Phenomenology and Biology

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Theory: Alex Lang, Javad Noorbakhsh, David Schwab

Experiments: Allyson Sgró, Thomas Gregor
The rapid rise of quantitative biology

**DATA EXPLOSION**

The amount of genetic sequencing data stored at the European Bioinformatics Institute takes less than a year to double in size.

Sequencers begin giving flurries of data

**Quantity**

**Quality**

Campas et al. Nature Methods 2014

New types of data
Bridging physics and biology

Q: How does a physicist milk a cow?
A: Well, first let us consider a spherical cow...

“All science is either physics or stamp collecting”-Ernest Rutherford

Genes, proteins, interactions, etc.
Unifying data with phenomenology

Phenomenological models can, and should, play a fundamental role in furthering our understanding of biological systems.

Generally accepted in terms of mechanical properties in biology

Extend to the realm of molecular biology, signaling networks, genetic networks
Example 1: Cellular Reprogramming

a) iPSC reprogramming and differentiation

- Fibroblast → KOSM (2–3 weeks) → iPSC → Conditioned medium → Desired cell type

b) Incomplete reprogramming and differentiation

- Fibroblast → KOSM (~1 week) → Unstable pluripotent state → Conditioned medium → Desired cell type

c) Direct conversion

- Fibroblast → Lineage-specific factors (1–3 weeks) → Desired cell type
An obtuse mathematical formulation

Effect of culture

\[ H = -\frac{N}{2} \sum_{\mu} a_{\mu} m^{\mu} + \sum_{\mu} a_{\mu} B^{\mu} + \sum_{\alpha \beta} G_{\alpha \beta} (\tilde{c}) S_i \xi_i^\alpha \]

\[ m^{\mu} = \frac{1}{N} \sum \xi_i^{\mu} S_i \]

Energy of gene expression state proportional to square of orthogonal distance to plane spanned by \textit{in vivo} cell types

(Details of mathematical construction in Lang et al PLoS Comp Bio 2014)
A simple reaction coordinate for reprogramming
Results VI: The "inverted funnel"

Number = Time in Days

Rais 2013
Polo 2012
Samavarchi 2010
Example 2: Collective behavior in *Dictyostelium*

Signaling through cyclic AMP (cAMP) and spiral formation

Example 2: Collective behavior in *Dictyostelium*
Collective behavior in *Dictyostelium*
Underlying networks are complicated
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BUT … network behavior undergoes bifurcation to oscillations
Cells lie near bifurcation

BUT ... network behavior undergoes bifurcation to oscillations
Inspirations from physics

concept of “universality” in statistical mechanics & dynamical systems

Systems with many interacting parts – collective properties often independent of many details

Near phase transitions or “bifurcation points” in dynamical system, only a few qualitative behaviors are possible.
Simple Universality-based Model

Universality Class: **Hopf Bifurcation** (many possible models but is excitable)

Simple two-dimensional model  (Fitz-Hugh Nagumo model)

\[
\frac{dA_i}{dt} = A_i - \frac{A_i^3}{3} - R_i + I(cAMP) + \sigma_i \eta
\]

\[
\frac{dR_i}{dt} = \epsilon_i (A_i - \gamma R_i + C)
\]

\[
I(S) = a \log \left( \frac{S}{K} + 1 \right)
\]

External cAMP plays the role of a bifurcation parameter
Fitz-Hugh Nagumo Model

Single spike in response to small steps
Tests of the single-cell model I

Spike for step but not for ramp

Oscillations for large enough ramp
Tests of the model II
Tests of the model III
Other Models of Dictyostelium


S.Han, Comp. Bio. And Chem. (2007)


Kessler Levine (1993)

Sawai and Cox (2005)
Back to molecules: origin of transients

Dominant paradigm employs feedforward excitation (fast) and inhibition (slow)

(a) 

Exitation

Signal 

Response

Inhibition

(b) 

Iglesias, Devreotes

Large transient response due to incoherent feedforward structure

Excitable system: Large transient response due to proximity to oscillations

Cannot oscillate without feedback
Modeling homogenous populations

- Single Cells
  - External signal
  - NETWORK

- Homogenous populations
  - Collective oscillations

- Spatially-structured populations
  - Chemotaxis/Aggregation Pattern formation

INCREASING COMPLEXITY
Overview of Experimental Set-up

Gregor, 2010
Multicellular Model

Logarithmic Input

Fitzhugh-Nagumo Model

Noise

Spike-Driven Secretion

Constant cAMP Secretion

\[
\begin{align*}
\frac{dA_i}{dt} &= A_i - \frac{1}{3}A_i^3 - R_i + a \log \left(1 + \frac{S}{K}\right) + \eta_i(t), \quad i = \{1, 2, 3, \ldots, N\} \\
\frac{dR_i}{dt} &= \epsilon (A_i - \gamma R_i + C) \\
\frac{dS}{dt} &= \alpha_f + \rho \alpha_0 + \rho D \frac{1}{N} \sum_{i=1}^{N} \Theta(A_i) - JS,
\end{align*}
\]
Density-dependent “Dynamical Quorum-Sensing” Transition
Phase Diagram

A

With noise + Logarithmic sensing

B

Without noise
Spatially Extended Multicellular Model

\[
\frac{dA}{dt} = A - \frac{1}{3} A^3 - R + I(S),
\]

\[
\frac{dR}{dt} = \epsilon (A - \gamma R + C)
\]

\[
\frac{dS}{dt} = \rho \alpha_0 + \rho D \Theta(A) - JS + \nabla^2 S
\]
Loss of Spirals

Model Conclusion

Single Cell

Step/Ramp Input (subthreshold)

Step/Ramp Input (suprathreshold)

Accommodation Spike Width

Oscillation Period

Entrainment
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