Introduction to modelling

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[1] The University of Manitoba campuses are located on original lands of Anishinaabeg, Cree, Oji-Cree, Dakota and Dene peoples, and on the homeland of the Métis Nation.

Outline

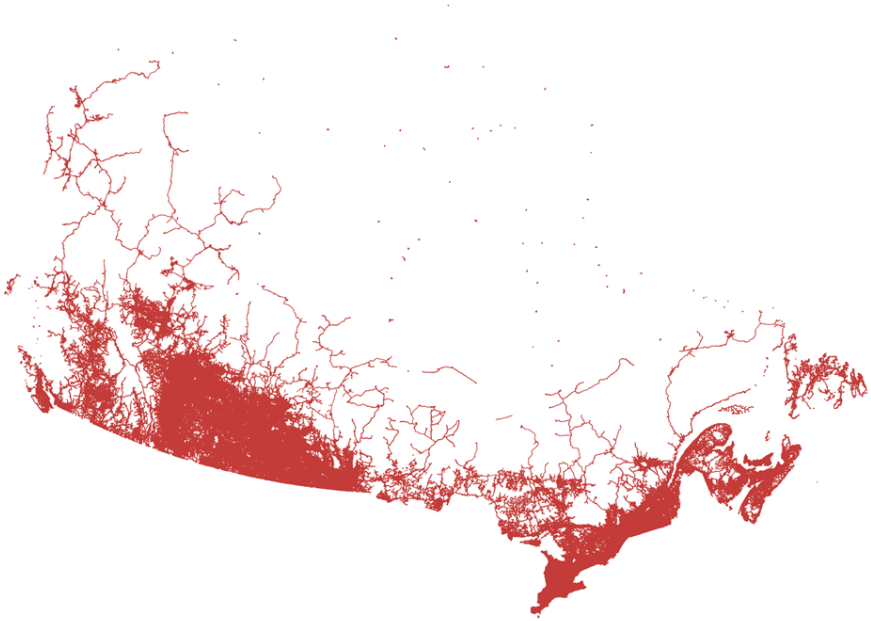
1. Introduction
   - Phenomenological approach
   - Mechanistic approach
2. Model formulation
   - Single population models
   - Interacting populations
   - Compartmental models
   - Structured populations
   - Spatial models
   - Stochastic approaches

Question

What do you need to cross Canada by bike ?

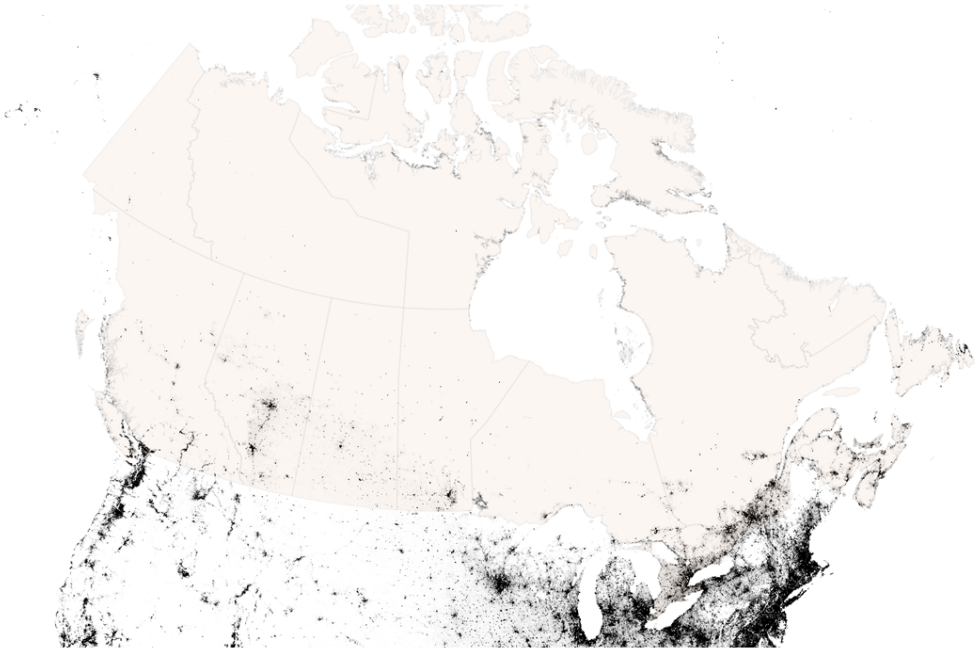
- a bike
-

Maps



Canada represented by
its road system

Canada represented by
its population density



Mathematical model

- A model is a map
- A model is a simplification of the reality (a map is not the territory it describes)

A model is an idealization of a real-world problem

> *It is a common fallacy to confuse scientists' models of reality with reality itself.* **A model is a map**. *A map is not the territory it describes. (Richard Casement)*

Modelling approaches: Phenomenological vs Mechanistic

Phenomenological approach: "A phenomenologically motivated approach generally constitutes a sketch or a summary of observations, and although it could be of high predictive utility, it is not directly connected to the underlying generative mechanism presumed to have produced available observations." $\Rightarrow$ **Descriptive models**

Mechanistic approach: ".. a mechanistically motivated approach is meant to constitute an explanation for observations, aimed at incorporating basic knowledge, and can typically be cast as a generalization or revision of a phenomenological approach." $\Rightarrow$ **Explanatory models**

N. Rodrigue, H. Philippe (2010) Trends in Genetics, 26: 248-252.

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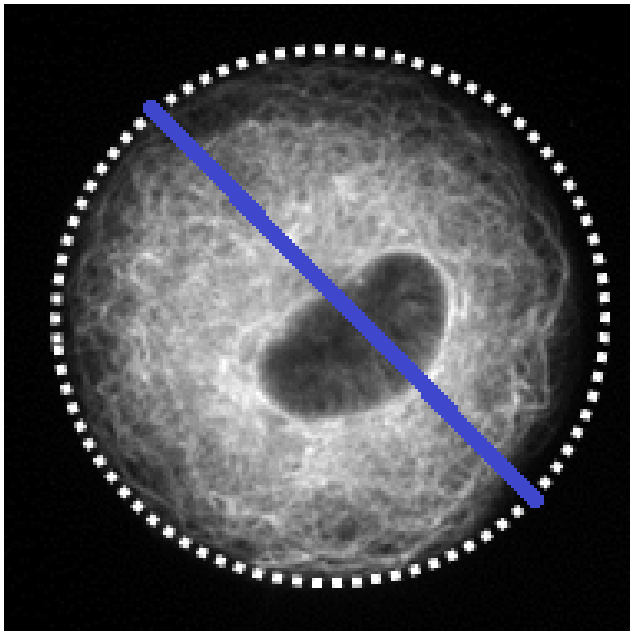
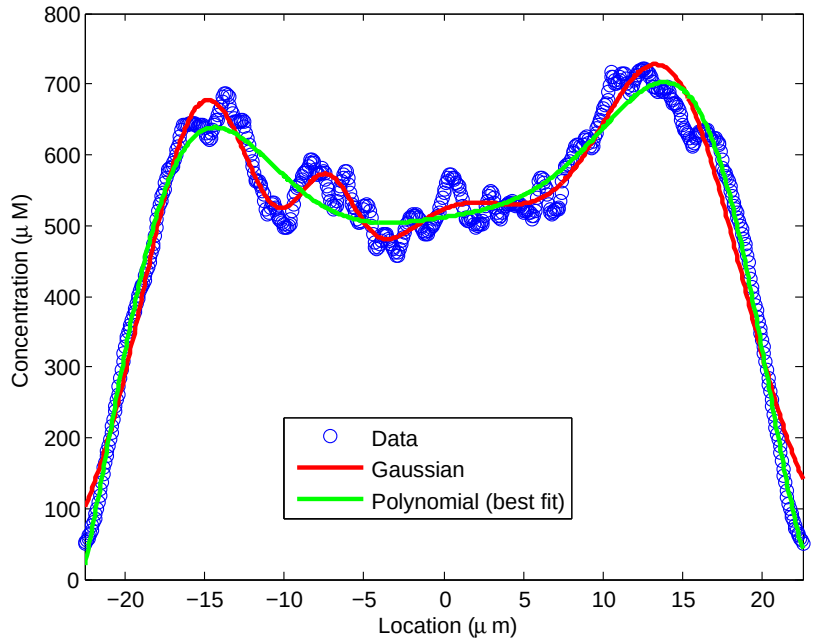
Phenomenological approach:

- **Data:** Limited number of data points representing values of a function for a limited number of values of the independent variable (e.g. time, space, ...)
- **Hypothesize the form of the function**
- **Interpolation:** estimate values of data for intermediate values of the independent variable
  $\Rightarrow$ **Curve fitting** (find the curve that has the best fit to data points)
  The best fit minimizes the difference between the actual value (data) and the predicted value (curve)

Example: Spatial profile of protein concentration in a cell





- **Gaussian function**: $\text{Concentration}(x) = \sum_{i=1}^{n} a_i e^{-((x-b_i)/c_i)^2}$
- **Polynomial function**: $\text{Concentration}(x) = \sum_{i=0}^{n} p_i x^i$

Phenomenological approach:

No model is formulated, but trend or main feature in data can be extracted

Descriptive aspect only

Predictive aspect

- Extrapolation (to find data points outside of the range of known data points)

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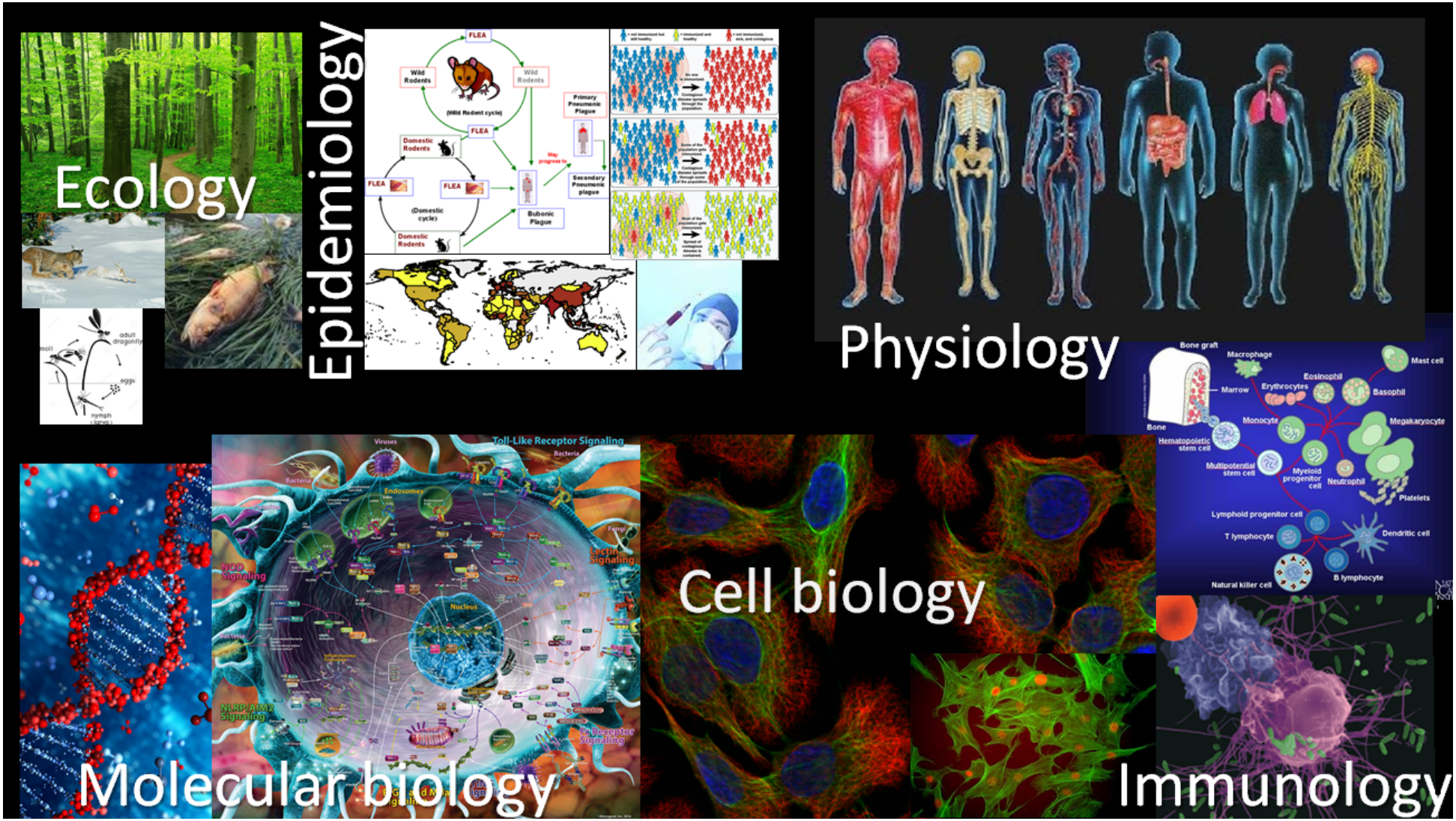
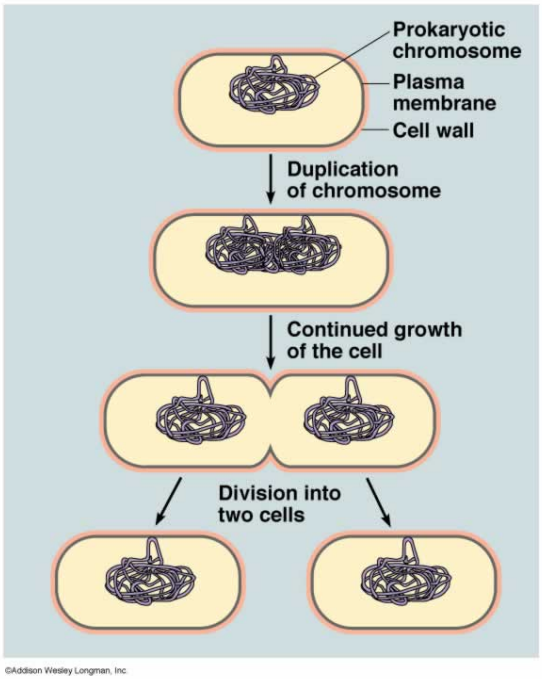
To write a mechanistic model

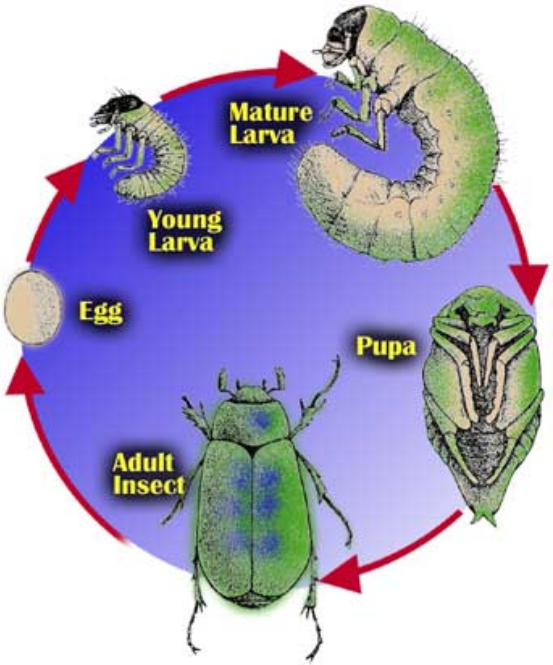
1. Identify the problem $\Rightarrow$ **Define the question to be answered**
2. **Define model variables and parameters** $\Leftarrow$ Experimental data
3. Identify the important processes governing the problem $\Rightarrow$ **Make assumptions**
4. Identify the **basic principles** that govern the quantities studied (physical laws, interactions..)
5. Express mathematically these principles $\Rightarrow$ **Choice of the formalism**
6. Verify that units are consistent
7. Verify that model is well-posed (existence of solutions, positivity of solutions..)

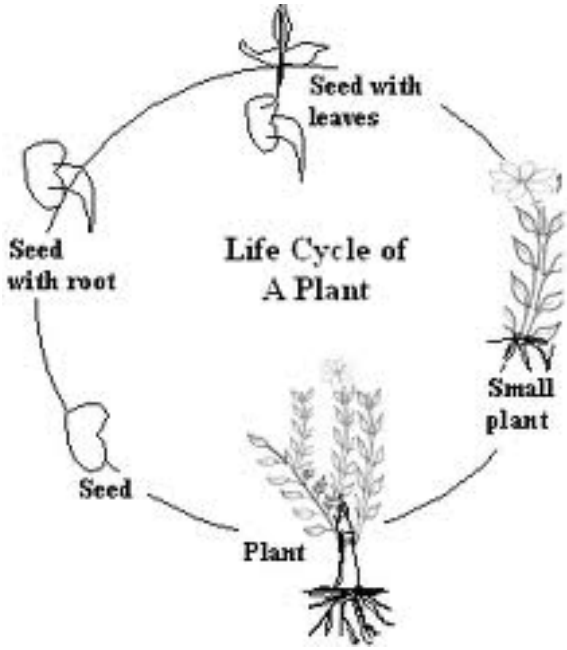
Idealization of real-world problems (never a completely accurate representation)


Ecology
Epidemiology
FLEA
Wild Rodents
(Wild Rodent cycle)
Primary Pneumonic Plague
Domestic Rodents
(Domestic cycle)
Secondary Pneumonic plague
Bubonic Plague
Physiology
Bone graft
Macrophage
Mast cell
Eosinophil
Erythrocytes
Basophil
Marrow
Bone
Monocyte
Megakaryocyte
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Neutrophil
Platelets
Lymphoid progenitor cell
T lymphocyte
Dendritic cell
Natural killer cell
B lymphocyte
Molecular biology
Toll-Like Receptor Signaling
Viruses
Bacteria
Endosomes
NOD Signaling
Lectin Signaling
Nucleus
NLRP1 AIM2 Signaling
Cell biology
Immunology

How does a population grow?







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How does a population grow? - Modelling change

Future value = Present value + Change

or

Change= Future value - Present value

$\Rightarrow$ Dynamical systems

How does a population grow?

- $N(t)$ population observed at time t
- Δt time interval
- r rate of growth per unit time

$$\begin{aligned} N(t+\Delta t) &= N(t) + r\Delta t N(t) \\ N(t+\Delta t) - N(t) &= r\Delta t N(t) \\ \frac{N(t+\Delta t) - N(t)}{\Delta t} &= rN(t) \end{aligned}$$

Assume that $\Delta t \to 0$

$$\begin{aligned} \lim_{\Delta t \to 0} \frac{N(t+\Delta t) - N(t)}{\Delta t} &= rN(t) \\ \frac{dN}{dt} &= rN \end{aligned}$$

How to represent time?

Time can be described as a

- discrete variable (time interval, generation..) $\Rightarrow$ **Difference equations**

$$N(t + \Delta t) = N(t) + r\Delta t N(t) = (1 + r\Delta t)N(t)$$

- continuous variable (instantaneous) $\Rightarrow$ **Differential equations**

$$\frac{dN}{dt} = rN$$

$\frac{dN}{dt}$ = instantaneous rate of change of the state variable N with respect to time t

Choice of formalism

How to represent a problem

- Static vs Dynamic
- Stochastic vs Deterministic
- Continuous vs Discrete
- Homogeneous vs Detailed

Formalism

Differential equations (ODE, PDE, DDE, SDE), difference equations, integral equations, integro-differential equations, Markov chains, game theory, graph theory, agent-based model, cellular automata, L-systems ...

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Malthus' population growth model

Consider a population with $N(t)$ individuals at time t. Suppose that

- individuals are born with rate constant b,
- individuals die with rate constant d.

Then the evolution of $N(t)$ over time is governed by an ODE, Malthus' equation:

$$\frac{dN}{dt} = bN - dN = (b-d)N \tag{1}$$

The solution is

$$N(t) = N(0)e^{(b-d)t}$$

- $b > d$, $\lim_{t\to\infty} N(t) = \infty$, the population grows,
- $b < d$, $\lim_{t\to\infty} N(t) = 0$, the population extincts.

Logistic equation: a refinement of Malthus' model

Assumptions

Additionally to birth and death, suppose that

- individuals are subject to *intraspecific competition* with other members of their species:
  - competition for food, competition for nesting space..
- intraspecific competition occurs with rate constant κ

Model: logistic equation

$$\frac{dN}{dt} = (b-d)N - \kappa N^2$$

by setting $r = b - d > 0$, $K = (b-d)/\kappa$,

$$\frac{dN}{dt} = r\left(1 - \frac{N}{K}\right)N \tag{2}$$

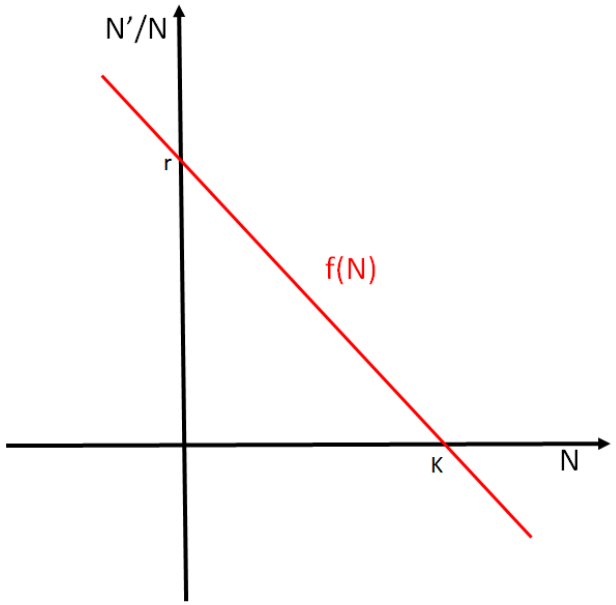
r: intrinsic rate of growth; K: environmental carrying capacity

Per capita growth rate depends on the population density

N'/N is the *per capita* instantaneous rate of growth:

$$\frac{N'}{N} = \underbrace{r}_{\text{Growth}} \underbrace{\left(1 - \frac{N}{K}\right)}_{\text{Regulation by crowding}} = r\left(1 - \frac{N}{K}\right) = f(N)$$

- $N < K$: population below carrying capacity, no regulation
- $N = K$: population at carrying capacity
- $N > K$: population over carrying capacity, crowding effects, population diminishes



Environment is capable of sustaining no more than a fixed number K of cells

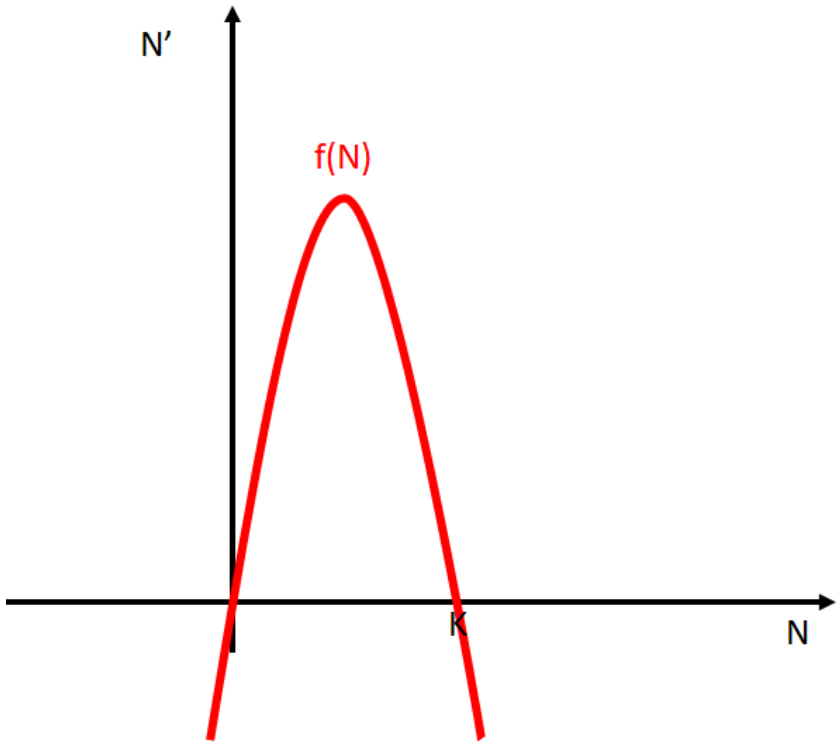
Solution of the logistic equation

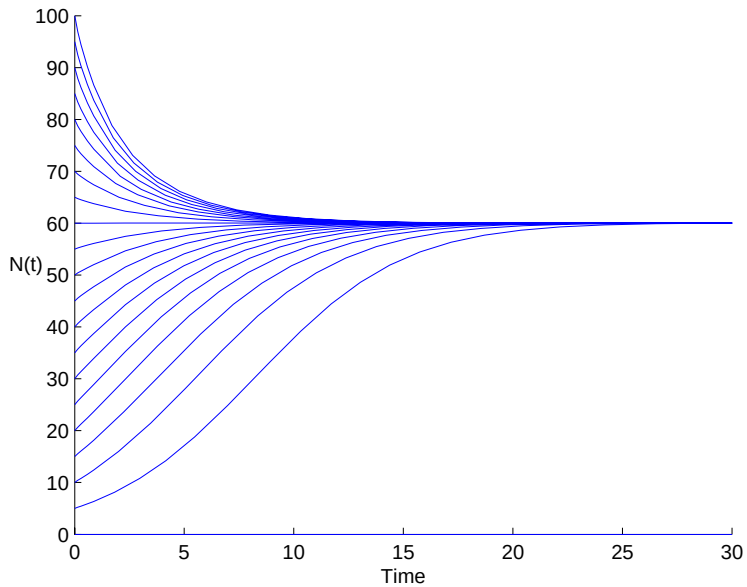
- Logistic equation is separable (or a Bernoulli equation with $n = 2$)

$$\frac{dN}{dt} = rN - \frac{r}{K}N^2 = f(N), \quad N_0 = N(0)$$

- Explicit solution

$$N(t) = \frac{KN_0}{N_0 + (K - N_0)e^{-rt}} \quad t \geq 0; \quad \lim_{t\to\infty} N(t) = K$$

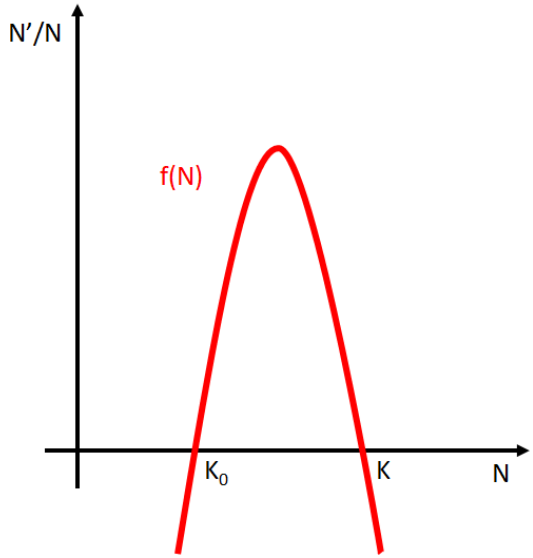




Other examples of non-constant per capita rate of growth

Allee effect

$$\frac{dN}{dt} = r\left(1 - \frac{N}{K}\right)\left(\frac{N}{K_0} - 1\right)N = f(N)N$$



Gompertz equation

$$\frac{dN}{dt} = re^{-\alpha t}N = f(t)N$$

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Mass Action law

The rate of an elementary reaction (defined by reduction of reactant or formation of product) is proportional to the concentration of each individual species involved in the elementary reaction.

Bimolecular reactions

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C$$

reversible reactions.

Dimerization

$$A + A \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C$$

Autocatalysis process whereby a chemical is involved in its own production.

$$A + X \underset{k_-}{\overset{k_+}{\rightleftharpoons}} X + X$$

Michaelis-Menten dynamics

Enzyme dynamics

$$C + X_0 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X_1$$

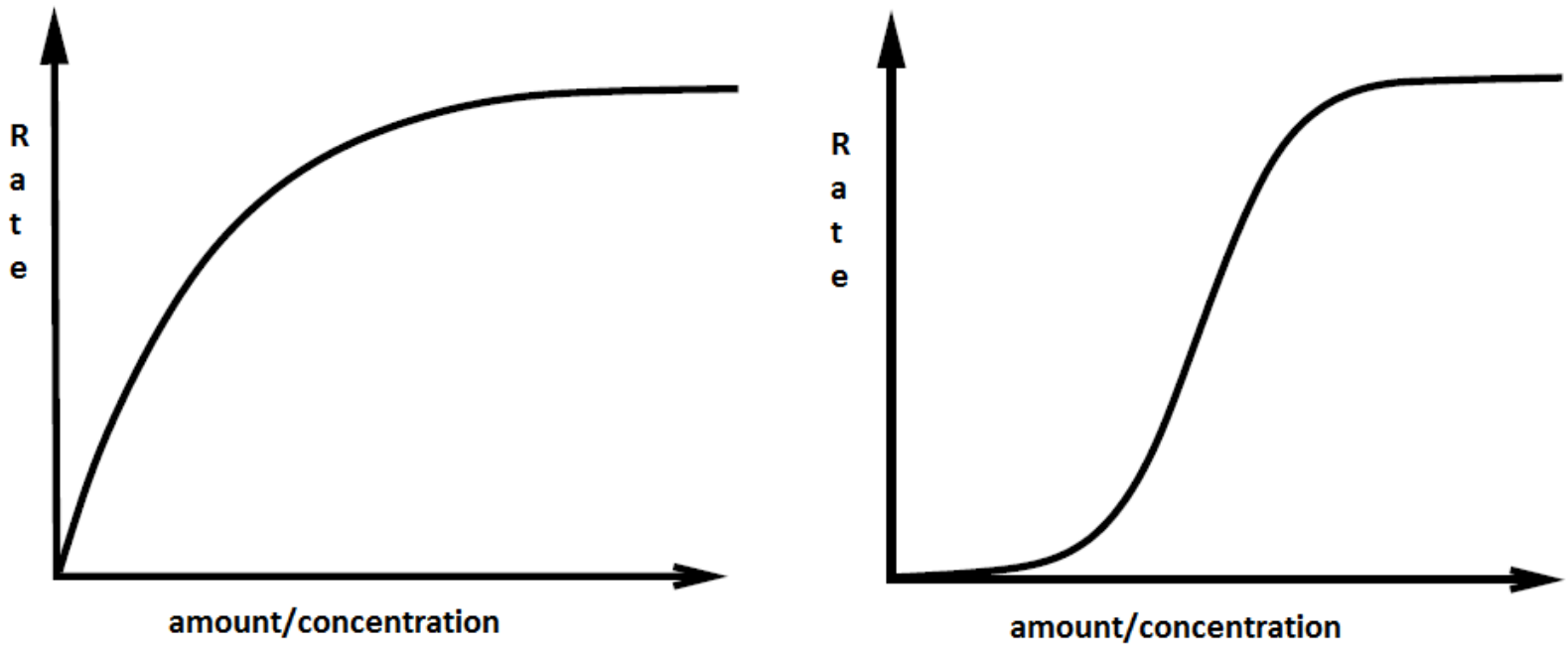
$$X_1 \xrightarrow{k_2} P + X_0$$

Michaelis-Menten law

$$-\frac{dC}{dt} = \frac{dP}{dt}$$
$$\frac{dP}{dt} = \frac{K_{max} C}{k_n + C}$$

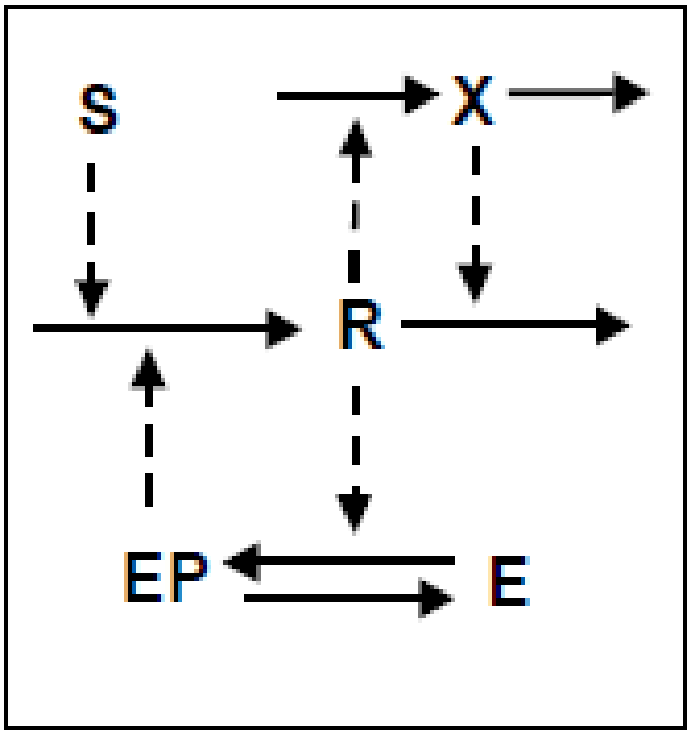
with $K_{max} = k_2 r$ ($r = X_0(0) + X_1(0)$), $k_n = \frac{k_{-1}+k_2}{k_1}$

Saturating rates



- Hyperbolic saturation: as the amount increases the rate increases but by slowing down (Michaelis-Menten dynamics)
- Sigmoidal saturation: from a slow to rapid rate, "switch-like" rise toward to the limiting value (Cooperativity)

Signalling pathways



$$\frac{dR}{dt} = k_0 \frac{2k_3 R J_4}{\Phi + \sqrt{\Phi^2 - 4(k_4 - k_3 R)k_3 R J_4}} + k_1 S - (k_2 + k_2' X)R$$

$$\frac{dX}{dt} = k_5 R - k_6 X$$

with $\Phi = k_4 - k_3 R + k_4 J_3 + k_3 R J_4$.

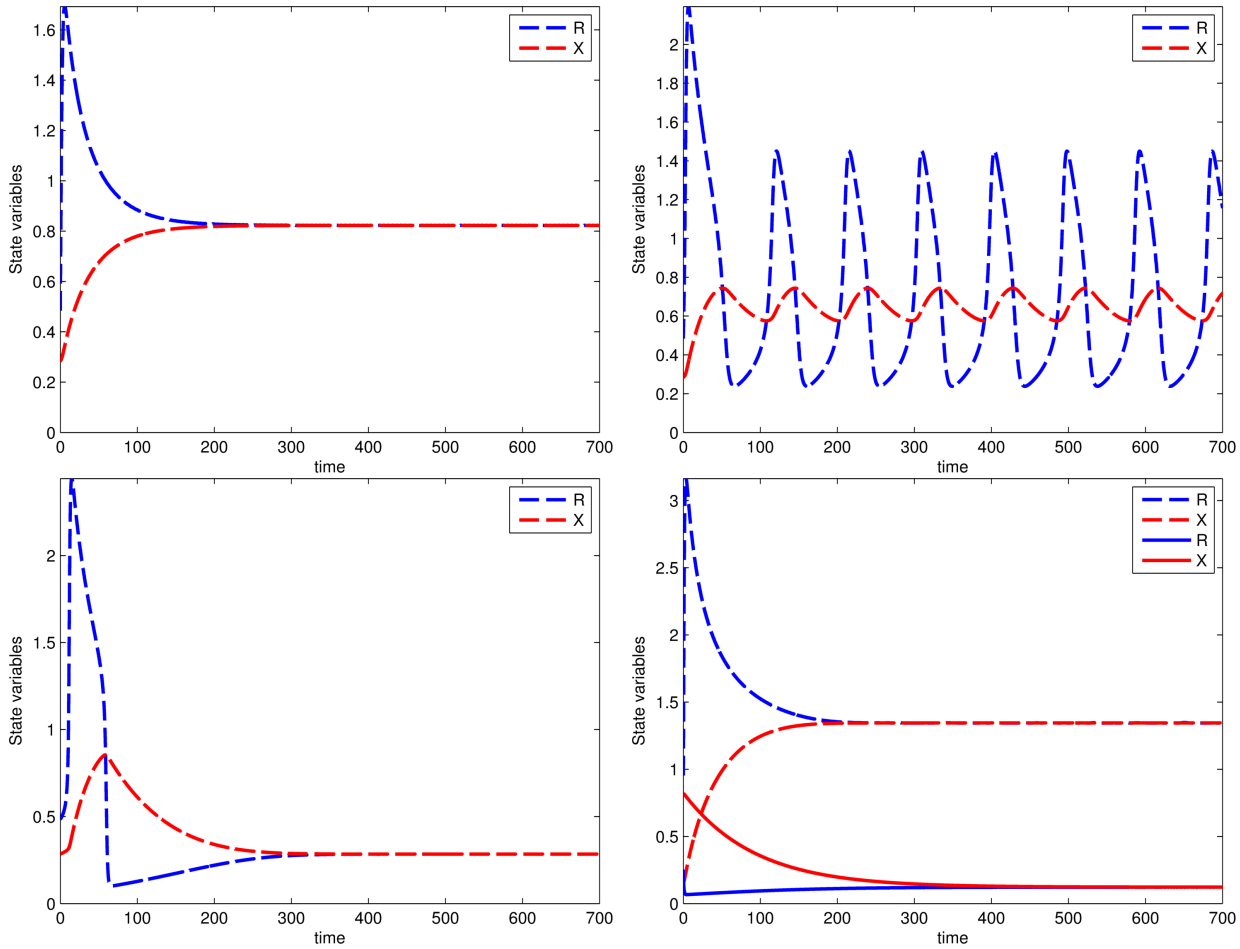
- S signal, R response
- X, E and EP other components of the network

Translation in mathematics $\Rightarrow$ model

[2] Tyson *et al.* (2003) Curr. Op. Cell Biol. 15:221-231.

Mathematical analysis shows that:

Depending on the concentration of the mediator, the pathway exhibits 4 types of regime/behaviour: stable steady-state, steady oscillation, excitability, bistability



Example for Michaelis-Menten growth rate

Assumption

The growth rate of the bacterial population is a saturating function of nutrient availability.

- $b(t)$ concentration of bacteria at time t (mass/volume)
- $n(t)$ concentration of nutrient at time t (mass/volume)

$$\frac{db}{dt} = \alpha \frac{k_{max} n}{k_n + n} b \cdots$$
$$\frac{dn}{dt} = -\frac{k_{max} n}{k_n + n} b \cdots$$

Parameters:

- k_{max} maximun rate of growth
- k_n half-saturation constant

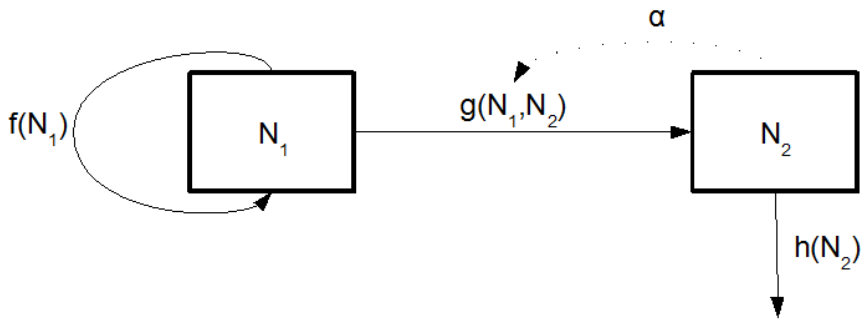
Michaelis-Menten growth rate, $K(n) = \frac{k_{max} n}{k_n + n}$

Consumer-Resource models

- N_1 resource
- N_2 consumer

$$\frac{dN_1}{dt} = \underbrace{f(N_1)}_{\text{resource-renewal}} - \underbrace{g(N_1, N_2)}_{\text{consumption of resource by consumers}}$$

$$\frac{dN_2}{dt} = \underbrace{\alpha}_{\text{conversion factor}} g(N_1, N_2) - \underbrace{h(N_2)}_{\text{change of consumers in absence of resource}}$$



Possible forms

Resource-renewal term

$f(N_1) = \pi$	Inflow of resources at a constant rate
$f(N_1) = -\pi$	Outflow of resources at a constant rate
$f(N_1) = rN_1$	Constant per capita growth of resource
$f(N_1) = rN_1(1 - \frac{N_1}{K})$	Per capita growth of resources declines linearly with resource level (Logistic)
$f(N_1) = rN_1 e^{-\beta N_1}$	Per capita growth of resources declines exponentially with resource level

Resource consumption term

$g(N_1, N_2) = acN_1N_2$	Linear rate of resource consumption
$g(N_1, N_2) = \frac{acN_1}{b+N_1}N_2$	Saturating rate of resource consumption
$g(N_1, N_2) = \frac{acN_1^k}{b+N_1^k}N_2$	Saturating rate of resource consumption

Change of consumers in absence of resource

$h(N_2) = dN_2$	Constant per capita death rate of consumers
$h(N_2) = (dN_2)N_2$	Per capita death rate of consumers increases linearly with consumer population size

Other types of interactions

$$\frac{dN_1}{dt} = r_1 N_1 \left(1 \underbrace{- \frac{N_1}{K_1}}_{\text{Intra-population}} + \underbrace{b_{12} \frac{N_2}{K_1}}_{\text{Inter-population}} \right)$$

$$\frac{dN_2}{dt} = r_2 N_2 \left(1 \underbrace{- \frac{N_2}{K_2}}_{\text{Intra-population}} + \underbrace{b_{21} \frac{N_1}{K_2}}_{\text{Inter-population}} \right)$$

b_{ij} strength of interaction exerted by an individual of species j on an individual of species i

b_{12}	b_{21}	Interactions
-	-	Competitive
+	+	Mutualistic
+	-	Parasitic
-	+	Parasitic

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Compartmental models

Definition

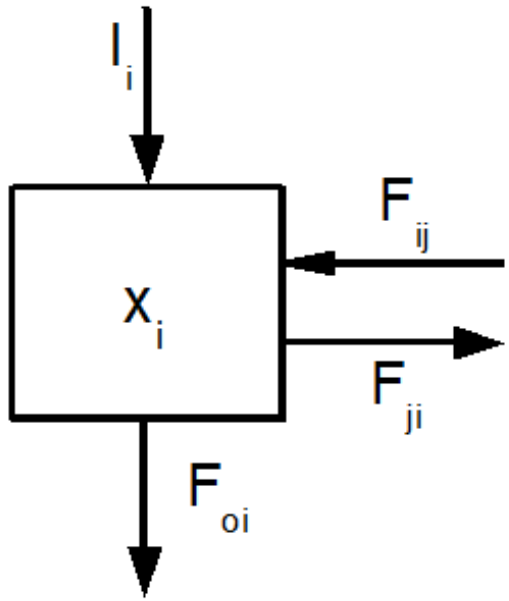
Systems in which there are flows of material between units called **compartments**

Compartments

A compartment is an amount of some material : the material of a compartment is at all times homogeneous; any material entering it is instantaneously mixed with the material of the compartment.

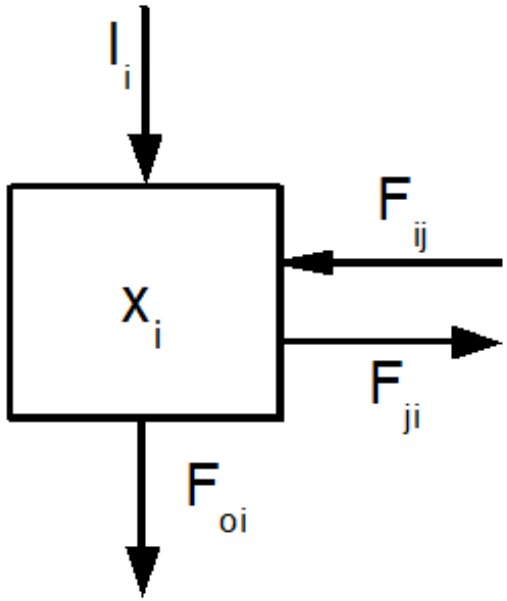
Dynamic models that depends on local mass balance conditions

The i^{th} compartment of a differential compartmental model



- x_i mass of compartment i
- I_i flows into the compartment i from the environment (**inflows**)
- F_{oi} **outflows** from compartment i to the environment (out of the system)
- F_{ji} transfers from compartment i to compartment j
- F_{ij} transfers from compartment j to compartment i

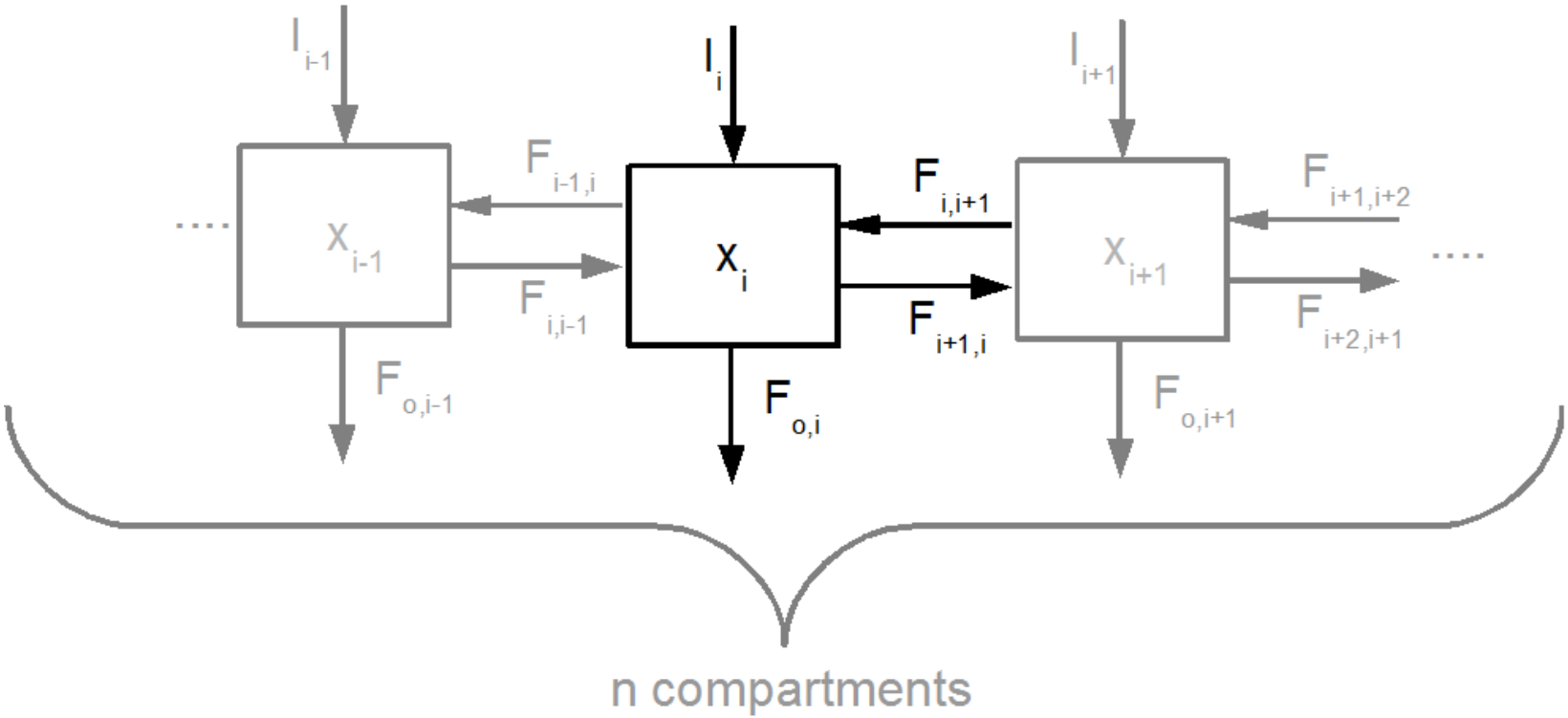
The i^{th} compartment of a differential compartmental model



$$\frac{dx_i}{dt} = \sum_{j \neq i} (-F_{j,i} + F_{i,j}) + I_i - F_{o,i}$$

- x_i nonnegative state variable
- all flows are nonnegative ($F_{i,j} \geq 0$, $I_i \geq 0$, $F_{o,i} \geq 0$, $\forall i, j$)
- sign in the equation translates the directions of flow
- if $x_i = 0$, then $F_{o,i} = 0$ and $F_{j,i} = 0$ $\forall j$

An example of model of n compartments



n state variables x_i for $i \in \{1, \cdots, n\}$

$$\frac{dx_i}{dt} = -F_{i-1,i} + F_{i,i-1} - F_{i+1,i} + F_{i,i+1} + I_i - F_{oi}$$

If $\mathbf{F}$ is C^k, then

$$F_{j,i}(\mathbf{x}) = f_{j,i}(\mathbf{x}) \cdot x_i$$

for some function $f_{j,i}(\mathbf{x})$ which is at least C^{k-1}.

System

$$\frac{dx_i}{dt} = \sum_{j \neq i} (-F_{j,i} + F_{i,j}) + I_i - F_{o,i}$$

can then be rewritten as

$$\frac{dx_i}{dt} = -\left(f_{o,i} + \sum_{j \neq i} f_{j,i} \right) x_i + I_i + \sum_{j \neq i} f_{i,j} x_j$$

- $f_{i,j}$ constants or functions only of time $\Rightarrow$ Linear system
- $f_{i,j}$ functions of $\mathbf{x}$ (not constant function) $\Rightarrow$ Nonlinear system

Compartmental models

$$\frac{dx}{dt} = \text{input rate} - \text{output rate}$$

Applications

- pharmacokinetics
- physiology
- immunology
- epidemiology
- ecology
- ..

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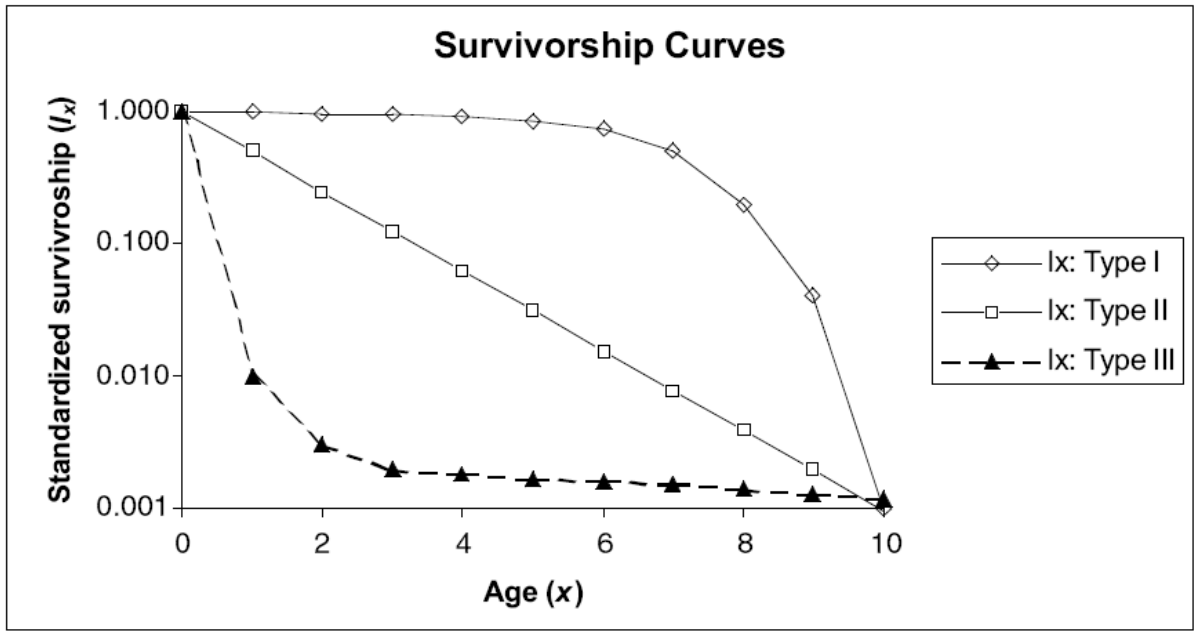
Structured populations

In some species, the amount of reproduction varies greatly with the age of individuals.

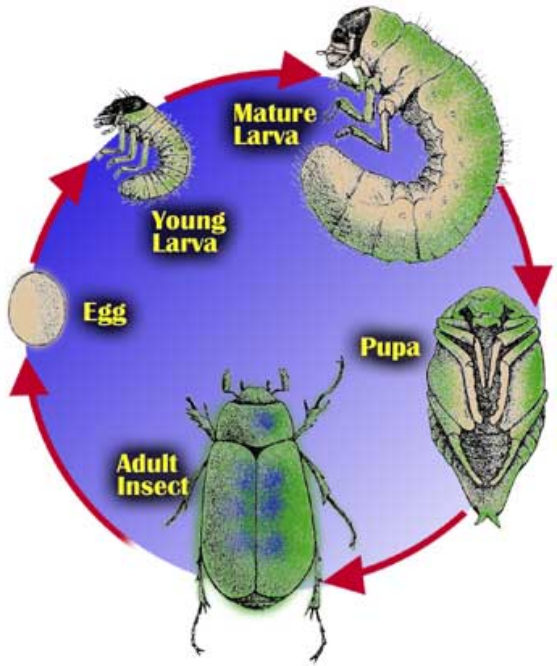


Type I: high survivorship throughout life until old age sets in, and then survivorship declines dramatically to 0. Humans are type I organisms. Type III: In contrast, very low survivorship early in life, and few individuals live to old age.

Age structure or developmental stage of population matters

Structured population models

used when the population can be organized or divided into various subclasses following traits such as age, life-stage or size. The variable that describes this trait is called the structuring variable.



The dynamic interactions among the stages, ages or sizes determine how the population structure changes over the time.

Structured population dynamics: discrete models

- Population categorized into a finite number of classes $i = 1, 2, \cdots, m$
- $x_i(t)$ number or density of individuals in the i^{th} class at time $t = 0, \Delta t, 2\Delta t, \ldots$
- If only birth and death processes (no migration):

$$x(t + \Delta t) = Px(t)$$

where $P = T + F$ is the projection matrix

$T = [t_{ij}]$ transition matrix, $0 \leq t_{ij} \leq 1$ and $\sum_{i=1}^{m} t_{ij} \leq 1$ for all j

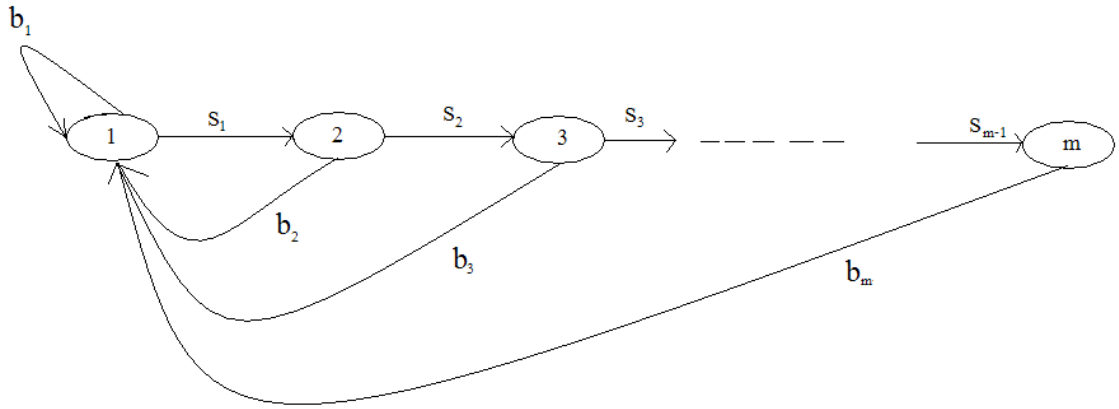
- t_{ij} fraction of $j-$class individual expected to survive and move to class i per unit of time
- t_{ii} fraction of individuals in class i that survive and remain in class i after one unit of time
- No individual can shrink or grow more than one class in one unit of time

$F = [f_{ij}]$ fertility matrix, $f_{ij} \geq 0$

- f_{ij} the expected number of (surviving) $i-$class offspring per $j-$class individual per unit of time

A particular case : Leslie model

(the time interval coincides with the structure interval)



$$
\begin{aligned}
x_1(t+1) &= b_1 x_1(t) + b_2 x_2(t) + b_3 x_3(t) + \ldots b_m x_m(t) \\
x_2(t+1) &= s_1 x_1(t) \\
&\vdots \\
x_m(t+1) &= s_{m-1} x_{m-1}(t)
\end{aligned}
$$

$$
X(t+1) = \begin{pmatrix} x_1(t+1) \\ x_2(t+1) \\ \vdots \\ x_m(t+1) \end{pmatrix} = \begin{pmatrix} b_1 & b_2 & \ldots & b_{m-1} & b_m \\ s_1 & 0 & \ldots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \ldots & s_{m-1} & 0 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ \vdots \\ x_m(t) \end{pmatrix} = LX(t)
$$

McKendrick–von Foerster equation

Model with age-structure

$$\frac{\partial N}{\partial t} + \frac{\partial N}{\partial a} + \mu(a)N(t,a) = 0$$

with boundary condition (birth function)

$$N(t,0) = \int_0^\infty b(a)N(t,a)da$$

and initial condition (initial age distribution)

$$N(0,a) = f(a)$$

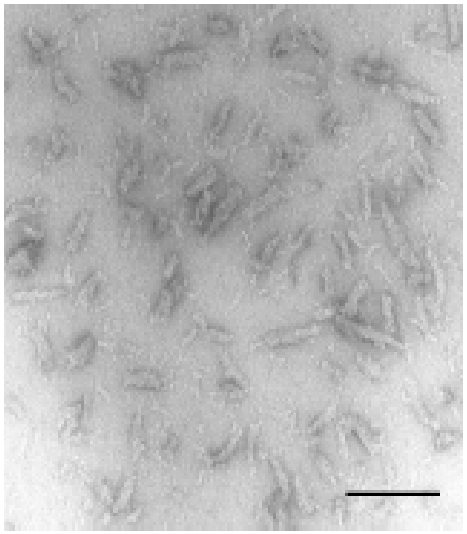
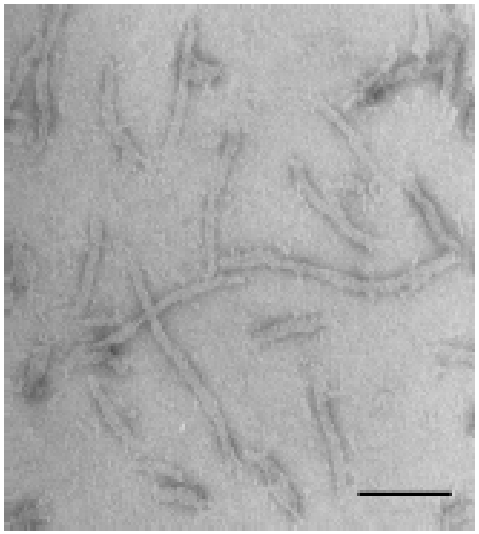
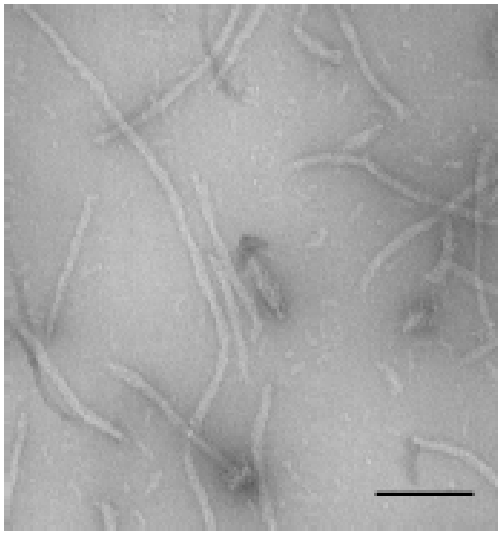
where

- $N(t,a)$ population density at time t and age a
- $b(a)$ birth rate of individuals of age a
- $\mu(a)$ death rate of individuals of age a
- $f(a)$ initial age distribution of population

What is the dynamics of length distributions?

Coagulation-fragmentation problems

describe the dynamics of cluster growth and the time evolution of a system of clusters under the combined effect of coagulation and fragmentation

A population of clusters which are free to move in space and may merge after collisions or spontaneously breakup.

A tool: coagulation-fragmentation equation

- **Reactions**
  Coagulation
  $$(i) + (j) \to (i + j)$$
  Fragmentation
  $$(i) \to (i - k) + (k)$$
- **Quantity of interest**: size profile
- **Size**: continuous or discrete variables?
- **Number of clusters**: finite or infinite?
- **Collision frequency expression (or rate constants)?** (from physical assumptions on the dynamics of interactions)

Continuous coagulation-fragmentation equation

- $C(x,t)$ concentration of clusters of size x ($x \in (0,\infty)$) at time $t \geq 0$
- $k(x,y)$ (non-negative function) coagulation kernel
- $f(x,y)$ (non-negative function) fragmentation kernel

$$\frac{\partial C(x,t)}{\partial t} = \underbrace{\frac{1}{2}\int_0^x k(x-y,y)C(x-y,t)C(y,t)dy}_{\text{formation of cluster of size x due to coagulation of smaller clusters}}$$

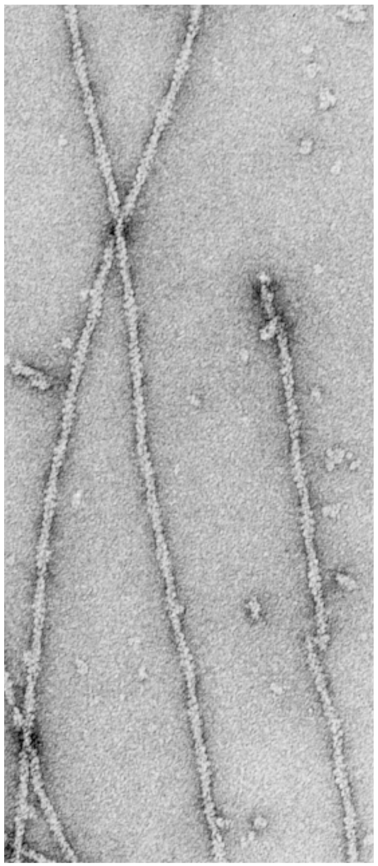
$$\underbrace{-\frac{1}{2}C(x,t)\int_0^x f(x-y,y)dy}_{\text{loss of cluster of size x due to breakup}} \quad \underbrace{-C(x,t)\int_0^\infty k(x,y)C(y,t)dy}_{\text{loss of cluster of size x due to coalescence}}$$

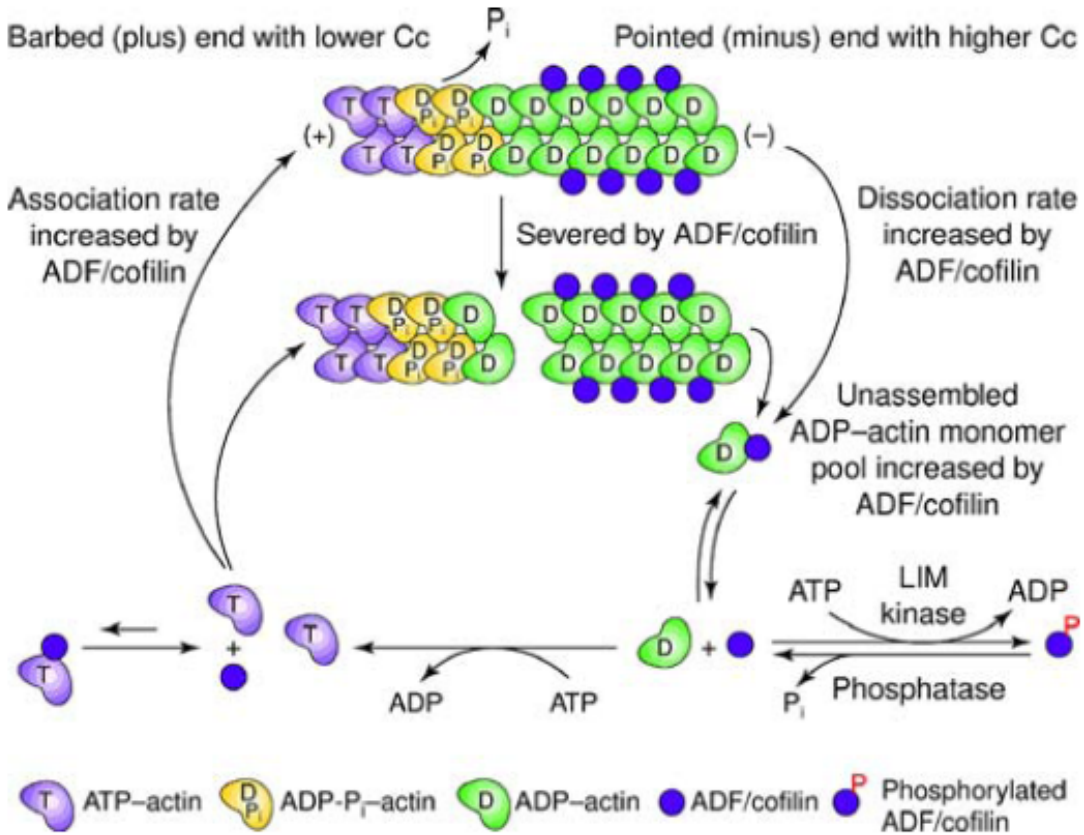
$$\underbrace{+\int_x^\infty f(x,y)C(x+y,t)dy}_{\text{formation of cluster of size x due to fragmentation of larger clusters}},$$

$$C(x,0) = C_0(x) \geq 0.$$

Z. A. Melzak. Trans. Amer. Math. Soc. (1957) 85:547.

Assembly dynamics of actin filaments





Hu, J. *et al.* J. Stats. Phys. (2007) 128:111.

Assembly dynamics of *in vitro* actin filaments

Assumptions

- size of filaments in numbers of subunits $\Rightarrow$ discrete version
- pool of monomers (closed system) $\Rightarrow$ finite system
- no distinction between barbed and pointed filament ends

Reactions

$\mathcal{M}_n$: filament of length n

$$\underbrace{\mathcal{M}_1 + \mathcal{M}_1 \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} \mathcal{M}_2 \underset{k_2^-}{\overset{k_2^+ \mathcal{M}_1}{\rightleftharpoons}} \mathcal{M}_3}_{\text{Nucleation}} \quad \underbrace{\underset{k_3^-}{\overset{k_3^+ \mathcal{M}_1}{\rightleftharpoons}} \mathcal{M}_4 \cdots \mathcal{M}_n \underset{k_n^-}{\overset{k_n^+ \mathcal{M}_1}{\rightleftharpoons}} \mathcal{M}_{n+1} \cdots}_{\text{Propagation}}$$

Hu, J. *et al.* J. Stats. Phys. (2007) 128:111.

Assembly dynamics of *in vitro* actin filaments

Variables

C_n: concentration of filaments of length n

Equations

$$\frac{dC_1}{dt} = -2(k_1^+ C_1^2 - k_1^- C_2) - \sum_{n=3}^{N}(k_{n-1}^+ C_1 C_{n-1} - k_{n-1}^- C_n)$$

$$\vdots$$

$$\frac{dC_n}{dt} = (k_{n-1}^+ C_1 C_{n-1} - k_{n-1}^- C_n) - (k_n^+ C_1 C_n - k_n^- C_{n+1})$$

$$\vdots$$

$$\frac{dC_N}{dt} = (k_{N-1}^+ C_1 C_{N-1} - k_{N-1}^- C_N)$$

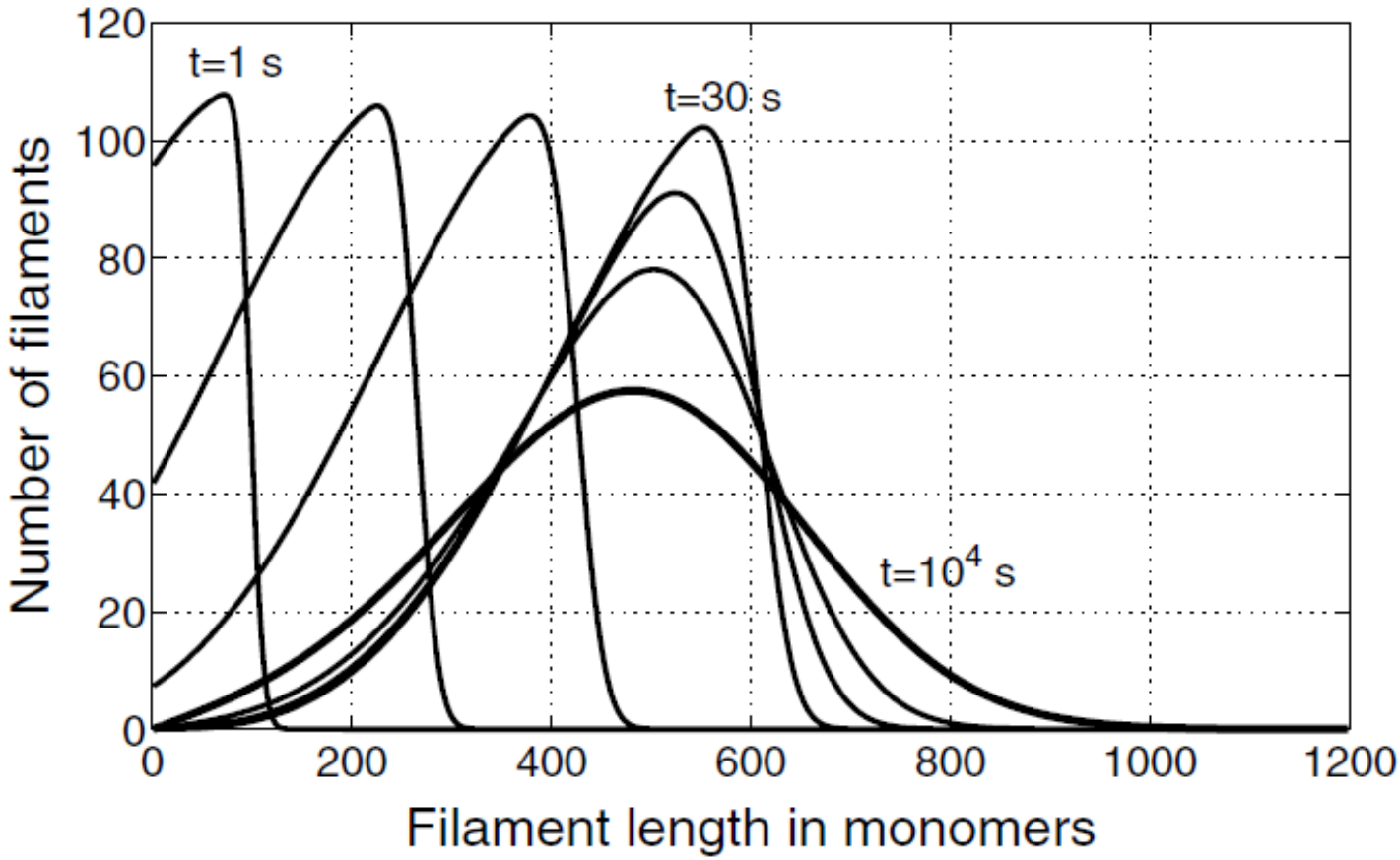
Mass conservation: $\sum_{n=1}^{N} nC_n = C_0$

Hu, J. *et al.* J. Stats. Phys. (2007) 128:111.

Assembly dynamics of *in vitro* actin filaments

Characterisation of time scale for establishing an equilibrium distribution

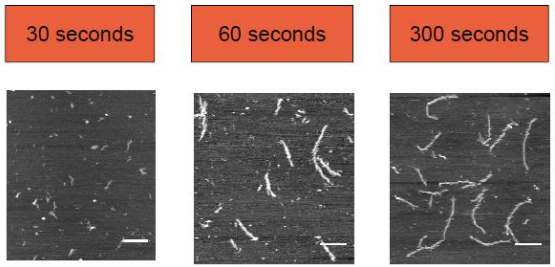
- distribution quickly evolves to a quasi-attractor for which the distribution has a maximum at an intermediate length



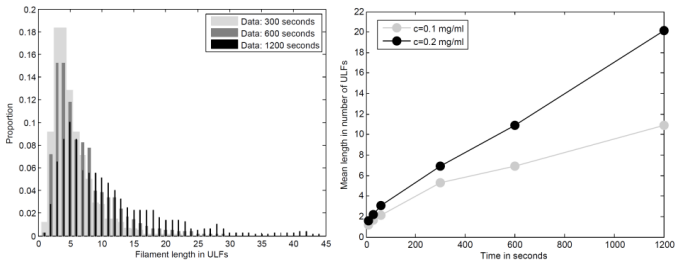
Hu, J. *et al.* J. Stats. Phys. (2007) 128:111.

Example: Dynamics of *in vitro* assembly of intermediate filaments

Experimental data



- In vitro assembly of filaments
- Imaging: EM, SFM, AFM, TIRF

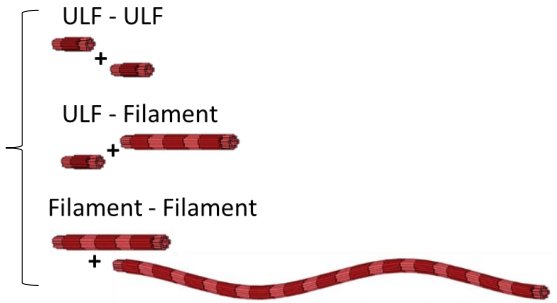


- Filament length distributions over time
- Mean lengths over time
- Lengths in # of ULFs

Model

- ULF = smallest structural stage
- Longitudinal annealing only

$$F_i + F_j \overset{k_0 \times k_{i,j}}{\longrightarrow} F_{i+j}$$



Effective association rates = $k_0 \times k_{i,j}$

- $k_{i,j}$ = diffusion-controlled association rates
- k_0 = intrinsic bimolecular rate constant (single free parameter)

Smoluchowski's coagulation equation =>

- F_i concentration of filaments composed of i ULFs over time
- Filament length distributions over time
- Mean lengths over time
- Lengths in # of ULFs

Find $k_0 \times k_{i,j}$ to best represent the data

Work in collaboration with H. Herrmann, N. Mücke (DKFZ, Heidelberg)

Example: Dynamics of *in vitro* assembly of intermediate filaments

Model depends on a single unknown parameter k_0

$$\frac{1}{k_0}\frac{\mathrm{d}F_i}{\mathrm{d}t} = \frac{1}{2}\sum_{j=1}^{i-1}(1+\delta_{j,i-j})\,k_{j,i-j}\,F_jF_{i-j} - \sum_{j=1}^{2N}(1+\delta_{j,i})\,k_{j,i}\,F_jF_i$$

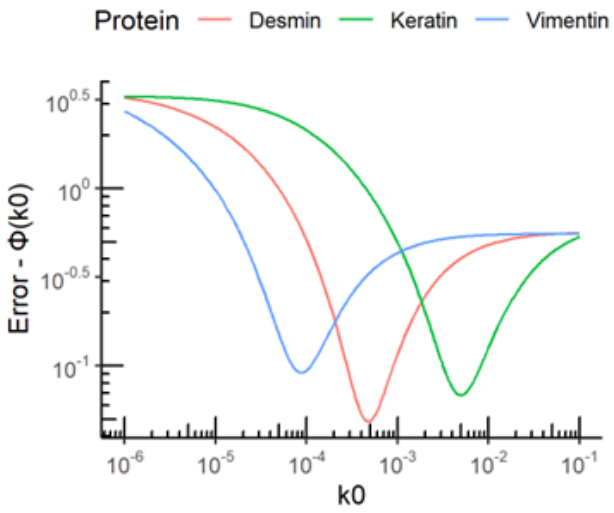
Observable function

$$ML(t) = \sum_{i=1}^{N} i\left[\frac{F_i(t)}{\sum_{i=1}^{N}F_i(t)}\right]$$

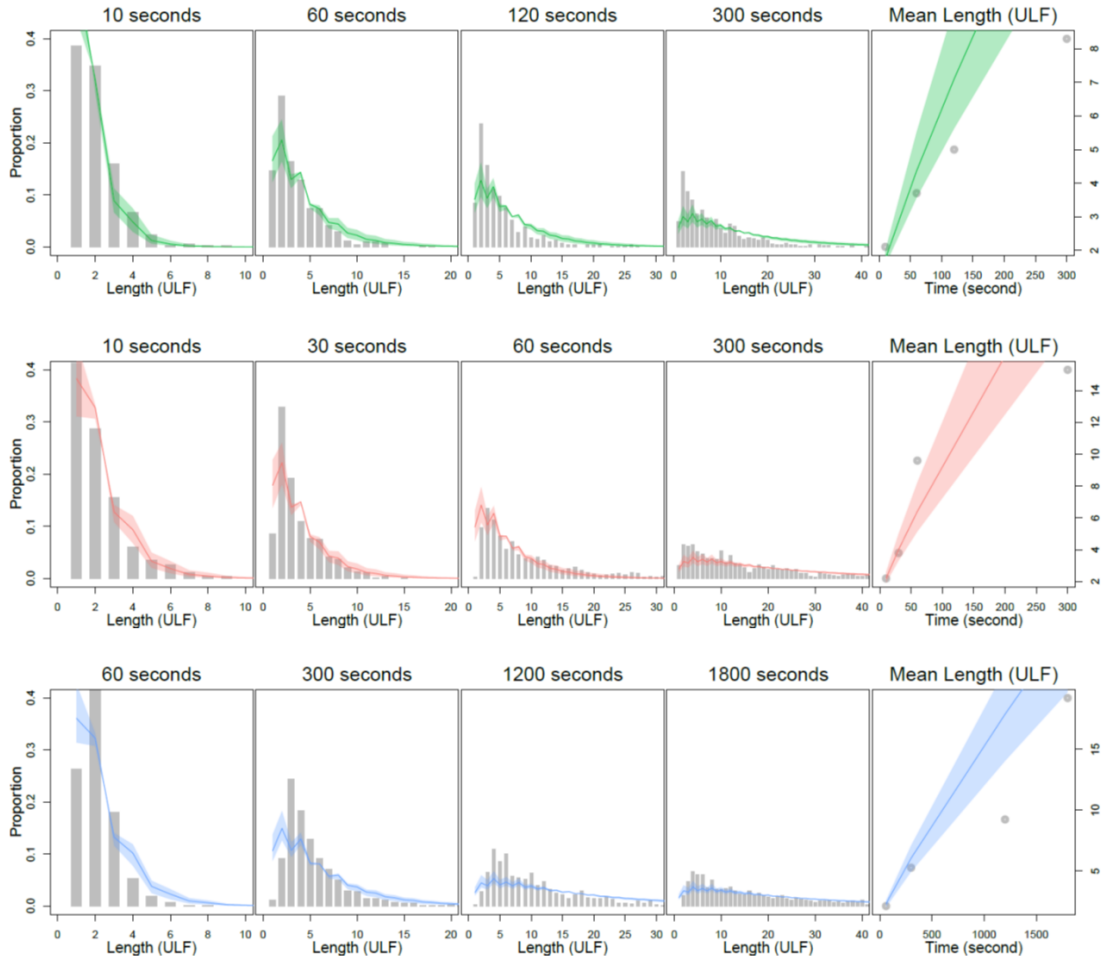
Error

$$\Phi(k_0) = \sum_{j=1}^{M}(ML_{model}(t_j,p) - ML_{data}(t_j))^2$$

Dynamics of *in vitro* assembly of intermediate filaments



	Keratin	Desmin	Vimentin
90% IC	$[3.6\text{x}10^{-3}, 7\text{x}10^{-3}]$	$[3.5\text{x}10^{-4}, 6.7\text{x}10^{-4}]$	$[6.6\text{x}10^{-5}, 1.1\text{x}10^{-4}]$
$\widehat{k_0}$	$5\text{x}10^{-3}$	$4.8\text{x}10^{-4}$	$8.9\text{x}10^{-5}$



Outline

1. Introduction
   - Phenomenological approach
   - Mechanistic approach
2. Model formulation
   - Single population models
   - Interacting populations
   - Compartmental models
   - Structured populations
   - Spatial models
   - Stochastic approaches

Spatial models

If the population/amount is not homogeneous in space $\Rightarrow$
Space-dependent processes + Movement/Motion

- **Discrete in space:** compartmental models, metapopulations, network models, cellular automata, lattice gas models, Potts model...
- **Continuous in space:** integro-differential equations, partial differential equations...

Different types of motions

- **Diffusion**: random motion of objects in a fluid
- **Advection**: objects are carried along by a current in the fluid
- **Taxis**: motion in response to a stimulus (environment sensing $\rightarrow$ respond to environment)
  - Chemotaxis: response to a chemical gradient
  - Phototaxis: response to a light source
  - Geotaxis: response to a gravitational field
  - Galvanotaxis: response to an electrical field (human skin cells migrate toward the negative pole in direct current electric fields of physiological strength (wound healing))
  - Haptotaxis: response to an adhesive gradient

Macroscopic theory – Conservation law

- $C(x,t)$ concentration of particles at location x at time t
- $J(x,t)$ (flux rate) rate at which C moves across the boundary at position x from left to right at time t (amount/area/time)
- $f(x,t,C)$ source function

The conservation law is

$$\frac{\partial C}{\partial t} + \frac{\partial J}{\partial x} = f(x,t,C)$$

(evolution equation for C)

(in $n-$dimension)

$$\frac{\partial C}{\partial t} + \nabla \cdot J = f(\mathbf{x},t,C)$$

Diffusive flux – Fick's law

"C moves from regions of high concentration to regions of low concentration", at a rate proprotional to the gradient concentration

$$J(x,t) = -D\frac{\partial C}{\partial x}$$

D is the diffusion coefficient.

Under Fick's law, C evolves as follows

$$\frac{\partial C}{\partial t} + \frac{\partial}{\partial x}\left(-D\frac{\partial C}{\partial x}\right) = f(x,t,C)$$

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} + f(x,t,C)$$

(in $n-$dimension)

$$\frac{\partial C}{\partial t} = \nabla\cdot(D\nabla C) + f(\mathbf{x},t,C) = D\nabla^2 C + f(\mathbf{x},t,C) = D\Delta C + f(\mathbf{x},t,C)$$

Advective flux

There is a uniform macroscopic flow of the solvent, with a speed u along the $x-$axis, which carries solutes along with it.

$$J(x,t) = uC(x,t)$$

So C evolves as follows

$$\frac{\partial C}{\partial t} + \frac{\partial uC}{\partial x} = f(x,t,C)$$

$$\frac{\partial C}{\partial t} = -u\frac{\partial C}{\partial x} + f(x,t,C)$$

(in $n-$dimension)

$$\frac{\partial C}{\partial t} = -\nabla \cdot (\mathbf{u}C) + f(\mathbf{x},t,C)$$

Attraction-Repulsion

Φ represents a source of attraction/repulsion for solutes/particles/cells. An attractive/repulsive force would pull/push particles towards/forwards the sites of greatest attraction/repulsion:

- direction and magnitude of motion is determined by the gradient of Φ,
- α a scalar to characterize the sensitivity of solutes/particles/cells to the attraction($\alpha > 0$)/repulsion($\alpha < 0$)

$$J(x,t) = \alpha C(x,t)\frac{\partial \Phi}{\partial x}$$

So C evolves as follows

$$\frac{\partial C}{\partial t} = -\frac{\partial}{\partial x}\left[\alpha C(x,t)\frac{\partial \Phi}{\partial x}\right] + f(x,t,C)$$

(in $n-$dimension)

$$\frac{\partial C}{\partial t} = -\nabla \cdot (\alpha C \nabla \Phi) + f(\mathbf{x},t,C)$$

Boundary conditions

Boundary conditions reflect certain physical conditions of the experiment.

One-dimensional case:

- Dirichlet boundary condition: C(L,t)=f(t)
- Neumann boundary condition: $J(L,t) = g(t)$
- Robin condition: $J(L,t) = h(t) - aC(L,t)$

(L is a boundary point)

Diffusion equation

$$\begin{aligned} \frac{\partial C}{\partial t} &= D\frac{\partial^2 C}{\partial x^2}, \quad -\infty < x < \infty, \quad t > 0, \\ C(x,0) &= C_0\delta(x), \\ \lim_{x\to\pm\infty} C(x,t) &= 0, \end{aligned}$$

where C_0 is the total amount of material, and $\delta(x)$ is the Dirac delta function.
The solution is

$$C(x,t) = \frac{C_0}{\sqrt{4\pi Dt}} exp^{-\frac{x^2}{4Dt}}.$$

(normal density function with mean 0 and variance $2Dt$)

Drift-diffusion equation

$$\begin{aligned} \frac{\partial C}{\partial t} &= -u\frac{\partial C}{\partial x} + D\frac{\partial^2 C}{\partial x^2}, \quad -\infty < x < \infty, \quad t > 0, \\ C(x,0) &= C_0\delta(x - x_0), \\ \lim_{x\to\pm\infty} C(x,t) &= 0, \end{aligned}$$

The solution is

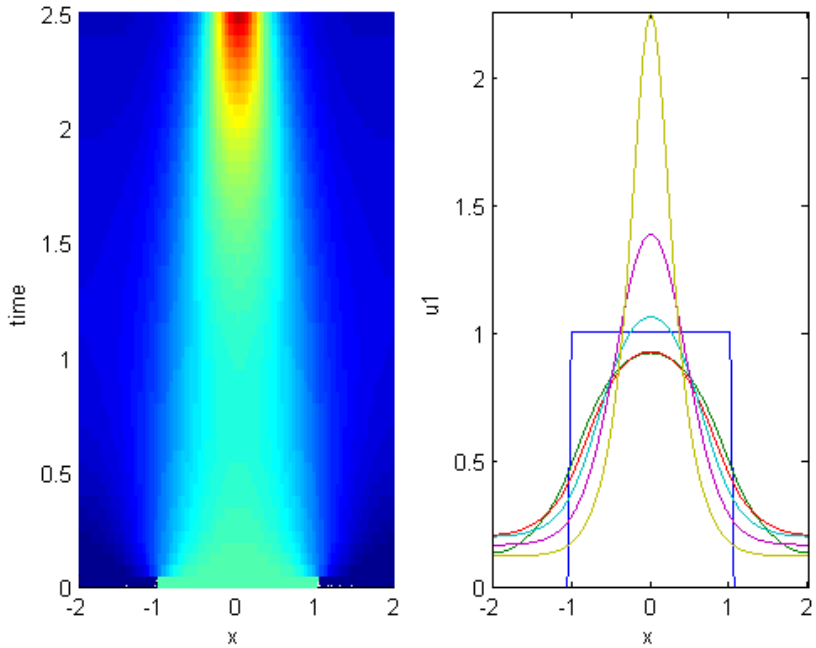
$$C(x,t) = \frac{C_0}{\sqrt{4\pi Dt}} exp^{-\frac{(x-x_0-ut)^2}{4Dt}}.$$

(normal density function with mean $x_0 + ut$ and variance $2Dt$)

Example: Chemotaxis

Keller-Segel model describes directed motion of cells stimulated by the chemical which they produce themselves.

$$\frac{\partial u}{\partial t} = -\nabla\left(-\mu\nabla u + \chi u \nabla v\right)$$
$$\frac{\partial v}{\partial t} = \nabla\left(D\nabla v\right) + fu - kv$$



Keller, E., Segel, L. (1970) J. Theor. Biol. 26:399-415.

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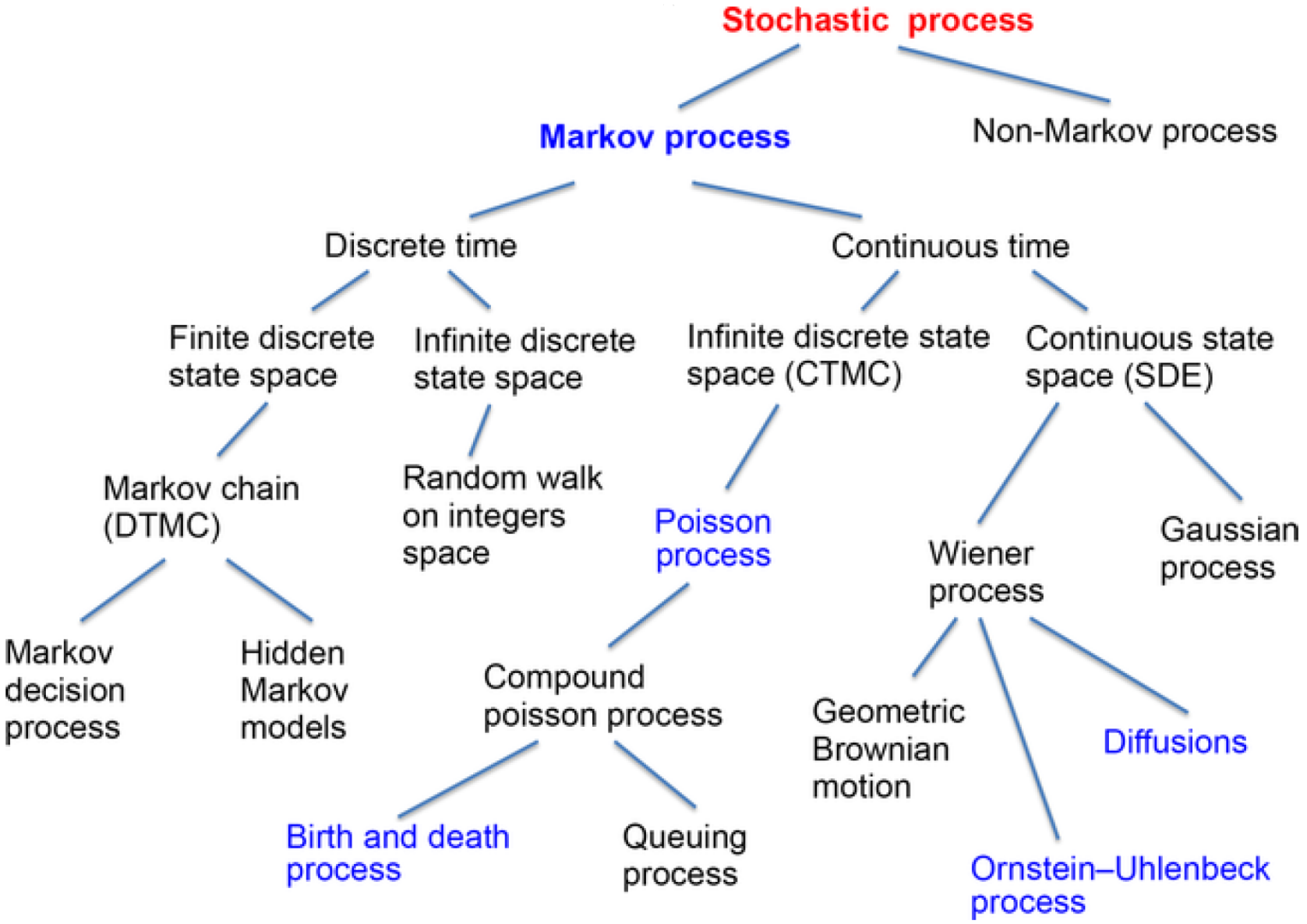
"The dynamics of real systems are often influenced by internal and external factors which are not completely understood and, therefore, cannot be described precisely. In order to understand such systems, **deterministic models** *(which explain broad overall behavior and growth patterns) are modified to incorporate complex variations in the mechanisms underlying the system. These variations, defined in terms of probabilities which evolve over time alongside the populations, result in new structures referred to as* **stochastic models***."*

Mubayi *et al. Handbook of Statistics*

Stochastic effects (variations)

- from differences among individuals (demographic stochasticity)
- from fluctuations in the environment (due to forces/mechanisms not described in the model), (environmental stochasticity)

Different types of stochastic processes



Mubayi *et al. Handbook of Statistics*

Stochastic differential equations

A SDE can be defined as a stochastic process $X_t = X(t)$ satisfying

$$dX_t = f(X_t, t)dt + g(X_t, t)dW_t$$

or

$$X_t = X_{t_0} + \int_{t_0}^{t} f(X_s, s)ds + \int_{t_0}^{t} g(X_s, s)dW_s$$

where

- $W_t = W(t)$ is the Wiener process (a Gaussian process with zero mean $E(W(t)) = 0$ and variance proportional to the elapsed time $Var(W(t)) = t$)
- $f(\cdot)$ the deterministic component
- $g(\cdot)$ the stochastic component
  - when $g(\dots)$ does not depend on $X_t \Rightarrow$ additive noise
  - when $g(\dots)$ depends on $X_t \Rightarrow$ multiplicative noise

SDE - Example

Stochastic logistic equation with multiplicative noise

$$dx_t = rx_t(1 - \frac{x_t}{k})dt + cx_t dw_t$$

Since a Wiener process is nondifferentiable, Ito's formula is often used to find the explicit solution of simple SDEs with a Wiener process.

When no explicit solution is available different characteristics of the process can be approximated by simulation, such as sample paths, moments, qualitative behavior..

Stochastic approach: Master Equation

Assume a system composed of N different types of molecules, and there exist M reactions.

- $\mathbf{X}(t) = [X_1(t), X_2(t), \ldots, X_N(t)]^T$ random variable
- $X_i(t)$ ($i \in \{1, \ldots, N\}$) the number of molecules of type i at time t
- $\mathbf{x} = [x_1, \ldots, x_N]^T$ state of system ($\mathbf{x} \in \mathbb{N}^N$)
- $p(\mathbf{x}, t) = Prob[\mathbf{X}(t) = \mathbf{x}]$ probability of the state $\mathbf{x}$ at time t

$$\frac{dp(\mathbf{x}, t)}{dt} = \sum_{j=1}^{M} [a_j(\mathbf{x} - \mathbf{v}_j)p(\mathbf{x} - \mathbf{v}_j, t) - a_j(\mathbf{x})p(\mathbf{x}, t)]$$

- $a_j(\mathbf{x})$ propensity function of j^{th} reaction at the state $\mathbf{x}$
- $\mathbf{v}_j$ j^{th} column of the stoichiometric matrix $\mathbf{v}$ (the reaction j will lead the system from the state $\mathbf{x}^i$ to the state $\mathbf{x}^i + \mathbf{v}_j$)

Propensity functions

- $a_j(\mathbf{x})\Delta t$ is the probability that reaction j will occur in $(t, t + \Delta t)$ when the system is at state $\mathbf{x}$
- $a_j(\mathbf{x})$ = rate of reaction j X number of reactant combinations available in the state $\mathbf{x}$ to allow reaction j

Chemical Master Equation $\rightarrow$ Forward Chapman Kolmogorov Equation

$P(t) = [p(\mathbf{x}^1, t), p(\mathbf{x}^2, t), \dots]^T$ vector whose the i^{th} entry is the probability of the i^{th} state $\mathbf{x}^i$ at time t

$$\frac{dP}{dt} = QP(t)$$

The solution is (if the number of states is finite)

$$P(t) = \exp(Qt)P(0)$$

A very simple chemical reaction: degradation

$$X \xrightarrow{k} \emptyset$$

- $X(t) = \#$ of molecule X at time $t =$ a discrete random variable
- Possible states: $\{0, 1, 2, \ldots, x_0\} \Rightarrow p(X = x, t | x_0, t_0)$?

Assumptions:

- At most 1 event occurs in $[t, t + \Delta t]$
- (Markov property) the state of the system at $t + \Delta t$ only depends on the state at time t
- Each one of the x molecules can degrade independently of the others with a probability $k\Delta t + O(\Delta t)^2$ in $[t, t + \Delta t]$
- Probability to have one degradation in $[t, t + \Delta t]$ is $k\Delta t x$ where x is the number of molecule at t
- Probability of no event in $[t, t + \Delta t]$ is $1 - k\Delta t x$ where x is the number of molecule at t

A very simple chemical reaction: degradation

$$X \xrightarrow{k} \emptyset$$

Deterministic approach: $X(t)$ concentration of molecule X at time t

$$\frac{dX}{dt} = -kX, \quad X(0) = x_0, \Rightarrow X(t) = x_0 \exp^{-kt}.$$

Stochastic approach: $X(t)$ number of molecule X at time t (random variable), $p(x, t|x_0, t_0) := Prob\{X(t) = x, given\, X(t_0) = x_0\}$

$$\frac{dp(x, t|x_0, t_0)}{dt} = k(x+1)p(x+1, t|x_0, t_0) - k(x)p(x, t|x_0, t_0).$$

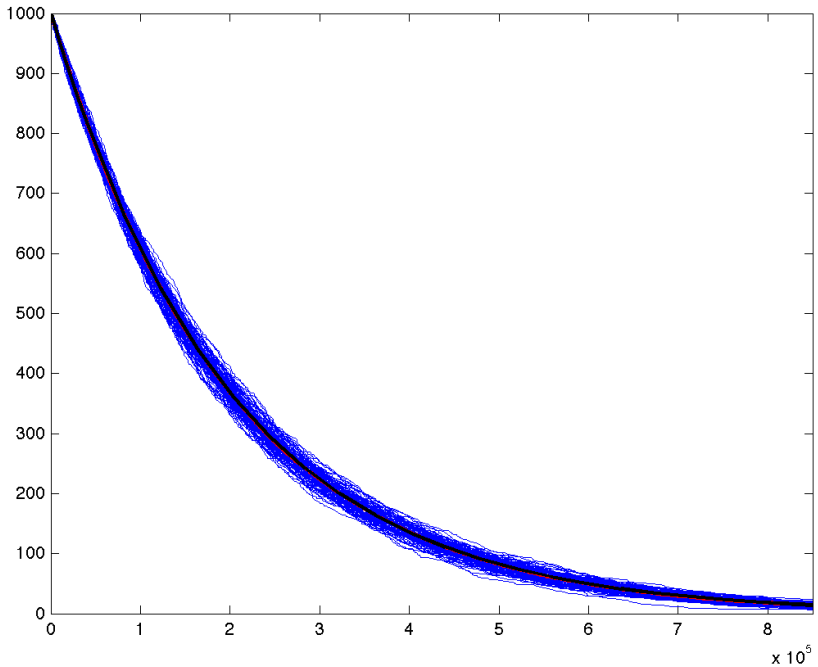
The solution is (Binomial probability density function)

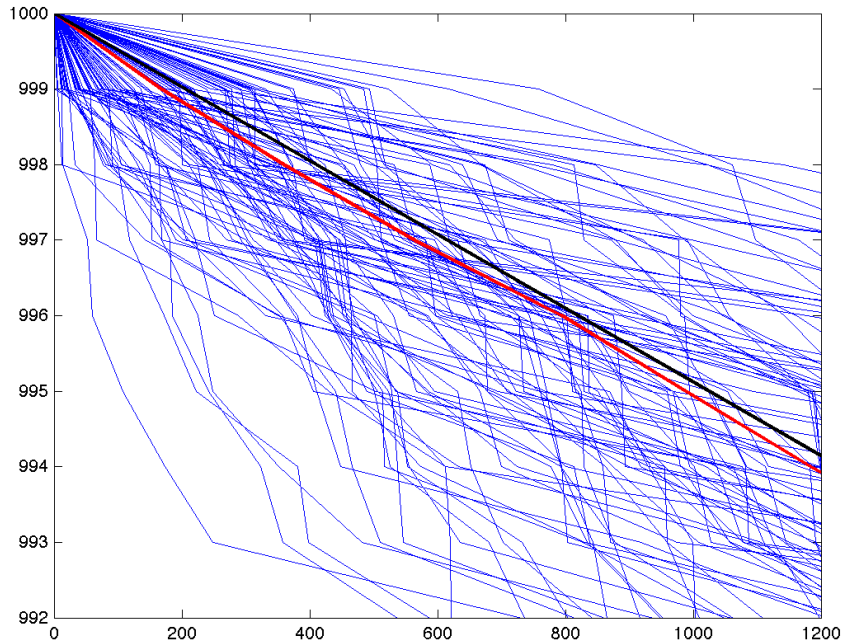
$$p(x, t|x_0, 0) = \frac{x_0!}{x!(x_0 - x)!} \exp^{-kxt}(1 - \exp^{-kt})^{x_0 - x}, \quad (x = 0, \ldots, x_0)$$

$$E(X) = x_0 \exp^{-kt}, \quad Var(X) = x_0 \exp^{-kt}(1 - \exp^{-kt})$$

$$X \xrightarrow{k} \emptyset$$

Simulations done with Gillespie's algorithm

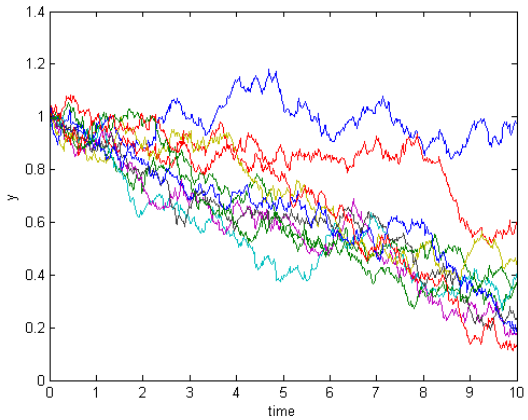


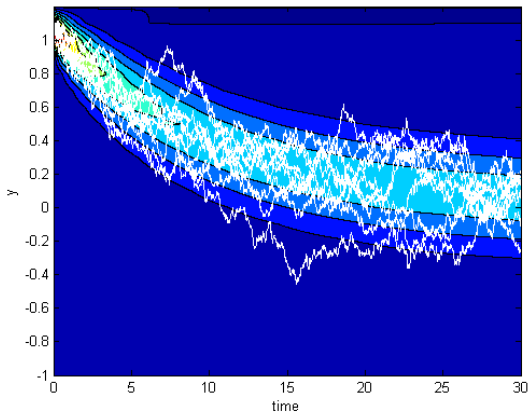


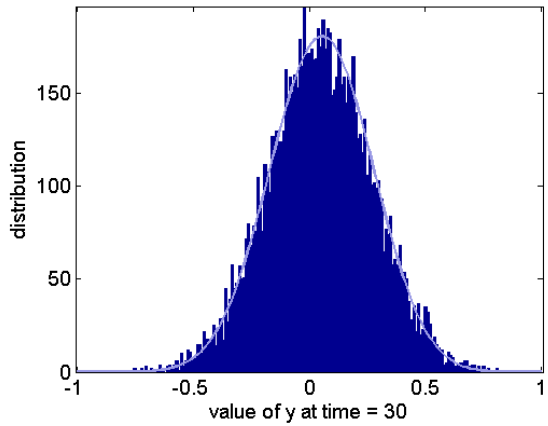
blue = realization, red = mean of realizations, black = ODE solution

Individual vs Population

Langevin equation: (stochastic equation of motion for the time evolution of y) motion of a particle in a viscous medium subject to friction and noise (white Gaussian noise).
Fokker-Planck equation: equation of motion for the time dependent probability distribution $p(y, t)$.







Deterministic vs Stochastic

- Deterministic model output is fully determined by the parameter values and the initial conditions
  - deterministic models capture the mean behavior of a system
- Stochastic models possess some inherent randomness. The same set of parameter values and initial conditions will lead to an ensemble of different outputs
  - stochastic models capture the ways that a system's behavior may deviate (variability) from the mean
  - small populations
  - when addressing questions related to variations in population

Once the model is written

Mathematical analysis: identify the type of mathematical techniques and theories required for the analysis of the model.. and characterize the behavior of the model

Numerical experiment: conduct numerical simulations of the model..

Model calibration: identify and estimate the values of parameters..

Sensitivity analysis: understand the effect of model inputs (parameters or initial conditions) on model outputs.. which parameter is the key driver of the model responses

Validation: model must represent accurately the real process, it must reproduce known states of the real process.. if several models are considered, model selection has to be used.