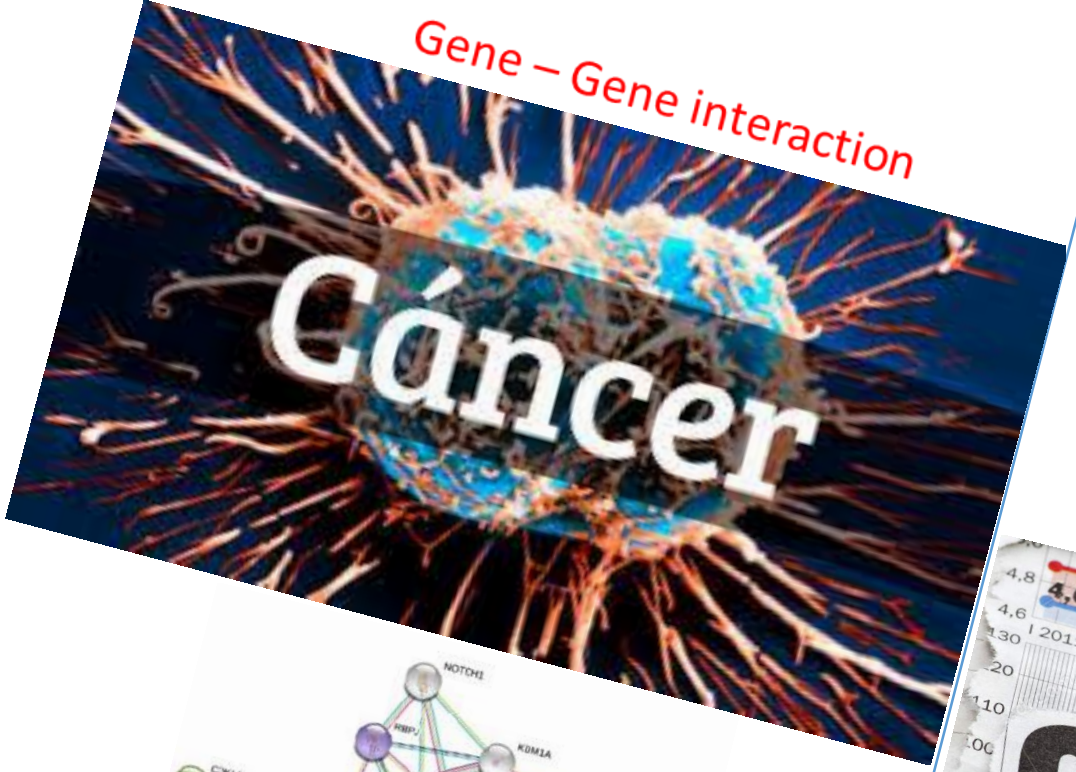
Hyperactive

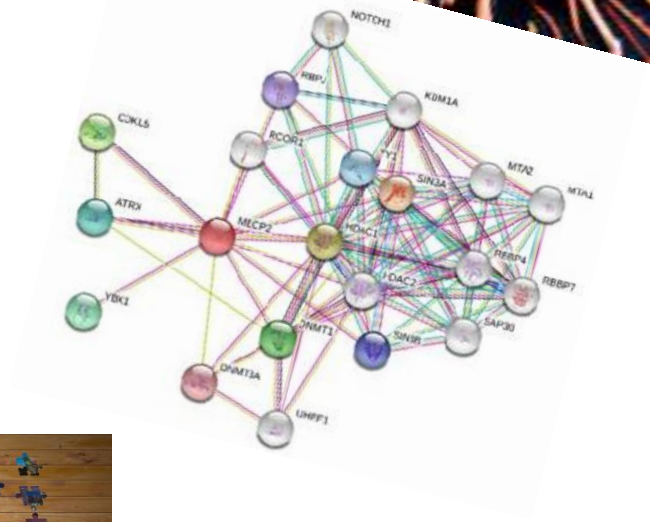


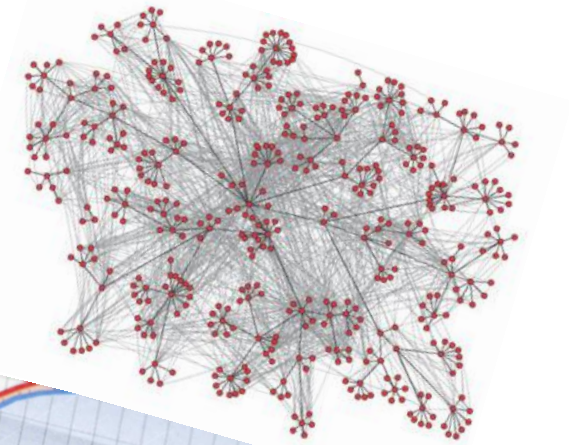
	$2 \times 10^{-4} < U$	$2 \times 10^{-4} \leq U < 4 \times 10^{-4}$	$4 \times 10^{-4} \leq U < 9.2 \times 10^{-4}$	$U > 9.2 \times 10^{-4}$
Autism				
Control				

[**Autism Brain Imaging Data Exchange II , The Longitudinal Collections**: http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html]

Gene – Gene interaction

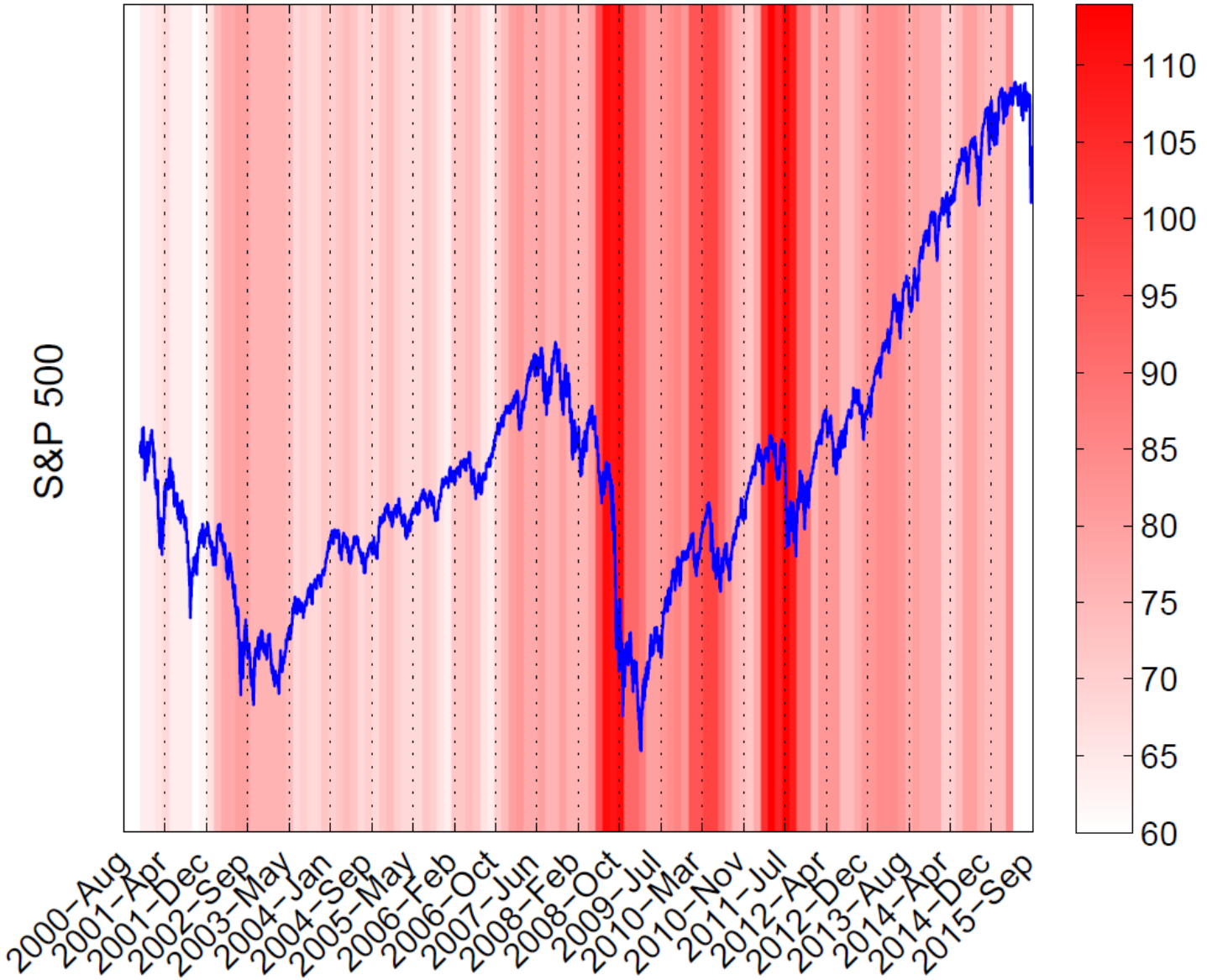






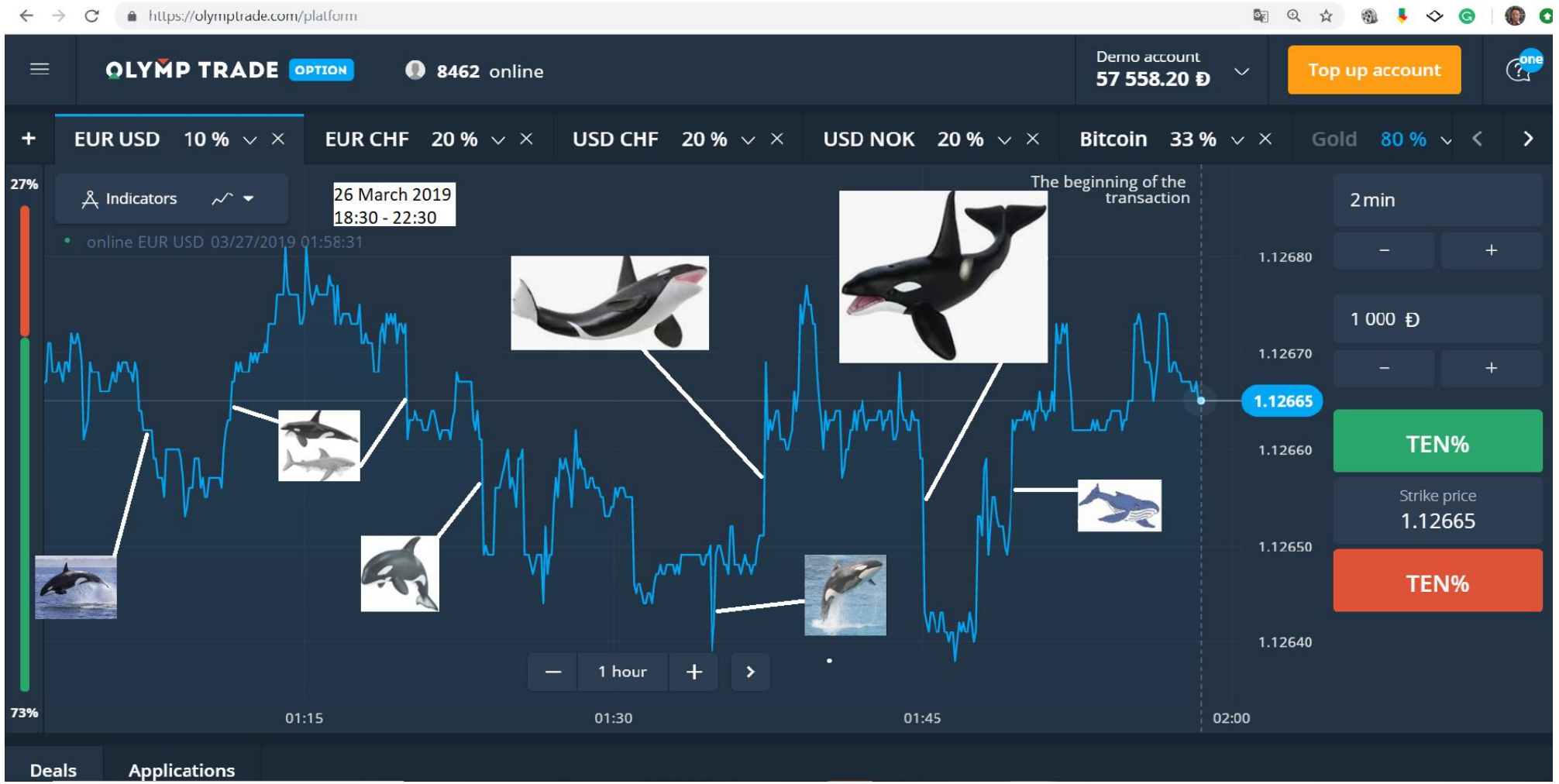
Market – Market interaction

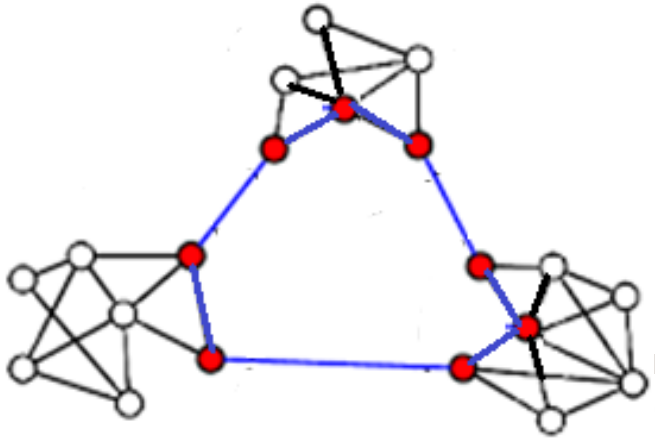
Heat map of S&P500

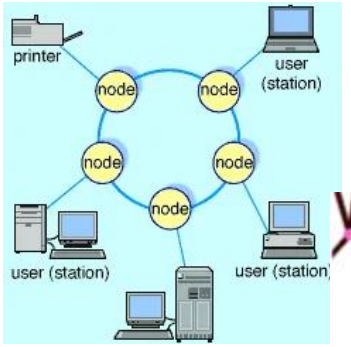


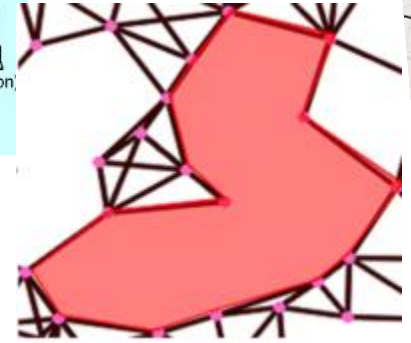
The Whales dance

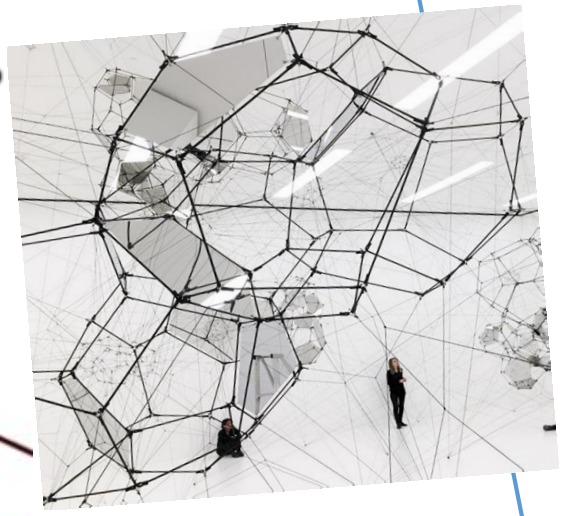
Quanta Trading Signals






printer
user (station)
node
node
node
node
node
user (station)
user (station)





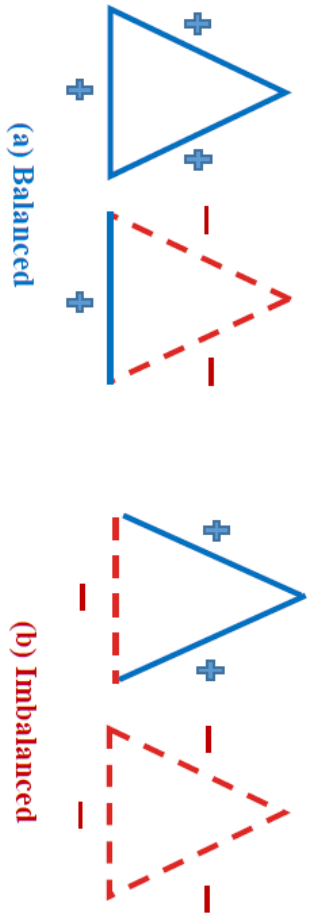

GROUND
FLOOR

Thanks

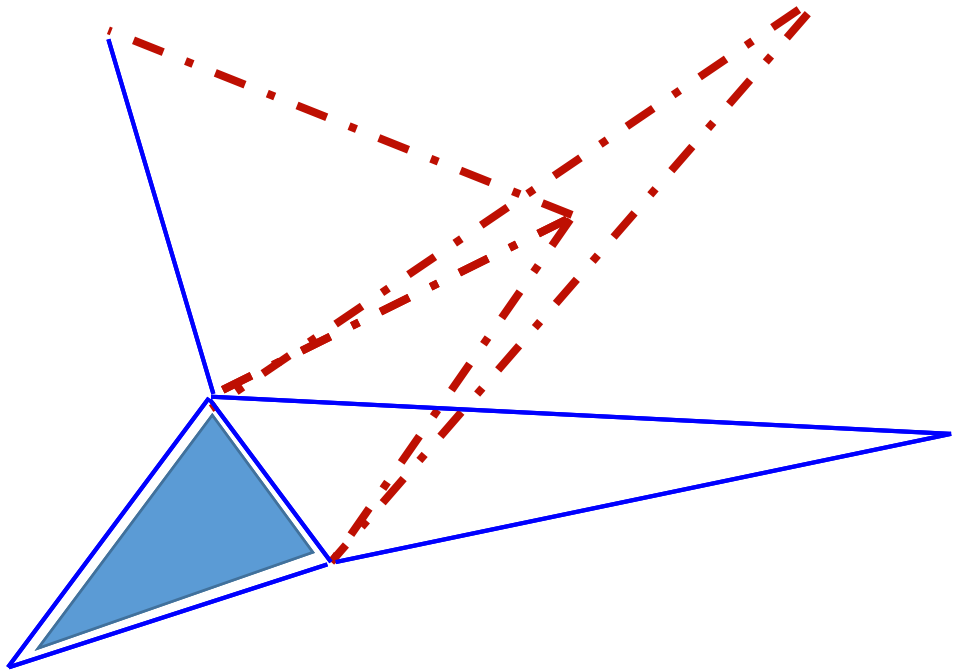
Compare the Balance states between 3th and 4th order interactions

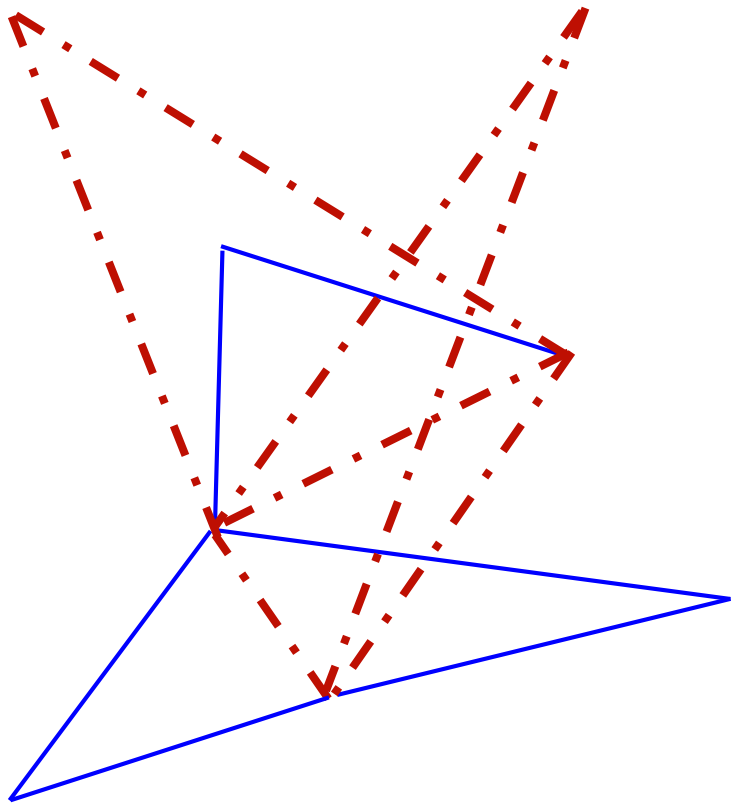
3th order interactions

$$\mathcal{H} = -\sum_{i<i<k} \Delta_{ijk}$$

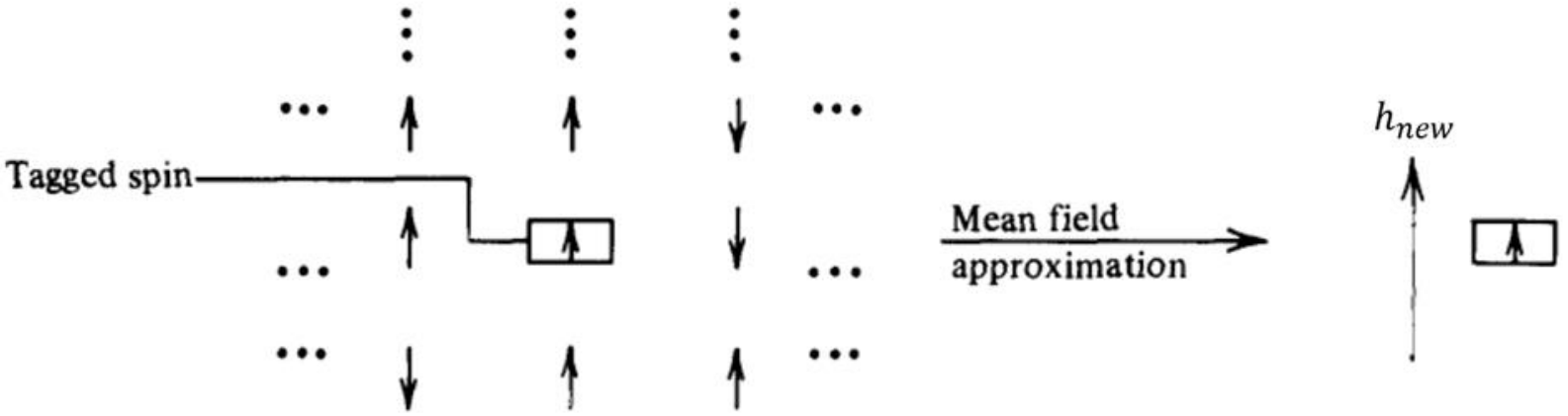


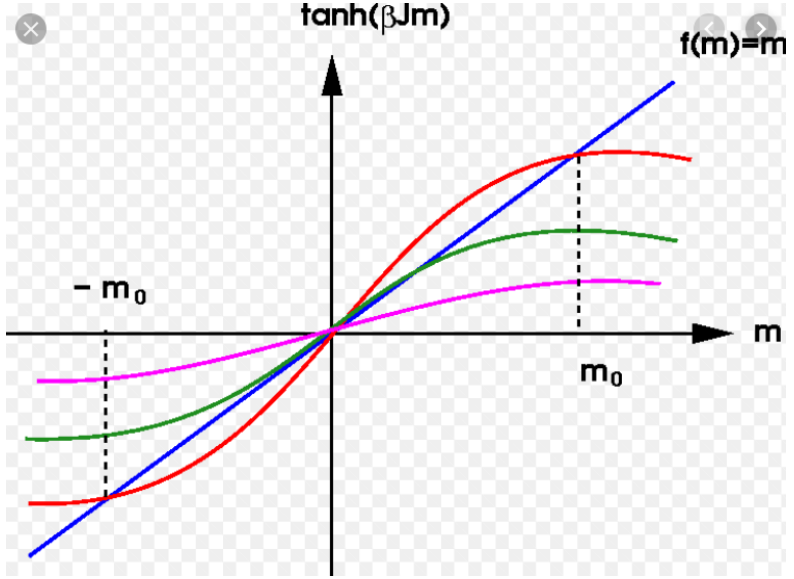
$$\mathcal{H} = -\sum_{i<i<k<\ell} \Delta_{ijk}\Delta_{ij\ell} \qquad = -\sum_{i<i<k<\ell} \Delta_{ijk}\Delta_{ij\ell}$$





Schematic mean field theory





$$H = -\mathrm{h}\sum_i^N S_i \; - \mathrm{J}\sum_{ij}^N S_i S_j$$

Mean field

$$H_i = -(\mathrm{h} + \mathrm{J} < S >)\, S_i$$

$$h_{new} = (\mathrm{h} - \mathrm{J} < S >)$$

$$H = \sum_i^N H_i$$

$$H = -\mathrm{h}\sum_i^N S_i \; - \mathrm{J}\sum_{ij}^N S_i S_j$$

$$Z = \sum e^{-\beta H}$$

$$\mathrm{m} = <S> = (1/\mathrm{N})\sum_i^N S_i$$

$$m = \tan(\beta J m)$$

Mean-field solution of structural balance dynamics in nonzero temperature

$$H = -\mathrm{J}\sum_{ij}^{N} S_{ij}S_{jk}S_{ki}$$

$$H_{ij} = -S_{ij}J\sum_{k}^{N} S_{jk}S_{ki}$$

$$P\{S_{ij}\rangle = P(S_{ij}=1)*(1) + P(S_{ij}=-1)*(-1)$$

$$= \left\langle \frac{e^{-\beta H_{ij}(S_{ij}=1)} - e^{-\beta H_{ij}(S_{ij}=-1)}}{e^{-\beta H_{ij}(S_{ij}=1)} + e^{-\beta H_{ij}(S_{ij}=-1)}} \right\rangle$$

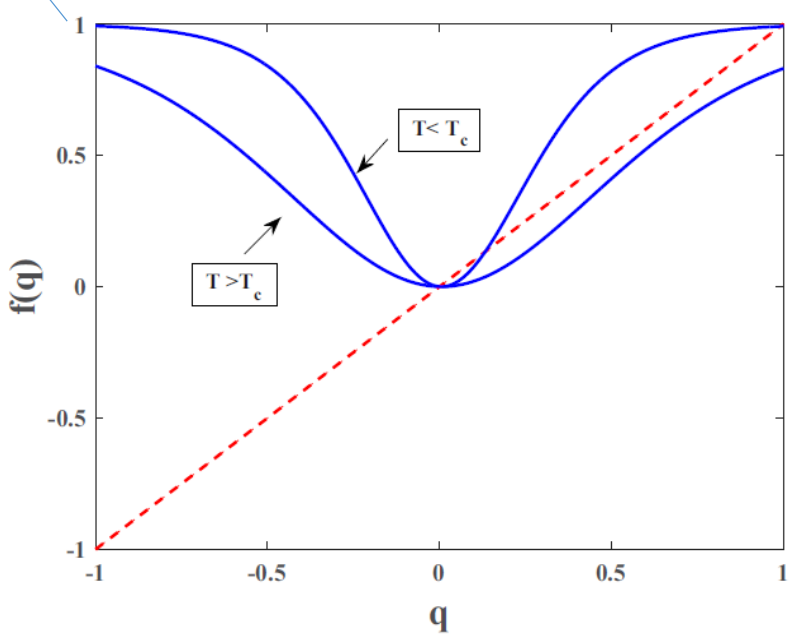
$$= \left\langle \frac{e^{\beta\sum_{k\neq i,j} S_{jk}S_{ki}} - e^{-\beta\sum_{k\neq i,j} S_{jk}S_{ki}}}{e^{\beta\sum_{k\neq i,j} S_{jk}S_{ki}} + e^{-\beta\sum_{k\neq i,j} S_{jk}S_{ki}}} \right\rangle$$

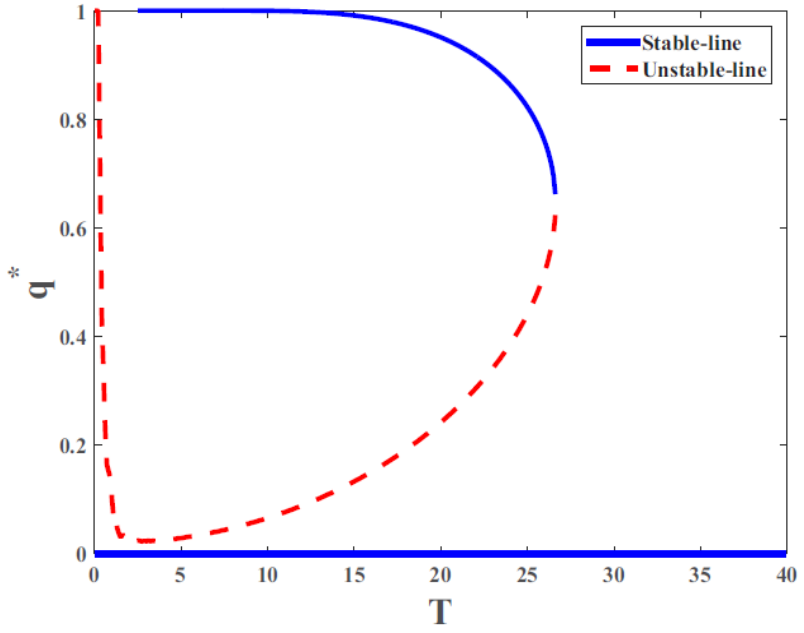
$$= \left\langle \tanh\left(\beta\sum_{k\neq i,j} S_{jk}S_{ki}\right)\right\rangle.$$

$$p = \tanh(\beta(N-2)q), \quad q = \left[\frac{e^{-\beta(N-3)(-2q)} - 2e^{-\beta(2p)} + e^{-\beta(N-3)(2q)}}{e^{-\beta(N-3)(-2q)} + 2e^{-\beta(2p)} + e^{-\beta(N-3)(2q)}}\right].$$

To solve these two equations with two unknowns, we use a self-consistency condition on q by substituting p into q:

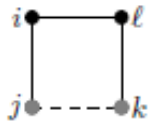
$$q \equiv \langle S_{ik}S_{kj}\rangle = \left[\frac{e^{-\beta(N-3)(-2q)} - 2e^{-2\beta\tanh(\beta(N-2)q)} + e^{-\beta(N-3)(2q)}}{e^{-\beta(N-3)(-2q)} + 2e^{-2\beta\tanh(\beta(N-2)q)} + e^{-\beta(N-3)(2q)}}\right] = f(q).$$

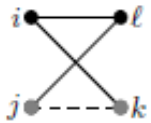




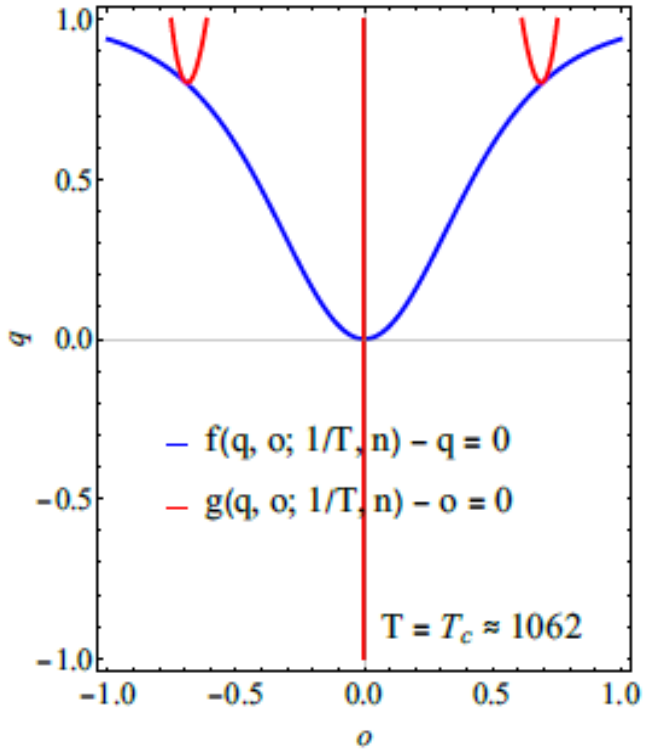
$$H = -\sum_{j<k<l} S_{jk}S_{kj}S_{jl}S_{lj}$$

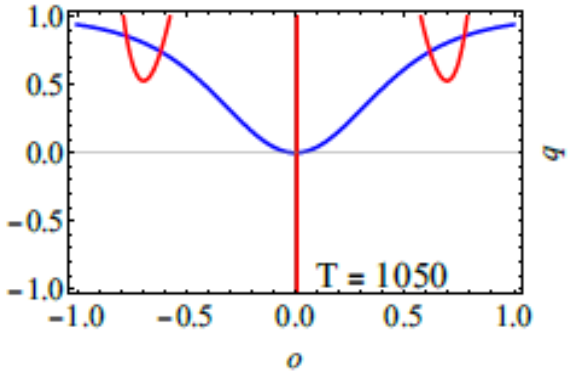
$$q \equiv \langle S_{ik}S_{kj} \rangle$$

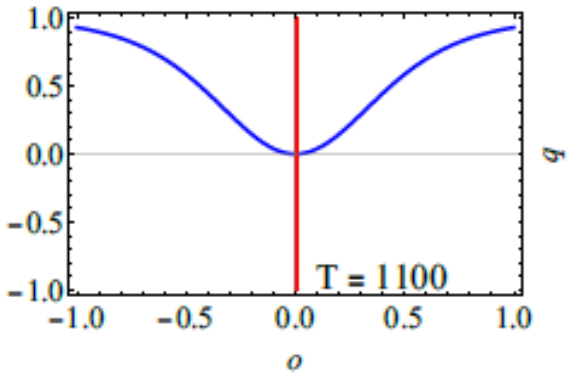


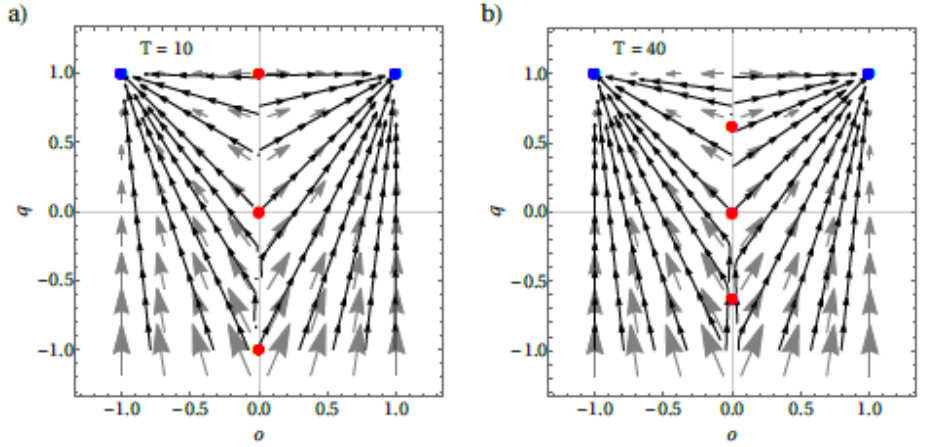


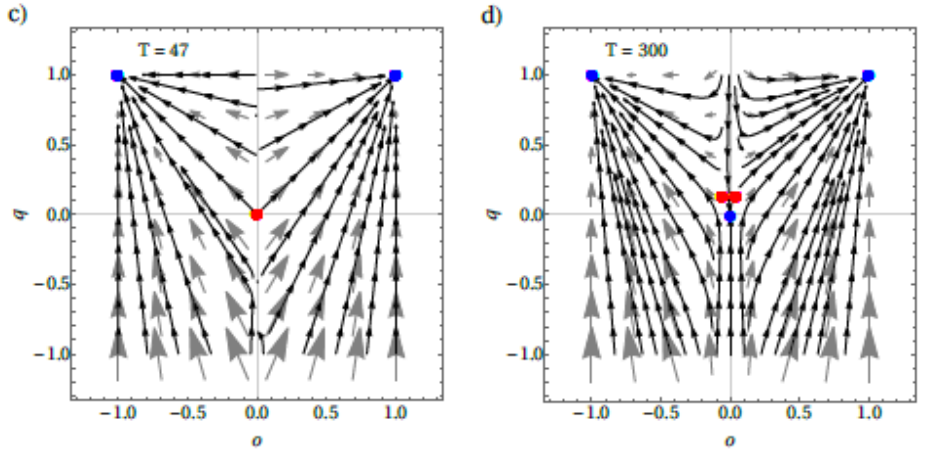
$$O = < S_{ij}S_{jk}S_{kl} >$$

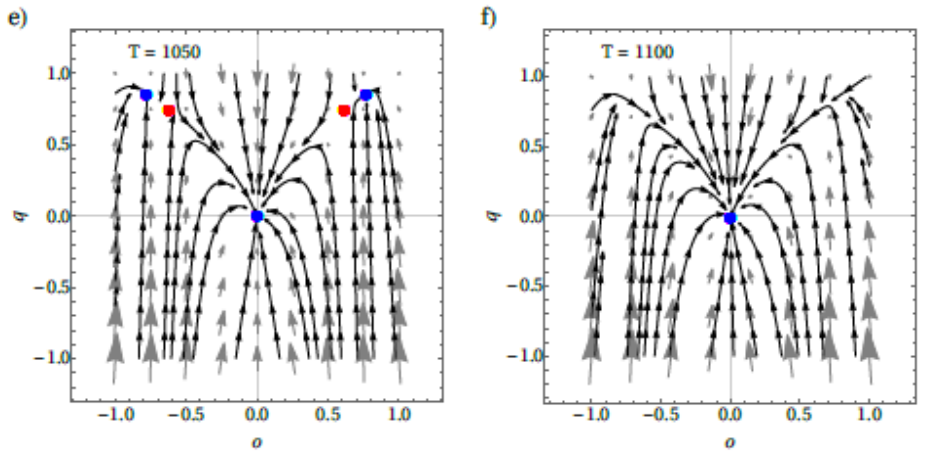




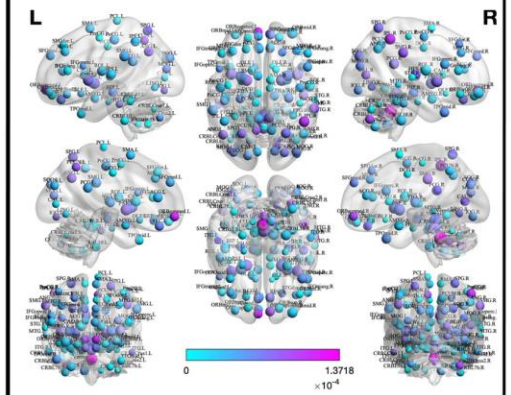
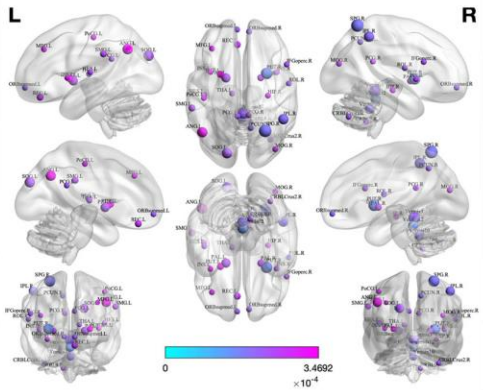
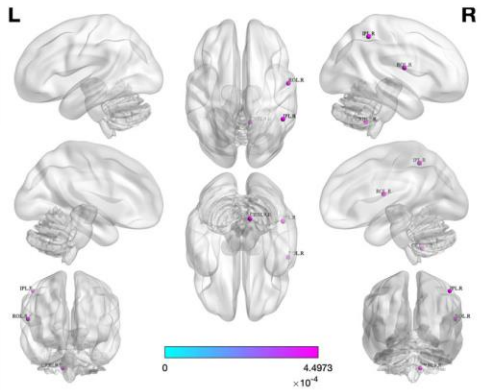
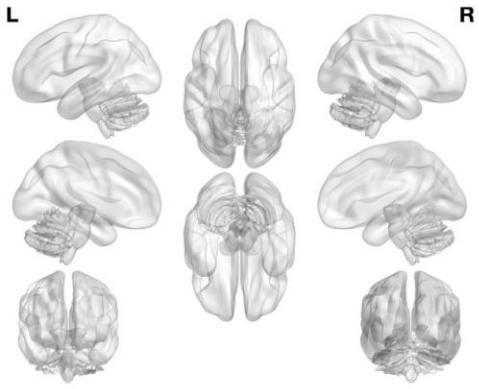
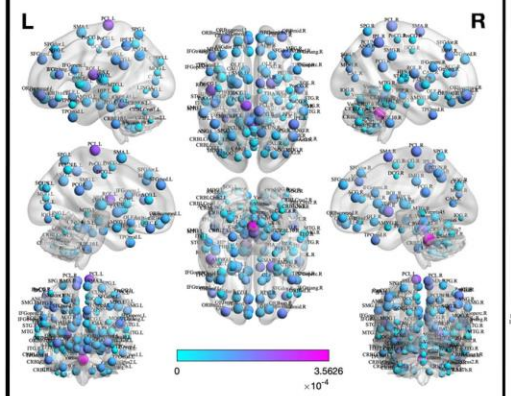
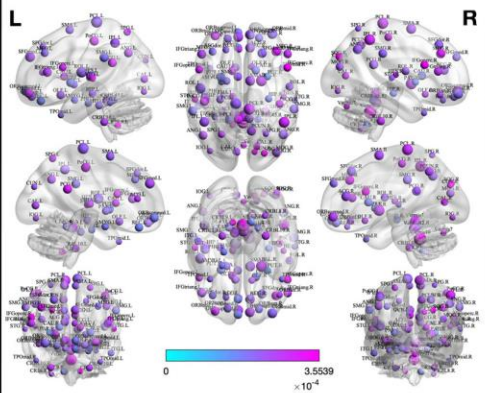
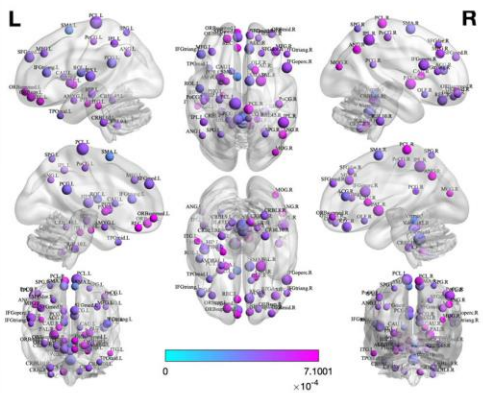
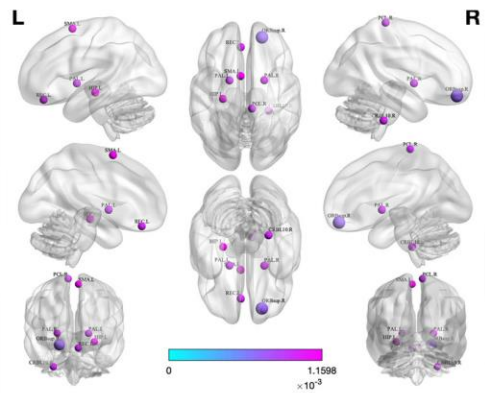








Session One

	$2 \times 10^{-4} < U$	$2 \times 10^{-4} \leq U < 4 \times 10^{-4}$	$4 \times 10^{-4} \leq U < 9.2 \times 10^{-4}$	$U > 9.2 \times 10^{-4}$
Autism				
Control				

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Thanks






Center for Complex Networks & Social Datascience (ccnsd.ir)