lecture 1
the role of mathematics in biology

jeremy gunawardena

department of systems biology
harvard medical school
200 longwood avenue
boston, ma 02115

jeremy@hms.harvard.edu
http://vcp.med.harvard.edu/

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0. what is systems biology?
“X-omics”

it is about using high-throughput technologies to acquire data on all X molecules and using computational algorithms to infer causality from correlation

“modelling”

it is about constructing mathematical models of biological systems so that biology becomes a predictive science like physics and engineering
but what are the questions

to which “omics” and “modelling” seek the answers?

systems biology

how do we get from dead molecules to living organisms?

how do the collective interactions of molecular components give rise to the phenotype of the organism?

1. The role of mathematics in biology has been a source of confusion.
what the biologists say

Chapter 5 – Diseases of the Will


Santiago Ramon y Cajal,
Advice for a Young Investigator,
MIT Press, 1999 (first published 1897)

“If ... you are a bit short in mathematical training, even very short, relax. You are far from alone ... many of the most successful scientists in the world today are mathematically no more than semiliterate.”

Edward Wilson
Letters to a Young Scientist
W W Norton, 2013

“I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics ... for men thus endowed seem to have an extra sense.”

Charles Darwin, Autobiography
W W Norton, 1958 (written in 1876)
what the mathematicians say

“The lack of real contact between mathematics and biology is either a tragedy, a scandal, or a challenge, it is hard to decide which.”


“Eugene Wigner wrote a famous essay on the unreasonable effectiveness of mathematics in natural sciences. He meant physics, of course. There is only one thing which is more unreasonable than the unreasonable effectiveness of mathematics in physics, and this is the unreasonable ineffectiveness of mathematics in biology.”

a revisionist view

- Jacques Monod: molecular biology
- James Till: stem cells
- Andrew Huxley: neuroscience
- Arthur Guyton: physiology
- Niels Jerne: immunology
- Sewall Wright: evolutionary genetics
- Rosalyn Yalow: immunoassays
- Conrad Waddington: developmental biology
- Otto Warburg: biochemistry
- Ronald Ross: epidemiology
- James Black: pharmacology

use of mathematics (a.u.)

- textbook average
- the good stuff
2. learning from an example
the michaelis-menten formula

\[
\frac{d[P]}{dt} = \frac{V_{max} [S]}{K_M + [S]}
\]


data do not support direct conversion

\[ \frac{d[P]}{dt} = \alpha[S] \]

**mass action**

**michaelis-menten data**

- Initial rate, \( \frac{dP}{dt} \) (t=0)
- Initial substrate concentration, \([S](0)\)

Graph showing the relationship between initial substrate concentration and initial rate, with data points plotted on a line.
the enzyme-substrate complex

\[ E + S \rightleftharpoons ES \rightarrow E + P \]

\[ \frac{d[P]}{dt} = \frac{V_{\text{max}}[S]}{K_M + [S]} \]

initial rate, \( \frac{dP}{dt} (t=0) \) vs. initial substrate concentration, \([S](0)\)
michaelis and menten did not identify the enzyme-substrate complex.

it was a hypothetical concept which, if it existed, could explain a great deal of experimental data (with the help of mathematics).
which remained theoretical for 30 years

\[
\text{Peroxidase} + \text{H}_2\text{O}_2 \xrightleftharpoons[k_2]{k_1} \text{peroxidase} \cdot \text{H}_2\text{O}_2
\]

“The reaction velocity constants are, however, lumped into one term, the Michaelis constant, and are not separately determined. It is the purpose of this research to determine these constants separately, and to show whether the Michaelis theory is an adequate explanation of enzyme mechanism. Moreover, studies on the over-all enzyme activity do not permit a determination of whether the enzyme-substrate compound exists in fact and, if it exists, whether such a compound is responsible for the enzyme activity”

\[k_1 = 1.2 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1}\quad k_2 = 0.2 \text{ sec}^{-1}\]

mathematics provides evidence for things unseen

“ion channels”

1952

1970

1976

“genes”

1866

1915

1953
Biology is more theoretical than physics

Jeremy Gunawardena
Department of Systems Biology, Harvard Medical School, Boston, MA 02115

ABSTRACT The word “theory” is used in at least two senses—to denote a body of widely accepted laws or principles, as in “Darwinian theory” or “quantum theory,” and to suggest a speculative hypothesis, often relying on mathematical analysis, that has not been experimentally confirmed. It is often said that there is no place for the second kind of theory in biology and that biology is not theoretical but based on interpretation of data. Here, ideas from a previous essay are expanded upon to suggest, to the contrary, that the second kind of theory has always played a critical role and that biology, therefore, is a good deal more theoretical than physics.

Mol Biol Cell, 24:1827-9, 2013
models are not descriptions of reality

michaelis & menten's data was so convincing because they used an acetate buffer to control pH (*)

![Graph showing initial rate vs. initial substrate concentration](image)

but ... there is no pH dependence in their mathematical model

\[
\frac{d[P]}{dt} = \frac{V_{\text{max}}[S]}{K_M + [S]}
\]

they describe our assumptions about reality

**REVIEW**

**Models in biology: ‘accurate descriptions of our pathetic thinking’**

Jeremy Gunawardena

Gunawardena *BMC Biology* 2014, 12:29
http://www.biomedcentral.com/1741-7007/12/29

“Models in (systems biology) are not meant to be descriptions, pathetic descriptions of nature; they are designed to be accurate descriptions of our pathetic thinking about nature.”

James Black, “Drugs from emasculated hormones: the principles of syntopic antagonism”, Nobel Lecture, 1988

Rob Phillips, “Theory in biology: Figure 1 or Figure 7”, TICB **25**:723-9 2015.
the dark side of the model

the most serious objection to darwin's theory of natural selection came from physics

in 1863 william thomson calculated that the age of the earth was no more than 100,000,000 years.

“I desire to point out that this seems to be one of the many cases in which the admitted accuracy of mathematical processes is allowed to throw a wholly inadmissible appearance of authority over the results obtained by them. Mathematics may be compared to a mill of exquisite workmanship, which grinds you stuff of any degree of fineness; but, nevertheless, what you get out depends on what you put in”.

Thomson, “On the secular cooling of the Earth”, Phil Mag 25:1-14 1863
1. models can provide evidence for things unseen

2. biology is more theoretical than physics

3. models describe our pathetic assumptions, not reality

4. models can make good tools but they are bad masters

“The guiding motto in the life of every natural philosopher should be, "Seek simplicity and distrust it."

Alfred North Whitehead, The Concept of Nature, CUP 1920
3. mathematics in modern biology
a taxonomy of models

FORWARD MODELS
starting from mechanism

REVERSE MODELS
starting from data

THICK MODELS
“all” the details

Covert et al, Cell 150:389-401 2012

THIN MODELS
answering a question

\[
\frac{d[P]}{dt} = \frac{V_{max} [S]}{K_M + [S]}
\]

Schiebinger et al, bioRxiv, https://doi.org/10.1101/191056

Mycoplasma genitalium

Schiebinger et al, bioRxiv, https://doi.org/10.1101/191056
Guyton's thick model for blood pressure regulation

The rise of the machines

deep learning in artificial neural networks (ANNs) – a paradigm change

“Humankind has accumulated Go knowledge from millions of games played over thousands of years, collectively distilled into patterns, proverbs and books. In the space of a few days, starting tabula rasa, AlphaGoZero was able to rediscover much of this Go knowledge, as well as novel strategies that provide new insights into the oldest of games.”

https://www.tensorflow.org/
ANNs are reverse models

“The CNN achieves performance on par with all tested experts across both tasks, demonstrating an artificial intelligence capable of classifying skin cancer with a level of competence comparable to dermatologists.”

ANNs are forward models

A LOGICAL CALCULUS OF THE IDEAS IMMANENT IN NERVOUS ACTIVITY*

Warren S. McCulloch and Walter Pitts

McCulloch & Pitts, Bull Math Biophys 5:115-33 1943
fake news of World Domination

The End of Theory: The Data Deluge Makes the Scientific Method Obsolete
By Chris Anderson  06.23.08

Wired Magazine, 16.07.
4. challenges for the future

levels of representation

the brain should be understood as a hierarchy of three levels of understanding

- **computational** behaviour, learning
  \[ Q^*(s,a) = \max_{\pi} \mathbb{E}_{s} \left[ r_t + \gamma r_{t+1} + \gamma^2 r_{t+2} + \ldots | s_t = s, a_t = a, \pi \right], \]

- **algorithmic** neural network

- **implementation** neuron, spikes
  \[ I = C_M \frac{dV}{dt} + g_K n^4 (V - V_K) + g_N a m^3 h (V - V_N) + g_l (V - V_l), \]


Willshaw, Dayan, Morris, Phil Trans Roy Soc B 370: 20140383 2015
what are the levels of representation in systems biology?