

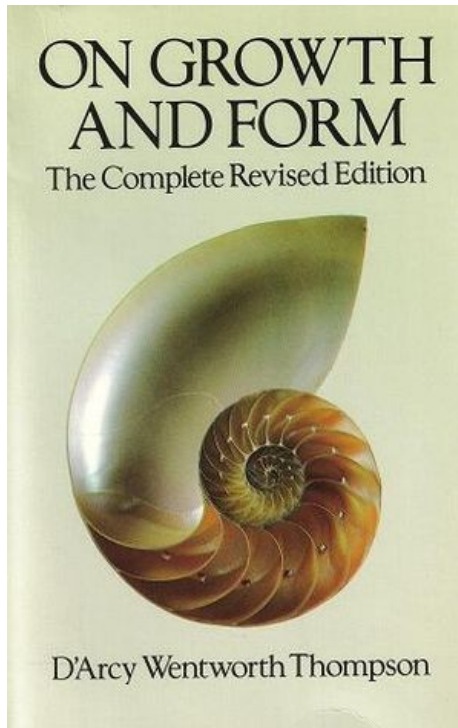
The many faces of modelling in biology

Nicolas Le Novère, The Babraham Institute

n.lenovere@gmail.com

What is the goal of using mathematical models?

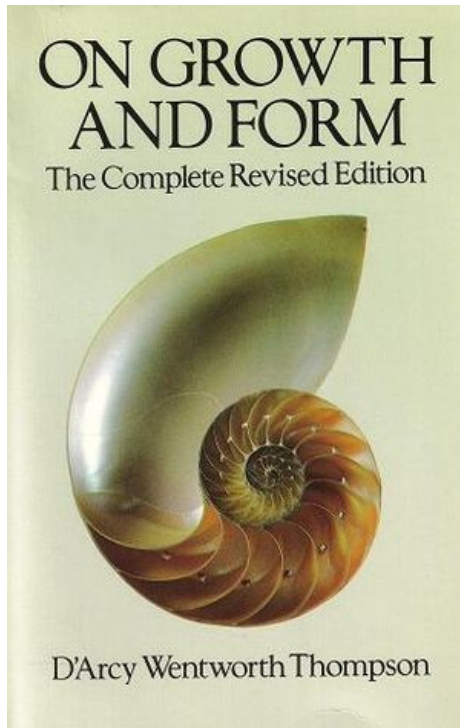
Describe



1917

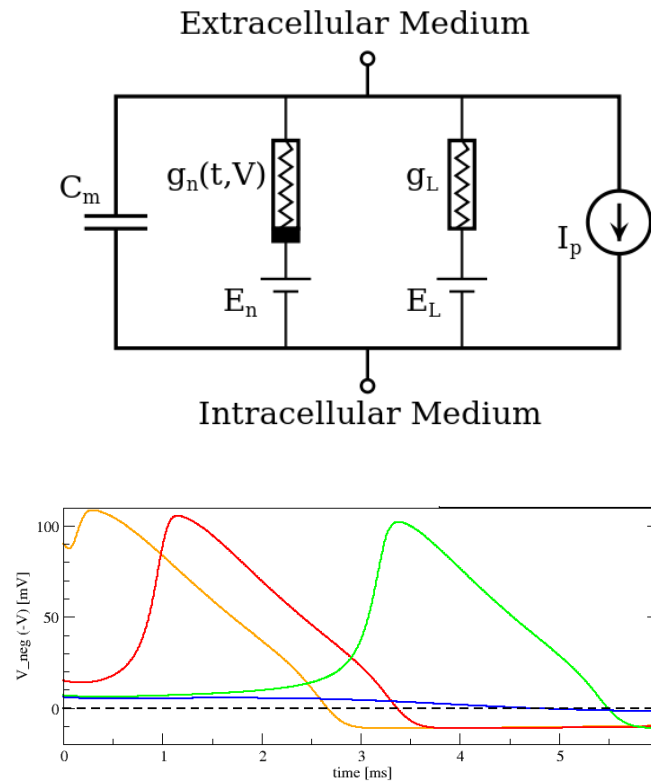
What is the goal of using mathematical models?

Describe



1917

Explain



1952

ON GROWTH
AND FORM
The Complete Revised Edition

D'Arcy Wentworth Thompson

Extracellular Medium

Intracellular Medium

C_m

$g_n(t, V)$

E_n

g_L

E_L

I_p



What is a mathematical model?

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

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variables

$[x]$

$V_{\max}$

K_d

EC_{50}

length

$t_{1/2}$

**What we want to know
or compare with experiments**

What is a mathematical model?

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$[X]$

$V_{\max}$

K_d

EC_{50}

length

$t_{1/2}$

relationships

$$K_d = \frac{[A] \cdot [B]}{[AB]}$$

$$d[X]/dt = k \cdot [Y]^2$$

$$\sum_i [X]_i - F(t) = 0$$

$$k(t) \sim N(k, \sigma^2)$$

If $\text{mass}_t > \text{threshold}$
then $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$

**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.”

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constraints

$$[X] \geq 0$$

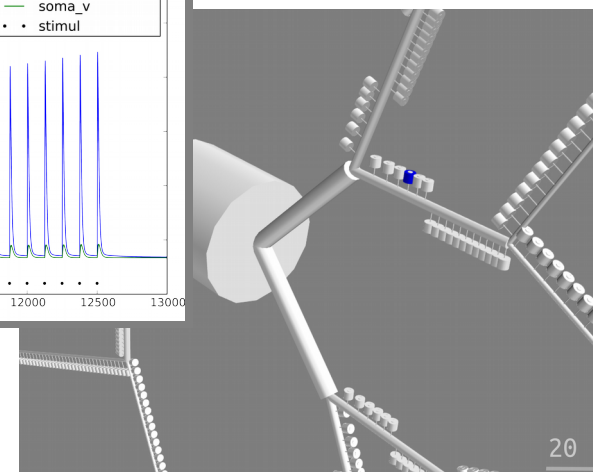
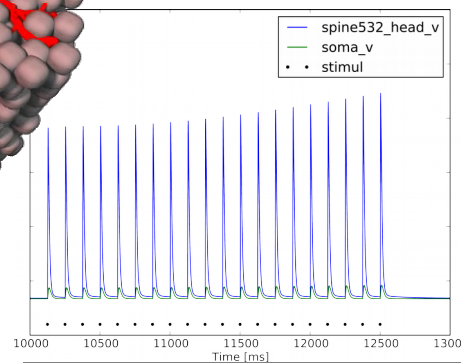
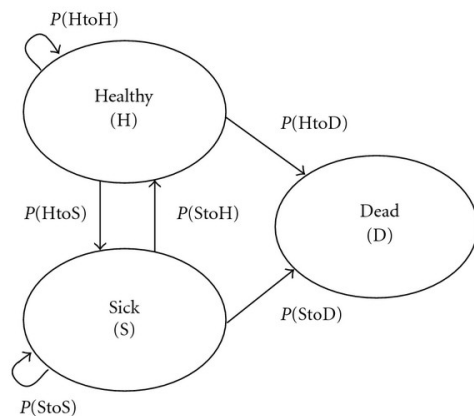
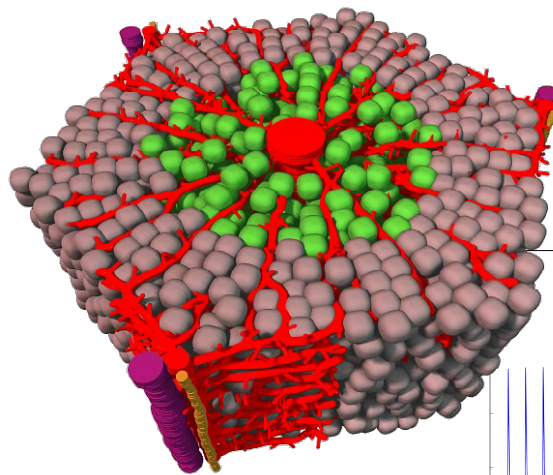
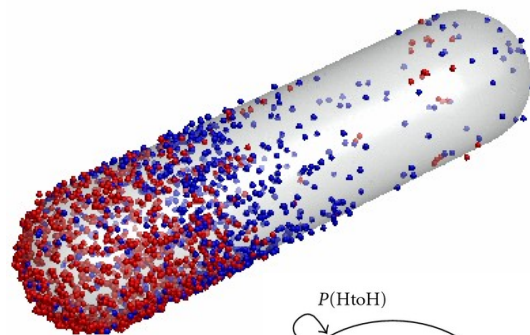
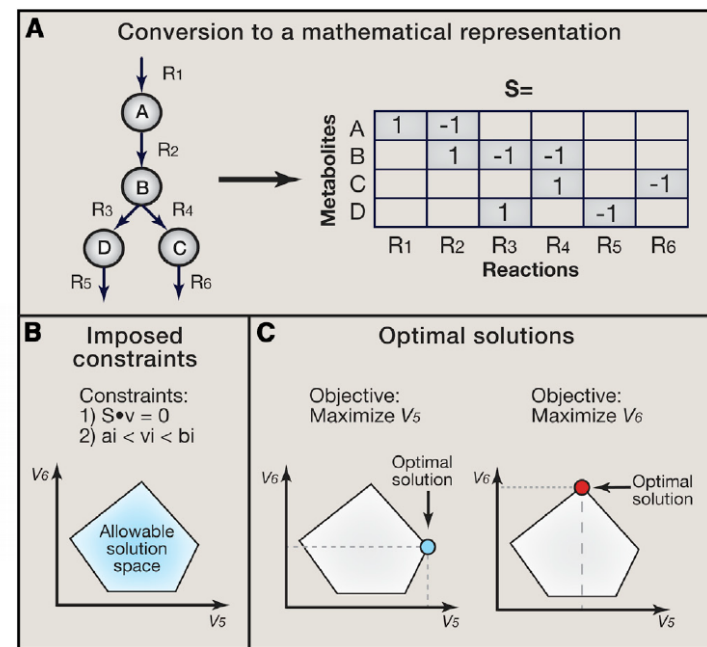
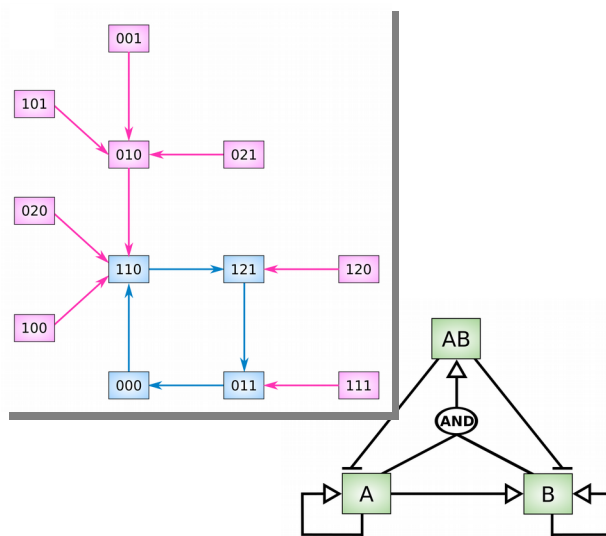
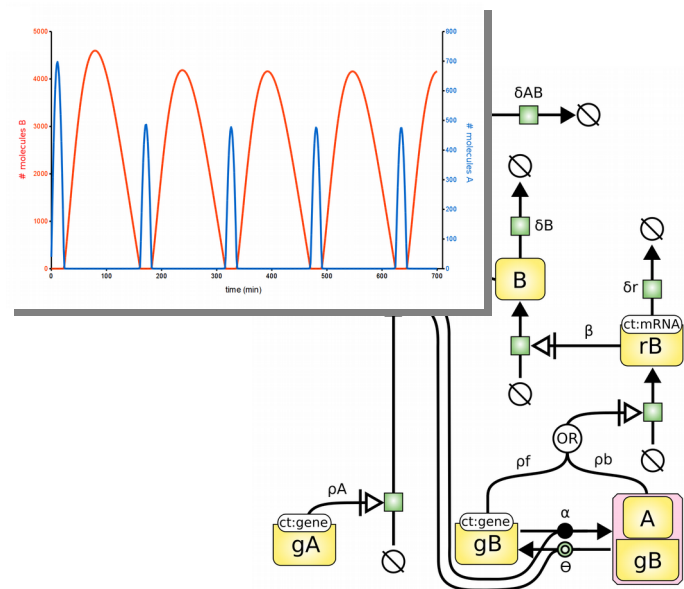
Energy conservation

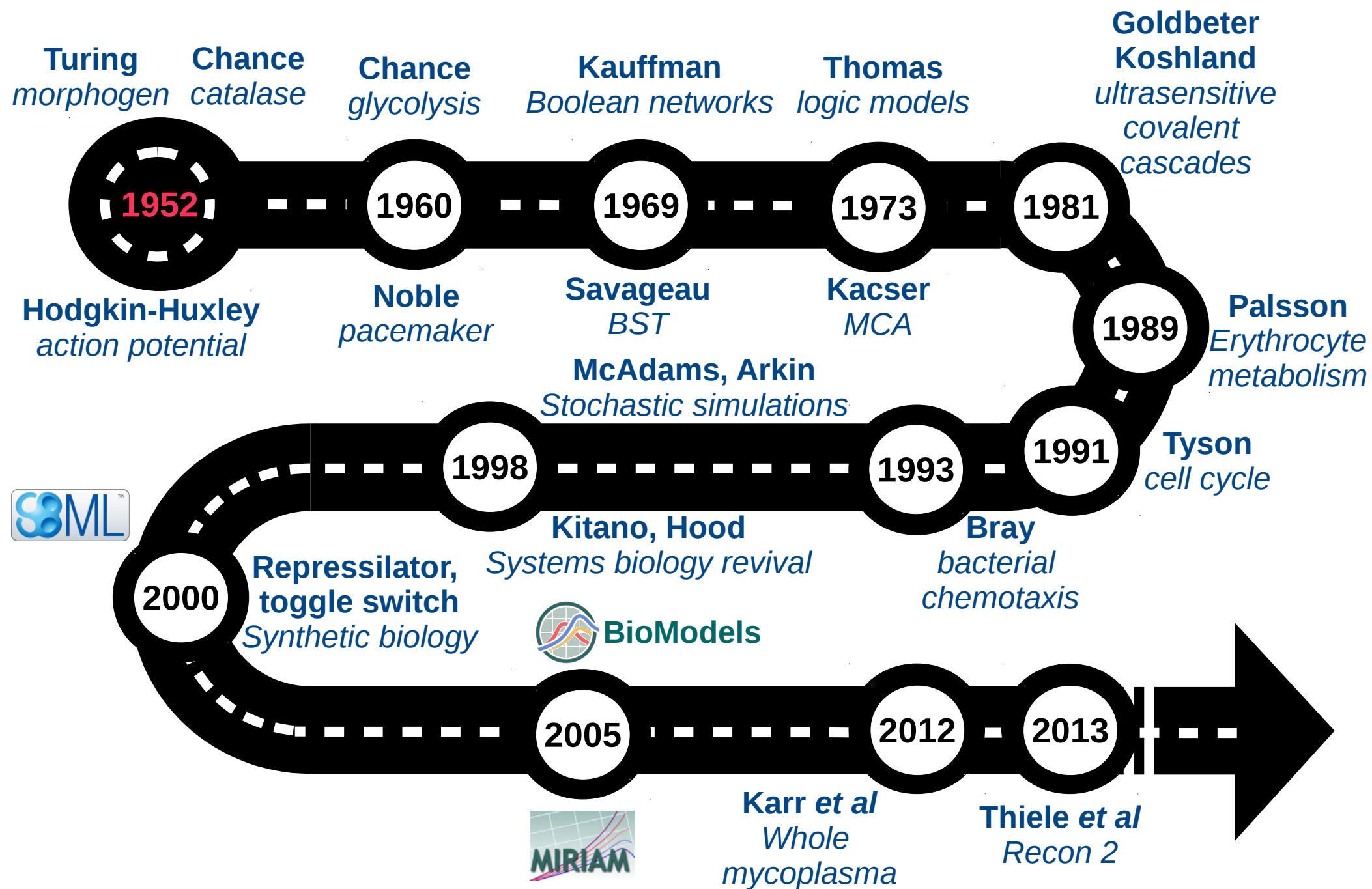
Boundary conditions
($v < \text{upper limit}$)

Objective functions
(maximise ATP)

Initial conditions

**The context or what
we want to ignore**





Computer simulations Vs. mathematical models

[37]

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

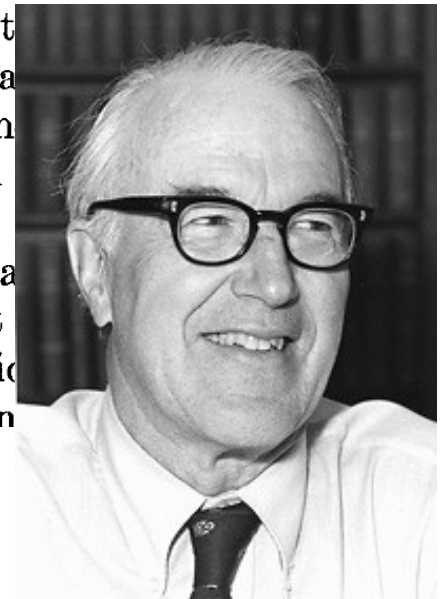
*From the Johnson Research Foundation, University of Pennsylvania,
Philadelphia, Pennsylvania*

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 sensitive spectrophotometric methods. Thus not only the steady-state but also the transient portions of the enzyme action are revealed. And the transient portions are very sensitive indicators of the mechanism which the enzyme acts.

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



Birth of Computational Systems Biology

J. Physiol. (1952) 117, 500–544

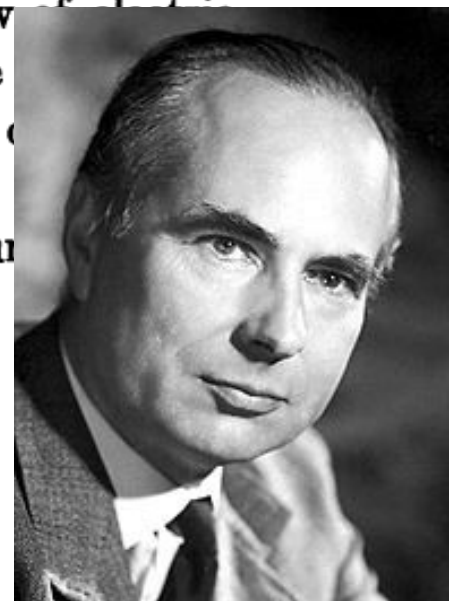
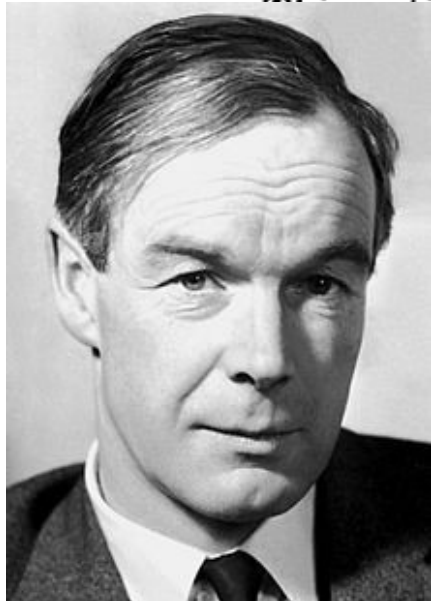
A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

BY A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(Received 10 March 1952)

This article concludes a series of papers concerned with the flow of ions through the surface membrane of a giant nerve fibre (Hodgkin & Katz, 1952; Hodgkin & Huxley, 1952 *a-c*). Its general object is to put the results of the preceding papers (Part I), to put them in mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).



The Computational Systems Biology loop

“biological” model

mathematical model

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

$$\frac{dn}{dt} = \alpha_n(1 - n) - \beta_n n,$$

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m,$$

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h,$$

$$\alpha_n = 0.01 (V + 10) / \left(\exp \frac{V + 10}{10} - 1 \right),$$

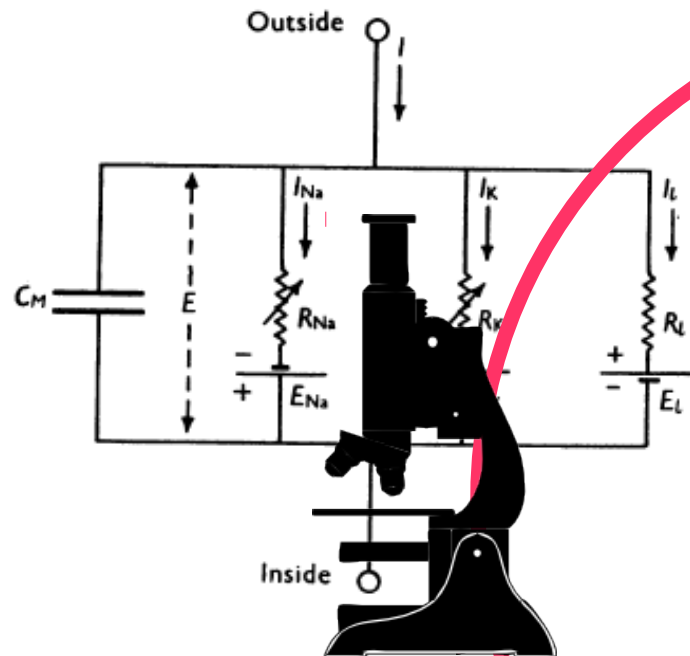
$$\beta_n = 0.125 \exp (V/80),$$

$$\alpha_m = 0.1 (V + 25) / \left(\exp \frac{V + 25}{10} - 1 \right),$$

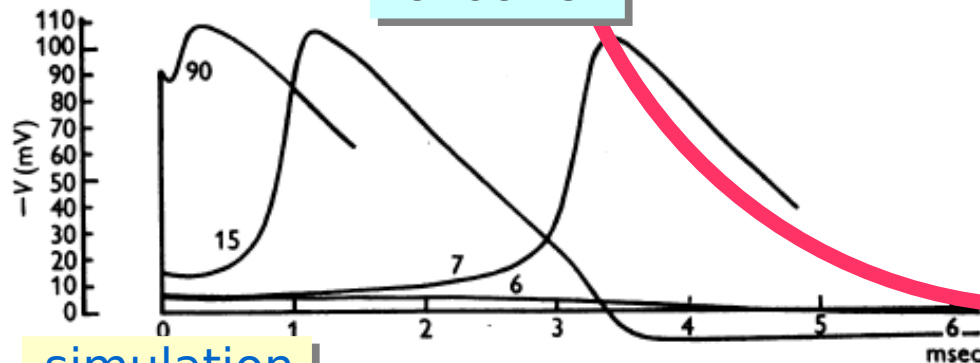
$$\beta_m = 4 \exp (V/18),$$

$$\alpha_h = 0.07 \exp (V/20),$$

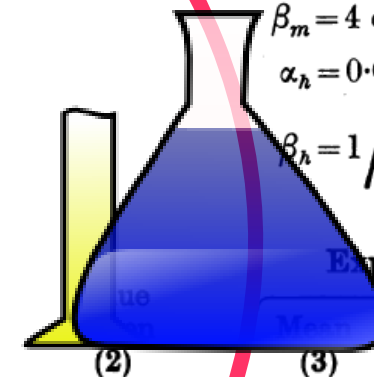
$$\beta_h = 1 / \left(\exp \frac{V + 30}{10} + 1 \right).$$



validation



simulation



Experimental values

parameterisation

Constant
(1)

C_M ($\mu\text{F}/\text{cm}^2$)

V_{Na} (mV)

V_K (mV)

V_l (mV)

$\bar{g}_{Na}$ (m.mho/cm²)

$\bar{g}_K$ (m.mho/cm²)

$\bar{g}_l$ (m.mho/cm²)

Range
(4)

0.8 to 1.5

-95 to -119

+9 to +14

-4 to -22

65 to 90

120 to 260

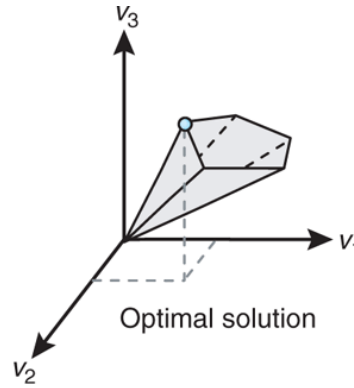
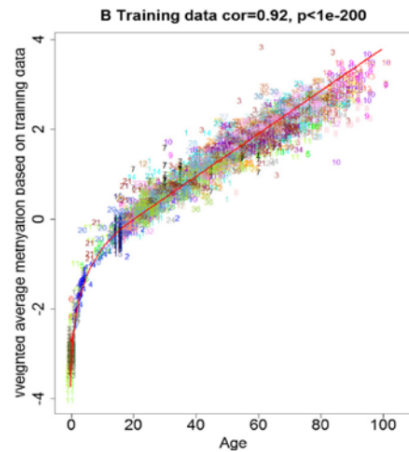
26 to 49

0.13 to 0.50

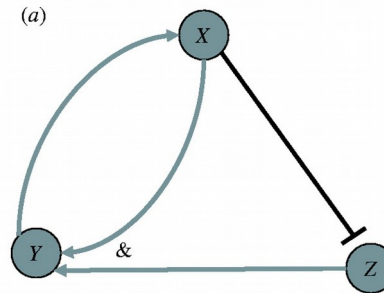
computational model



Representation of time



No time: correlations, steady-states

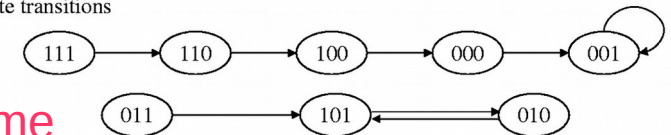


(b) $Y=X \& Z, X=Y, Z=\neg X$

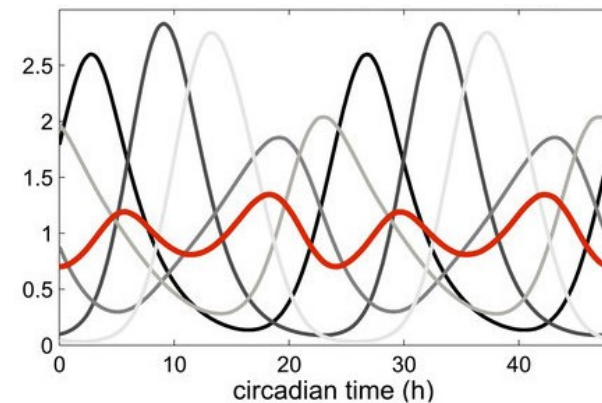
(c)

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
($t_4 - t_0$ is not $2 \times t_2 - t_0$): Logic models

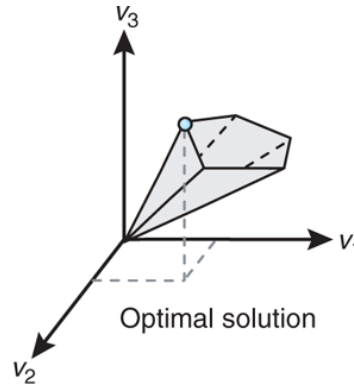
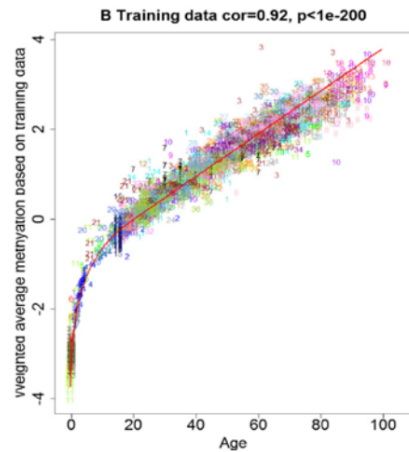


Continuous time

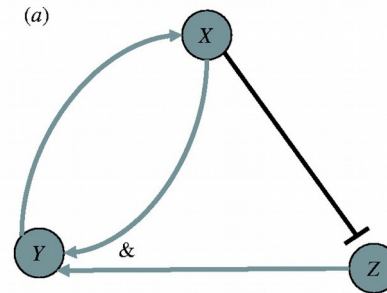
Discrete time



Representation of time



No time: correlations, steady-states

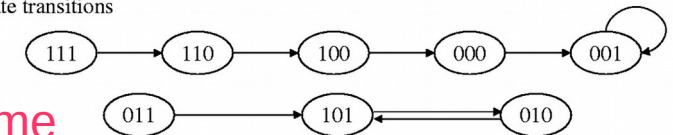


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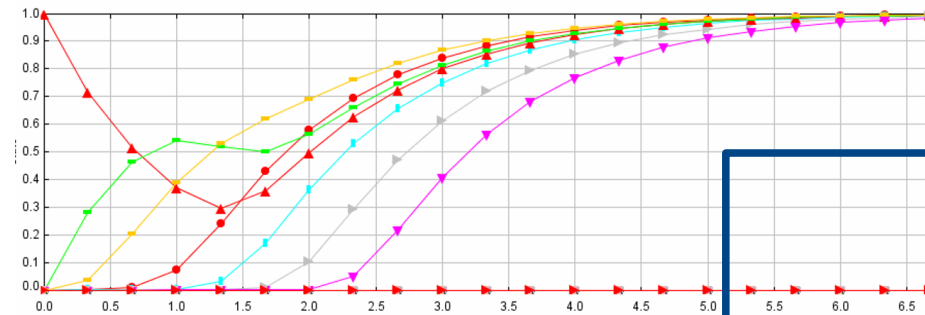
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t				$t+1$		
X	Y	Z		X	Y	Z
0	0	0		0	0	1
0	0	1		0	0	1
0	1	0		1	0	1
0	1	1		1	0	1
1	0	0		0	0	0
1	0	1		0	1	0
1	1	0		1	0	0
1	1	1		1	1	0

(d) state transitions

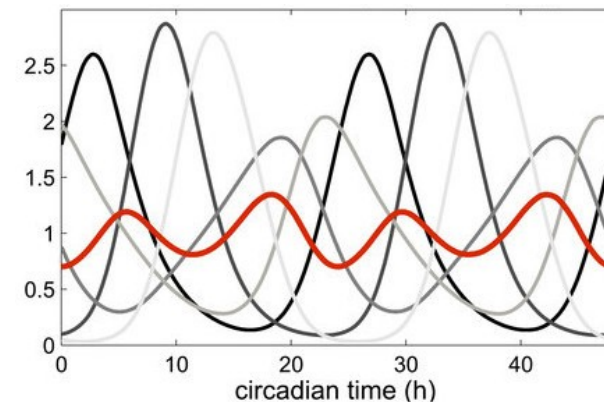


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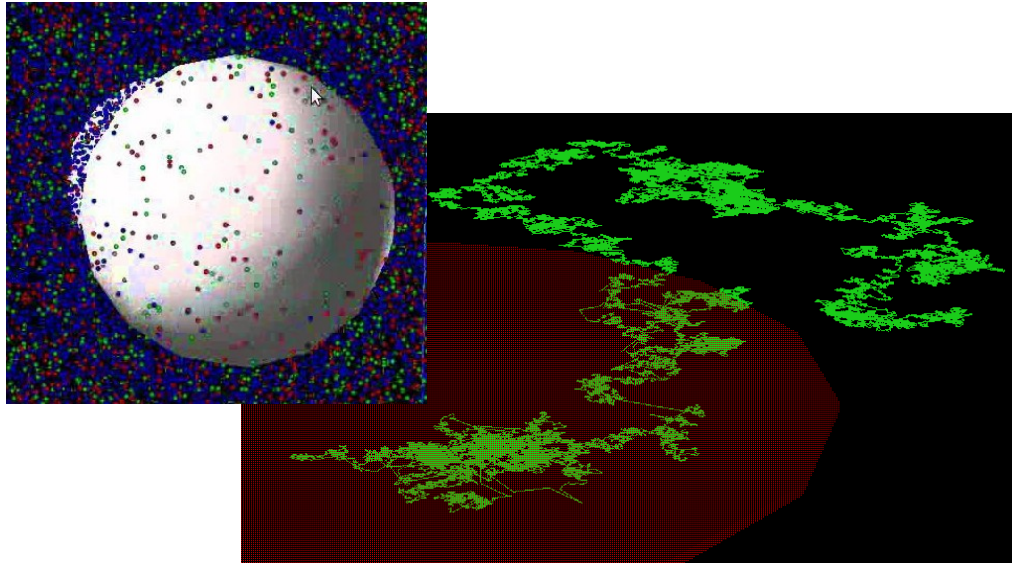
Discrete time

Continuous time

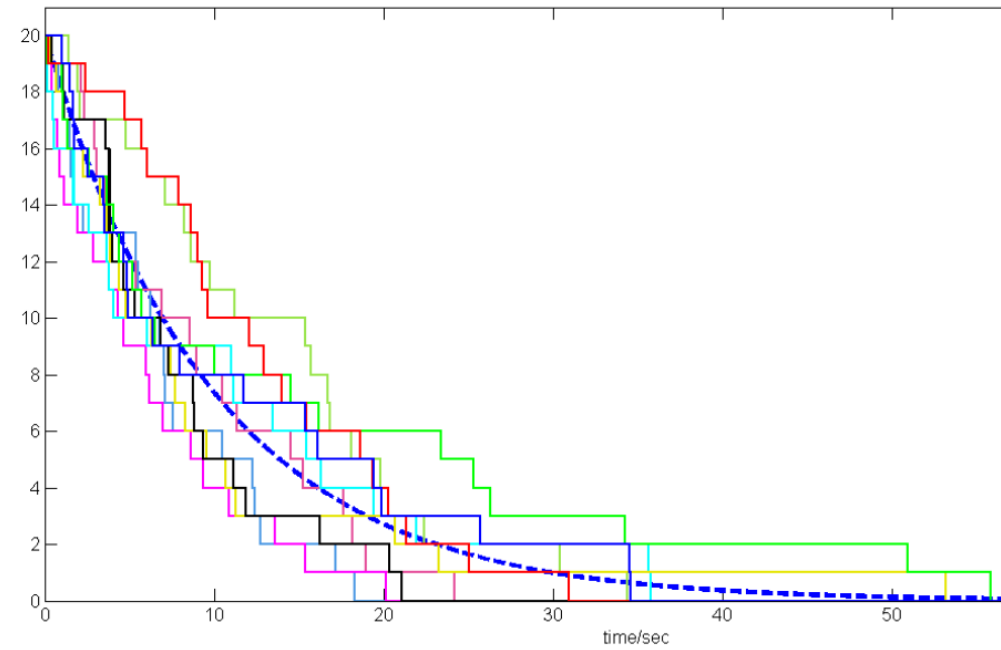


Variable granularity

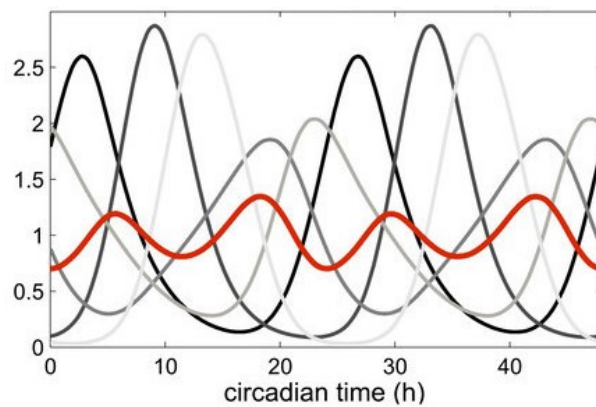
Single particles



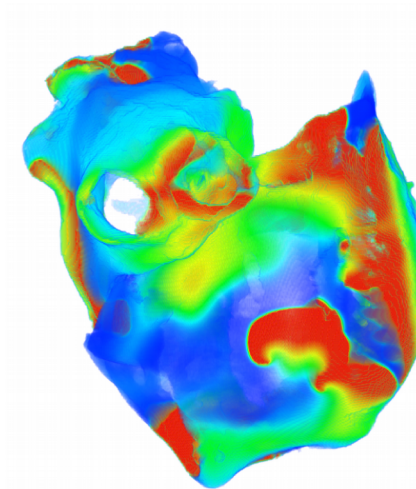
Discrete populations



Continuous populations

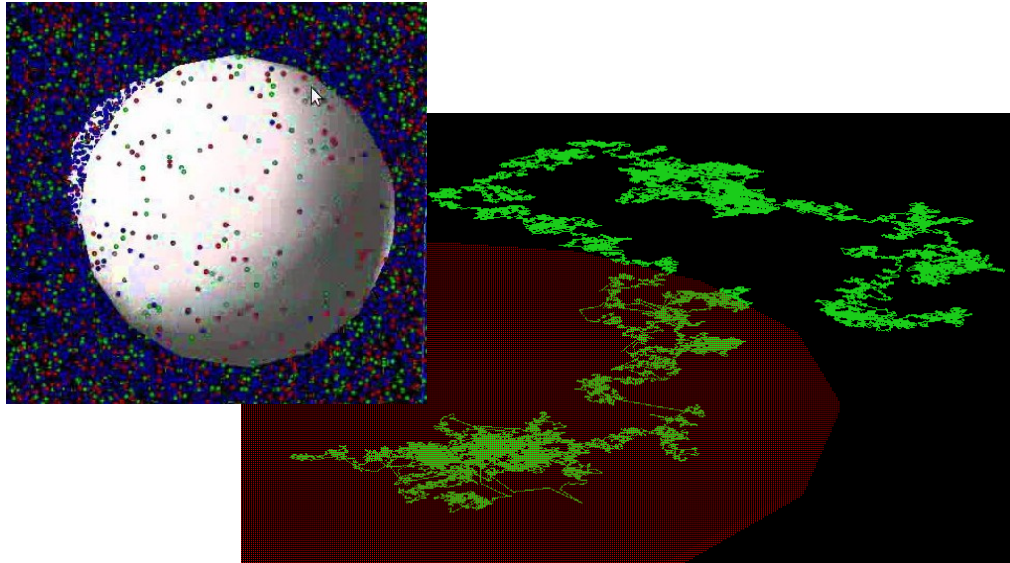


Fields

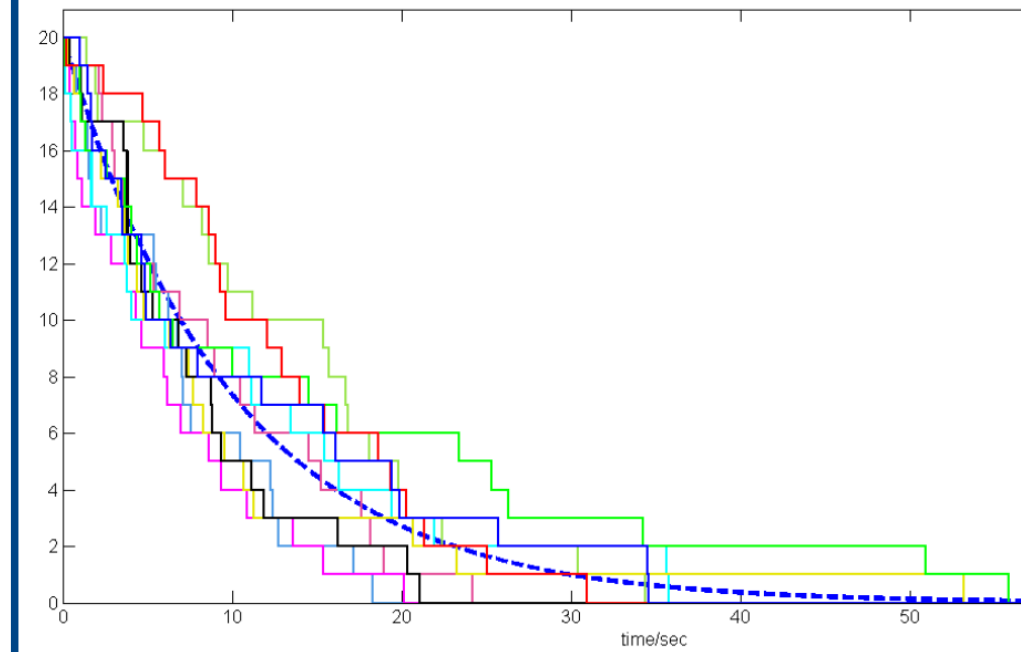


Variable granularity

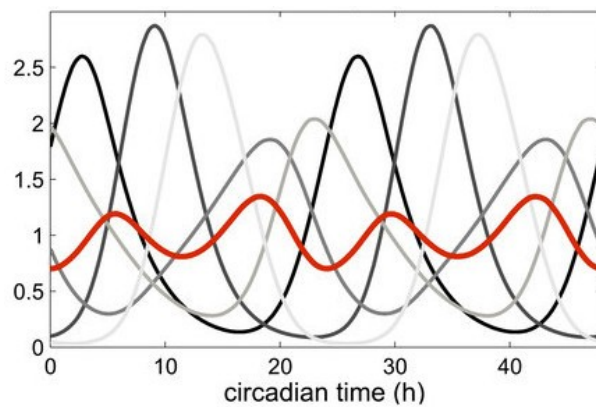
Single particles



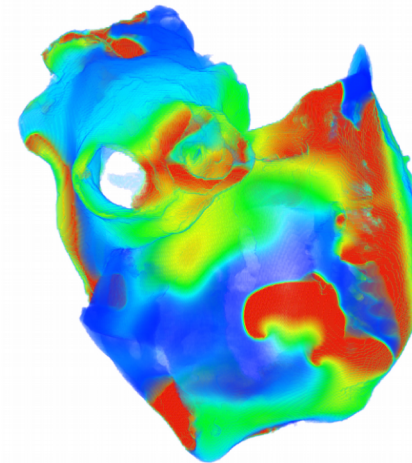
Discrete populations



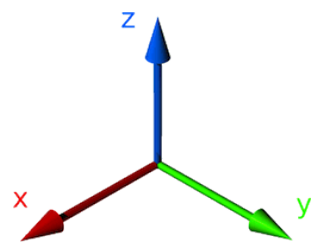
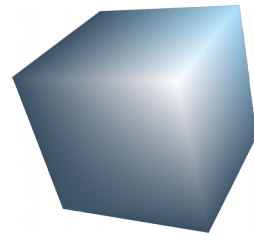
Continuous populations



Fields



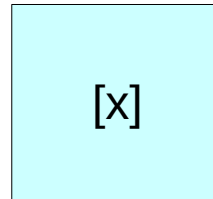
Spatial representation



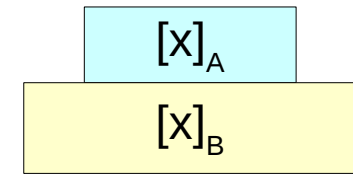
No dimension



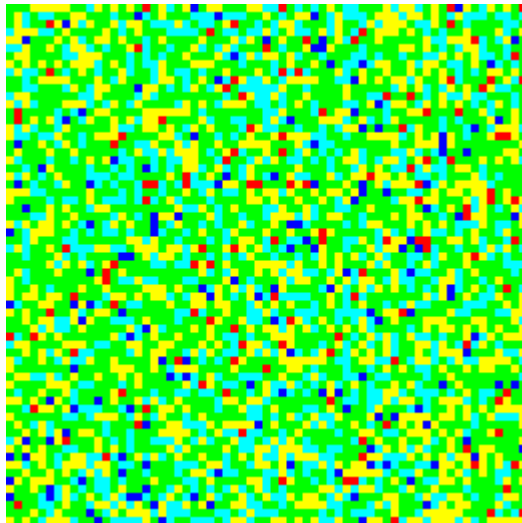
Homogeneous
(well-stirred, isotropic)



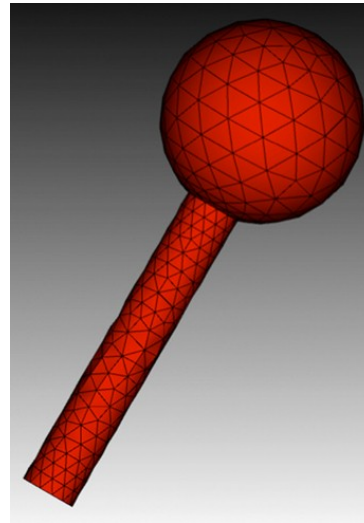
Compartments



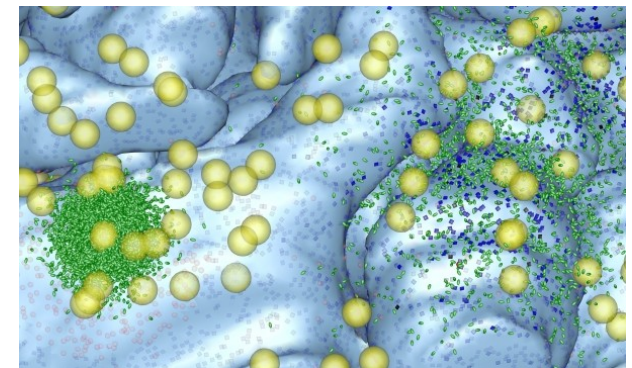
Cellular automata



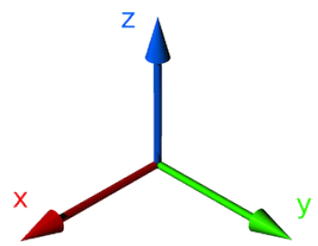
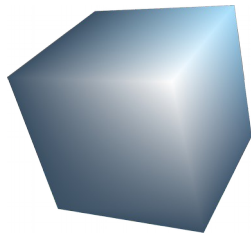
Finite elements



Real space



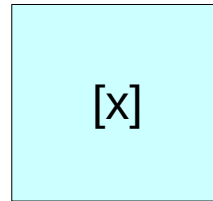
Spatial representation



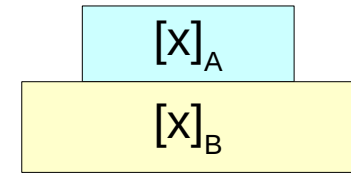
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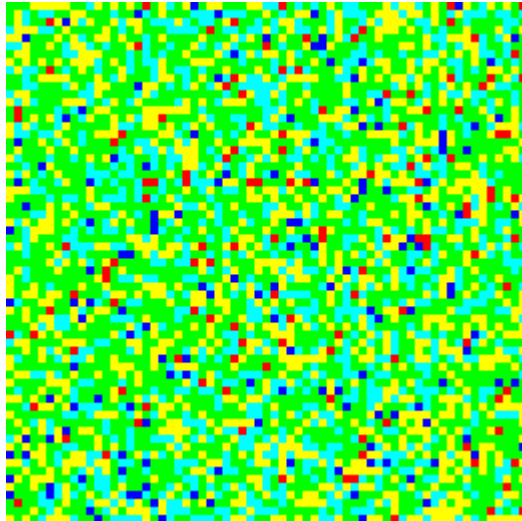
Homogeneous
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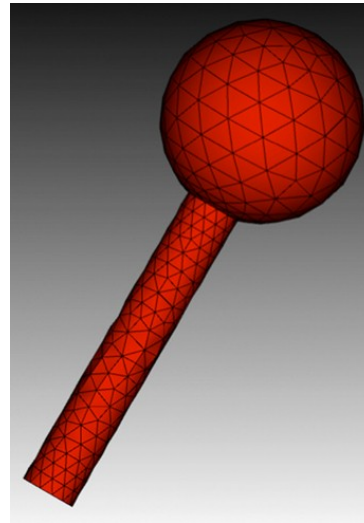
Compartments



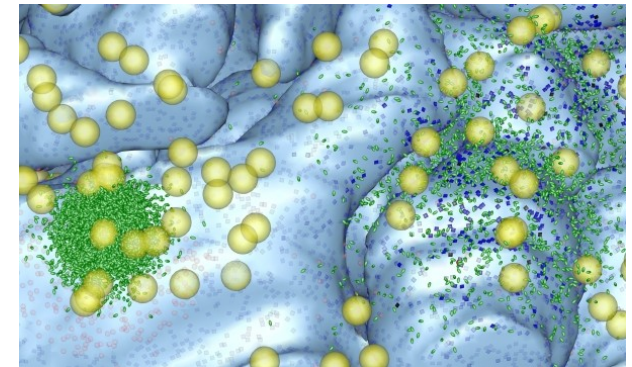
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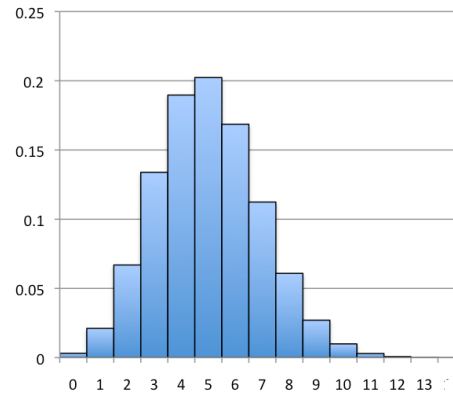
Real space



Stochasticity



Ensemble models (distributions)



Initial conditions
Parameter values

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

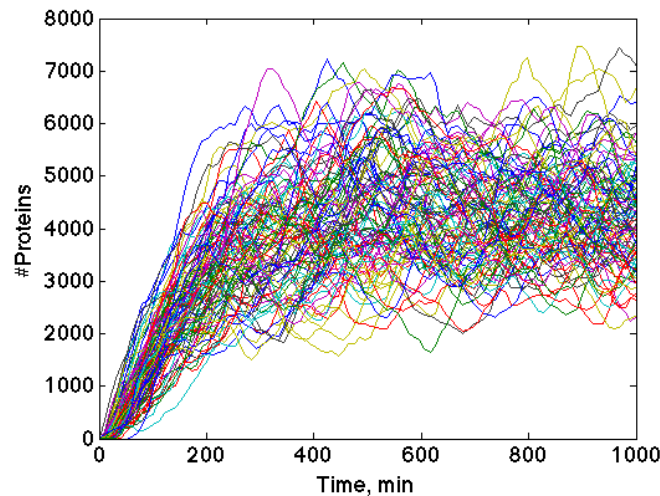
Deterministic simulation

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

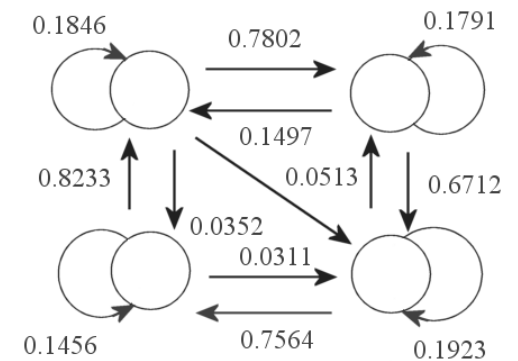
Stochastic differential equations

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

Stochastic simulations (SSA, "Gillespie")



Probabilistic models



Stochasticity



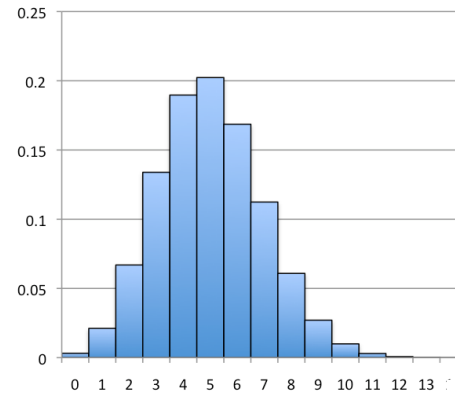
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$$\dot{x}_i = \sum_j n_{ij} k_j \prod_i X_i^{n_{ij}}$$

Stochastic differential equations

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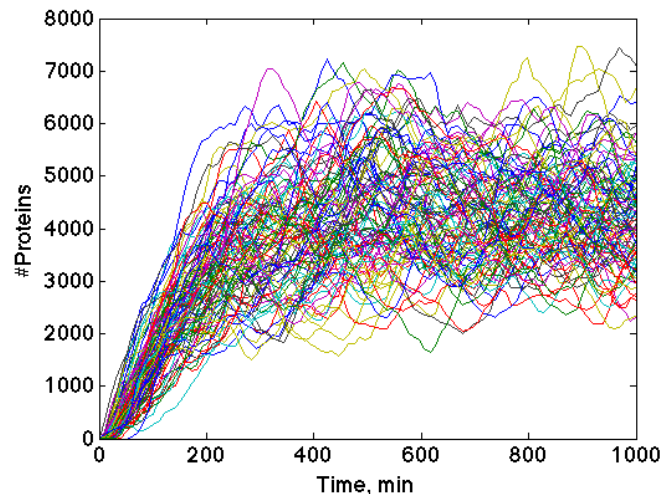
Ensemble models (distributions)



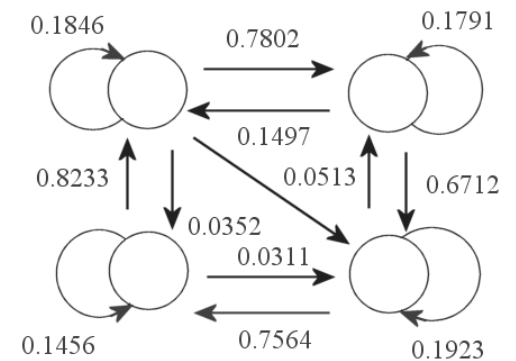
Initial conditions
Parameter values

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

Stochastic simulations (SSA, "Gillespie")

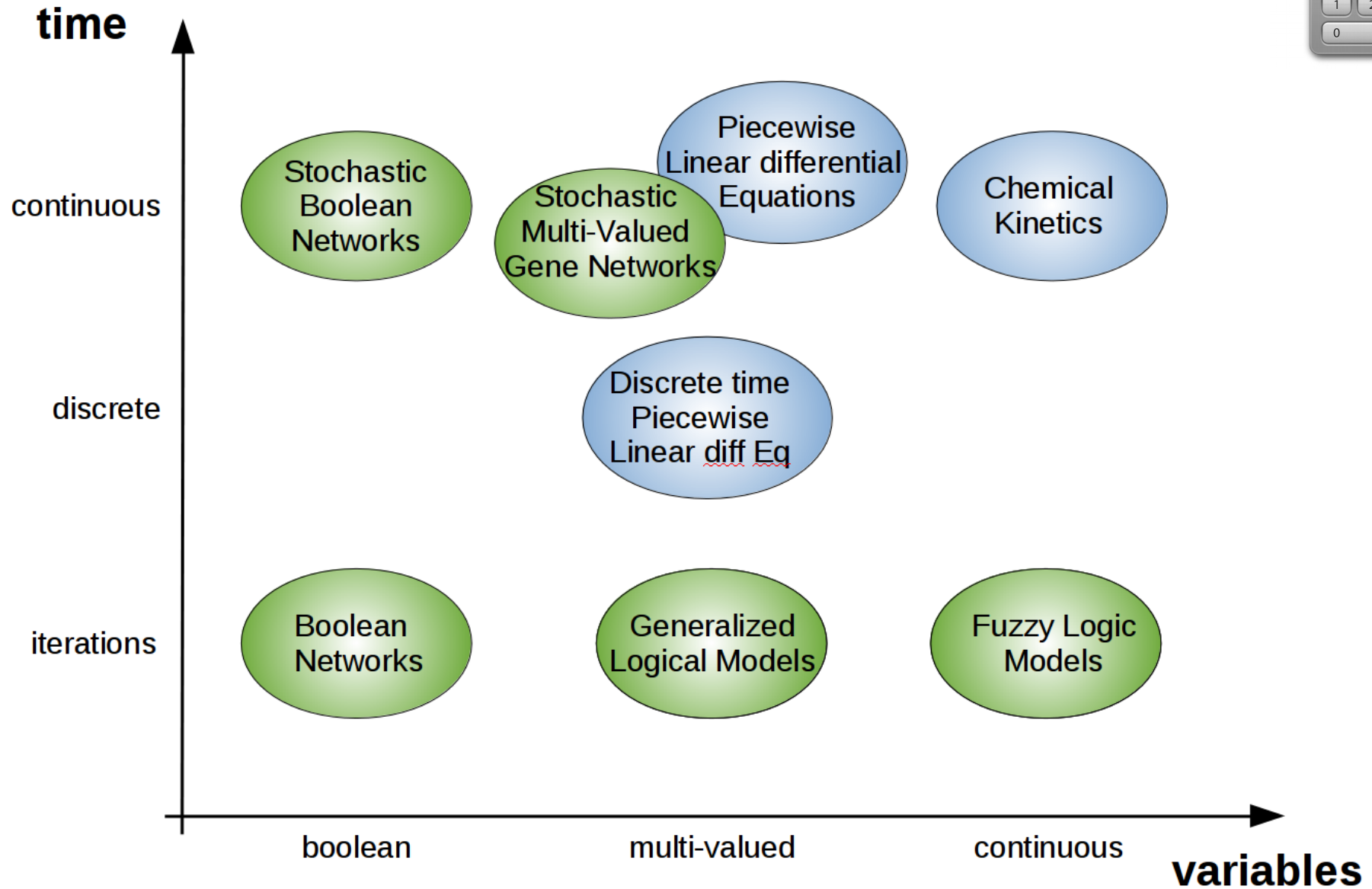
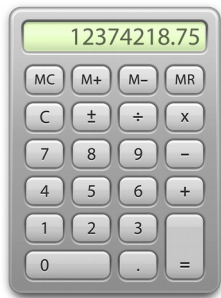


Probabilistic models



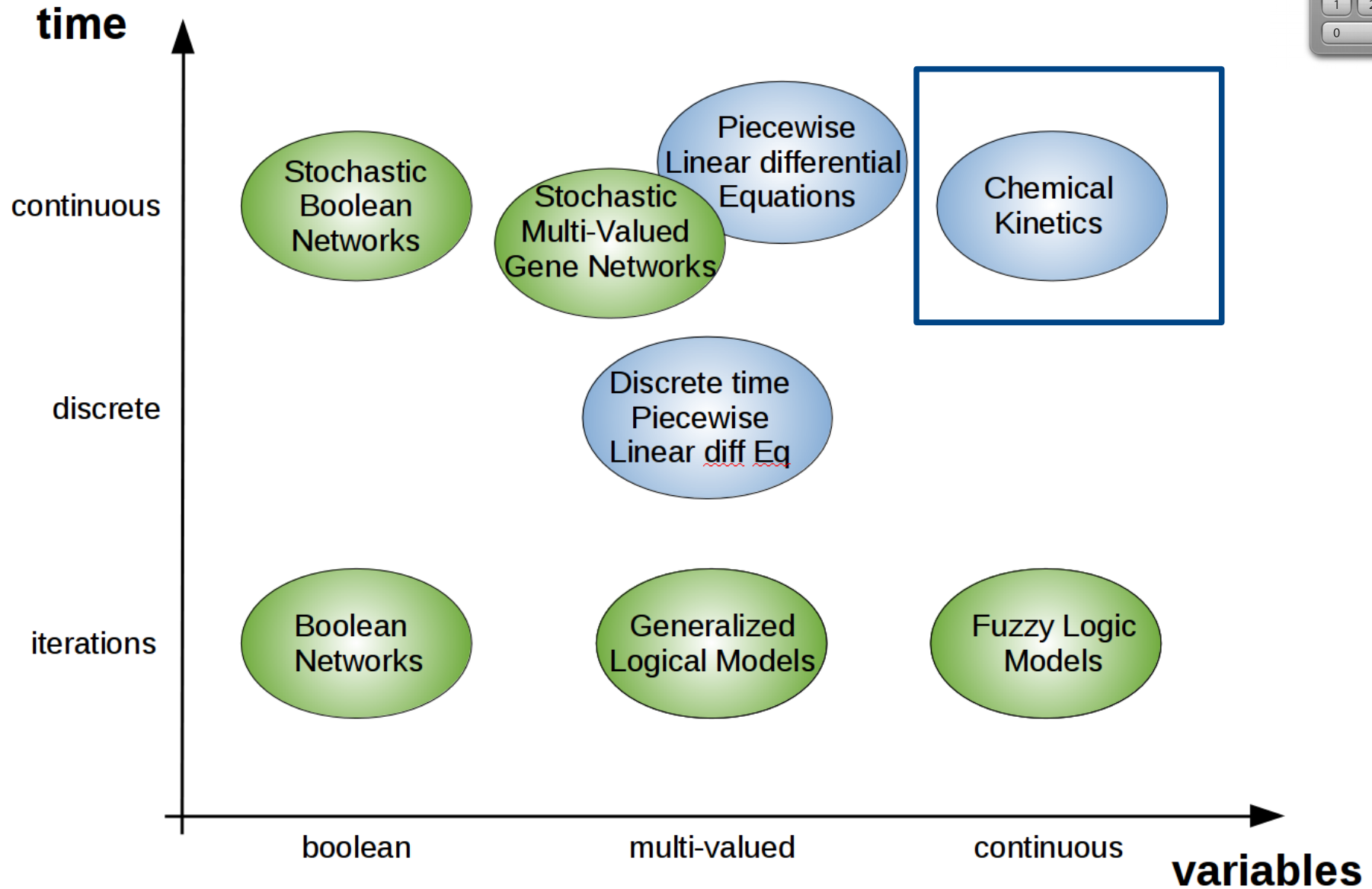
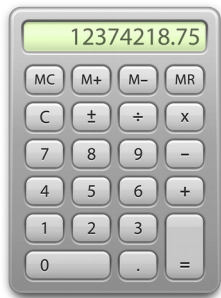


Logic versus numeric



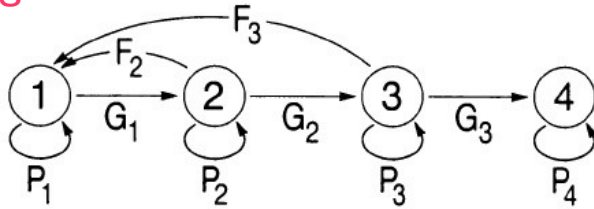


Logic versus numeric

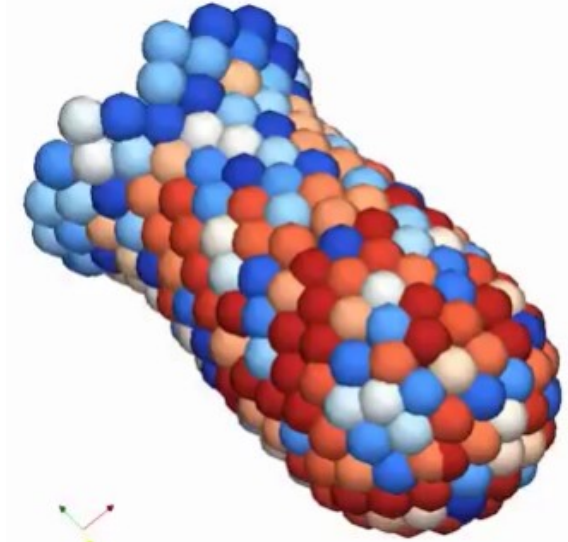


Many other types of models

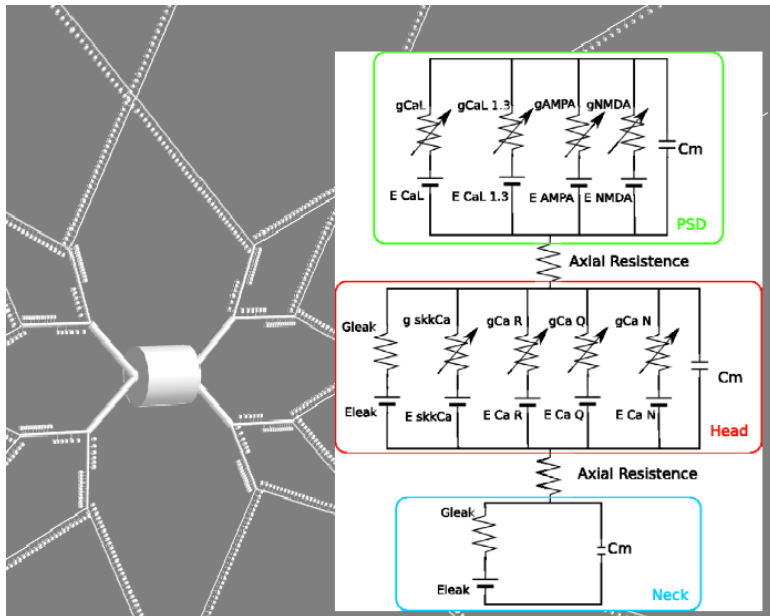
Matrix models



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



Multi-agents models (cellular potts)



Cable approximation

