Mathematical models of gene regulation: Biology drives new mathematics

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Statistical Physics of Complex Systems
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"Schrödinger: Life and Thought", Walter Moore
WHAT IS LIFE?

The Physical Aspect of the Living Cell

BY

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Based on Lectures delivered under the auspices of the Institute at Trinity College, Dublin, in February 1943.

- Timofeeff-Ressovsky: describes the mutagenic effects of x-rays and gamma rays on *Drosophila melanogaster*
- Zimmer: analyzes Timofeeff-Ressovsky’s results theoretically
- Delbruck: puts forth a model of genetic mutation based on atomic physics
- Their conclusion: a mutation is a molecular rearrangement within a particular molecule, and the gene a union of atoms in which a mutation can occur
Schrödinger’s recruits

A most impressive list of molecular biologists

- Seymour Benzer
- Francis Crick
- Walter Gilbert
- Leo Szilard
- James D. Watson— the only ‘real’ biologist
- Maurice Wilkins
The operon concept

Two basic motifs
- Inducible—the lac (lactose) operon (positive feedback)
- Repressible—the trp (tryptophan) operon (negative feedback)

Early mathematical modeling: Totally deterministic

Later embellishments
- Delays from transcription and/or translation

Poorly charted territory: New mathematics
- State dependent transcriptional/translational delays
- Stochastic effects
  - Bursting production of mRNA and protein
  - Stochastic delays
The Operon Concept

The key paper (lactose operon)
Jacob, Perrin, Sanchez, Monod: (1960) C. R. Acad. Sci. 250, 1727-29

lac I Promoter O lac Z lac Y lac A

DNA
Transcription
mRNA
Translation

R.A^n → R

B P LT
The feedback nature of the lactose (lac) operon
Essential reading: Early models

- Tyson & Othmer: (1978) Prog. Biophy. 5, 1. Early and still valuable modeling review/summary
Simple Model Equations

The players

- $M =$ mRNA: $\bar{b}_d =$ transcription level; $\bar{\varphi}_m =$ transcription rate
- $I =$ intermediate (protein): $\beta_I =$ prod rate; $\gamma_I =$ destruct rate
- $E =$ effector: $\beta_E =$ prod rate; $\gamma_E =$ destruct rate

The equations

$$\frac{dM}{dt} = \bar{b}_d \bar{\varphi}_m f(E) - \gamma_M M$$
$$\frac{dI}{dt} = \beta_I M - \gamma_I I$$
$$\frac{dE}{dt} = \beta_E I - \gamma_E E$$

Feedback

$f(E)$: inducible (positive) or repressible (negative) feedback
Inducible operon: $f(E)$ is monotone increasing

$$f(E) = \frac{1 + K_1 E^n}{K + K_1 E^n}$$
The bistability data

Source: Gardiner, Cantor, & Collins: Nature, 2000
Repressible operon: $f(E)$ is monotone decreasing

\[ f(E) = \frac{1 + K_1 E^n}{1 + K E^n} \]
Repressible operon model behaviours

There is a single steady state that is either

- Globally stable, or
- Unstable and replaced with a globally stable limit cycle

Embellishments: Delays in transcription/translation

The equations are altered

\[
\frac{dM}{dt} = \bar{b}_d \bar{\varphi}_m f(e^{-\mu \tau_M} E_{\tau_M}) - (\gamma_M + \mu) M
\]

\[
\frac{dl}{dt} = \beta_I e^{-\mu \tau_I} M_{\tau_I} - (\gamma_I + \mu) I
\]

\[
\frac{dE}{dt} = \beta_E I - (\gamma_E + \mu) E
\]

The new players

- \(\tau_M(\tau_I)\): transcription (translation) delays; \(\mu\) is cell growth rate
- \(E_{\tau_M}(t) \equiv E(t - \tau_M)\) and \(M_{\tau_I}(t) \equiv M(t - \tau_I)\)

The effects

- Delays in inducible operons do not affect qualitative dynamics
- Delays in repressible operons can dramatically affect dynamics
New aspects fall into two broad categories:

State dependent delays

Stochastic effects

As well: How to describe populations in which both are present
State dependent delays

Biologically we expect that

- Rate of DNA transcription (to produce mRNA) and/or mRNA translation (to produce protein) can depend on the level of intermediates and/or effectors
- Implication: there are state dependent delays in gene regulation

So this leads to

- Question: “How do these behave based on experimental observation?”
- This is a totally unexplored area of gene regulation dynamics
- Virtually nothing is known about the effects of state dependent delays on dynamics
- Or the effects on function!
The delays (transcriptional as well as translational) should be:

- Increasing functions of concentrations for inducible operons
- Decreasing functions of concentrations for repressible operons

We have found a variety of new behaviours:

- Multiple bifurcations for inducible operons including Hopf bifurcations (totally new and unexpected) as well as
- Multiple bifurcations for repressible operons including multiple locally stable steady states (again, totally new and unexpected)

We are still in the process of exploring and untangling these behaviours to characterize what is going on.
So called extrinsic noise is just the typical noise studied by physicists and mathematicians. It is there because of fluctuations in the number of particles and typically the amplitude scales as

\[ \frac{1}{\sqrt{\text{Number of particles}}} \]

There has been a great deal of (rather silly) debate in the biology literature about ‘extrinsic’ versus ‘intrinsic’ noise that has generated more smoke/heat than light.
Stochastic aspects: ‘Extrinsic’ noise

Example of ‘extrinsic’ noise in effector degradation rate

- **Stochastic equation**

  \[
  dE(t) = \gamma [\kappa_d f(E) - E] + \sigma \sqrt{E} \, dw(t)
  \]

  \(w(t)\) is a standard Wiener process (delta correlated, Gaussian distributed)

- **The corresponding Fokker-Planck equation is**

  \[
  \frac{\partial P(E, t)}{\partial t} = -\frac{\partial (E - \gamma \kappa_d f(E))P(E, t))}{\partial E} + \frac{\sigma^2}{2} \frac{\partial^2 (EP(E, t))}{\partial E^2}
  \]

- **Fokker-Planck equation stationary solution for the density is**

  \[
  P_\star(E) = \frac{C}{E} e^{-2\gamma E/\sigma^2} \exp \left[ \frac{2\gamma \kappa_d}{\sigma^2} \int_{-\infty}^{E} \frac{f(y)}{y} \, dy \right]
  \]

Stochastic aspects: ‘Intrinsic’ noise

‘Intrinsic’ noise from bursting production of mRNA and protein

Protein degradation is interrupted at random times to produce random amounts of protein distributed with density

\[ h(E) = \frac{1}{b} e^{-E/b} \]

\( E(t) \) is a solution of the stochastic equation

\[ \frac{dE}{dt} = -\gamma E + \Xi(h, \varphi(E)) \]

\( \Xi(h, \varphi) \) is a jump Markov process, occurring at a rate \( \varphi \), whose amplitude is distributed with density \( h \)
Stochastic aspects: Intrinsic noise

Fokker-Planck like equation

\[
\frac{\partial P(E, t)}{\partial t} - \gamma \frac{\partial (EP(E, t))}{\partial E} = -\varphi(E)P(E, t) \\
+ \int_0^E \varphi(y)P(y, t)h(E - y)dy.
\]

Stationary solution

\[
P_*(E) = \frac{C}{E} e^{-E/b} \exp \left[ \int_0^E \frac{\varphi(y)}{\gamma y} dy \right]
\]

NB Identical in form to the stationary solution for extrinsic noise!
Can’t distinguish between noise sources based on stationary protein distribution
Fokker-Planck like equation pretty much as you would expect: A sum of those from the extrinsic and intrinsic cases.

We know that under very mild conditions the stationary density exists, is unique, and is asymptotically stable (i.e. all system preparations will converge to it).

But we have been unable to obtain an analytic solution in any but the most elementary situations.

This leads us to consider stochastic bifurcations.

- Only rudimentary results in a virgin field.
Molecular biology, like many of the other biological sciences, owes its development and form to physicists and mathematicians.

Mathematical modeling of gene regulation has played an important role in our understanding of dynamics at the molecular level.

The experimental demonstration of unknown aspects of gene regulation highlights new and unexplored areas of mathematics that have yet to be clearly defined and developed:

- State dependent delays: Much to be done here
- The role of both extrinsic and intrinsic noise in gene dynamics in shaping gene responses to the environment: In need of a coherent treatment
- How can we describe populations in which there are both delays and stochasticity, i.e. how to derive Fokker-Planck like equations?
Further details to be found in

Lecture Notes on Mathematical Modelling in the Life Sciences
Michael C. Mackey
Moisés Santillán
Marta Tyran-Kamińska
Eduardo S. Zeron

Simple Mathematical Models of Gene Regulatory Dynamics
In conclusion

- Thank you for the invitation to speak
- The NSERC of Canada for their financial support as well as
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- And a very special thank you to the organizing committee for a job well done!