Introduction to Mathematical Models

23 Feb, 2017
Jörg Stelling, D-BSSE

Content:

- Why formal models in biology?
- Systems analysis: An example
- Origins of enzyme kinetics

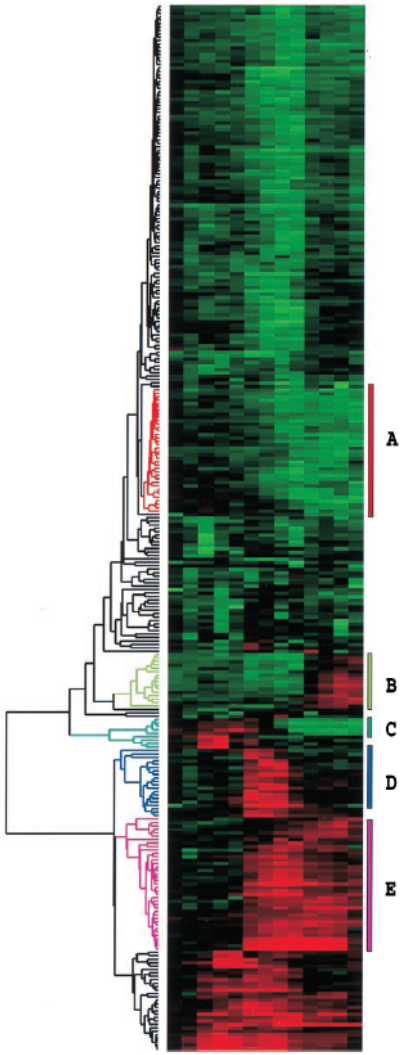
Modeling (Encyclopedia Britannica)

"**Scientific modeling**, the generation of a physical, conceptual, or mathematical representation of a real phenomenon that is difficult to observe directly.

Scientific models are used to explain and predict the behaviour of real objects or systems ...

Although modeling is a central component of modern science, scientific models at best are approximations of the objects and systems that they represent—they are not exact replicas. Thus, scientists constantly are working to improve and refine models ..."

Models are Used Everywhere in Biology



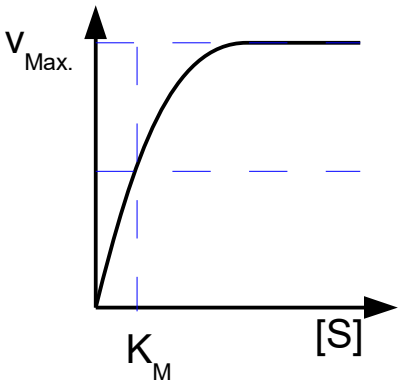
M. Eisen *et al.* (1998).
PNAS **95**, 14863-68.

- **Verbal models:**

  "Co-expressed genes have a common regulator."

- **Mathematical models:**

  Formalizations of hypotheses.



$$\frac{dY}{dt} = f_1(I) - a_1 Y,$$

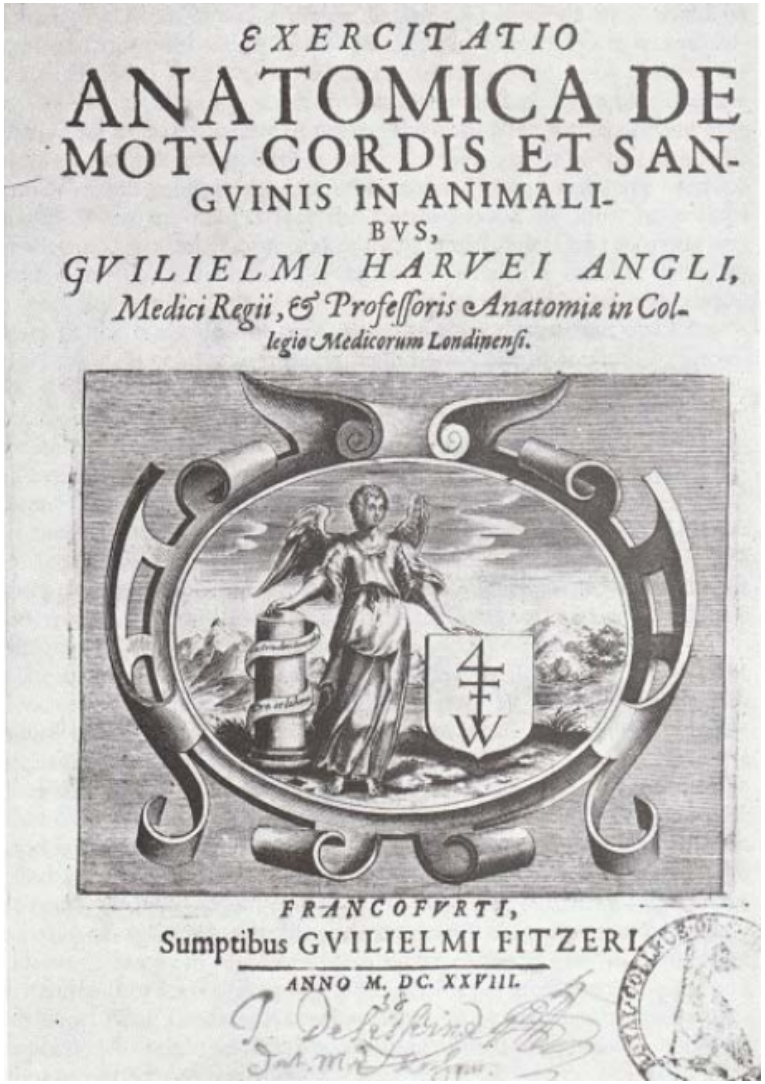
$$\frac{dY_f}{dt} = b_1 Y - a_2 Y_f,$$

$$\frac{dI}{dt} = [f_2(I_{ex}) - f_3(I)]Y_f + b_2 I_{ex} - a_3 I,$$

$$\frac{dZ}{dt} = g\, f_1(I) - a_3 Z.$$

J. Vilar *et al.* (2003). *J. Cell Biol.* **161**, 471-76

Mathematical Modeling in Biology is Not New


EXERCITATIO
ANATOMICA DE
MOTV CORDIS ET SAN-
GVINIS IN ANIMALI-
BVS,
GVILIELMI HARVEI ANGLI,
Medici Regii, & Professoris Anatomiæ in Col-
legio Medicorum Londinensi.
FRANCOFVRTI,
Sumptibus GVILIELMI FITZERI.
ANNO M. DC. XXVIII.

"On this assumption of the passage of blood, made as a basis for argument, and from the estimation of the pulse rate, it is apparent that the entire quantity of blood passes from the veins to the arteries through the heart, and likewise through the lungs."

Systems analysis of physiology by William Harvey, 1628

Systems Biology: The Modern Version

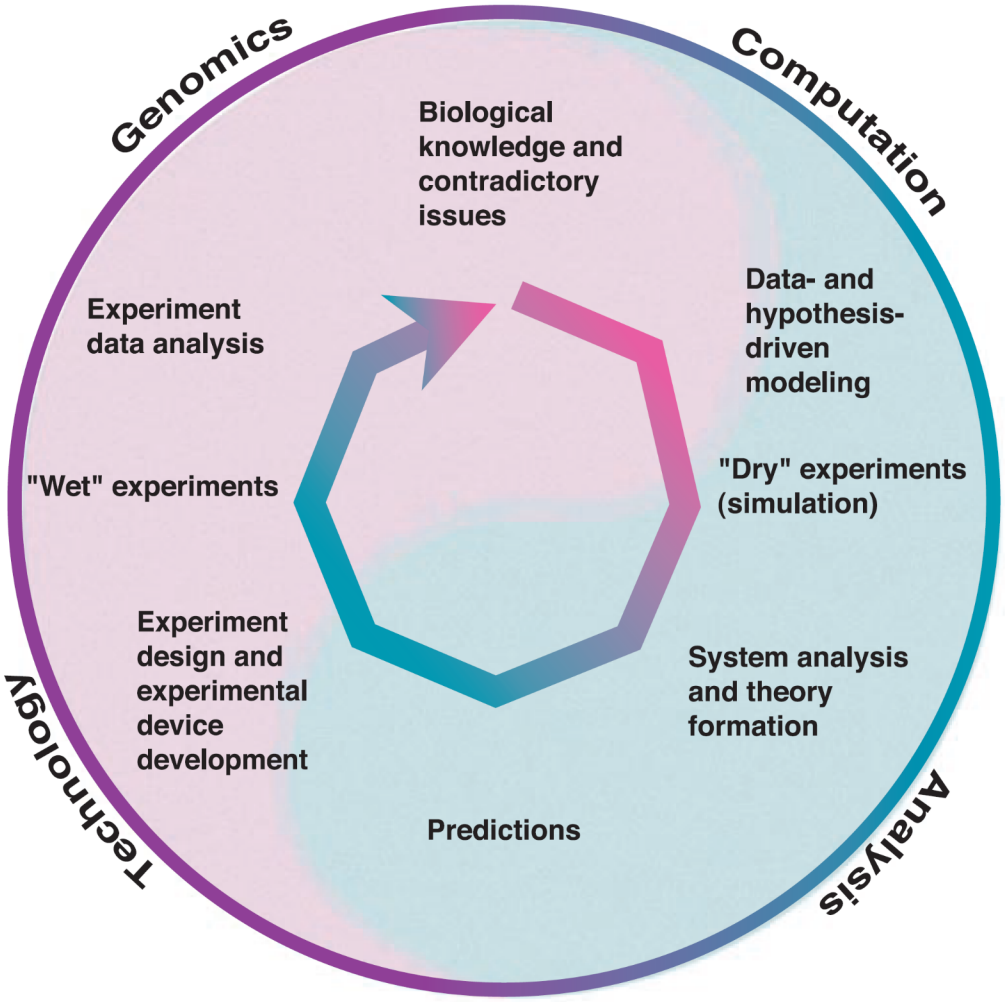


Figure from: H. Kitano (2002) Science 295: 1662

“All models are wrong

but some models are useful.”

George Box (1979)

Robustness in the strategy of scientific model building

Introduction to Mathematical Models

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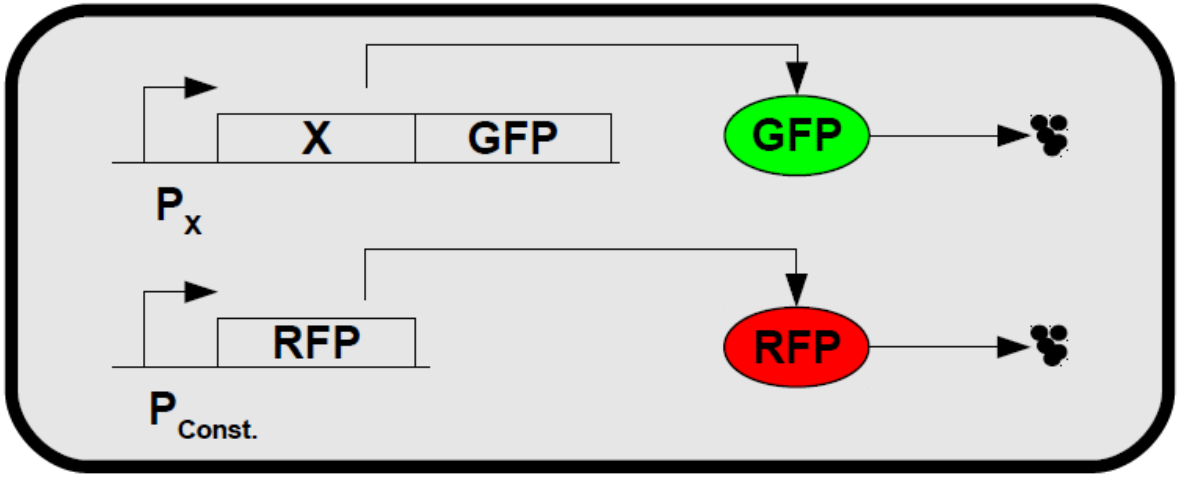
- Systems analysis: An example
- Origins of enzyme kinetics

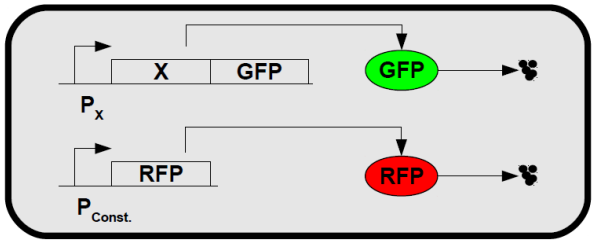
Systems Analysis: Metabolic Example



- **Aim:** Identify genes regulated by amino acid availability.
- **Approach:** Engineered *E. coli* strain with GFP fused to gene of interest (X) and constitutive RFP as control.
- **Experiment:** Measure fluourescence +/- amino acid.

Metabolic Example: 'Experimental' Data

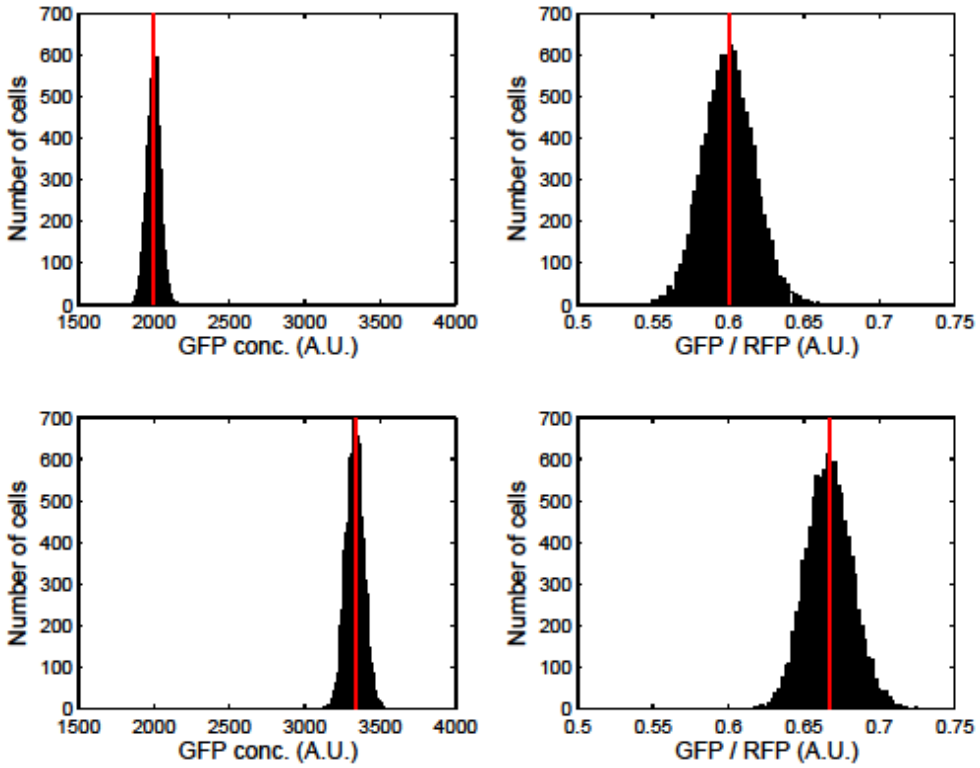
apply statistics to figure out whether it is significant



perhaps, it's X that is regulated directly, but a signaling pathway.

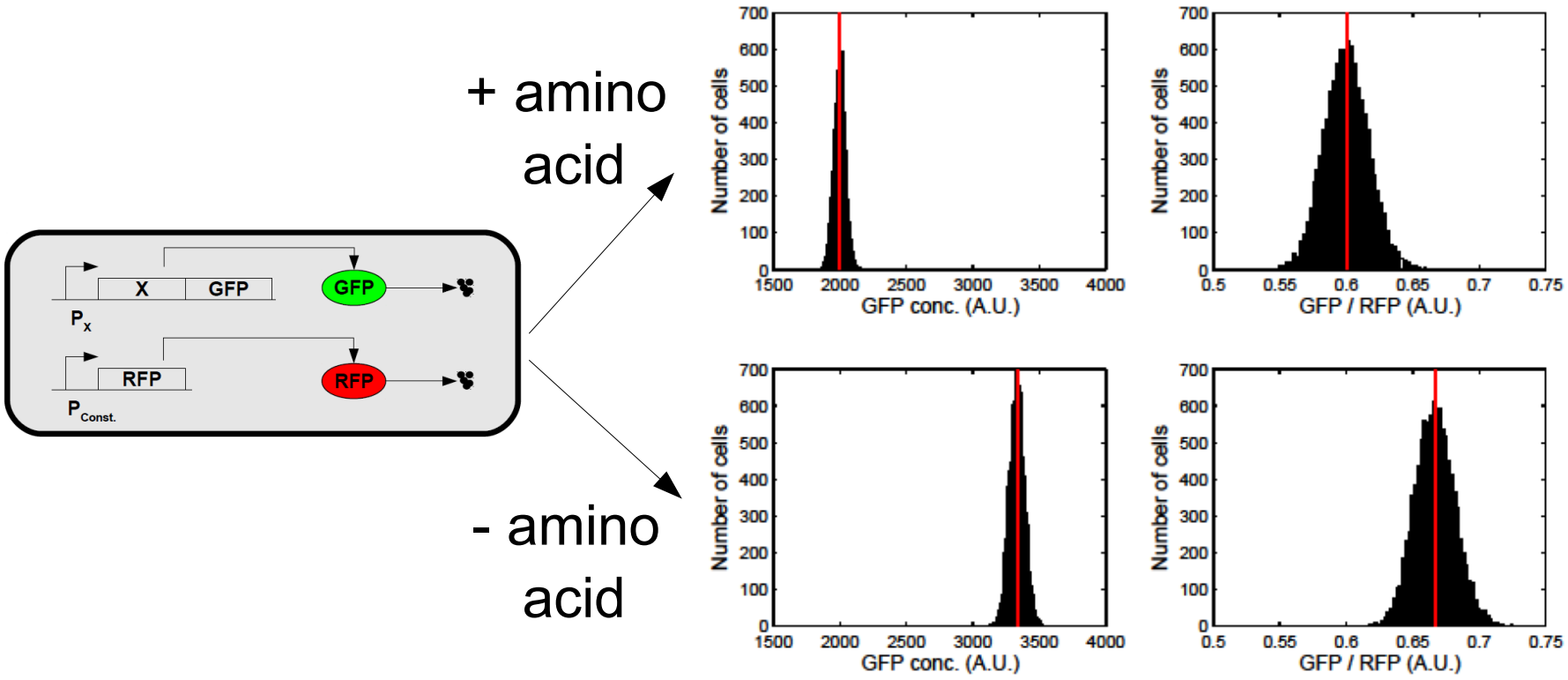
+ amino acid

- amino acid



- **Experiment:** Measure fluourescences +/- amino acid in single cells during exponential culture growth.
- Is gene X regulated by amino acid availability?

Metabolic Example: Statistical Analysis



- **Is gene X regulated by amino acid availability?**
- **Statistical analysis:** Distribution means are significantly different (Student's t-test, $P<10^{-15}$).

Metabolic Example: Interpretation of Data

Molecular Systems Biology 7; Article number 493; doi:10.1038/msb.2011.24
Citation: *Molecular Systems Biology* **7:493**

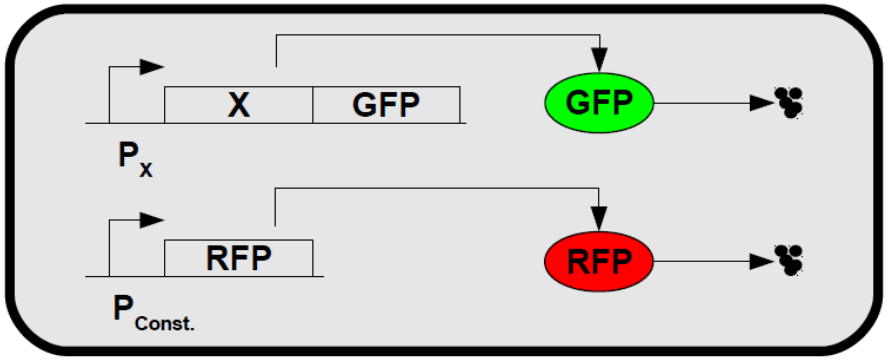
www.molecularsystemsbiology.com

molecular systems biology

Adaptation by stochastic switching of a monostable genetic circuit in *Escherichia coli*

- Claim by this paper: Expression of gene X is regulated (adapts to environment) **without** explicit signalling pathways or genetic control.
- Is this correct? Are alternative hypotheses possible?

Metabolic Example: Null Model

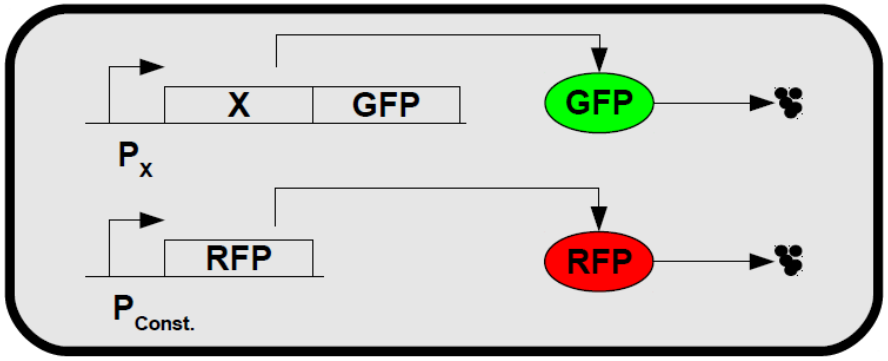


(not regulated)

- **Null hypothesis:** Gene X is constitutively expressed.
- **Assumptions:** All cells are equal, fluorescence measures gene expression, cells are in steady state.
- **Model:** Mass balance for each fluorescent protein:

$$\begin{matrix} Rate\ of \\ change\ of \\ fluorescence \end{matrix} = FP\ production - FP\ degradation = 0$$

Metabolic Example: Null Model



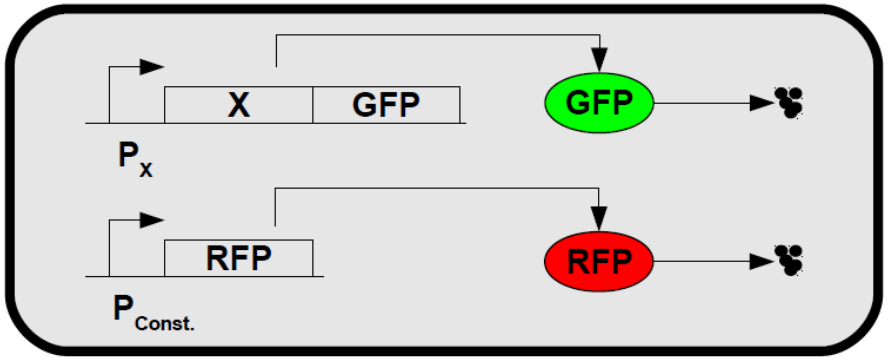
- **Model:** Mass balance for each fluorescent protein:

$$\frac{d[GFP]}{dt} = k_{P,GFP} - k_{D,GFP} \cdot [GFP] = 0$$

$$\frac{d[RFP]}{dt} = k_{P,RFP} - k_{D,RFP} \cdot [RFP] = 0$$

with **model parameters** (k_P for production, k_D for degradation) and **model states** ($[GFP]$ and $[RFP]$).

Metabolic Example: Null Model



- **Model:** Mass balance for each fluorescent protein:

$$\frac{d[GFP]}{dt} = k_{P,GFP} - k_{D,GFP} \cdot [GFP] = 0$$

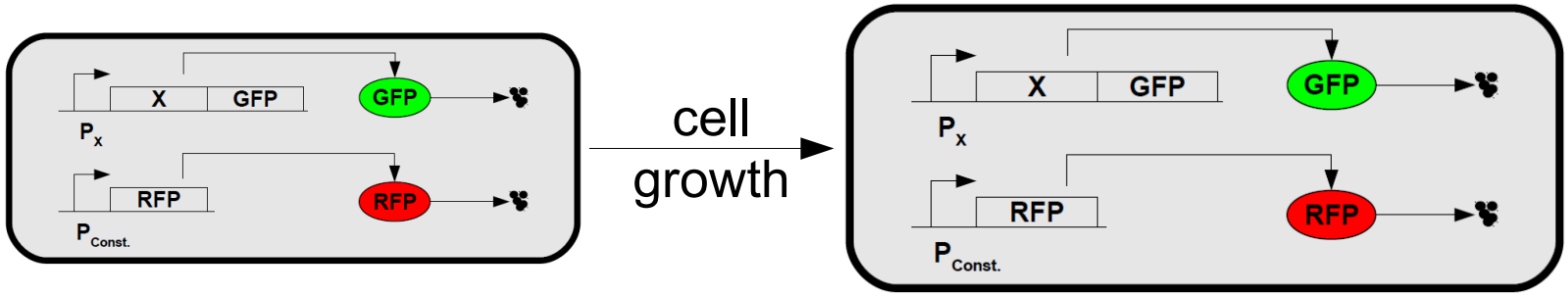
$$\frac{d[RFP]}{dt} = k_{P,RFP} - k_{D,RFP} \cdot [RFP] = 0$$

Assumptions can be wrong. there can be interference in floursescne or degradation etc.

- **Contradiction** with experimental observations:

$$[GFP] = \frac{k_{P,GFP}}{k_{D,GFP}}, \quad [RFP] = \frac{k_{P,RFP}}{k_{D,RFP}} \quad \Rightarrow \quad \frac{[GFP]}{[RFP]} = \frac{k_{P,GFP} \cdot k_{D,RFP}}{k_{D,GFP} \cdot k_{P,RFP}}$$

Metabolic Example: Alternative Model



- **Hypothesis**: Amino acid availability affects growth rate (μ), and cell growth dilutes protein content:

$$\frac{d[GFP]}{dt} = k_{P,GFP} - (k_{D,GFP} + \mu) \cdot [GFP] = 0$$

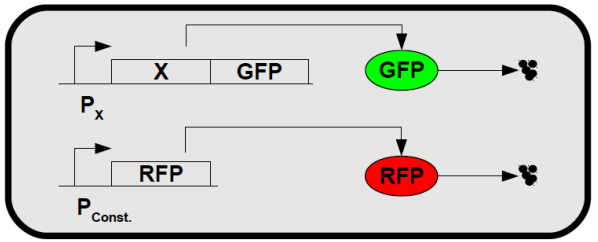
$$\frac{d[RFP]}{dt} = k_{P,RFP} - (k_{D,RFP} + \mu) \cdot [RFP] = 0$$

- The GFP/RFP ratio then depends on the growth rate:

$$[GFP] = \frac{k_{P,GFP}}{k_{D,GFP} + \mu}, \quad [RFP] = \frac{k_{P,RFP}}{k_{D,RFP} + \mu} \quad \Rightarrow \quad \frac{[GFP]}{[RFP]} = \frac{k_{P,GFP}}{k_{D,GFP}} \frac{k_{D,RFP} + \mu}{k_{D,GFP} + \mu}$$

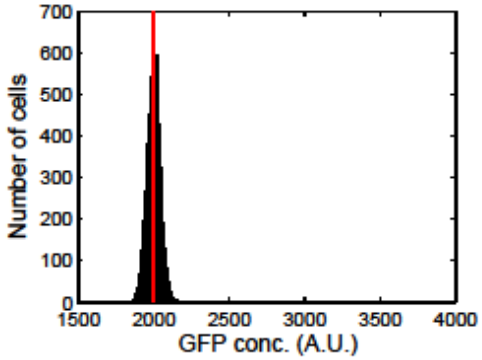
Metabolic Example: Alternative Model

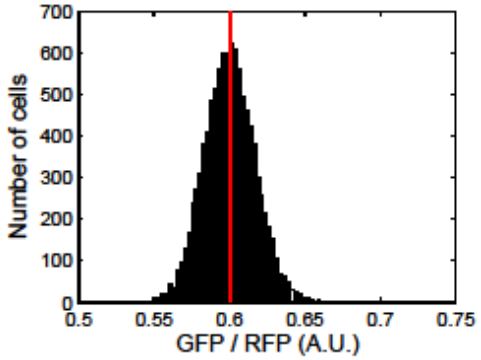
cells have an increased grwoth rate with amino acid availability of course.

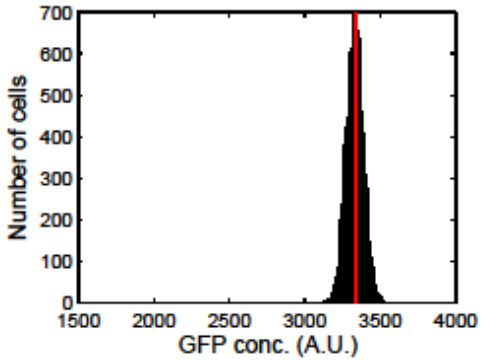


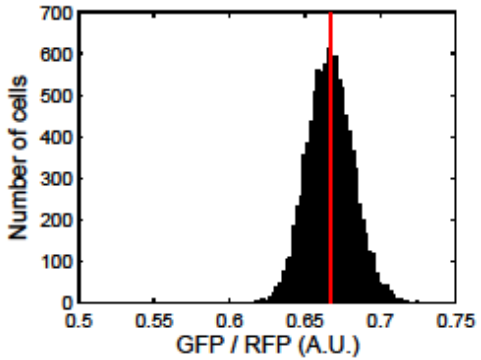
fast growth

slow growth





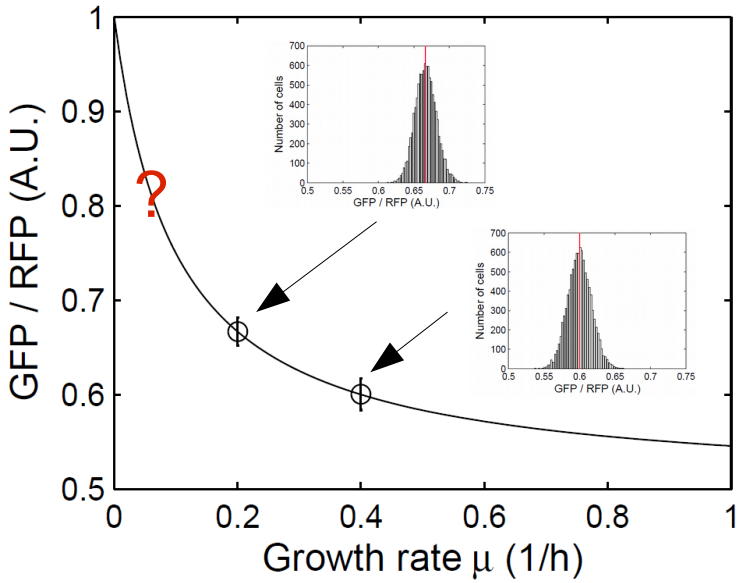




- The GFP/RFP ratio then depends on the growth rate:

$$[GFP]=\frac{k_{P,GFP}}{k_{D,GFP}+\mu},\quad [RFP]=\frac{k_{P,RFP}}{k_{D,RFP}+\mu}\quad\Rightarrow\quad \frac{[GFP]}{[RFP]}=\frac{k_{P,GFP}}{k_{D,GFP}}\frac{k_{D,RFP}+\mu}{k_{D,GFP}+\mu}$$

Metabolic Example: Conclusions



- The model can predict the growth rate dependency:

$$\frac{[GFP]}{[RFP]} = \frac{k_{P,GFP}}{k_{D,GFP}} \frac{k_{D,RFP}+\mu}{k_{D,GFP}+\mu}$$

- Gene X may be unregulated → Further experiments (e.g., different modulation of growth) are required.

Metabolic Example: Why Care About It?

- Critical thinking:

Molecular Systems Biology 7; Article number 493; doi:10.1038/msb.2011.24
Citation: *Molecular Systems Biology* **7:493**

www.molecularsystemsbiology.com

molecular systems biology

Adaptation by stochastic switching of a monostable genetic circuit in *Escherichia coli*

- Biological reality:

Growth Rate-Dependent Global Effects on Gene Expression in Bacteria

Stefan Klumpp,[1,2,4,*] Zhongge Zhang,[3] and Terence Hwa[1,2,3,*]
[1]Center for Theoretical Biological Physics
[2]Department of Physics
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University of California, San Diego, La Jolla, CA 92093-0374, USA
[4]Max Planck Institute of Colloids and Interfaces, 14424 Potsdam, Germany
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DOI 10.1016/j.cell.2009.12.001

Cell

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Revisiting Michaelis-Menten Kinetics

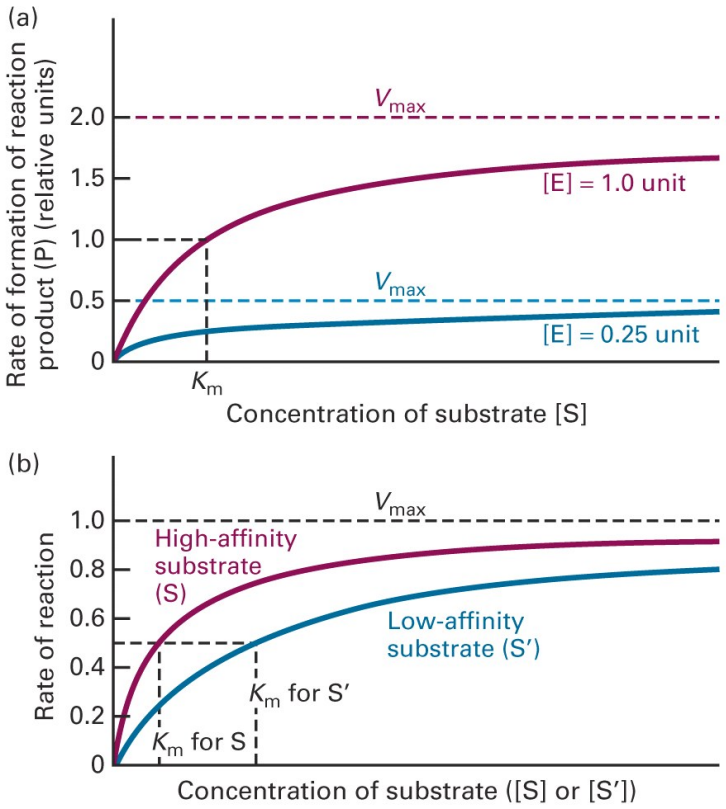
Die Kinetik der Invertinwirkung.

Von

L. Michaelis und Miß Maud L. Menten.

(Eingegangen am 4. Februar 1913.)

$$v = \frac{v_{max}[S]_0}{[S]_0 + K_M}$$



H. Lodish et al., *Molecular Cell Biology*, 5th ed., 2004.

- v_{max} : Maximal reaction rate (velocity).
- K_M : Affinity enzyme-substrate (subtrate conc. for 50% v_{max}).

Michaelis-Menten: What is the Model?

Die Kinetik der Invertinwirkung.

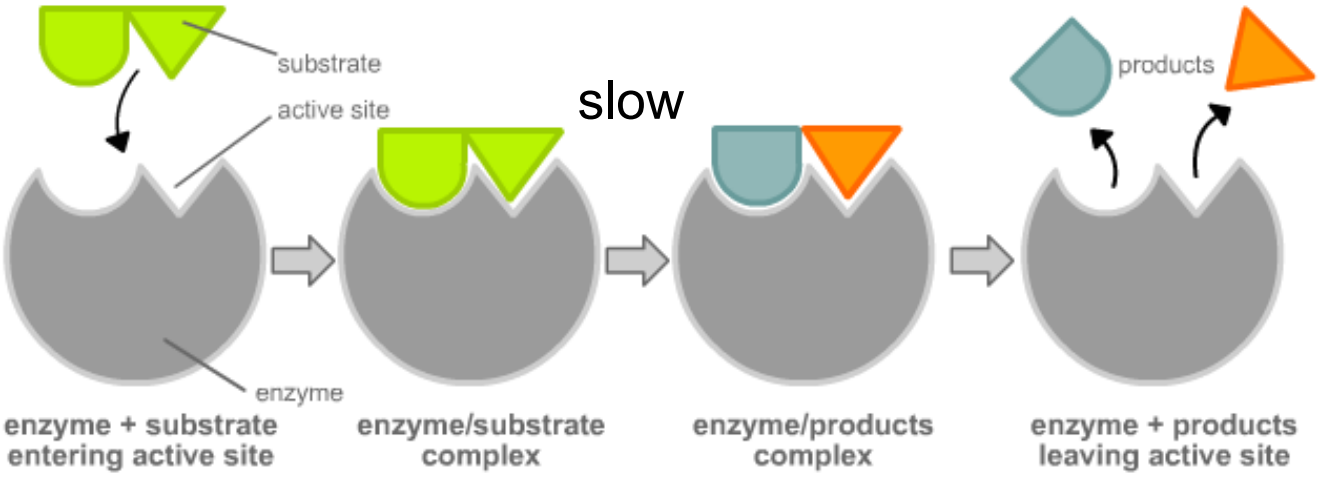
Von

L. Michaelis und Miß Maud L. Menten.

(Eingegangen am 4. Februar 1913.)

$$v = \frac{v_{max}[S]_0}{[S]_0 + K_M}$$

- Basic scheme: $[E] + [S] \rightleftharpoons [E \bullet S] \longrightarrow [E] + [P]$



Reaction Kinetics: Law of Mass Action

- Law of mass action (at constant temperature, without catalyst): Chemical reaction rates are proportional to products of concentrations of reacting molecules.

- Derived from chemical collision theory:

$$p(\text{reaction}) = const.(\text{energy, orientation, ...}) \cdot \prod n_{molecules}$$

- **Statistical approach** → Large numbers of molecules.

- **'Well-mixed system'** → Cell as a 'bag of enzymes'.

Enzyme Kinetics: Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{\cdot}S \xrightarrow{k_2} E + P$$

- Dynamic (ODE) system for enzyme (E), substrate (S), enzyme-substrate complex (E·S) and product (P):

$$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[E \cdot S]$$

$$\frac{d[E]}{dt} = -k_1[E][S] + \left(k_{-1} + k_2\right)[E \cdot S]$$

$$\frac{d[E \cdot S]}{dt} = +k_1[E][S] - \left(k_{-1} + k_2\right)[E \cdot S]$$

$$\frac{d[P]}{dt} = +k_2[E \cdot S] \equiv v$$

- Simplification #1: No feedback by product → Ignore first.

Enzyme Kinetics: Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{\cdot}S \xrightarrow{k_2} E + P$$

- Simplification #2: Total enzyme amount is conserved:

$$[E]^T = [E] + [E \cdot S]$$

- Eliminate one dynamic variable from the ODE system:

$$\frac{d[S]}{dt} = -k_1[E]^T[S] + (k_1[S] + k_{-1})[E \cdot S]$$

$$\frac{d[E \cdot S]}{dt} = +k_1[E]^T[S] - (k_1[S] + k_{-1} + k_2)[E \cdot S]$$

- Analytic solution ... needed 80 years to come up with ...

Enzyme Kinetics: Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{\cdot}S \xrightarrow{k_2} E + P$$

- Assumption #1: Quasi steady-state approximation because of time-scale separation ($k_1, k_{-1} >> k_2$):

$$\frac{d[E \cdot S]}{dt} \approx 0$$

- Reduction to algebraic equation in two variables:

$$[E \cdot S] = \frac{[S][E]^T}{[S] + \frac{k_2 + k_{-1}}{k_1}}$$

assumption: there is a lot more substrate than enzymes (=infinite pool of substrate). Doesn't hold for all problems.

Enzyme Kinetics: Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{\cdot}S \xrightarrow{k_2} E + P$$

- Assumption #2: Excess of substrate over enzyme (e.g., for start of the reaction with initial concentration $[S]_0$):

$$[S] \approx [S]_0$$

- Enzyme-substrate complex in terms of initial substrate:

$$[E \cdot S] = \frac{[S]_0 [E]^T}{[S]_0 + \frac{k_2 + k_{-1}}{k_1}}$$

Enzyme Kinetics: Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{\cdot}S \xrightarrow{k_2} E + P$$

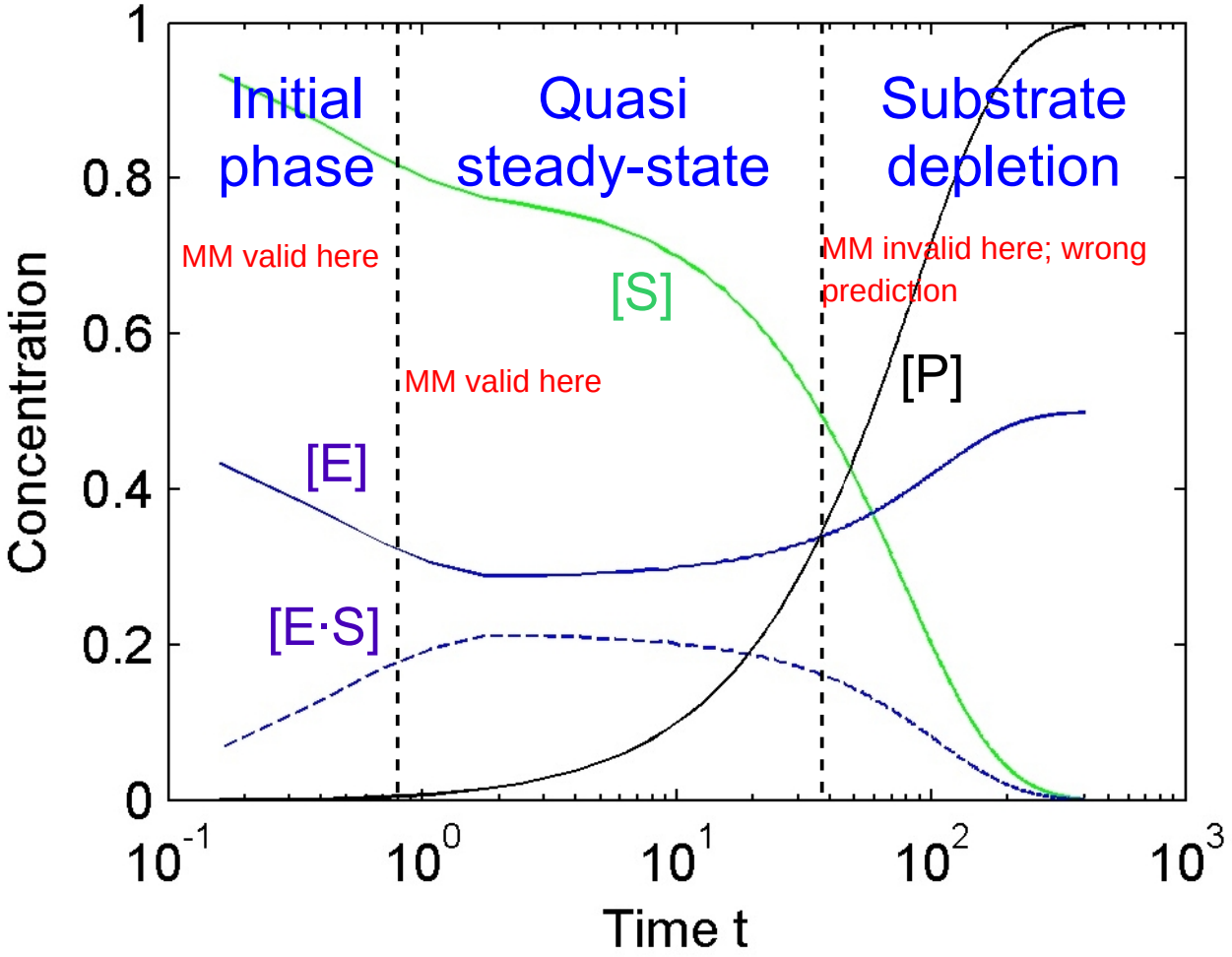
- Kinetic law capturing product formation rate v:

$$\frac{d[P]}{dt} = +k_2[E \cdot S] = \frac{k_2[S]_0[E]^T}{[S]_0 + \frac{k_2 + k_{-1}}{k_1}} \equiv v$$

- Michaelis-Menten kinetics with maximal reaction rate v_{max} and Michaelis-Menten constant K_M:

$$v = \frac{v_{max}[S]_0}{[S]_0 + K_M}$$

Michaelis-Menten Kinetics Approximate



model only viable in a spefific range (middle part and beginning; substrate depletion is predicted worngly)

- **Full dynamics** → Approximations (quasi steady-state, substrate excess) valid only in a time window.

Reaction Kinetics Can Be Generalized

- Derivation of rate laws or equilibrium binding concentrations for structurally similar reaction networks, using the same assumptions, yields similar functions.

- Example: Gene G bound by transcription factor T:
  - Without repression: $[G \cdot T] = \frac{[G]^T [T]}{[T] + K}$
  - Competitive repressor R: $[G \cdot T] = \frac{[G]^T [T]}{[T] + K\left(1 + [R]/K_I\right)}$
  - Cooperative binding: $[G \cdot T] = \frac{[G]^T [T]^n}{[T]^n + K^n}$

Summary: Teaching Goal II

- Models (abstractions from reality) are central to any scientific endeavour.
- Interpretation of data and hypotheses often requires formal models: even ‘simple’ biological systems can show unintuitive behaviour (see metabolic example).
- Realistic models can be used for data interpretation, hypothesis testing, design of new experiments, ...

(What does ‘realistic’ mean for a given biological problem?)

Summary: Teaching Goal III

- Different assumptions on biology lead to different types of mathematical formalisms and abstractions (see full enzyme kinetics vs. Michaelis-Menten rate law).

- The logic of deriving the Michaelis-Menten rate law generalizes to other rate laws in enzyme kinetics as well as to other biological phenomena such as control of gene regulation.