Living Software

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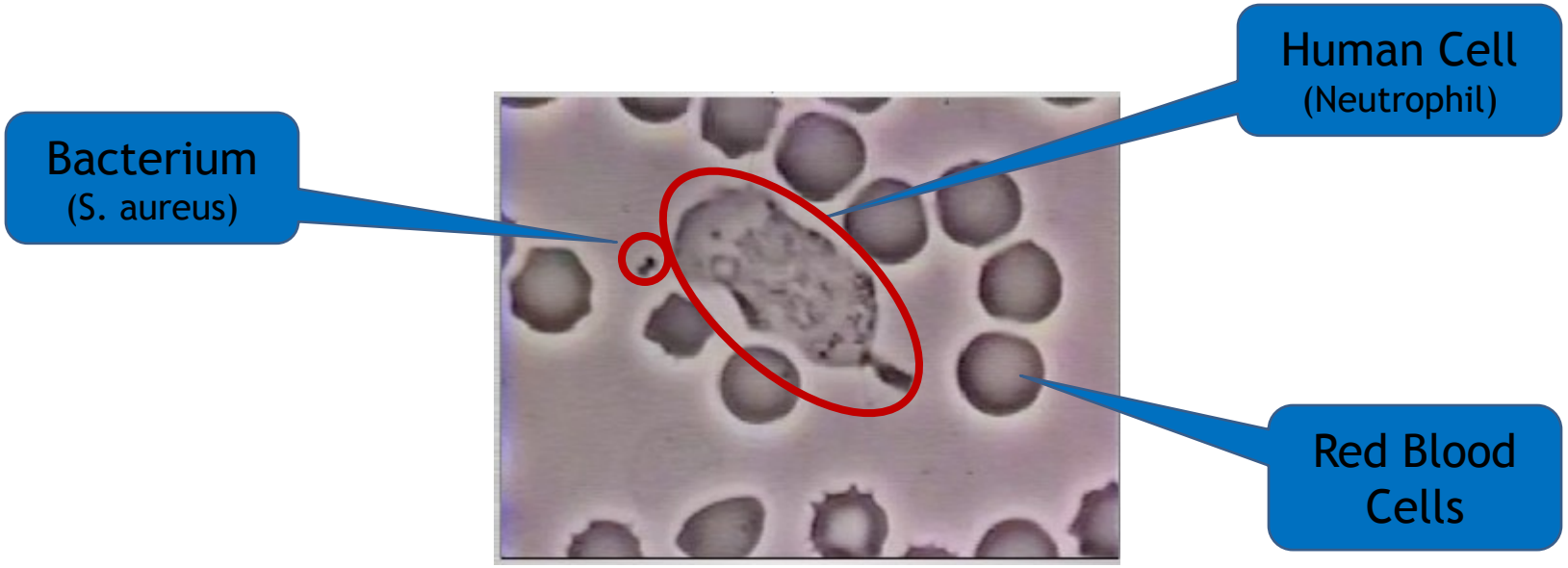
Crawling Neutrophil Chasing a Bacterium

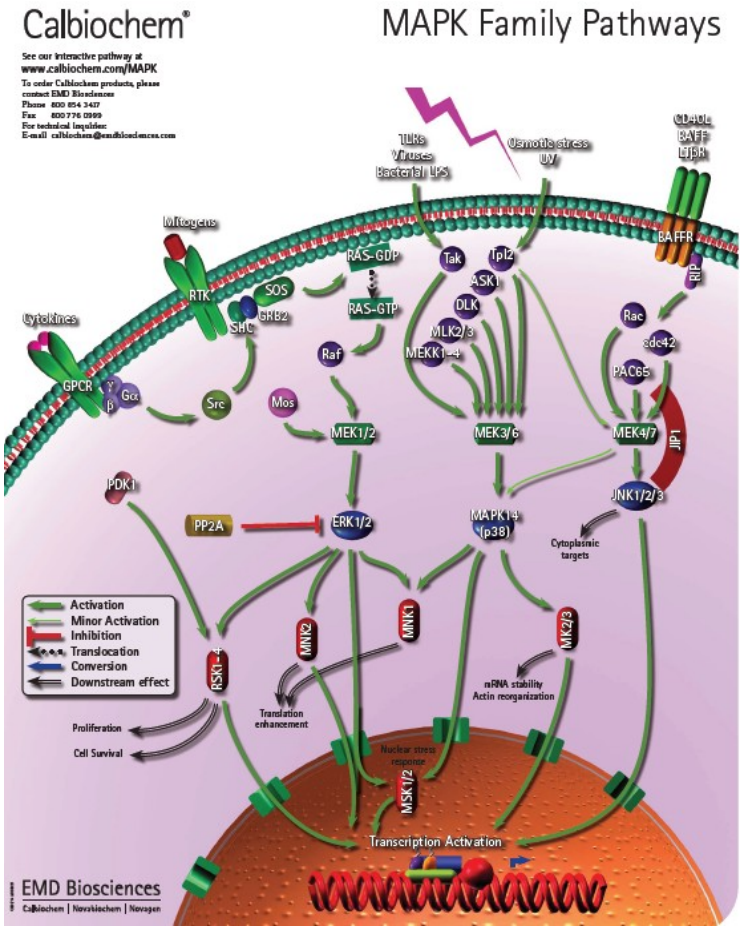


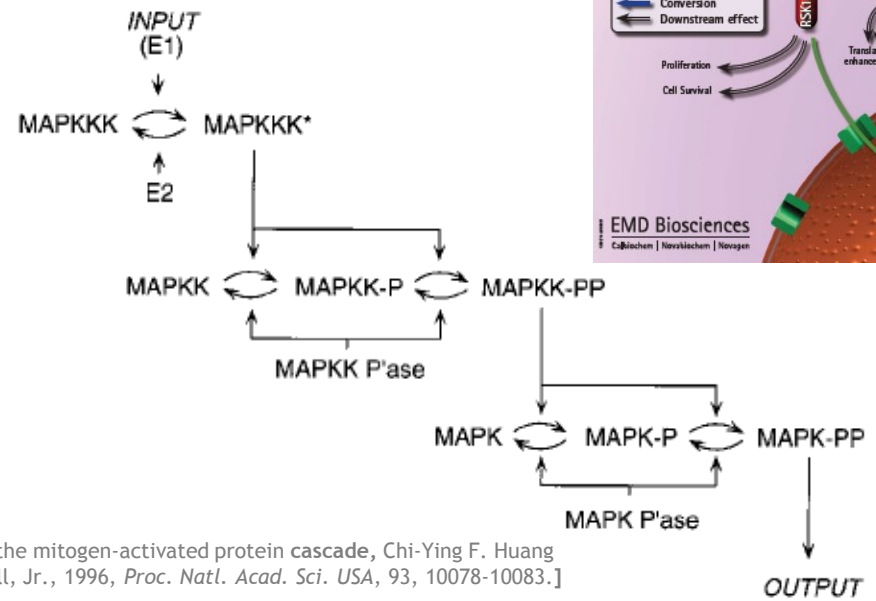
[www.biochemweb.org/fenteany/research/cell_migration/neutrophil.html]

How does it do it?

Cells Compute

- No survival without computation!
  - Finding food
  - Avoiding predators
- How do they compute?
  - Proteins: what kind of circuits?
  - Genes: what kind of software?

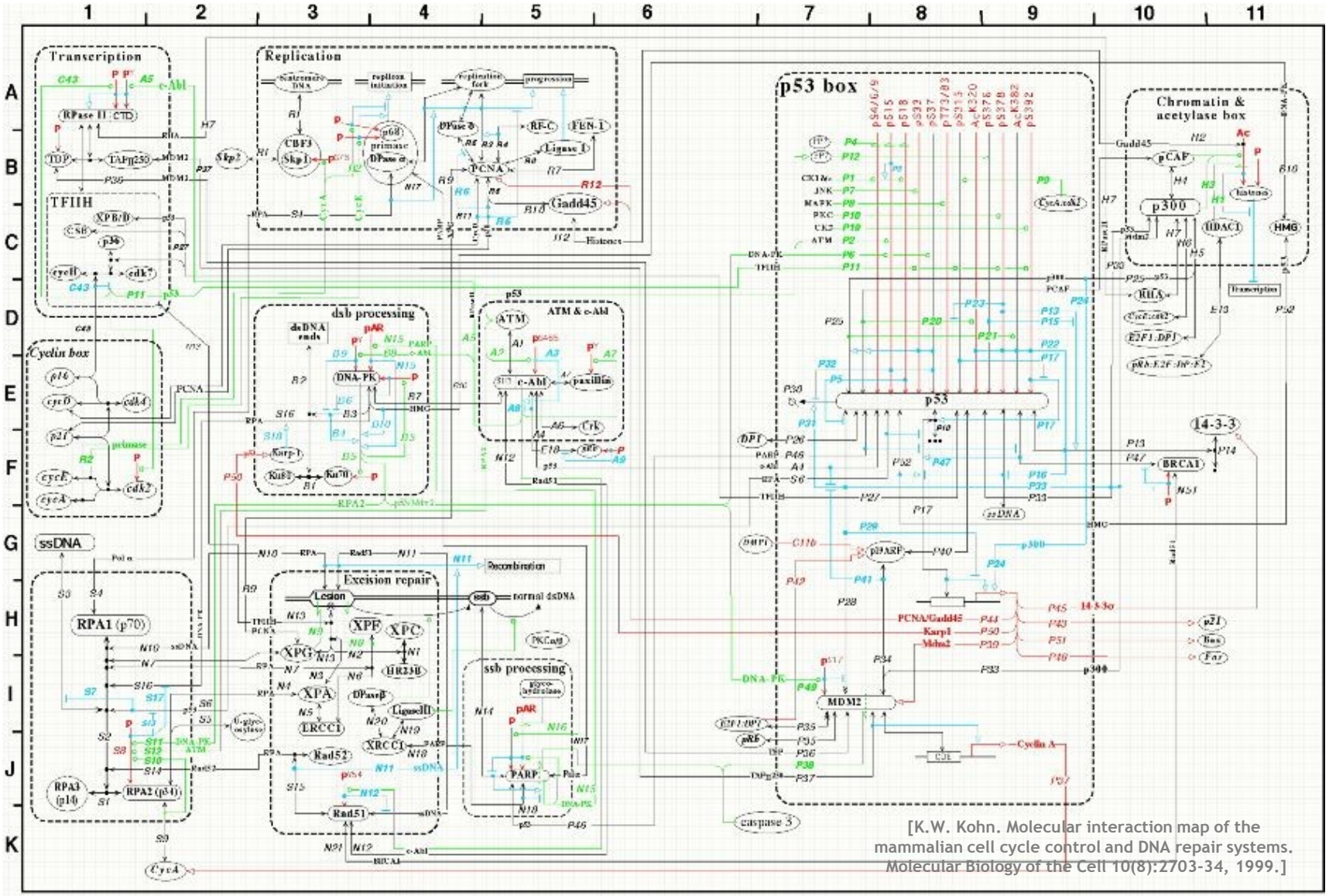




[Ultrasensitivity in the mitogen-activated protein **cascade**, Chi-Ying F. Huang and James E. Ferrell, Jr., 1996, *Proc. Natl. Acad. Sci. USA*, 93, 10078-10083.]

Protein Networks = Circuits?

The p53-Mdm2 and DNA Repair Regulatory Network



[K.W. Kohn. Molecular interaction map of the mammalian cell cycle control and DNA repair systems. Molecular Biology of the Cell 10(8):2703-34, 1999.]

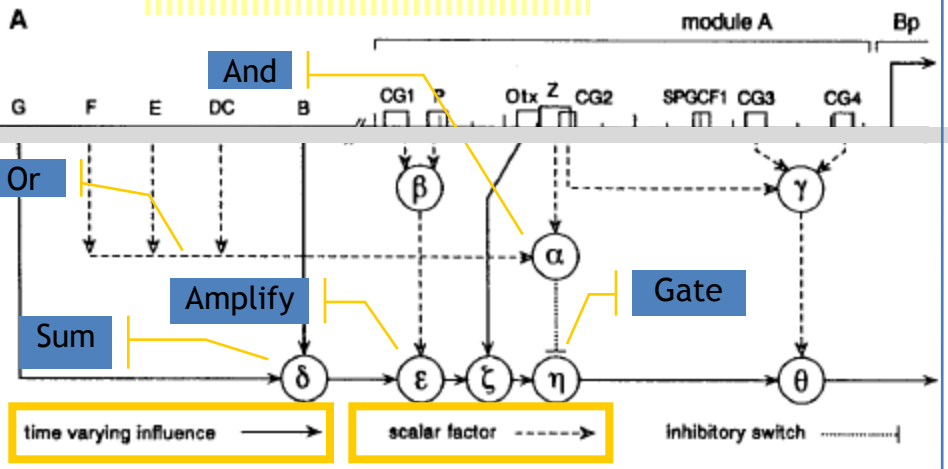
Figure 6B: The p53-Mdm2 and DNA repair regulatory network (version 2p - May 19, 1999)

Gene Networks = Software?

regulatory region

protein coding region

DNA



Control diagram
of a sea urchin gene

as a *program*

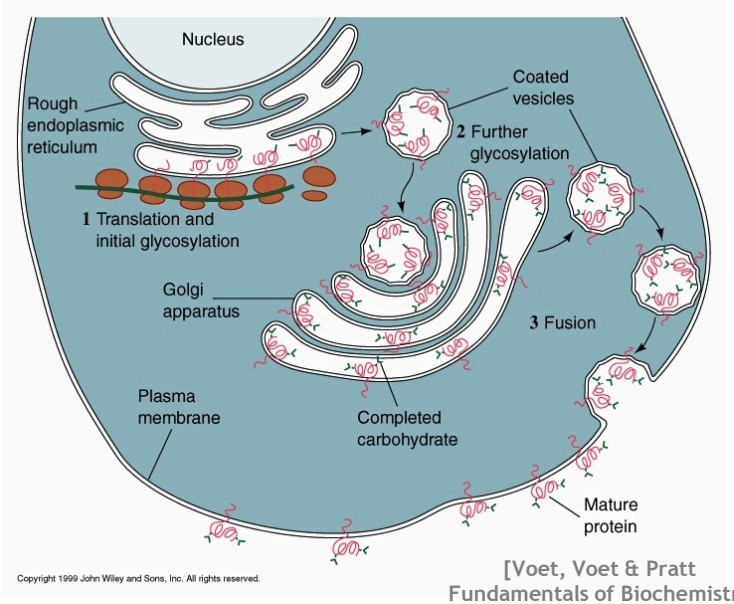
B

if (F = 1 or E = 1 or CD = 1) and (Z = 1)	Repression functions of modules F, E, and DC mediated by Z site
α = 1	
else α = 0	
if (P = 1 and CG_1 = 1)	
β = 2	
else β = 0	
if (CG_2 = 1 and CG_3 = 1 and CG_4 = 1)	Final step up of system output
γ = 2	
else γ = 1	
δ(t) = B(t) + G(t)	Positive input from modules B and G
ε(t) = β*δ(t)	Synergistic amplification of module B output by CG_1-P subsystem
if (ε(t) = 0)	Switch determining whether Otx site in module A, or upstream modules (i.e., mainly module B), will control level of activity
ξ(t) = Otx(t)	
else ξ(t) = ε(t)	
if (α = 1)	Repression function inoperative in endoderm but blocks activity elsewhere
η(t) = 0	
else η(t) = ξ(t)	
Θ(t) = γ*η(t)	Final output communicated to BTA

[C-H.Yuh, H.Bolouri, E.H.Davidson. Genomic Cis-Regulatory Logic: Experimental and Computational Analysis of a Sea Urchin Gene. Science 279:1896-1902, 1998]

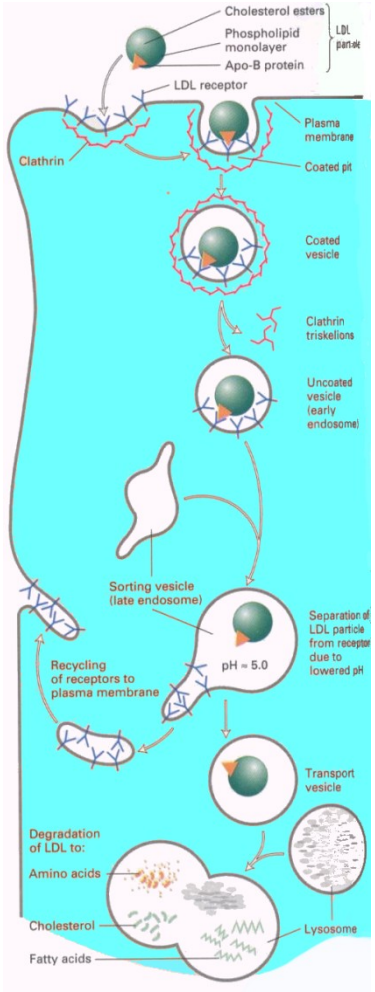
Biological Algorithms

Protein Production and Secretion



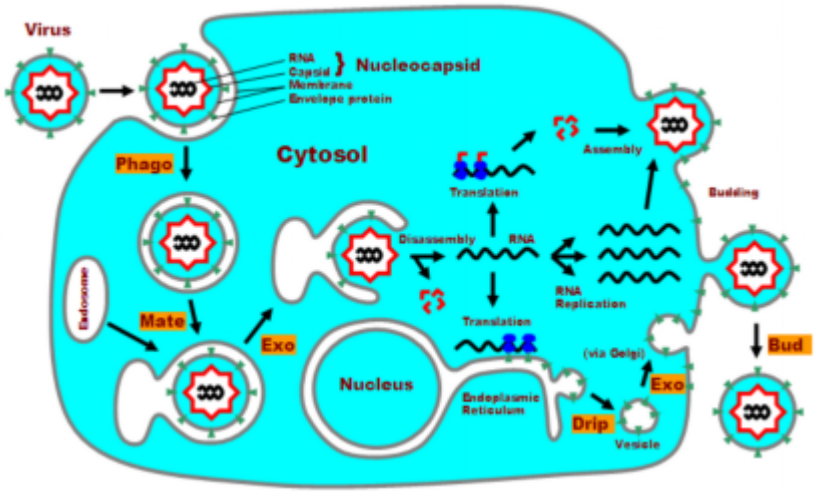
[Voet, Voet & Pratt Fundamentals of Biochemistry Wiley 1999. Ch10 Fig 10-22.]

LDL-Cholesterol Degradation



[H.Lodish et al. Molecular Cell Biology. 4th Ed. p.730.]

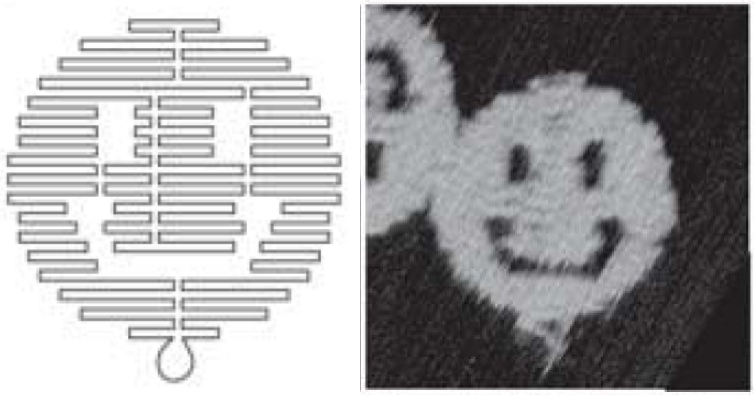
Viral Replication



[Adapted from: B.Alberts et al. Molecular Biology of the Cell 3rd Ed. p.279.]

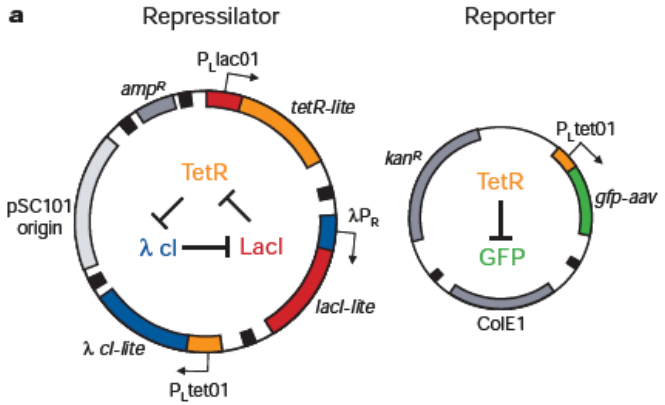
Understanding by Direct Engineering

- If we could manipulate molecules as well as nature, what would we do?
  - Nanomaterials Engineering



[Folding DNA to create nanoscale shapes and patterns, Paul W. K. Rothemund, Nature Vol 440|16 March 2006]

  - Genetic Engineering

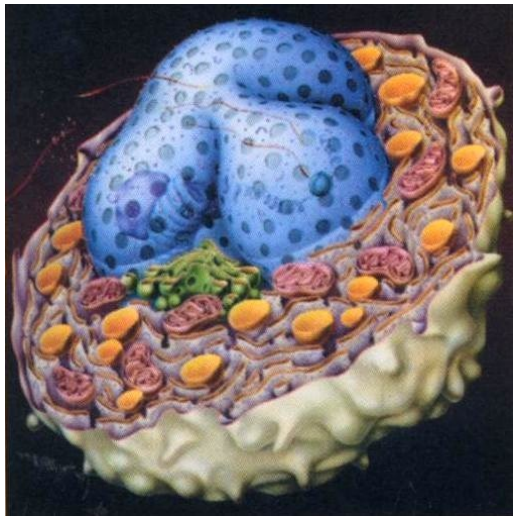


[A synthetic oscillatory network of transcriptional regulators, Michael B. Elowitz & Stanislas Leibler, NATURE |VOL 403 | 20 JANUARY 2000]

- How does nature do it?

Understanding by Reverse Engineering

Biological Organism



[H.Lodish et al. Molecular Cell Biology, 4th Ed. p.1]

Technological Organism

[www.tamagotchi.com]

Software:	~3MB (yeast) - ~650MB (human)	~1MB (?)
Hardware:	~10^{10} protein molecules (~5000 species)	~10^{5} transistors (?)
	~10^{12} other organic (~250 species)	

[www.foresight.org/Nanomedicine/Ch03_1.html]

Every known living autonomous entity has at least 150KB of software (M. genitalium); and usually a lot more.

Reverse Engineering an Organism

- Understanding the principles
  - What does a Tamagotchi compute?

Reverse Engineering an Organism

- ~~Understanding the principles~~
  - ~~What does a Tamagotchi compute?~~

- Understanding the mechanism
  - How are the parts connected to the cyberpet on the screen?

Reverse Engineering an Organism

- ~~Understanding the principles~~
  - ~~What does a Tamagotchi compute?~~
- ~~Understanding the mechanism~~
  - ~~How are the parts connected to the cyberpet on the screen?~~
- Understanding the behavior
  - How does it react to stimuli?

"How often do I have to exercise my Tamagotchi?"

"Every Tamagotchi is different. However we do recommend exercising at least three times a day."

Reverse Engineering an Organism

- ~~Understanding the principles~~
  - ~~What does a Tamagotchi compute?~~
- ~~Understanding the mechanism~~
  - ~~How are the parts connected to the cyberpet on the screen?~~
- ~~Understanding the behavior~~
  - ~~How does it react to stimuli?~~
- Understanding the interactions with the environment
  - How did it evolve from the Japanese culture and economy?

Reverse Engineering an Organism

- ~~Understanding the principles~~
  - ~~What does a Tamagotchi compute?~~
- ~~Understanding the mechanism~~
  - ~~How are the parts connected to the cyberpet on the screen?~~
- ~~Understanding the behavior~~
  - ~~How does it react to stimuli?~~
- ~~Understanding the interactions with the environment~~
  - ~~How did it arise from the Japanese culture and economy?~~
- Understanding the math
  - What differential equations does it obey?

$$\frac{d\,\text{Tamagotchi}}{dt} = ???$$

Reverse Engineering an Organism

- ~~Understanding the principles~~
  - ~~What does a Tamagotchi compute?~~
- ~~Understanding the mechanism~~
  - ~~How are the parts connected to the cyberpet on the screen?~~
- ~~Understanding the behavior~~
  - ~~How does it react to stimuli?~~
- ~~Understanding the interactions with the environment~~
  - ~~How did it arise from the Japanese culture and economy?~~
- ~~Understanding the math~~
  - ~~What differential equations does it obey?~~
- Now what?

Reverse *Software* Engineering

- Understanding the hardware is not enough
  - *Everything* interesting a Tamagotchi does is defined by its software
  - The hardware is completely generic: e.g. ~same as in a digital watch

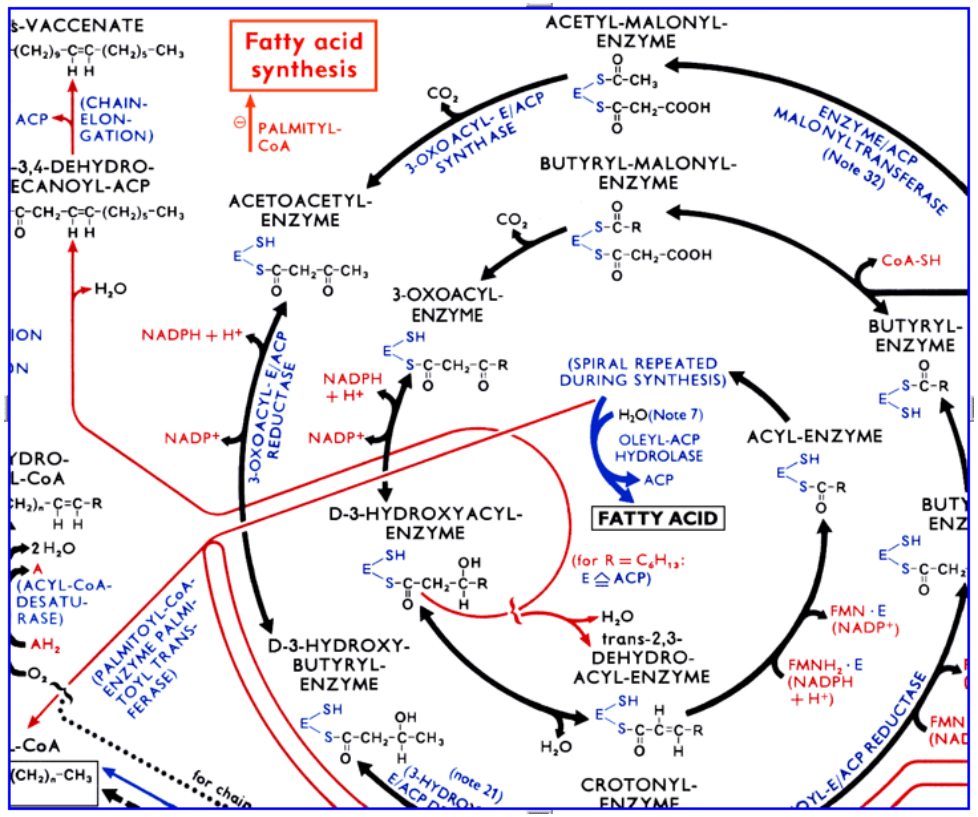
- Understanding the software, and how it controls the hardware
  - Dumping the raw code *(genomics)*
  - Taking stack traces *(transcriptomics)*
  - Taking core dumps *(proteomics)*
  - Monitoring the heap size and power supply *(metabolomics)*
  - Sniffing the network packets *(systems biology)*

A Cell is:

- Living chemistry

Yes, but chemistry is there to implement *function*

Roche Applied Sciences biochemical pathways wall chart



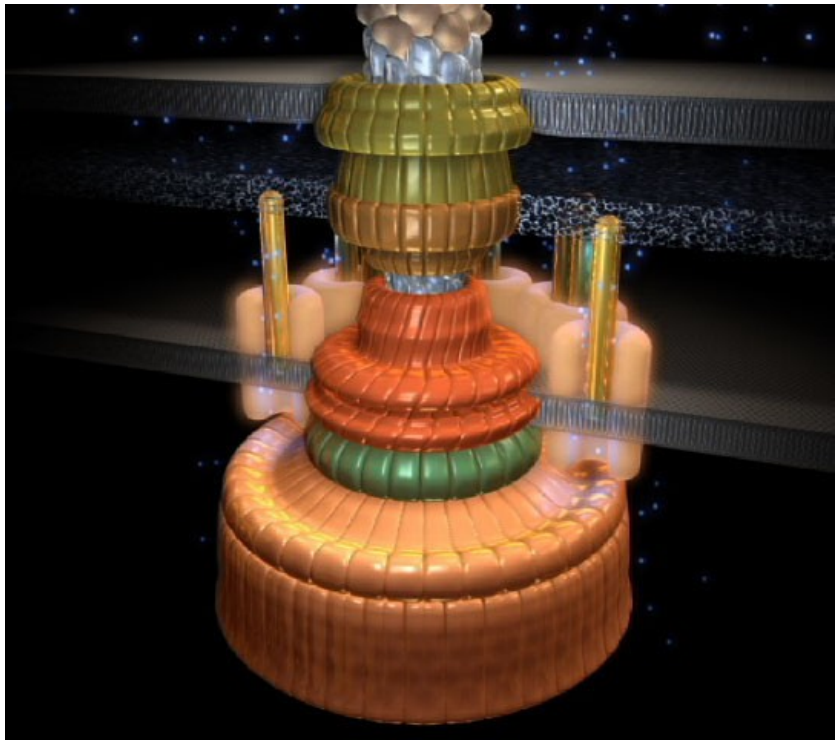
[www.expasy.ch/cgi-bin/show_thumbnails.pl]

A Cell is:

- ~~Living chemistry~~
- A living machine

Yes, but machinery needs *control*

Schematic diagram of the flagellar motor



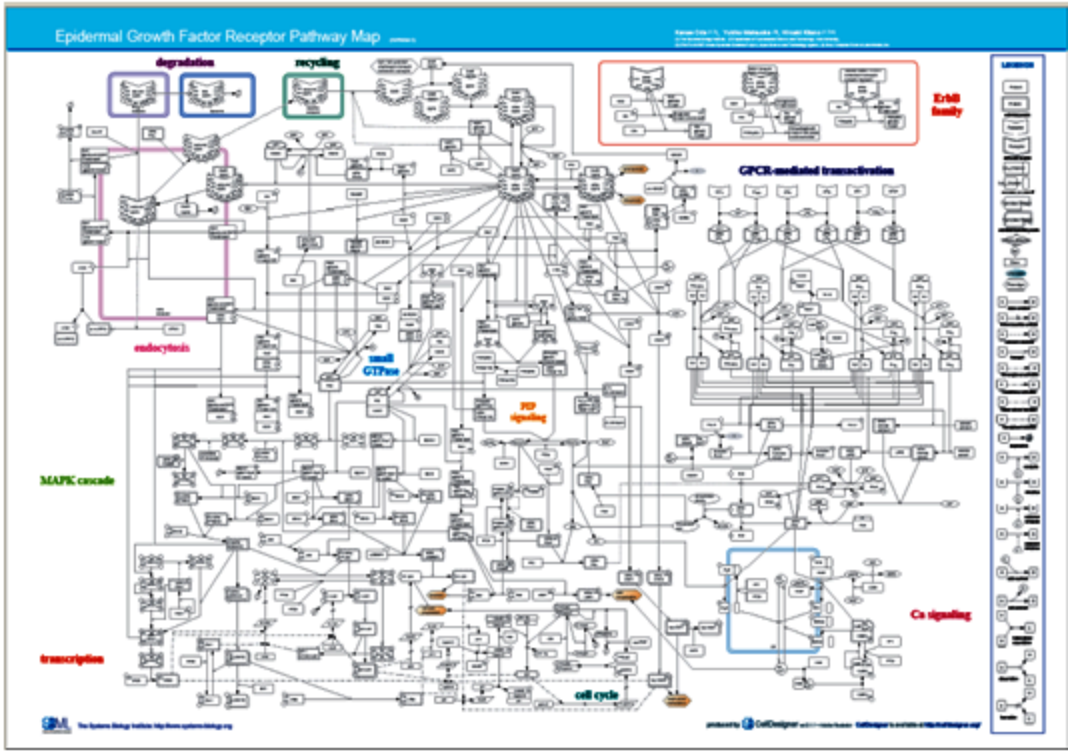
[Keiichi NAMBA, Osaka University, JAPAN NANONET BULLETIN - 11th Issue - February 5, 2004]

A Cell is:

- ~~Living chemistry~~
- ~~A living machine~~
- A living computer

Yes, but cellular circuits need to be built and reconfigured from *blueprints*

Epidermal Growth Factor Receptor pathway map



[A comprehensive pathway map of epidermal growth factor receptor signaling. Oda K, Matsuoka Y, Funahashi A, Kitano H. Mol Syst Biol. 2005;1:2005.0010. Epub 2005.]

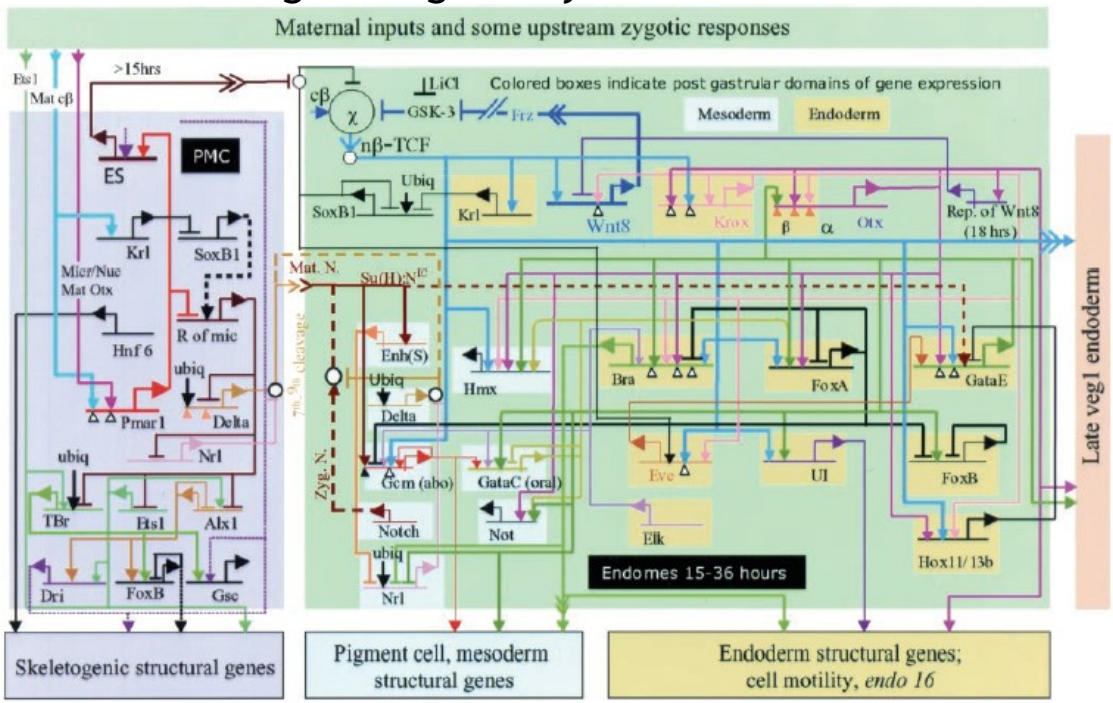
A Cell is:

- ~~Living chemistry~~
- ~~A living machine~~
- ~~A living computer~~
- Living software

Without understanding the software of life, ultimately, we cannot understand/repair cells.

Even if we understood all the chemistry, mechanics, and circuitry.

Portion of the sea urchin embryo endomesoderm gene regulatory network



[E.H.Davidson, D.R.McClay, L.Hood. Regulatory gene networks and the properties of the developmental process. PNAS 100(4):1475-1480, 2003.]

Conclusions

- Biology and Computing will ultimately converge
  - Nanomachines are the ultimate hardware
  - "*How does a cell work*" has to be answered at many levels and ultimately at the "software" (dynamic control) level