Making Headway into the Complexity of Biology

Systems Approaches in Understanding Evolution and Evolvability

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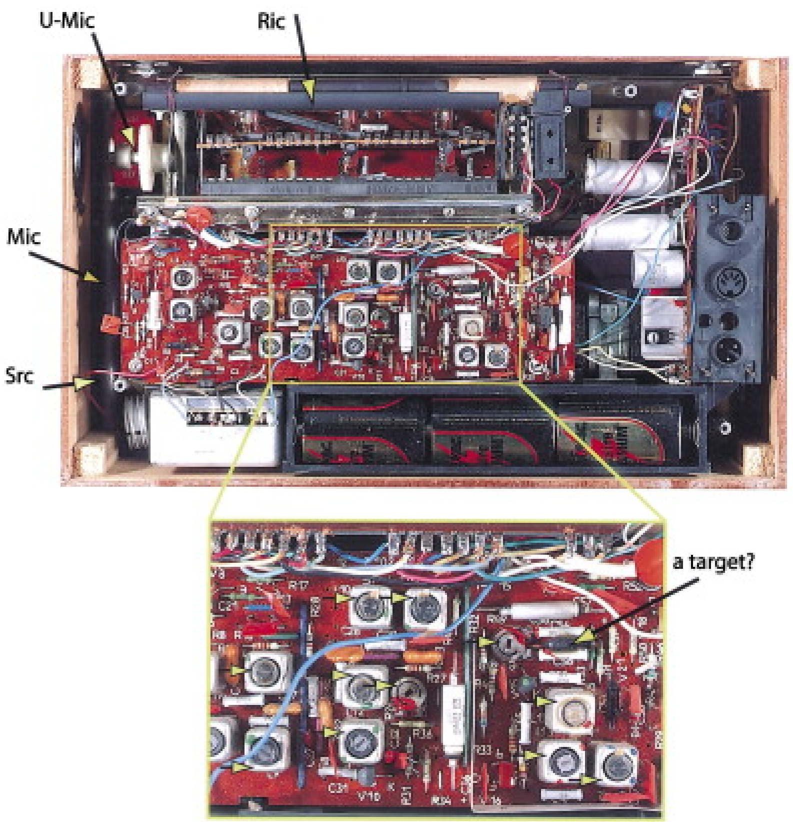
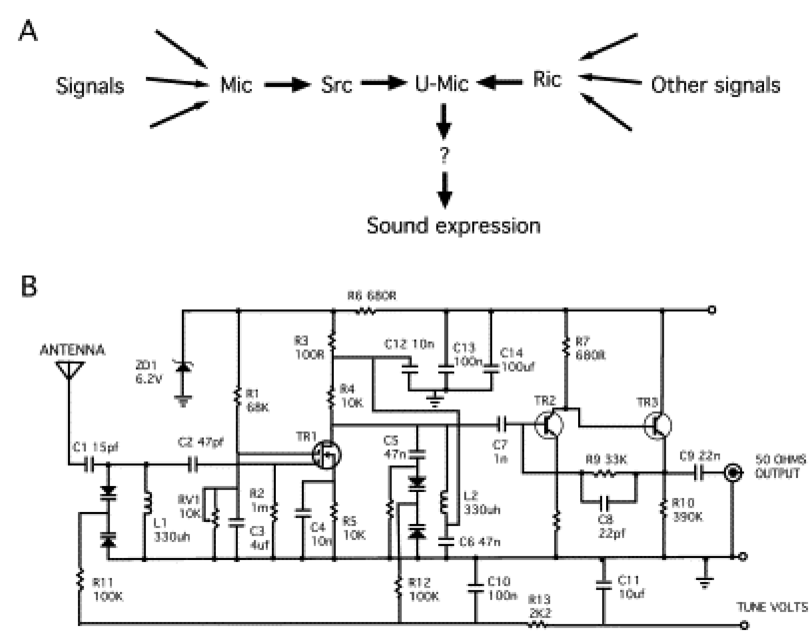
Systems Biology

- Seeks to take a more 'holistic' (as opposed to 'reductionist') approach to biology
- “Can a biologist fix a radio?” [Yuri Lazebnik]

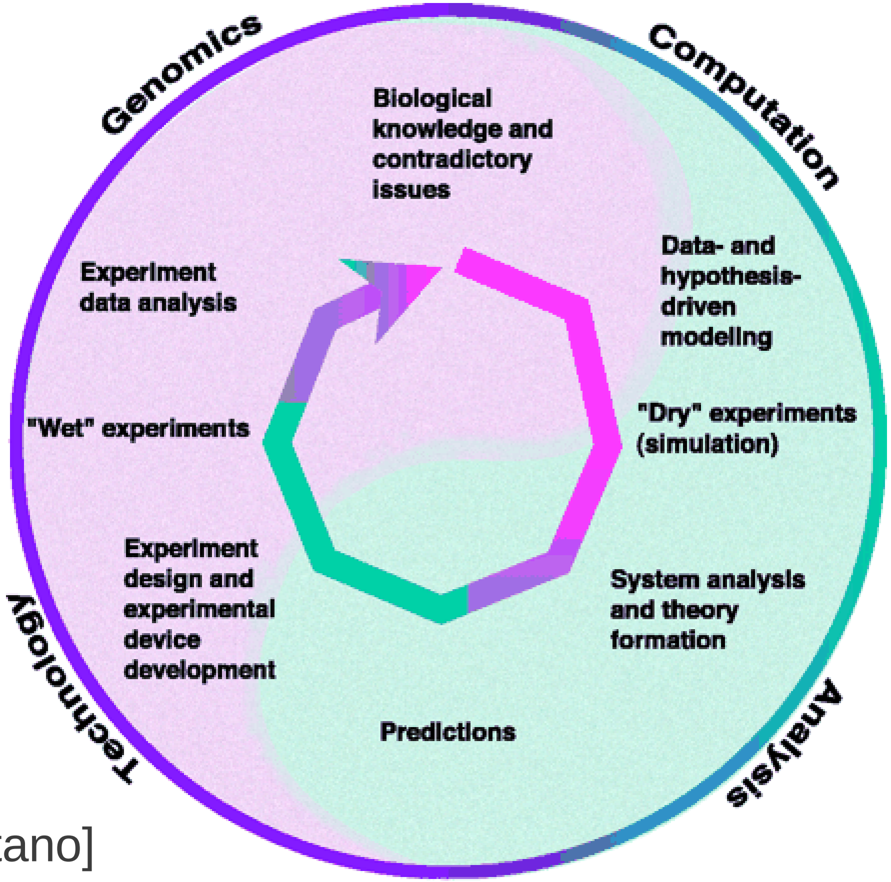




Systems Biology

- Seeks to use mathematical modelling to *quantitatively* understand interactions between different system components and their respective roles

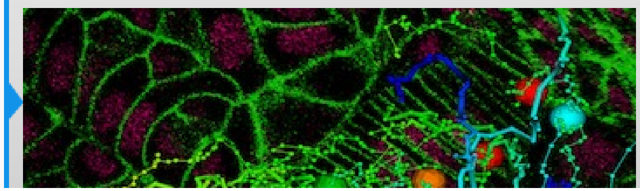
- Feedback loop between modelling and experimentation is critical



[Kitano]

Growing a spine

Neuron precursors undergo dramatic spatial rearrangements during development, prompting a reassessment of the model for how morphogen gradients determine cell fate and spatial organization.



Upcoming Events

01/21/2014 - 1:00pm
Student Defense - Tami

02/04/2014 - 12:30pm
Pizza Talk - Robert Bao

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Job Focus

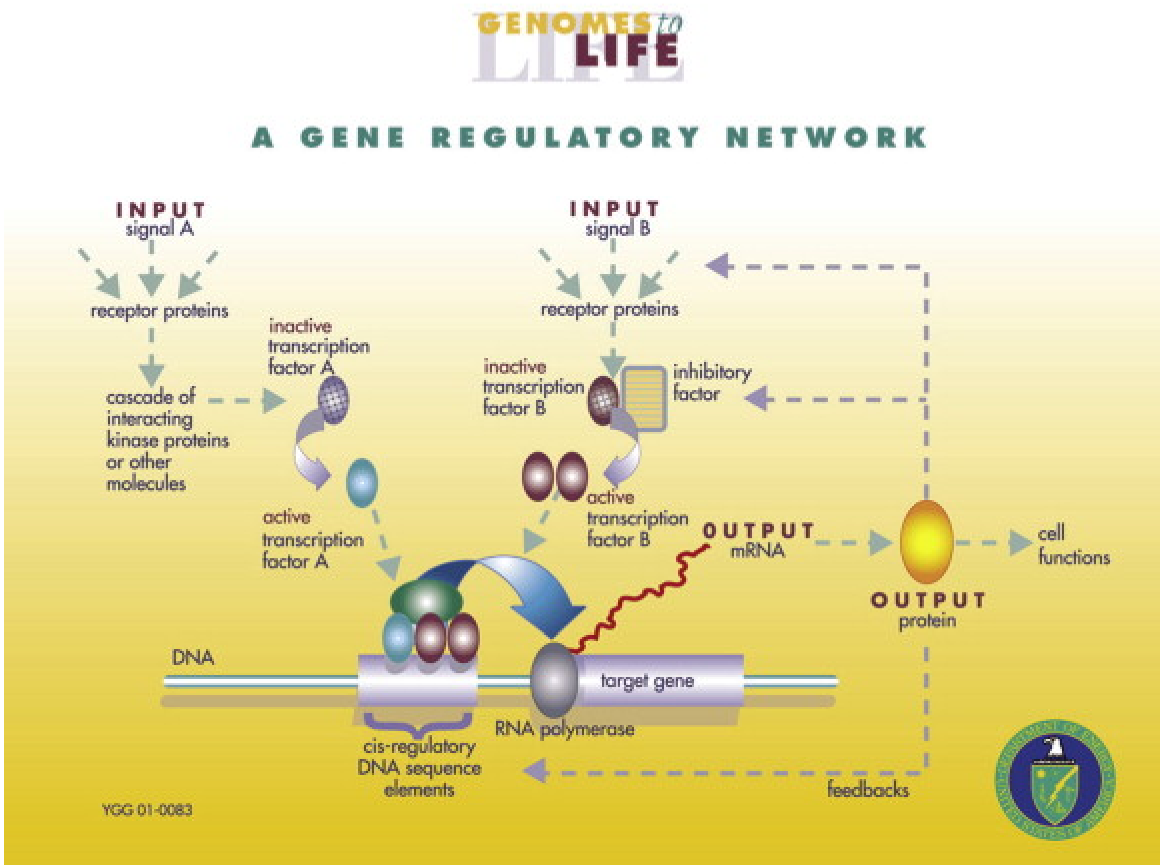
Working with colleagues from Clinical Pharmacology; Pharmacokinetics, Dynamics and Metabolism; and the Computational Sciences Center of Excellence, the successful candidate and the Systems Biology group will increase the efficiency of clinical development and new target selection by developing and analyzing mathematical models of biological networks/pathways/complex systems including disease mechanisms.

The Systems Biology and Whole-Body Physiology group of Pfizer's Cardiovascular, Metabolic, and Endocrine Diseases

Gene Regulatory Networks

- Perhaps the most prominent example of 'systems biology'

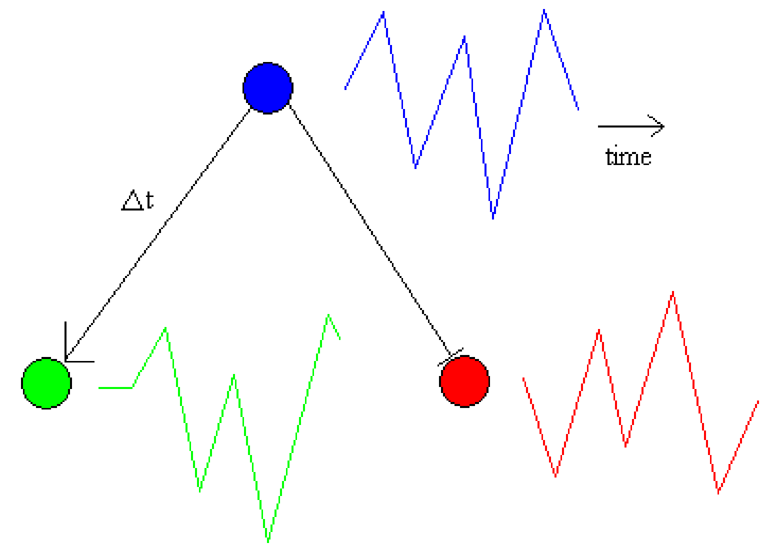
- Can we mathematically model genetic circuits; and even predict their response to perturbations?

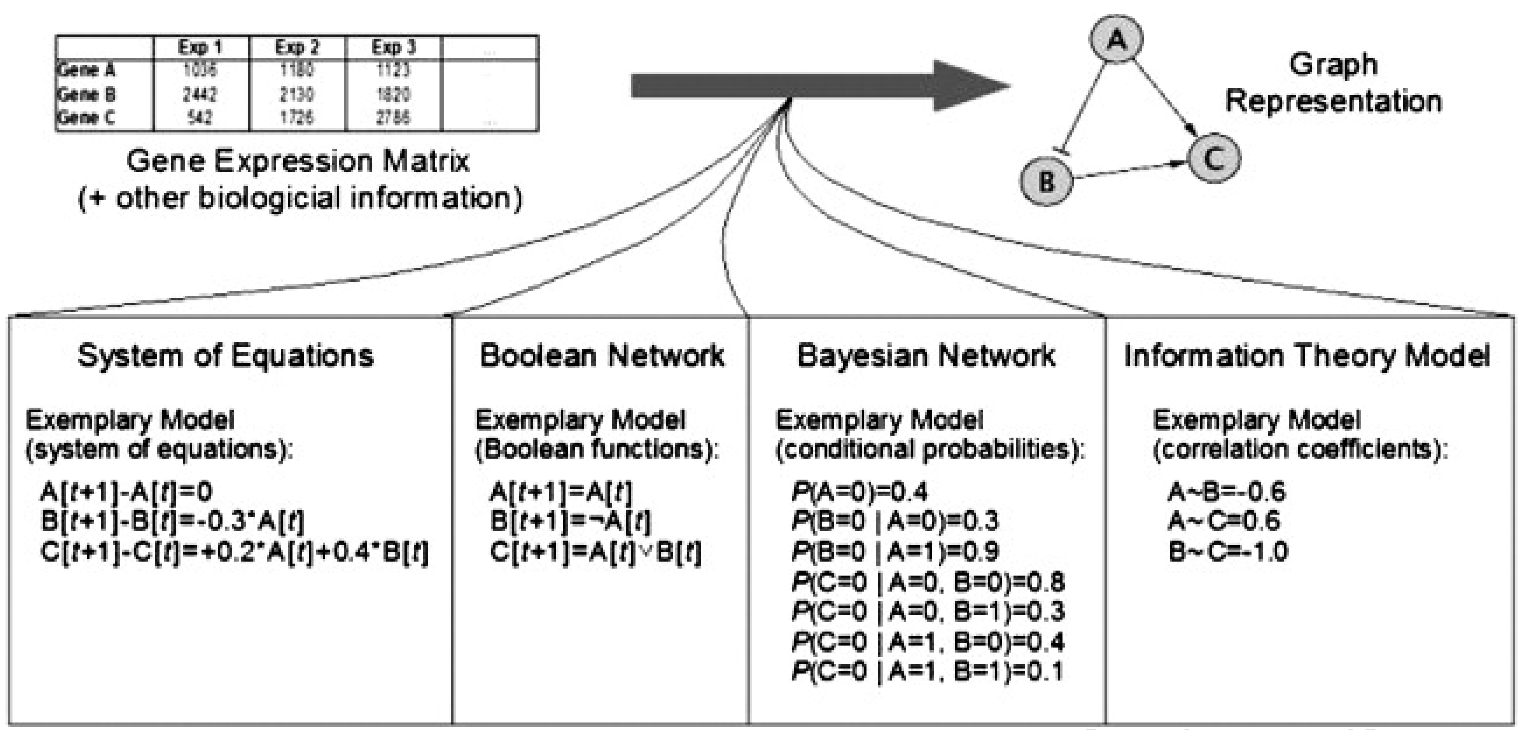


[http://genomics.energy.gov]

Modelling Dynamics

- Many approaches, ranging from simple ON/OFF models of genes to full-fledged differential equations





[Hecker *et al.*]

Evolution & Evolvability

- We can try to model systems dynamics; but can we also say something about *how* and *why* certain kinds of systems have evolved?
- On top of the dynamical models, we can also model and simulate the process of their evolution (evolutionary computing / genetic algorithms)
- This may allow us to study the conditions under which systems properties like modularity and robustness can emerge

Wagner model

- A simple model for dynamics and evolution proposed by Andreas Wagner
- Each gene is always ON (+1) or OFF (-1); the state of a gene at a given time is determined by the states of other genes at the previous time step

$$x_i(t+\tau) = \sigma\left[\sum_{j=1}^{N} w_{ij} x_j(t)\right].$$

- w_{ij} is the strength of the effect of gene j on gene i; σ is the sign function, so that $\sigma(y) = +1$ for $y>0$ and -1 for $y<0$

Wagner model

- Evolution: Suppose there is an ideal/optimal equilibrium expression state; the fitness for a given individual network can be defined as the Hamming distance from the optimum

Gene no.	1	2	3	4	5
$\mathbf{x}^{opt}$	+1	+1	-1	+1	-1
x	+1	-1	-1	+1	+1

Hamming distance = 2

- Given a fitness function, we can apply natural selection over populations to simulate evolution

Results: Modularity & Robustness

- Kashtan & Alon [2005]: Modular network structures emerge under *modularly varying goals*
- *E.g.* (X XOR Y) AND (Z XOR W) vs.
  (X XOR Y) OR (Z XOR W)
- Siegal & Bergman [2002]: Waddington's *canalisation* can also emerge from such models, just from the need for developmental stability

Evolution as Learning

- Valiant [2009]: Suggests that we can think of evolution as a kind of *learning from the environment*
- We can use a branch of computer science called *computational learning theory* to understand what kinds of functionality can evolve in feasible time and resources
- E.g., given some assumptions, monotone conjunctions/disjunctions evolvable (x OR y OR z), but not parity functions (an even number of genes should be ON)

Connections / Future work

- Modular gene networks are more efficient at certain tasks
- Can Valiant approach be used to show that modularity enhances evolvability?
- Certain information flow or communication tasks on networks shown to be easier for modular networks [Agarwal; Bui-Xuan & Jones]; is this relevant to biology?

Conclusions

- Systems approaches can give us a quantitative handle on the behaviour of complex biological systems
- We can begin to ask questions about the nature of evolution (what are its powers and limits?) in a more precise fashion
- Still a lot of work to bridge the gap between simple abstractions and real-world messiness

References

- Yuri Lazebnik. Can a biologist fix a radio?—Or, what I learned while studying apoptosis. *Cancer Cell* **2:**179–182, 2002.
- Hiroaki Kitano. Systems biology: a brief overview. *Science* **295:**1662–1664, 2002.
- M. Hecker *et al*. Gene regulatory network inference: data integration in dynamic models—a review. *Biosystems* **96:**86–103, 2009.
- Andreas Wagner. Does evolutionary plasticity evolve? *Evolution* **50:**1008–1023, 1996.
- N. Kashtan and U. Alon. Spontaneous evolution of modularity and network motifs. *PNAS* **102:**13773–13778, 2005.
- M. L. Siegal and A. Bergman. Waddington's canalization revisited: developmental stability and evolution. *PNAS* **99:**10528–10532, 2002.
- L. G. Valiant. Evolvability. *Journal of the ACM* **56:**3:1–3:21, 2009.
- Sumeet Agarwal. *Networks in Nature: Dynamics, Evolution, and Modularity.* D.Phil. Thesis, University of Oxford, 2012.
- B. M. Bui-Xuan and N. S. Jones. How Modular Structure Can Simplify Tasks on Networks. *arXiv*:1305.4760, 2013.