Systems biology and evolution

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Definition (1)

- why “systems biology”?
- doesn't all biology study “systems”?
  - cell
  - tissue
  - organ
  - organism
  - ecosystem
- “systems biology” in practice focuses on the cell

Definition (2)

- “structure and dynamics of cellular and organismal function” (Kitano 2002)
- “studies biological systems by systematically perturbing them ... integrating ... data .. formulating mathematical models” (Ideker, Galitski & Hood 2001)

Definition (3):

- quantitative study of cellular processes:
  - measuring interactions (data)
  - building models (theory)
- kinds of networks
  - gene networks (e.g., sea squirt mesoderm development)
  - metabolic networks (cellular respiration)
  - signal transduction (e.g., cascade of events triggered by external hormone)

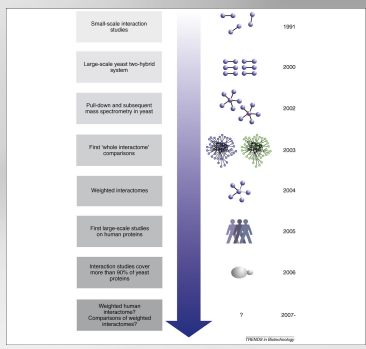
Goal:

- What are the molecules involved
- Which molecules interact with which
- How interactions lead to cell function
- Spatial-temporal organization
- Analyze cell response to perturbation
- Modeling for hypothesis testing
- General principles that apply across many taxa

History: molecular biology

- sequencing projects (late 1980s)
  - genomics (mid-late 1990s)
  - proteomics late (1990s-early 2000s)
  - “interactomics” (early-mid 2000s) which is characterizing how elements interact (normally proteins)
- focus on high-throughput data generation
- Shifted focus from molecules to networks

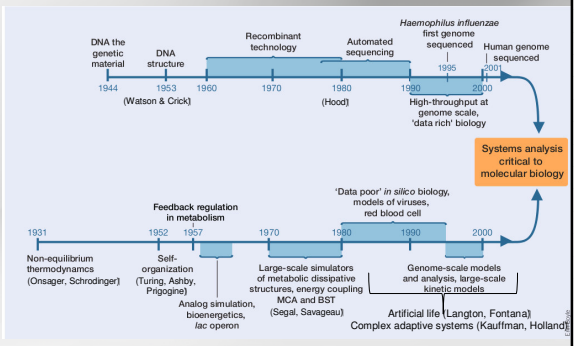
Example "-omics": protein "interactomics"



History: other disciplines

- Development of techniques from
  - mathematics (non-linear dynamics 1970-80s)
  - statistics (Bayesian 1990s)
  - engineering (control theory, metabolic engineering)
  - physics (enzyme kinetics)
- Cultural cross-talk between mathematicians & biologists has increased

History: other branches



History: systems tradition

- non-equilibrium thermodynamics
- self-organization
- 1960s systems theory
- 1980s genetic and biochemical systems, more abstract:
  - e.g. biochemical systems theory (BST), metabolic control analysis (MCA)
- late 1980s – present
  - artificial life (cellular automata)
  - complex adaptive systems (NK-landscapes, emergence)

Molecular biology vs. systems biology

- Molecular biology: how molecules work one by one
- Systems biology: predicts consequences of networks for the cell as a whole
- DNA + protein structure does not equalsystems biology

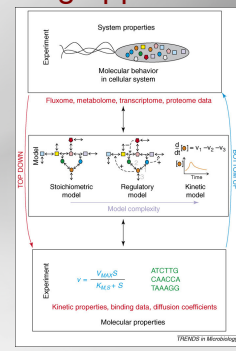
Top-down modeling:

- measures of genome-wide experimental data (microarrays)
- aims to reconstruct networks using data mining/statistical inference
  - e.g. correlation of gene expression in microarray to find gene network
- mostly phenomenological
  - mechanism of regulation is not specified

Bottom-up modeling

- mechanistic-oriented
- model formulates the interactions between the components
- dynamic modeling (includes time)
  - deterministic (e.g. metabolism has large # of molecules)
  - stochastic (e.g. transcription involves small # molecules)
- typically simulation-based
- mostly data-poor:
  - kinetic for in vivo are hard to measure

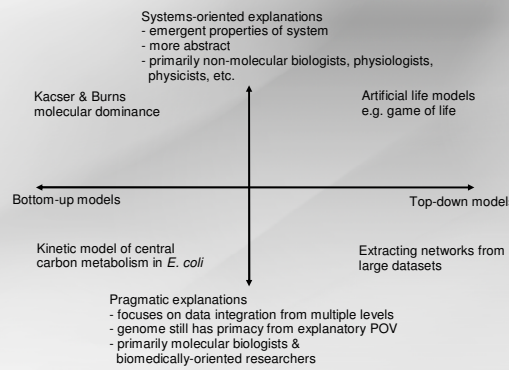
Modeling approaches (2)



Cautionary notes:

- "top-down": not able to get to molecular level
- "bottom-up": proof of principle is not enough, need to show it occurs in nature

Modes of explanation



Systems biology & evolutionary biology

- Is a network/system biology approach useful or necessary in evolutionary biology?
- Wilkins (2007) argues that it is useful based on:
  - network properties constrain paths evolution can take
  - single gene approaches

Is evolution "design" or "bricolage"?

- Biologists must explain how species are so well designed for specific tasks without an omnipotent Designer.
- In fact, many organisms well "designed" for one task may be suboptimal for others.
- "Tradeoffs"

Is evolution "design" or "bricolage"?

- "Bricolage" may connote a haphazard throwing together of things.
- A better metaphor may be "tinkering".

How does network constrain paths of evolution?

- Two kinds of general constraint must operate
  - Set of preexisting conditions of the recruited molecule, permitting its adoption for new roles
    - Eg. A transcription factor must have properties not shared with other TFs.

How does network constrain paths of evolution?

- Recruited gene must already be expressed in site where new function already takes place.
  - Or mutation must be one that prompts *de novo* expression of recruited TF, for new use
  - In this case additional mutations could be needed to optimize expression or function of recruited molecule
  - No evidence of this as of yet.

How does recruitment occur?

- We often think of this process as a gene at time
- In fact, it may often be a module at a time.
  - E.g. *Six-Dacha-eya* functional ensemble of TF in fruit flies.

Combination of modules used that determines the composition of an entire gene network governing a trait.

Questions and Discussions