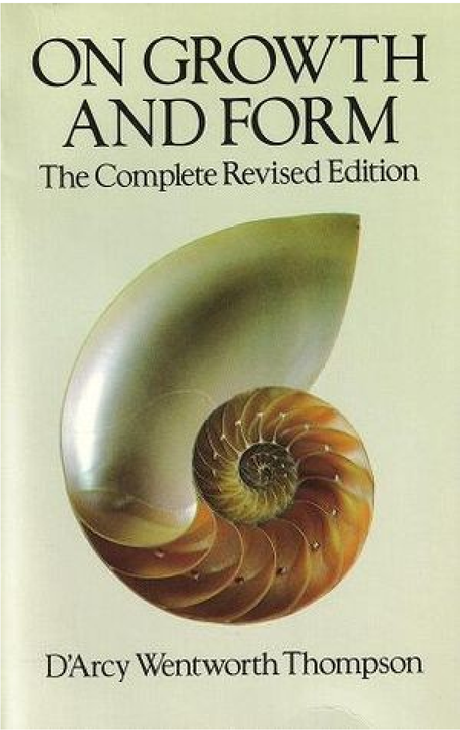
The many faces of modelling in biology

Nicolas Le Novère, The Babraham Institute

n.lenovere@gmail.com

What is the goal of using mathematical models?

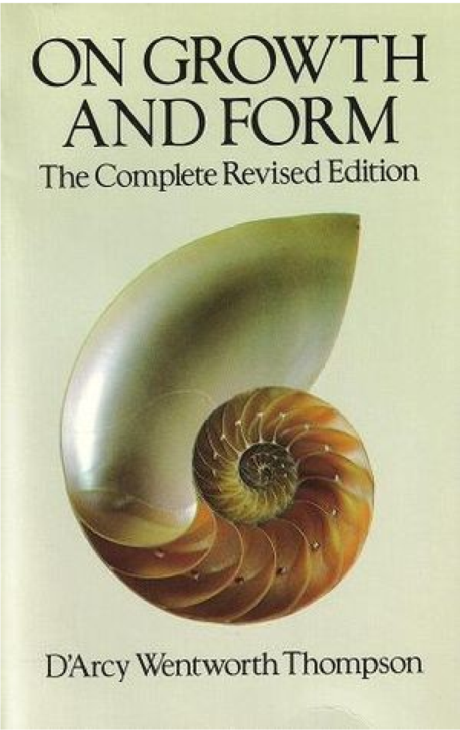
Describe

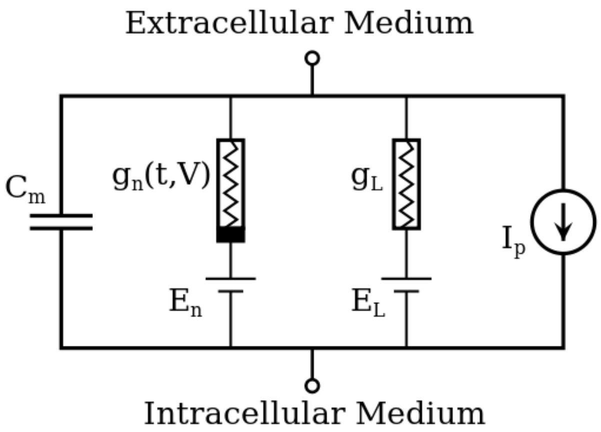


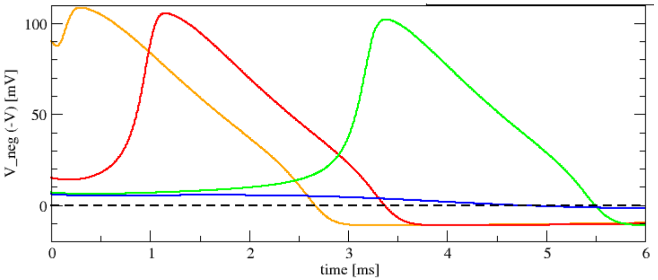
1917

What is the goal of using mathematical models?

Describe	Explain



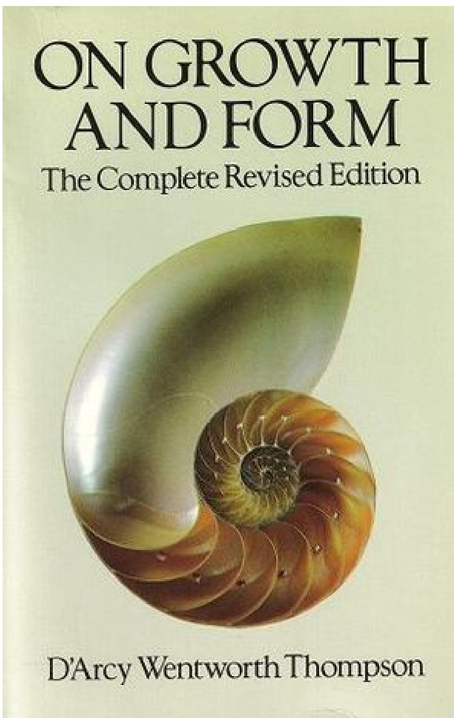


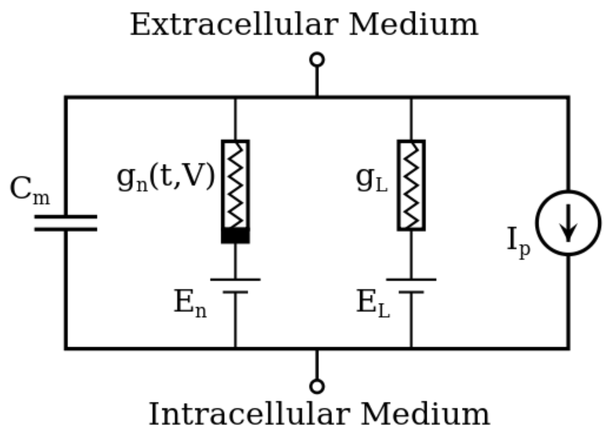


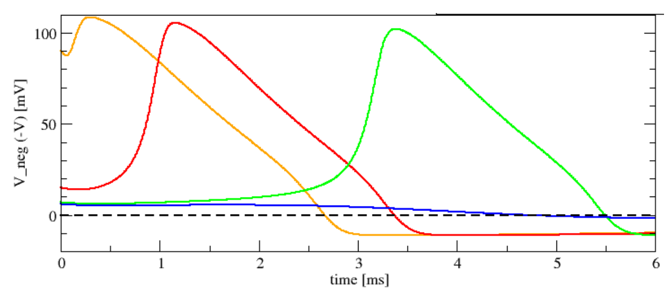
1917 **1952**

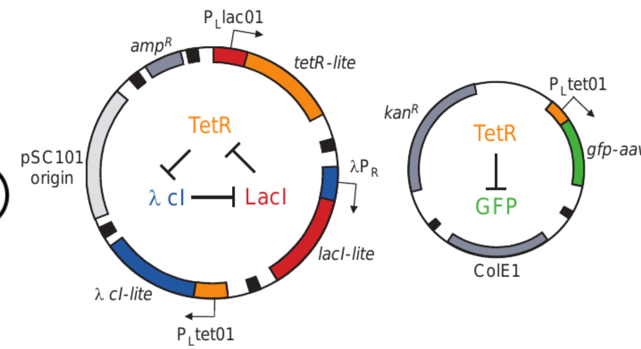
What is the goal of using mathematical models?

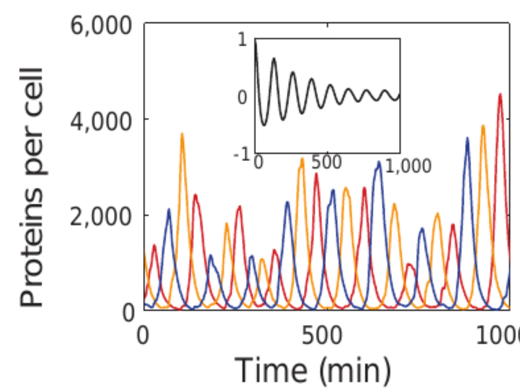
Describe	Explain	Predict











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 $\text{mass}_{t+\Delta t} = 0.5 \cdot \text{mass}$
$t_{1/2}$	

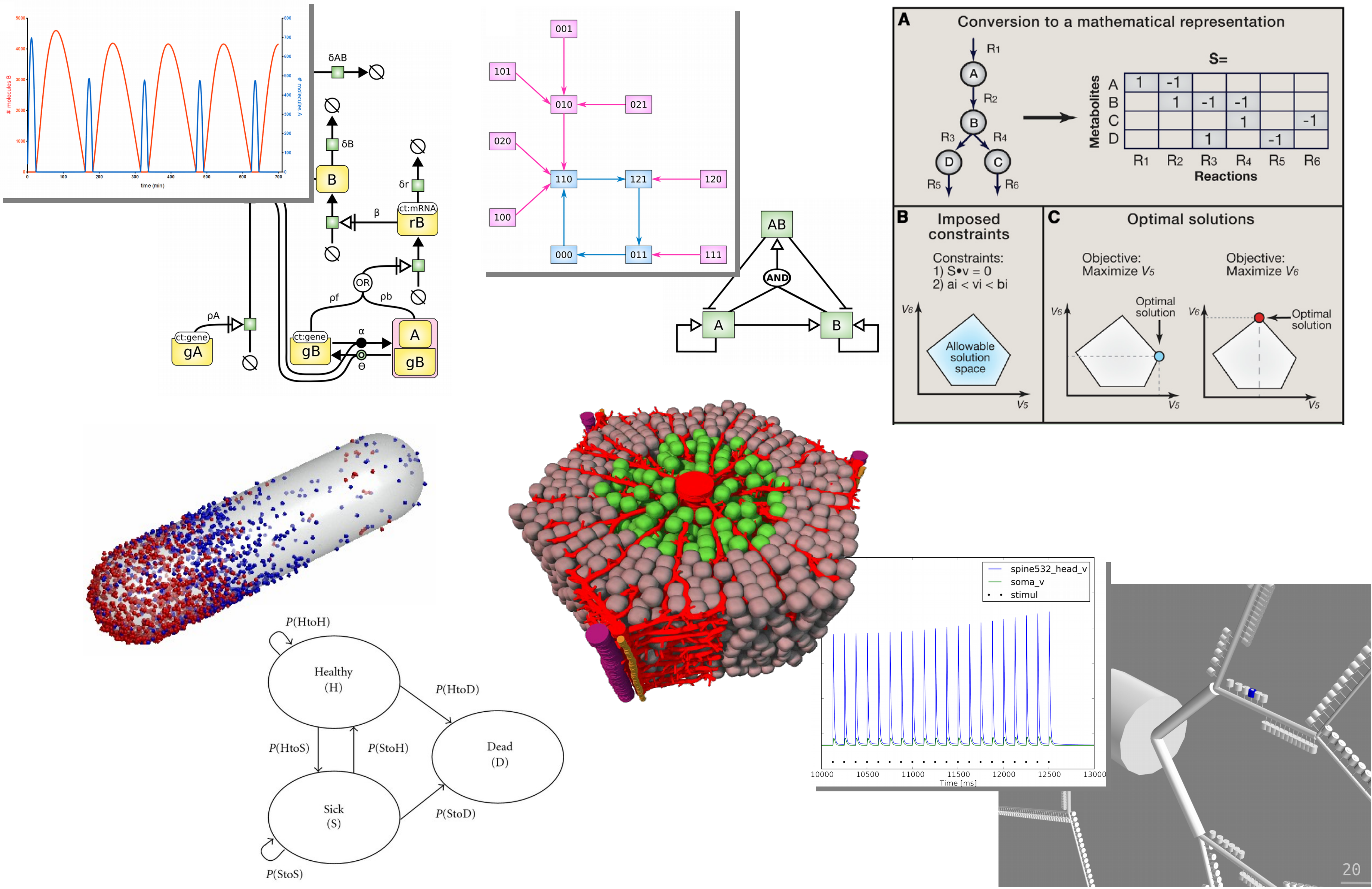
What we already know or want to test

What is a mathematical model?

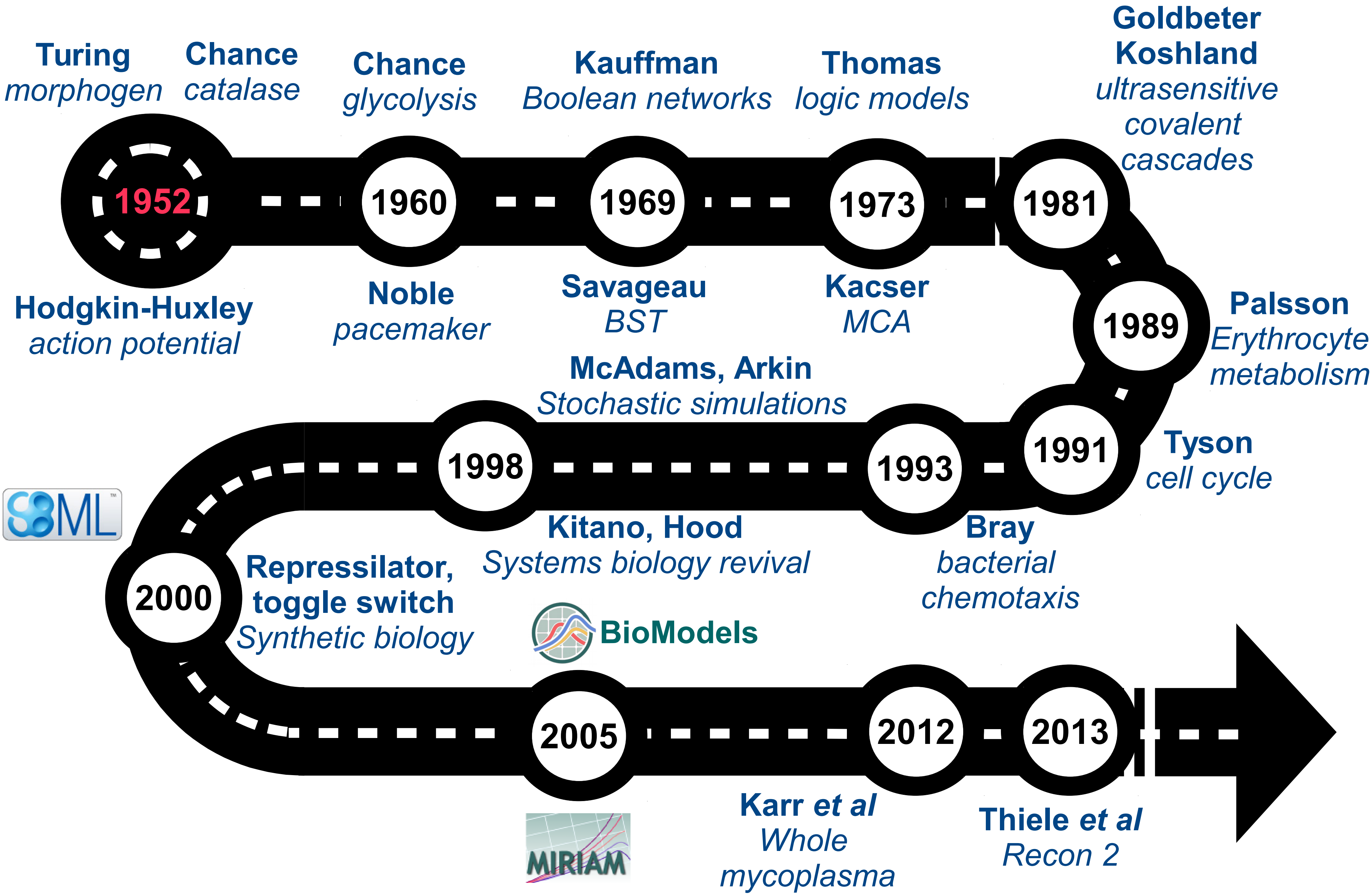
Wikipedia (October 14th 2013): "A mathematical model is a description of a system using mathematical concepts and language."

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
$t_{1/2}$		

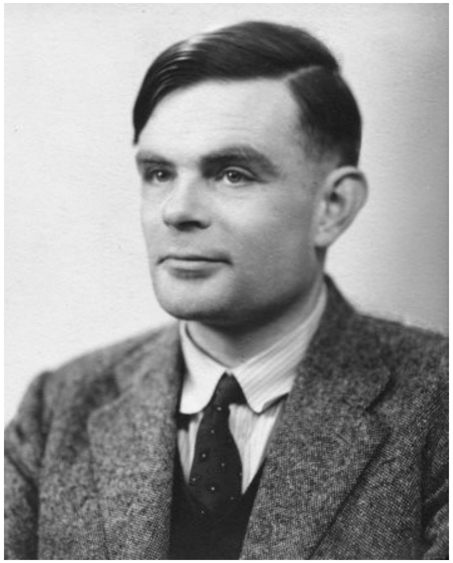
The context or what we want to ignore



time (min)
molecules B
molecules A
δAB
δB
δr
β
B
rB
ct:mRNA
ρA
ρf
ρb
OR
α
θ
ct:gene
gA
gB
A
001
101
010
021
020
110
121
120
100
000
011
111
AB
AND
A
Conversion to a mathematical representation
S=
Metabolites
Reactions
R1 R2 R3 R4 R5 R6
B
Imposed constraints
Constraints:
1) S•v = 0
2) ai < vi < bi
Allowable solution space
C
Optimal solutions
Objective:
Maximize V5
Objective:
Maximize V6
Optimal solution
P(HtoH)
Healthy
(H)
P(HtoD)
Dead
(D)
P(HtoS)
P(StoH)
Sick
(S)
P(StoD)
P(StoS)
spine532_head_v
soma_v
stimul
Time [ms]


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



[37]

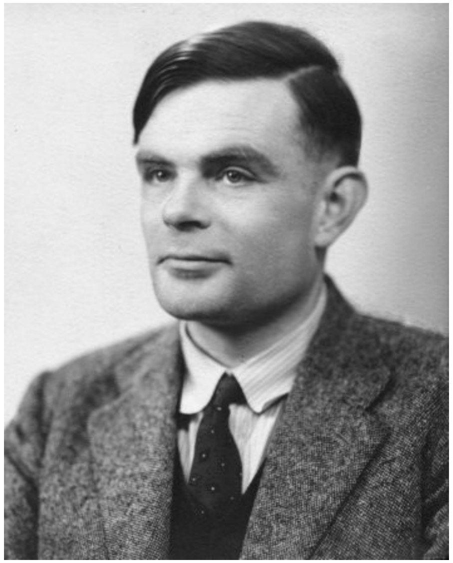
THE CHEMICAL BASIS OF MORPHOGENESIS

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

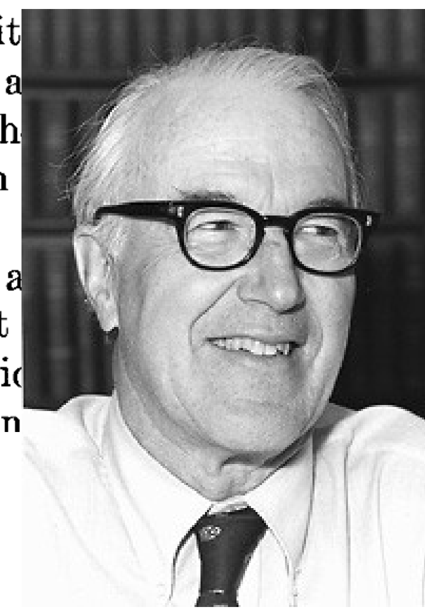
From the Johnson Research Foundation, University of Pennsylvania, Philadelphia, Pennsylvania

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 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 solutic of these equations are readily obtained for the special and often un



Birth of Computational Systems Biology

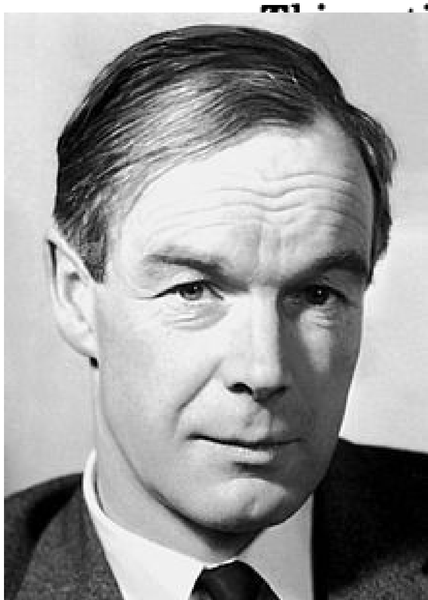
J. Physiol. (1952) 117, 500–544

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

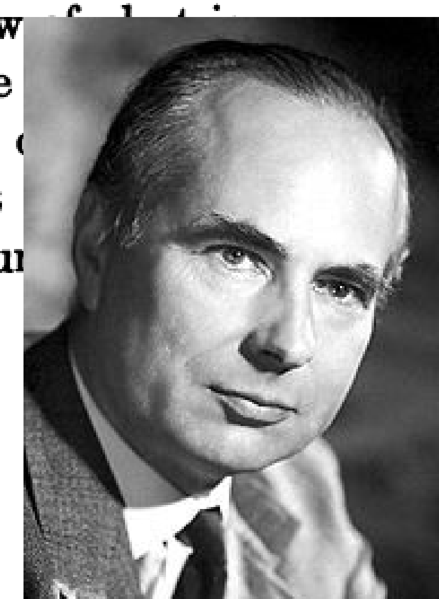
By A. L. HODGKIN and A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

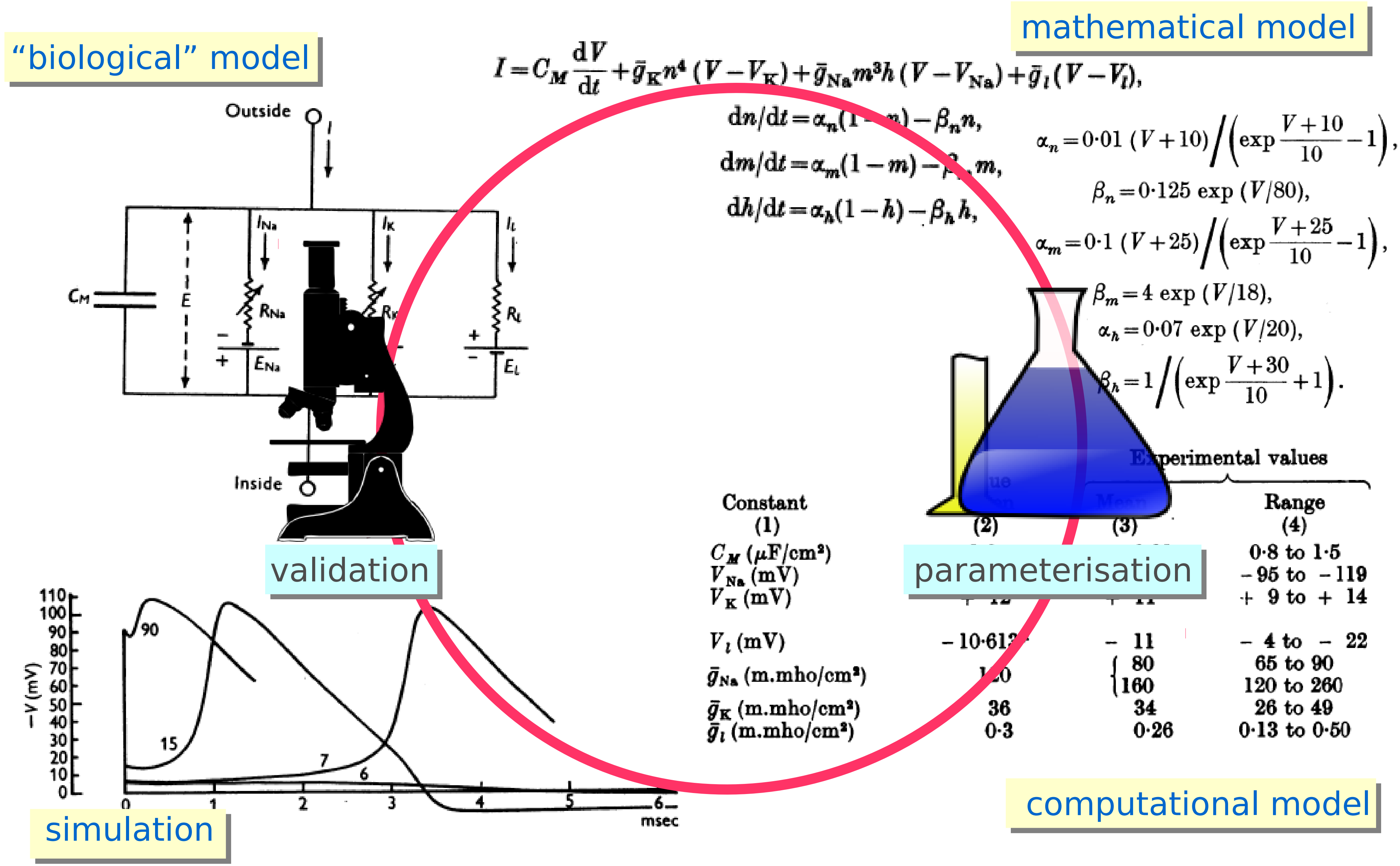
(*Received* 10 *March* 1952)



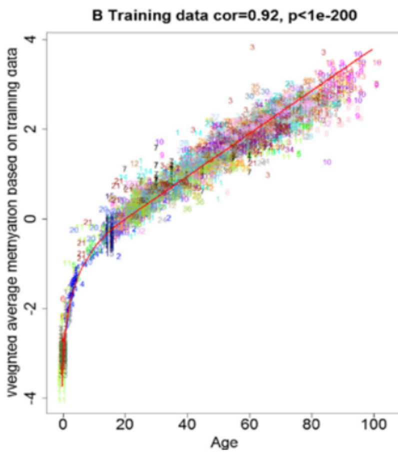
Th… …icle concludes a series of papers concerned with the flow … through the surface membrane of a giant nerve fibre … & Katz, 1952; Hodgkin & Huxley, 1952 *a–c*). Its general … the results of the preceding papers (Part I), to put … …atical form (Part II) and to show that they will accou… …and excitation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

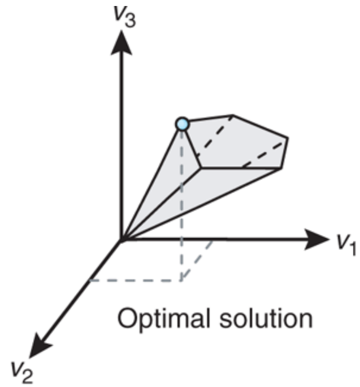


The Computational Systems Biology loop

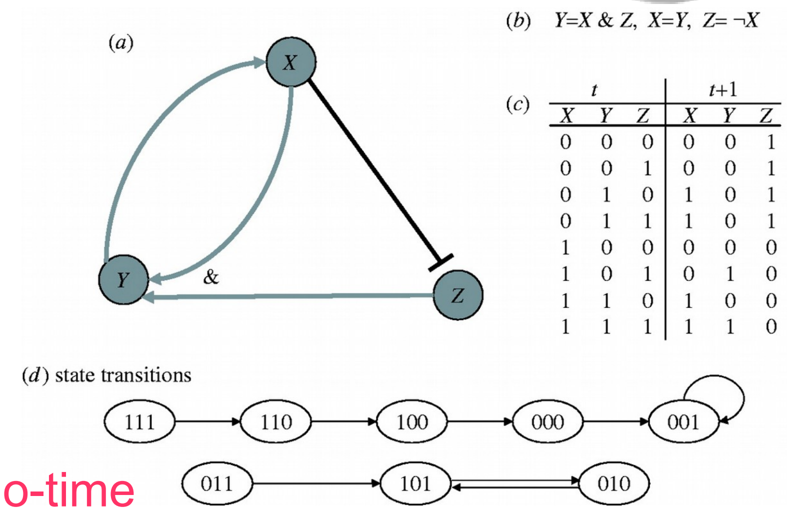


Representation of time



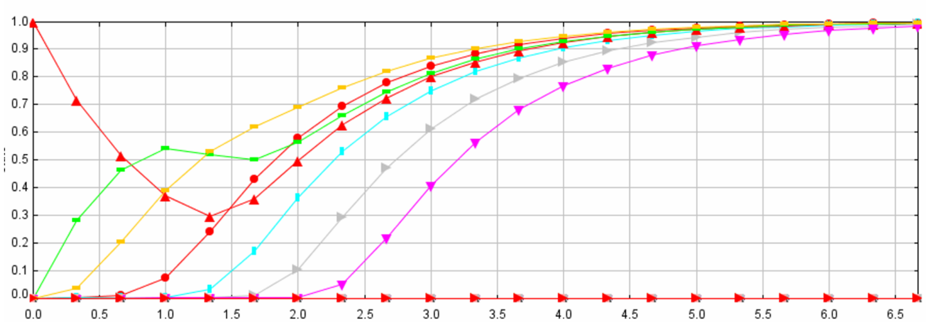


No time: correlations, steady-states

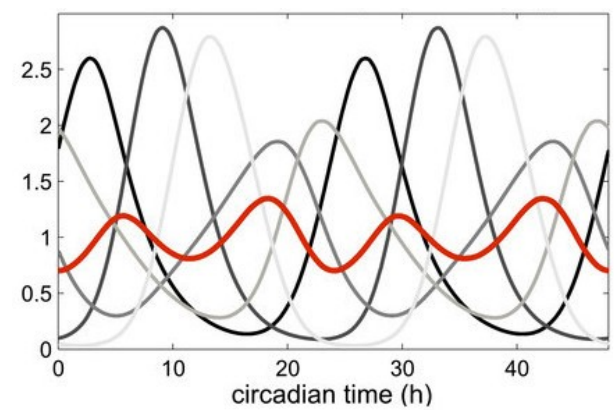


t			t+1		
X	Y	Z	X	Y	Z
0	0	0	0	0	1
0	0	1	0	0	1
0	1	0	1	0	1
0	1	1	1	0	1
1	0	0	0	0	0
1	0	1	0	1	0
1	1	0	1	0	0
1	1	1	1	1	0

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



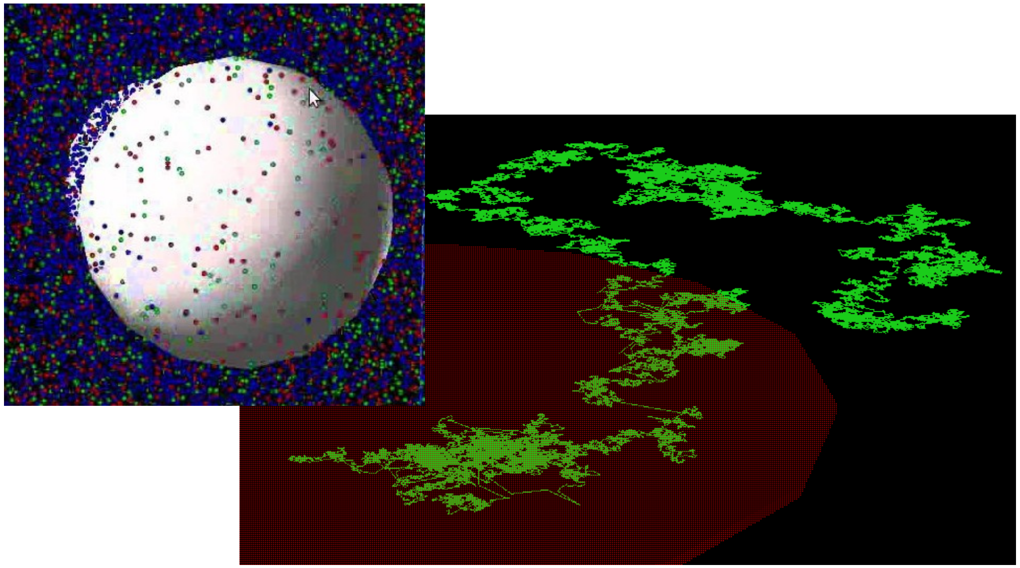
Discrete time



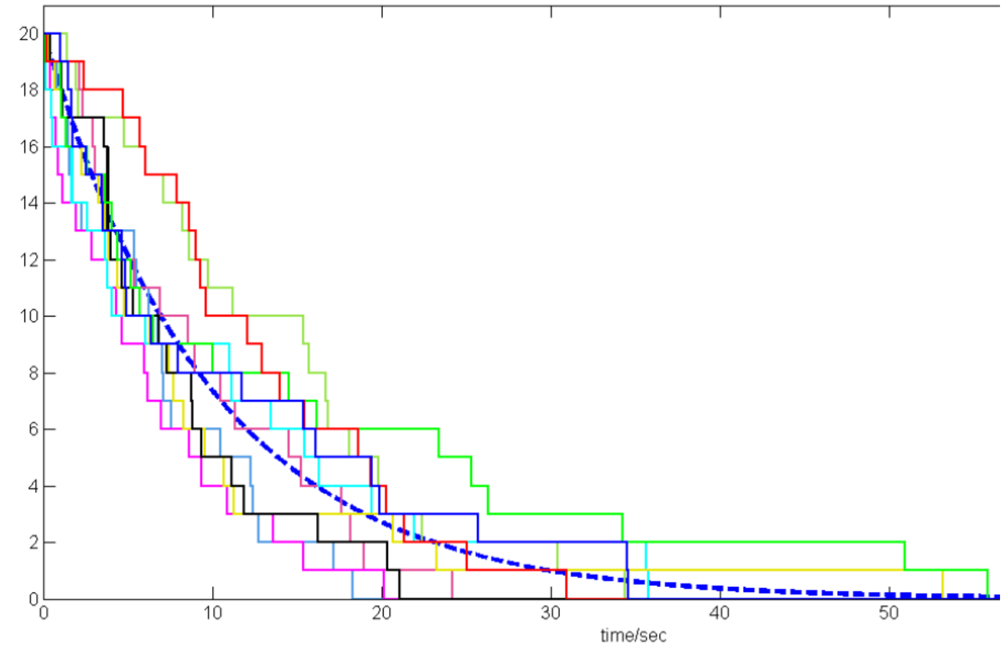
Continuous time

Variable granularity

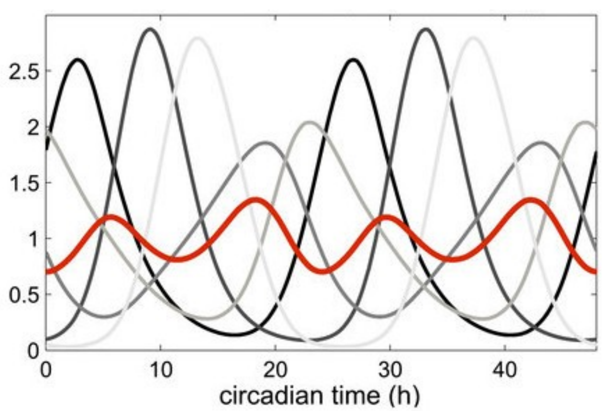
Single particles



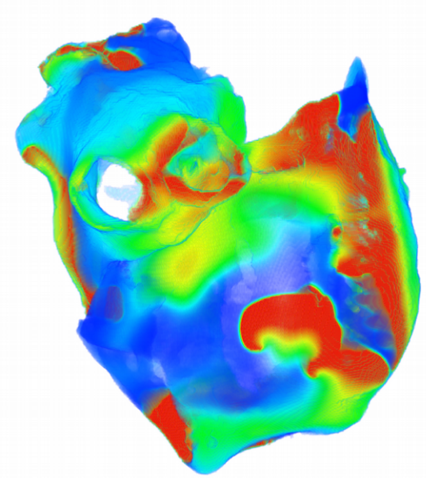
Discrete populations

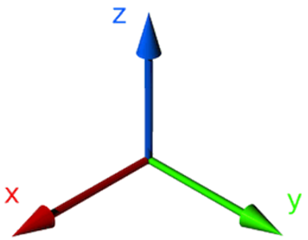


Continuous populations

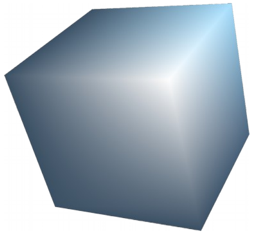


Fields





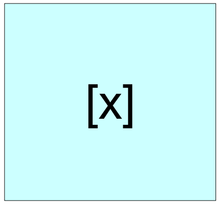
Spatial representation



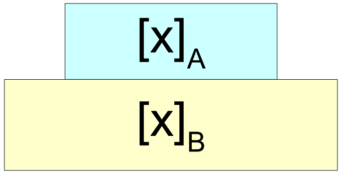
No dimension

•

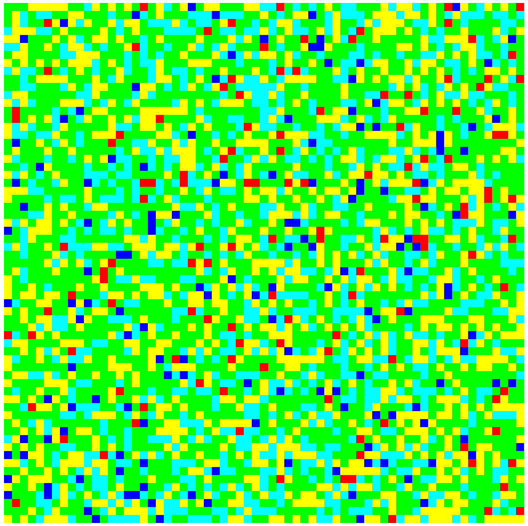
Homogeneous
(well-stirred, isotropic)



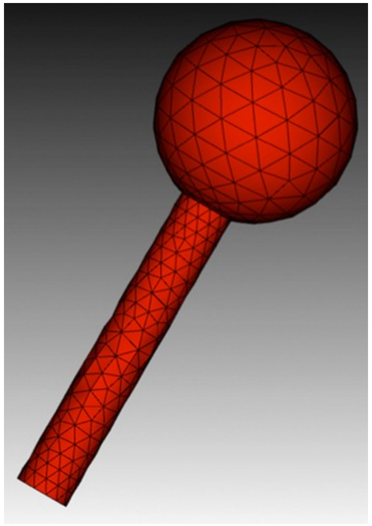
Compartments



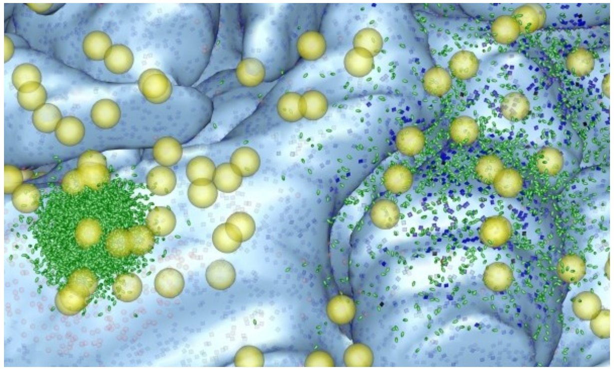
Cellular automata

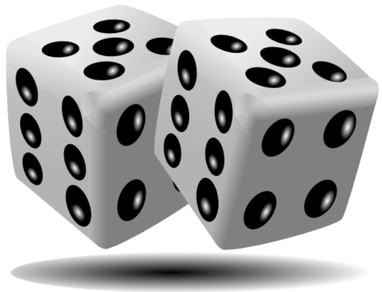


Finite elements



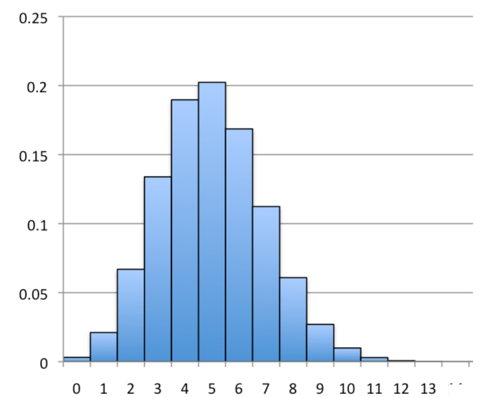
Real space





Stochasticity

Ensemble models (distributions)



Initial conditions
Parameter values

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

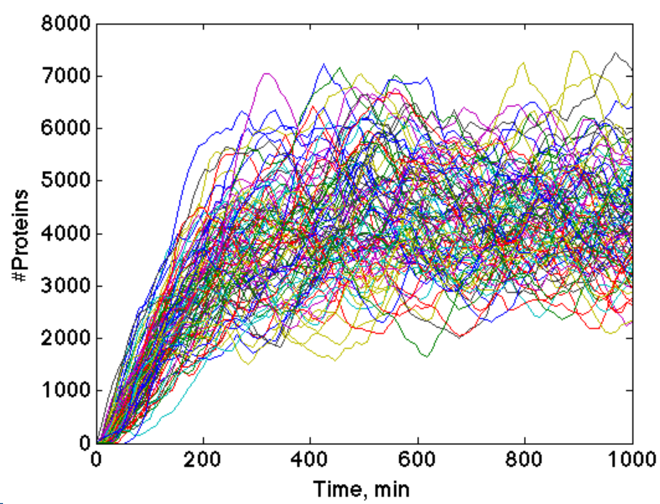
Deterministic simulation

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

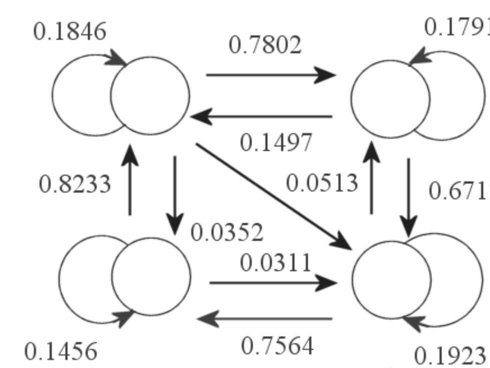
Stochastic differential equations

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

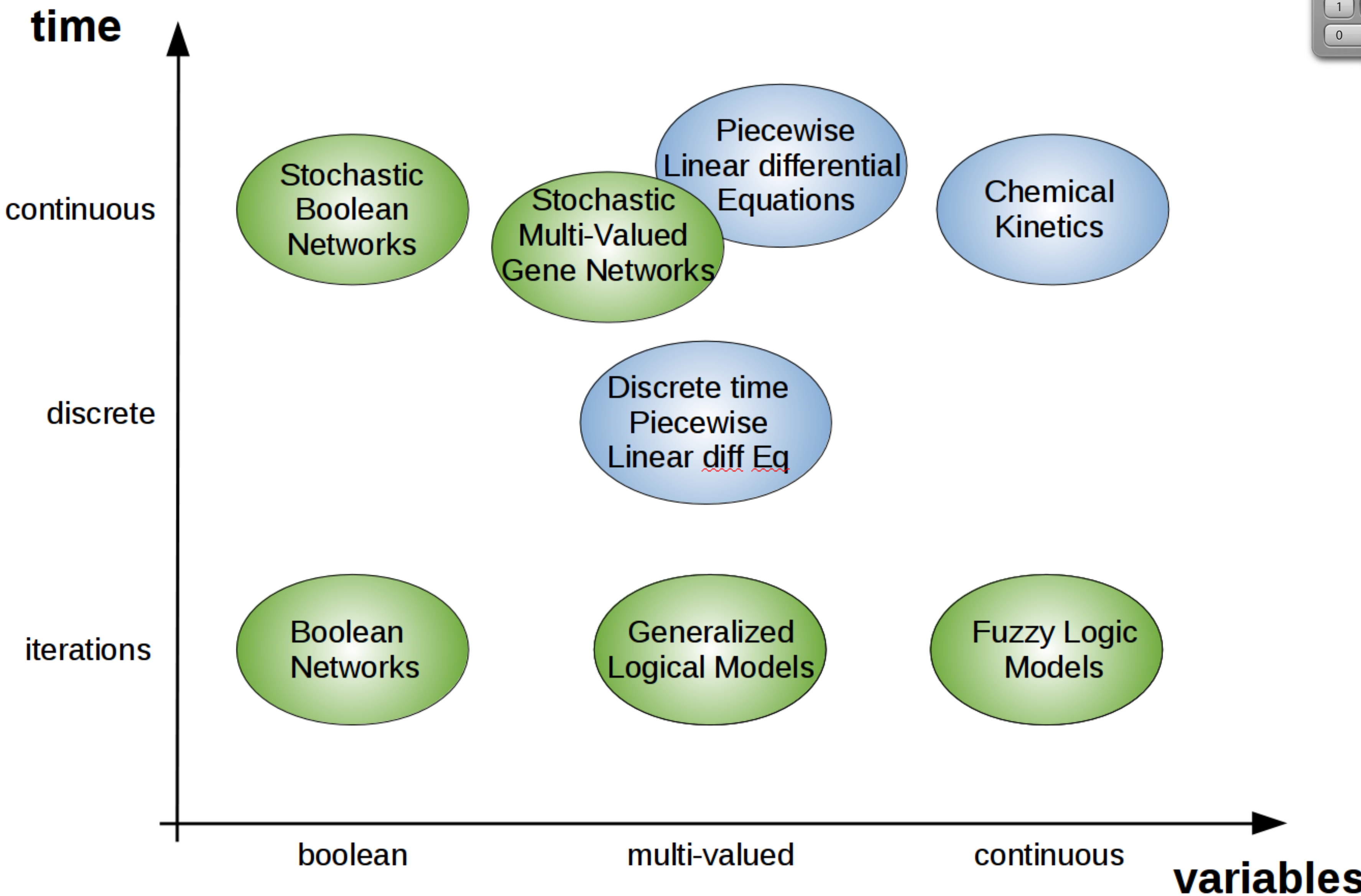
Stochastic simulations (SSA, “Gillespie”)



Probabilistic models

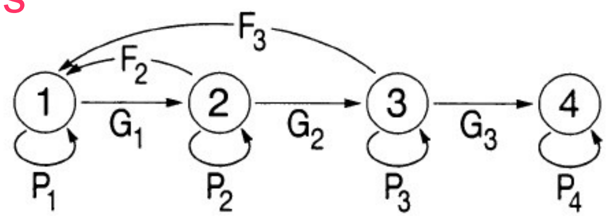


Logic versus numeric

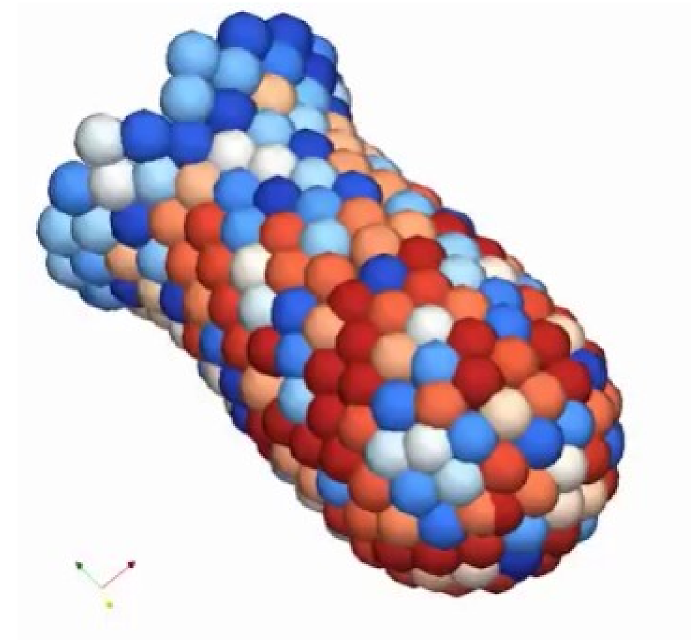


Many other types of models

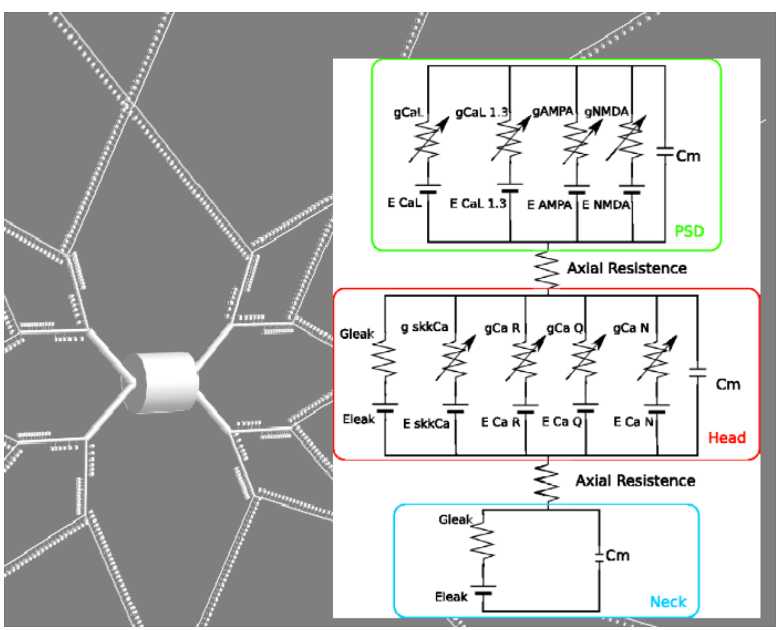
Matrix models



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



Multi-agents models (cellular potts)



Cable approximation