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THE ELISHA YEGAL BAR-NESS CENTER FOR WIRELESS COMMUNICATIONS AND SIGNAL PROCESSING RESEARCH

5G is Man-Made Cells, 1G in Human Cells!

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CWCSPR Research Day

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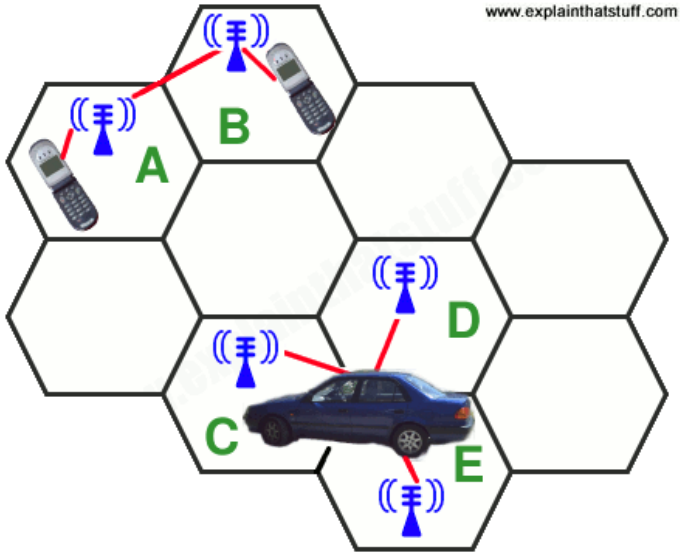
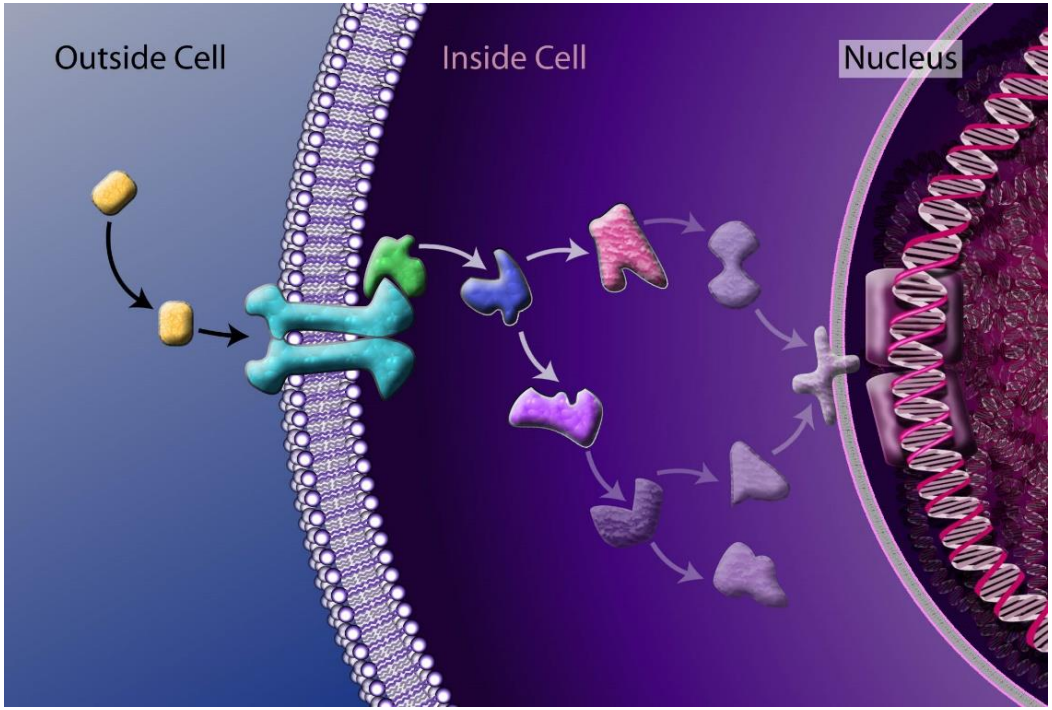
Man-Made Cells



A Human Cell



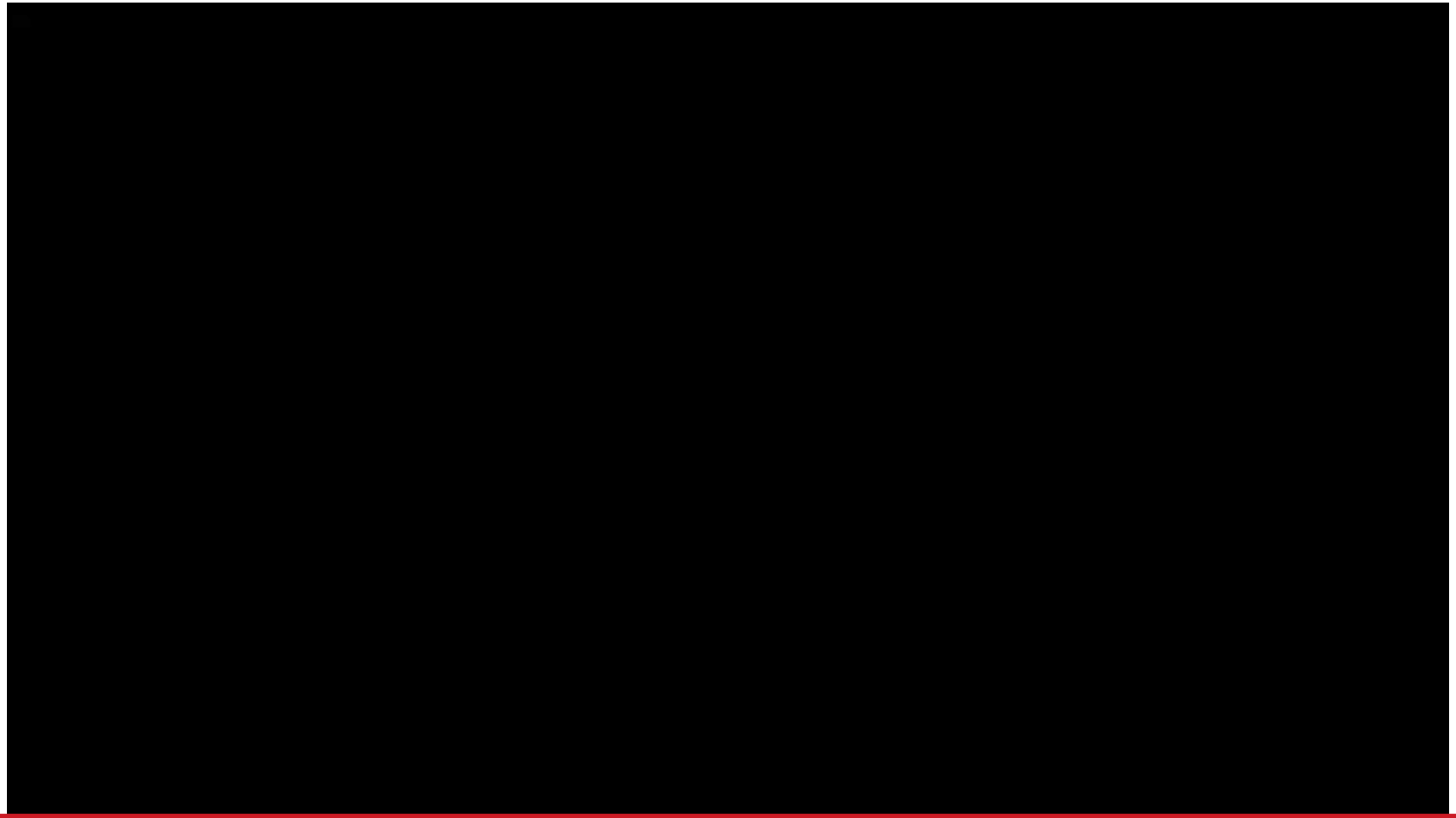
- Trillions of cells in a human body
- Billions of molecules in a cell
- Biochemical molecular networks perform a variety of tasks (cell death, cell division, cell growth, etc.)

http://phys.org/news/2013-05-rapid-threat-mitigate-danger-chemical.html

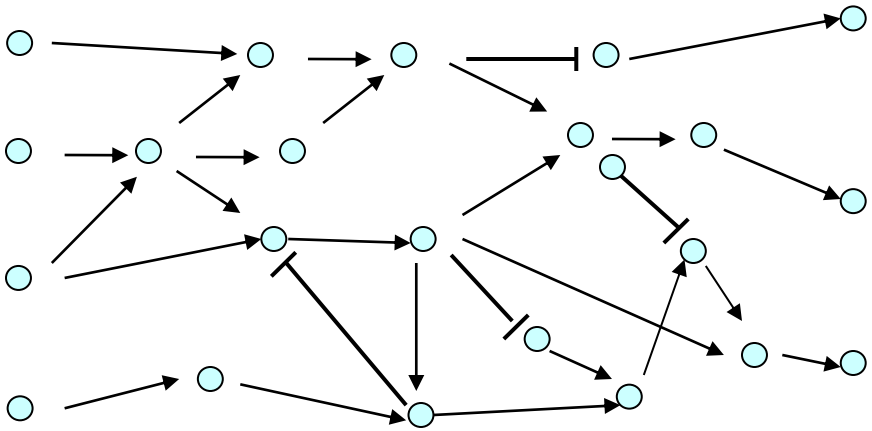
Molecular Systems Biology: A New Paradigm

- Living organisms are composed of cells.
- Molecular networks within cells regulate cellular functions.
- Molecular Systems Biology: Analysis of the orchestrated function of systems and networks of molecules in a cell.
- Dysfunction of some molecules may contribute to the development of some diseases (cancer, mental disorders such as schizophrenia, metabolic diseases such as diabetes, …).
- In many complex diseases we do not know the dysfunction of which molecules may have causative effects.
- ***Our Goal: Find critical molecules whose dysfunction seriously affects the whole function of a molecular network.***

An Example of How a Small Molecular Network Works



Molecular Network Graphical Representation



- Nodes
  - Protein or non-protein biomolecules.
- Edges
  - Biochemical interactions, such as activation and inhibition.

Construction of a Molecular Network Model

1. Specify input and output nodes as well as the intermediate molecules in the network

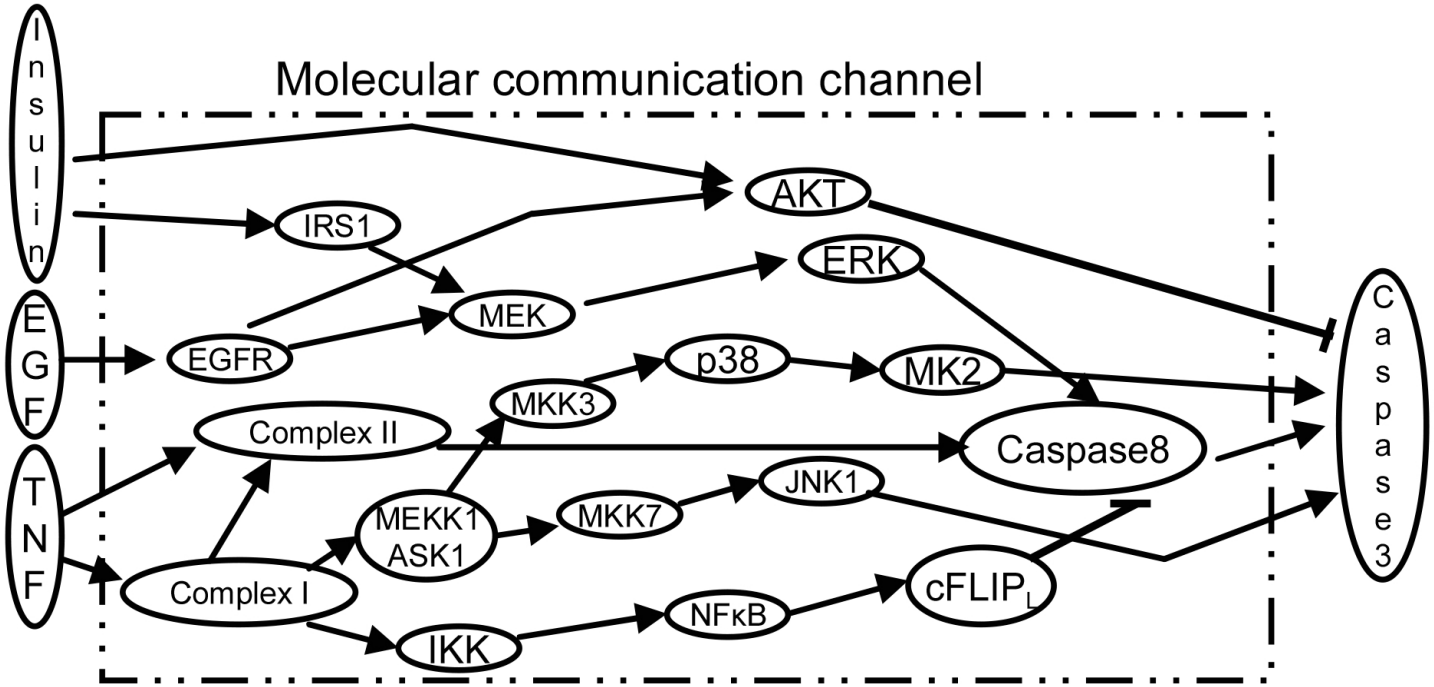
2. Specify types of the interactions among the molecules in the network

3. Simulate the network by computing outputs in response to inputs

4. Compare the model response with experimental data

The Caspase3 Network

- **Input molecules: insulin, EGF, TNF**
- **Output: Caspase3**



Binary Equations for the Caspase3 Network

	Molecules	Equations
Internal molecules of the channel (listed alphabetically)	AKT	AKT=EGFR+insulin
	caspase8	caspase8=$cFLIP_L$'×(ComplexII+ERK)
	$cFLIP_L$	$cFLIP_L$=NFκB
	ComplexI	ComplexI=TNF
	ComplexII	ComplexII=TNF+ComplexI
	EGFR	EGFR=EGF
	ERK	ERK=MEK
	IKK	IKK=ComplexI
	IRS1	IRS1=Insulin
	JNK1	JNK1=MKK7
	MEK	MEK=EGFR+IRS1
	MEKK1ASK1	MEKK1ASK1=ComplexI
	MK2	MK2=p38
	MKK3	MKK3=MEKK1ASK1
	MKK7	MKK7=MEKK1ASK1
	NFκB	NFκB=IKK
	p38	p38=MKK3
Channel output	caspase3	caspase3=AKT'×(caspase8+JNK1+MK2)

(Operations ', + and ×, represent NOT, OR and AND, respectively)

Input–Output Relationships for the Caspase3 Network

EGF	insulin	TNF	caspase3
0	0	0	0
0	0	1	1
0	1	0	0
0	1	1	0
1	0	0	0
1	0	1	0
1	1	0	0
1	1	1	0

The network transition probability matrix M

$$\mathbf{M} = \begin{bmatrix} P(0|000) & P(1|000) \\ P(0|001) & P(1|001) \\ P(0|010) & P(1|010) \\ P(0|011) & P(1|011) \\ P(0|100) & P(1|100) \\ P(0|101) & P(1|101) \\ P(0|110) & P(1|110) \\ P(0|111) & P(1|111) \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 1 & 0 \end{bmatrix} \cdot \begin{matrix} \text{EGF, insulin, TNF} \\ \begin{matrix} 0 & 0 & 0 \\ 0 & 0 & 1 \\ 0 & 1 & 0 \\ 0 & 1 & 1 \\ 1 & 0 & 0 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \\ 1 & 1 & 1 \end{matrix} \end{matrix}$$

$$\text{caspase3} = \begin{matrix} 0 & 1 \end{matrix}$$

A Simple Model for Signaling Failures and Network Dysfunction

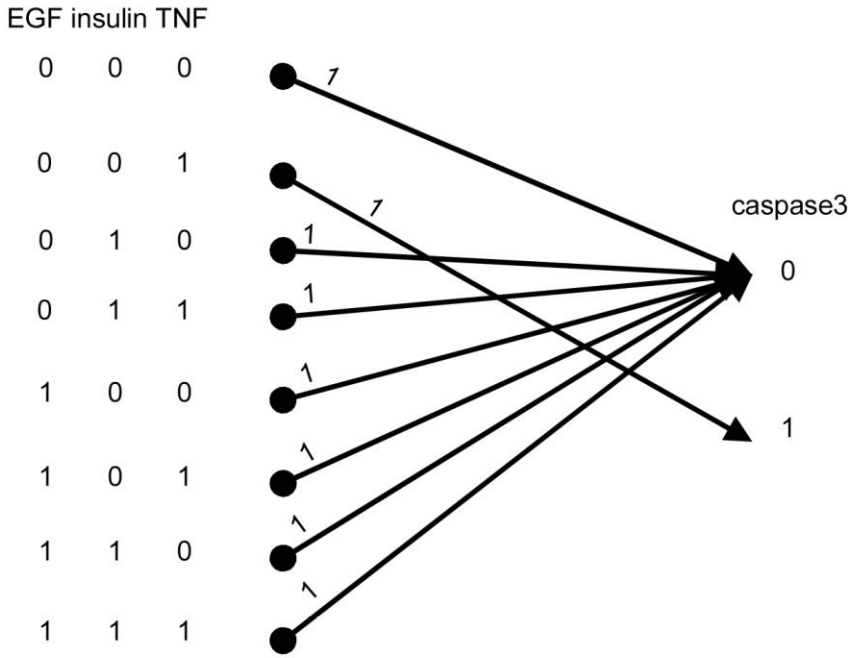
- Probability of each molecule being dysfunctional β
- A dominant molecule is k times more probable to be dysfunctional
- A faulty molecule is either stuck-at-0 or stuck-at-1

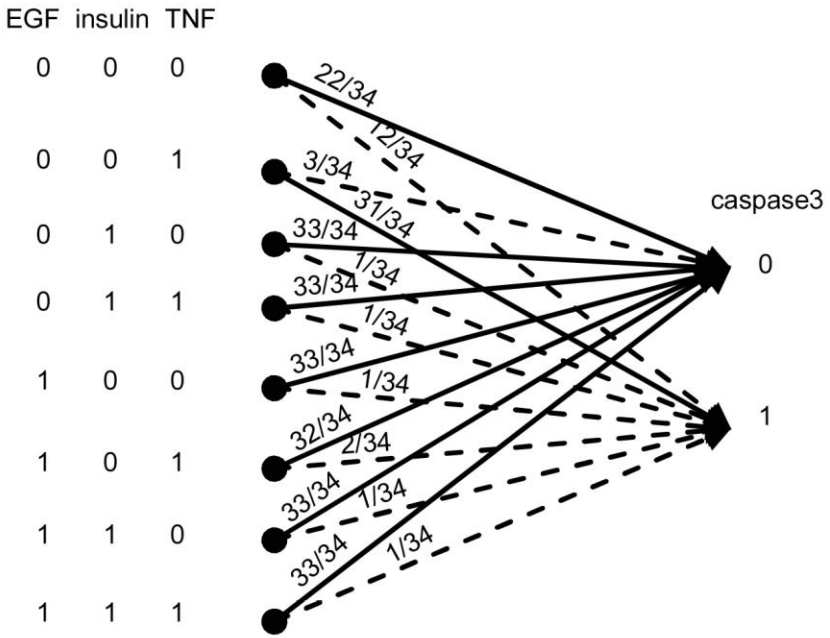
Habibi, I., Emamian, E. S., & Abdi, A. (2014). **Quantitative analysis of intracellular communication and signaling errors in signaling networks.** BMC systems biology, 8(1), 89.

Transition Probability Diagrams for Normal & Abnormal Caspase3 Networks

Normal network

All the molecules in the network are equally likely to be dysfunctional (k=1)





Transition Probability Matrices for the Abnormal Caspase3 Network

caspase8 or ComplexI or ComplexII or ERK or IRS1 or JNK1or MEK or MK2 or MKK3 or MKK7 or p38 is dominant:

$$\mathbf{M}_{abnormal\ channel} = \frac{1}{2k+32}\begin{bmatrix} k+21 & k+11 \\ 3 & 2k+29 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ 2k+30 & 2 \\ 2k+31 & 1 \\ 2k+31 & 1 \end{bmatrix}$$

$cFLIP_L$ or IKK or NFκB is dominant :

$$\mathbf{M}_{abnormal\ channel} = \frac{1}{2k+32}\begin{bmatrix} 2k+20 & 12 \\ 3 & 2k+29 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ 2k+30 & 2 \\ 2k+31 & 1 \\ 2k+31 & 1 \end{bmatrix}$$

Transition Probability Matrices for Abnormal Caspase3 Network

AKT is dominant :

$$\mathbf{M}_{abnormal\ channel} = \frac{1}{2k+32}\begin{bmatrix} 2k+20 & 12 \\ k+2 & k+30 \\ k+32 & k \\ k+32 & k \\ k+32 & k \\ k+31 & k+1 \\ k+32 & k \\ k+32 & k \end{bmatrix}$$

EGFR is dominant :

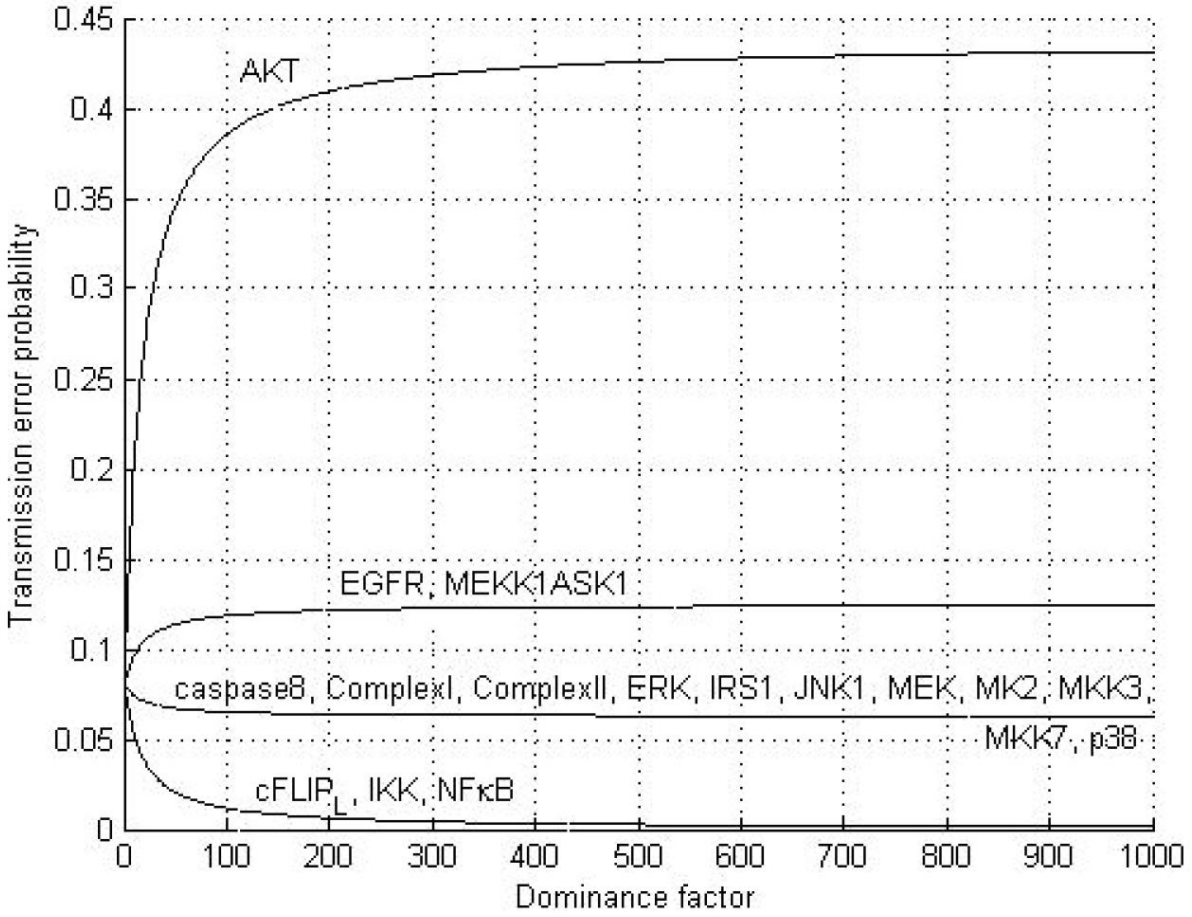
$$\mathbf{M}_{abnormal\ channel} = \frac{1}{2k+32}\begin{bmatrix} 2k+20 & 12 \\ k+2 & k+30 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ k+31 & k+1 \\ 2k+31 & 1 \\ 2k+31 & 1 \end{bmatrix}$$

MEKK1ASK1 is dominant :

$$\mathbf{M}_{abnormal\ channel} = \frac{1}{2k+32}\begin{bmatrix} k+21 & k+11 \\ k+2 & k+30 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ 2k+31 & 1 \\ 2k+30 & 2 \\ 2k+31 & 1 \\ 2k+31 & 1 \end{bmatrix}$$

Transmission Error Probability of the Caspase3 Network

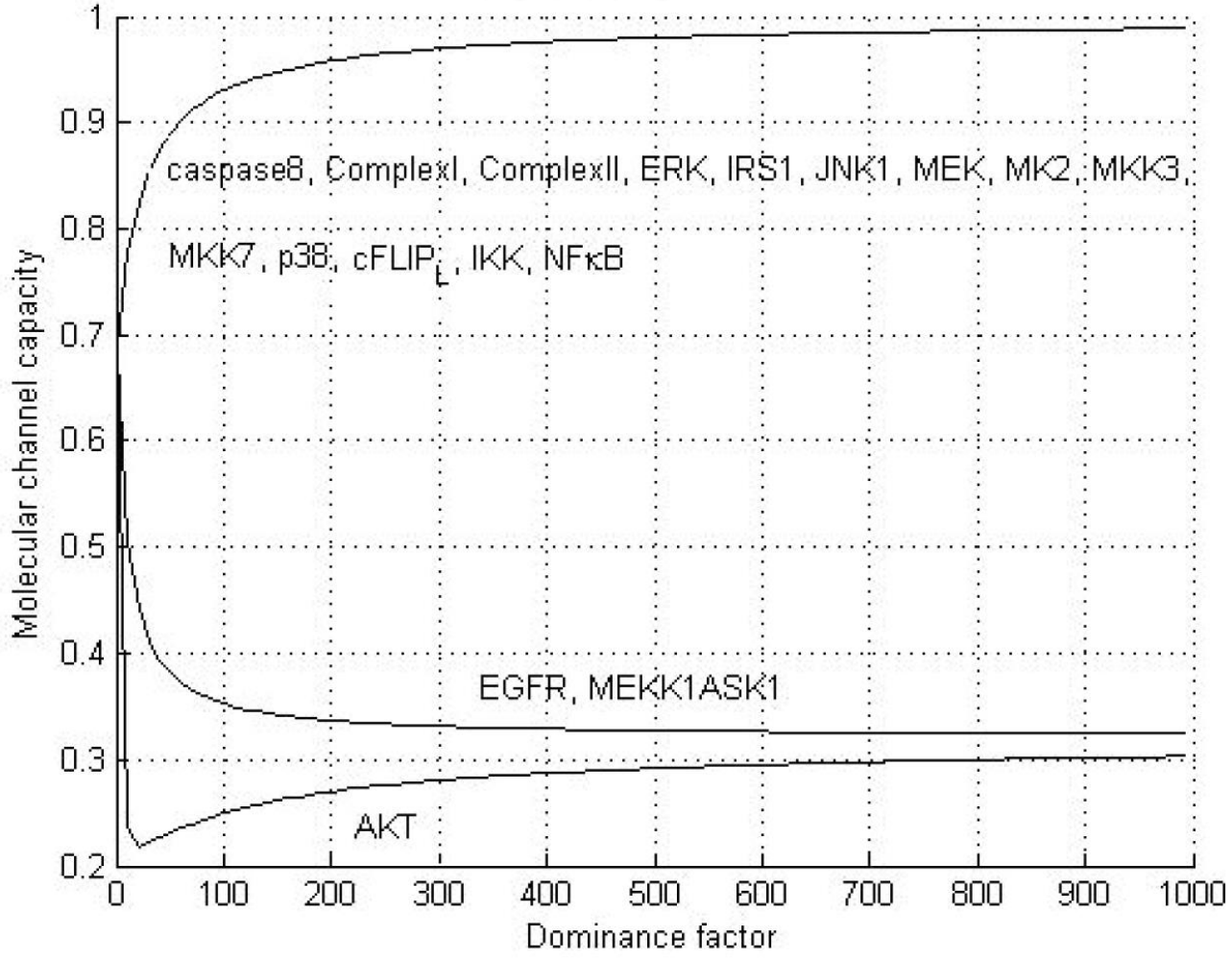
Error probability is the probability of having network responses different from expected (normal) responses.



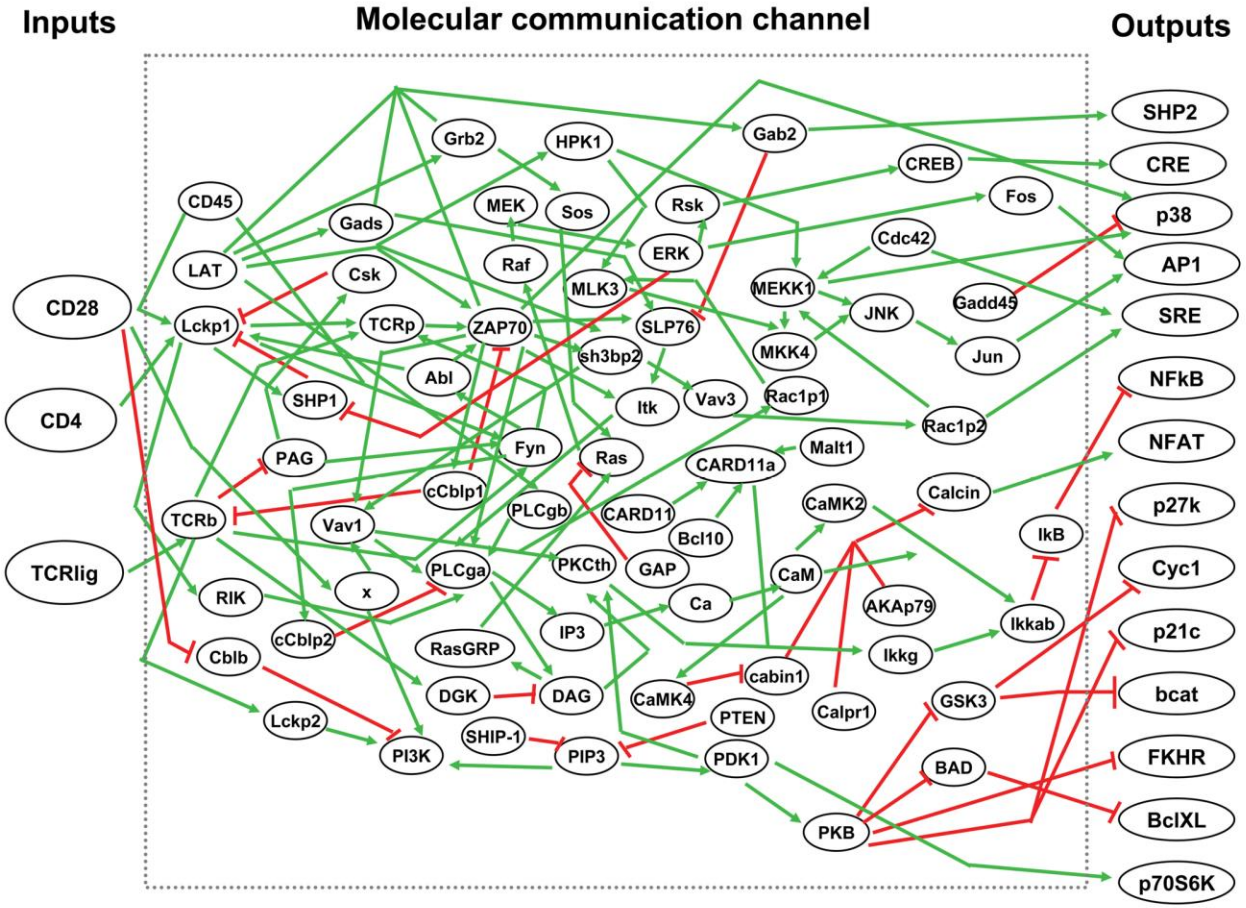
Biological Observations

- The caspase3 network shows different fault behaviors depending on the faulty molecule.
- When AKT is faulty, transmission error probabilities are high (critical role of AKT).
- Some molecules such as EGFR or MEKK1ASK1 cause small transmission error probabilities.
- Many molecules do not cause any transmission error!

Signaling Capacity of the Caspase3 Network



The T Cell Network



Habibi, I., Emamian, E. S., & Abdi, A. (2014). **Quantitative analysis of intracellular communication and signaling errors in signaling networks.** BMC systems biology, 8(1), 89.

Saez-Rodriguez et al. (2007). **A logical model provides insights into T cell receptor signaling.** PLoS Comput Biol 3:1580–27 1590.

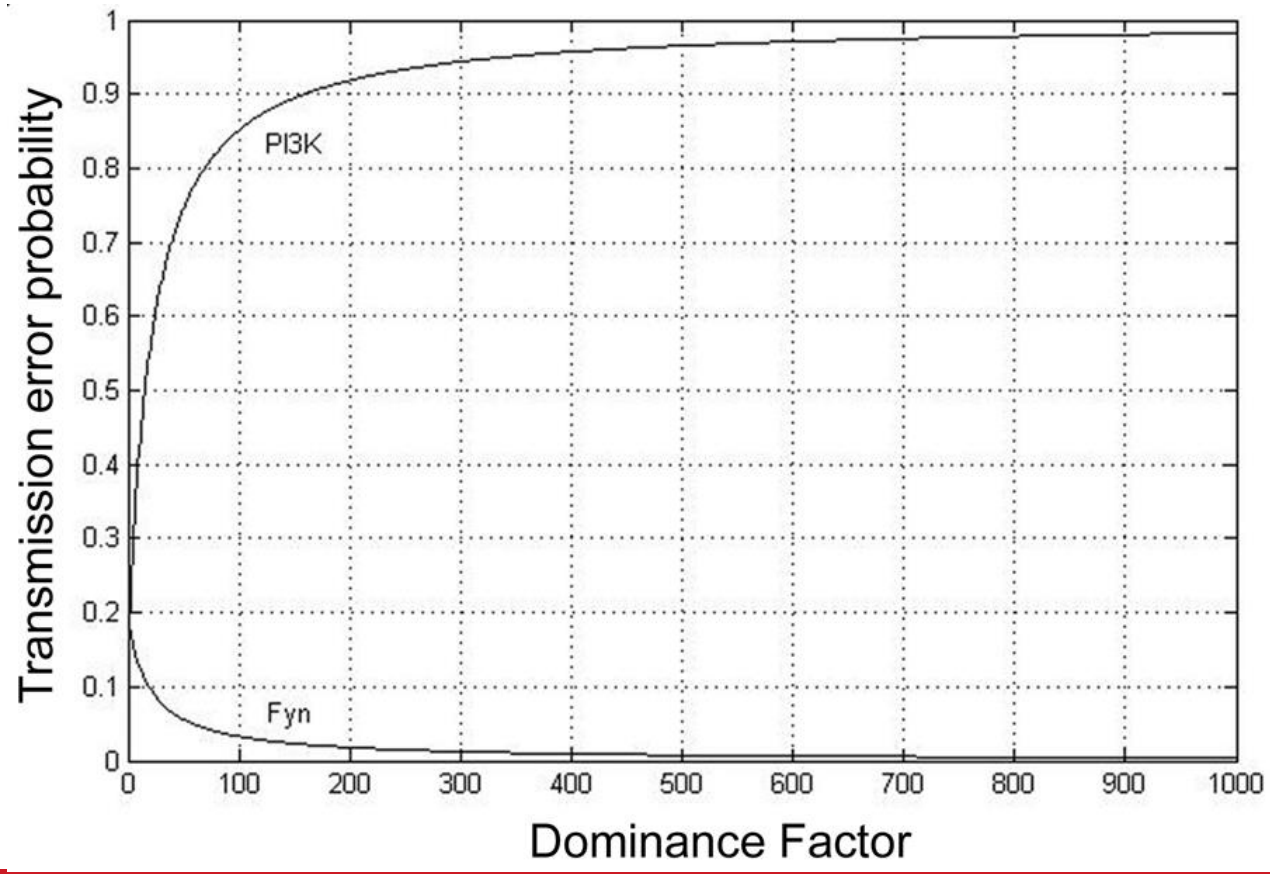
Analysis of the T Cell Network

The output node is SHP2:

Node	P_e	Capacity
Gab2	0.5	0
TCRb	0.5	0
ZAP70	0.5	0
Abl	0.25	0.3219
cCblp1	0.25	0.3219
LAT	0.25	0.3219
TCRp	0.25	0.3219
Fyn	0.125	1

Transmission Error Probability for T Cell Network

The output node is PKB:



Summery and Conclusions

- Several network models developed to analyze signaling errors and possible dysfunction of molecular networks.
- Signaling errors and capacities where calculated for multiple biologically-verified networks.
- Networks show different fault behaviors depending on the faulty molecules.
- Only few molecules generate large signaling errors.
- Such molecules are suitable targets for therapeutic drug development.

Questions?

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THE EDGE IN KNOWLEDGE