dynamic processes in cells
(a systems approach to biology)

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lecture 1

3 september 2015

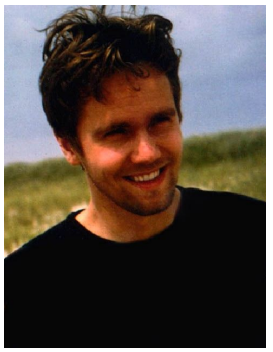
sb200 – “dynamic and stochastic processes in cells”

aka: “a systems approach to biology”

part 1 (SB303)

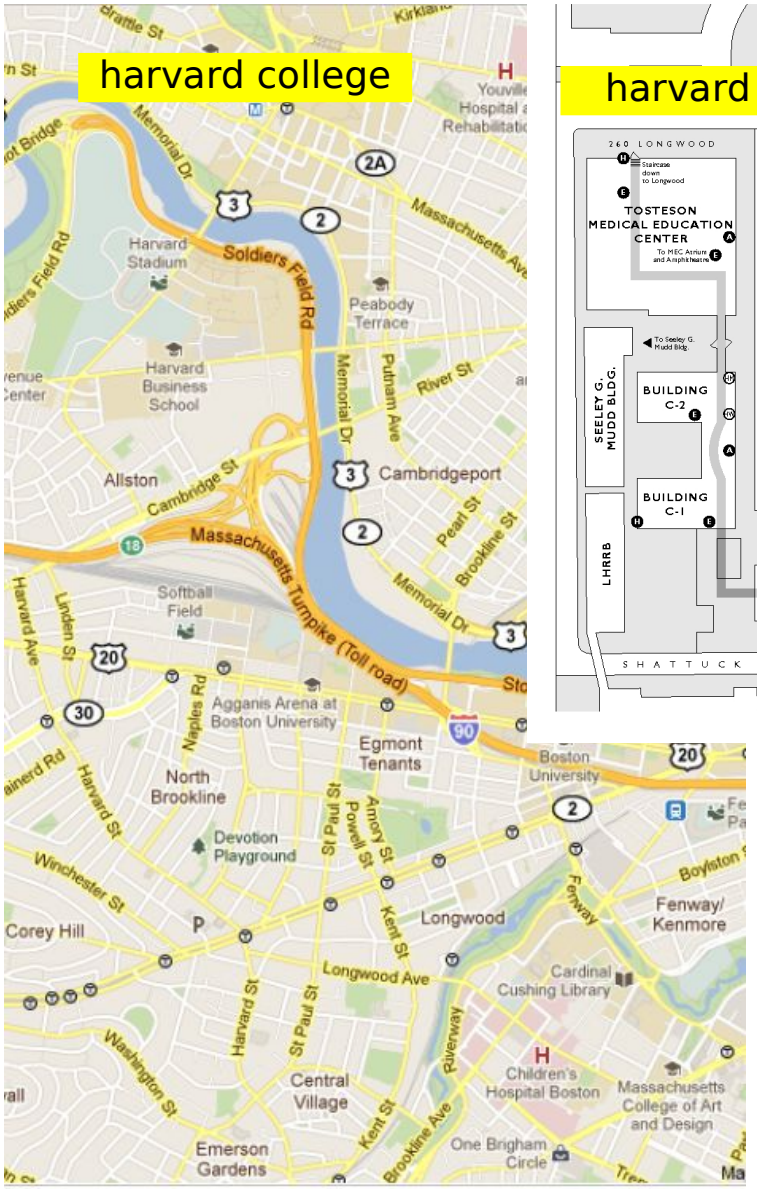
“deterministic dynamics”

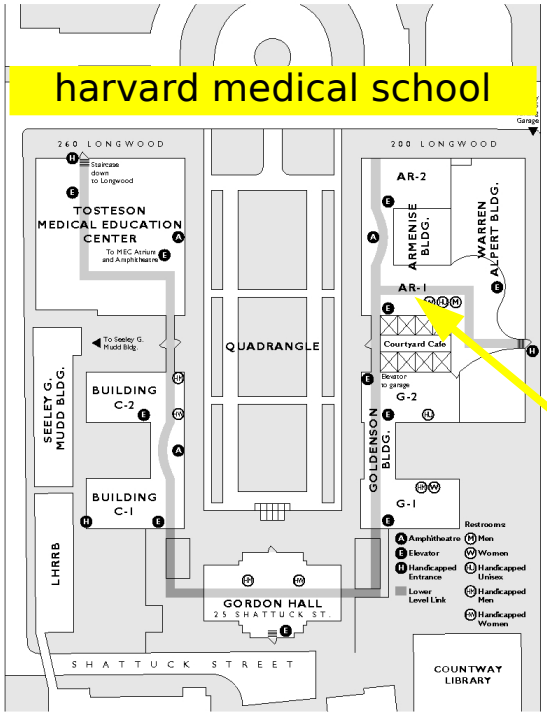
part 2 (SB304)



“stochastic dynamics”

isites.harvard.edu/k112757





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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?

molecular biology

characterising the molecular components

systems biology

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

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

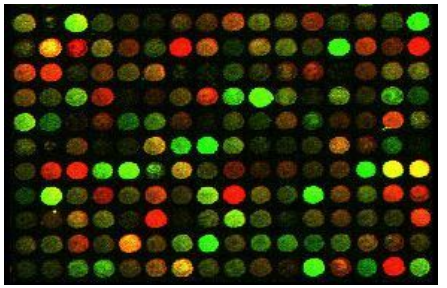
what is systems biology?

top-down, "-omics", data-centric

system = cell / organism

model = statistical correlations

data = high-throughput, poor quality



too much data, not enough analysis

bottom-up, mechanism-centric

system = molecular network

model = mechanistic, biophysical

data = quantitative, single-cell

$$\frac{d}{dt}[ES] = a[E][S] - (b + c)[ES]$$

not enough data, too much analysis

collective interactions need mathematical tools

Leading Edge

In This Issue

Cell

Finding Strength in Numbers (and Equations)

As much as any discipline in modern biology, systems biology relies on computation and mathematics to collect data, build models, and make predictions. In their Minireview, Trey Ideker, Janusz Dutkowski, and Leroy Hood (page 860) introduce strategies for leveraging accumulated knowledge about biological systems to boost signal-to-noise in analyzing large-scale datasets. To illustrate the power of these tools and concepts, they cite key studies that range from genome-wide association studies of disease to kinase-phosphatase signaling networks. In a similar vein, Dana Pe'er and Nir Hacohen (Perspective, page 864), using cancer as an example, outline strategies and principles for identifying gene networks relevant to disease phenotypes and discuss the prospects of network modeling for personalizing cancer treatment.

Taking their turn at the chalkboard, James Ferrell, Tony Tsai, and Qiong Yang (Primer, page 874) guide us step-by-step through equations that model the cell cycle to explain why certain circuits oscillate. Their demonstration highlights the power of integrating knowledge gleaned from biochemistry and molecular biology with mathematical modeling. Some problems, however, require greater computing power. On this topic, Olga Troyanskaya (Book Review, page 842) comments on a recently published advanced computing how-to guide aimed at biologists. She discusses the book's strengths and weaknesses, while encouraging bench researchers to embrace complex computation and quantitative experiments.

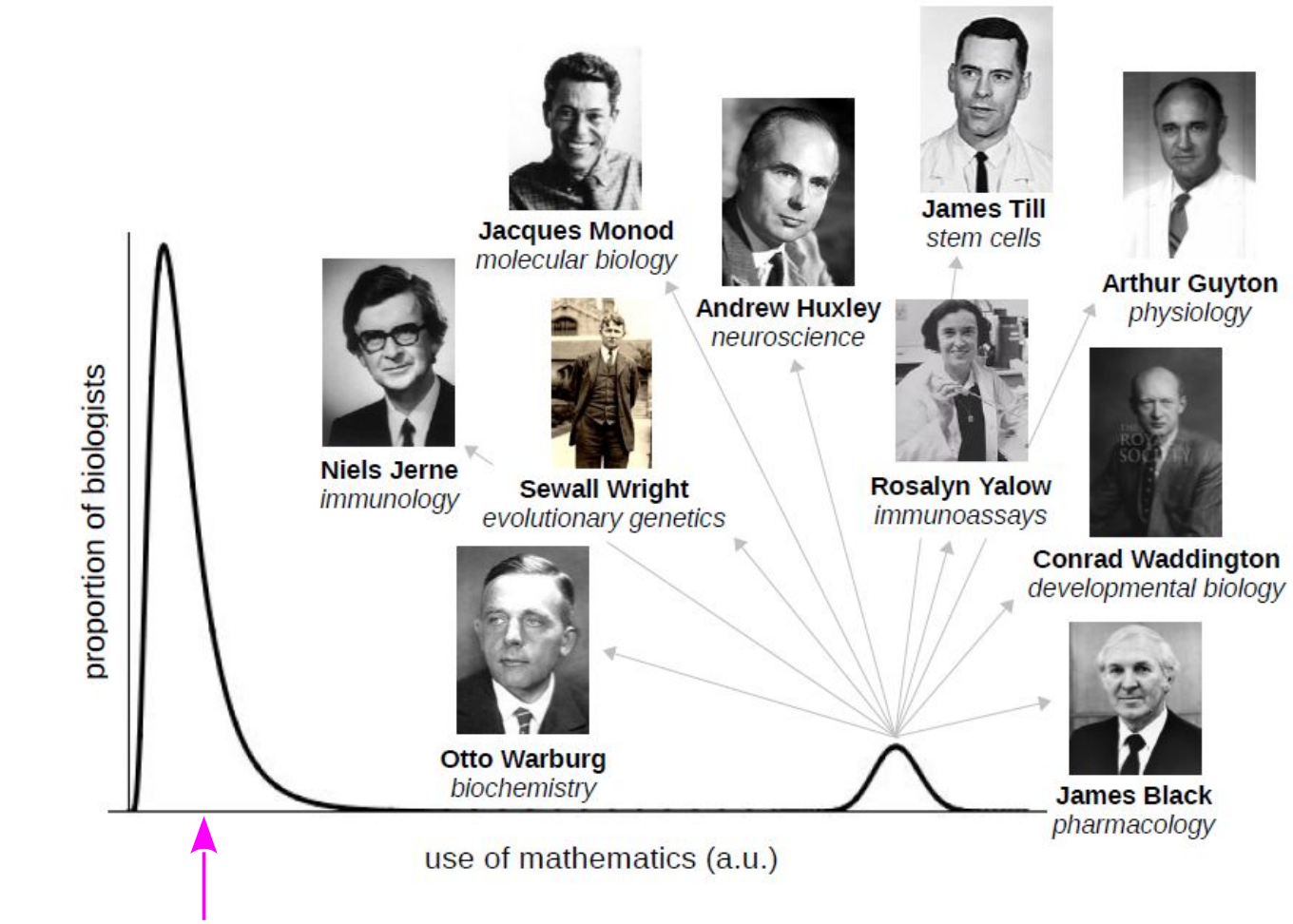
Cell **144(6)** 18 March 2011

syllabus

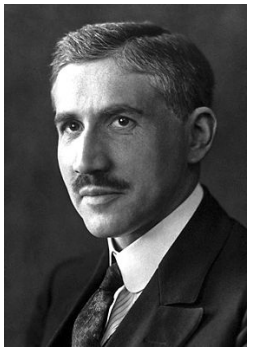
topics	*lectures*
0. why mathematics?	1
1. homeostasis & microscopic cybernetics	2-4
2. evolution, modularity & weak linkage	5
3. time-scale separation & the linear framework	6
4. cellular identity & gene regulatory networks	7-9
5. signal transduction & information processing	10-12

0. why mathematics?

a revisionist history of biology



otto warburg



otto meyerhoff

hans krebs

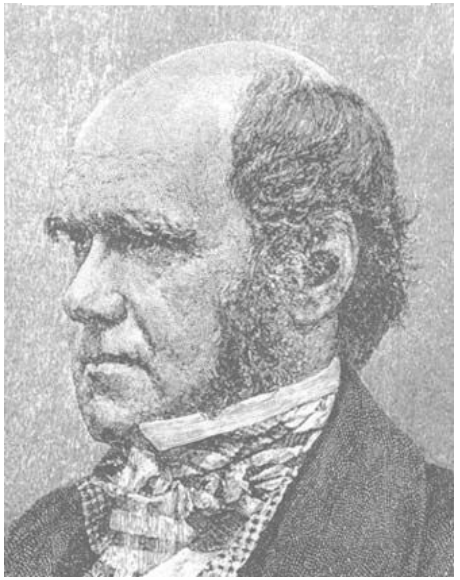
hugo theorell

But to devise and to carry out the experiments and to develop the mathematical analysis of the measurements required very exceptional experimental and theoretical skill.

Hans Krebs, **Otto Warburg: Cell Physiologist, Biochemist and Eccentric**, OUP 1981

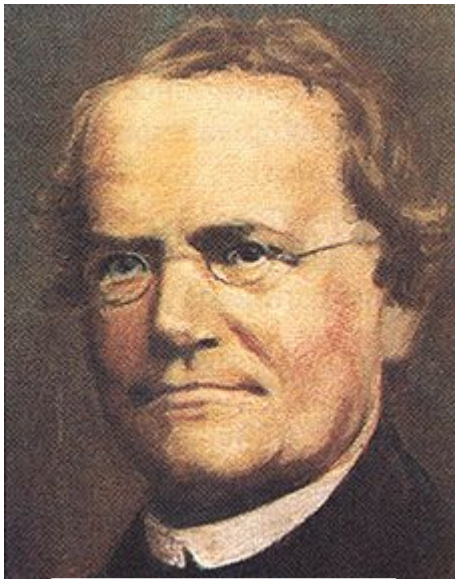
two methodologies in biology

descriptive



1809-1882

analytical



1822-1884

two methodologies in biology

descriptive

analytical

1813-1878

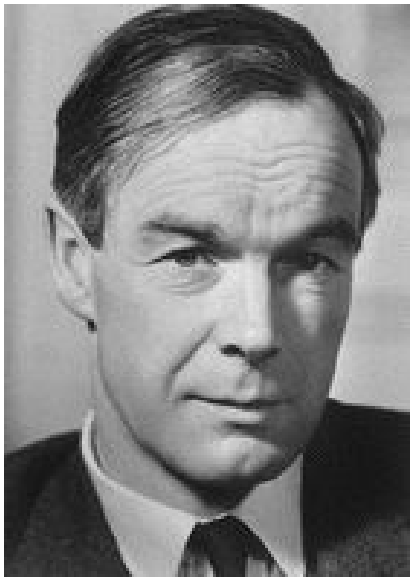
1821-1894

two methodologies in biology

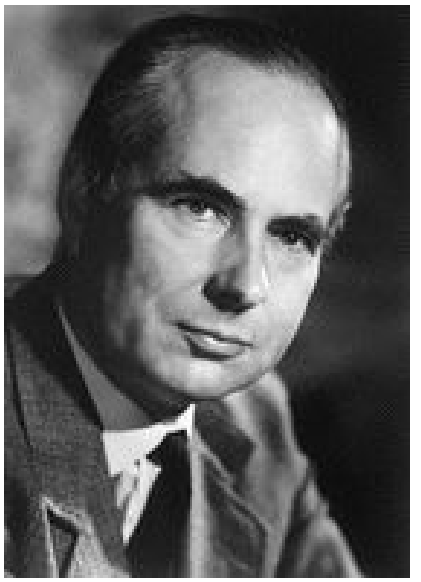
descriptive

1852-1934

analytical



1914-1998



1917-2012

a revisionist history of biology

quantitative analysis and the use of mathematical methods is not something new, imported into biology by physical scientists, but is part of a long tradition within biology, developed and exploited by biologists to answer some of the deepest questions in biology ... we are merely following that tradition

a case study in using mathematics

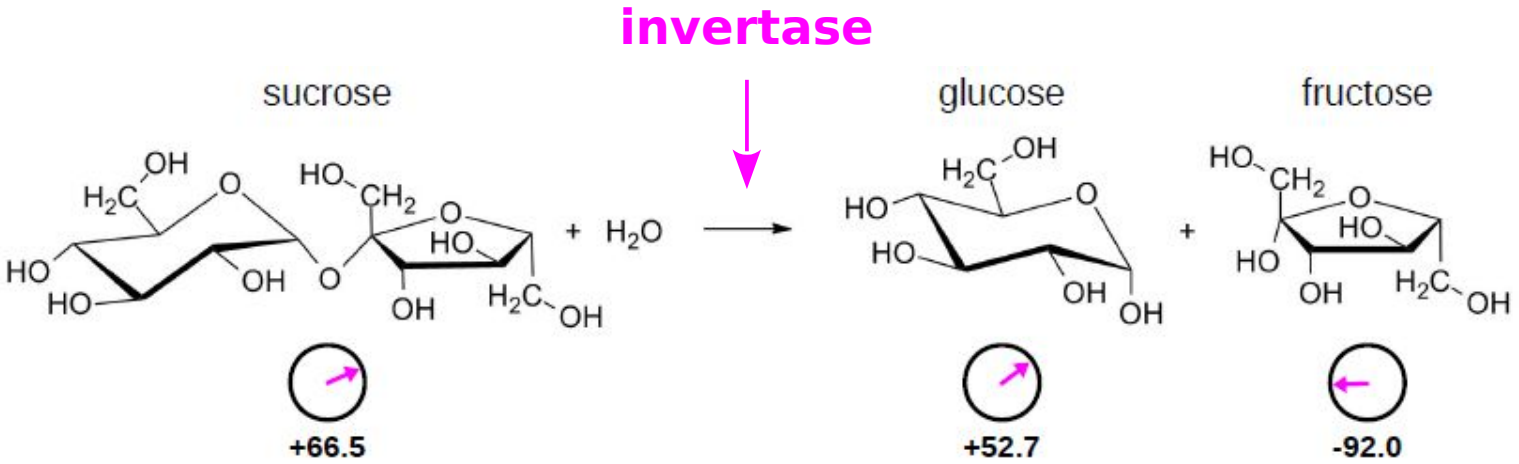
1879-1960 *1875-1949*

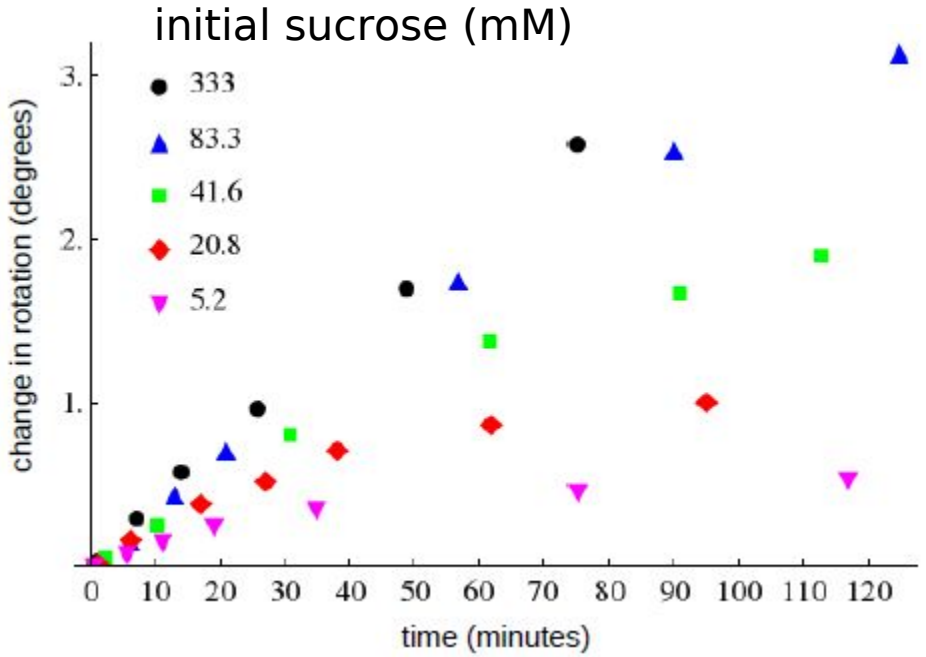
Michaelis & Menten, *"Die kinetik der Invertinwirkung"*, Biochem Z, **49**:333-69, 1913

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

Gunawardena, *"Some lessons about models from Michaelis and Menten"*, Mol Biol Cell, **23**:517-9, 2012

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

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

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

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

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

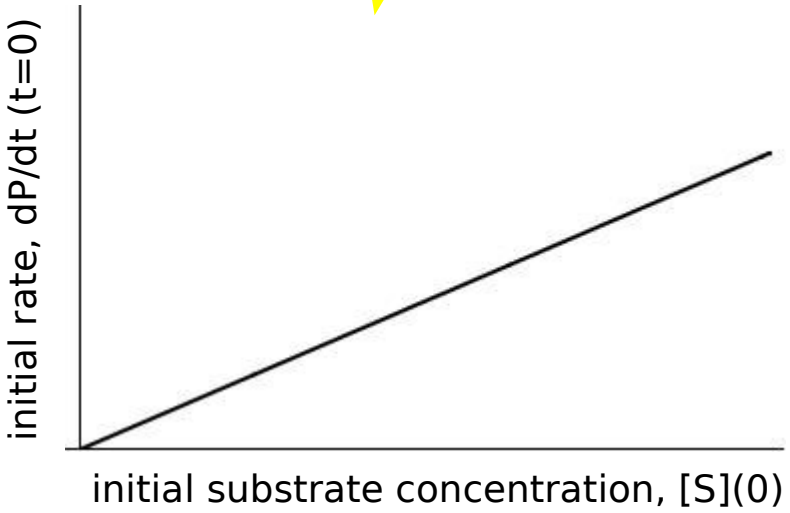
1836-1902 1833-1900

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.

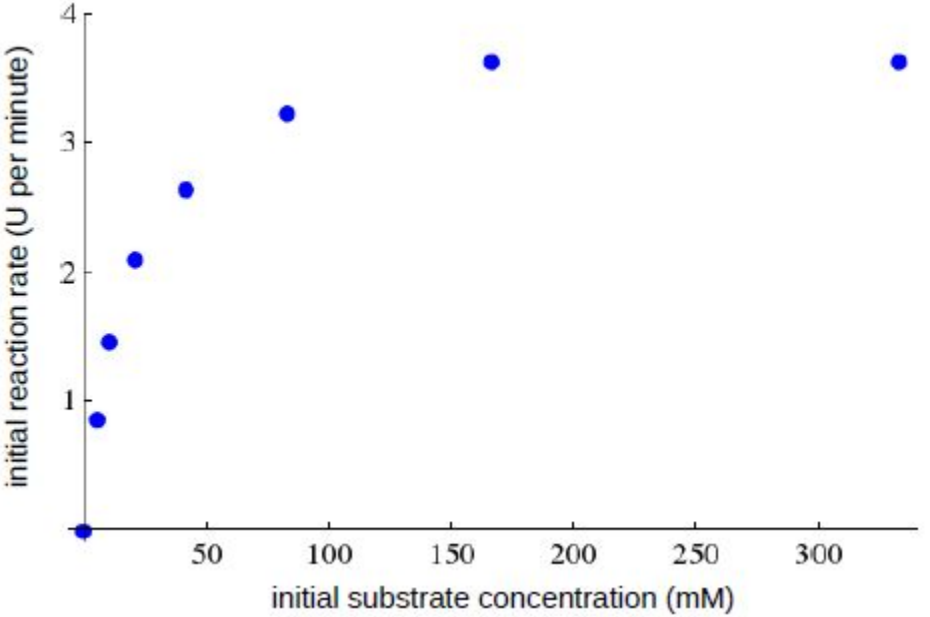
enzyme mechanism

rate constant

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



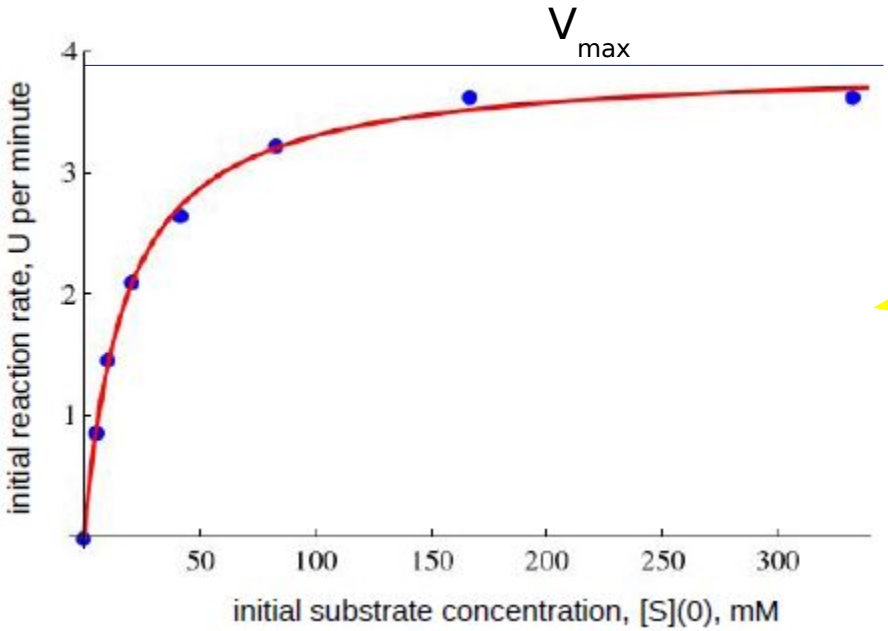
Michaelis-Menten data



michaelis-menten formula

enzyme-substrate complex

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



explains all the data

Michaelis-Menten differential equation

$$\frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]} \qquad [S](t) + [P](t) \approx S_{tot}$$

can be solved

$$[S](t) + K_M \ln([S](t)) = -V_{max}t + c$$

and fits the time-course data very well

but

Michaelis and Menten did not show that an enzyme-substrate complex existed and did not measure the rates of association of dissociation.

the enzyme-substrate complex was a hypothetical entity which, using mathematics, could explain a great deal of experimental data

30 years later ...

1913-2010

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

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.

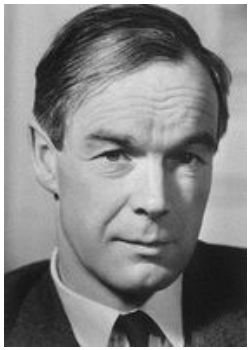
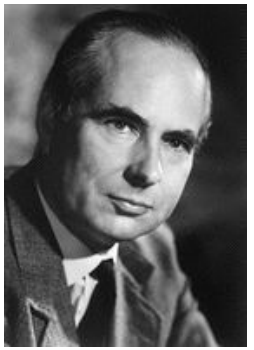
A conclusive proof of the Michaelis theory rests on such evidence.

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

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

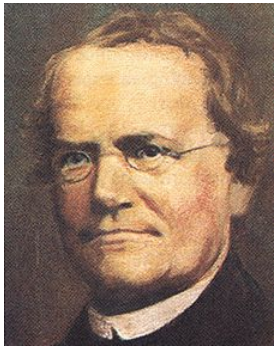
mathematics provides evidence for things unseen

“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 [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.

in lecture 6 we will discuss the “linear framework” for doing such eliminations systematically

models are not descriptions of reality

Michaelis was one of the first to understand that enzymes were sensitively dependent on pH and ionic balance (*)

Michaelis and 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

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

they describe our assumptions about reality

1924-2010

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.

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

Gunawardena, *"Models in biology: 'accurate descriptions of our pathetic thinking"*, BMC Biol, **12**:29, 2014

michaelis-menten, in summary

1. evidence for things unseen
2. time-scale separation eliminates internal complexity
3. models are not descriptions of reality

Gunawardena, *"Some lessons about models from Michaelis and Menten"*, Mol Biol Cell, **23**:517-9, 2012; *"Biology is more theoretical than physics"*, Mol Biol Cell, **24**:1827-9, 2013; *"Models in biology: 'accurate descriptions of our pathetic thinking"*, BMC Biol, **12**:29, 2014

back to the present

these days, (we think) we know most of the molecular components

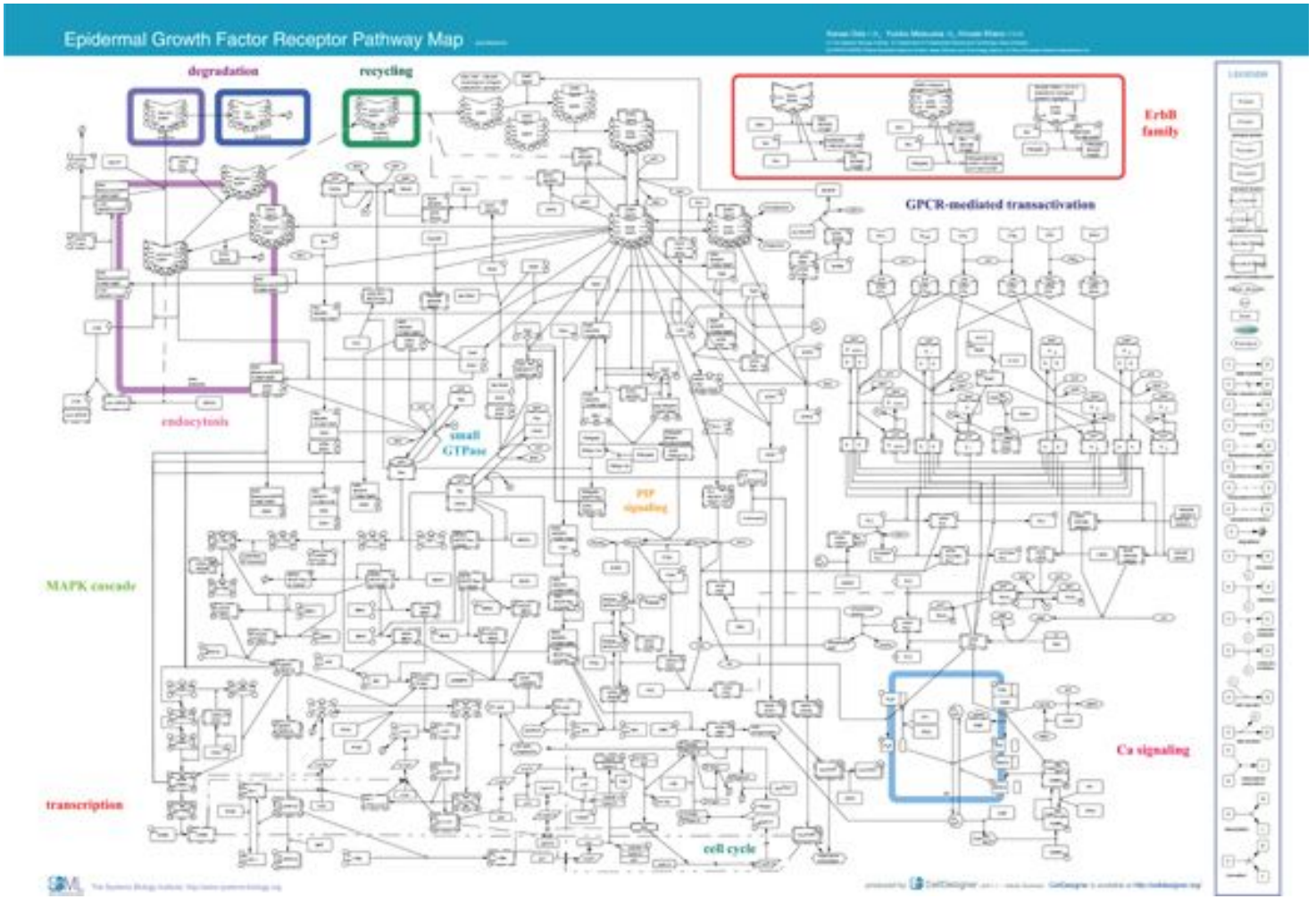
what are models good for in the age of systems biology?

they provide evidence relating mechanism to function

however, the interpretation of a mechanism can be more elusive than finding something unseen because it can depend on our state of knowledge

they help us to think – to know whether our conclusions are justified by our assumptions

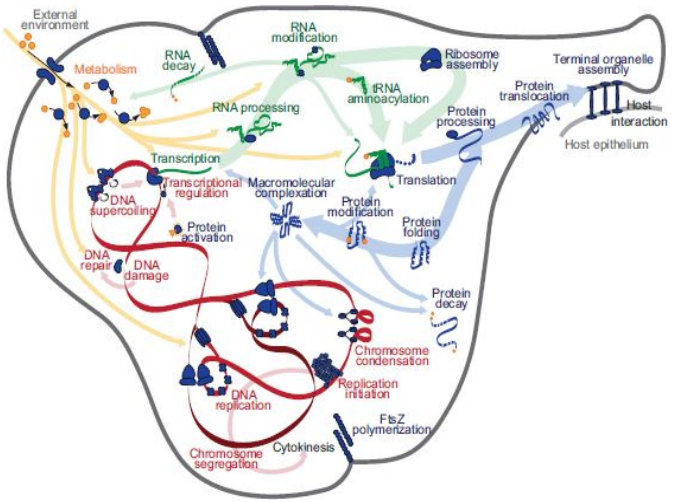
confronting molecular complexity

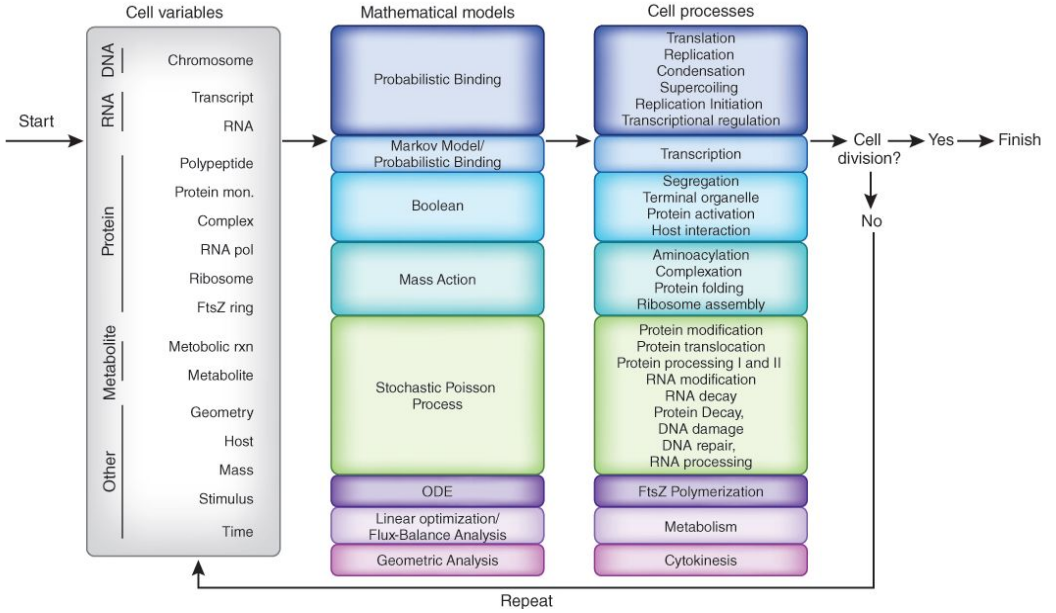


thick models – embrace the details

a computational grand challenge

Mycoplasma genitalium



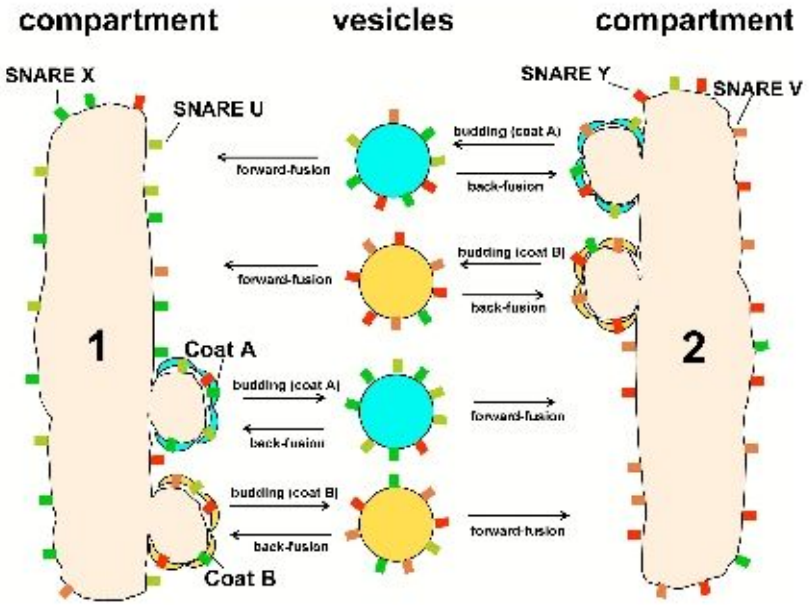


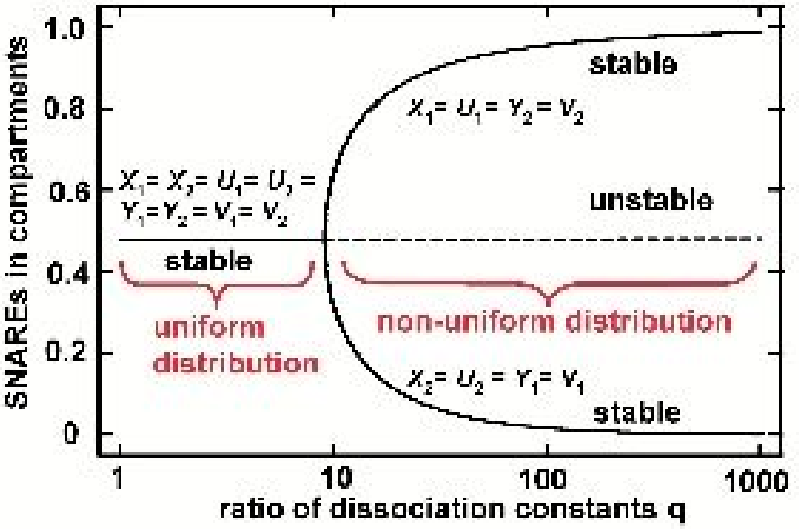
Karr, Sanghvi, Macklin, Gutschow, Jacobs, Bolival, Assad-Garcia, Glass, Covert, *"A whole-cell computational model predicts phenotype from genotype"*, Cell **150**:389-401 2012

Gunawardena, *"Silicon dreams of cells into symbols"*, Nature Biotech, **30**:838-40, 2012

thin models – abstract the details

asking a biological question





our analysis provides the first self-consistent explanation for the generation of distinct, stable compartments.

Reinhart Heinrich & Tom Rapoport, *"Generation of non-identical compartments in vesicular transport systems"*, J Cell Biol **168**:271-80 2005.