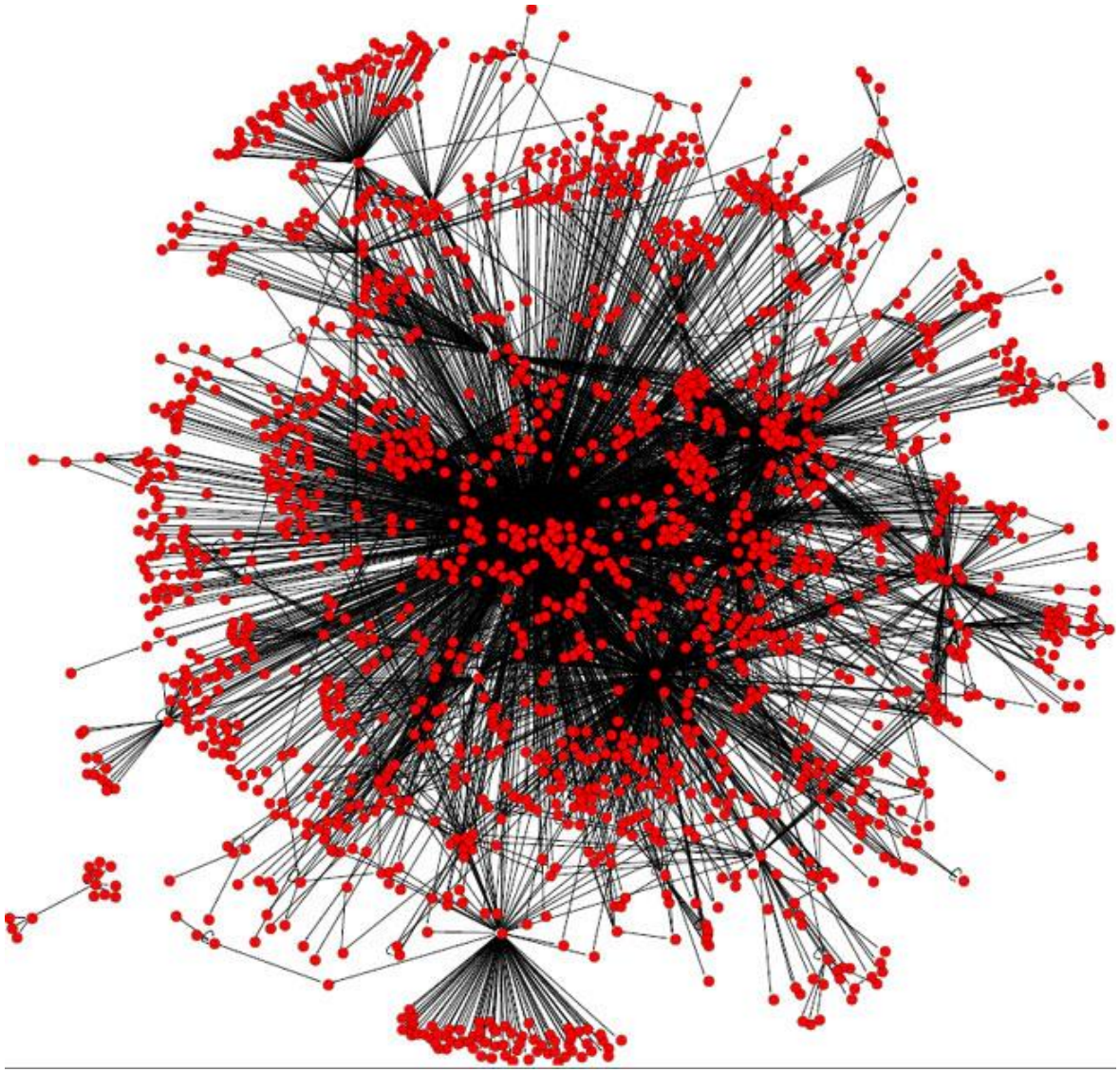
Towards a Roadmap to Executable Biology : On a Tower of Abstractions for Biology

Moshe Y. Vardi

Rice University

Collaborators: J. Fisher & N. Piterman

Regulary Networks in Bacteria

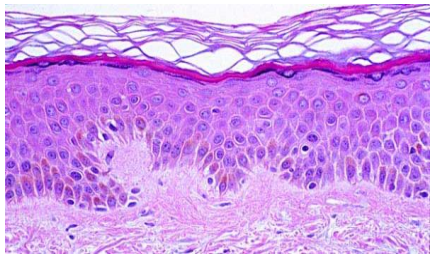


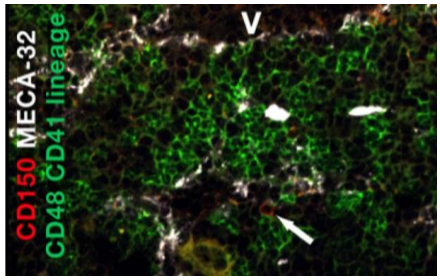
Mathematical System Biology

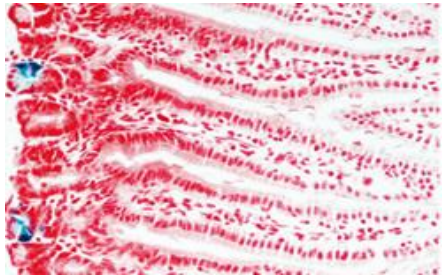
- Abstract mathematical models for biological systems, e.g., Regulatory Networks
- Boolean networks
- Qualitative networks
- Continuous networks
- Stochastic gene networks
- Coupled ODEs
- …
- Abstraction is key to quantitative analyzability! ***Abstraction tames complexity***!

Skin Cancer

Tissue homeostasis is critical



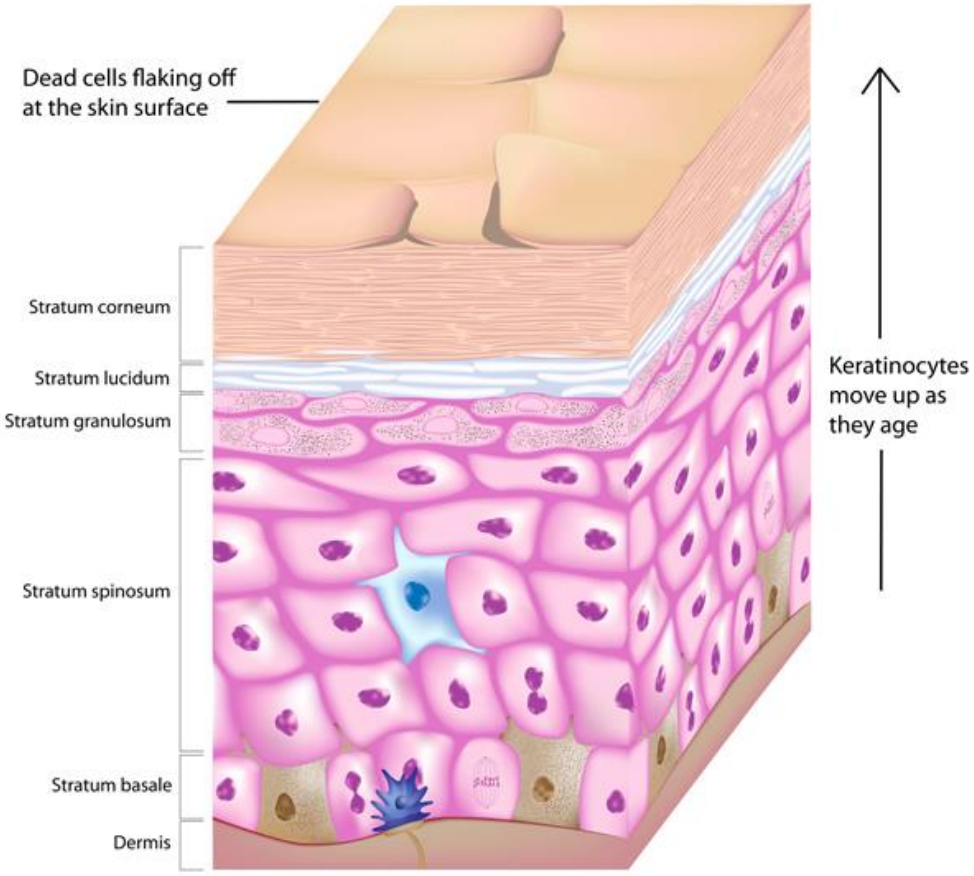


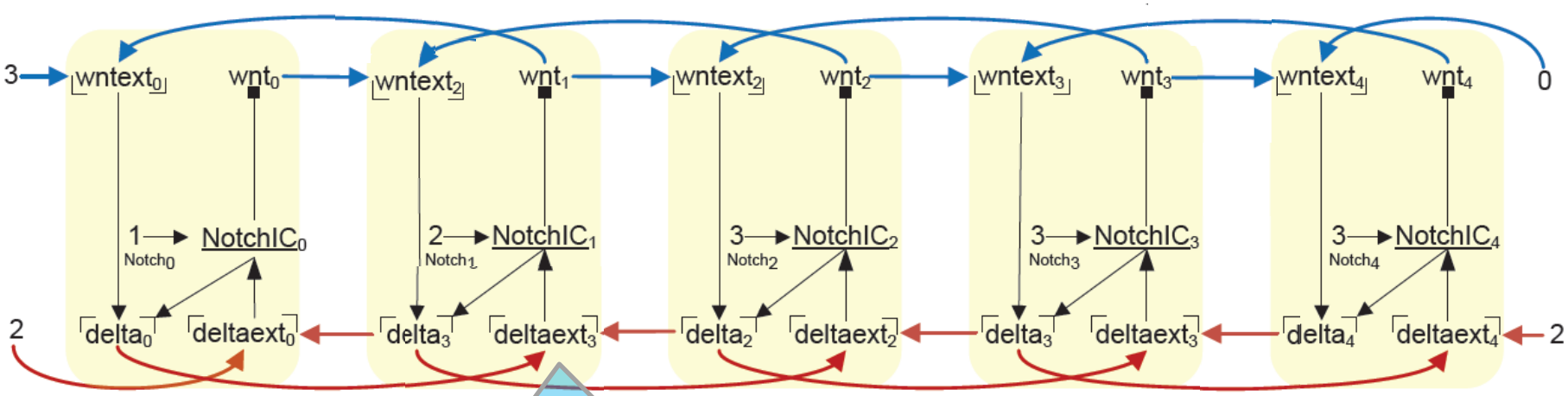


Cells lost = new cells made

Cells lost > new cells made FAILURE

New cells made > cells lost CANCER


Dead cells flaking off at the skin surface
Stratum corneum
Stratum lucidum
Stratum granulosum
Stratum spinosum
Stratum basale
Dermis
Keratinocytes move up as they age




```
deltaext1 :=
 if (deltaext0 + deltaext2 > 2 * deltaext1)
   deltaext1 + 1
 else if (deltaext0 + deltaext2 < 2 * deltaext1)
   deltaext1 - 1
 else
   deltaext1
```

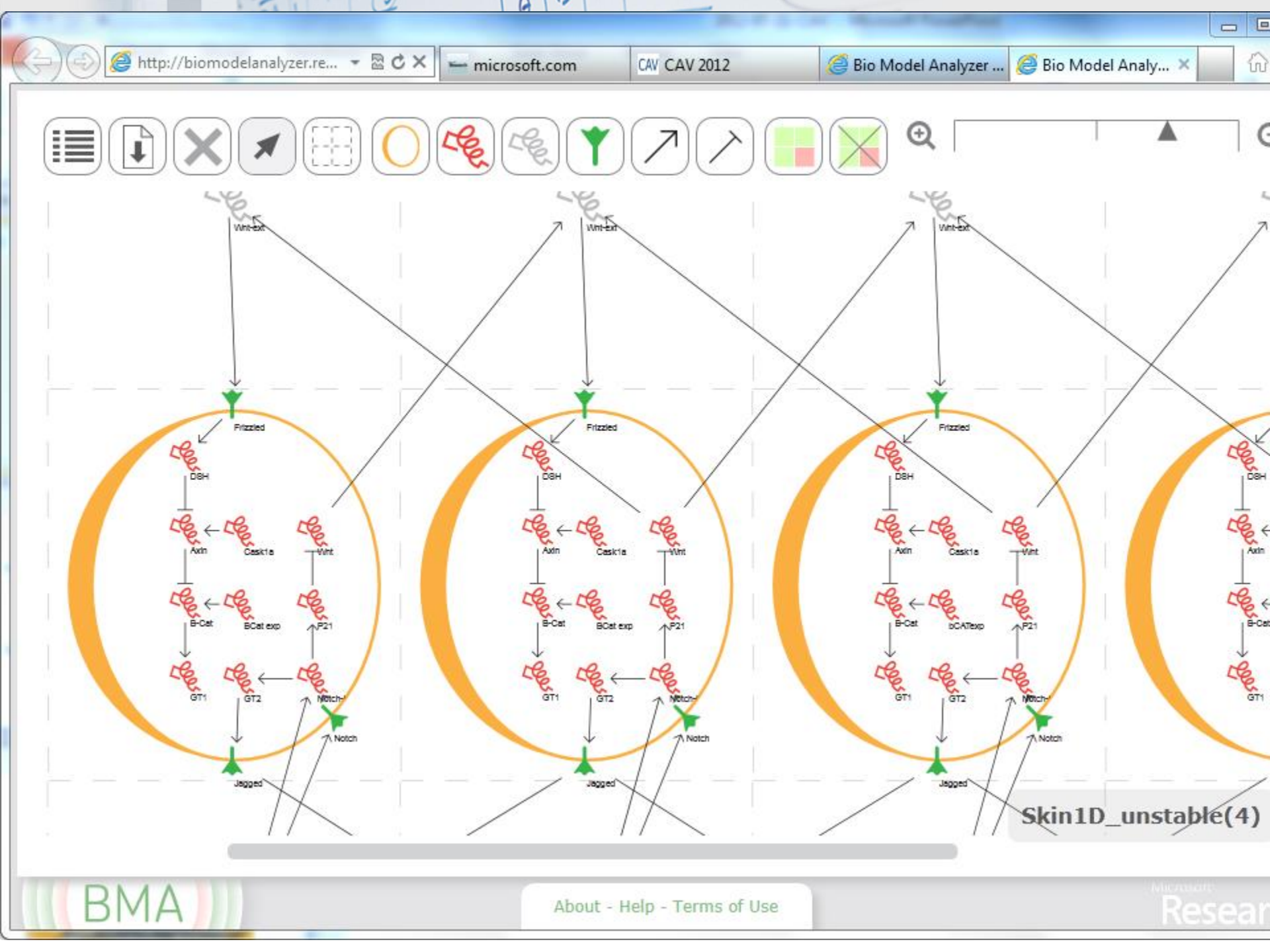
Microsoft Research

BMA: A TOOL FOR MODELING AND ANALYSIS OF BIOLOGICAL NETWORKS

David Benque, Sam Bourton, Caitlin Cockerton, Byron Cook, Jasmin Fisher, **Samin Ishtiaq**, Nir Piterman, Alex Taylor and Moshe Vardi

http://biomodelanalyzer.research.microsoft.com

CAV 2012, 11 July 2012


http://biomodelanalyzer.re...
microsoft.com
CAV 2012
Bio Model Analyzer ...
Bio Model Analy...
Wnt-ext
Frizzled
DSH
Axin
Cask1a
Wnt
B-Cat
BCat exp
bCATexp
P21
GT1
GT2
Notch
Jagged
Skin1D_unstable(4)
BMA
About - Help - Terms of Use

Abstraction is not enough!

- ***Abstraction by itself cannot tame complexity!***
  - *Highly complex abstract models are not useful.*

- **Thesis**: system biology needs a ***tower of abstractions***; that is, a *sequence of models of increasing degree of abstraction, each level building on the level below it.*

Biology and Computer Hardware

- A natural analogy (see "Algorithmic Systems Biology", "Executable Biology", …)
  - Transistors vs. proteins/genes/metabolites
  - Logic gates vs biologic gates
  - Concurrent execution
  - Emergent behavior: computing vs life

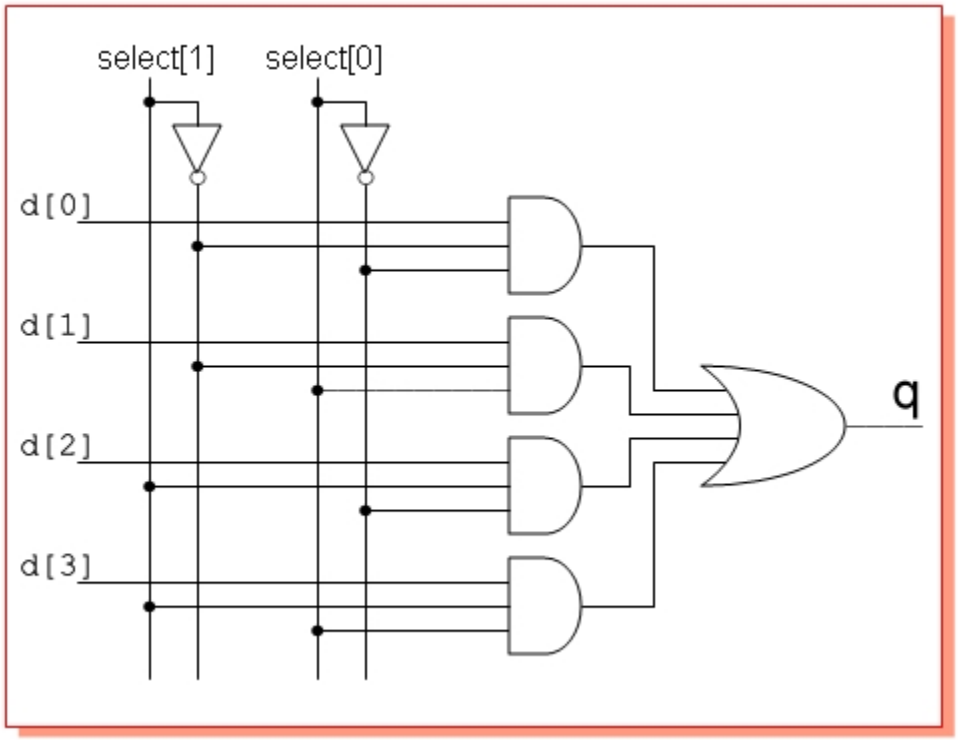
Hardware Design Process, I

- Design requirements: implement a 32-bit integer multiplier
- Software model: K=I*J
- Hardware Description Language (HDL): multiplication via iteration addition
  - K:=0
  - While I>0 do
  - {K:=K+J;
  - I=I-1}

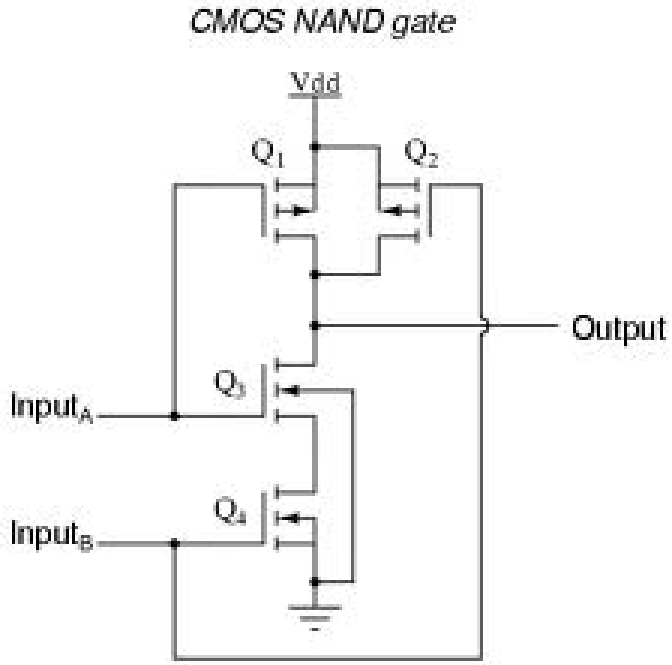
Hardware Design Process, II

- **Gate level**: translate + and – to Boolean gates (and, or, not)
- **Transistor level**: implement Boolean gates and registers by means of transistors
- **Silicon level**: implement transistors by silicon patterns

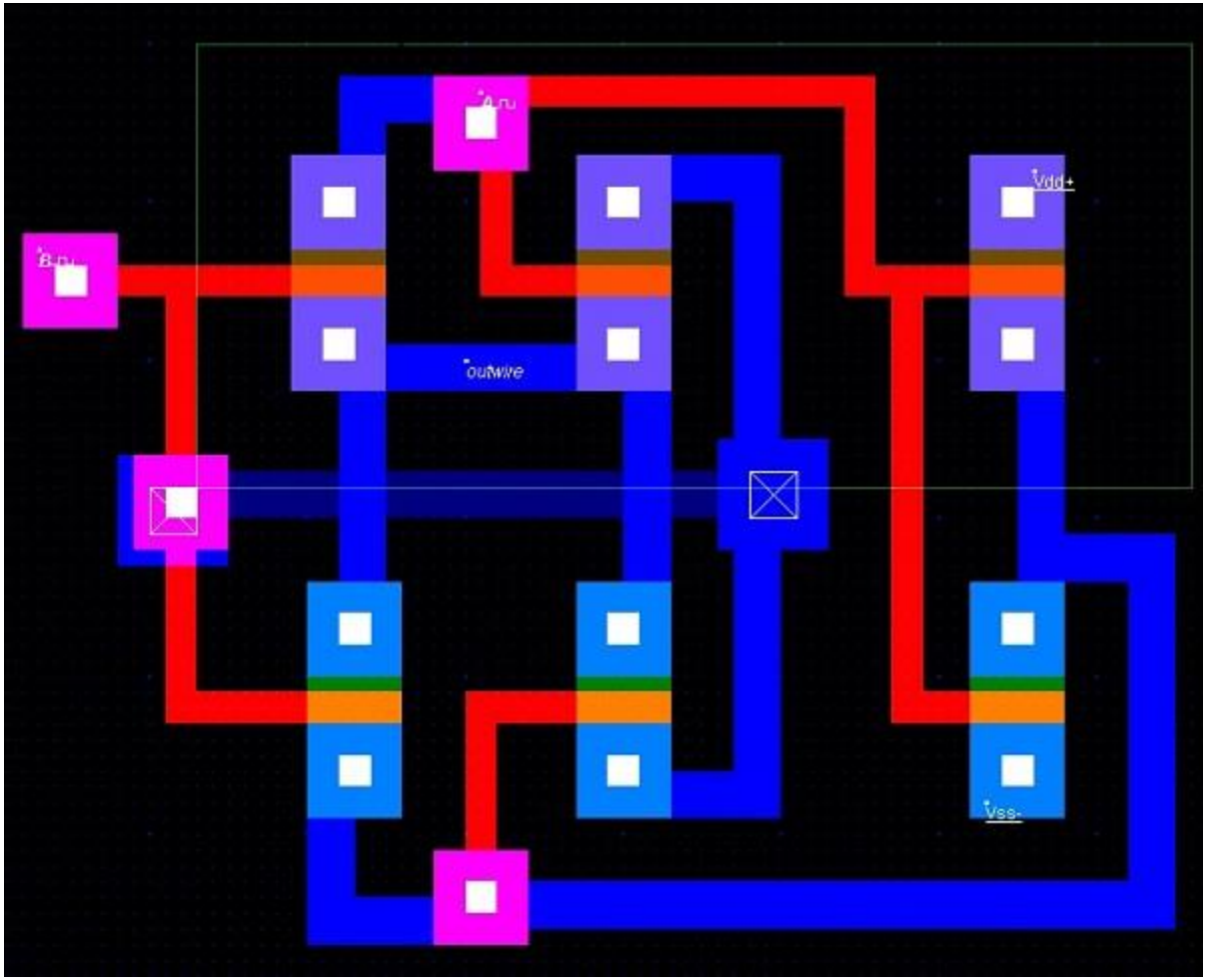
Gate-Level Model



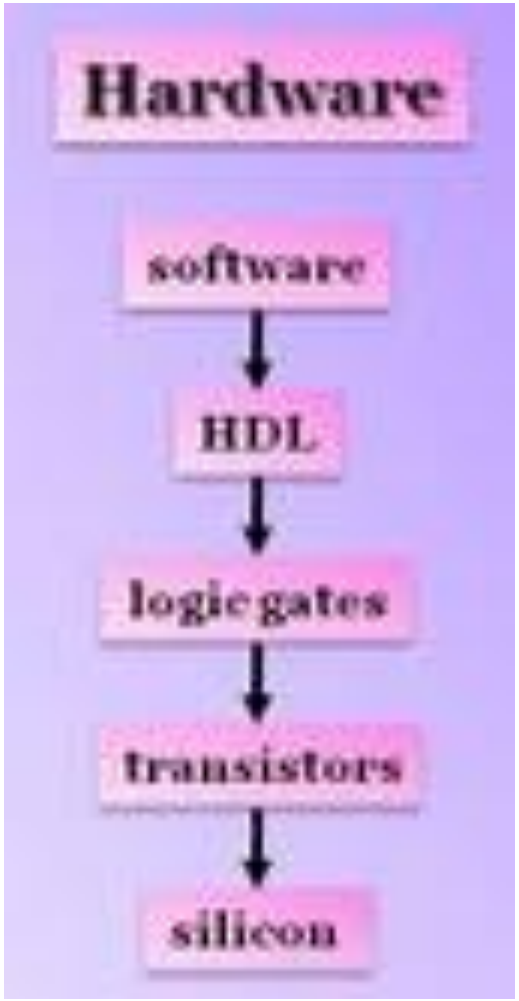
Transistor-Level Model



Silicon Mask



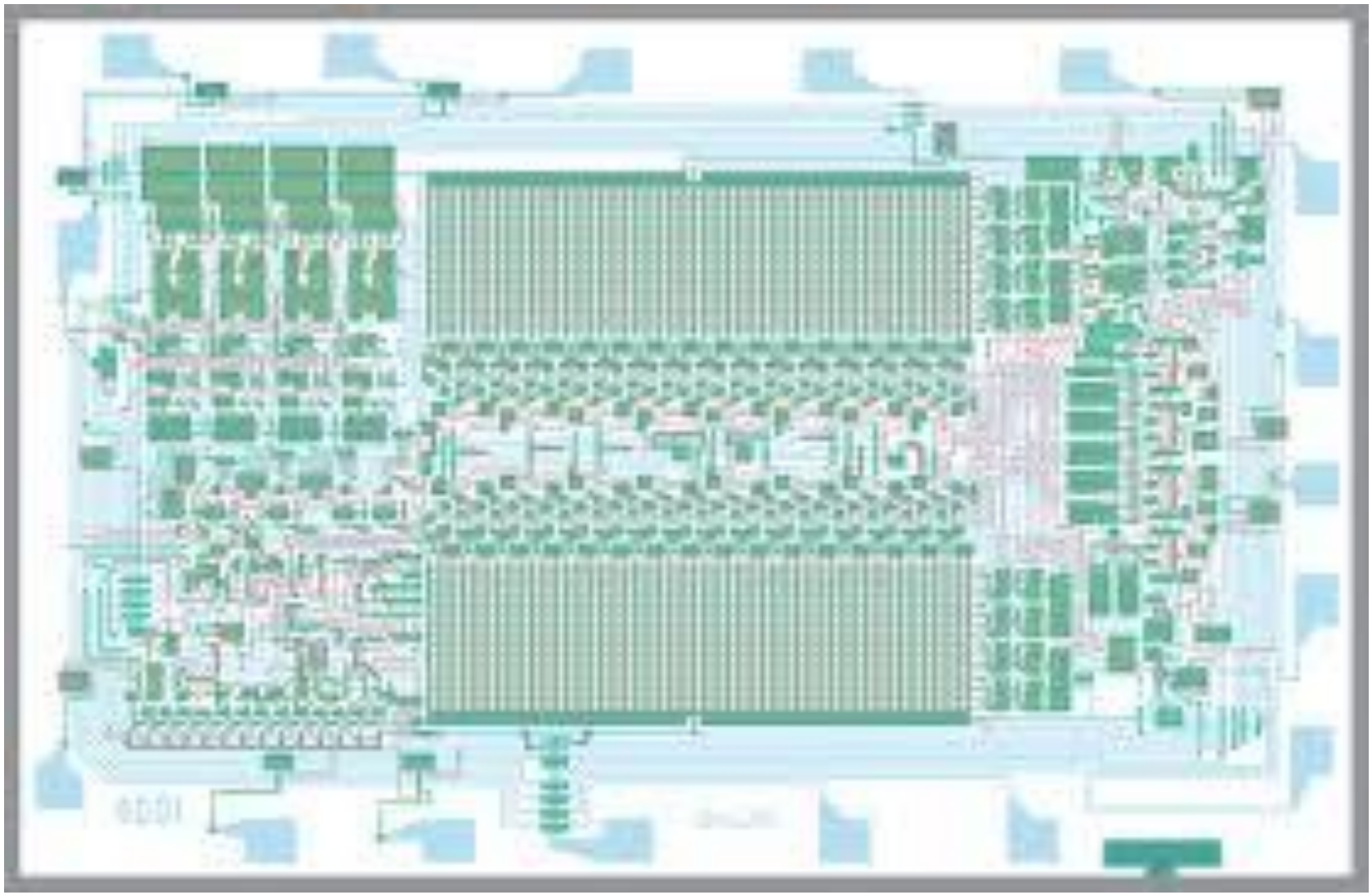
HW ToA



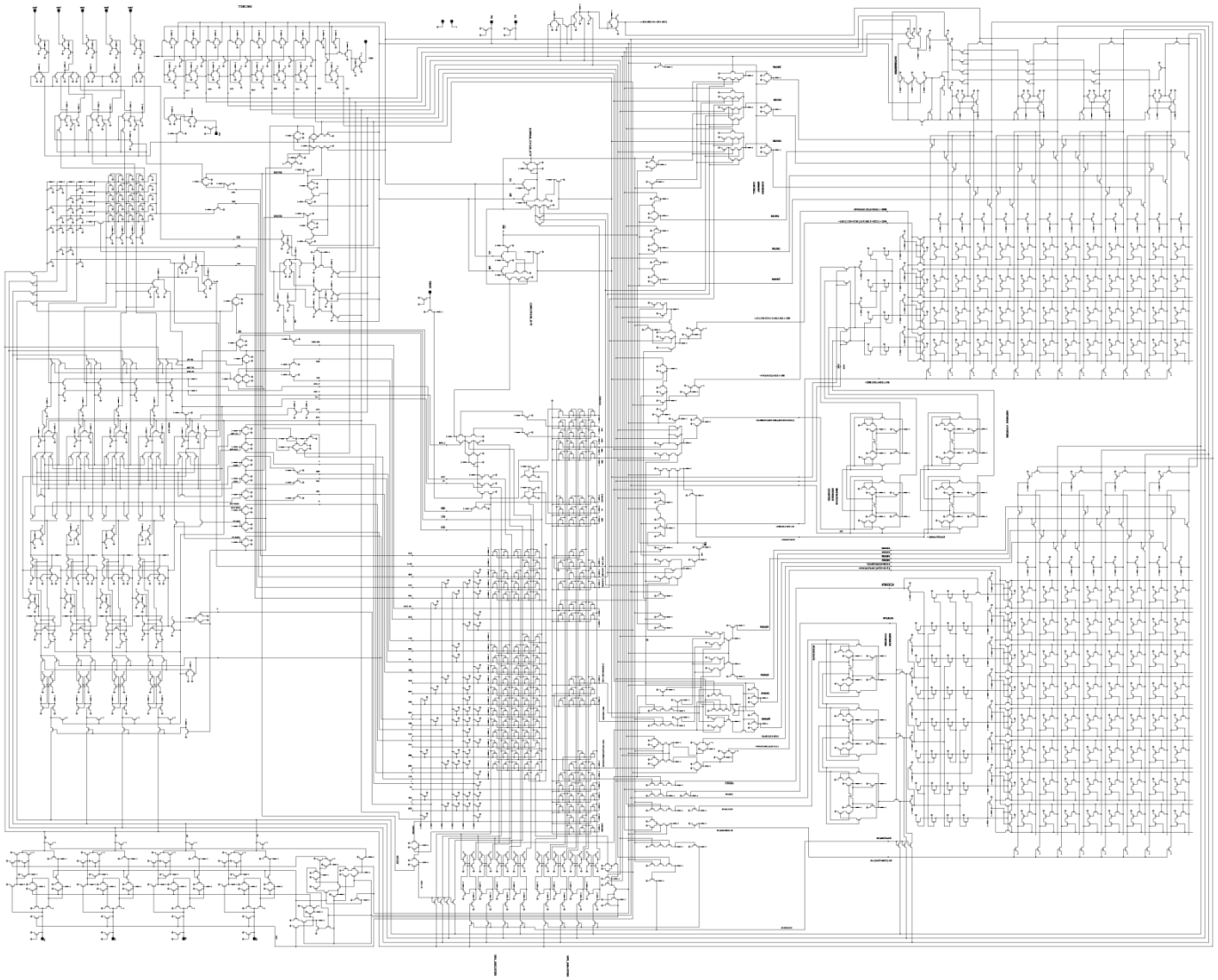
Intel 4004

- Intel's first microprocessor (1971)
- 4-bit CPU
- 2300 transistors
- 1MHz
- 10μM
- Designed by hand!

Intel 4004: Mask



Intel 4004: Transistor Level



Can One Reverse Engineer the 4004?

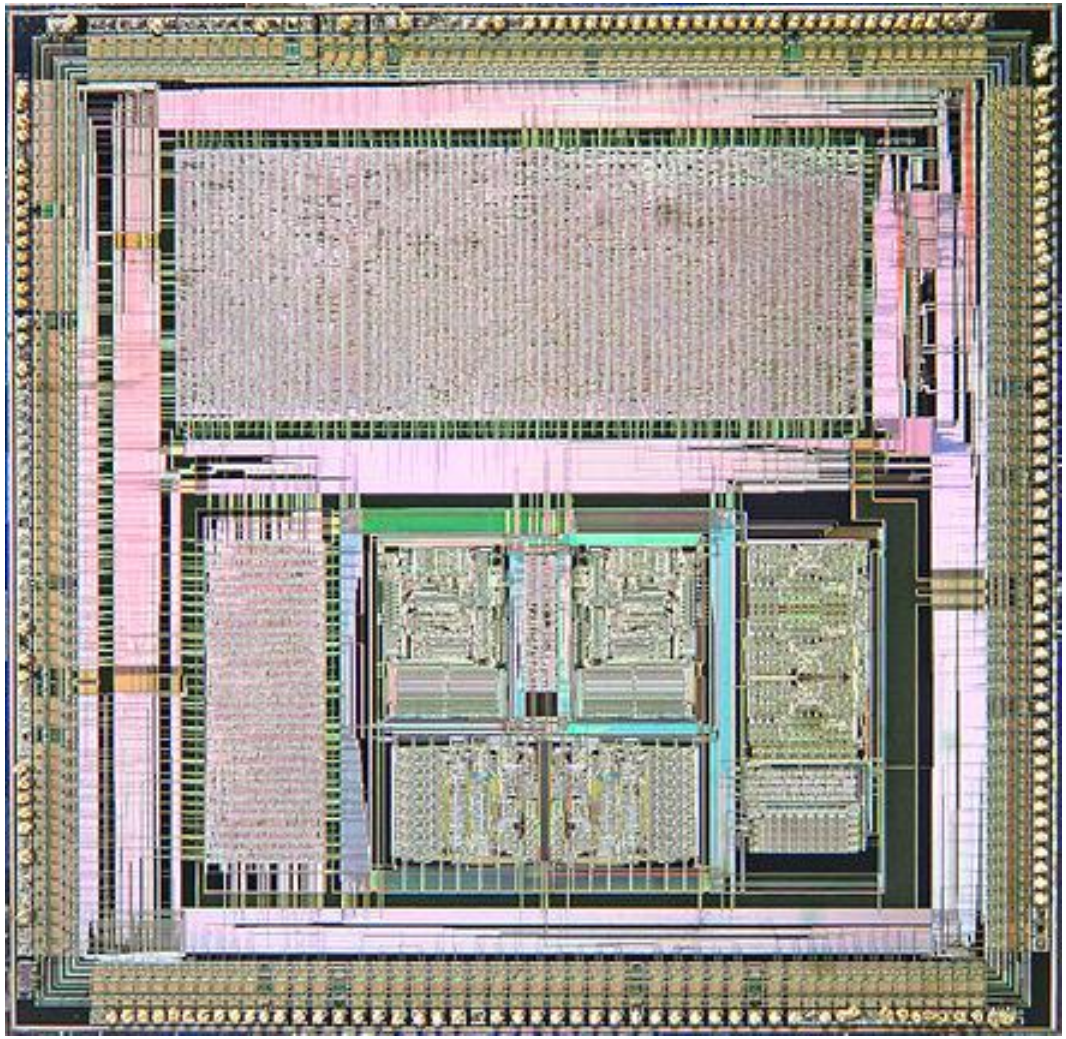
- The 4004 was designed for the Busicom 141-PF calculator.
- The designers chose to implement as CPU, with calculator implemented in software.
- *Impossible to reverse engineer* w/o understanding the 4004 ***architecture***: memory, I/O ports, registers, instruction set, addressing modes.

Higher-level concepts!

Intel Xeon Haswell-EX

- 18 cores
- 64-bit CPU
- 5.6B transistors
- 3.3GHz
- 22nm transistors
- 662 mm2 die size (about 1 sq inch)
- Designed using sophisticated CAD tools

Modern Microprocessor

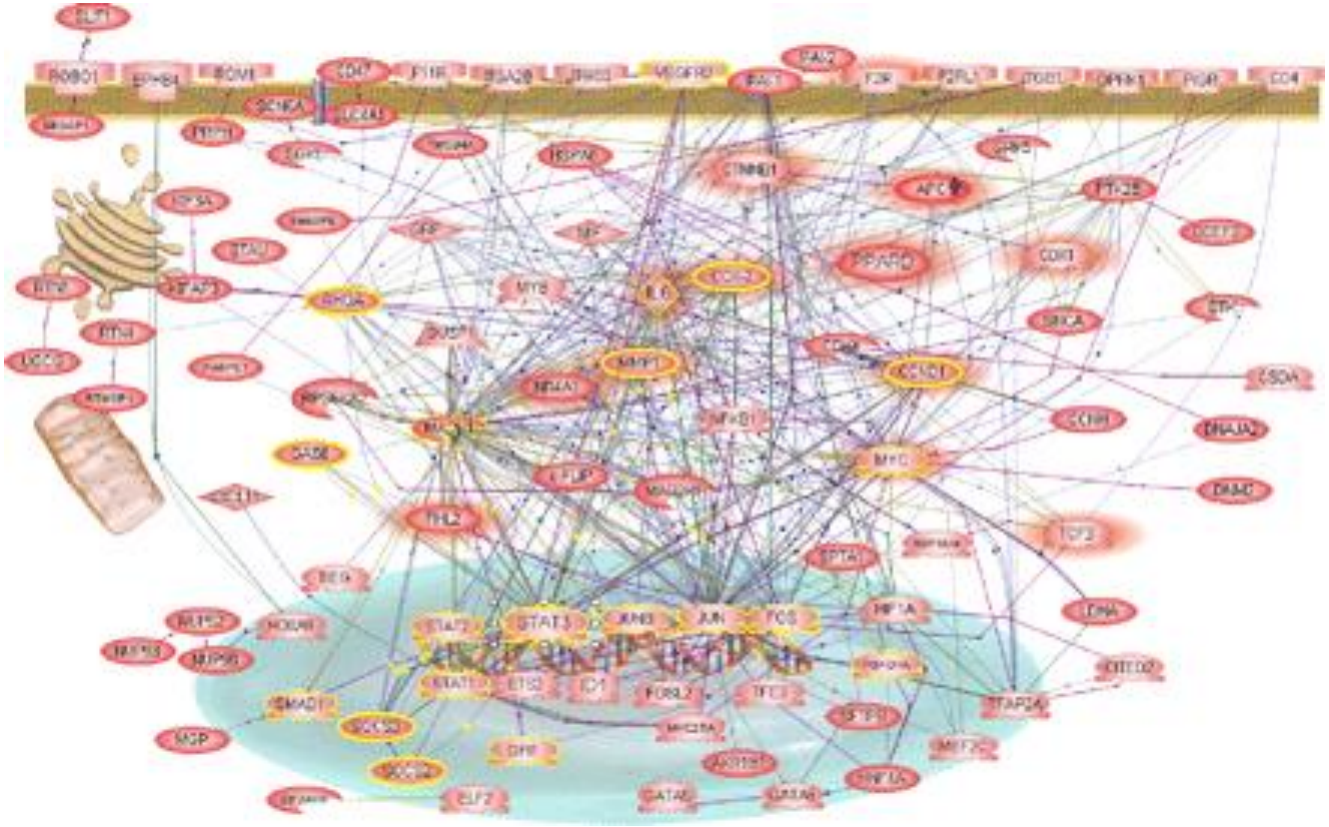


Taming Complexity

- Modern HW systems are highly complex.
- Designing a modern CPU is like designing NYC to the level of individual light switches and door knobs!
- Tower of abstractions is necessary!
  - For design
  - For reverse engineering

Gene Regulatory Networks

- "Transcriptional network governing the angiogenic switch in human pancreatic cancer"



System Biology Needs a ToA!

- Phenotype
- …
- Mechanisms
- …
- Functional modules
- Biologic gates
- Signaling pathways
- Genes, proteins, metabolites

Level of Abstraction

- S. Brenner: "While the genome sequence is central, it is a level of abstraction that is too cryptic to be used for the organization of data and derivation of theoretical models."
- S. Bornholdt: Less Is More in Modeling Large Genetic Networks – "Is coarse-graining of genetic network models possible?"
- Our thesis: ***multiple levels of abstraction needed!***

Physical vs Conceptual ToA

- Classical ToA: tower of physical ***scales*** –
  - Molecular
  - Cellular
  - Organ
  - …
- Conceptual ToA:
  - Silicon patterns
  - Transistors
  - Gates
  - Registers
- **Challenge**: *Identify conceptual levels in SB!*

Example: Segmentation Clock

K. Horikawa, K. Ishimatsu, E. Yoshimoto, S. Kondo, & H. Takeda:

"Periodic somite segmentation in vertebrate embryos is controlled by the 'segmentation clock', which consists of numerous cellular oscillators. Although the properties of a single oscillator, driven by a hairy negative-feedback loop, have been investigated, the system-level properties of the segmentation clock remain largely unknown."

(Nature, 2006)

Evolutionary Perspective

Q: But biological systems are not designed, they are evolved! Why should evolution prefer a ToA?

A: **Evolution** occurs at the *genotype* level. But **selection** occurs at the *phenotype* level, and higher-level constructs are closer to the phenotype.

Analogy: 32-bit register is closer to multiplication that a single transistor.

In Conclusion

J. Gunawardena: "Molecular biology was reductionism finest hour. Now there is nowhere left to go but up!"

References

http://www.cs.rice.edu/~vardi/papers

1. "The Only Way Is Up"
2. " BMA: Visual Tool for Modeling and Analyzing Biological Networks"