# *six lectures on systems biology*

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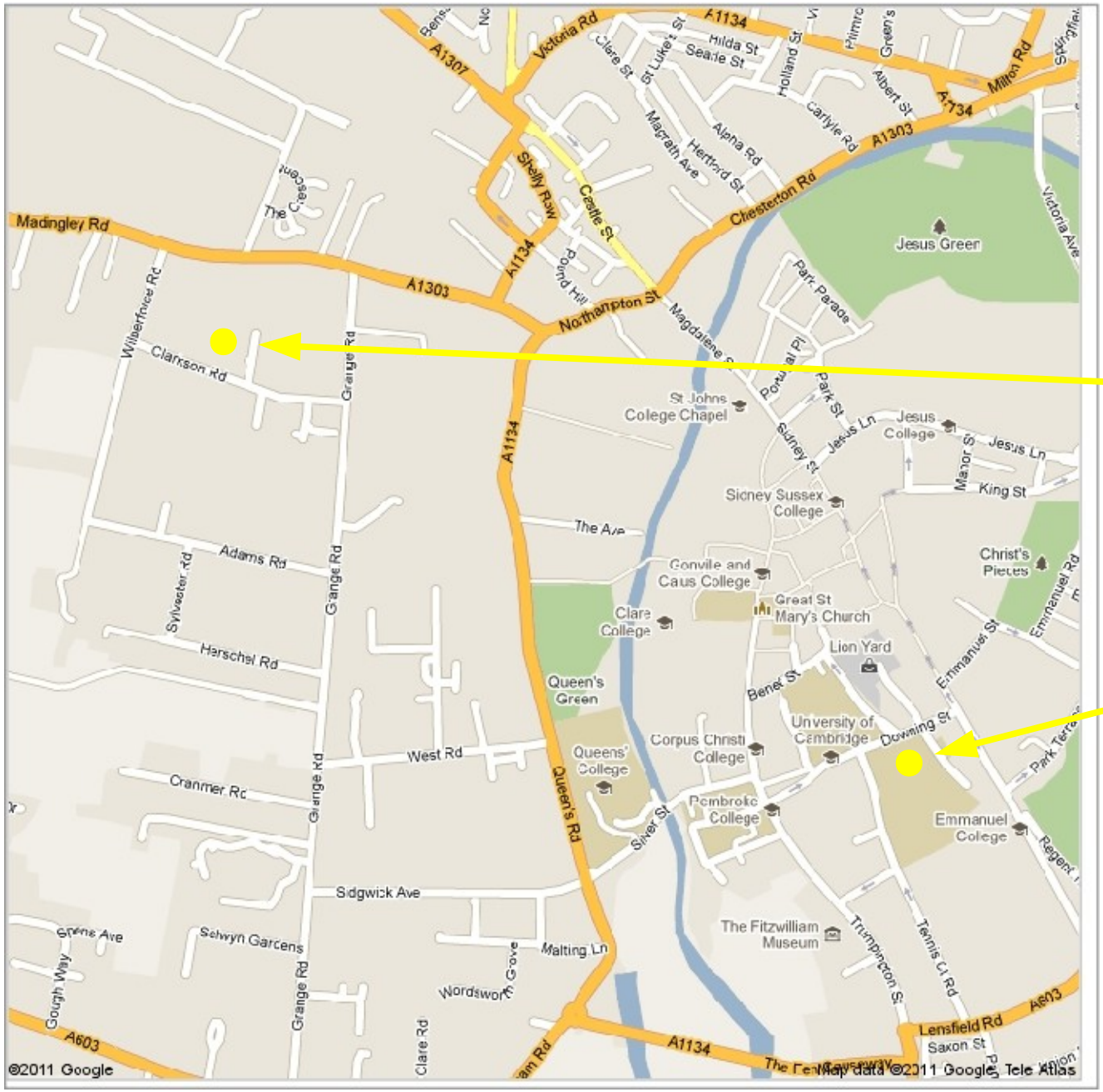
lecture 1
29 march 2011

part 2 seminar room, department of genetics

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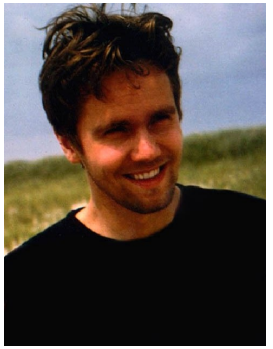
# systems biology courses in harvard

SB200 – “a systems approach to biology”

jg



johan paulsson



http://vcp.med.harvard.edu/teaching.html

12 lectures, handouts, preprints

# systems biology courses in the real cambridge

SB200 is diffusing across the pond ...

MPhil in Computational Biology

**3.7 SB — Systems Biology**

*Johan Paulsson and Andreas Hilfinger (Harvard Systems Biology)*

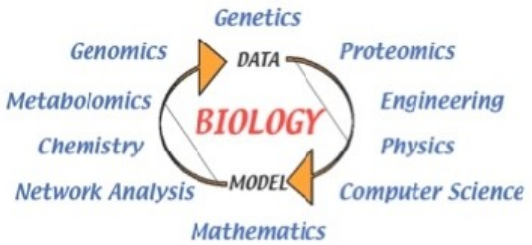
Detecting regulatory networks. Inverse engineering. Scale-free networks. Modeling frameworks: Boolean logic, deterministic rate equations and stochastic processes - analytically and computationally. Kinetic design principles, e.g feedback loops, metabolic phase transitions, multi-stability, and order versus disorder. Systematic kinetic approaches, e.g. metabolic control analysis and biochemical systems theory. Biological model systems, e.g. the lac operon, phages, plasmids and chemotaxis. Single cell and single molecule experiments. Synthetic biology.

steve oliver's part III course

**Part III Course in Systems Biology**

***Part III Systems Biology really gives you a great insight into the current state of the field, putting you ahead in the quest for understanding how biological components come together to form lif***
*Peter Ackermann, Part III Systems Biology Student*

Systems Biology is an integrated approach to the study of biology through experiment and the use of computer models with both predictive and explanatory power. It is interdisciplinary, requiring the participation of biological, physical, mathematical, engineering and computational sciences.



***molecular biology***

characterising the molecular components

***systems biology***

putting Humpty Dumpty back together again

*how do the collective interactions of the components give rise to the physiology and pathology of the system?*

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

# 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.

## a rather provisional syllabus

0. why mathematical models?
1. post-translational modification of proteins
2. microscopic cybernetics
3. development and evolution

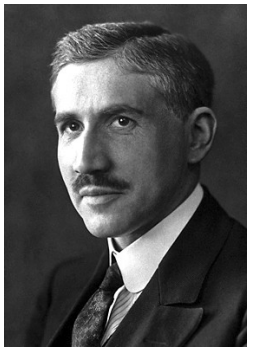
# 0. why mathematical models?

## a revisionist history of biology

... suggests that it has some of the finest examples of how quantitative reasoning and mathematical analysis have been used to uncover how the world works

| | |
|---|---|
| thomas hunt morgan | walter cannon |
| ernest starling | paul weiss |
| charles sherrington | conrad waddington |
| august krogh | arthur guyton |
| archibald vivian hill | alan hodgkin |
| leonor michaelis | andrew huxley |
| david keilin | ernest mcculloch |
| otto warburg | james till |
| j b s haldane | niels jerne |
| r a fisher | peter mitchell |
| sewall wright | james black |

# 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

# michaelis-menten revisited

***principle of mass action***

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

rate constant

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

$$\frac{dC}{dt} = kA^2B^3$$

$$\frac{dA}{dt} = -2kA^2B^3$$

$$\frac{dB}{dt} = -3kA^2B^3$$

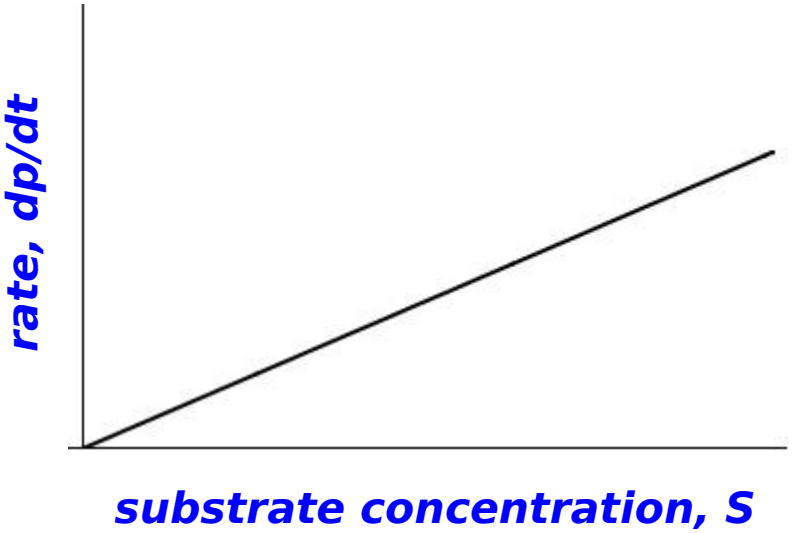

P Waage & C Guldberg, *"Studies concerning affinity"*, J Chem Edu 63:1044-7 1986. English translation by H Abrash of original 1866 paper in Norwegian.

JG, *"Modelling of interaction networks in the cell: theory and mathematical methods"*, to appear in E Egelman (editor), Comprehensive Biophysics Volume 9, Elsevier, 2011.

# enzyme rates

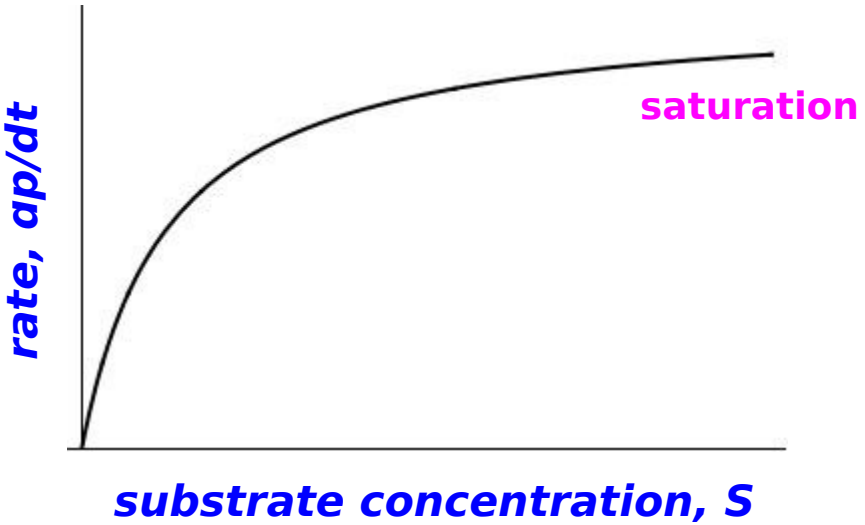
S → P

mass action ⟹




***invertase***

sucrose → fructose + glucose



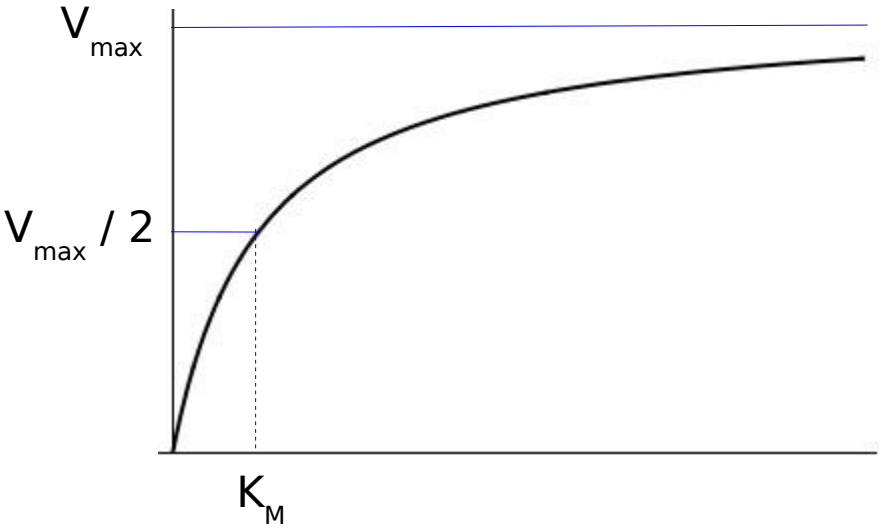
# leonor michaelis and maud menten

enzyme-substrate complex

$$E + S \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + P$$

$$\frac{dP}{dt} = \frac{V_{max} S}{K_M + S}$$

$$V_{max} = E_{tot} k_{cat} \qquad K_M = \frac{k_{off} + k_{cat}}{k_{on}}$$




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

# britton chance

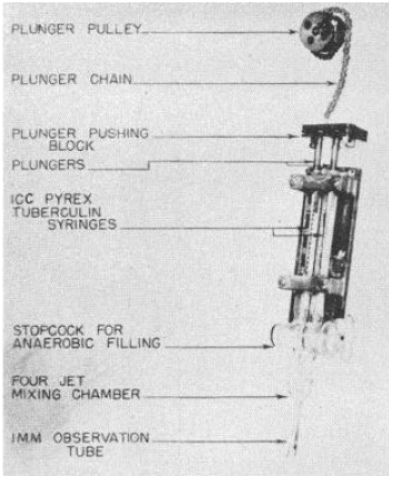
was the first to isolate an enzyme-substrate complex and to measure on- and off-rates

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.

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

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

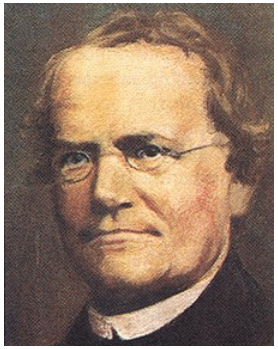
$k_2 = 0.2\ sec^{-1}$

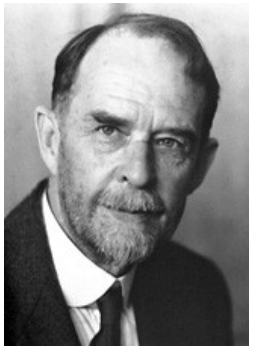


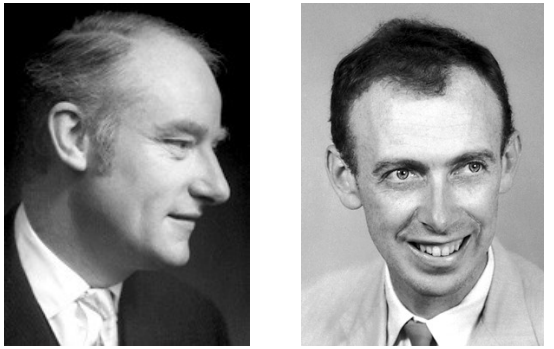

B Chance, *"The kinetics of the enzyme-substrate compound of peroxidase"*, J Biol Chem, **151**:553-77 1943

# mathematics provides evidence for things unseen

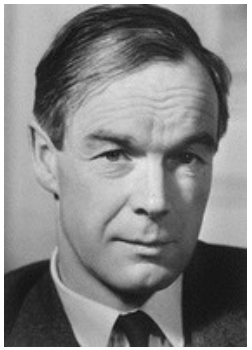
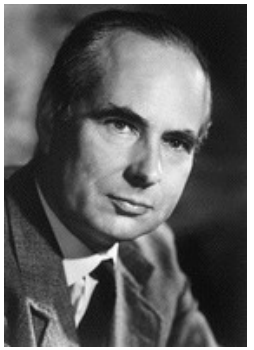
“genes”


1866


1915

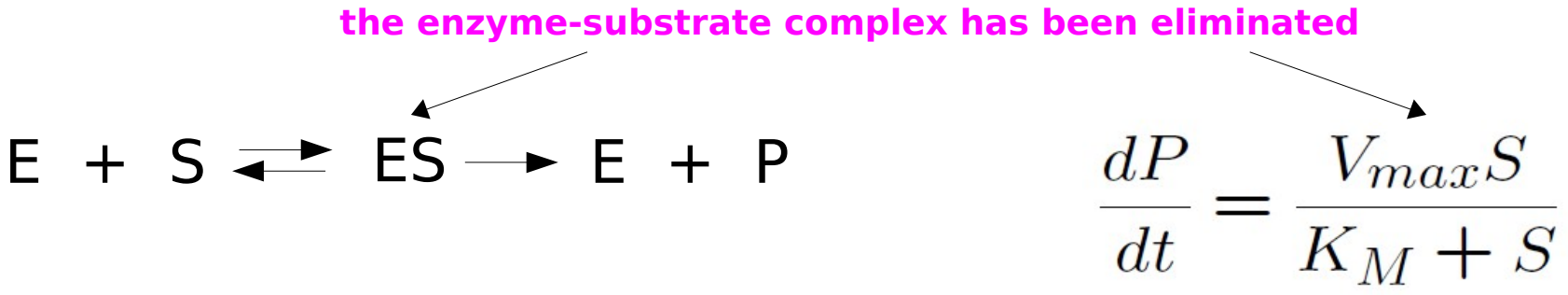

1953

“ion channels”



1952


1976

# time-scale separation eliminates internal complexity



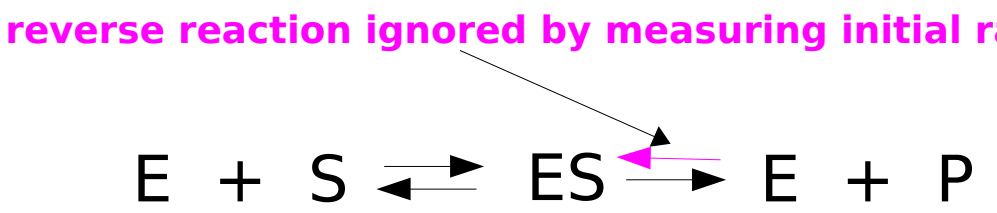

the complex is assumed to come rapidly to steady-state

$$\frac{dES}{dt} = 0$$

in comparison to slower catalytic activity

*there is a framework for doing such calculations, that we will discuss later*

# unrealistic models can be (much) better




**dependence of rates on pH and ionic strength ignored by buffering**

***careful arrangement of experimental conditions makes it feasible to get away with an unrealistic model***

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

## michaelis-menten, in summary

1. evidence for things unseen
2. time-scale separation eliminates internal complexity
3. unrealistic models can be better

what is important about a model is not merely that it fits the data (its output) but the assumptions made to achieve that (its input)

## back to the present

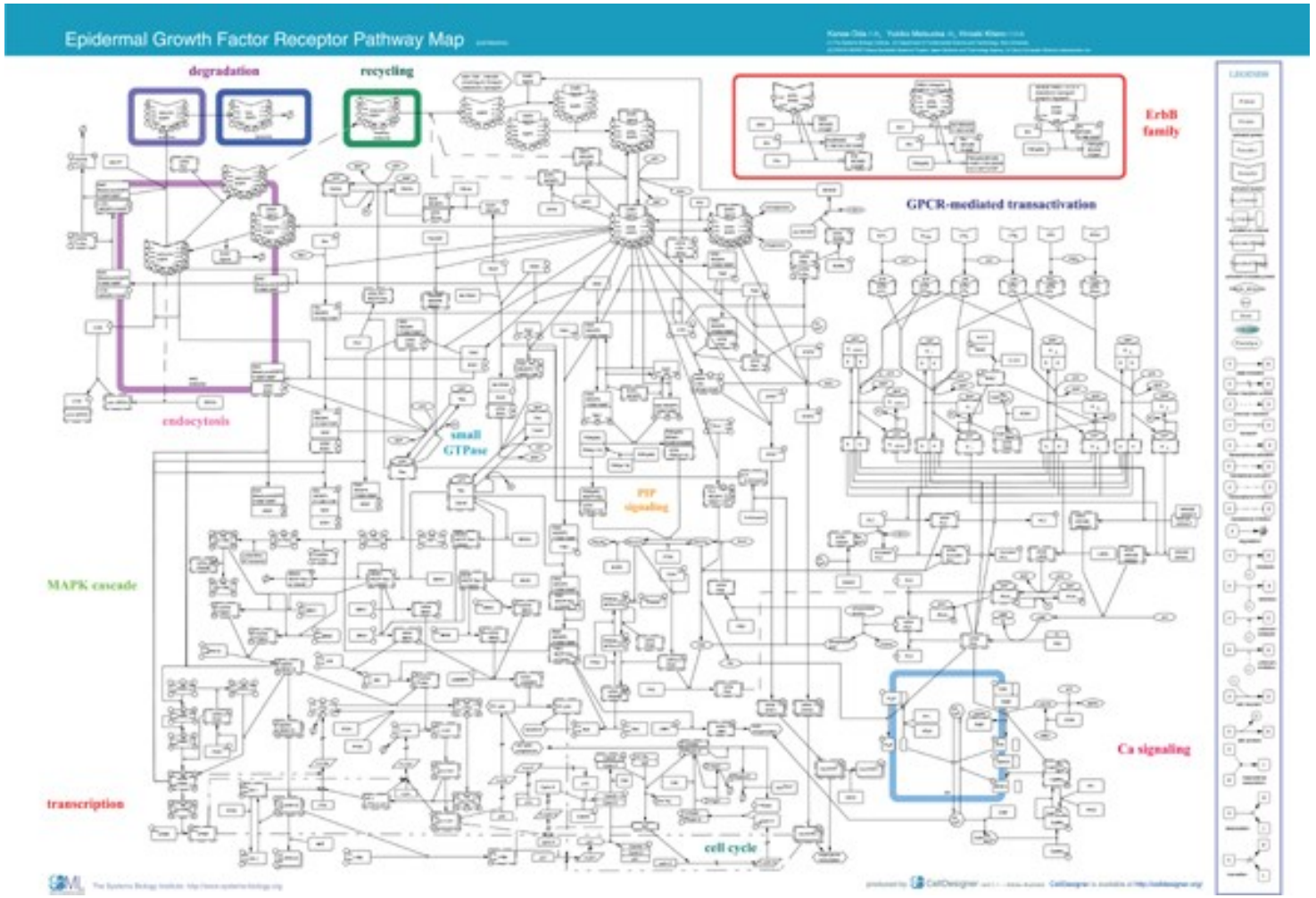
these days, (we think) we (sometimes) know most of the molecular components

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

***models provide evidence relating mechanism to function***

***and the means to interpret data mechanistically***

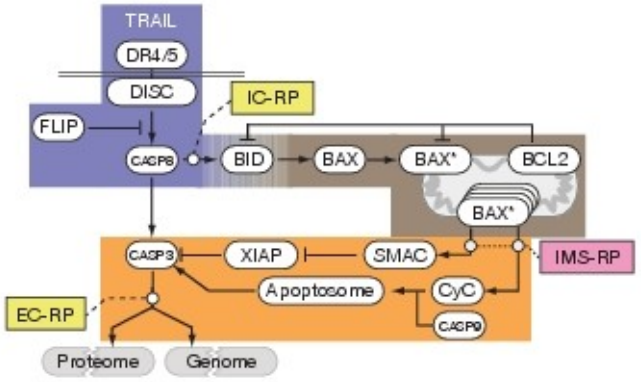
# evidence relating mechanism to function ...

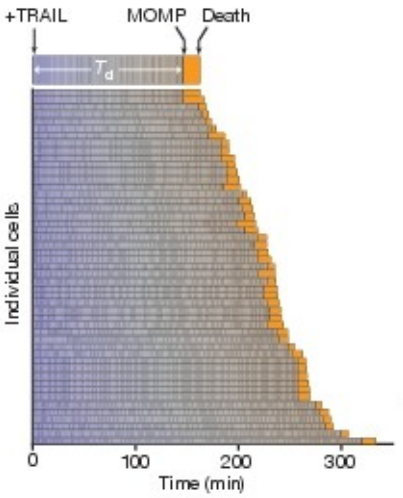



how do we deal with this overwhelming molecular complexity?

# thick models – embrace the details

*more detail may lead to improved experimental prediction, in specific biological contexts, but requires complementary datasets to deal with the "parameter problem". it also becomes harder to see the wood for the trees*




Spencer, Gaudet, Albeck, Burke, Sorger, *"Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis"*, Nature **459**:428-33 2009

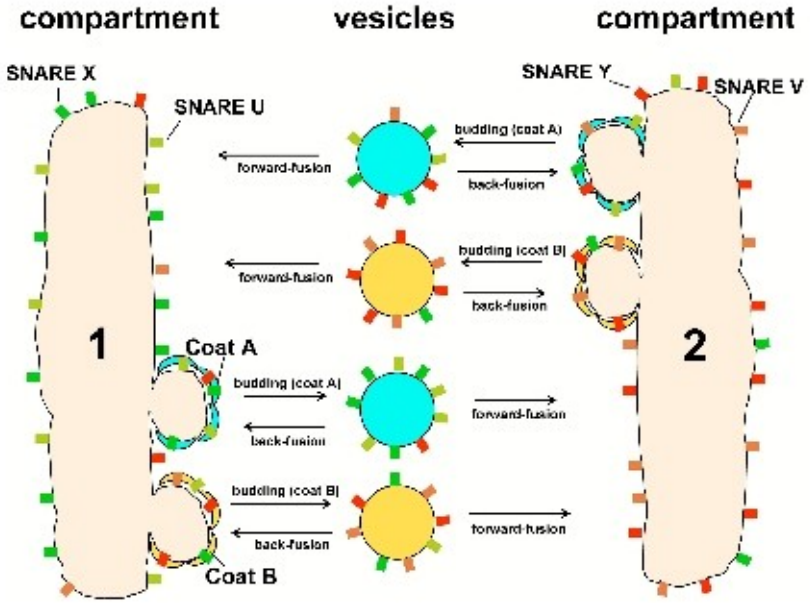
Albeck, Burke, Spencer, Lauffenburger, Sorger, *"Modelling a snap-action, variable delay switch controlling extrinsic cell death"*, PLoS Biol **6**:2831-52 2008

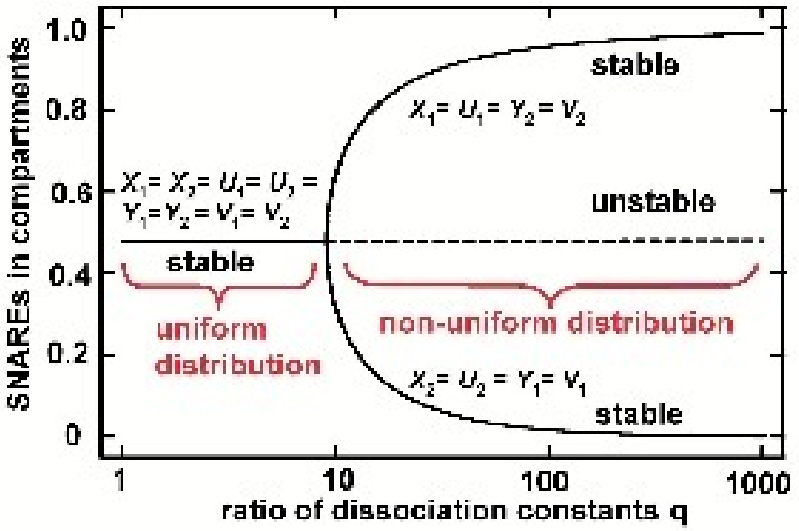
Table S2. EARM v1.0 Biochemical Equations

| Reaction | Ref |
|---|---|
| $L + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} L:R \xrightarrow{\kappa_1} R^*$ | (1) |
| $R^* + flip \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R^*:flip$ | (2) |
| $R^* + C8 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} R^*:C8 \xrightarrow{\kappa_3} R^* + C8^*$ | (3) |
| $C8^* + Bar \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} C8^*:Bar$ | (4) |
| $C8^* + C3 \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} C8^*:C3 \xrightarrow{\kappa_5} C8^* + C3^*$ | (5) |
| $C3^* + C6 \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} C3^*:C6 \xrightarrow{\kappa_6} C3^* + C6^*$ | (6) |
| $C6^* + C8 \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} C6^*:C8 \xrightarrow{\kappa_7} C6^* + C8^*$ | (7) |
| $C3^* + XIAP \underset{k_{-8}}{\overset{k_8}{\rightleftharpoons}} C3^*:XIAP \xrightarrow{\kappa_8} C3^*_{Ub} + XIAP$ | (8,9) |
| $C3^* + PARP \underset{k_{-9}}{\overset{k_9}{\rightleftharpoons}} C3^*:PARP \xrightarrow{\kappa_9} C3^* + cPARP$ | (10) |
| $C8^* + Bid \underset{k_{-10}}{\overset{k_{10}}{\rightleftharpoons}} C8^*:Bid \xrightarrow{\kappa_{10}} C8^* + tBid$ | (11,12) |
| $Bid + Bcl2_c \underset{k_{-11}}{\overset{k_{11}}{\rightleftharpoons}} Bid:Bcl2_c$ | (13) |
| $tBid + Bax \underset{k_{-12}}{\overset{k_{12}}{\rightleftharpoons}} tBid:Bax \xrightarrow{\kappa_{12}} tBid + Bax^*$ | (14) |
| $Bax^* \underset{k_{-13}}{\overset{k_{13}}{\rightleftharpoons}} Bax^*_m$ | (14) |
| $Bax^*_m + Bcl2 \underset{k_{-14}}{\overset{k_{14}}{\rightleftharpoons}} Bax^*_m:Bcl2$ | (15) |
| $Bax^*_m + Bax^*_m \underset{k_{-15}}{\overset{k_{15}}{\rightleftharpoons}} Bax_2$ | (16) |
| $Bax_2 + Bcl2 \underset{k_{-16}}{\overset{k_{16}}{\rightleftharpoons}} Bax_2:Bcl2$ | |
| $Bax_2 + Bax_2 \underset{k_{-17}}{\overset{k_{17}}{\rightleftharpoons}} Bax_4$ | (17) |
| $Bax_4 + Bcl2 \underset{k_{-18}}{\overset{k_{18}}{\rightleftharpoons}} Bax_4:Bcl2$ | |
| $Bax_4 + M \underset{k_{-19}}{\overset{k_{19}}{\rightleftharpoons}} Bax_4:M \xrightarrow{\kappa_{19}} M^*$ | (17) |
| $M^* + CyC_m \underset{k_{-20}}{\overset{k_{20}}{\rightleftharpoons}} M^*:CyC_m \xrightarrow{\kappa_{20}} M^* + CyC_r$ | (18) |
| $M^* + Smac_m \underset{k_{-21}}{\overset{k_{21}}{\rightleftharpoons}} M^*:Smac_m \xrightarrow{\kappa_{21}} M^* + Smac_r$ | (19,20) |
| $CyC_r \underset{k_{-22}}{\overset{k_{22}}{\rightleftharpoons}} CyC$ | |
| $CyC + Apaf \underset{k_{-23}}{\overset{k_{23}}{\rightleftharpoons}} CyC:Apaf \xrightarrow{\kappa_{23}} CyC + Apaf^*$ | (21) |
| $Apaf^* + C9 \underset{k_{-24}}{\overset{k_{24}}{\rightleftharpoons}} Apop$ | (18) |
| $Apop + C3 \underset{k_{-25}}{\overset{k_{25}}{\rightleftharpoons}} Apop:C3 \xrightarrow{\kappa_{25}} Apop + C3^*$ | (18) |
| $Smac_r \underset{k_{-26}}{\overset{k_{26}}{\rightleftharpoons}} Smac$ | |
| $Apop + XIAP \underset{k_{-27}}{\overset{k_{27}}{\rightleftharpoons}} Apop:XIAP$ | (22,23) |
| $Smac + XIAP \underset{k_{-28}}{\overset{k_{28}}{\rightleftharpoons}} Smac:XIAP$ | (19,20) |

# thin models – abstract the details

*abstracting may give independence from details whose correctness is uncertain or whose validity is context-specific, allowing general principles to emerge more easily, but at the risk of becoming detached from experimental interpretation*



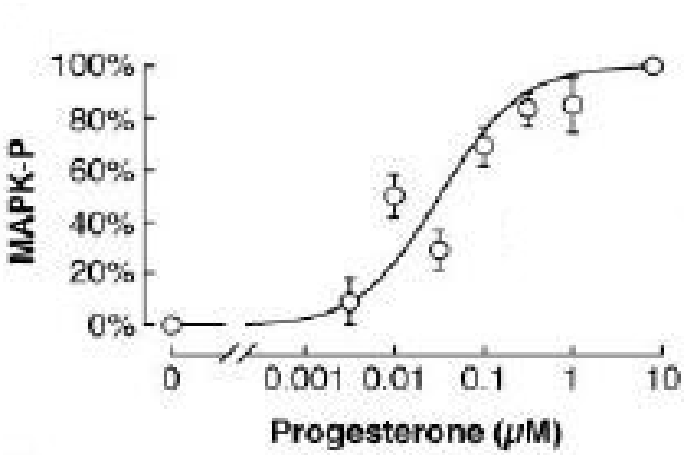

our analysis provides the first self-consistent explanation for the generation of distinct, stable compartments.

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

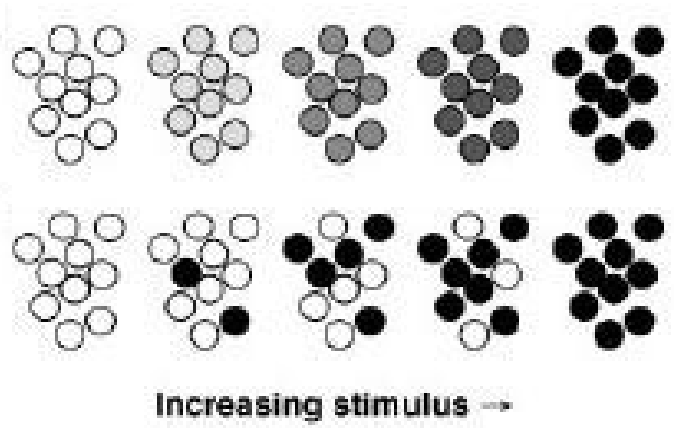
# interpeting data mechanistically

*the data that we have is rarely the data that we want. for instance, we often have to average over cellular populations but molecular mechanisms take place in individual cells. a population average may not be representative of any cell in the population.*

dose response
averaged over the population



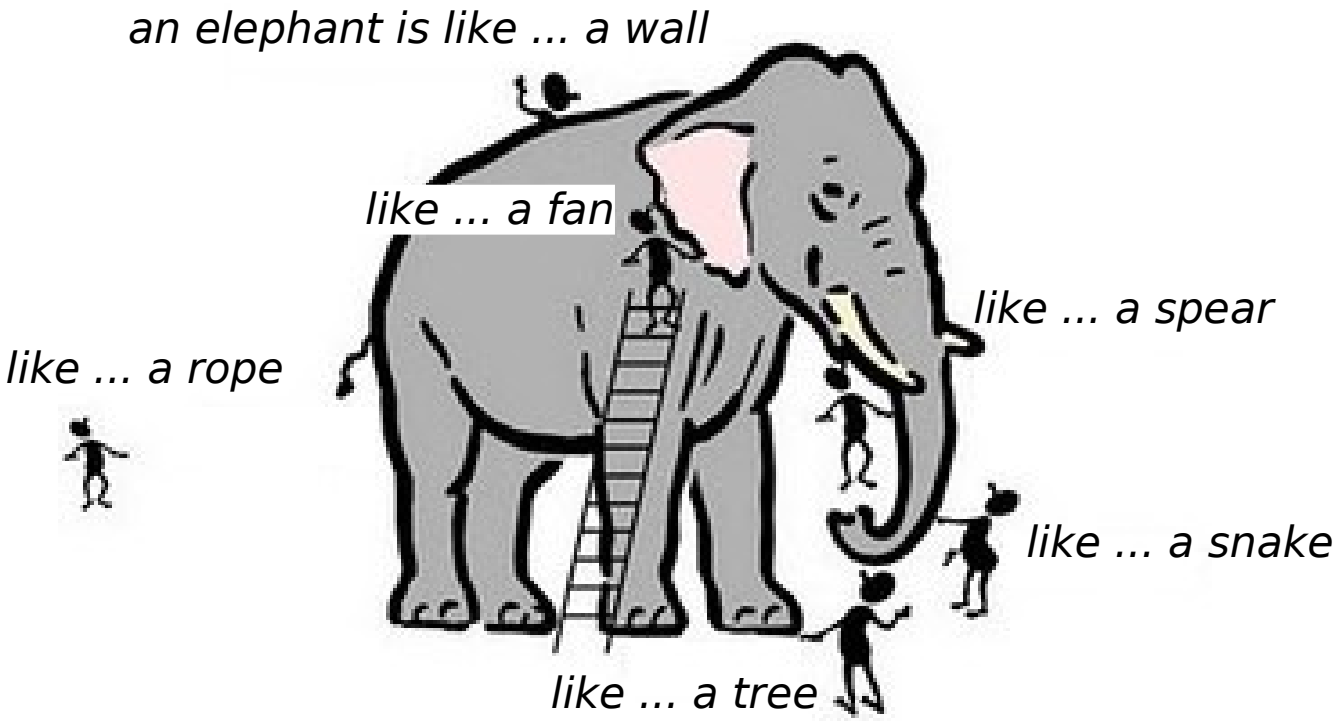

different mechanisms at
the single cell level




data never “speaks for itself” - it is always interpreted, by us!

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

# elephant reconstruction for the visually challenged



# the physiologists were here before us ...

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