Computing, Communication and Control

The view from Systems Biology

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Systems Biology

• A philosophical shift in biological and biomedical research
  – Acknowledges complexity
  – Takes account of dynamics
  – Reliant on modeling and simulation

Computing → Biology
Systems Biology

• A philosophical shift in biological and biomedical research
  – Acknowledges the existence of design, as it arises through natural selection
  – Seeks to elucidate design principles ("strategies")

Biology    Computing
Biological Strategies

- Ultimately, all species “seek” to maximize reproductive fitness within a given environment
  - Energy efficiency
  - Environmental sensing/measuring
  - Foraging
  - Cooperating
  - Remembering
  - Copying
  - Learning
  - Adapting
Does biology come up with the same strategies as engineers?

Integral feedback control underlies high-sensitivity signal detection over a wide dynamic range.
Does biology come up with the same strategies as engineers?

The same control strategy, implemented in a completely different way, enables tissues to growth to a predetermined size despite environmental fluctuations.
Does biology come up with the same strategies as engineers?

Analog-to-digital conversion for reducing signal degradation during information transfer
Biology routinely ventures where engineers don’t often go

- The nano-world
- The spatial world
- The “highly optimized” world

Can the strategic successes of biology in these areas teach us “new” engineering?
Biology and the nano-world

• Single-celled organisms are the oldest, most diverse and most abundant life forms on this planet.
  – A huge number of biological strategies are based on mechanisms that operate on the molecular-to-cellular scales.
  • Gene regulation
  • Cellular signaling
  • Molecular motors
  • Metabolism
Issues and constraints at the nano-scale

- Stochasticity
- Component unreliability
- Energy efficiency
- Environmental lability
- Evolvability/Adaptability
- Transport limitations
The same issues are faced by nano-electronics today

- Stochasticity
- Component unreliability
- Energy efficiency
- Environmental lability
- Evolvability/Adaptability
- Transport limitations

Martorelli and Rubio, 2008, Microelectronics J.
Intrinsic stochasticity in biological systems

- Subcellular components are often present at levels where deterministic chemistry is not a good approximation

  - DNA a prime example: Genes tend to be present at 1 or 2 copies per cell. Genes do not express at a steady rate, but flip back and forth between “on” and “off” states.
Why don’t biological systems avoid intrinsic stochasticity by just using more “stuff”?

• Transport limitations
  – To lower Poissonian fluctuations by a factor 2, you must increase “stuff” by a factor of 4, which increases system linear dimensions by a factor of $4^{1/3}$, which means that averaging times due to diffusion go up by a factor of $4^{2/3}=2.5$
Why don’t biological systems avoid intrinsic stochasticity by just using more “stuff”?

• Redundancy hinders evolution
  – Evolution depends upon random variations at the molecular level (DNA mutation). If you have too many copies of the same gene, individual mutations have little effect, good or bad
So do biological systems actively suppress intrinsic noise?

- Sometimes, but very often not.

Elowitz et al., 2002, Science
Noise can do useful things

- Stochasticity can power switches, create switches, synchronize networks, increase the sensitivity of input/output relationships, and enable adaptive responses to novel stimuli.

Wang et al., 2007
BMC Systems Bio
Noise can do useful things

• Stochasticity can power switches, create switches, synchronize networks, increase the sensitivity of input/output relationships, and enable adaptive responses to novel stimuli.

Schultz et al., 2008 PNAS
Noise can do useful things

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q = \frac{1}{1 + [s]/K}
\]

Paulsson et al., PNAS, 2000
Noise can do useful things

- Stochasticity can power switches, create switches, synchronize networks, increase the sensitivity of input/output relationships, and enable adaptive responses to novel stimuli.

Kashiwagi et al., 2006 PLoS ONE
Stochasticity in Biology

- Stochastic behavior is a fact of life in the nano-world.
- Rather than treat noise as a liability, biology has learned to build useful strategies around it.
Biology and the Spatial World

- In human-designed computers, information is encoded in temporal strings, even spatial information (e.g. images).
- In biological “computing”, space (like noise) is not necessarily treated as a liability.
Copying maggots

Maternal morphogen gradients
e.g. nanos, bicoid

Gap genes
e.g. Kruppel

Pair-rule genes
e.g. even-skipped

Segment polarity genes
e.g. engrailed, wingless

Hox genes
e.g. Ultrabithorax, abdominal A

Fruitfly embryos
Copying maggots

• Spatial pattern emerges out of an interaction between spatially non-uniform initial conditions, gene-regulatory networks, and physical laws of molecular transport through space.

Fruitfly embryos
Morphogens specify pattern at a distance
Morphogens specify pattern at a distance

TGFβs, Wnts, Hhs, EGFs, FGFs, retinoids

Gene expression
Fundamentally, morphogens are strategies for getting cells to cooperate over distances

- Information is transported by molecular diffusion (not targeted)
- Transport is affected by the cells around which the morphogen passes (cells take up and destroy morphogen in a regulatable fashion)
- Enormous opportunity for feedback control of transport arise
Emergent properties can appear as a result of feedback.
Features of cellular stochasticity can also be extracted from spatial noise.

Input morphogen gradient

“Perceived” by cells
Biology and the Spatial World

• Spatial inhomogeneity, regulated transport, and cell-neighbor interactions are intimately connected with biological sensing, responding, replicating and storing of information.
Biology and the “highly-optimized” world

• When we say an organism is adapted to its environment, what we mean is it has been optimized over some function of a huge number of performance objectives.

• Engineers know that optimizing over many objectives at once is inherently difficult due to inevitable tradeoffs
Highly optimized tolerance (HOT)  
Carlson, Doyle, et al.

• Optimizing for many performance objectives at the same time necessitates complexity of design
• Fragility to unplanned-for events is unavoidable.
Are there rules underlying HOT?

• Are there strategies for combining strategies?
• If there are, biology is surely the place to look for them.
Summary

• Biology inhabits the nano-world, the spatial world, and the highly-optimized world, and manages to communicate and compute quite well!

• Key to the success of biology is its ability to take advantage of noise, space, and tradeoffs, rather than treat them as liabilities.

Can we learn from what biology is telling us?