Systems Biology: Dynamics

Systems Biology

- Wolkenhauer’s definition of systems biology:
  - “Systems biology is the science that studies how biological function emerges from the interactions between the components of living systems and how these emergent properties enable and constrain the behavior of those components.”
  - “Systems biology is thus an approach to understanding complex, i.e., non-linear spatio-temporal phenomena, across multiple levels of structural and functional organization.”
- Where does computational modeling fit into this understanding of systems biology?

Clicker Question

Which of the following does not count as a model for Wolkenhauer?

A computational model
A mechanism diagram
An experimental system
A physical model

Why do (Computational) Modeling

- "all alternatives for understanding the system involve creating a model of some sort. We cannot understand complex systems without modeling. For example, even a diagram that identifies the components of a system (e.g., a network or pathway) and has arrows to indicate interactions between them is a conceptual model. For complex systems, new understanding about how the system might work is generated by transforming one reality into another."
- Computational models belong to a broader category of models
  - diagrams
  - physical models
  - computational models

Clicker Question

What is the point of computational modeling for Wolkenhauer?

A good computational model is the ultimate objective of inquiry

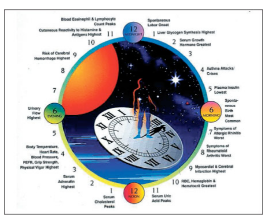
A computational model can confirm the mechanistic hypotheses experimentalists construct

A computation model can help guide further experimentation

There is no point to it—it is a worthless pursuit

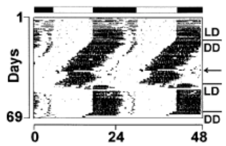
Dynamical Phenomenon: Circadian Rhythms

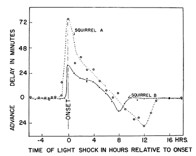
- Many physiological processes and behaviors of a very large percentage of organisms on earth are regulated by circadian rhythms
  - Endogenously generated oscillations with a period of approximately 24-hours
  - Entrainable to the local light-dark regime by a variety of Zeitgebers
  - Temperature compensated



Representing Dynamic Phenomena

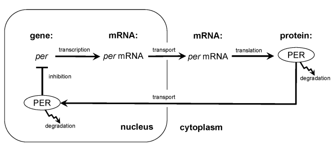
- Although at a global level we may speak of the phenomenon of circadian rhythmicity, much scientific research is directed at establishing and explaining far more specific phenomena
  - After establishing that circadian rhythms are endogenously generated, much research was devoted to how they are entrained
  - Researchers presented light pulse at different times and observed how they advanced or delayed the phase of rhythms





Constructing and Mentally Animating Diagrams

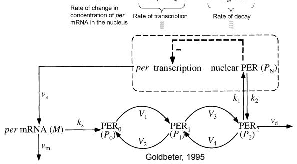
- In the period 1970-1990 the first clock gene, per and the first account of the clock mechanism were put forward:
  - *per* is transcribed into mRNA, which is translated into PER
  - PER returns to the nucleus and inhibits its own transcription
    - When operations are feedforward and linear, one can mentally step through the operations to show how the effect is produced
    - Even with a single feedback loop, one can still mentally rehearse the operations



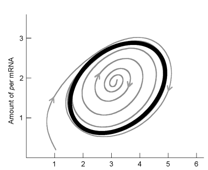
From Mental Animations to Computational Models

- While mental rehearsal could reveal that the mechanism would oscillate
  - it could not demonstrate that it would produce sustained oscillations
- Goldbeter (1995) developed a computational model demonstrating that with appropriate parameters, this type of mechanism would generate sustained oscillations (e.g., generate a limit cycle)

(Eq.1) $$\underbrace{\frac{dM}{dt}}_{\text{Rate of change in concentration of } per \text{ mRNA in the nucleus}} = \underbrace{v_s \frac{K_I^n}{K_I^n + P_N^n}}_{\text{Rate of transcription}} - \underbrace{v_m \frac{M}{K_m + M}}_{\text{Rate of decay}}$$

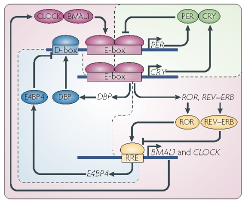


Goldbeter, 1995



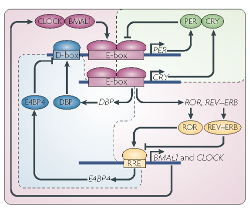
More Complicated and Complex Mechanisms

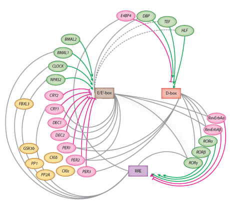
- No sooner than the original model was advanced, then researchers started identifying many more parts
  - The model was getting complicated
- These parts fit into multiple feedback loops, making the model
  - more complex
  - perhaps more complex
- One modeling strategy:
  - Add more and more differential equations to describe each operation
  - Run the simulation to show it would generate oscillations
  - What function does such a model play?
    - Show that the proposed mechanism *could* generate the phenomenon



Alternative: Abstract/Simplify to Find Basic Principles

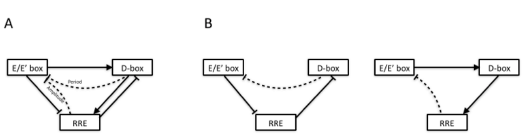
- In an attempt to explain why such a mechanism would generate endogenous rhythms, Ueda re-represented the mechanism by making
  - the promoter boxes central
  - collapsing the distinction between genes and proteins





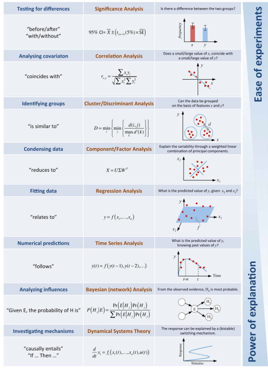
Abstracting Further

- Ueda then replaced all connections from one promoter via a gene/protein to another promoter with an arrow or an end-edged line (repressor) between the promoters
- He then decomposed the result into two motifs, both known to generate sustained oscillations
  - a repressilator
  - a delayed negative feedback loop



Using Mathematics to Understand Biology

- Tests of causation
  - Significance testing
  - Correlation analysis
  - Regression analysis
- Analyzing mechanisms
  - Time series equations
  - Bayesian networks
  - Differential equation models



Interaction Between Modeling and (Mechanistic) Experimentation

- As Wolkenhauer discusses them, models start with experimental results
- The models represent the proposed mechanisms in mathematical form that allow one to make predictions
  - Often used in simulations that step through the operations proposed in a mechanistic account
- They can help establish that the mechanism could produce the phenomenon
  - They can also guide new experimentation either
    - When they go beyond the known mechanism and propose additions
    - When they fail, and require a search for more components

Clicker Question

What do Green et al. mean by (neo-)rationalist approaches?

Approaches that appeal to universal organizing laws in explaining biological phenomena

Another name for mechanistic approaches

Approaches that seek to identify the specific selections factors that figure in the evolution of organisms

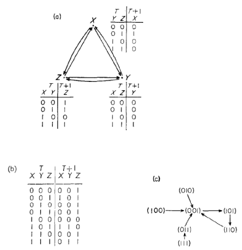
Approaches that use complex statistical measures to predict the features of living organisms

Alternative Strategies for Understanding Evolution: Rationalist vs. Darwinian

- Rational morphology: emphasize the principles of organism organization that, for example, explain their stability
  - How the parts of the organism support each other and compensate for local failures
- Darwinism: put the emphasis on explaining the adaptedness of traits as products of a specific history of variation and selective retention

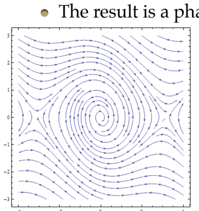
Systems Resilient To Change

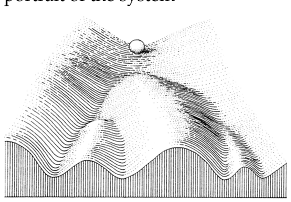
- Kauffman developed a simple Boolean network model of a gene network
  - Each node updates according to a simple rule
- One can calculate for each starting configuration how the network will evolve
  - One cyclic attractor
    - Once the system enters the attractor, it cannot escape
      - it is stable



Phase Portraits

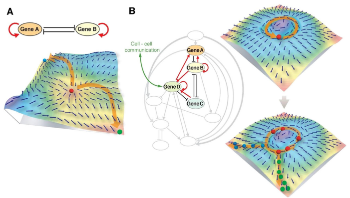
- State space: multidimensional space (one dimension for each variable)
  - Each possible state of the system is identified by a point
  - From each point there is a trajectory to another point
  - One can identify attractors and their basins
  - The result is a phase portrait of the system





Phase Portrait of Gene Regulatory Networks

- Stem cells: poised to divide into more stem cells or into specialized cells
- Theorists proposed a double negative feedback model, each node self-activating but inhibiting the other
  - Two attractors, each with a basin of attraction
  - Represent different cell types



Does Such a Model Explain?

- "DS theorists claim that such simple network models **explain** a number of characteristic features of stem cells: wide differentiation potential, low levels of "promiscuous" gene expression, the balance of differentiation and self-renewal that maintains a stem cell population, and the transition between stem cells and cells "committed" to a particular pathway. In this framework, these features are understood by virtue of being reproduced (or "recapitulated") by a simple model, the network circuit." (Green et al., 2014)

Explanation From First Principles

- "Whatever stem cells do, the fundamental laws governing the underlying regulatory systems must be obeyed. These, in turn, impose constraints on cell behaviour that cannot be conceived in the ad hoc schemes of causal arrows or through metaphors, for the latter are malleable and not anchored in mathematical principles. In contrast, if explanations are rooted in a set of first principles, then the very exis- tence of particular stem cell behaviours, such as the robustness of multi-potency and its destabilization preceding cell-fated decisions, the binary nature of the latter, etc., will follow as inevitable, necessary consequence from the mathematics and physics of gene-regulatory networks." (Huang 2011, p. 2249)

Mechanists and Dynamicists Don’t Play Well Together

- Competing accounts of explanations
  - Mechanistic explanations emphasize the actual parts, the operations they perform, and how they are organized
  - Dynamicists emphasize general principles from which one can derive what will happen under specific (initial) conditions

Neo-Rationalists vs. Neo-Darwinists Revisited

- Green et al. identify the same divide between neo-rationalists and neo-Darwinists:
  - “For the neo-rationalist, the primary aim is to identify general organizational principles that define possible and non-possible forms, while neo-Darwinians aim to identify genetic mechanisms to account for heredity of specific traits”

Forward Modeling vs. Reverse Engineering

- Forward modeling
  - Start with detailed measurements of system variables over time (time-series) and discover parameters
  - Develop computational models to capture this data using these parameters
    - Complaint: such models are difficult to generalize
- Reverse engineering
  - Emphasize coarse-grained models constructed without knowing specific parameter values
  - Test these model by the results derived from them (and revise when they give erroneous results)

Clicker Question

What is meant by a *how-possibly* model?

- An organism that is engineered to have traits different than those of naturally occurring organisms
- A hypothesized model that is not intended to describe how things happen in this world, but only in a world that might exist
- A hypothesized model that offers an account of what might explain what happens in this world
- A dynamical model for which we do not know how to solve the equations

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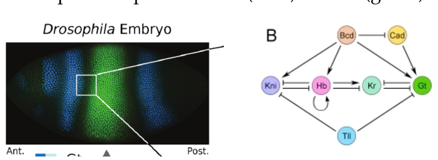
How-possibly vs. How-actually Models

- Some mechanists criticize mathematical models, especially those offered by dynamical systems theorists, as *how-possibly models*
  - The idea is that they sketch one way a process might be brought about, but because they are not grounded in the actual parts and operations of a mechanism, they don't really explain
  - Explanation requires a *how-actually model*—an account in terms of the parts, operations, and organization of a mechanism

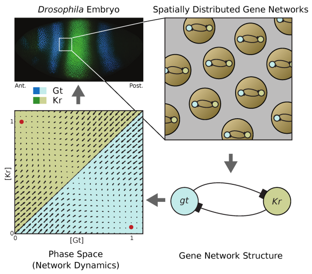
Example: Modeling Drosophila gap gene systems

- In developing fruit flies, gap genes are regulated by protein concentrations controlled by the mother
- There are differential concentrations of these proteins along the anterior-posterior axis of the embryo, which cause expression of different gap genes, which serve as transcription factors controlling other genes
  - Expression pattern of Gt (blue) and Kr (green)



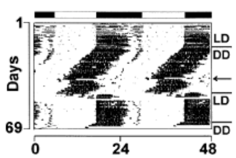
Develop a Phase Portrait of the Interaction of Gt and Kr

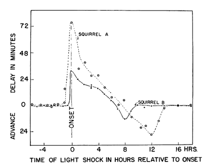
- The genes Gt and Kr each inhibit the other (double negative feedback loop motif)
- Plot the behavior of that interaction in phase space
  - System of two attractors
  - Whichever gene begins with greater expression it will push the system to its attractor



Another Circadian Example

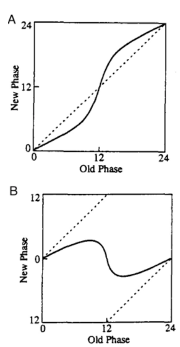
- In addition to maintaining 24-hour oscillations, an important feature of circadian rhythms is that they can be entrained to time cues (Zeitbebers) such as light
- Light at different times of day has different effects on the core clock
  - During expected daytime it does nothing
  - Just before expected dawn it advances the clock
  - Just after expected sunset in retards the clock





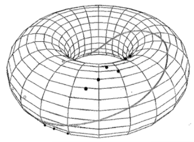
Type 1 vs. Type 0 Entrainment

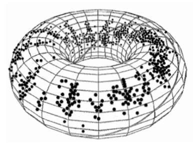
- Entrainment experiments revealed two different patterns of entrainment, which appear very different in phase transition curves (PTCs: plot the new phase in terms of the old phase at which the stimulus was presented)
  - Type 1: The new phase = old phase plus some variability (slope ≈ 1)
  - Type 0: The new phase is largely independent of the old phase at which the stimulus was presented (slope ≈ 0)



No Continuous Transition Between the Two Types of Entrainment

- Winfree (1970) determined that both types of entrainment can occur in the same organism (depending on the strength of the light stimulus or its duration)
  - But he also recognized that there cannot be a continuous transition from one to the other
- Geometric demonstration: Roll the PTC into a torus
  - Type 1 Entrainment passes through the center
  - Type 2 Entrainment does no
  - Without breaking the trajectory, cannot change one into the other



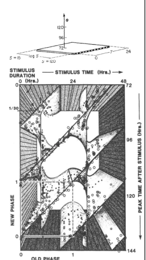


There Must Be a Singularity

- From this result, Winfree inferred that there has to be a singularity: a point in phase space corresponding to the abrupt transition from Type 1 to Type 0 entrainment
  - The singularity is a point at which one cannot infer, by extending the patterns observed elsewhere, what will happen
- Winfree not only predicted the singularity, but can be viewed as explaining its existence
  - His geometric argument demonstrates that there is no possibility of a continuous transition in any system exhibiting both types of entrainment

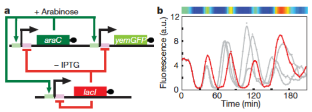
Investigating the Singularity Empirically

- From the demonstration that a singularity had to exist, Winfree could not determine what would happen at it
  - This required experimentation
- By plotting the phase change at each of many points in phase space, Winfree located the singularity
- When he presented a stimulus corresponding to the singularity, he discovered that the clock stopped
- While Winfree could not explain why the clock stopped, he had explained why there had to be a singularity



Synthetic Biology: From Computational Models Back to Biology

- The best way to show that you understand a complex system is that you can build it
- Hasty and his colleagues at UCSD set out to build a synthetic oscillator—inserting genes into *E. coli* according to a design for an oscillator
  - In their computational model, oscillation was sensitive to parameter values
  - The synthesized mechanism generated oscillations under a broad range of parameter values



From Synthesized Organism Back to a Computational Model

- In the attempt to understand why the synthesized organism produced robust oscillations, Hasty and his collaborators looked to other parts of the mechanism they had not modeled
- When they added these components to the model, the oscillations became robust
- One computational model guided the construction
  - but another was required to explain it