dynamic processes in cells
(a systems approach to biology)

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harvard medical school

lecture 1

1 september 2016

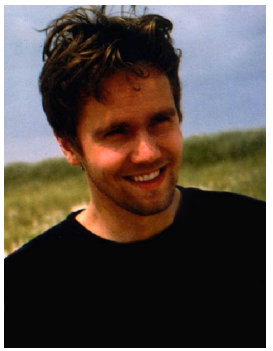
sb200 – “dynamic and stochastic processes in cells”

aka: “a systems approach to biology”

part 1 (SB303)

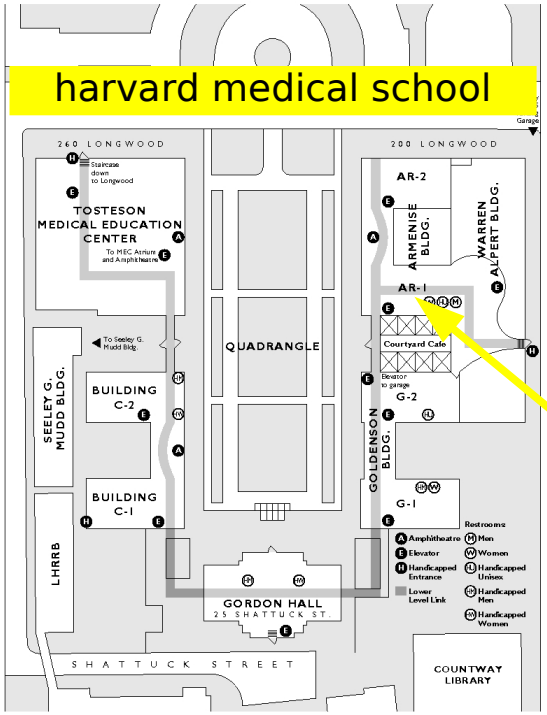
“deterministic dynamics”

part 2 (SB304)



“stochastic dynamics”

https://canvas.harvard.edu/courses/14151



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i do not hold formal office hours but am always happy to discuss the course.
please send me an e-mail to arrange a time to meet.

what is systems biology?

you might get the following answers:

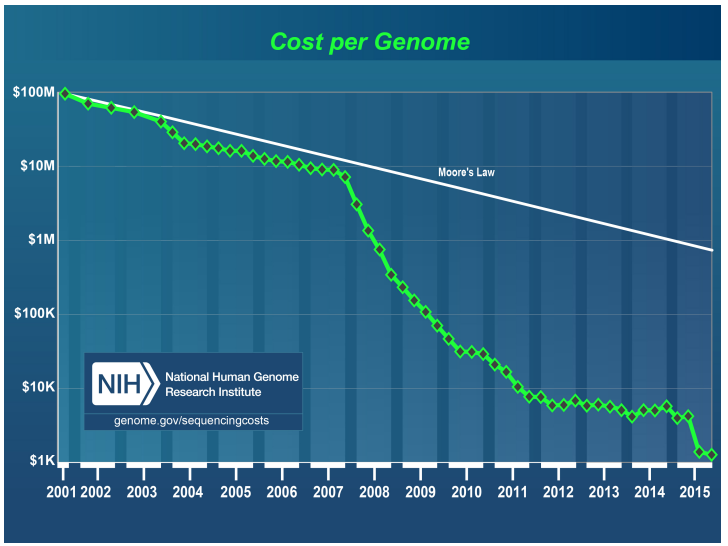
"X-omics"

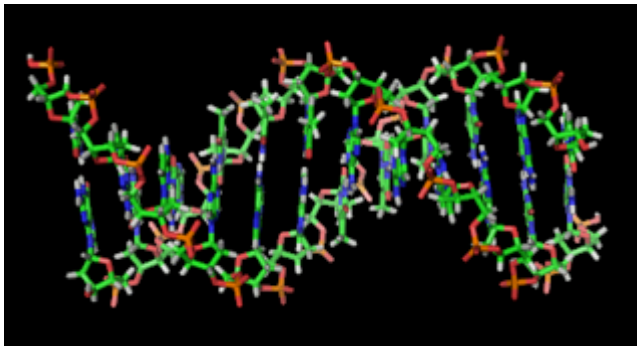
it is about using high-throughput technologies to acquire data on all X molecules and using computational algorithms to infer causality from correlation

"modelling"

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

the genomic revolution





... ATGACGTGGTGCACCT ...

but what are the questions

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

systems biology

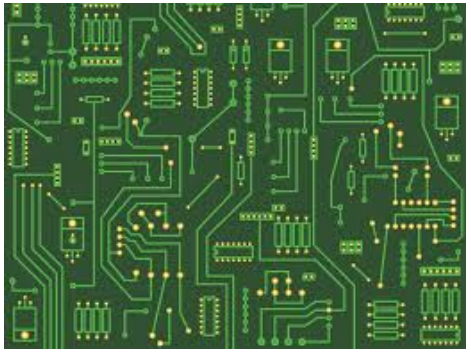
how do we get from dead molecules to living organisms?

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

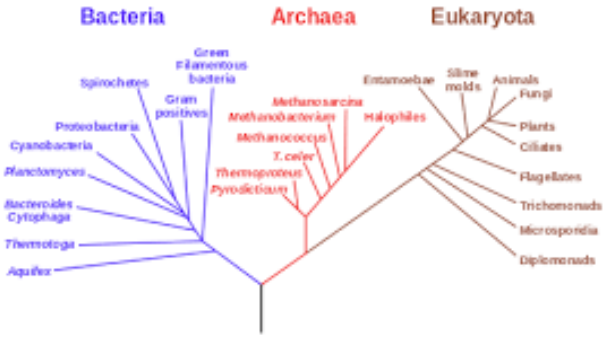
Marc Kirschner, *“The meaning of systems biology”*, Cell **121**:503-4 2005.

different views of the organism

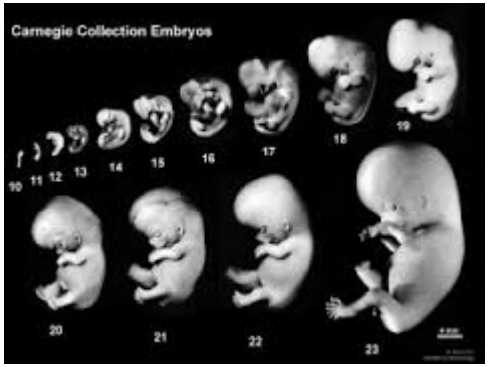
entity that resembles a human-made machine



entity that evolves by descent with modification



entity that develops through epigenetic self-organisation

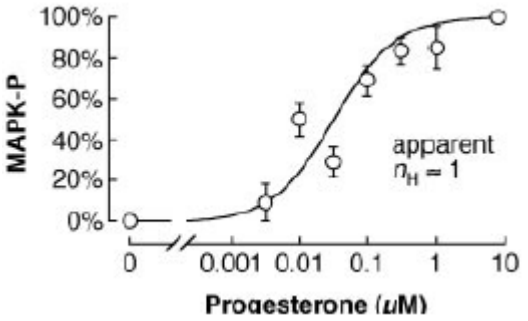


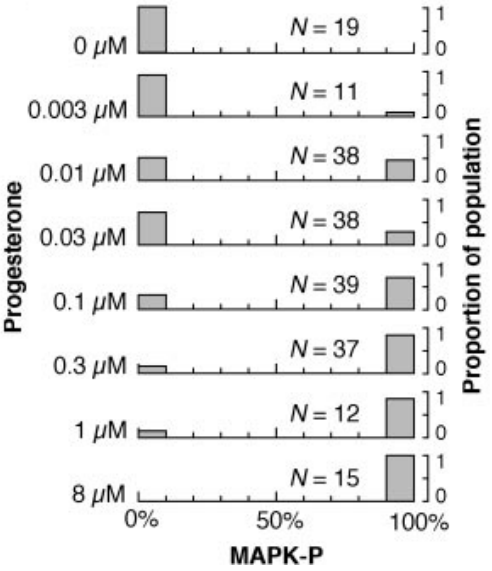
systems biology is diffusion, not explosion

it is learning how to think in a different way

for example:

the average may not represent the distribution





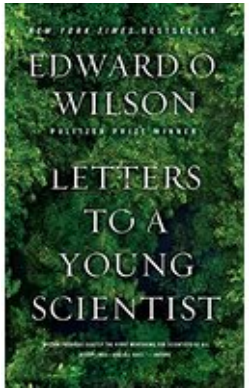
Ferrell, Machleder, *"The biochemical basis of an all-or-none cell fate switch in Xenopus oocytes"*, Science **280**:895-8 1998

systems biology is diffusion, not explosion

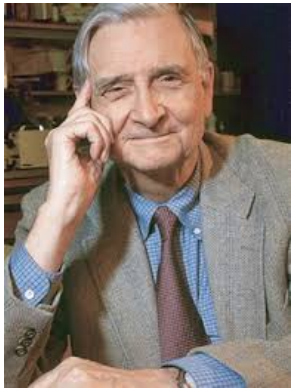
Exceptional Responders Initiative:

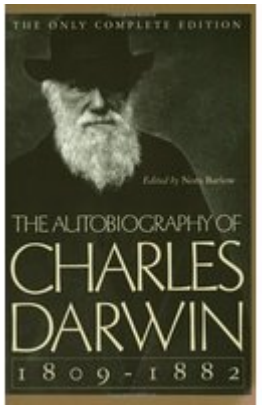
The National Cancer Institute (NCI) has embarked on the Exceptional Responders Initiation to understand the molecular underpinnings of exceptional responses to treatment ... Exceptional responders are patients who have a unique response to treatments that are not effective for most other patients.

collective interactions need mathematical tools



"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."





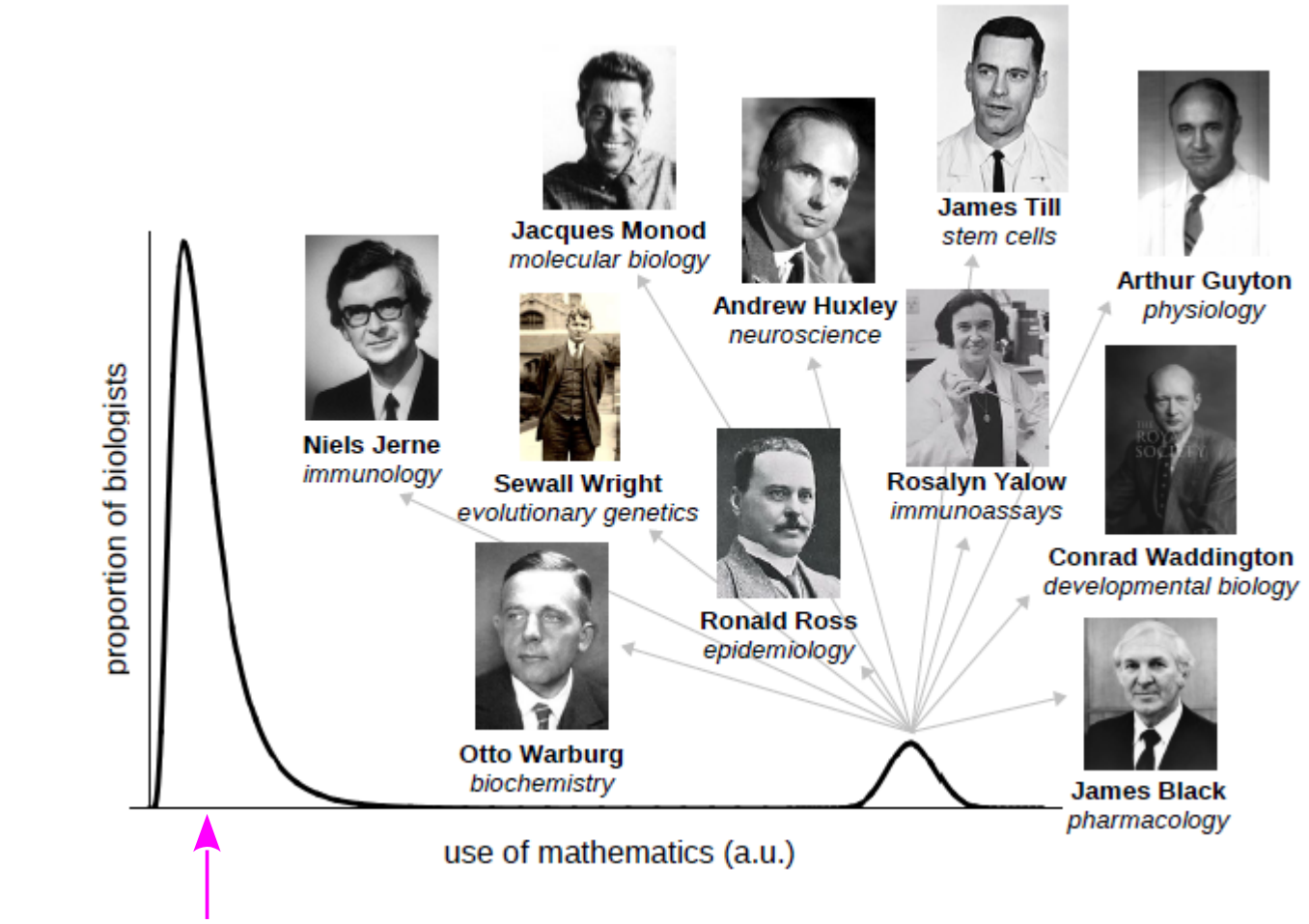
"I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics ... for men thus endowed seem to have an extra sense."

syllabus for part I

	topics	*lectures*
0.	systems biology and the role of mathematics	1
1.	homeostasis & microscopic cybernetics	2-4
	linear dynamical systems, control theory	
2.	evolution of complexity	5-6
3.	cellular identity & gene regulatory networks	7-9
	nonlinear dynamical systems	
4.	signal transduction & information processing	10-12

0. the role of mathematics

a revisionist history of biology



textbook average

example: the michaelis-menten formula

MBoC | PERSPECTIVE

Some lessons about models from Michaelis and Menten

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

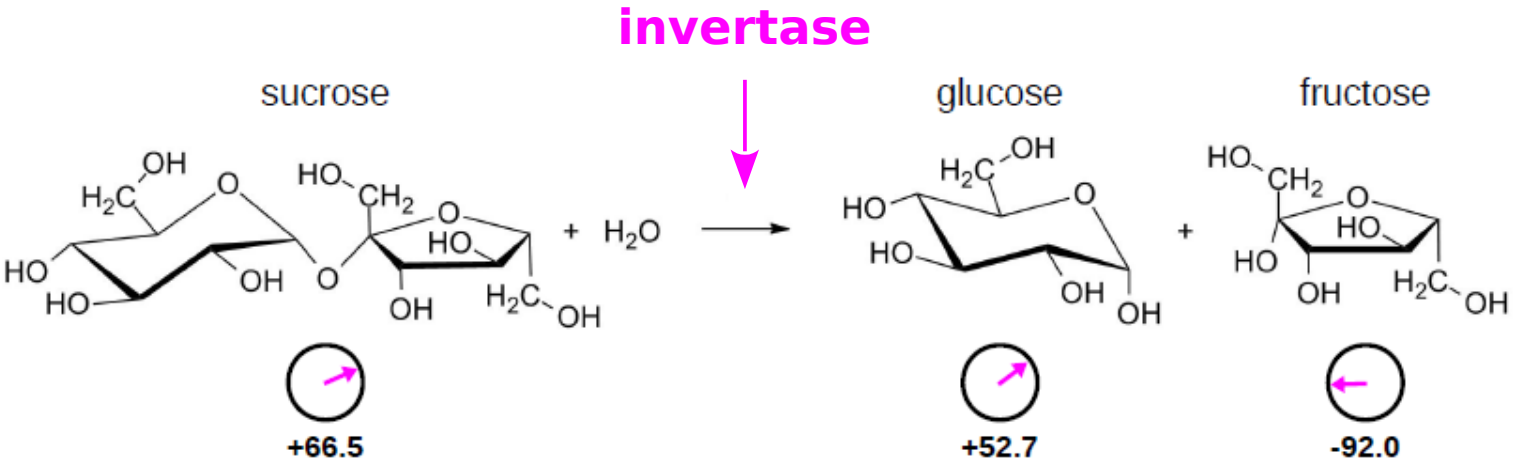
ABSTRACT Michaelis and Menten's classic 1913 paper on enzyme kinetics is used to draw some lessons about the relationship between mathematical models and biological reality.

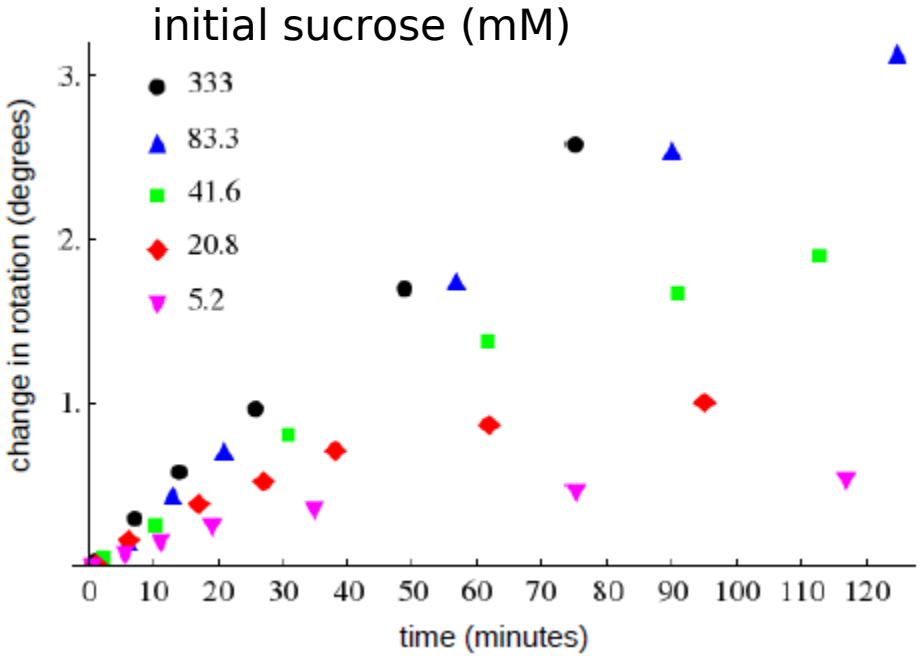
Mol Biol Cell, **23**:517-8, 2012

Michaelis & Menten, *"Die kinetik der Invertinwirkung"*, Biochem Z, **49**:333-69, 1913

Johnson & Goody, *"The original Michaelis constant: translation of the 1913 Michaelis-Menten paper"*, Biochemistry, **50**:8264-9 2011

how do enzymes work?





principle of mass action

the rate of an elementary reaction is proportional to the product of the concentrations of the substrates, taking stoichiometry into account

rate constant

$$2A + 3B \xrightarrow{k} C$$

$$\frac{d[C]}{dt} = k[A]^2[B]^3$$

$$\frac{d[A]}{dt} = -2k[A]^2[B]^3$$

$$\frac{d[B]}{dt} = -3k[A]^2[B]^3$$

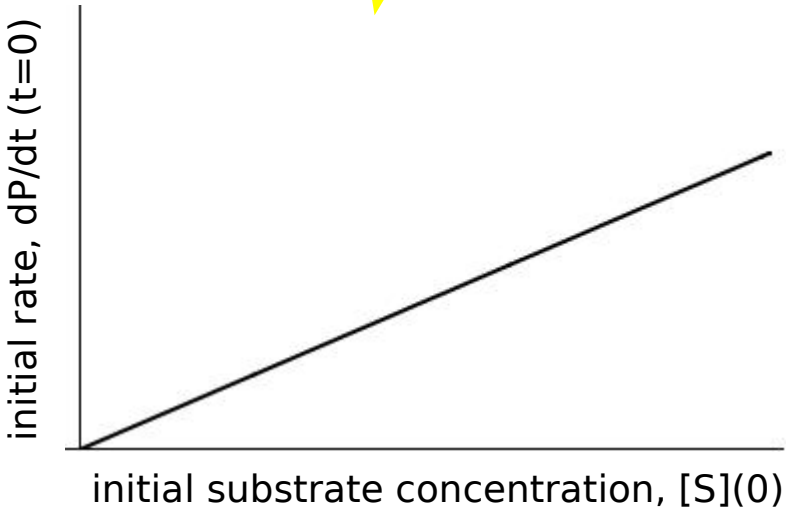
1836-1902 1833-1900

P Waage & C Guldberg, *"Studies concerning affinity"*, J Chem Edu 63:1044-7 1986. English translation by H Abrash of original 1866 paper in Norwegian.

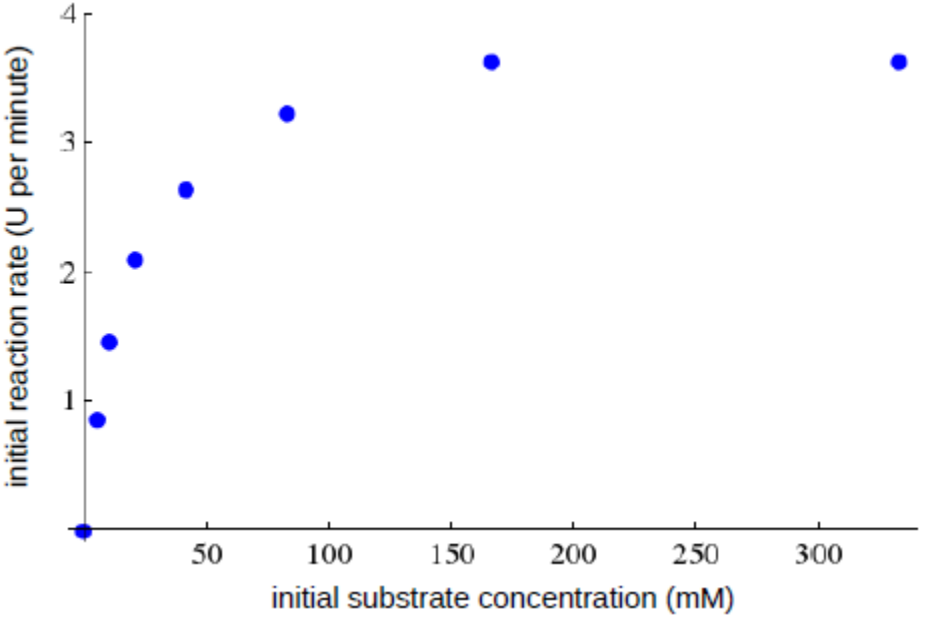
direct conversion?

rate constant

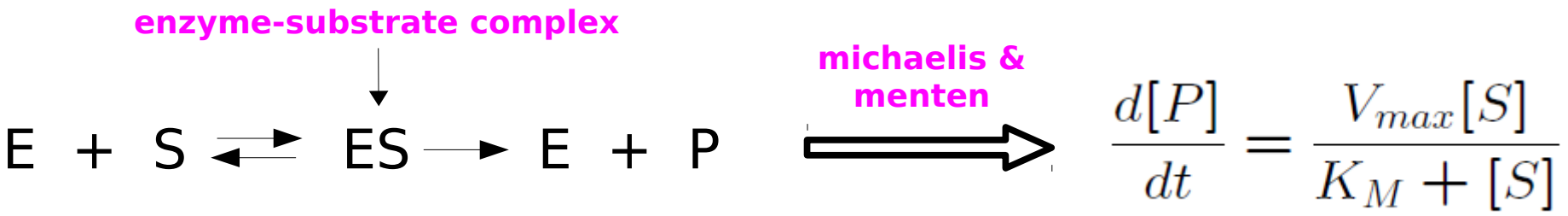
S → P mass action ⟹ $\frac{d[P]}{dt} = \alpha[S]$

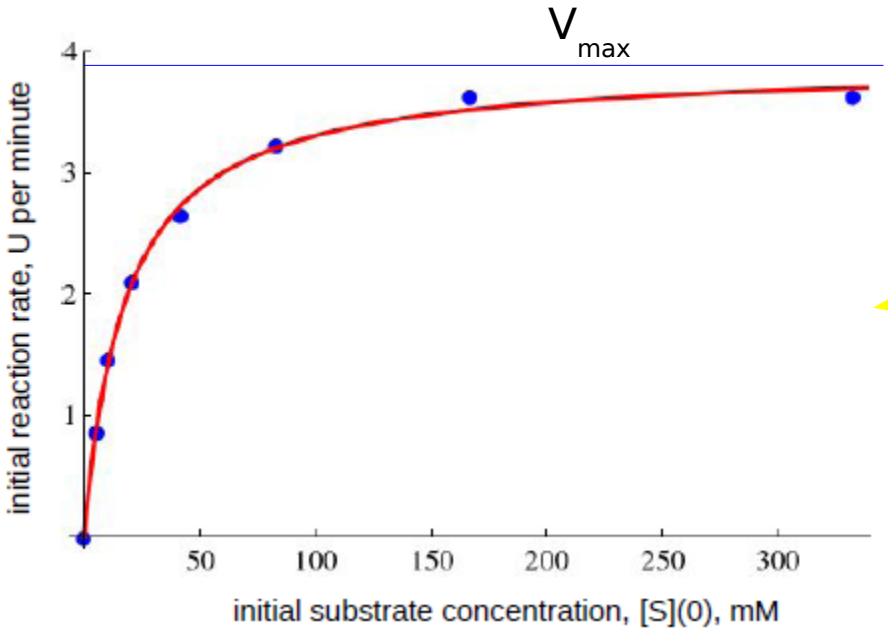


michaelis-menten data

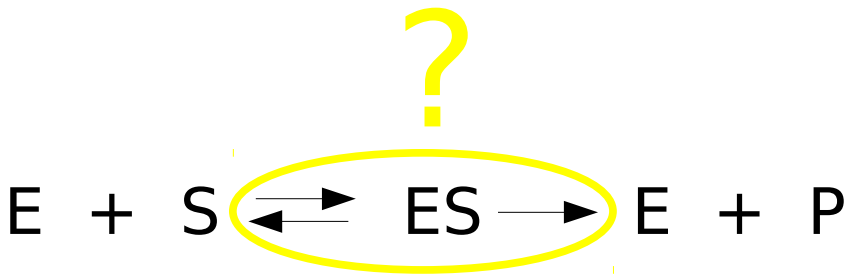


bottleneck – the enzyme-substrate complex





but what is an “enzyme-substrate” complex?



michaelis and menten did not identify the enzyme-substrate complex. it was a purely hypothetical concept which could explain a great deal of experimental data with the help of mathematics.

the concept was so useful that biochemists used it as the foundation for understanding how enzymes worked, without an enzyme-substrate complex being experimentally identified

30 years after michaelis & menten ...

$$\text{Peroxidase} + H_2O_2 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{peroxidase}\cdot H_2O_2$$

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. A conclusive proof of the Michaelis theory rests on such evidence.

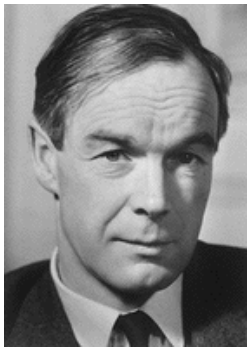
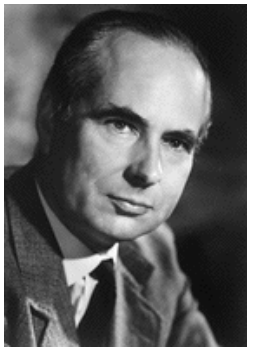
1913-2010

$k_1 = 1.2 \times 10^7\ M^{-1}\ sec^{-1}$ $k_2 = 0.2\ sec^{-1}$

B Chance, *"The kinetics of the enzyme-substrate compound of peroxidase"*, J Biol Chem, **151**:553-77 1943

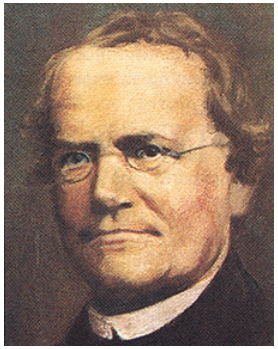
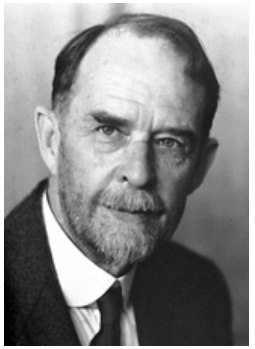
mathematics provides evidence for things unseen

“ion channels”


1952 1970 1976

“genes”

1866 1915 1953

a revisionist history of biology

MBoC | PERSPECTIVE

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

time-scale separation

steady-state assumption

$$\frac{d[ES]}{dt} = 0$$

allows steady-state [ES] and [E] to be eliminated

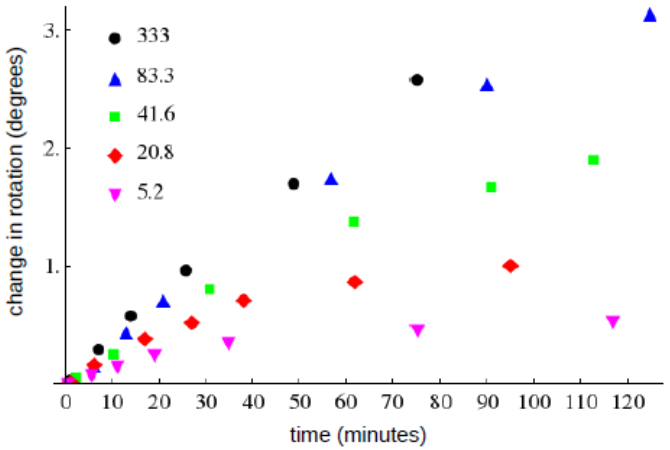
$$\frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

[ES] and [E] are assumed to be “fast” variables, which rapidly reach steady state, to which the “slow” variables, [S] and [P], gradually adapt. the fast variables can be eliminated, leaving only the slow variables.

later, we will introduce the “linear framework” for doing such eliminations systematically

models are not descriptions of reality

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



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

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

X

(*) L Michaelis, **Die Wasserstoffionen-Konzentration: Ihre Bedeutung Fur Die Biologie Und Die Methoden Ihrer Messung**. 1914.

they describe our assumptions about reality

REVIEW

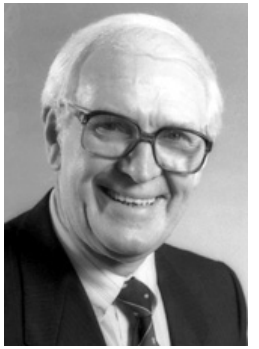
Models in biology: 'accurate descriptions of our pathetic thinking'

Jeremy Gunawardena

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

BMC Biology

"Models in (analytical pharmacology) are not meant to be descriptions, pathetic descriptions of nature; they are designed to be accurate descriptions of our pathetic thinking about nature."



1924-2010

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

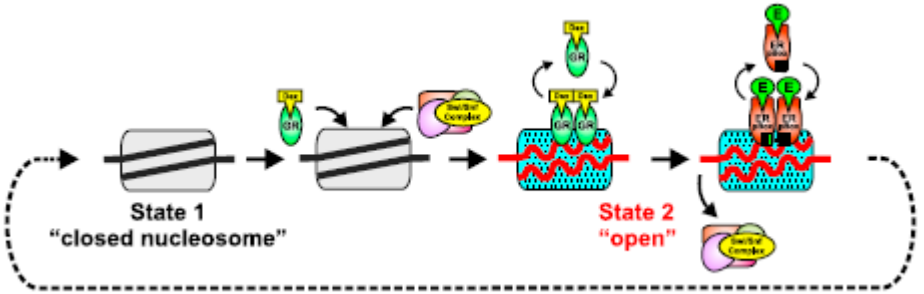
formal vs informal models

formal model

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

permits rigorous reasoning
conclusions logically guaranteed
narrow and “brittle”
assumptions must be precise
and cannot be changed
only as good as its assumptions

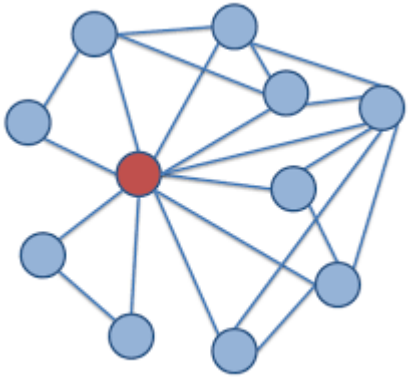
informal model



accommodates uncertainty
judgement and
new assumptions
broad and robust
but imprecise and “fuzzy”
relies on intuition and analogy

we will mostly use forward models

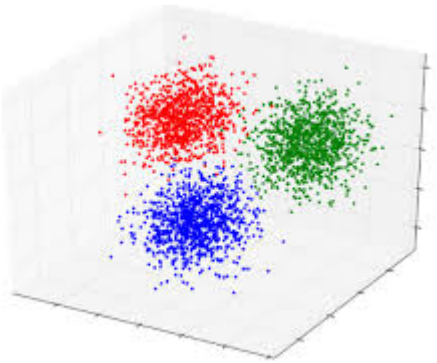
molecular interactions



forward model

$$\frac{\partial \phi}{\partial t} = \nabla.(D\nabla\phi) + S$$

experimental data



reverse model