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        <listOfProducts>
          <speciesReference species="B"/>
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              <times/>
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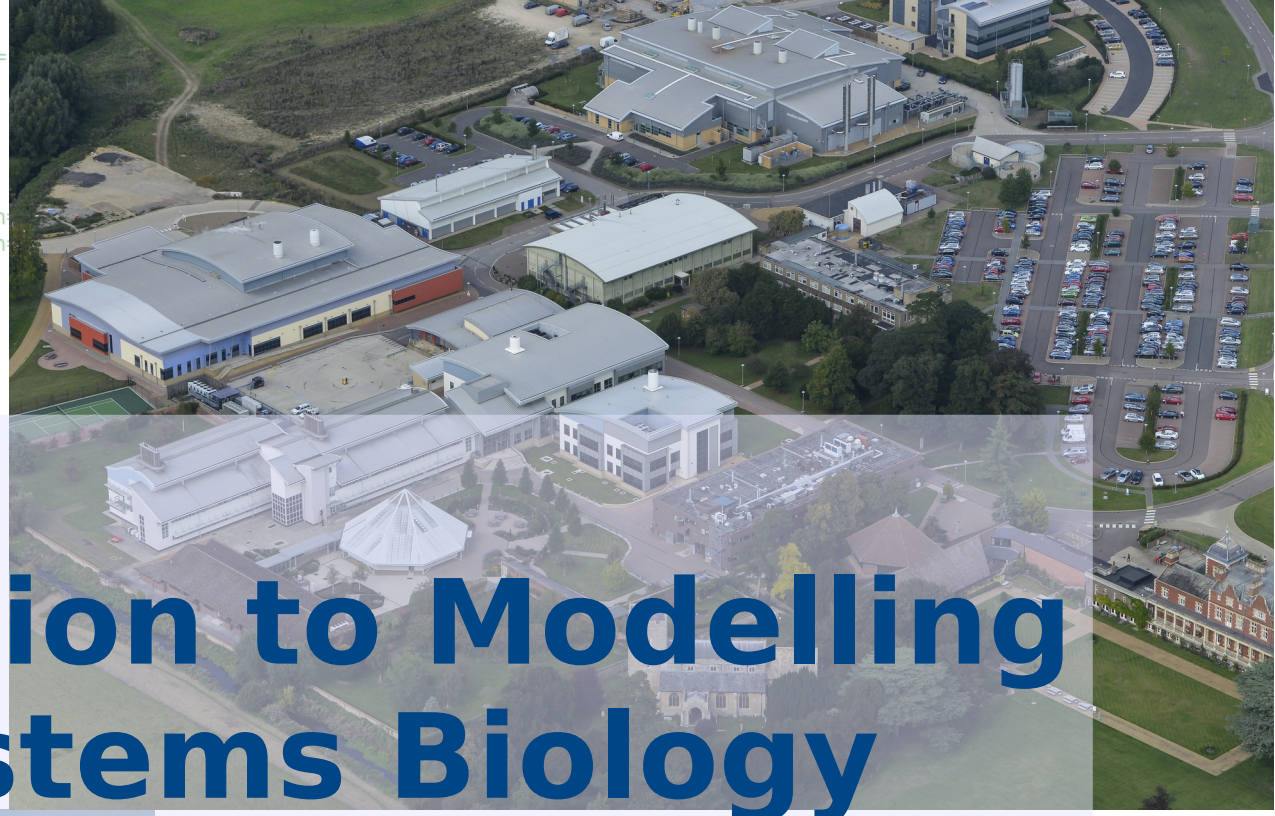
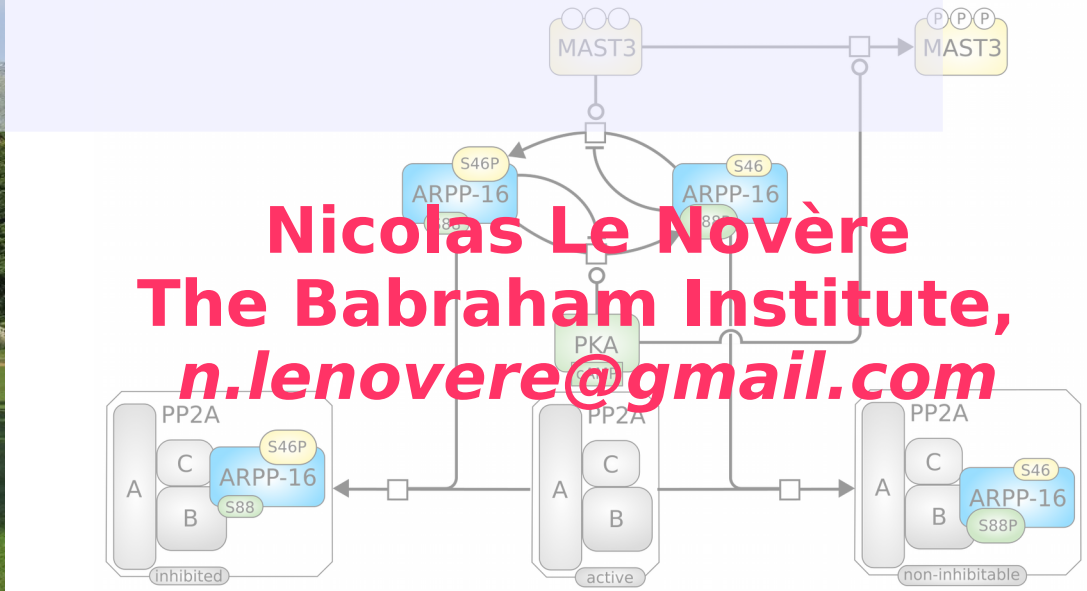


Introduction to Modelling In Systems Biology



Nicolas Le Novère
The Babraham Institute,
n.lenovere@gmail.com

University of Cambridge, 14 March 2017

Babraham Institute

eulife

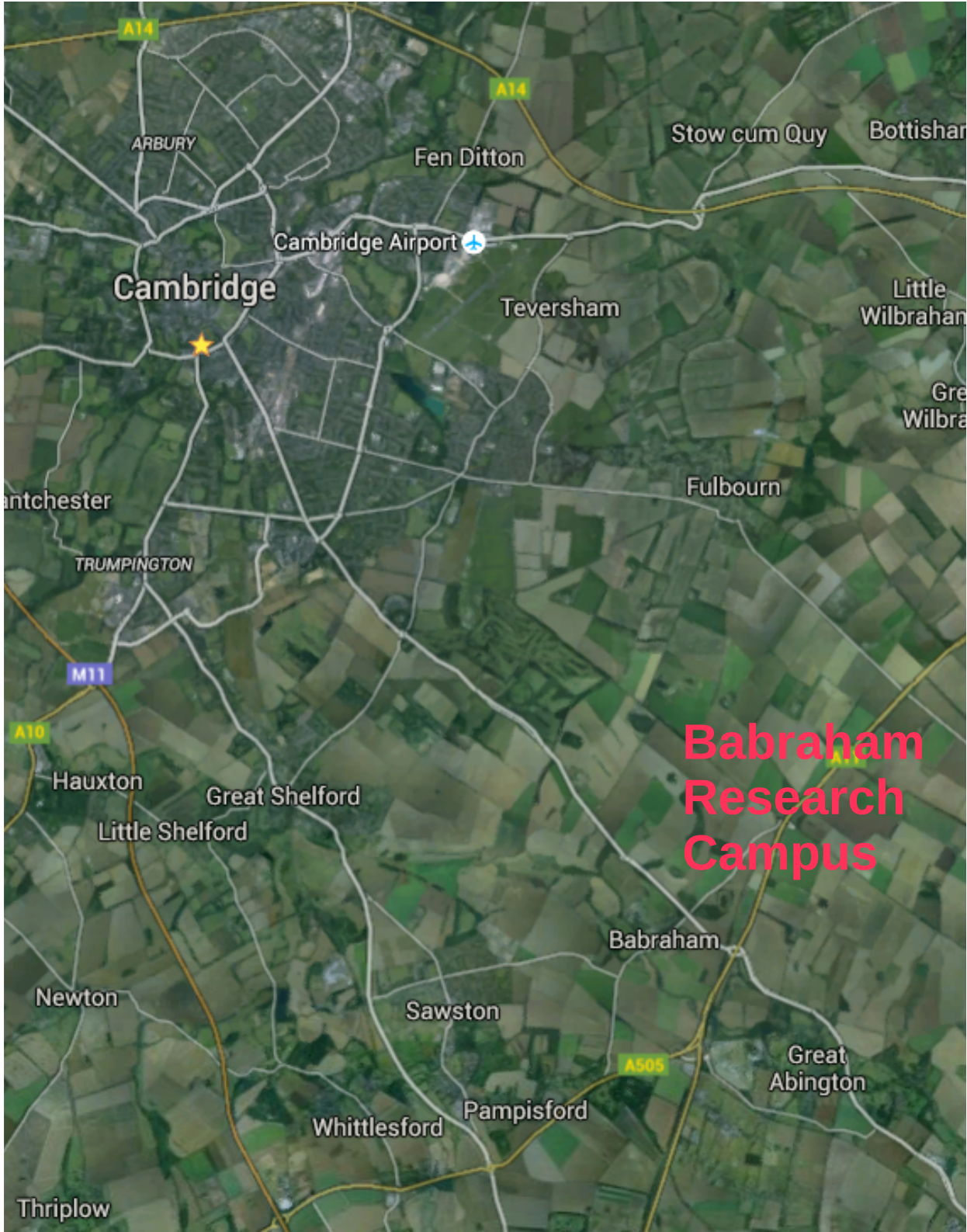
BBSRC
bioscience for the future

Programmes in:

- **Signalling**
- **Immunology**
- **Epigenetics**
- **Nuclear Dynamics**

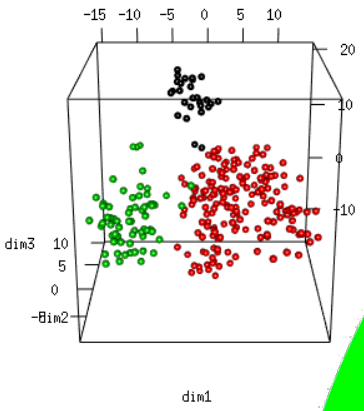
Plateforms including:

- **Bioinformatics**
- **Imaging**
- **FACS**
- **Lipidomics**
- **Mouse facilities**
- **Sequencing**



Some of Babraham Institute's historical fame

- Discovery of the liposome
  Bangham AD, Standish MM, Watkins JC (1965) Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Mol Biol* 13, 238–252
- Discovery of IP3 signalling and release of internal calcium stores
  H Streb, RF Irvine, MJ Berridge, I SchulzH Streb, RF Irvine, MJ Berridge, I Schulz (1983) Release of Ca2+ from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1, 4, 5-trisphosphate. *Nature* 306, 67-69
- DNA methylation responsible of parental imprinting
  W Reik, A Collick, ML Norris, SC Barton, MA Surani (1987) Genomic imprinting determines methylation of parental alleles in transgenic mice. *Nature* 328, 248-251
- Phosphorylation of PIP2 into PIP3 by PI3K
  PT Hawkins, TR Jackson, LR Stephens (1992) Platelet-derived growth factor stimulates synthesis of PtdIns(3,4,5)P3 by activating a PtdIns(4,5)P2 3-OH kinase. *Nature* 358, 157-159



Metabolism

Lipids in infections and cancer

Whole genome metabolism
(ageing, stem cell differentiation)

Epigenetics
Stem-Cells

Stem cell differentiation

Neuronal specification

Responses to PI signals

Immune response and ageing

Signalling

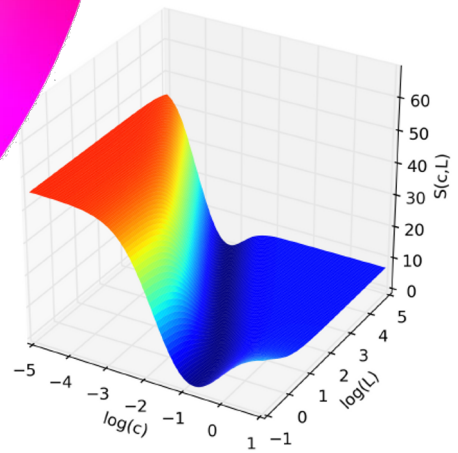
Calcium in synapses

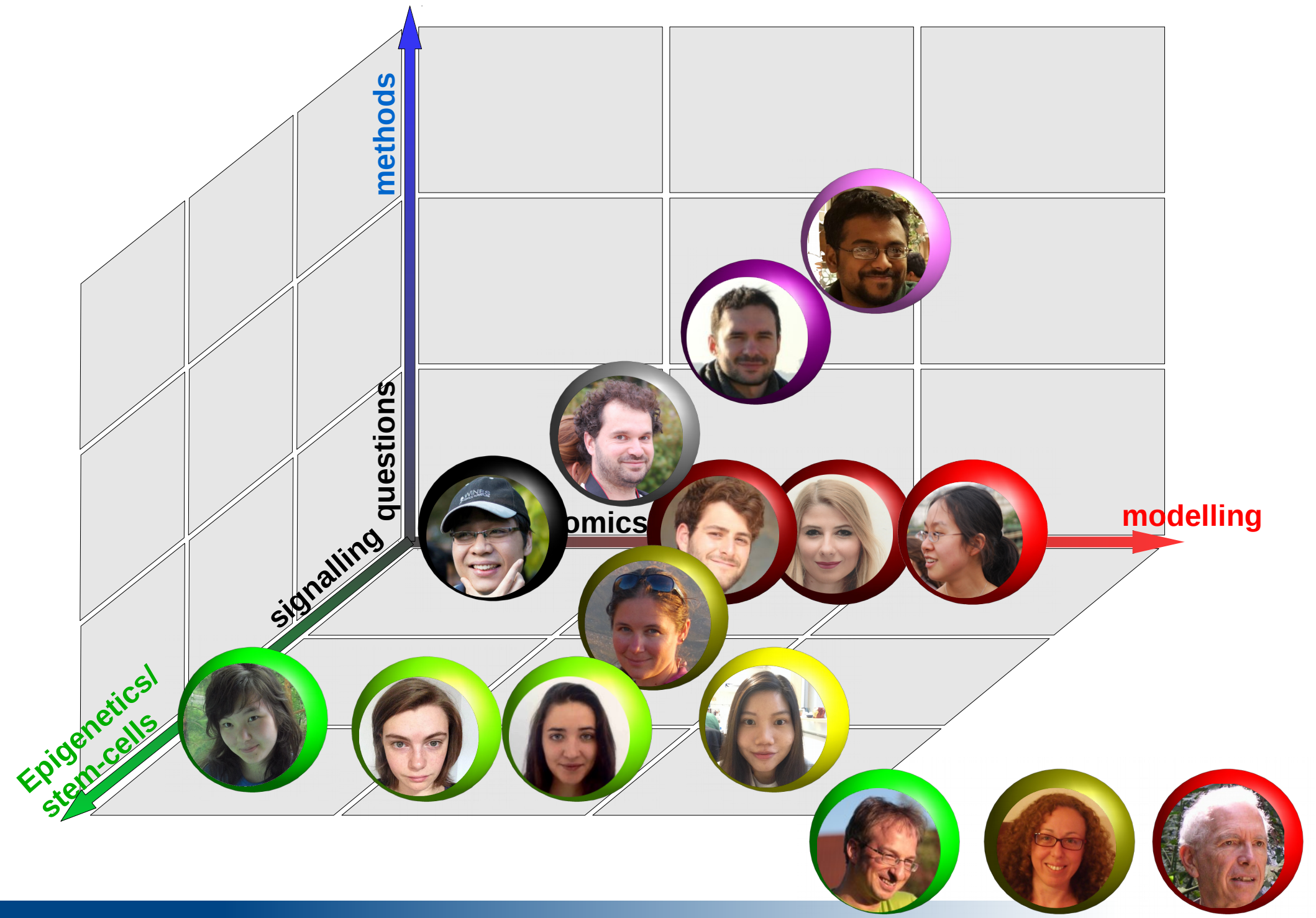
Phosphatase in neurons

Phophoinositides

Inflammation

Tools




methods
signalling questions
omics
modelling
Epigenetics/
stem-cells

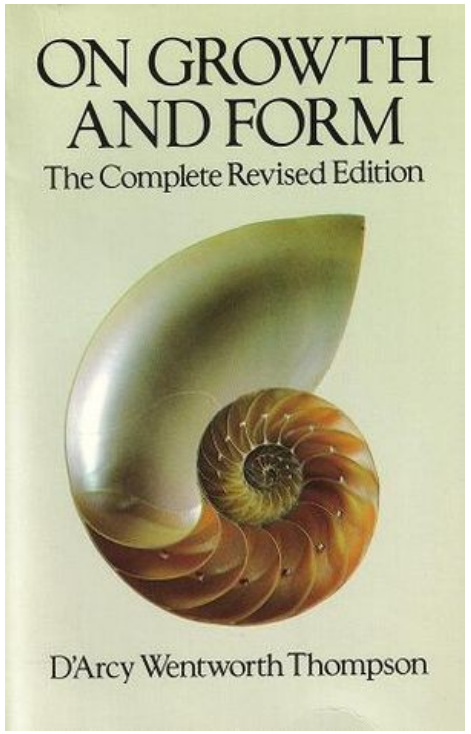
Babraham Institute

BBSRC bioscience for the future

The many faces of modelling in biology

What is the goal of using mathematical models?

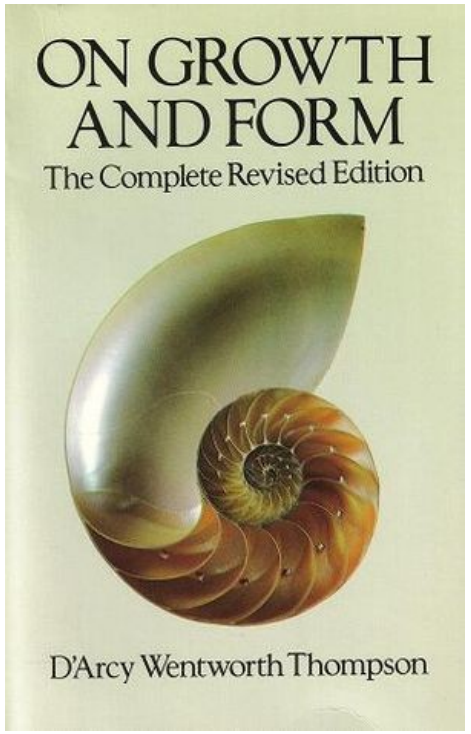
Describe



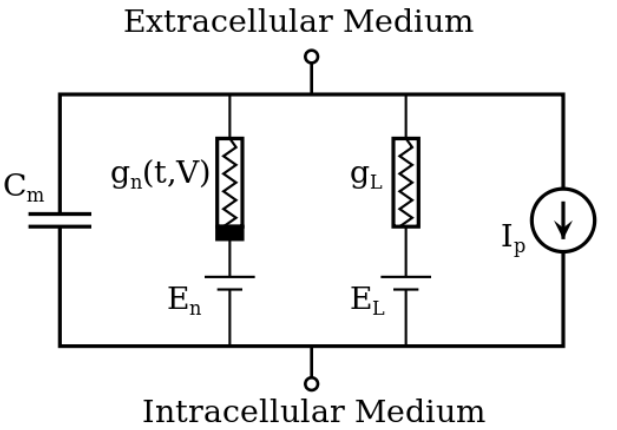
1917

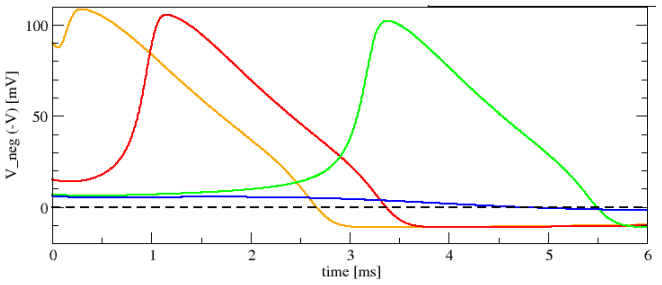
What is the goal of using mathematical models?

Describe	Explain



1917

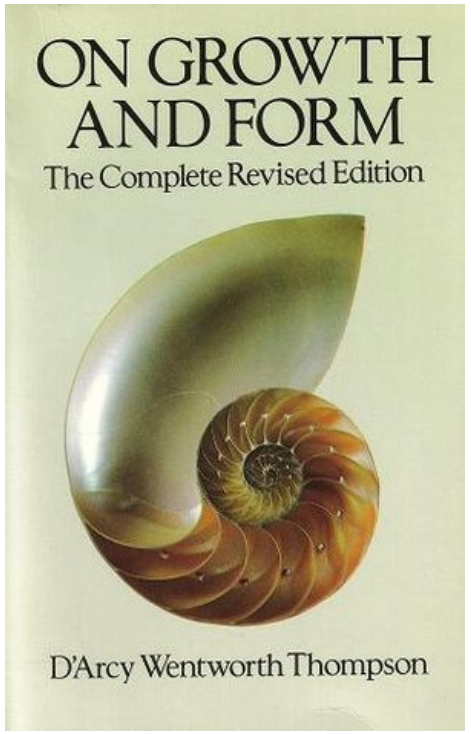


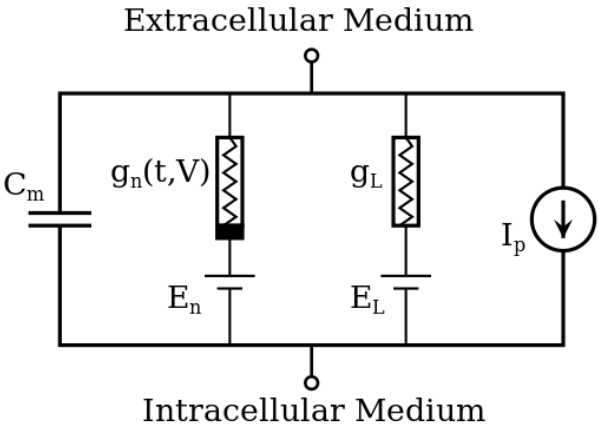


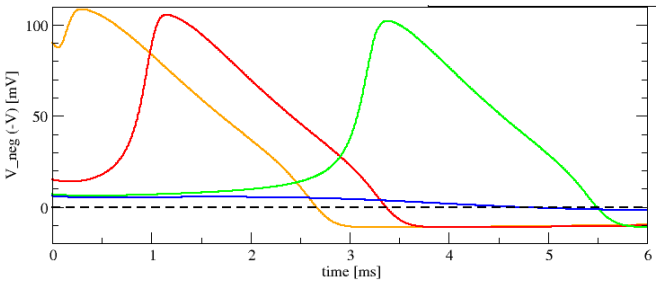
1952

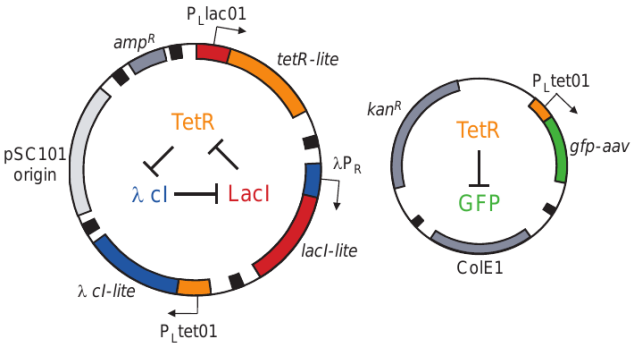
What is the goal of using mathematical models?

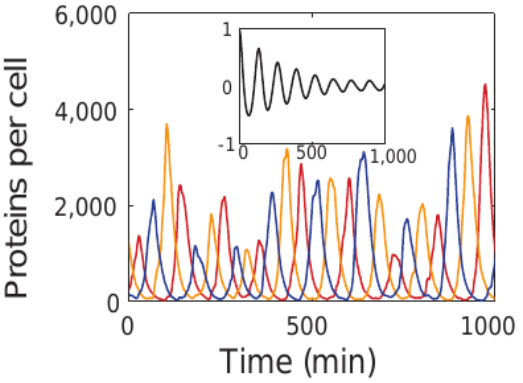
Describe	Explain	Predict











1917 **1952** **2000**

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables
[x]
Vmax
Kd
EC_{50}
length
$t_{1/2}$

What we want to know or compare with experiments

What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

variables	relationships
[x]	$K_d = \frac{[A] \cdot [B]}{[AB]}$
Vmax	$d[X]/dt = k \cdot [Y]^2$
Kd	$\sum_i [X]_i - F(t) = 0$
EC_{50}	$k(t) \sim N(k, \sigma^2)$
length	If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$
$t_{1/2}$	

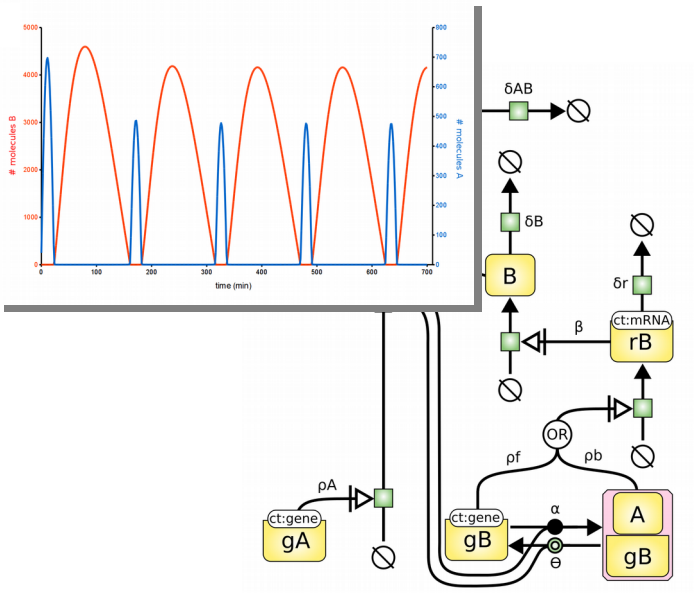
What we already know or want to test

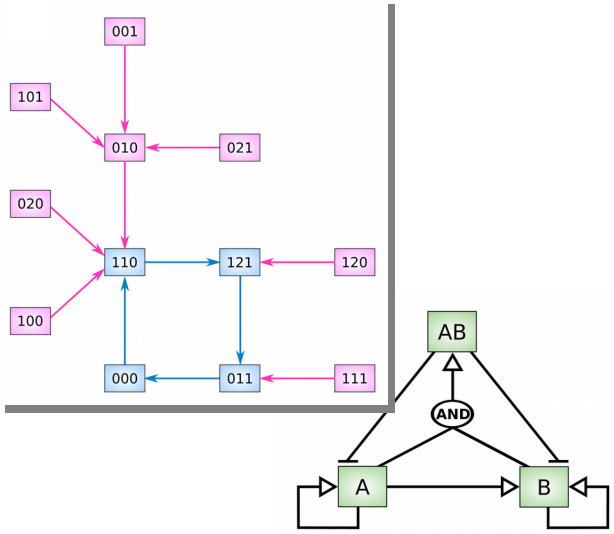
What is a mathematical model?

Wikipedia (October 14th 2013): “A mathematical model is a description of a system using mathematical concepts and language.”

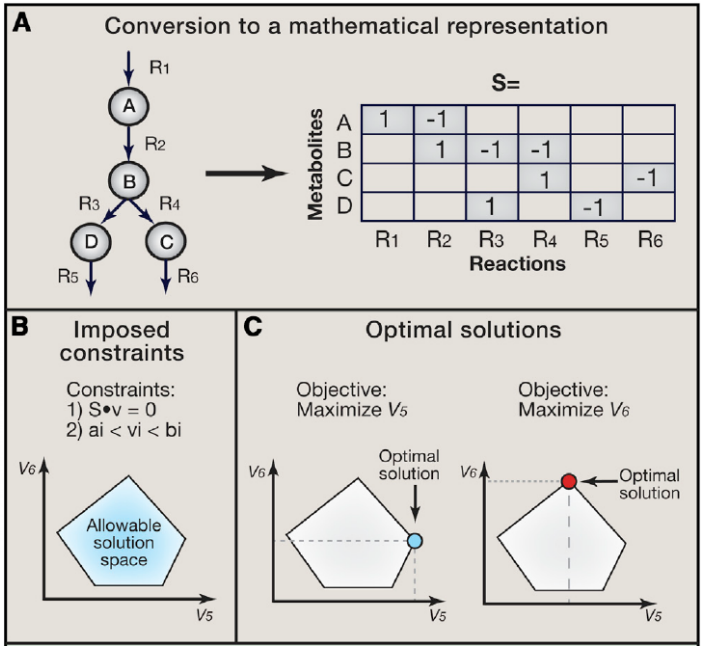
variables	relationships	constraints
[x]	$K_d = \frac{[A] \cdot [B]}{[AB]}$	[x]≥0
Vmax	$d[X]/dt = k \cdot [Y]^2$	Energy conservation
Kd	$\sum_i [X]_i - F(t) = 0$	Boundary conditions (v < upper limit)
EC_{50}	$k(t) \sim N(k, \sigma^2)$	Objective functions (maximise ATP)
length	If $\text{mass}_t > \text{threshold}$ then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$	Initial conditions
$t_{1/2}$		

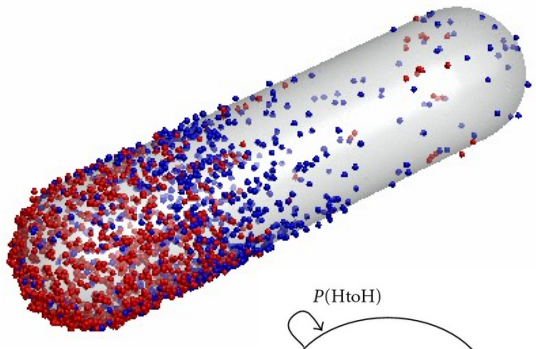
The context or what we want to ignore

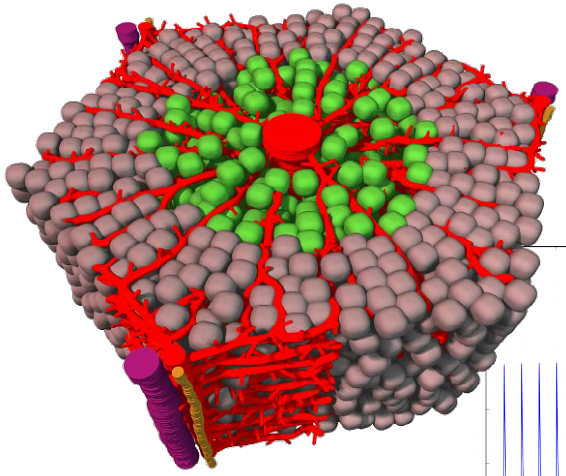

δAB
δB
B
δr
β
ct:mRNA
rB
OR
ρf
ρb
ρA
ct:gene
gA
ct:gene
gB
α
θ
A
gB

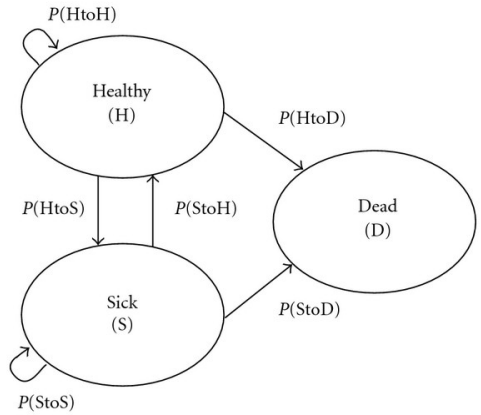

001
101
010
021
020
110
121
120
100
000
011
111

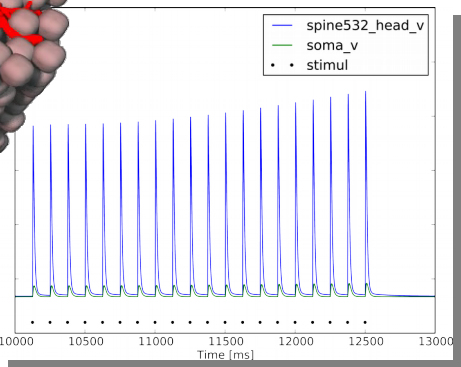
AB
AND
A
B

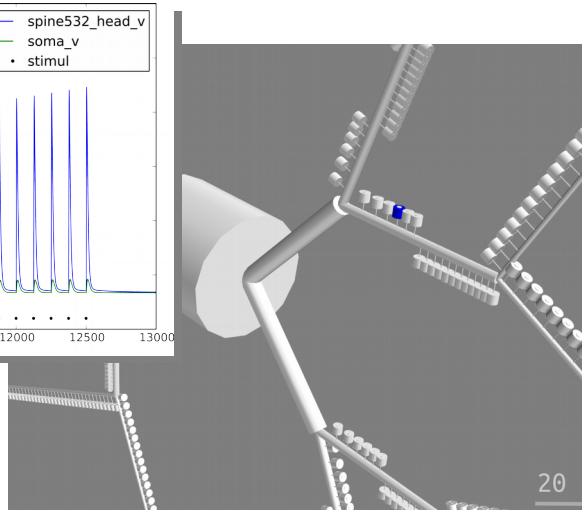

A
Conversion to a mathematical representation
R1
A
R2
B
R3
R4
D
C
R5
R6
S=
Metabolites
A
B
C
D
R1 R2 R3 R4 R5 R6
Reactions
B
Imposed constraints
Constraints:
1) S•v = 0
2) ai < vi < bi
V6
Allowable solution space
V5
C
Optimal solutions
Objective: Maximize V5
Objective: Maximize V6
Optimal solution
Optimal solution

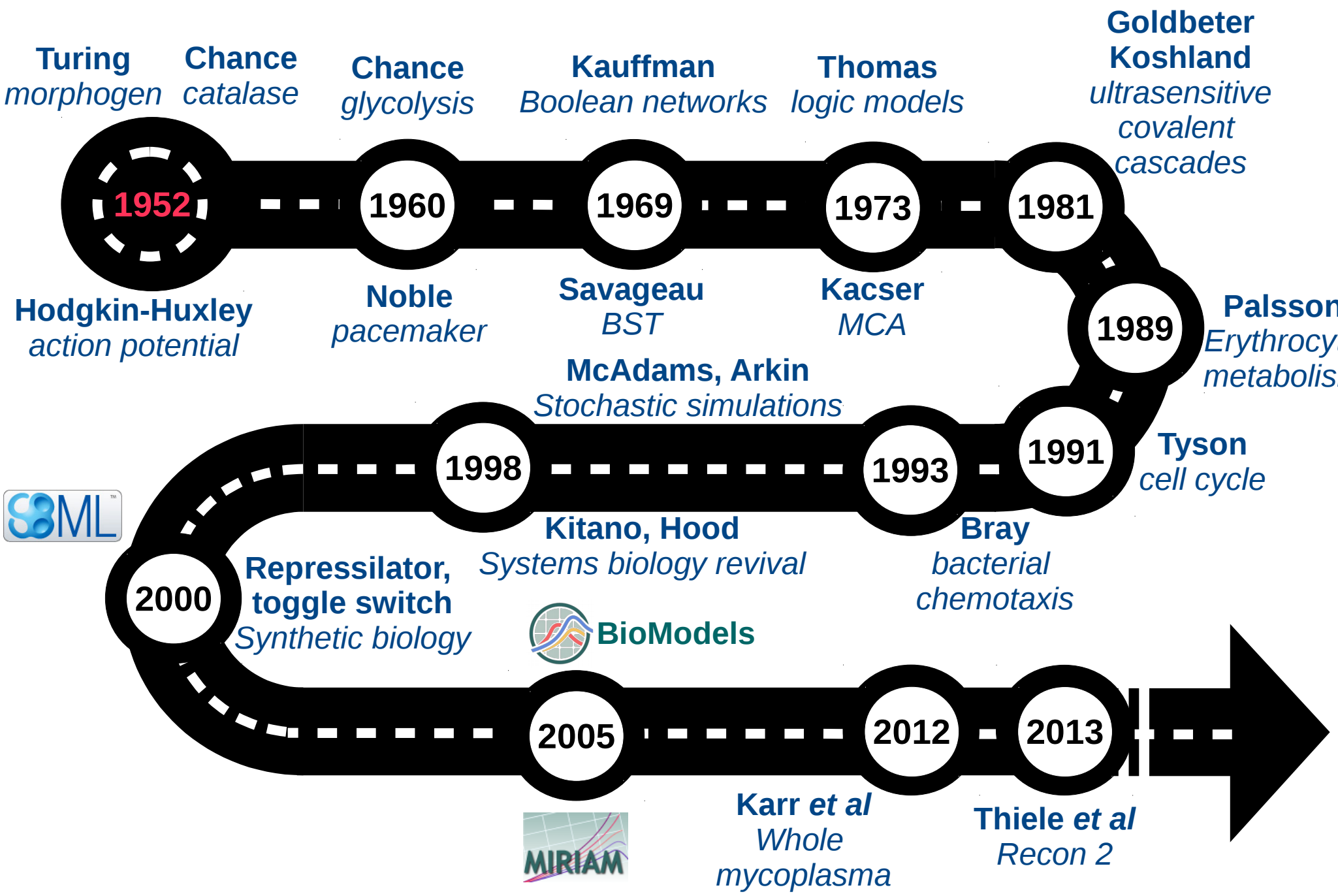




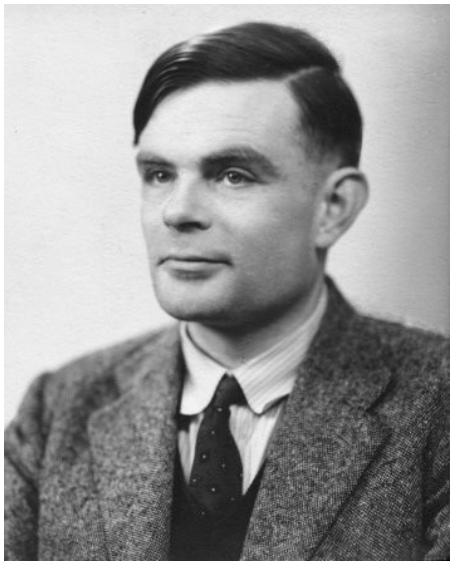

P(HtoH)
Healthy
(H)
P(HtoD)
P(HtoS)
P(StoH)
Dead
(D)
Sick
(S)
P(StoD)
P(StoS)


spine532_head_v
soma_v
stimul
10000
10500
11000
11500
12000
12500
13000
Time [ms]


20


Turing
morphogen
Chance
catalase
Chance
glycolysis
Kauffman
Boolean networks
Thomas
logic models
Goldbeter
Koshland
ultrasensitive
covalent
cascades
1952
1960
1969
1973
1981
Hodgkin-Huxley
action potential
Noble
pacemaker
Savageau
BST
Kacser
MCA
1989
Palsson
Erythrocyte
metabolism
McAdams, Arkin
Stochastic simulations
1998
1993
1991
Tyson
cell cycle
SBML
Kitano, Hood
Systems biology revival
Bray
bacterial
chemotaxis
2000
Repressilator,
toggle switch
Synthetic biology
BioModels
2005
2012
2013
MIRIAM
Karr et al
Whole
mycoplasma
Thiele et al
Recon 2

Computer simulations Vs. mathematical models



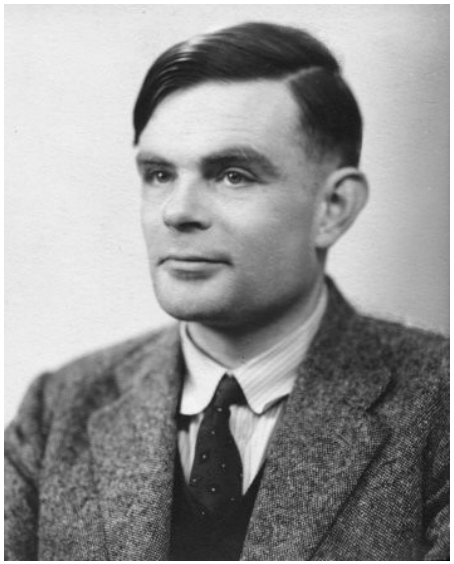
THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two

Computer simulations Vs. mathematical models



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It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis.

One would like to be able to follow this more general process mathematically also. The difficulties are, however, such that one cannot hope to have any very embracing theory of such processes, beyond the statement of the equations. It might be possible, however, to treat a few particular cases in detail with the aid of a digital computer. This method has the advantage that it is not so necessary to make simplifying assumptions as it is when doing a more theoretical type of analysis.

Birth of Computational Systems Biology

The Mechanism of Catalase Action. [1]

II. Electric Analog Computer Studies

Britton Chance, David S. Greenstein, Joseph Higgins and C. C. Yang

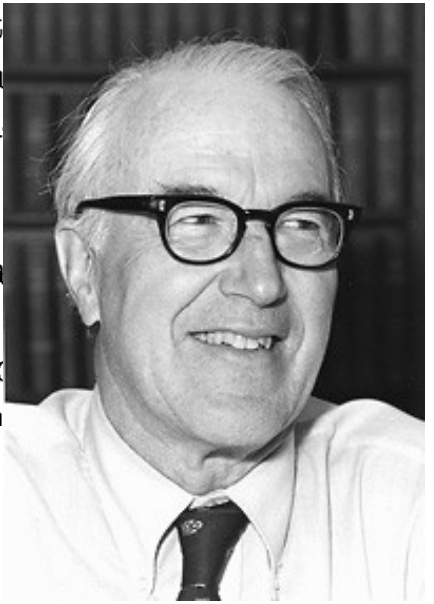
From the Johnson Research Foundation, University of Pennsylvania, Philadelphia, Pennsylvania

Received October 26, 1951

Introduction

In early studies of enzyme reactions only the disappearance of substrate could be measured and only the steady-state operation of the enzyme could be studied. We can now study directly the formation and disappearance of compounds of enzyme and substrate by sensit spectrophotometric methods. Thus not only the steady-state but a the transient portions of the enzyme action are revealed. And th transient portions are very sensitive indicators of the mechanism which the enzyme acts.

Differential equations representing the transient formation a disappearance of an enzyme-substrate complex can readily be set for enzyme reactions that follow the law of mass action, and solutio of these equations are readily obtained for the special and often un



Birth of Computational Systems Biology

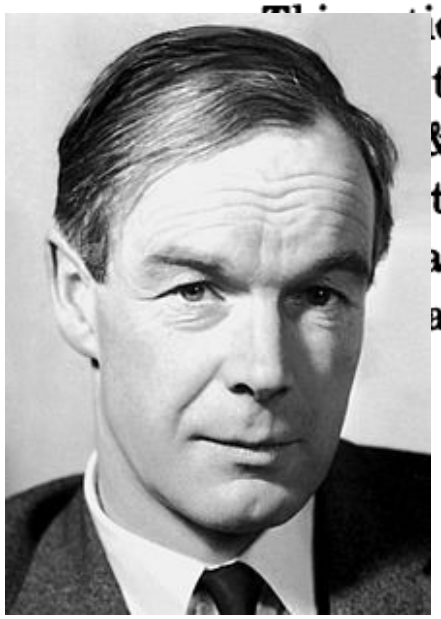
J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

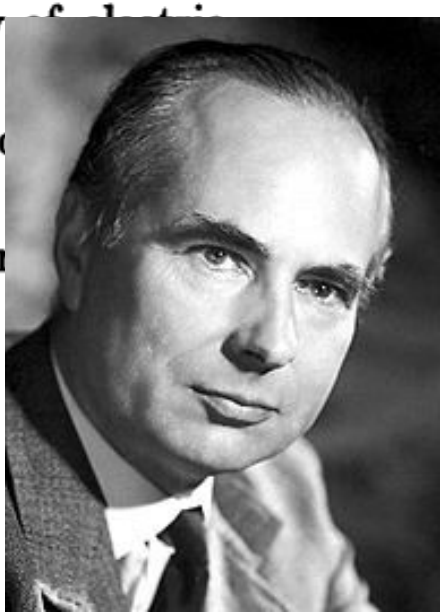
By A. L. HODGKIN and A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)



icle concludes a series of papers concerned with the flow
through the surface membrane of a giant nerve fibre
& Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general
the results of the preceding papers (Part I), to put
atical form (Part II) and to show that they will accou
and excitation in quantitative terms (Part III).



The Computational Systems Biology loop

"biological" model

mathematical model

validation

parameterisation

simulation

computational model

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$dn/dt = \alpha_n (1 - n) - \beta_n n,$$

$$dm/dt = \alpha_m (1 - m) - \beta_m m,$$

$$dh/dt = \alpha_h (1 - h) - \beta_h h,$$

$$\alpha_n = 0{\cdot}01\,(V + 10) \Big/ \left(\exp \frac{V + 10}{10} - 1\right),$$

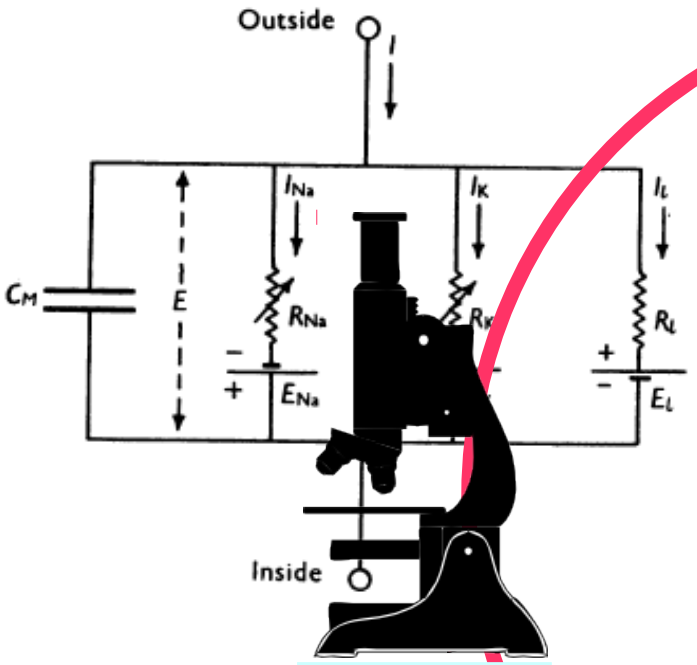
$$\beta_n = 0{\cdot}125 \exp (V/80),$$

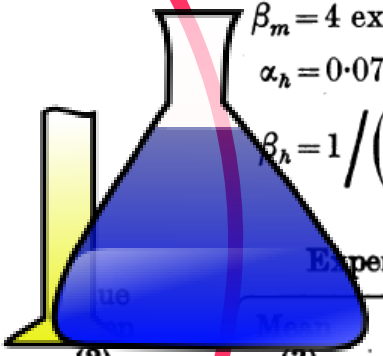
$$\alpha_m = 0{\cdot}1\,(V + 25) \Big/ \left(\exp \frac{V + 25}{10} - 1\right),$$

$$\beta_m = 4 \exp (V/18),$$

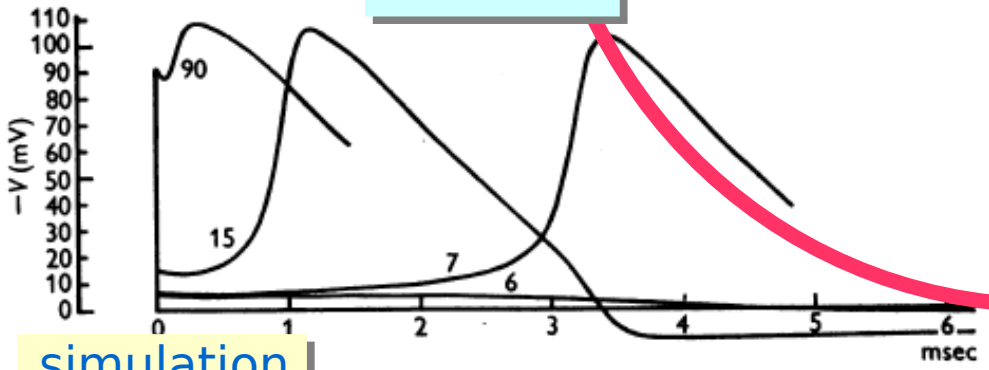
$$\alpha_h = 0{\cdot}07 \exp (V/20),$$

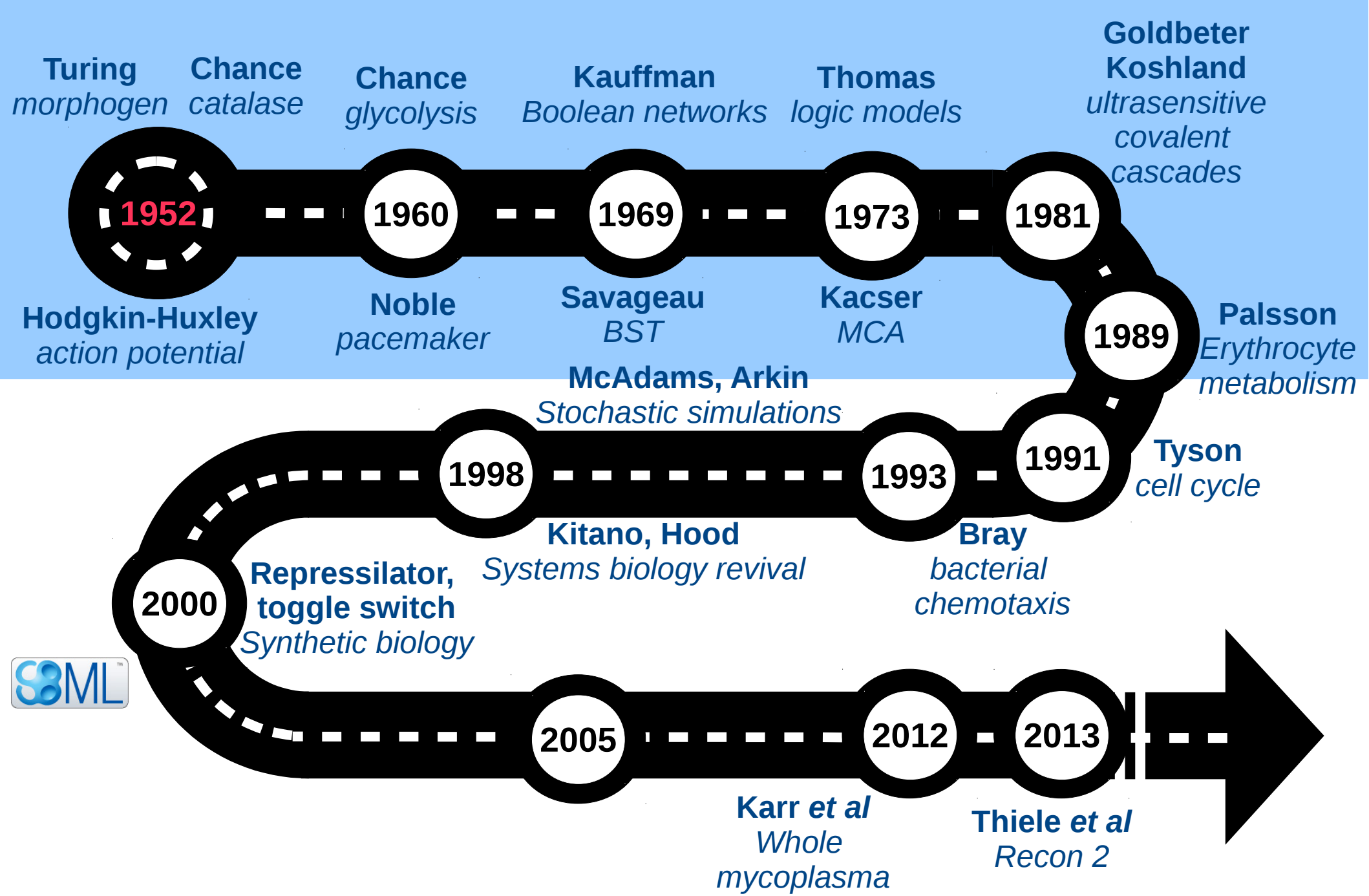
$$\beta_h = 1 \Big/ \left(\exp \frac{V + 30}{10} + 1\right).$$





Constant (1)	Experimental values (2)	(3)	Range (4)
C_M (μF/cm²)			0·8 to 1·5
V_{Na} (mV)			−95 to −119
V_K (mV)			+ 9 to + 14
V_l (mV)	−10·613	− 11	− 4 to − 22
$\bar{g}_{Na}$ (m.mho/cm²)	120	80 160	65 to 90 120 to 260
$\bar{g}_K$ (m.mho/cm²)	36	34	26 to 49
$\bar{g}_l$ (m.mho/cm²)	0·3	0·26	0·13 to 0·50




Turing
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catalase
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Kauffman
Boolean networks
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1952
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1973
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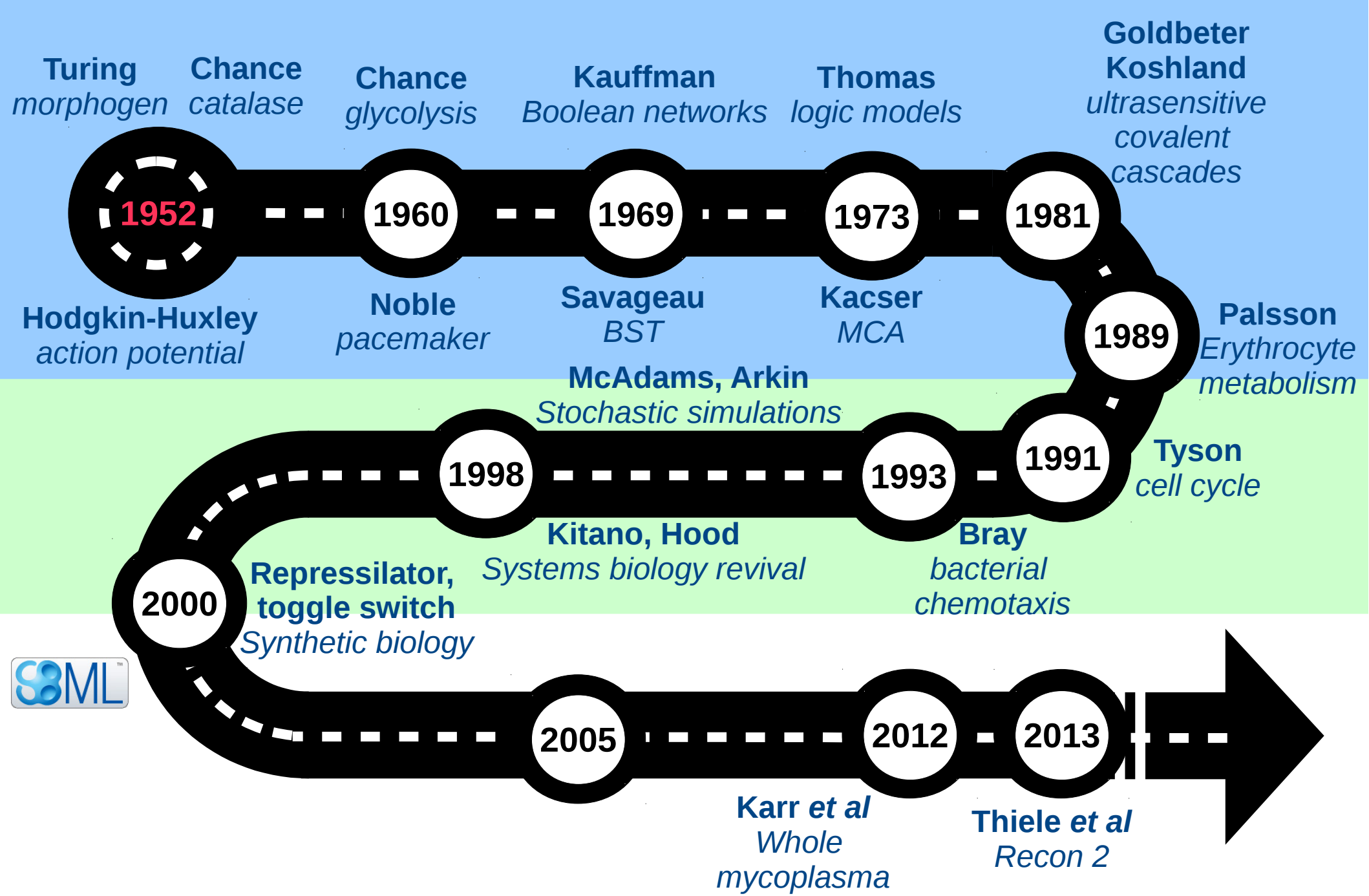
Hodgkin-Huxley
action potential
Noble
pacemaker
Savageau
BST
Kacser
MCA
1989
Palsson
Erythrocyte
metabolism
McAdams, Arkin
Stochastic simulations
1998
1993
1991
Tyson
cell cycle
Kitano, Hood
Systems biology revival
Bray
bacterial
chemotaxis
2000
Repressilator,
toggle switch
Synthetic biology
SBML
2005
2012
2013
Karr et al
Whole
mycoplasma
Thiele et al
Recon 2


Turing
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Chance
catalase
Chance
glycolysis
Kauffman
Boolean networks
Thomas
logic models
Goldbeter
Koshland
ultrasensitive
covalent
cascades
1952
1960
1969
1973
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Hodgkin-Huxley
action potential
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toggle switch
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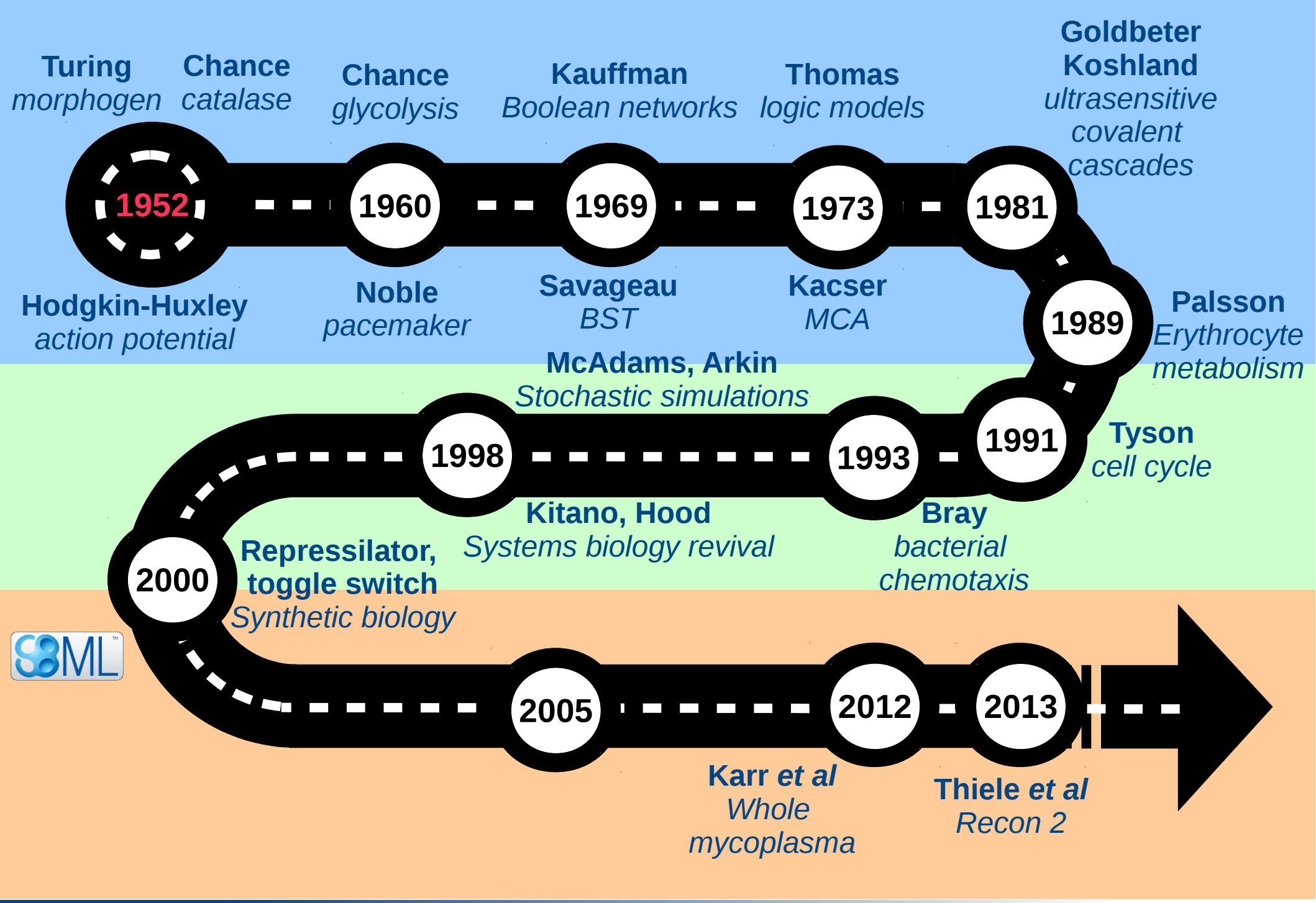
Recon 2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mycoplasma
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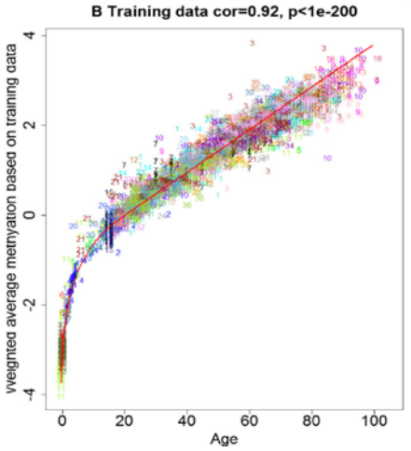
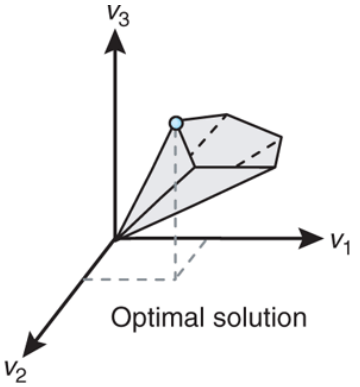
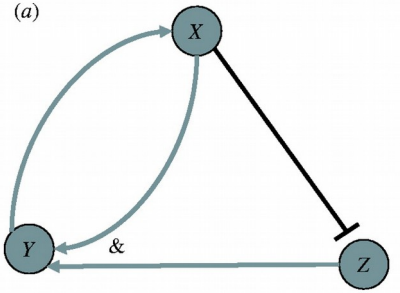
Recon 2

Representation of time





No time: correlations, steady-states

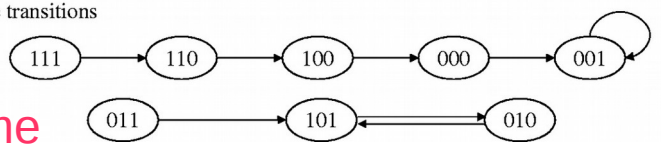


(b) $Y=X \,\&\, Z,\ X=Y,\ Z=\neg X$

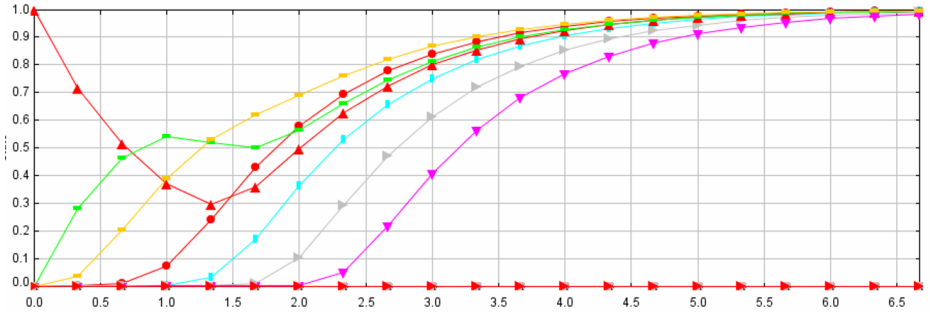
(c)

t			$t+1$		
X	Y	Z	X	Y	Z
0	0	0	0	0	1
0	0	1	0	0	1
0	1	0	1	0	1
0	1	1	1	0	1
1	0	0	0	0	0
1	0	1	0	1	0
1	1	0	1	0	0
1	1	1	1	1	0

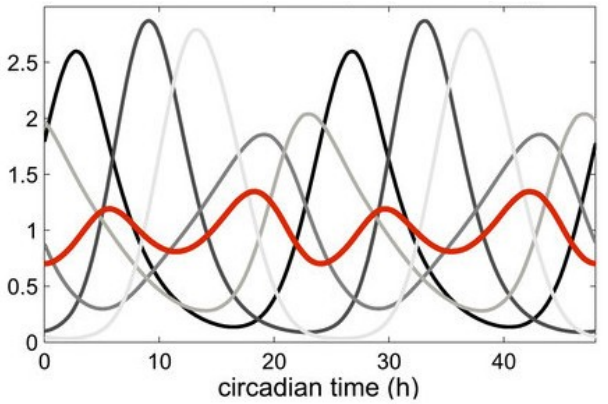
(d) state transitions



Pseudo-time
(t4 – t0 is not 2 x t2 -t0): Logic models

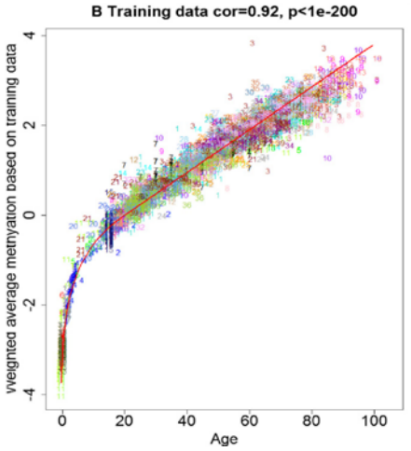


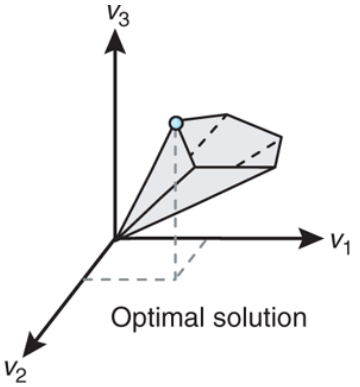
Discrete time



Continuous time

Representation of time





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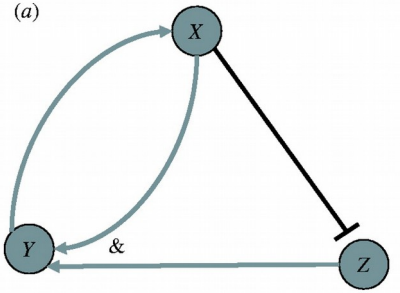
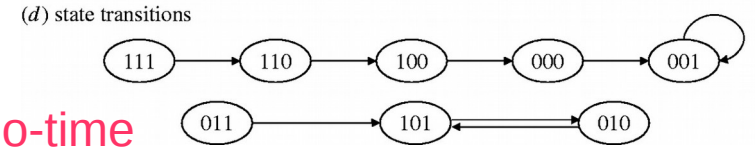


(c)

t			t+1		
X	Y	Z	X	Y	Z
0	0	0	0	0	1
0	0	1	0	0	1
0	1	0	1	0	1
0	1	1	1	0	1
1	0	0	0	0	0
1	0	1	0	1	0
1	1	0	1	0	0
1	1	1	1	1	0



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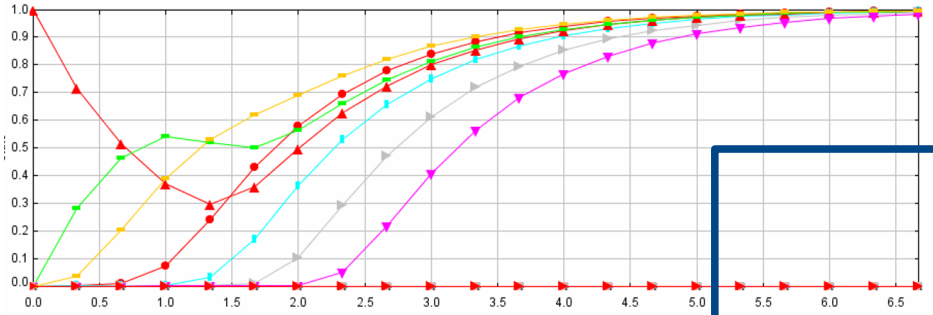
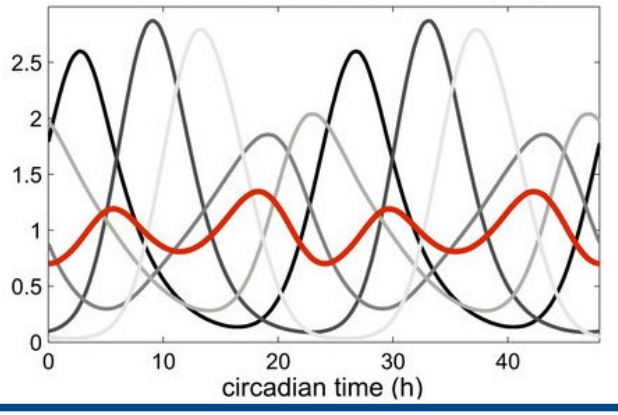


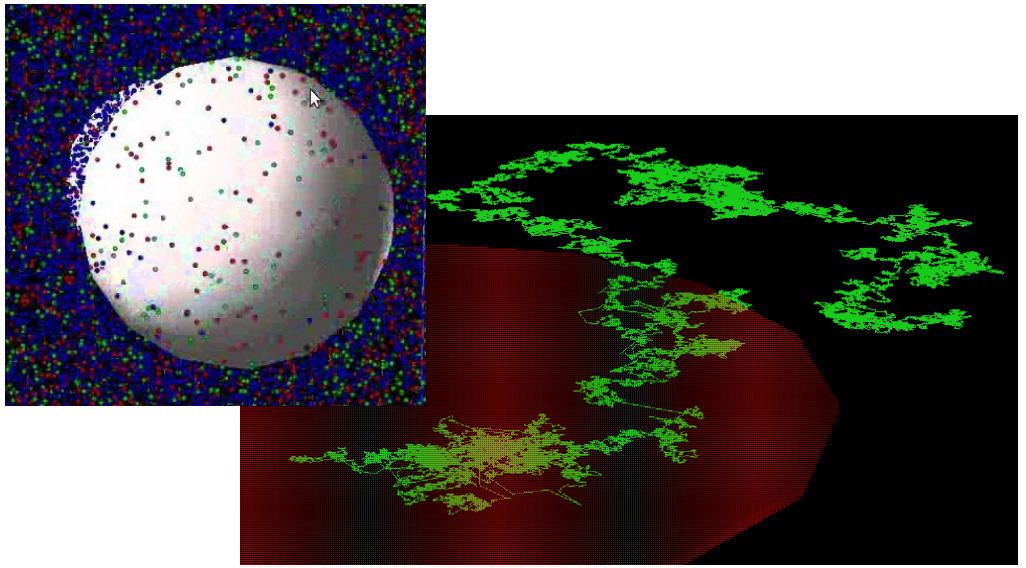
Discrete time

Continuous time

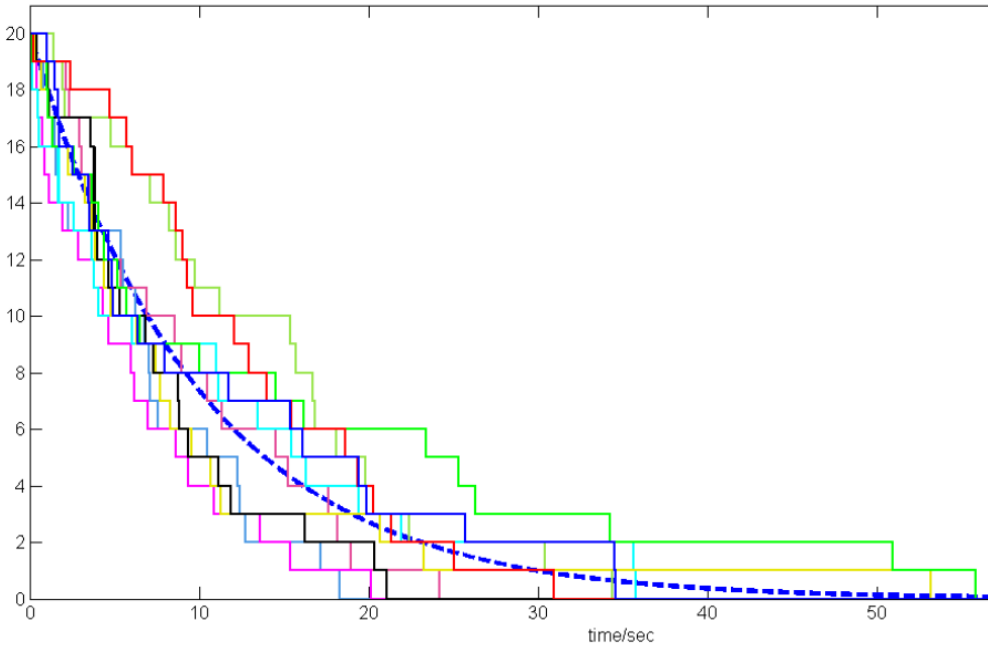


Variable granularity

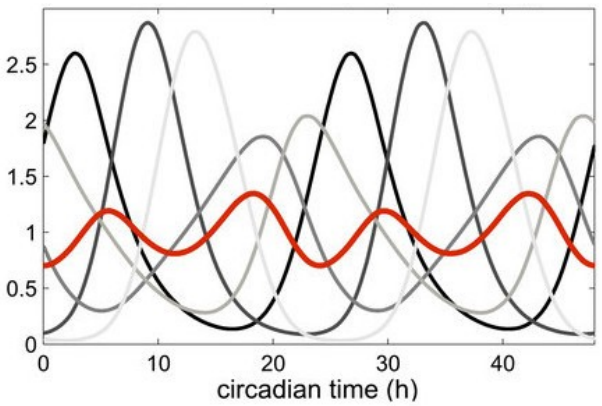
Single particles



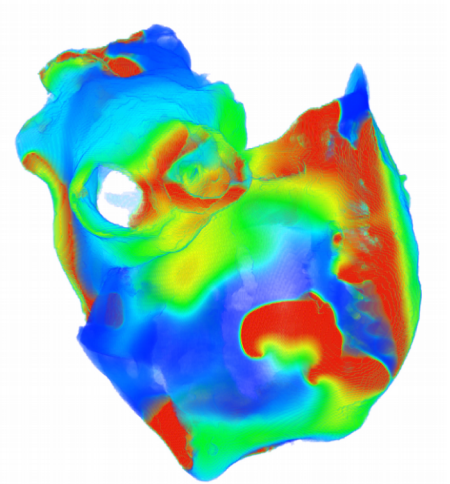
Discrete populations



Continuous populations

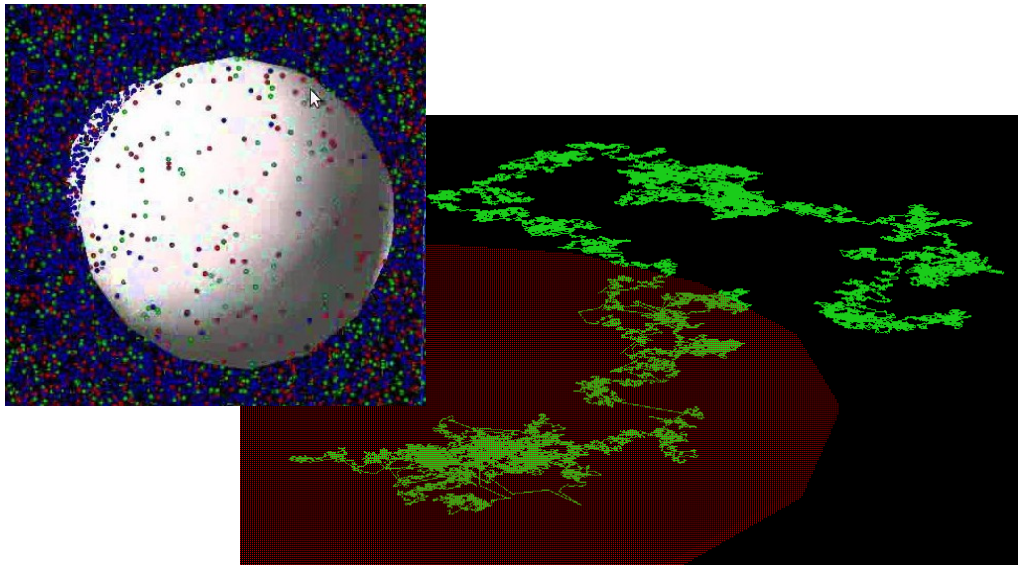


Fields

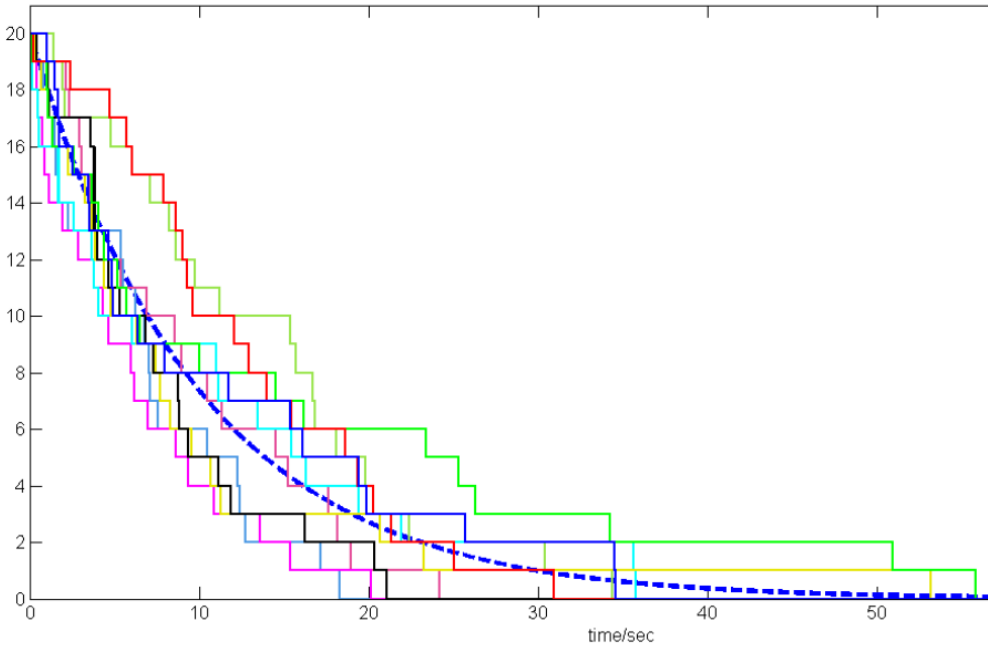


Variable granularity

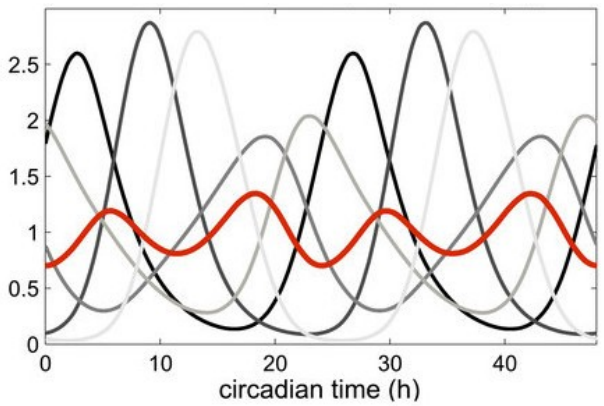
Single particles



Discrete populations



Continuous populations



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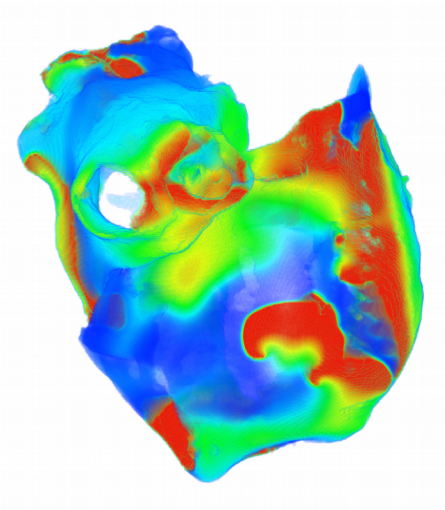
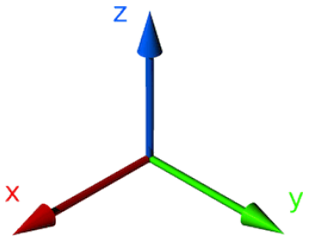
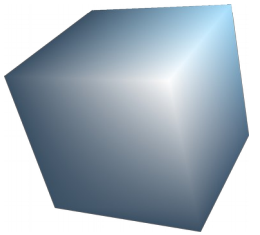




Spatial representation



No dimension

Homogeneous
(well-stirred, isotropic)

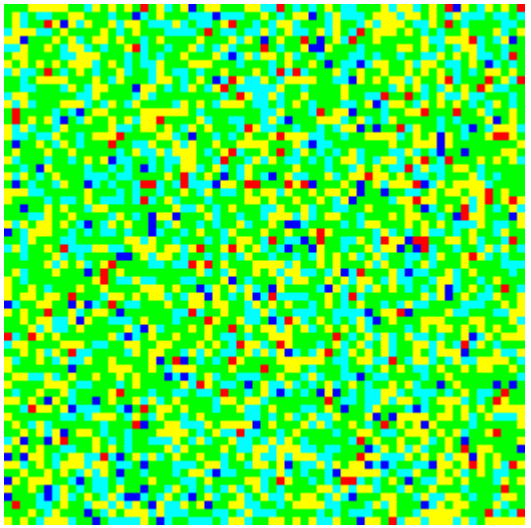
[x]

Compartments

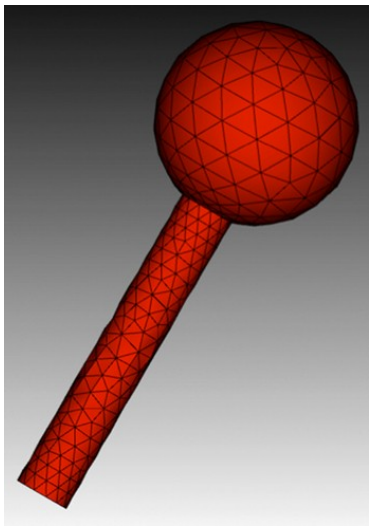
$[x]_A$

$[x]_B$

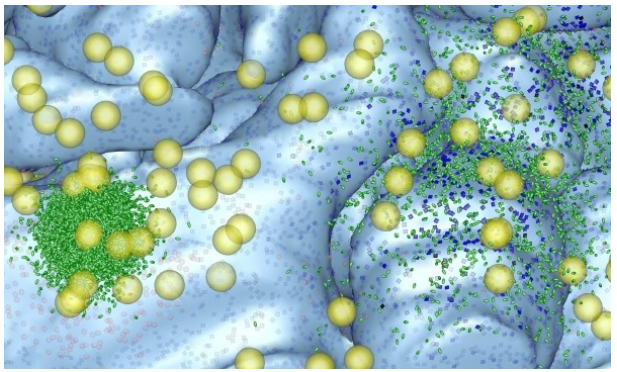
Cellular automata

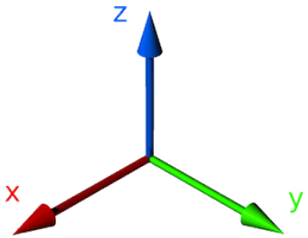


Finite elements

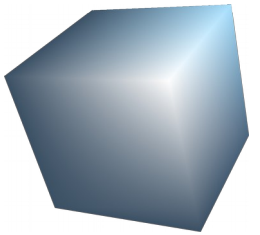


Real space





Spatial representation



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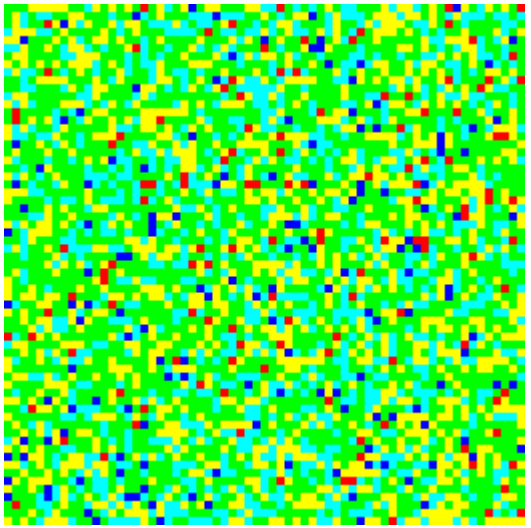

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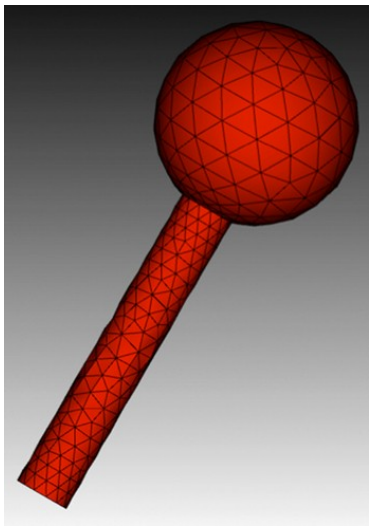

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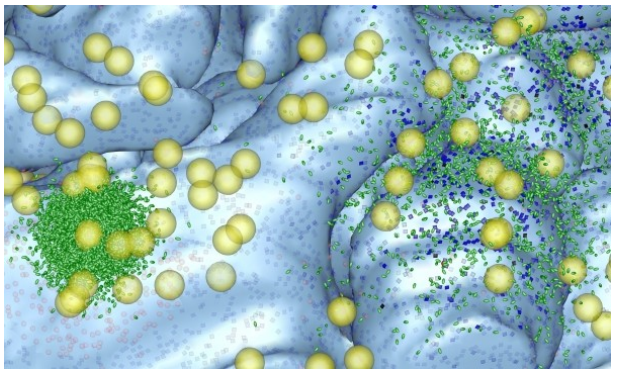
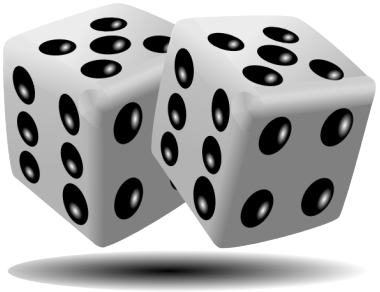


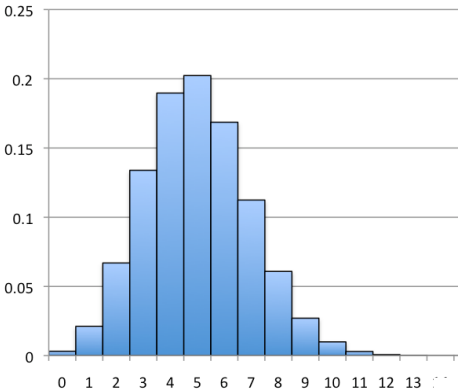


Stochasticity

Deterministic simulation

$$\dot{x}_i = \sum_j n_{ij} k_j \prod_i X_i^{n_{ij}}$$

Ensemble models (distributions)



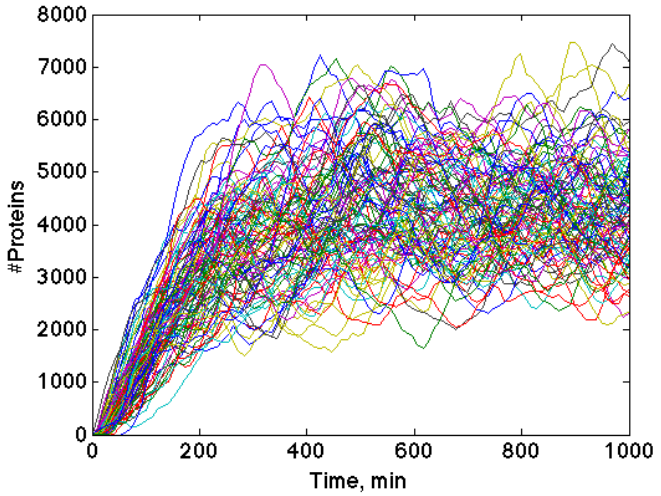
Initial conditions
Parameter values

$$\dot{x}_i = \sum_j n_{ij} k_j \prod_i X_i^{n_{ij}}$$

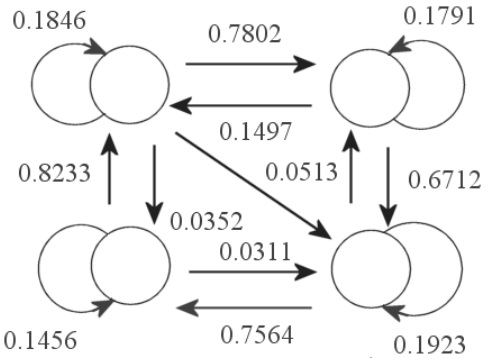
Stochastic differential equations

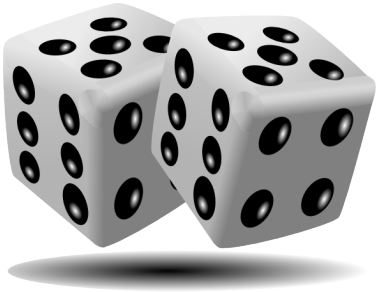
$$\dot{x}_i = f(X) + \sum_j g_j(x_i) n_j(t)$$

Stochastic simulations (SSA, “Gillespie”)



Probabilistic models





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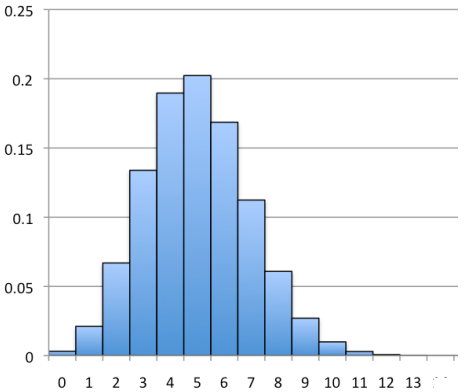

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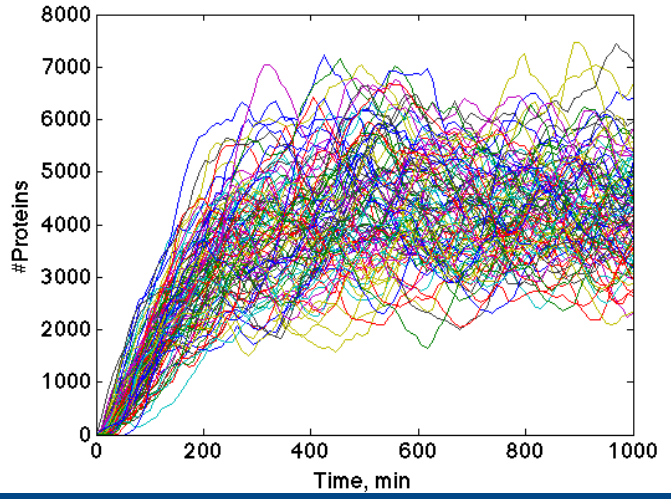

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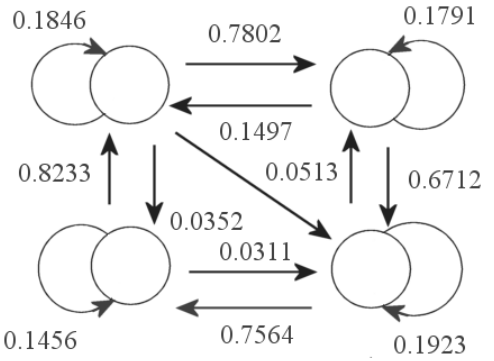
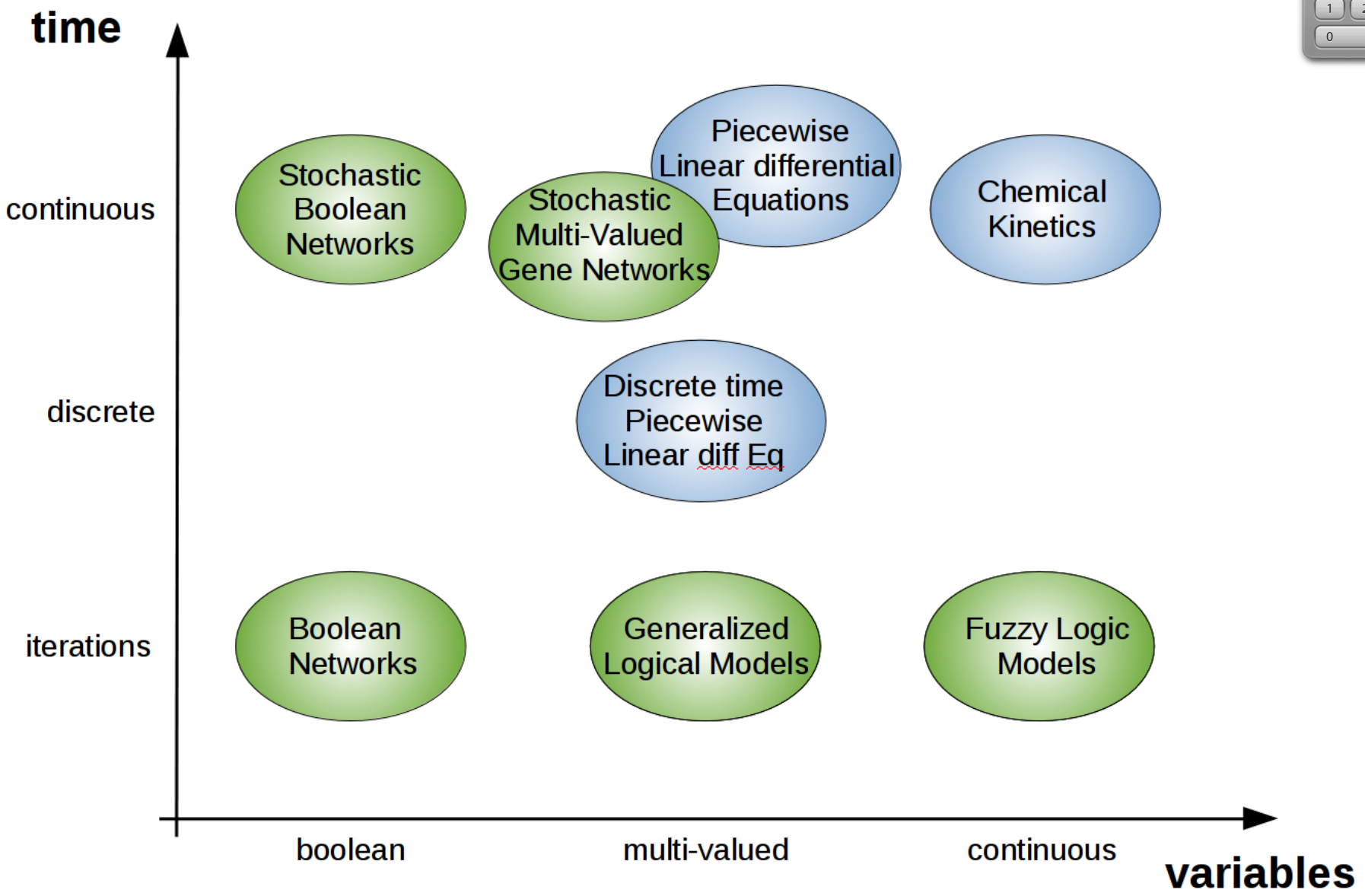


Logic versus numeric



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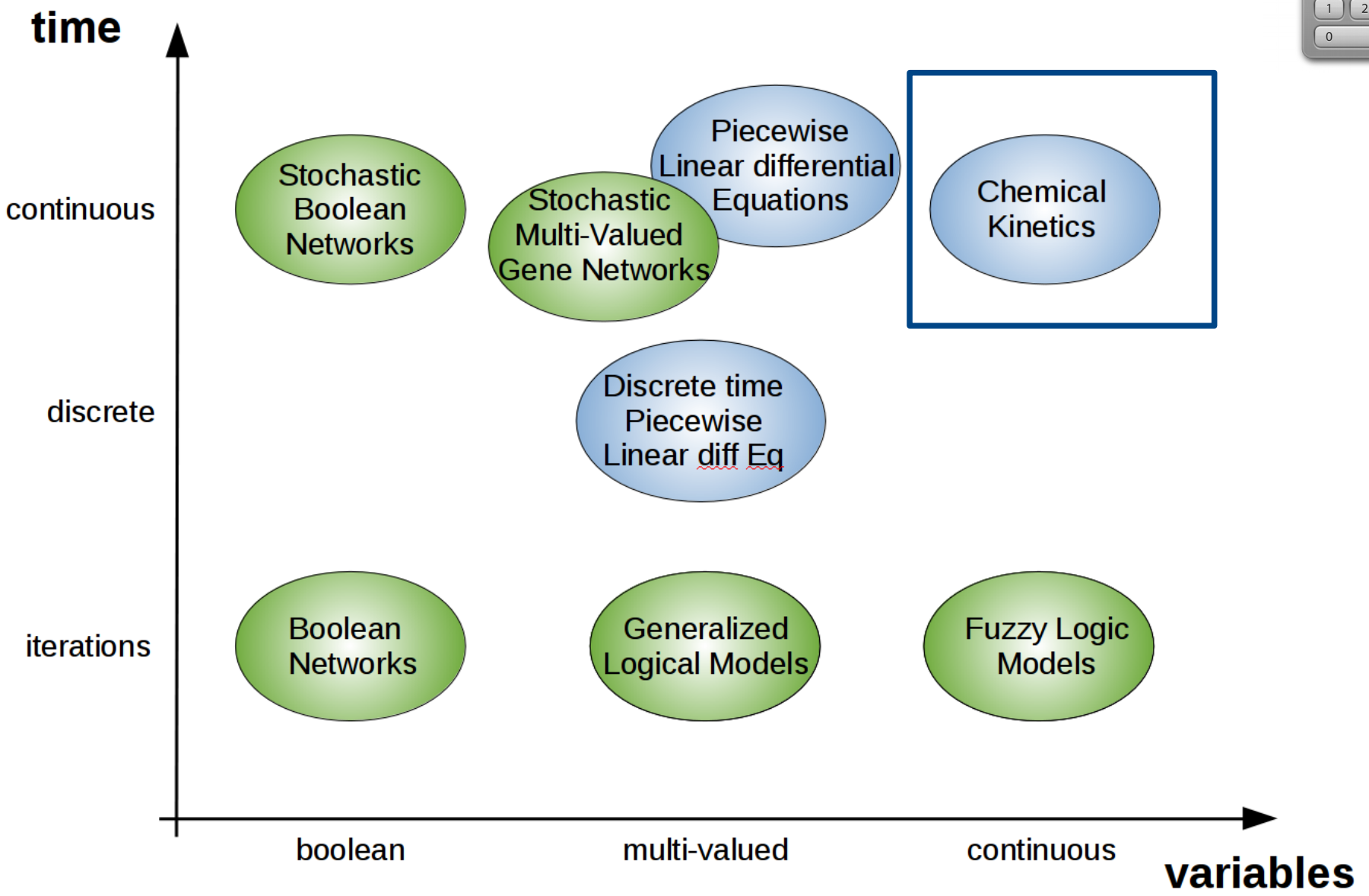
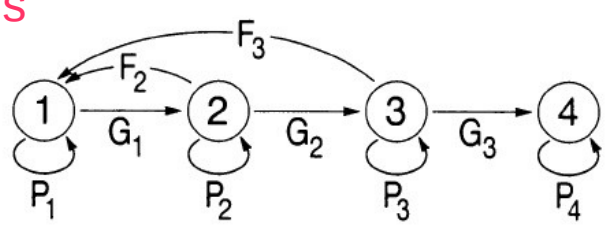
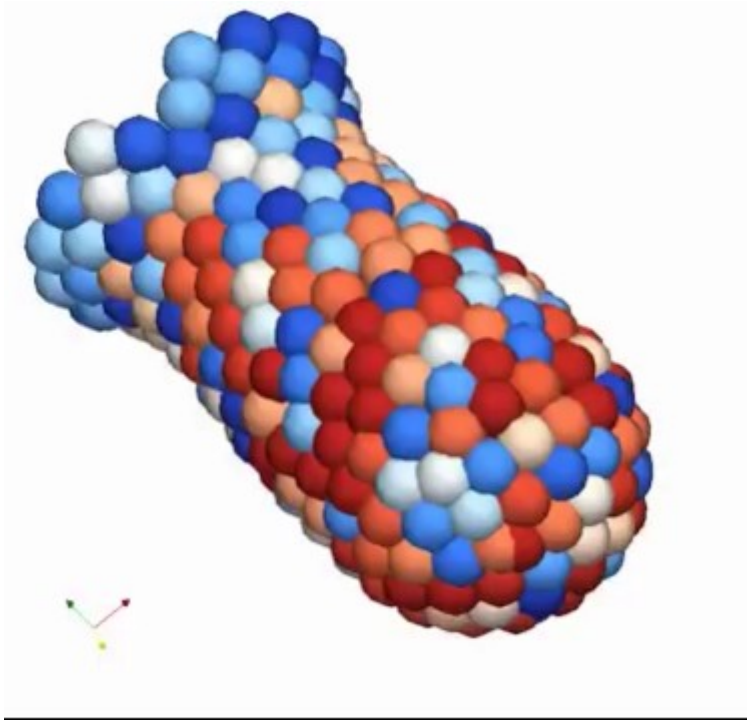


Many other types of models

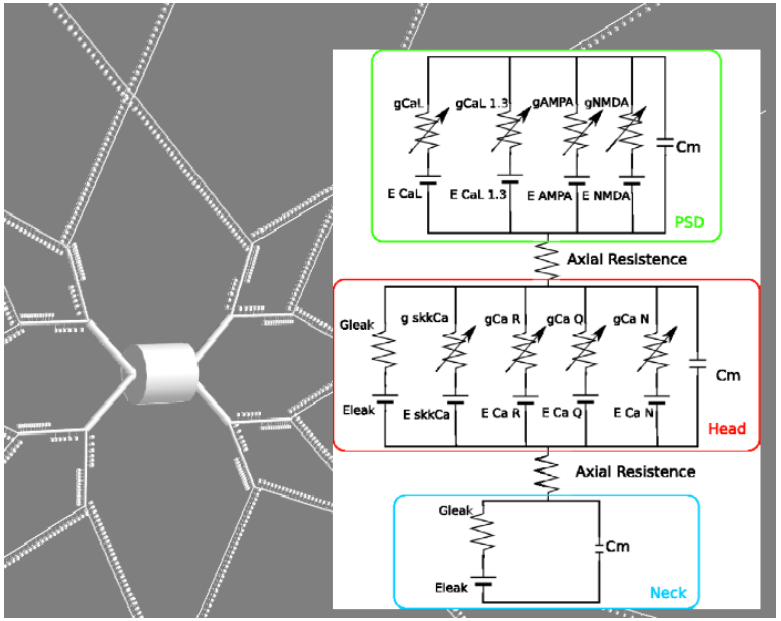
Matrix models



$$\begin{pmatrix} N_1(t+1) \\ N_2(t+1) \\ N_3(t+1) \\ N_4(t+1) \end{pmatrix} = \begin{pmatrix} 0 & F_2 & F_3 & 0 \\ G_1 & P_2 & 0 & 0 \\ 0 & G_2 & P_3 & 0 \\ 0 & 0 & G_3 & P_4 \end{pmatrix} \begin{pmatrix} N_1(t) \\ N_2(t) \\ N_3(t) \\ N_4(t) \end{pmatrix}$$



Multi-agents models (cellular potts)



Cable approximation

Babraham Institute

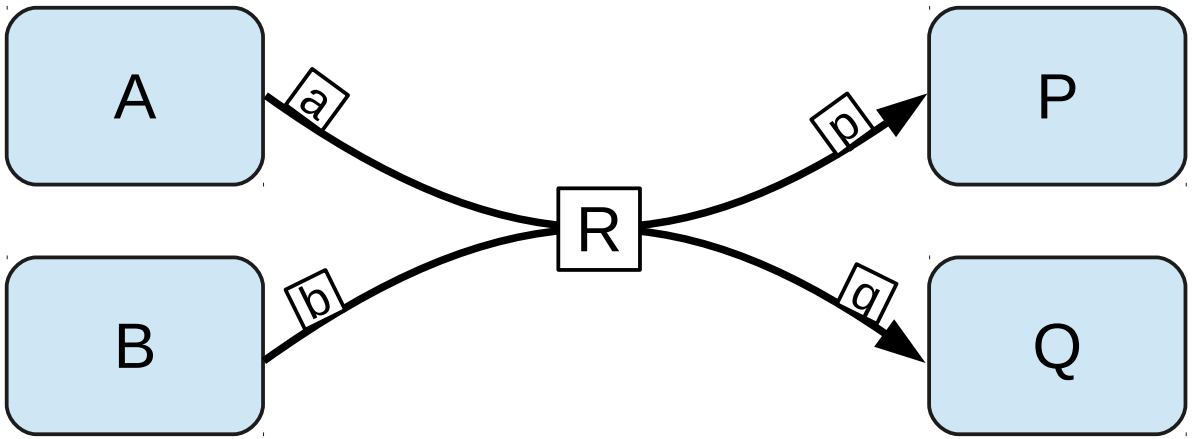
BBSRC bioscience for the future

Modelling chemical kinetics

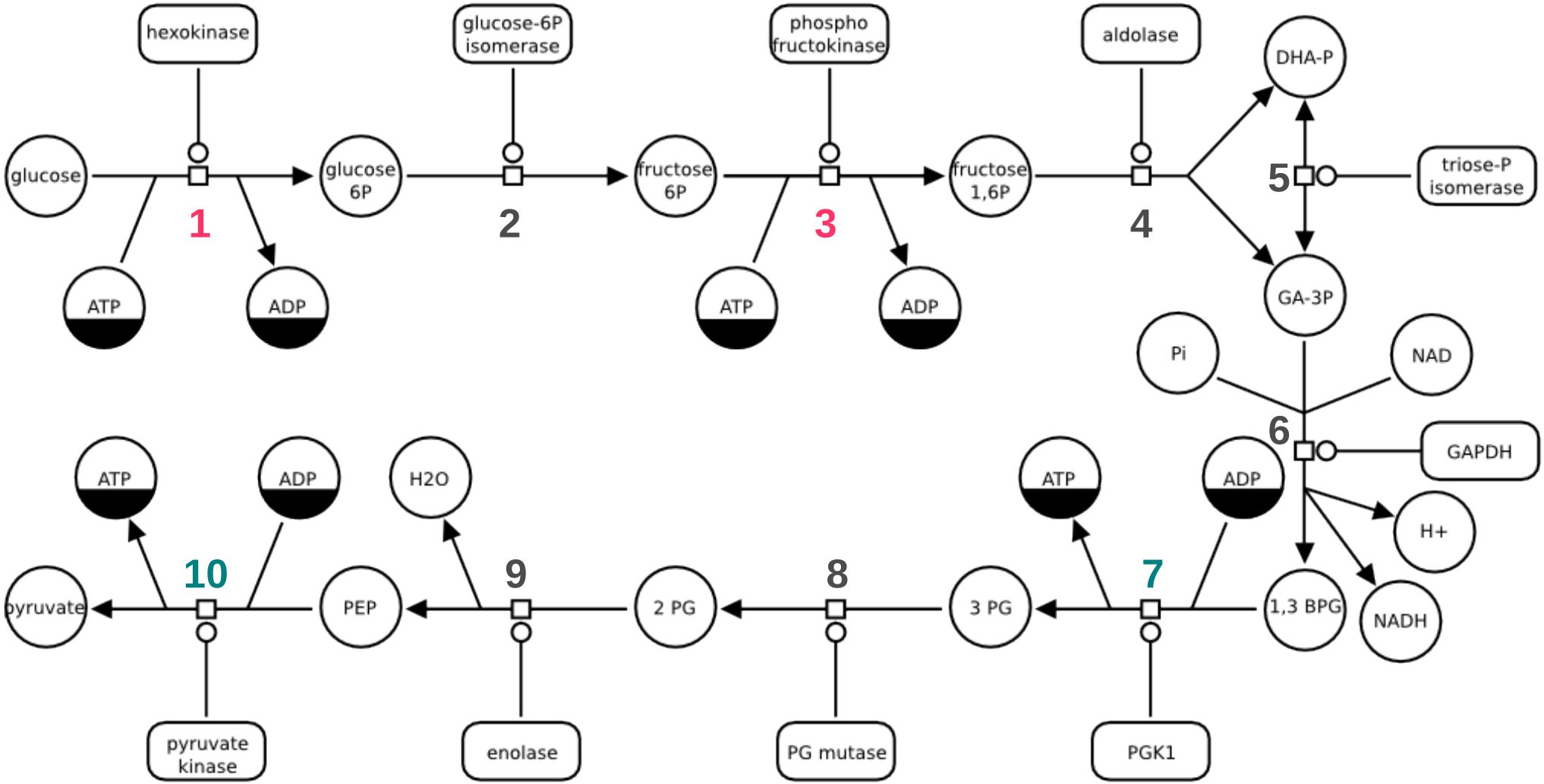
Systems Biology models ≠ ODE models

→ Reconstruction of state variable evolution
from process descriptions:

- Processes can be combined in ODEs (for deterministic simulations); transformed in propensities (for stochastic simulations)
- Systems can be reconfigured quickly by adding or removing a process

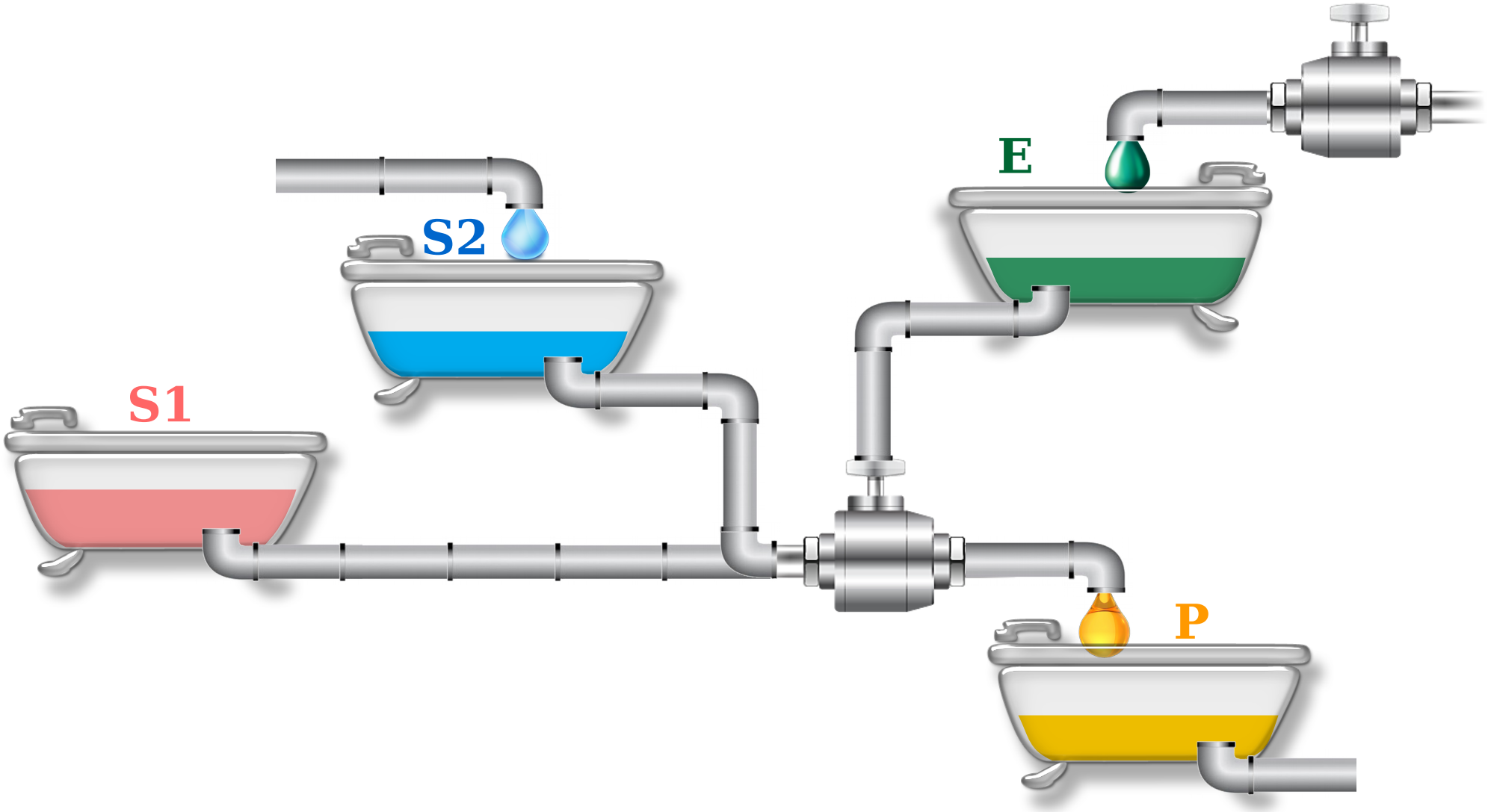


substances A and B are consumed by reaction R that produces substances P and Q

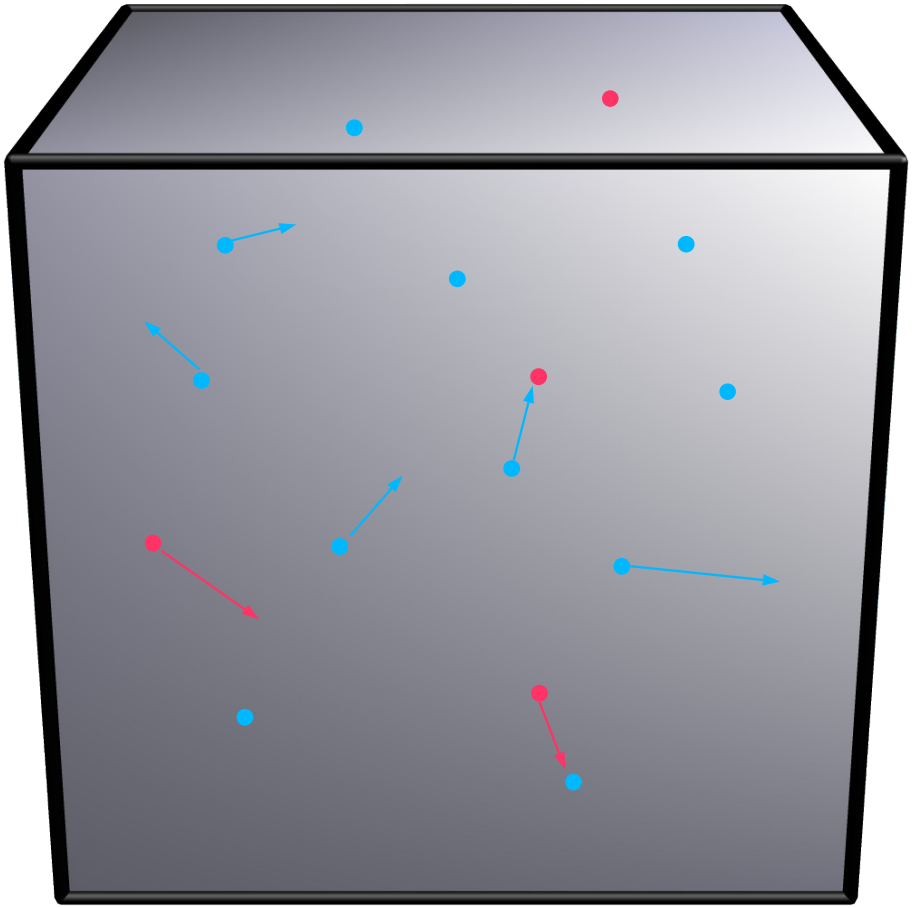


ATP is consumed by processes 1 and 3, and produced by processes 7 and 10 (for 1 reactions 1 and 3, there are 2 reactions 7 and 10)

Chemical kinetics and fluxes



Statistical physics and chemical reaction



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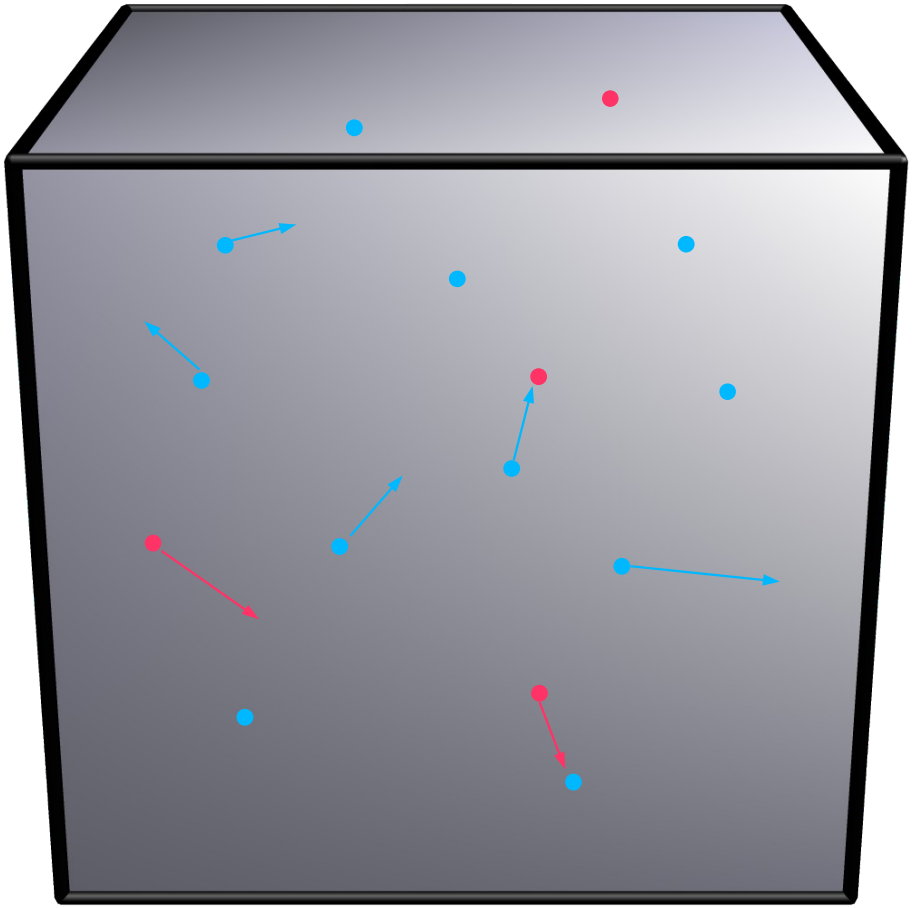
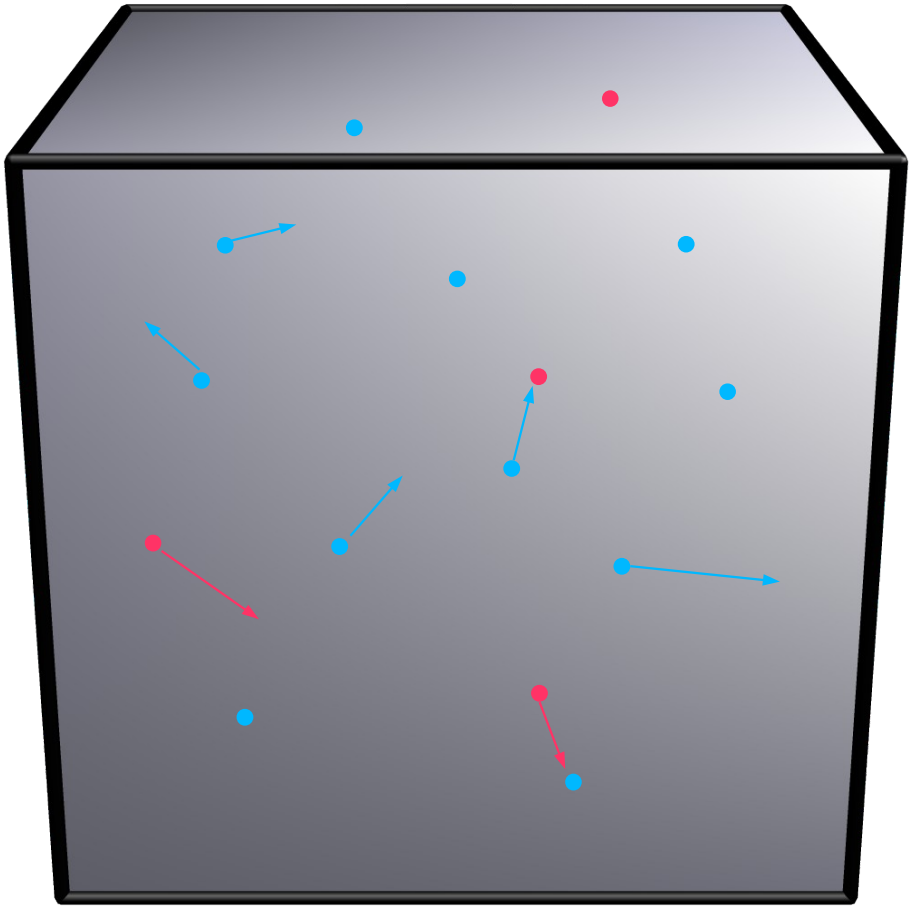


Probability to find an object in a container within an interval of time

$$P(\cdot) \propto \frac{n(\cdot)}{V} = [\cdot]$$

Statistical physics and chemical reaction



Probability to find an object in a container within an interval of time

$$P(\cdot) \propto \frac{n(\cdot)}{V} = [\cdot]$$

$$P(\text{reaction } \cdot) = P(\cdot) \times P(\cdot \text{reacts})$$
$$P(\text{reaction } \cdot + \cdot) = P(\cdot) \times P(\cdot) \times P(\cdot \text{reacts with } \cdot)$$
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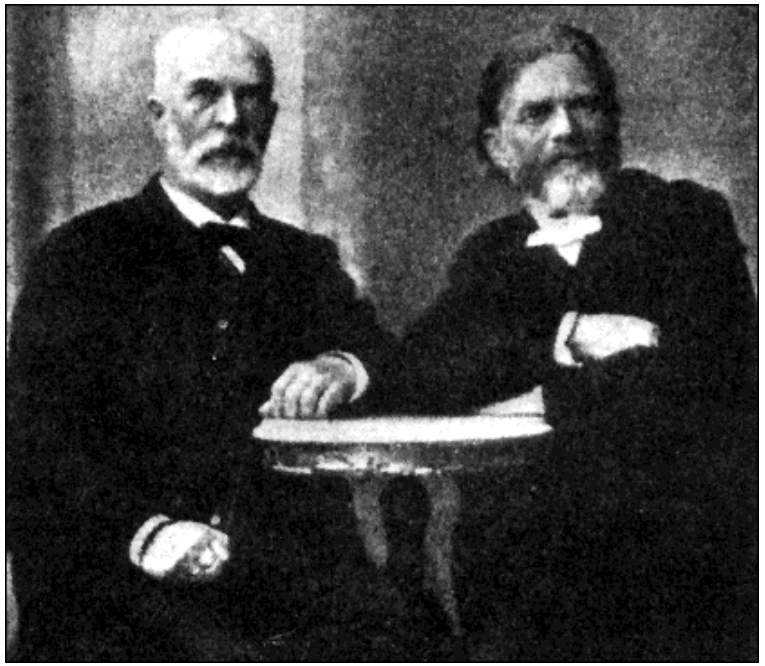
Law of Mass Action

Waage and Guldberg (1864)



activity

rate-constant

stoichiometry

$$v = k \cdot \prod_i {a_i}^{n_i}$$

velocity

Law of Mass Action

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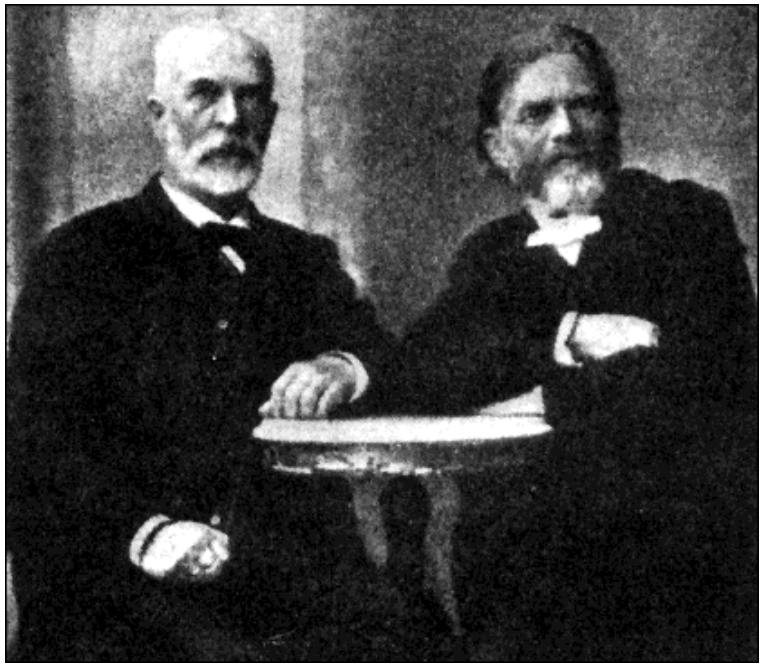

activity

rate-constant

stoichiometry

$$v = k \cdot \prod_i {a_i}^{n_i}$$

velocity

$$v = k \cdot \prod_i {P_i}^{n_i} \quad \text{gas}$$

$$v = k \cdot \prod_i [X_i]^{n_i} \quad \text{solution}$$

Evolution of a reactant

- Velocity multiplied by stoichiometry
- negative if consumption, positive if production
- Example of a unimolecular reaction $x \xrightarrow{k} y$

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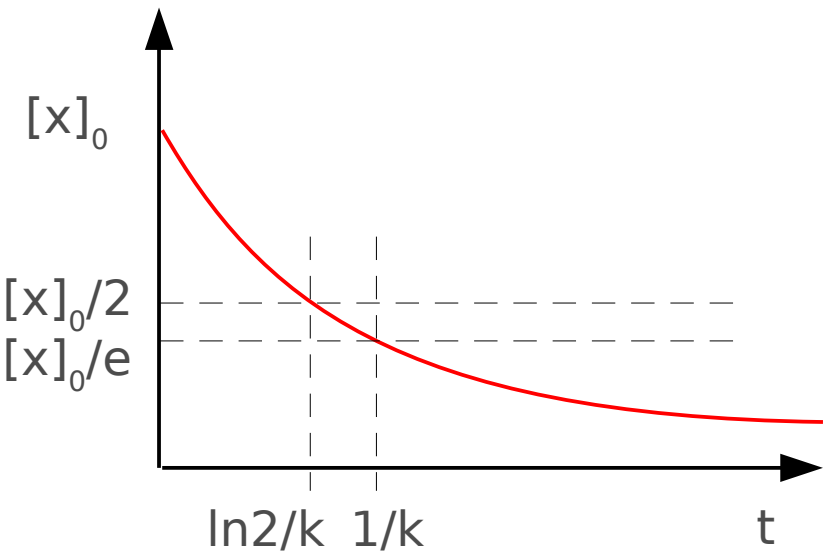
$$x(t) = [x]_0 \cdot e^{-kt}$$



Reversible reaction

$$2x \underset{k2}{\overset{k1}{\rightleftharpoons}} y$$ is equivalent to

$$2x \rightarrow y; v1 = k1 \cdot [x]^2$$

$$y \rightarrow 2x; v2 = k2 \cdot [y]$$

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$$\frac{d[x]}{dt} = -2 \cdot v1 + 2 \cdot v2 = -2 \cdot k1 \cdot [x]^2 + 2 \cdot k2 \cdot [y]$$

$$\frac{d[y]}{dt} = +1 \cdot v1 - 1 \cdot v2 = +1 \cdot k1 \cdot [x]^2 - 1 \cdot k2 \cdot [y]$$

Example of an enzymatic reaction

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

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d[S]/dt &= -k_1[E][S] + k_2[ES] \\
d[ES]/dt &= +k_1[E][S] - k_2[ES] - k_3[ES] \\
d[P]/dt &= +k_3[ES]
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d[P]/dt &= + k_3[ES]
\end{aligned}$$

$$\begin{pmatrix} d[E]/dt \\ d[S]/dt \\ d[ES]/dt \\ d[P]/dt \end{pmatrix} = \begin{pmatrix} -1 & +1 & +1 \\ -1 & +1 & 0 \\ +1 & -1 & -1 \\ 0 & 0 & +1 \end{pmatrix} \times \begin{pmatrix} k_1[E][S] \\ k_2[ES] \\ k_3[ES] \end{pmatrix}$$

$$\mathbf{S} = \mathbf{N} \cdot \mathbf{v}$$

Example of an enzymatic reaction

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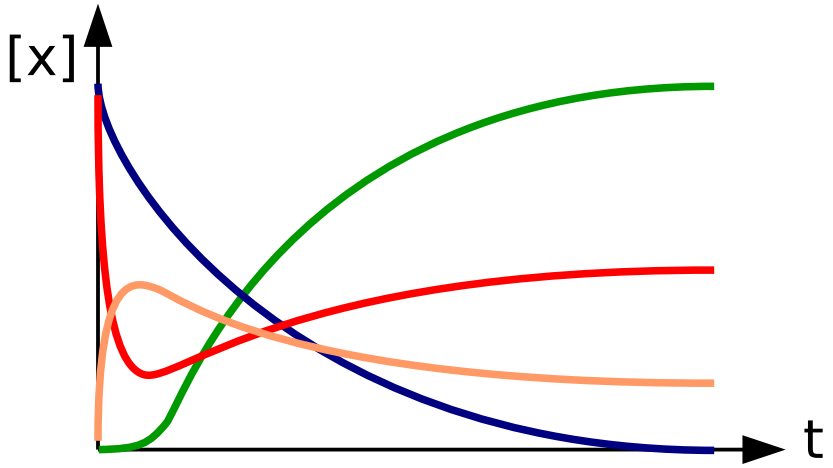


Not feasible in general

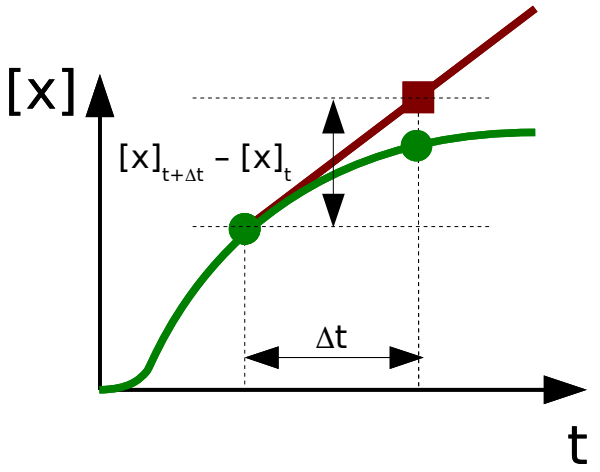
→ Numerical integration

Numerical integration

Euler method:

$$d[x]/dt \approx ([x]_{t+\Delta t} - [x]_t)/\Delta t$$

$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \cdot \Delta t$$



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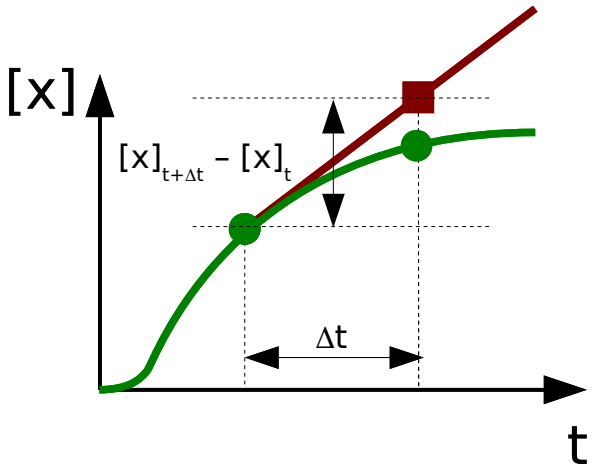

$$\begin{aligned}
[E]_{t+\Delta t} &= [E]_t + ((k_2 + k_3)[ES]_t - k_1[E]_t[S]_t) \cdot \Delta t \\
[S]_{t+\Delta t} &= [S]_t + (k_2[ES]_t - k_1[E]_t[S]_t) \cdot \Delta t \\
[ES]_{t+\Delta t} &= [ES]_t + (k_1[E]_t[S]_t - (k_2 + k_3)[ES]_t) \cdot \Delta t \\
[P]_{t+\Delta t} &= [P]_t + k_3[ES]_t \cdot \Delta t
\end{aligned}$$

Choose the right formalism

$$E + S \underset{k_{ds}}{\overset{k_{as}}{\rightleftharpoons}} ES \underset{k_{catp}}{\overset{k_{cats}}{\rightleftharpoons}} EP \underset{k_{ap}}{\overset{k_{dp}}{\rightleftharpoons}} E + P \qquad \frac{d[P]}{dt} = k_{dp}[EP] - k_{ap}[E][P]$$

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irreversible catalysis

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product escapes before rebinding

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irreversible catalysis

$$E + S \underset{k_{ds}}{\overset{k_{as}}{\rightleftharpoons}} ES \xrightarrow{k_{cats}} E + P$$

product escapes before rebinding

$$S \xrightarrow{k_{cats}} P$$

quasi-steady-state

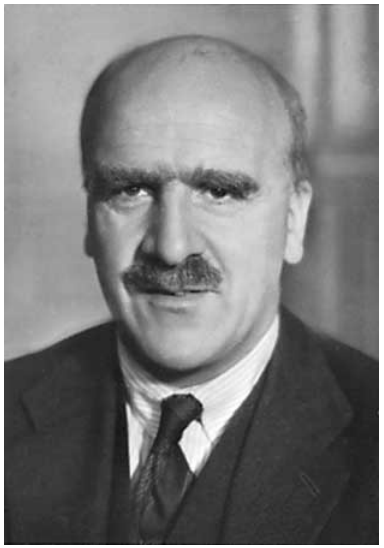
$$\frac{d[P]}{dt} = [E] k_{\mathrm{cat}} \frac{[S]}{K_m + [S]}$$

Enzyme kinetics

Victor Henri (1903) Lois Générales de l'Action des Diastases. Paris, Hermann.

Leonor Michaelis, Maud Menten (1913). Die Kinetik der Invertinwirkung, Biochem. Z. 49:333-369

George Edward Briggs and John Burdon Sanderson Haldane (1925) A note on the kinetics of enzyme action, Biochem. J., 19: 338-339



Briggs-Haldane on Henri-Michaelis-Menten
(only for info. Not needed)

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

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

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

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$[E]=[E_0]-[ES]$$

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

Briggs-Haldane on Henri-Michaelis-Menten
(only for info. Not needed)

$$E + S \underset{k_{-1}}{\overset{k1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} E + P$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

$$[E]=[E_0]-[ES]$$

steady-state!!!

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

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

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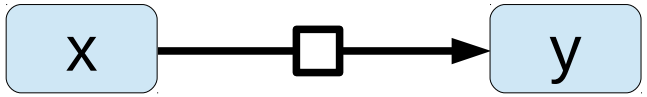
Generalisation: activators



$$\frac{d[y]}{dt} = v(= k \cdot [x])$$

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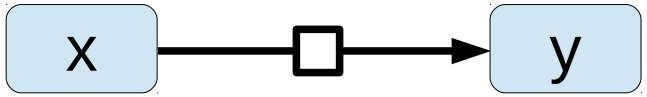

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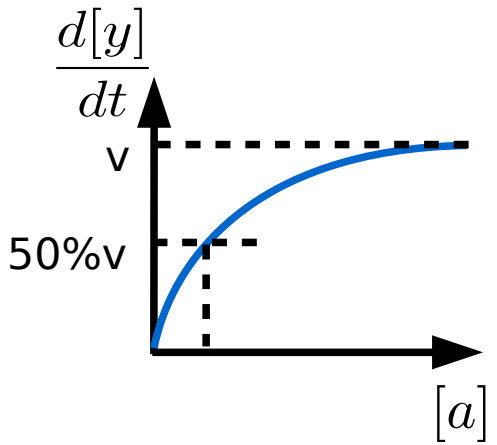
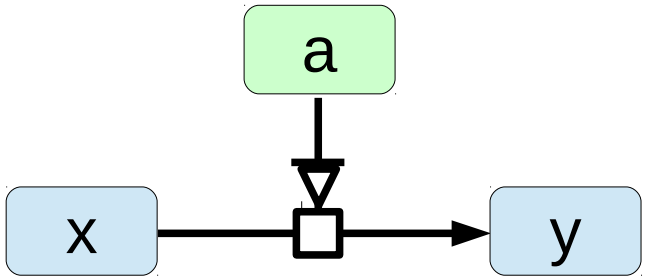
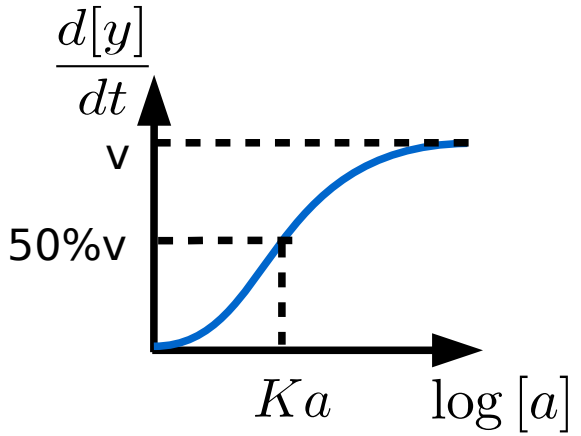




$$\frac{d[y]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



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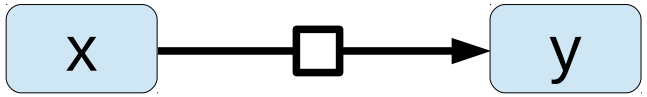

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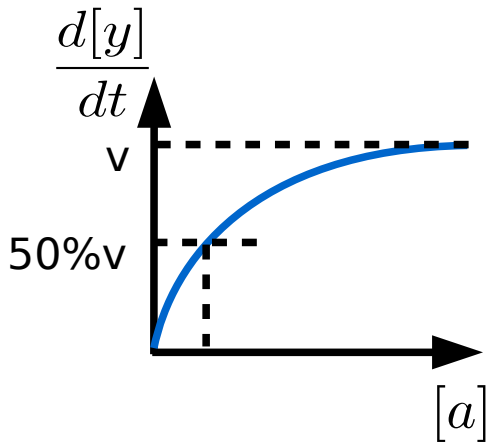

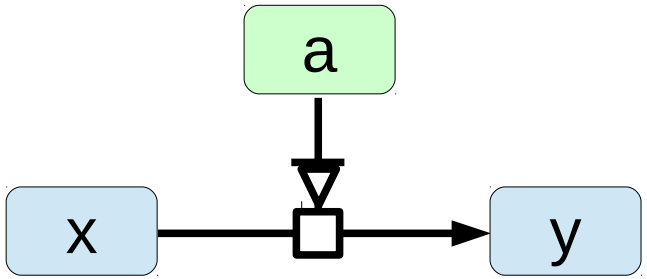

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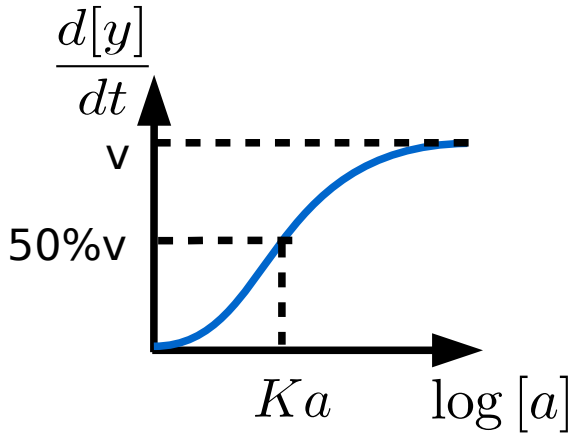


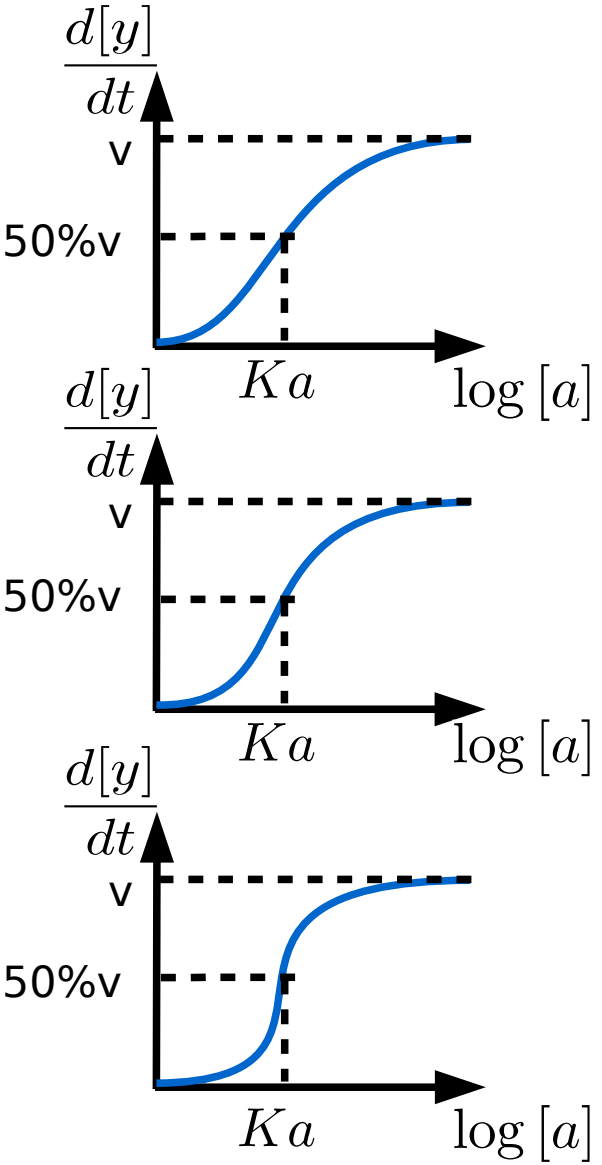
(NB: You can derive that as the fraction of target bound to the activator)

Phenomenological ultrasensitivity

$$\frac{d[y]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$

$$\frac{d[y]}{dt} = v \cdot \frac{[a]^2}{Ka^2 + [a]^2}$$

$$\frac{d[y]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n}$$



The Hill function

The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves. By A. V. HILL.

In a previous communication Barcroft and I gave evidence which seemed to us to prove conclusively that dialysed hæmoglobin consists simply of molecules containing each one atom of iron. The molecular weight is therefore Hb = 16,660. These experiments have not been published yet, but I shall assume the results.

Other observers (Reid, Roaf, Hüfner and Gansser) working on different solutions have obtained divergent results. The method used by all of them was the direct estimation of the osmotic pressure, by means of a membrane permeable to salts, but not to hæmoglobin. The method involves a relatively large error, because the quantity measured is small. It is doubtful however whether this can explain the discordant results.

Our work led me to believe that the divergence between the results of different observers was due to an aggregation of the hæmoglobin molecules by the salts present in the solution, a consequent lowering of the number of molecules, and an increase in the average molecular weight as observed by the osmotic pressure method. To test this hypothesis I have applied it to several of the dissociation curves obtained by Barcroft and Camis with hæmoglobin in solutions of various salts, and with hæmoglobin prepared by Bohr's method.

The equation for the reaction would be

$$\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2},$$
$$\mathrm{Hb}_n + n\mathrm{O_2} \rightleftarrows \mathrm{Hb}_n\mathrm{O}_{2n},$$

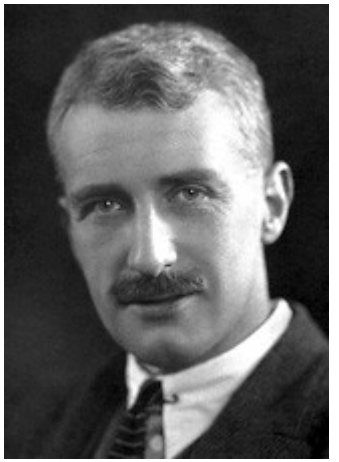
where Hb_n represents the aggregate of n molecules of Hb. I have supposed that in every solution there are many different sized aggregates, corresponding to many values of n.

If there were in the solution only Hb and $\mathrm{Hb_2}$ the dissociation curve would be

$$y = \lambda \frac{K'x^2}{1+K'x^2} + (100-\lambda)\frac{Kx}{1+Kx} \quad \ldots\ldots\ldots\ldots\ldots\ldots(\mathrm{A}),$$

where λ % is as $\mathrm{Hb_2}$, $(100-\lambda)$ % as Hb, K' is the equilibrium constant of the reaction $\mathrm{Hb_2} + 2\mathrm{O_2} \rightleftarrows \mathrm{Hb_2O_4}$ and K that of $\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2}$: K has the value ·125 (Barcroft and Roberts).

Hill (1910) *J Physiol* 40: iv-vii.



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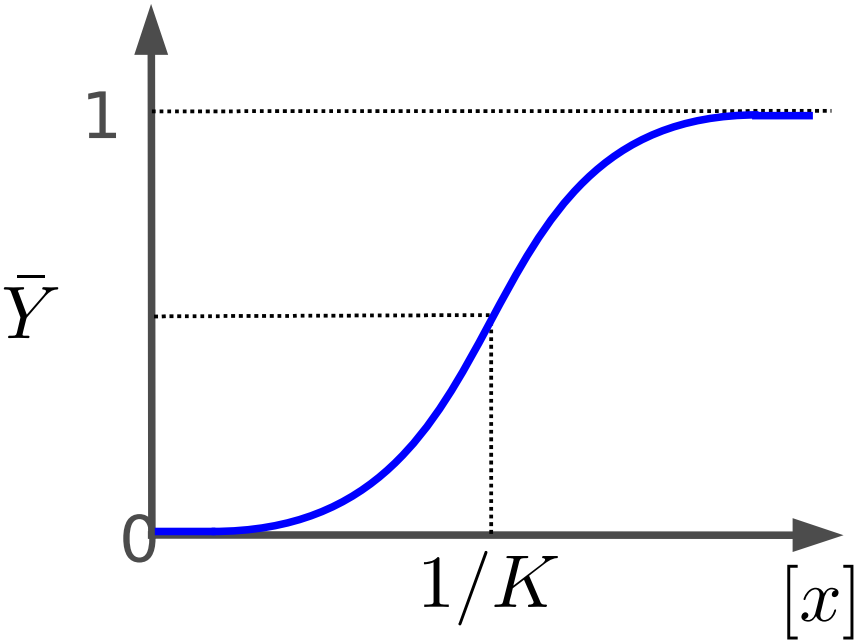
Hill (1910) *J Physiol* 40: iv-vii.

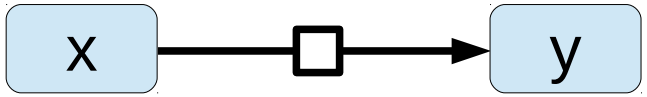
Now it is unlikely that in either of these cases there is only Hb and $\mathrm{Hb_2}$: and as the calculation of the constants in these equations is very tedious I decided to try whether the equation

$$y = 100\frac{Kx^n}{1+Kx^n} \quad \ldots\ldots\ldots\ldots\ldots\ldots(\mathrm{B})$$

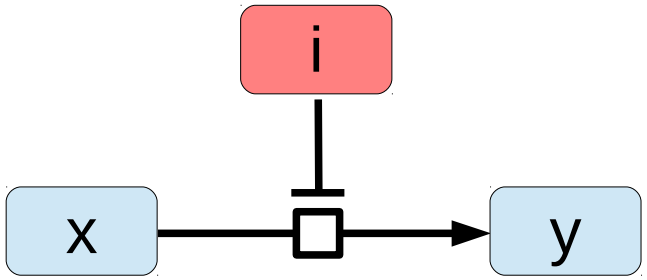
would satisfy the observations.



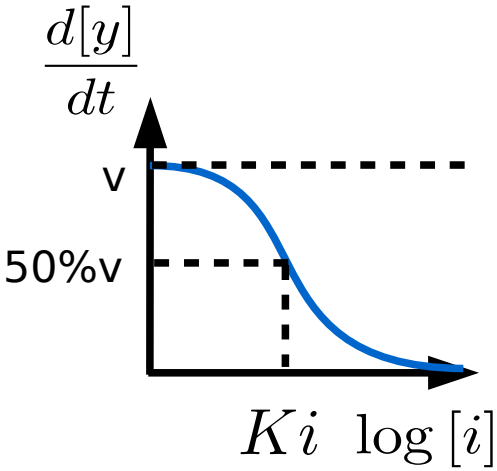
Generalisation: inhibitors



$$\frac{d[y]}{dt} = v(= k \cdot [x])$$

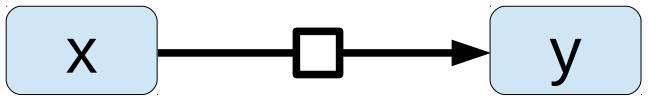


$$\frac{d[y]}{dt} = v \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

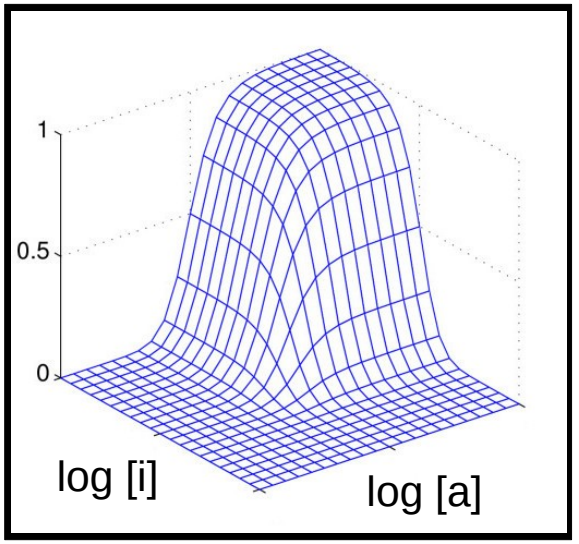


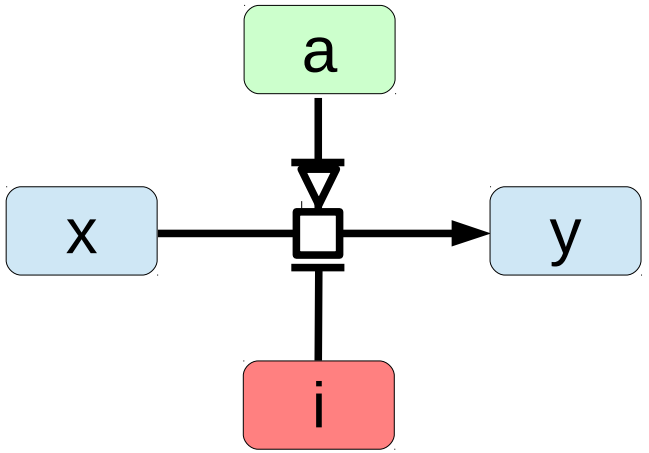
(NB: You can derive that as the fraction of target not bound to the inhibitor)

Generalisation: activators and inhibitors



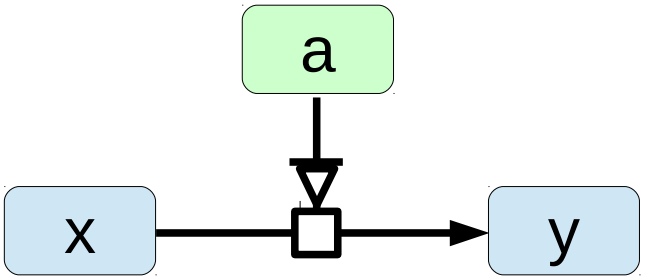
$$\frac{d[y]}{dt} = v(= k \cdot [x])$$



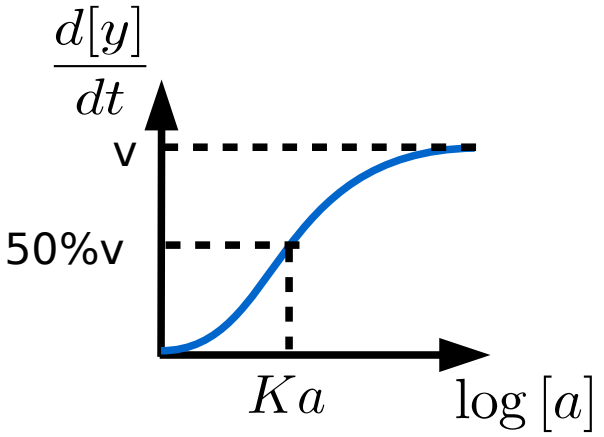


$$\frac{d[y]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n} \cdot \frac{Ki^m}{Ki^m + [i]^m}$$

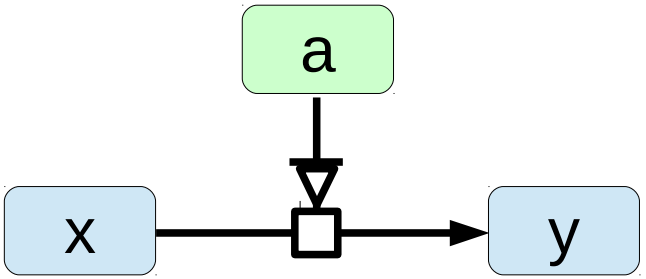
absolute Vs relative activators

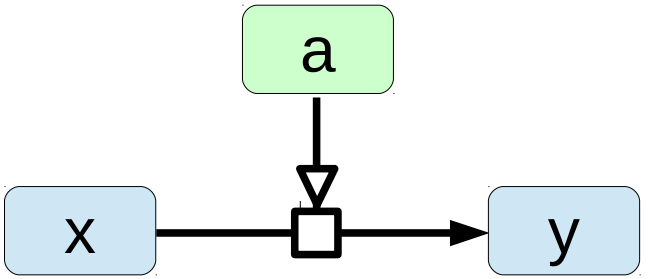


$$\frac{d[y]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



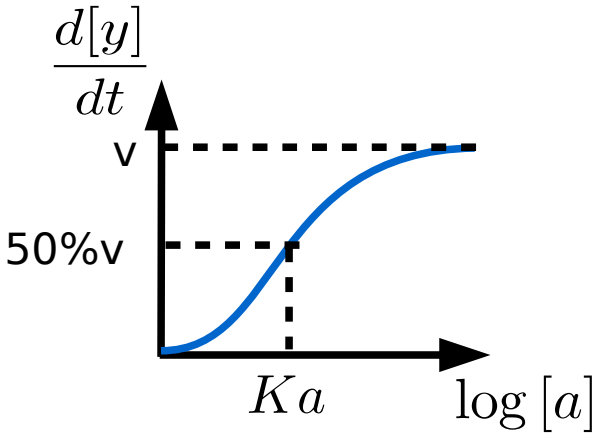
absolute Vs relative activators

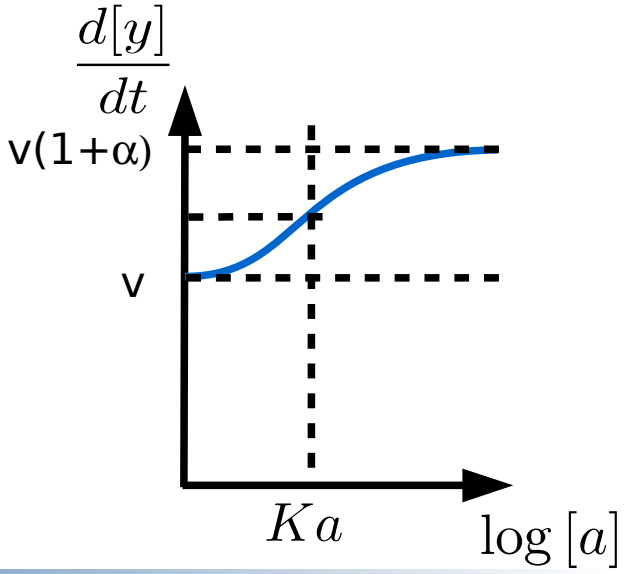




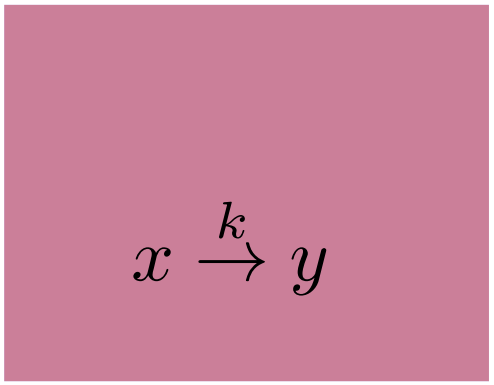
$$\frac{d[y]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$

$$\frac{d[y]}{dt} = v \cdot (1 + \alpha \cdot \frac{[a]}{Ka + [a]})$$





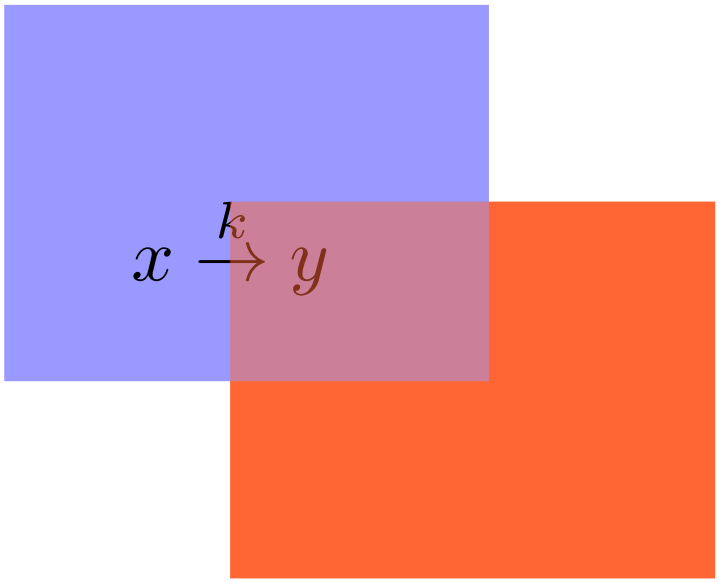
1 compartment



$$\frac{d[x]}{dt} = -1 \cdot k \cdot [x]$$

$$\frac{d[y]}{dt} = +1 \cdot k \cdot [x]$$

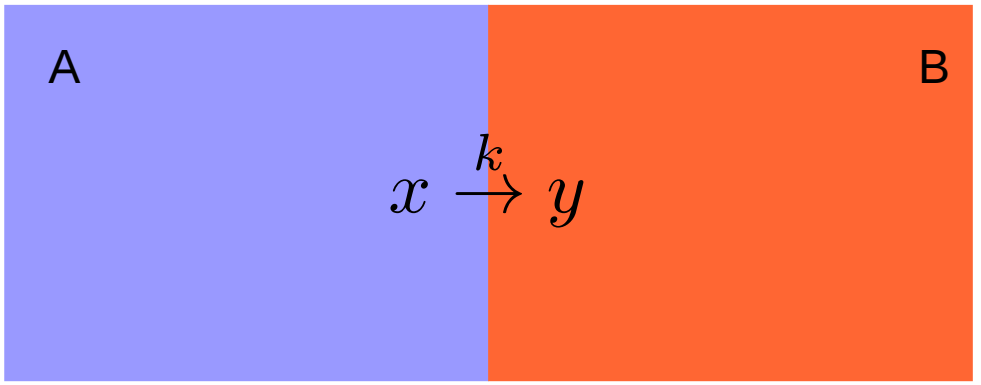
2 compartments



$$\frac{d[x]}{dt} = -1 \cdot k \cdot [x]$$

$$\frac{d[y]}{dt} = +1 \cdot k \cdot [x]$$

2 compartments



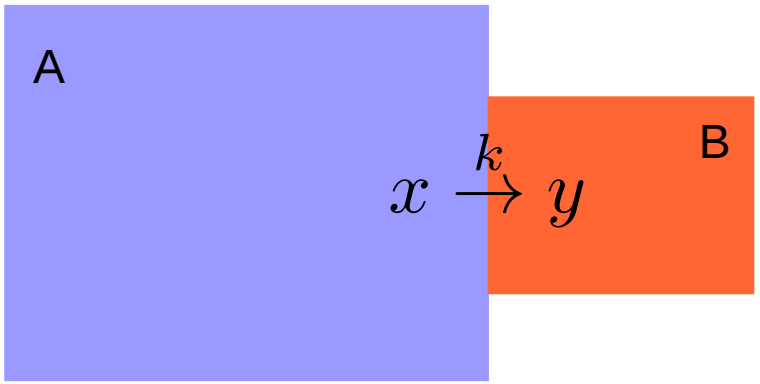
Per unit of time

$$\frac{d[x]_A}{dt} = -1 \cdot k \cdot [x]_A \qquad nx_A = -1 \cdot k \cdot [x]_A \cdot V_A$$

$$\frac{d[y]_B}{dt} = +1 \cdot k \cdot [x]_A \qquad ny_B = +1 \cdot k \cdot [x]_A \cdot V_B$$

$$V_A = V_B \Rightarrow nx_A = ny_B$$

2 compartments … with different volumes

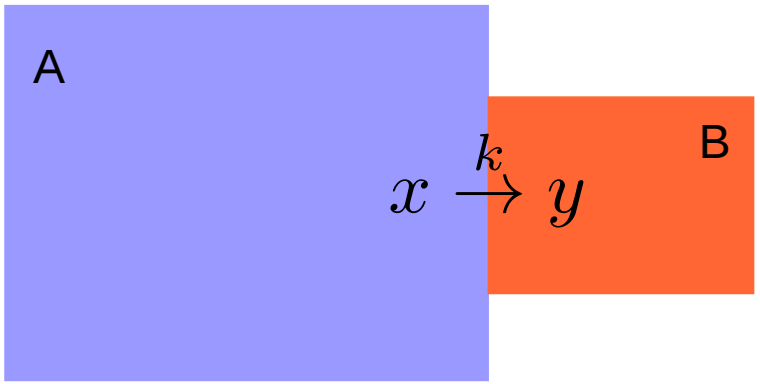


$$V_A = 4 \cdot V_B$$

$$\frac{d[x]_A}{dt} = -1 \cdot k \cdot [x]_A$$

$$\frac{d[y]_B}{dt} = +1 \cdot k \cdot [x]_A$$

2 compartments … with different volumes



$$V_A = 4 \cdot V_B$$

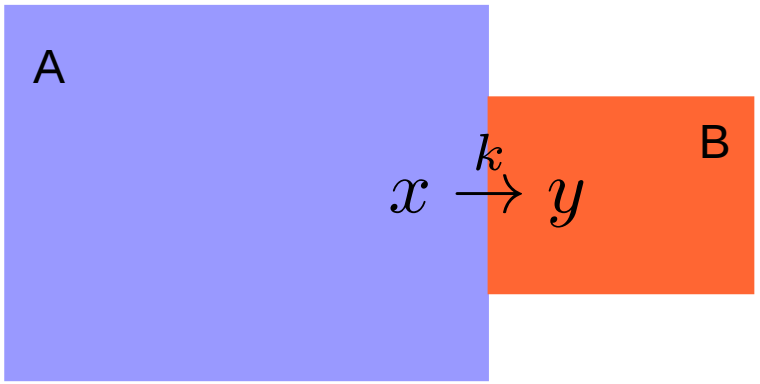
Per unit of time

$$\frac{d[x]_A}{dt} = -1 \cdot k \cdot [x]_A \qquad nx_A = -1 \cdot k \cdot [x]_A \cdot V_A$$

$$\frac{d[y]_B}{dt} = +1 \cdot k \cdot [x]_A \qquad ny_B = +1 \cdot k \cdot [x]_A \cdot V_B$$

$$nx_A = 4 \cdot ny_B$$

2 compartments … with different volumes



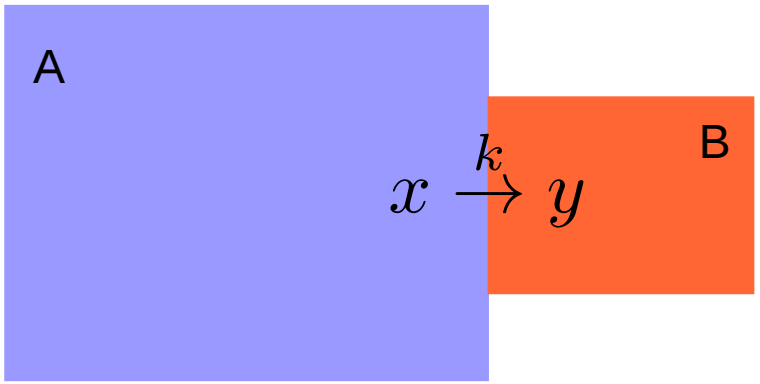
$$V_A = 4 \cdot V_B$$

Per unit of time

$$\frac{d[x]_A}{dt} = -1 \cdot k \cdot [x]_A \cdot \frac{V_A}{V_A} \qquad nx_A = k \cdot [x]_A \cdot \frac{V_A}{V_A} \cdot V_A$$

$$\frac{d[y]_B}{dt} = +1 \cdot k \cdot [x]_A \cdot \frac{V_A}{V_B} \qquad ny_B = k \cdot [x]_A \cdot \frac{V_A}{V_B} \cdot V_B$$

2 compartments … with different volumes



$$V_A = 4 \cdot V_B$$

Per unit of time

$$\frac{d[x]_A}{dt} = -1 \cdot k \cdot [x]_A \cdot \frac{V_A}{V_A}$$

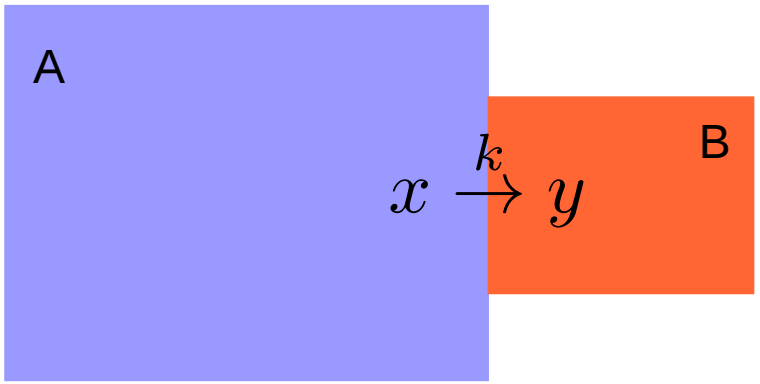
$$\frac{d[y]_B}{dt} = +1 \cdot k \cdot [x]_A \cdot \frac{V_A}{V_B}$$

$$nx_A = k \cdot [x]_A \cdot \frac{V_A}{\cancel{V_A}} \cdot \cancel{V_A}$$

$$ny_B = k \cdot [x]_A \cdot \frac{V_A}{\cancel{V_B}} \cdot \cancel{V_B}$$

$$nx_A = ny_B$$

2 compartments … with different volumes



$$V_A = 4 \cdot V_B$$

Kinetic constants must be scaled with volumes:

$$k_{A \to B} = k \cdot \frac{V_A}{V_A}$$

$$k_{B \to A} = k \cdot \frac{V_A}{V_B}$$

Per unit of time

$$\frac{d[x]_A}{dt} = -1 \cdot k \cdot [x]_A \cdot \frac{V_A}{V_A}$$

$$\frac{d[y]_B}{dt} = +1 \cdot k \cdot [x]_A \cdot \frac{V_A}{V_B}$$

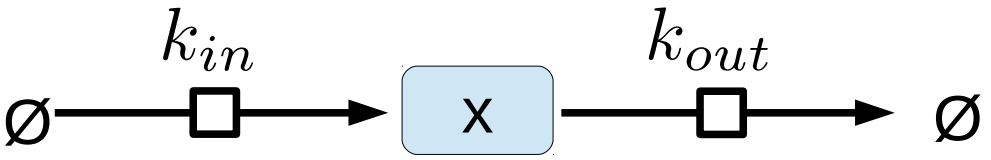
$$nx_A = k \cdot [x]_A \cdot \frac{V_A}{\cancel{V_A}} \cdot \cancel{V_A}$$

$$ny_B = k \cdot [x]_A \cdot \frac{V_A}{\cancel{V_B}} \cdot \cancel{V_B}$$

$$nx_A = ny_B$$

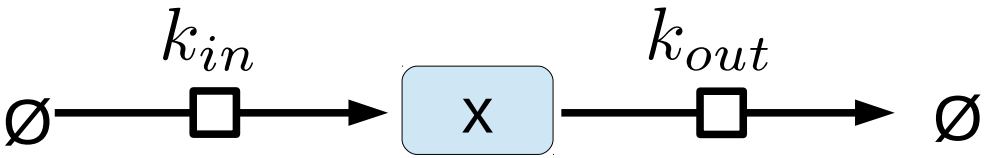
Homeostasis

How can-we maintain a stable level with a dynamic system?



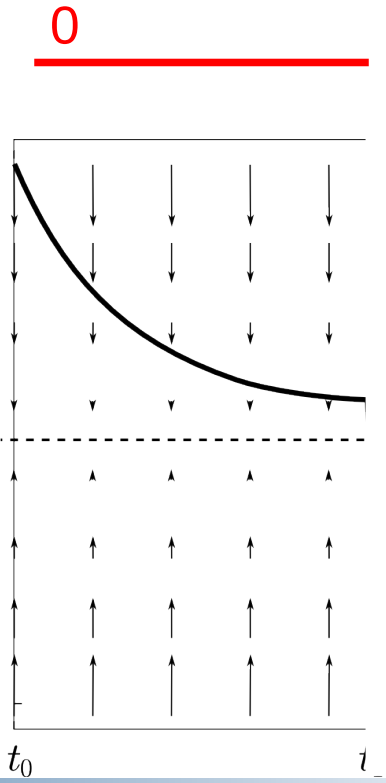
Homeostasis

How can-we maintain a stable level with a dynamic system?



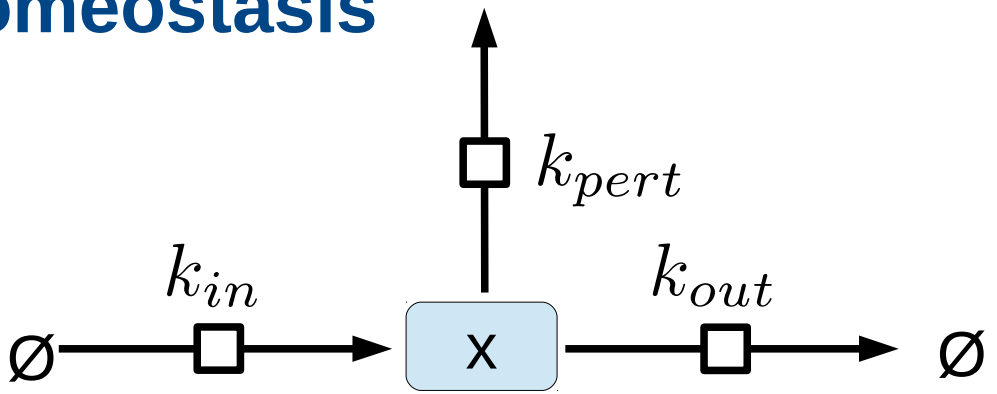
$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$

$$[x]_{eq} = \frac{k_{in}}{k_{out}}$$

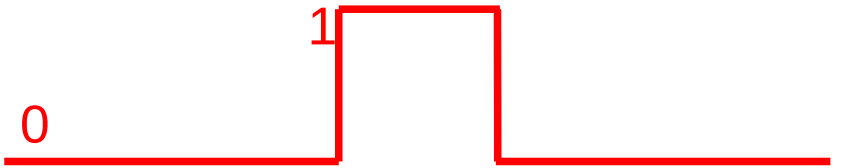


Homeostasis

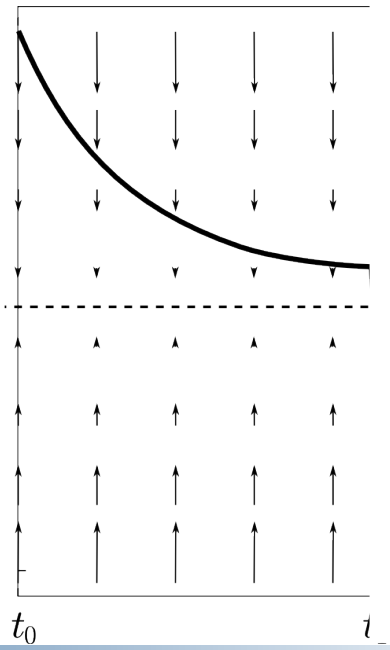
How can-we maintain a stable level with a dynamic system?



$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$

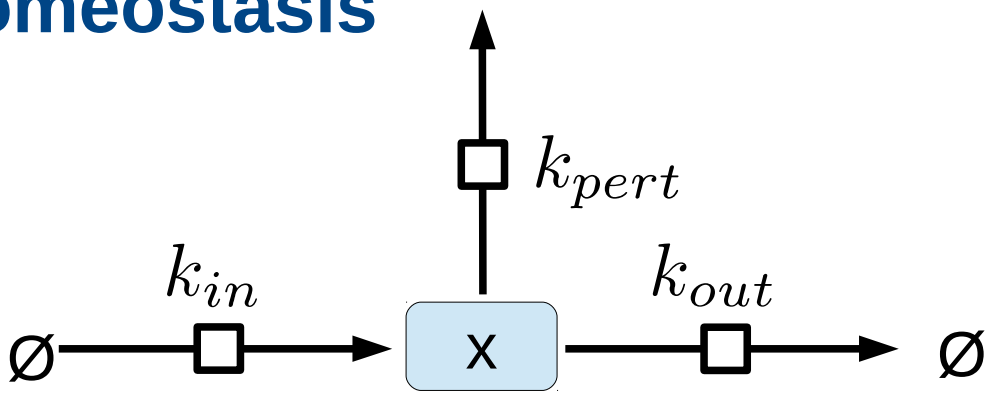


$$[x]_{eq} = \frac{k_{in}}{k_{out}}$$

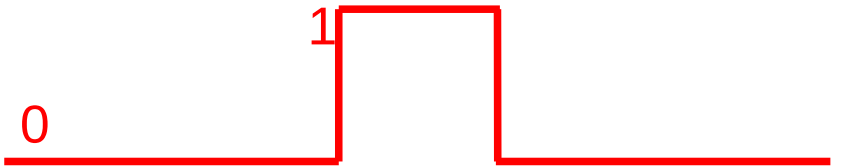


Homeostasis

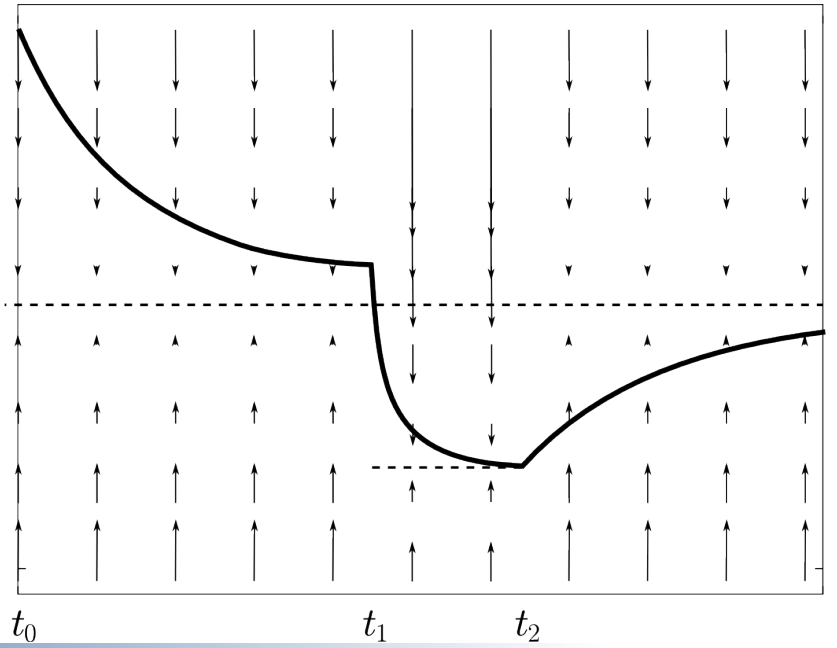
How can-we maintain a stable level with a dynamic system?



$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x] - k_{pert} \cdot [x]$$



$$[x]_{eq} = \frac{k_{in}}{k_{out}}$$



Babraham Institute

BBSRC bioscience for the future

Building and simulating Models with COPASI

COPASI: Biochemical System Simulator

COPASI is a software application for simulation and analysis of biochemical networks and their dynamics.

COPASI is a stand-alone program that supports models in the SBML standard and can simulate their behavior using ODEs or Gillespie's stochastic simulation algorithm; arbitrary discrete events can be included in such simulations. A list of the many features can be found here.

Most recent News

COPASI is part of de.NBI

Frank T. Bergmann: 2017-01-25 11:05:00 +0000

COPASI is part of de.NBI, the 'German Network for Bioinformatics Infrastructure'.

COPASI is part of de.NBI, the 'German Network for Bioinformatics Infrastructure' (for further information visit de.NBI homepage). The network provides comprehensive first-class bioinformatics services to users in life sciences research, industry and medicine. The de.NBI program coordinates bioinformatics training and education and the cooperation of the German bioinformatics community with international bioinformatics network structures including ELIXIR.

In order to improve COPASI, we would like to ask you to fill out the de.NBI user survey for COPASI to collect ideas for improvements.

Thanks in advance for your help and support.

The COPASI Team.

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Language Bindings: Java	Mac OS X	COPASI-4.19.140-Java-Bindings-Darwin.tar.gz

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 10078–10083, September 1996
Biochemistry

Ultrasensitivity in the mitogen-activated protein kinase cascade

CHI-YING F. HUANG AND JAMES E. FERRELL, JR.†

Department of Molecular Pharmacology, Stanford University School of Medicine, Stanford, CA 94305-5332

Communicated by Daniel E. Koshland, Jr., University of California, Berkeley, CA, May 16, 1996 (received for review January 22, 1996)

ABSTRACT **The mitogen-activated protein kinase (MAPK) cascade is a highly conserved series of three protein kinases implicated in diverse biological processes. Here we demonstrate that the cascade arrangement has unexpected consequences for the dynamics of MAPK signaling. We solved the rate equations for the cascade numerically and found that MAPK is predicted to behave like a highly cooperative enzyme, even though it was not assumed that any of the enzymes in the cascade were regulated cooperatively. Measurements of MAPK activation in *Xenopus* oocyte extracts confirmed this prediction. The stimulus/response curve of the MAPK was found to be as steep as that of a cooperative enzyme with a Hill coefficient of 4–5, well in excess of that of the classical allosteric protein hemoglobin. The shape of the MAPK stimulus/response curve may make the cascade particularly appropriate for mediating processes like mitogenesis, cell fate induction, and oocyte maturation, where a cell switches from one discrete state to another.**

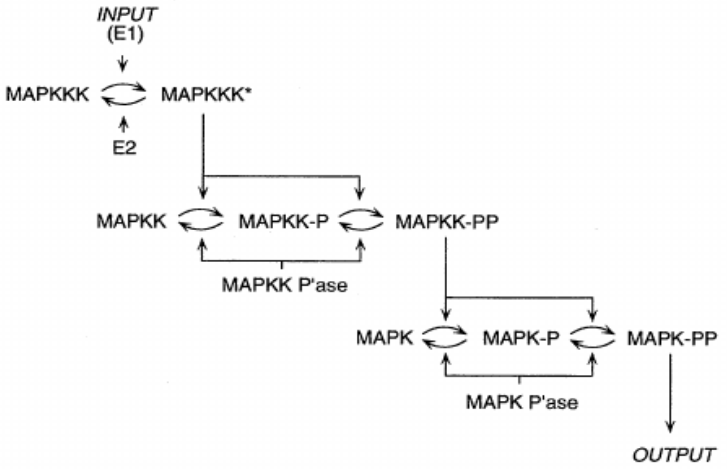

FIG. 1. Schematic view of the MAPK cascade. Activation of MAPK depends upon the phosphorylation of two conserved sites

Eur. J. Biochem. **267**, 1583–1588 (2000) © FEBS 2000

Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades

Boris N. Kholodenko

Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA

Functional organization of signal transduction into protein phosphorylation cascades, such as the mitogen-activated protein kinase (MAPK) cascades, greatly enhances the sensitivity of cellular targets to external stimuli. The sensitivity increases multiplicatively with the number of cascade levels, so that a tiny change in a stimulus results in a large change in the response, the phenomenon referred to as ultrasensitivity. In a variety of cell types, the MAPK cascades are im
terminal kinase stimulates o
feedback loop combined w
oscillations in MAPK phospl
period of oscillations can ran
and almost 100% of the total
in the cytoplasm can lead to

Keywords: signal transductio

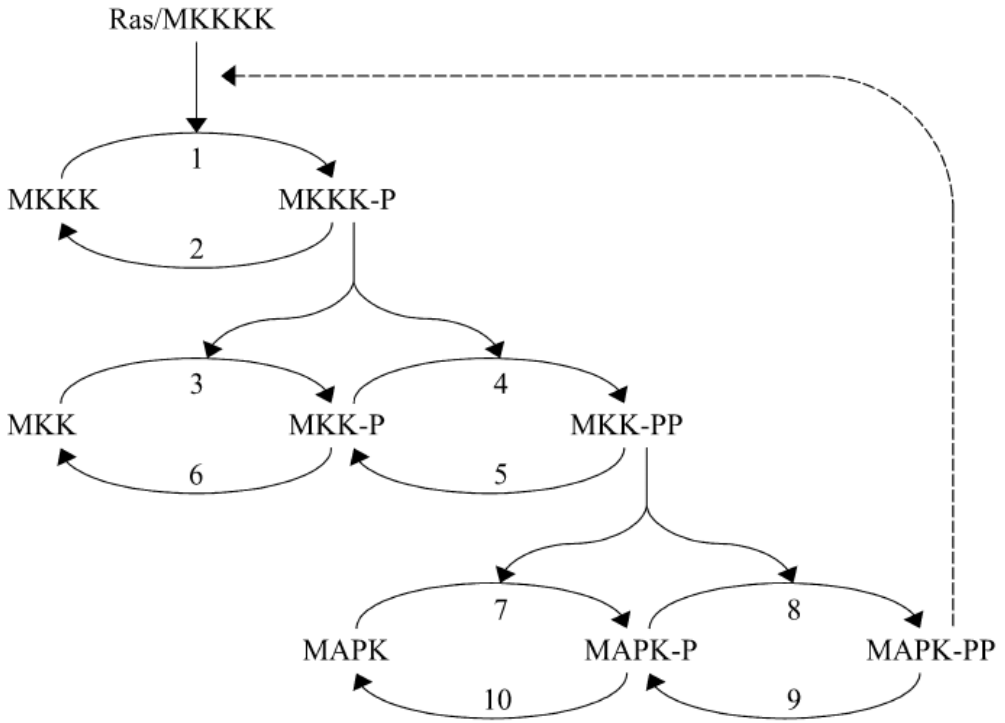

Fig. 1. Kinetic scheme of the MAPK cascade. Feedback effect of MAPK on the rate of MKKK phosphorylation is shown schematically by the dashed line. Numbering of individual steps corresponds to kinetic equations in Tables 1 and 2.

Mathematics are beautiful

$$1 - \frac{[I]^m}{K_i^m + [I]^m} = \frac{K_1^m}{K_i^m + [I]^m} = \frac{[I]^{-m}}{K_i^{-m} + [I]^{-m}}$$