

Modeling and Simulation in Computational Biology 2

BCB 5250 Introduction to Bioinformatics II

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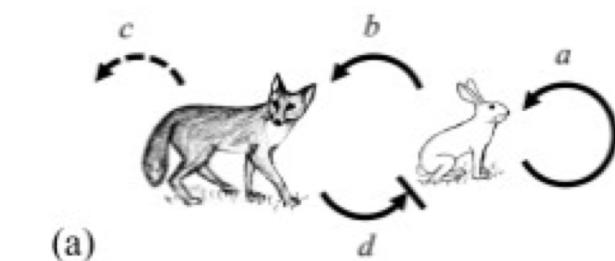
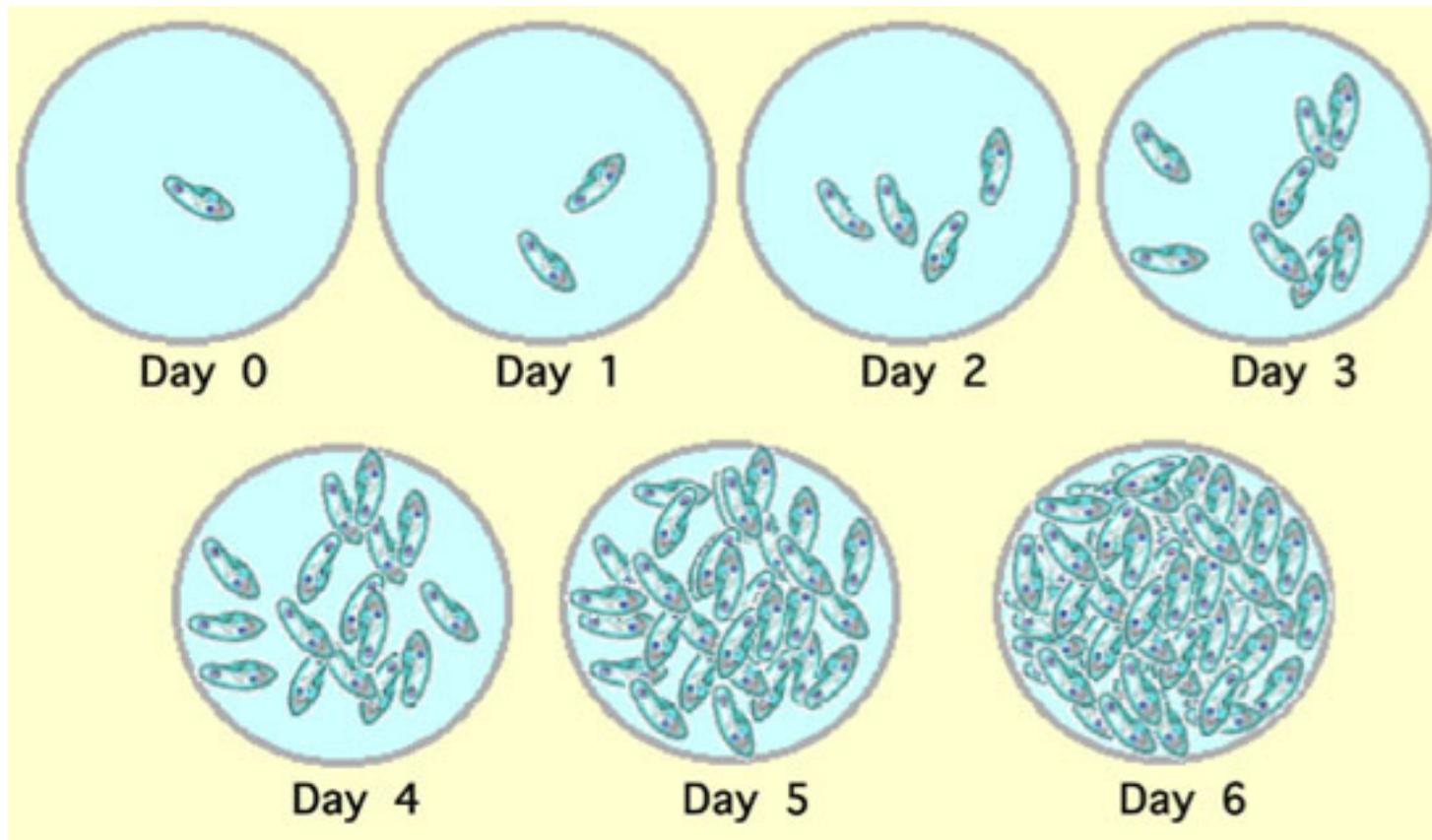


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— EST. 1818 —

Modeling Population Growth

What are the underlying principles of how populations change over time? Two basic principles are involved, **the idea of exponential growth and its ultimate control.**

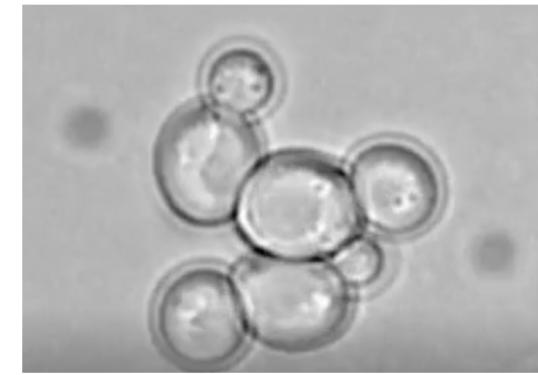
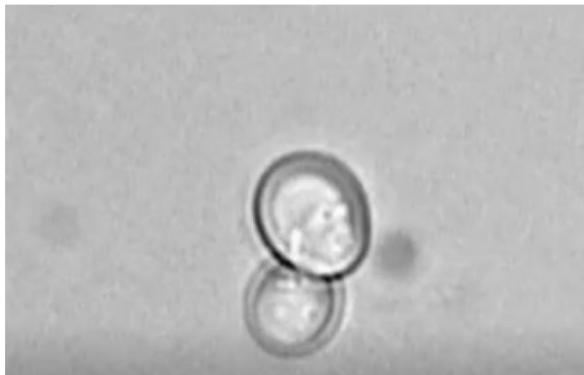


<https://www.nature.com/scitable/knowledge/library/how-populations-grow-the-exponential-and-logistic-13240157>

<https://www.sciencedirect.com/topics/mathematics/lotka-volterra-model>

Yeast Doubling Time

- Yeast are easy to grow and yeast plasmids and strains are commercially available.
- In biology, growth curves represent the change in cell population over a period of time. In yeast, the growth curve is generated by plotting the optical density, or "OD", of cell culture at 600 nm in the y axis and time on the x axis.



- Wild type **yeast** should give a **doubling time** value of approximately 90 minutes

Mathematical Modeling: From Your Note to Equations

Observed

Start with one yeast

After 90 min: 2

After 91 min: 4

After 89 min: 8

After 90 min: 16

So, I hypothesis the
doubling-time is 90 min

Equations

t = time in minutes

$X(t)$ = yeast population size of t minutes

$X(0) = 1, X(t + 90) = 2 X(t)$

$X(t + 90) - X(t) = X(t)$

$X(t + 45) - X(t) = 0.5 X(t)$

...

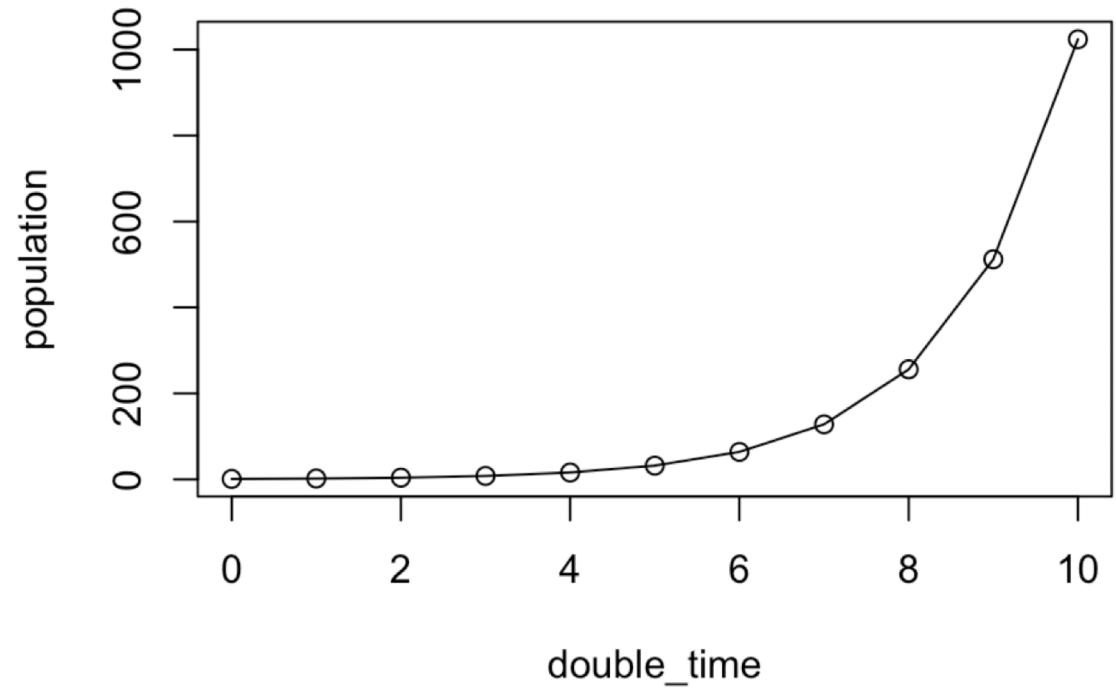
$X(t + 1) - X(t) = 0.011 X(t)$

When it goes to 1024?

- You can use R or any scientific calculator

```
double_time <- seq(0,10,1)
rate <- 1
population<- 1*2^(rate*double_time)
plot(double_time, population)
lines(double_time, population)
```

- $10 \times \text{double_time}$ (90 min) = 15 hours



Malthus Model

Thomas Robert Malthus

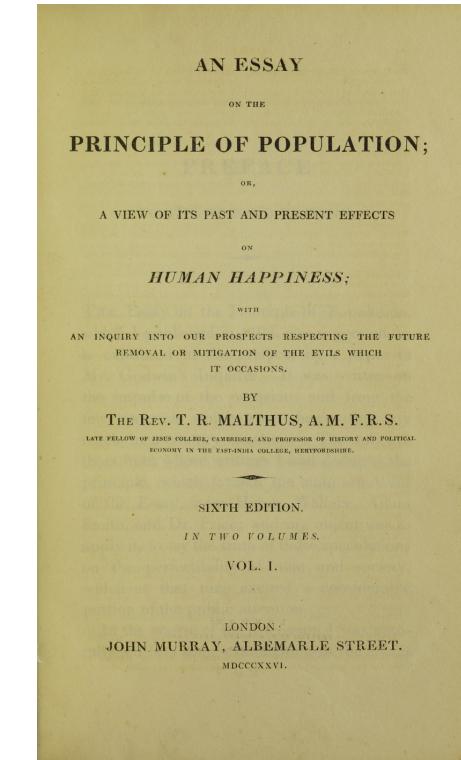


“Population, when unchecked,
increases in a geometrical ratio”

(Thomas Robert Malthus, 1798)

A Malthusian growth model, sometimes called a **simple exponential** growth model, is essentially exponential growth based on the idea of the function being proportional to the speed to which the function grows. The model is named after Thomas Robert Malthus, who wrote An Essay on the Principle of Population (1798), one of the earliest and most influential books on population.

https://en.wikipedia.org/wiki/Malthusian_growth_model



Population Dynamics

- Let $x(t)$ = population at time t
- Let r = rate constant for growth
- Assumption: No death
- Observe bacterial cell density at times t and $(t+dt)$. Then

$$x(t+dt) \approx x(t) + r x(t) dt$$

Total density
at time $t+dt$

=

Total density at time t + increase in density
due to reproduction during time interval dt

- Rewrite:

$$\frac{x(t + dt) - x(t)}{dt} \approx r x(t)$$

Population Dynamics

- The model:

$$\frac{dx}{dt} = r x$$

- Analytic solution possible here.

$$x = x_0 e^{rt}$$

Ordinary Differential Equations (ODEs)

- Mathematical equations used to **study time dependent phenomena**
- A “**differential equation**” of a function = an algebraic equation involving the *function and its derivatives*
- A “**derivative**” is a function representing the *change* of a dependent variable with respect to an independent variable. (Often thought of as representing a slope.)
- Example:

$$\frac{dX}{dt} = 5x$$

$$x(2) = 1$$

Malthus Population Dynamics

$b(t)$ **BIRTH RATE**

$d(t)$ **DEATH RATE**

$r(t)$ **GROWTH RATE**

**Malthus
ASSUMED
CONSTANT
RATES**

$b(t) \equiv b_0$

$d(t) \equiv d_0$

$r(t) \equiv r_0 = (b_0 - d_0)$

$$\frac{d}{dt} p(t) = r_0 p(t)$$

$$p(t) = e^{r_0 t} p_0$$

DO AN EXPERIMENT

$$p(0) = p_0 = 10$$

$$p(1) = 10e^{r_0 1} = 25$$

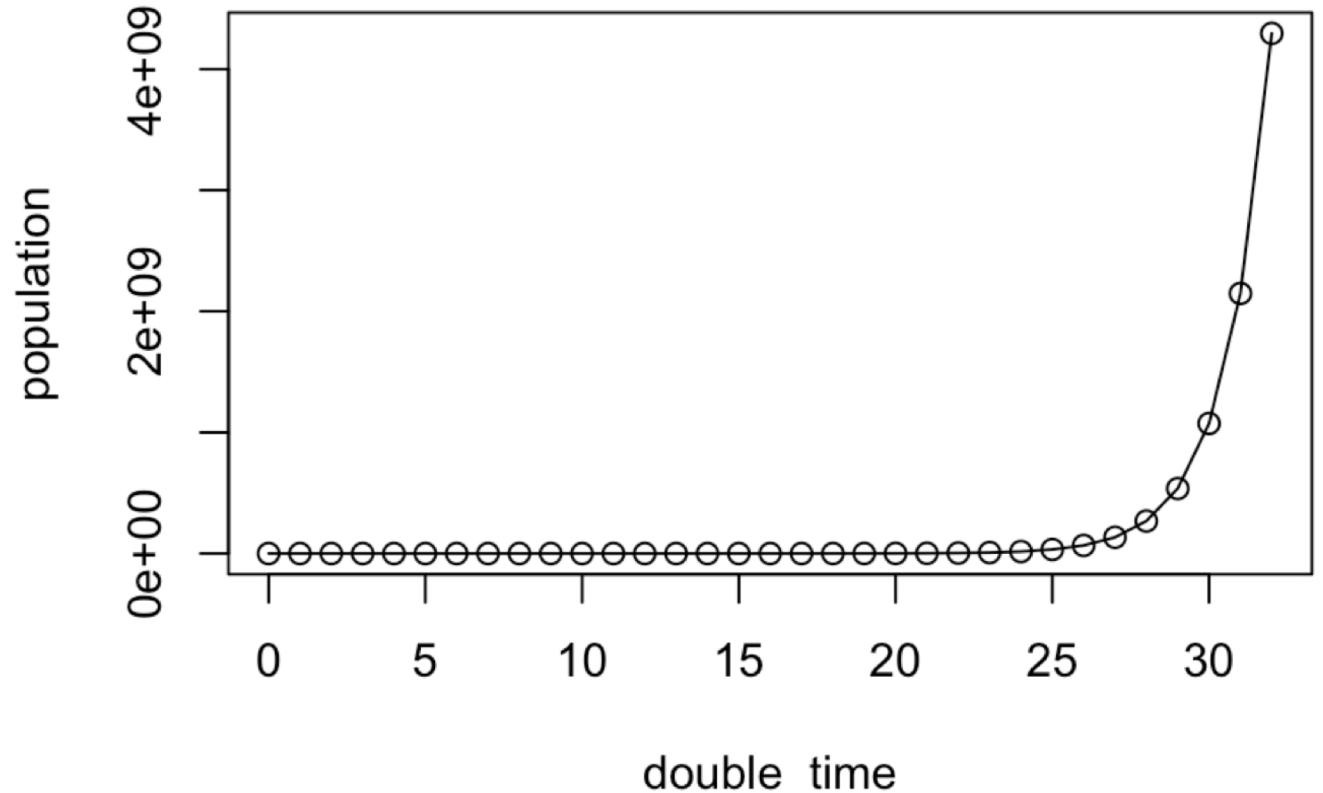
$$e^{r_0} = \frac{25}{10} = 2.5$$

$$r_0 = \ln e^{r_0} = \ln(2.5)$$

$$r_0 \cong 0.9163$$

Realistic?

- After 1 day: 65536
- After 2 days: 4294967296
- After 5 days: ???????



Logistic Population Model

- Developed by Belgian mathematician Pierre Verhulst (1838) in 1838
- The rate of population increase may be limited, i.e., it may depend on population density

COMPETITION FOR FOOD AND SPACE

$$b(t) \equiv b_0 - b_1 p(t), \quad d(t) \equiv d_0 + d_1 p(t)$$

$$r(t) \equiv b(t) - d(t) = (b_0 - d_0) - (b_1 + d_1)p(t)$$

$$r(t) \equiv r_0 \left(1 - \frac{(b_1 + d_1)}{r_0} p(t) \right) \stackrel{\Delta}{=} r_0 \left(1 - \frac{1}{K} p(t) \right)$$

Malthus vs Logistic Population Model

Malthus

$$\frac{dx}{dt} = r x$$

Logistic

$$\frac{dx}{dt} = r \left(1 - \frac{x}{K}\right) x$$

Let $x(t)$ = population at time t

Let r = rate constant for growth

Let K = carrying capacity

Malthus vs Logistic Population Model

Malthus

$$\frac{dx}{dt} = r x$$

$$x = x_0 e^{rt}$$

Logistic

$$\frac{dx}{dt} = r \left(1 - \frac{x}{K}\right) x$$

$$x = \frac{K}{1 + \left(\frac{K}{x_0} - 1\right)e^{-rt}}$$

Let $x(t)$ = population at time t

Let r = rate constant for growth

Let K = carrying capacity

Malthus vs Logistic Population Model

Malthus

$\frac{d}{dt} p(t) = r_0 p(t)$ where $p(0) = 10$ and $p(1) = 25$.

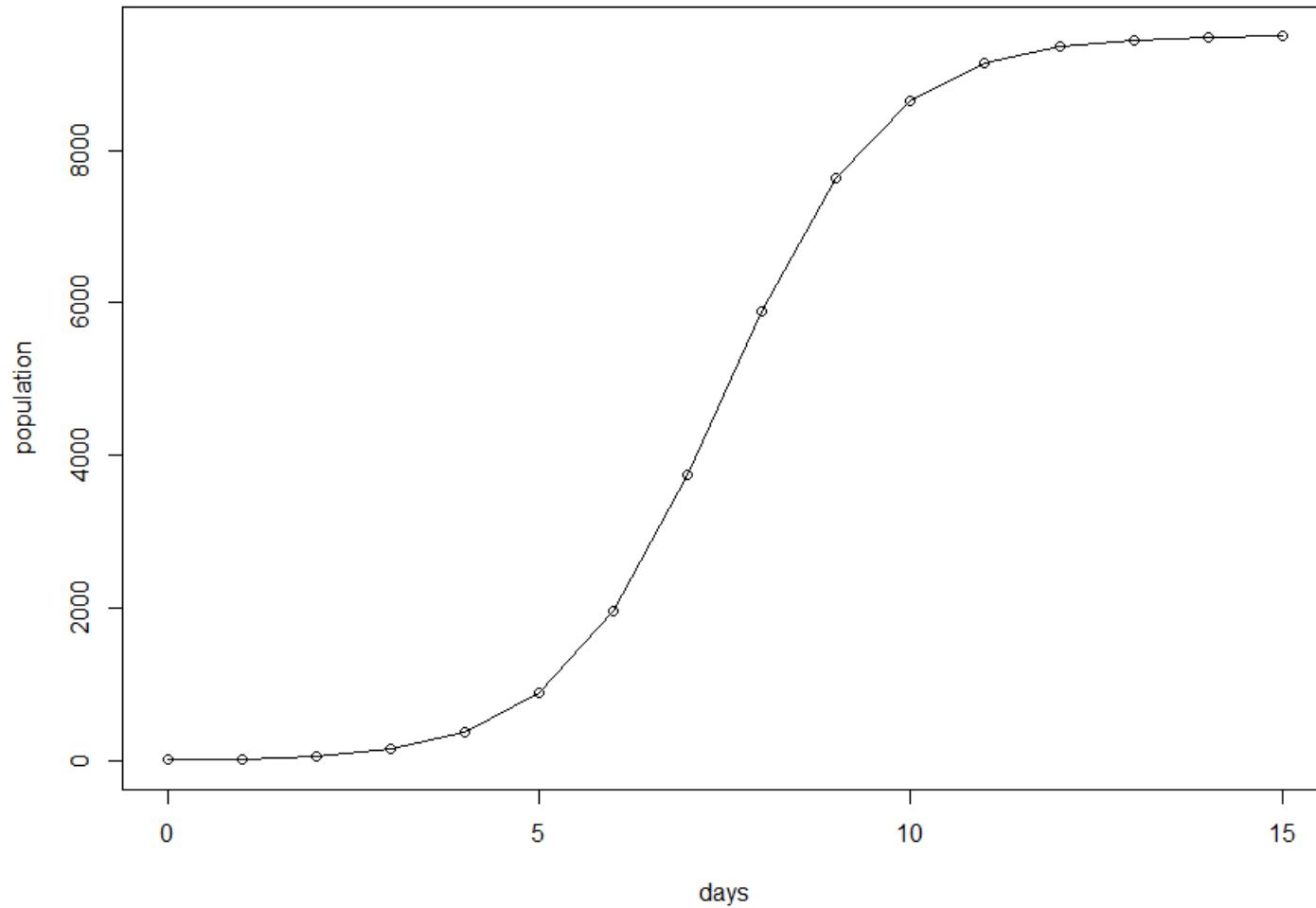
Then, $p(t) = 10e^{r_0 t}$ with $r_0 = 0.9163$.

Logistic

$\frac{d}{dt} p(t) = r_0 \left(1 - \frac{1}{K} p(t)\right) p(t)$ where $p(0) = 10$, $p(1) = 25$, and $K = 9500$.

Then, $p(t) = \frac{K}{\frac{K}{10.01054} e^{-r_0 t} + 1}$ with $r_0 = 0.9178723$.

Logistic Population Model



Population Model

- **Malthus Population Model**

$$\frac{d}{dt} p(t) = r_0 p(t)$$

- **Logistic Population Model**

$$\frac{d}{dt} p(t) = r_0 \left(1 - \frac{1}{K} p(t)\right) p(t)$$

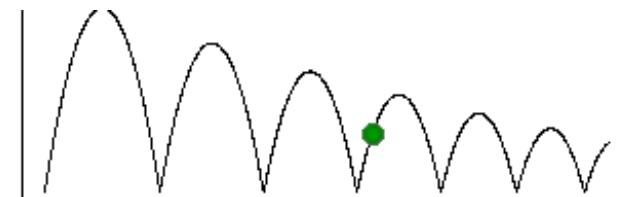
- Question: Is this a **discrete** form or **continuous** form?
- **Discrete Dynamical Systems to Continuous Dynamical Systems”?**

Numerical Simulation

- Why numerical solutions?
 - Not all systems have an analytical solution.
 - Not all analytical solutions can be derived.

Numerical solution is required.

Continuous Numerical Solution



deSolve - Differential Equations in R

'deSolve' is an add-on package for the open source data analysis system **R** for the numerical treatment of systems of differential equations

What is in deSolve?

deSolve contains functions that solve initial value problems of a system of first-order ordinary differential equations (ODE), of partial differential equations (PDE), of differential algebraic equations (DAE), and of delay differential equations (DDE). The functions provide an interface to the FORTRAN functions lsoda, lsodar, lsode, lsodes of the ODEPACK collection, to the FORTRAN functions dvode, zvode, daspk and radau5, and a C-implementation of solvers of the Runge-Kutta family with fixed or variable time steps.

The package contains also routines designed for solving ODEs resulting from 1-D, 2-D and 3-D partial differential equations (PDE) that have been converted to ODEs by numerical differencing.

Project web pages

- The package at CRAN
- The project [summary page](#) at R-Forge.
- [Download](#)

Continuous Plot

Logistic Population Model

$$\frac{d}{dt} p(t) = r_0 \left(1 - \frac{1}{K} p(t)\right) p(t) \text{ where } p(0) = 10, p(1) = 25, \text{ and } K = 9500.$$

Then, $p(t) = \frac{K}{\frac{K}{10.01054} e^{-r_0 t} + 1}$ with $r_0 = 0.9178723$.

R program

```
library(deSolve)

LogisticPopulation <- function (Time, State, Params) {
  with(as.list(c(State, Params)), {
    dx <- r*x*(1-(1/K)*x)
    return(list(c(dx)))
  })
}

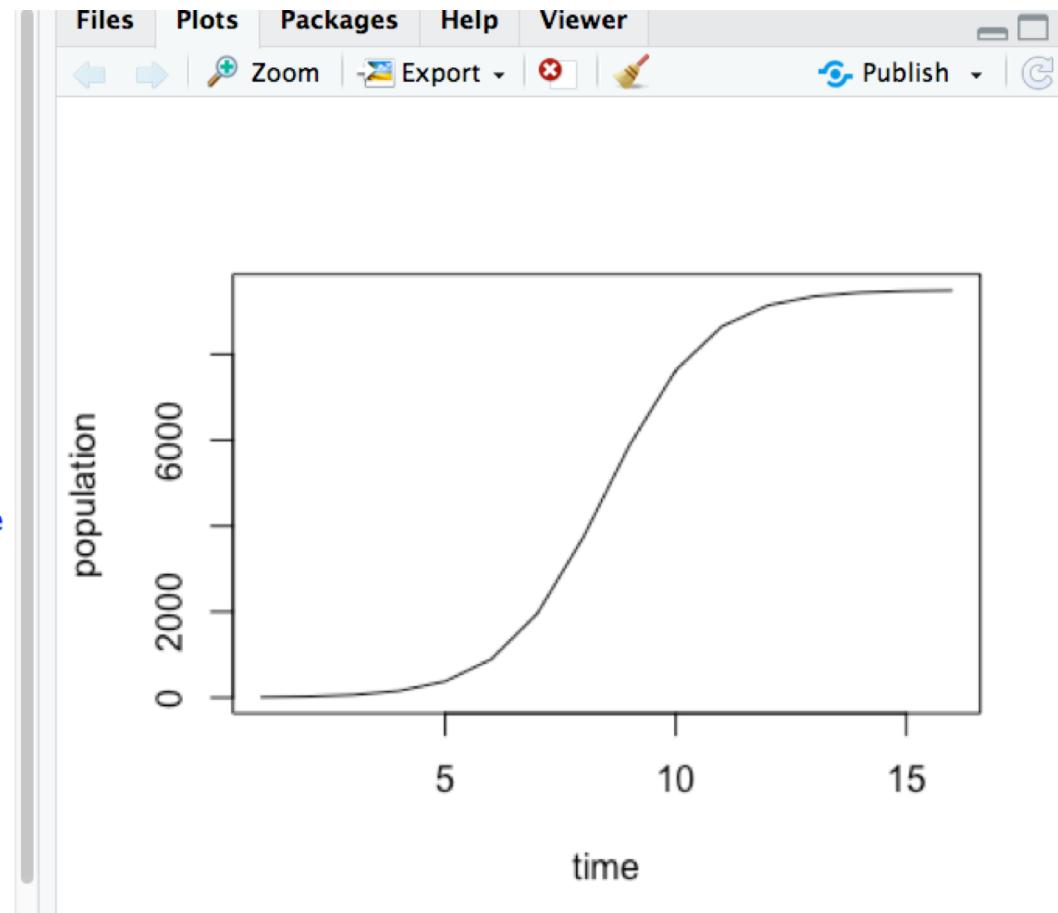
Params <- c(K=9500, r=0.9178723)
State <- c(x = 10)
Time <- seq(0, 15, by = 1)

out <- as.data.frame(ode(func = LogisticPopulation, y = State, parms = Params, times = Time))

matplot(out[,-1], type = "l", xlab = "time", ylab = "population")
```

Continuous Plot

```
> library(deSolve)
>
> LogisticPopulation <- function (Time, State, Params) {
+   with(as.list(c(State, Params)), {
+     dx <- r*x*(1-(1/K)*x)
+     return(list(c(dx)))
+   })
+ }
>
> Params <- c(K=9500,r=0.9178723)
> State <- c(x = 10)
> Time <- seq(0, 15, by = 1)
>
> out <- as.data.frame(ode(func = LogisticPopulation, y = State, parms = Params, times = Time
))
>
> matplot(out[,-1], type = "l", xlab = "time", ylab = "population")
>
>
>
>
>
>
```

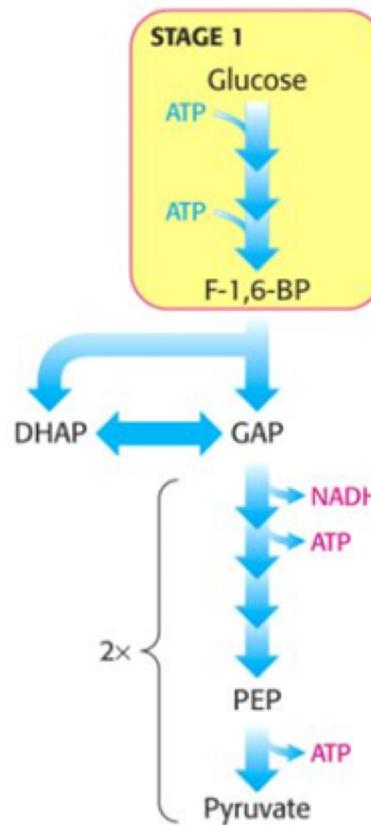


Now, it's time for Model Development

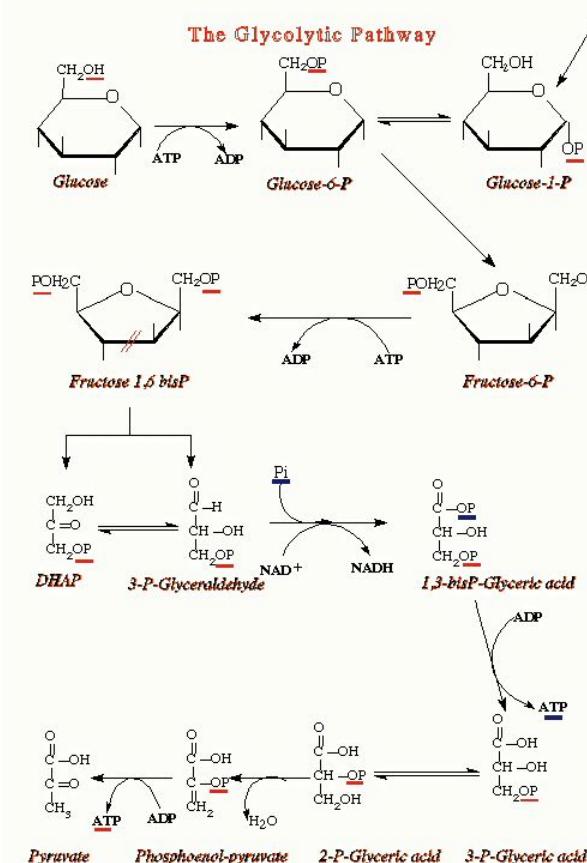
- The modeler must choose an appropriate level of abstraction

Glycolysis: Metabolic pathway that convert glucose into pyruvate

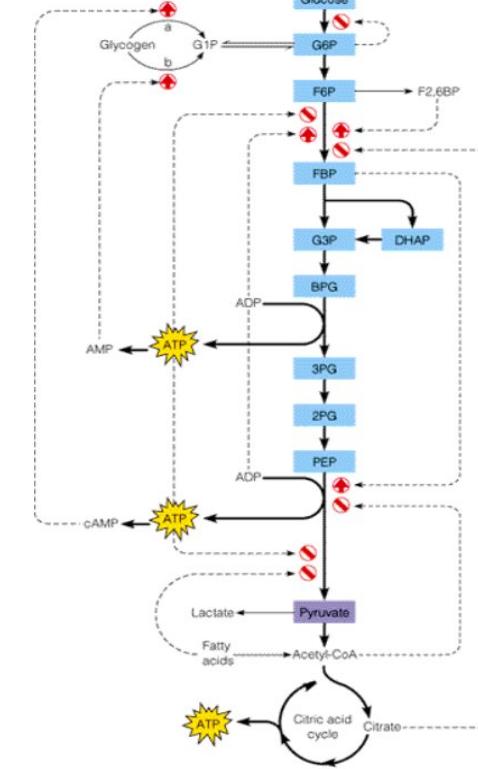
Flow of metabolites



Chemistry

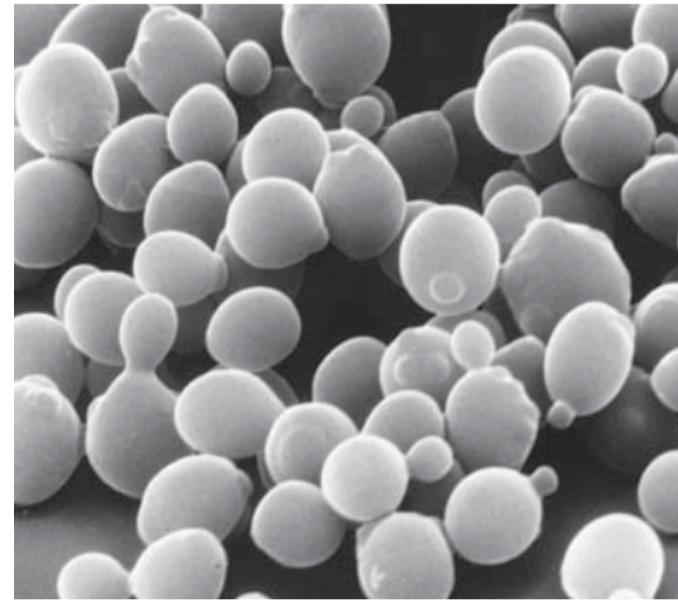


Regulation



Units

- Budding yeast cell
 - Cell diameter: 4~6 μm
 - Cell volume: $42 \pm 2 \mu\text{m}^3$
 - Cell mass: 60 pg (pico = 10^{-12})
- ODE model is based on “concentration”
- Molar concentration
 - The molar concentration c_i is defined as the amount of a constituent n_i (in moles) divided by the volume of the mixture V :
 - $$c_i = \frac{n_i}{V}$$
 - The SI unit is mol/m³. However, more commonly the unit mol/L (= mol/dm³) is used.



10 μm

Units

Name	Abbreviation	Concentration	Concentration (SI unit)
millimolar	mM	10^{-3} mol/dm ³	10^0 mol/m ³
micromolar	μ M	10^{-6} mol/dm ³	10^{-3} mol/m ³
nanomolar	nM	10^{-9} mol/dm ³	10^{-6} mol/m ³
picomolar	pM	10^{-12} mol/dm ³	10^{-9} mol/m ³
femtomolar	fM	10^{-15} mol/dm ³	10^{-12} mol/m ³
attomolar	aM	10^{-18} mol/dm ³	10^{-15} mol/m ³
zeptomolar	zM	10^{-21} mol/dm ³	10^{-18} mol/m ³
yoctomolar	yM ^[3]	10^{-24} mol/dm ³ (1 particle per 1.6 L)	10^{-21} mol/m ³

https://en.wikipedia.org/wiki/Molar_concentration

Mass Action Kinetic

- Mass action kinetics is a kinetic scheme for chemical reaction networks which says that the rate of a chemical reaction is proportional to the product of the concentrations of the reacting chemical species.
- Deterministic modeling

For example,



Let $[A]$ and $[B]$ denote the concentration of A and B respectively.

Then the reaction occurs at a rate proportion to $[A][B]$.

That is to say, we have [rate of reaction] = $k[A][B]$.

k is the proportional rate (or rate constant).

Mass Action Kinetic

- Deterministic modeling

For example,



Since each instance of the reaction produces a net decrease of one molecule of A and B each, and an increase of one molecule of C , we can model the reaction as

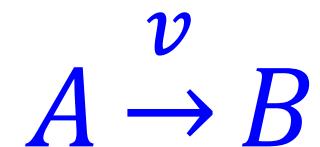
$$\frac{d[A]}{dt} = -k[A][B]$$

$$\frac{d[B]}{dt} = -k[A][B]$$

$$\frac{d[C]}{dt} = k[A][B]$$

Simple Chemical Reaction

- Irreversible Isomerization



Qualitative description: the rate ν of the reaction $A \rightarrow B$ increases as the concentration of A increases

A quantitative description: mass action

$$\nu = k[A]$$

$$\frac{d[A]}{dt} = -k[A]$$

mass action

$$\frac{d[B]}{dt} = k[A]$$

Irreversible Isomerization

- This quantitative description of the reaction rate can be used to characterize the rates of change of the chemical species in the network:

$$\frac{d}{dt}[A](t) = -k_1[A](t)$$

$$\frac{d}{dt}[B](t) = k_1[A](t)$$

$\underbrace{\qquad}_{\uparrow}$ $\underbrace{\qquad}_{\uparrow}$

rate of change of
concentration

+/- rate of reaction

Numerical Simulation

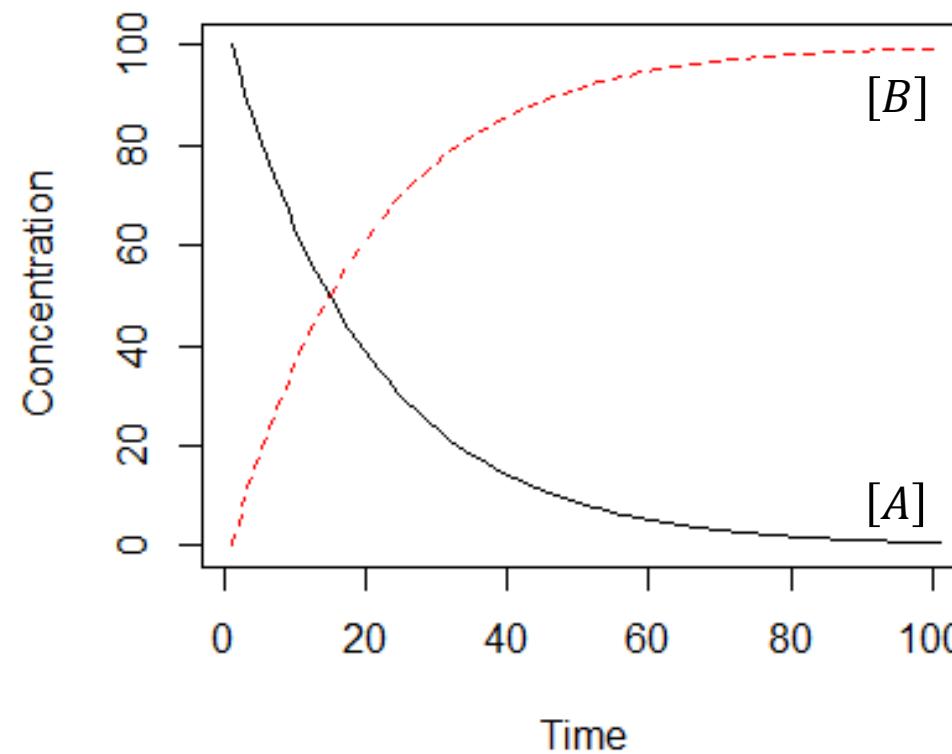
- Irreversible Isomerization

$$\frac{d[A]}{dt} = -k[A]$$

$$\frac{d[B]}{dt} = k[A]$$

where $[A](0) = 100$,

$[B](0) = 0$, and $k = 0.05$



Numerical Simulation

- Irreversible Isomerization (IrreversibleIsomerization.r)

$$\frac{d[A]}{dt} = -k[A]$$

$$\frac{d[B]}{dt} = k[A]$$

where $[A](0) = 100$,

$[B](0) = 0$, and $k = 0.05$

```
library(deSolve)

IrreversibleIsomerization <- function (Time,
State, Params) {
  with(as.list(c(State, Params)), {
    dA <- -k1*A
    dB <- k1*A
    return(list(c(dA,dB)))
  })
}

Params <- c(k1=0.05)
State <- c(A = 100, B = 0)
Time <- seq(0, 100, by = 1)

out <- as.data.frame(ode(func =
IrreversibleIsomerization, y = State, parms =
Params, times = Time))

matplot(out[,-1], type = "l", xlab = "Time",
ylab = "Concentration")
```

Simple Term

To simplify, let's just use rate constant and concentration in the reaction

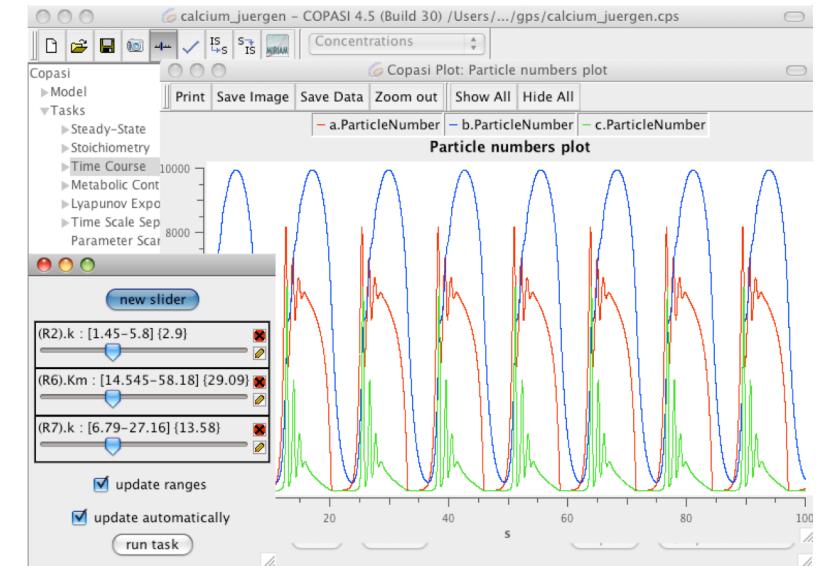
$$\frac{dA}{dt} = -kAB$$

not

$$\frac{d[A](t)}{dt} = -k[A](t)[B](t)$$

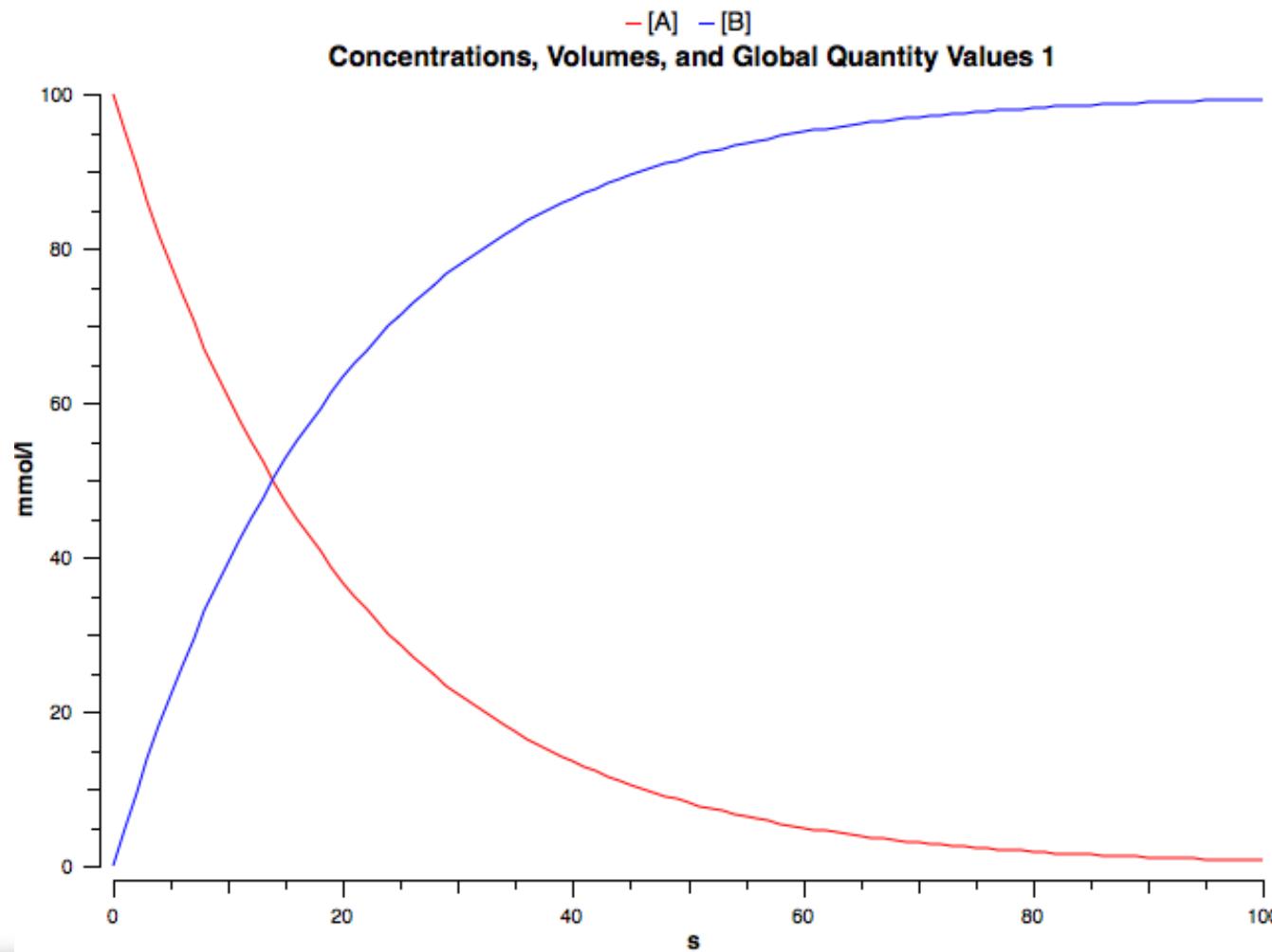
COPASI

- <http://copasi.org/>
- Models in **COPASI** are **based on reactions** that convert a set of *species* into another set of *species*.
- Each *species* is located in a **compartment**, which is a physical location with a size (volume, area, etc).
- COPASI **automatically converts** the reaction network to a set of differential equations or to a system of stochastic reaction events.
- COPASI can import and export models in the **SBML** format.



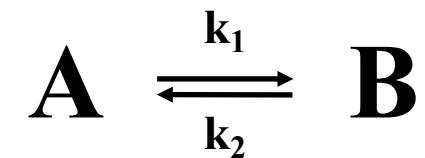
COPASI Lab

- Run COPASI and get the plot as below:



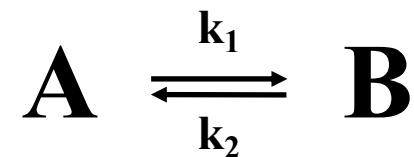
Reversible Isomerization

- Reversible Isomerization



Reversible Isomerization

- Reversible Isomerization



$$\frac{dA}{dt} = -k_1 A + k_2 B$$

$$\frac{dB}{dt} = k_1 A - k_2 B$$

Reversible Isomerization

- Reversible Isomerization

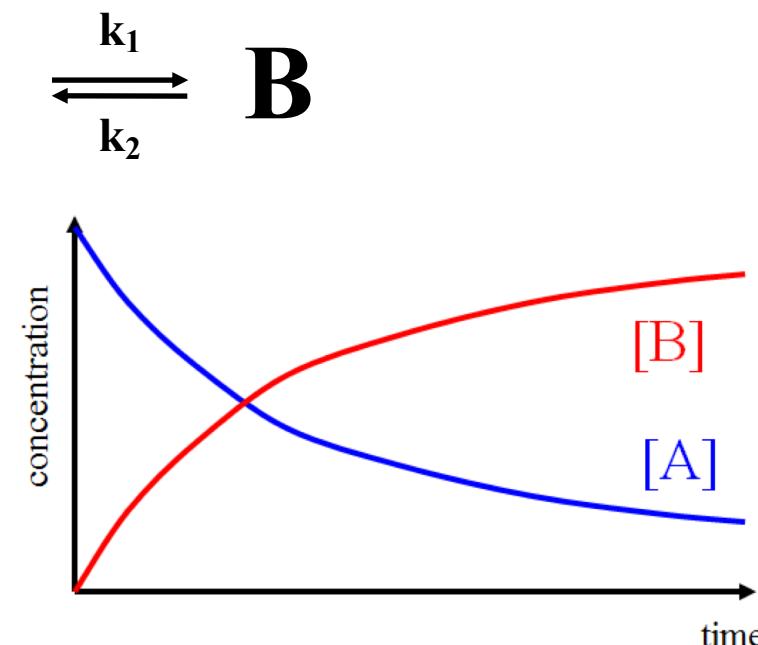
$$\frac{dA}{dt} = -k_1 A + k_2 B$$

$$\frac{dB}{dt} = k_1 A - k_2 B$$

Steady state → Derivate should be 0

$$0 = -k_1 A + k_2 B$$

$$0 = k_1 A - k_2 B$$



Steady state (equilibrium ratio):

$$\frac{B}{A} = \frac{k_1}{k_2}$$

Biochemical Reactions

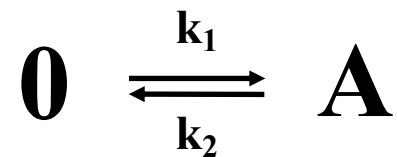
- Foundation: **Law of Mass Action**

Rate of a reaction is proportional to the product of the concentrations of the reactants

- Key assumptions:
 - Well mixed environment (no spatial effects)
 - Large numbers of molecules (continuum of concentrations)

Biochemical Reactions

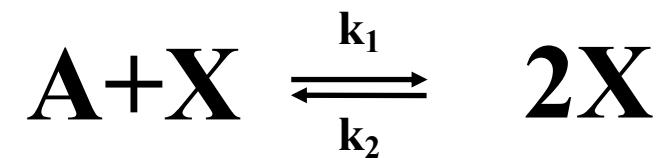
- Creation and degradation of a molecule



$$\frac{dA}{dt} = k_1 - k_2 A$$

Biochemical Reactions

- Autocatalysis



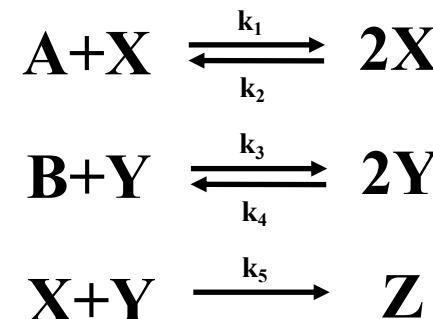
$$\frac{dX}{dt} = k_1 AX - k_2 X^2$$

In this case, we assume that there is a surplus of molecule A resulting in that its concentration can be assumed to be constant.

$$\frac{dX}{dt} = KX - k_2 X^2 = X(K - k_2 X)$$

Biochemical Reactions

- Two autocatalysing molecules that forms a complex



In this case, we assume that there is a surplus of molecule A and B resulting in that their concentrations being constant.

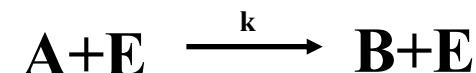
$$\frac{dX}{dt} = k_1AX - k_2X^2 - k_5XY$$

$$\frac{dY}{dt} = k_3BY - k_4Y^2 - k_5XY$$

$$\frac{dZ}{dt} = k_5XY$$

Enzyme Kinetic

- Many reactions have a far too high activation energy to ever occur spontaneously.
- A common type of reaction is an enzyme reaction, where a helper molecule (the enzyme)
- Facilitate a reaction to occur. The enzyme is not used up in the reaction itself.



$$\frac{dA}{dt} = -\frac{dB}{dt} = -kAE, \quad \frac{dE}{dt} = 0$$

Enzyme Kinetic

- Michaelis-Menten kinetics



$$\frac{d[S]}{dt} = -k_1[S][E] + k_2[SE]$$

$$\frac{d[E]}{dt} = -k_1[S][E] + k_2[SE] + k_3[SE]$$

$$\frac{d[SE]}{dt} = k_1[S][E] - k_2[SE] - k_3[SE]$$

$$\frac{d[P]}{dt} = k_3[SE]$$

Enzyme Kinetic

- Michaelis-Menten kinetics



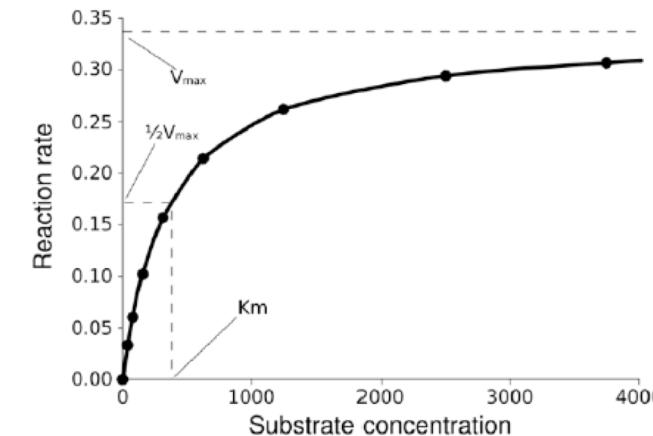
Equilibrium approximation

- The first reaction is assumed to be fast (and in equilibrium) and we assume that $k_1[S][E]=k_2[SE]$.
- If we also assume a constant amount of total enzyme, $[E] + [SE] = E_0$, the complex concentration can be written as a function of the substrate concentration.

$$k_2[SE] = k_1[S](E_0 - [SE])$$

$$[SE] = \frac{E_0[S]}{(K_m + [S])} \text{ where } K_m = \frac{k_2}{k_1}$$

$$\text{Finally, } v = \frac{d[P]}{dt} = \frac{V_{max}[S]}{(K_m + [S])} \text{ where } V_{max} = k_3 E_0$$



Quasi-steady-state approximation

assumed that the concentration of the intermediate complex does not change on the time-scale of product formation

Chemical Kinetics

- Kinetics is the study of the rates of chemical reactions.

For example,



Since each instance of the reaction produces a net decrease of one molecule of A and B each, and an increase of one molecule of C , we can model the reaction as

$$\frac{d[A]}{dt} = -k[A][B]$$

$$\frac{d[B]}{dt} = -k[A][B]$$

$$\frac{d[C]}{dt} = k[A][B]$$

with reaction rate constant k .

Chemical Kinetics

- Reaction rate: the change in concentration of a substance divided by the time interval during which this change is observed

$$rate = \frac{\Delta \text{concentration}}{\Delta \text{time}}$$

For a reaction $A + B \rightarrow C$, the rate

$$rate = -\frac{\Delta[A]}{\Delta t} = -\frac{\Delta[B]}{\Delta t} = \frac{\Delta[C]}{\Delta t}$$

Consider $A + 3B \rightarrow 2D$

Consider $4A + 3B \rightarrow 2C + 6D$

Chemical Kinetics

For a reaction $aA + bB \rightarrow cC$, the general rate law is expressed as:

$$\text{rate} = k[A]^a[B]^b$$

Here k is reaction rate constant. This can be noted as $k(T)$ as it depends on temperature.

[A] and [B] are the molar concentrations of substances A and B in moles per unit of volume. Simply 1 molar = 1 M = 1 mole/litre

Reaction Order (Order of Reaction) = $a + b$

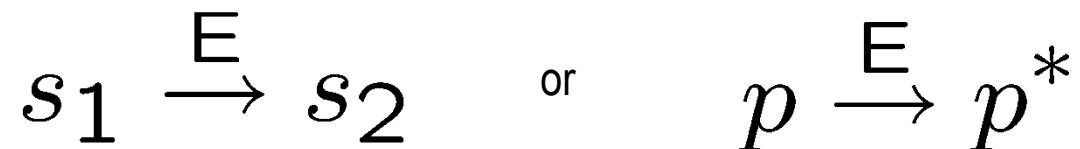
Reaction Order

The next few slides illustrate different type of reactions.

	Zero-Order	First-Order	Second-Order
Rate Law	Rate= k	Rate= k[A]	Rate= $k[A]^2$
Integrated Rate Law	$[A]_t = -kt + [A]_0$	$\ln[A]_t = -kt + \ln[A]_0$	$\frac{1}{[A]_t} = -kt + \frac{1}{[A]_0}$
Units of Rate Constant (k):	$\text{mol L}^{-1} \text{s}^{-1}$	s^{-1}	$\text{L mol}^{-1} \text{s}^{-1}$
Linear Plot to Determine (k):	[A] versus time	$\ln[A]$ versus time	$\frac{1}{[A]}$ versus time

Michaelis-Menten Kinetics

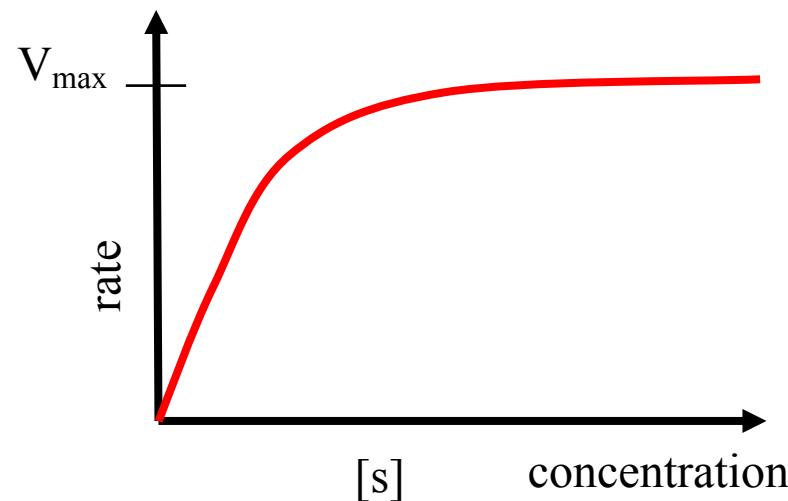
Michaelis-Menten Kinetics:



Enzyme-catalysed reaction (metabolic, signal transduction, active transport)

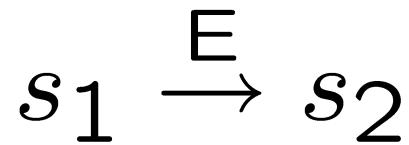
Rate:

$$v = \frac{V_{\max}s}{K_m + s} = \frac{k_{\text{cat}}Es}{K_m + s}$$



Hill-type Kinetics

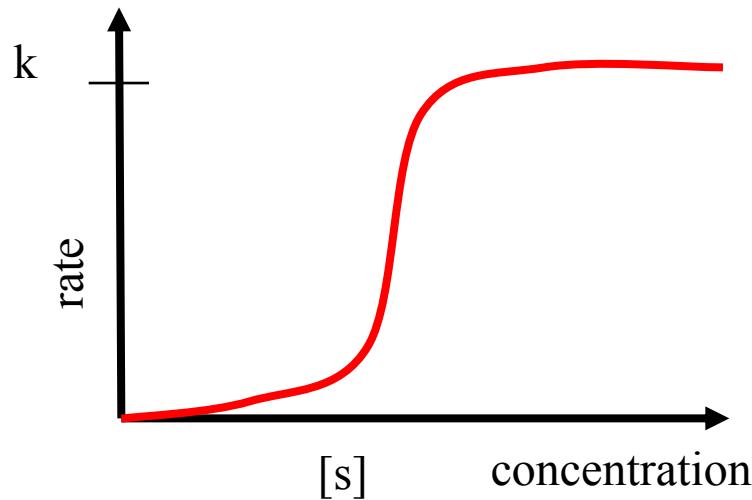
Hill-type Kinetics:



Catalysis by cooperative enzyme or lumped description of multi-step process

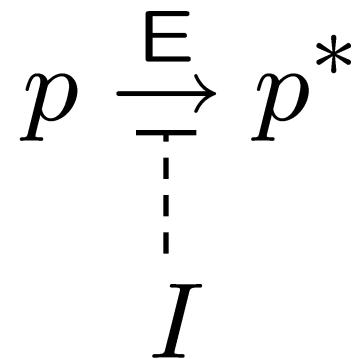
Rate:

$$v = \frac{ks^n}{K_m^n + s^n}$$



Allosteric inhibition

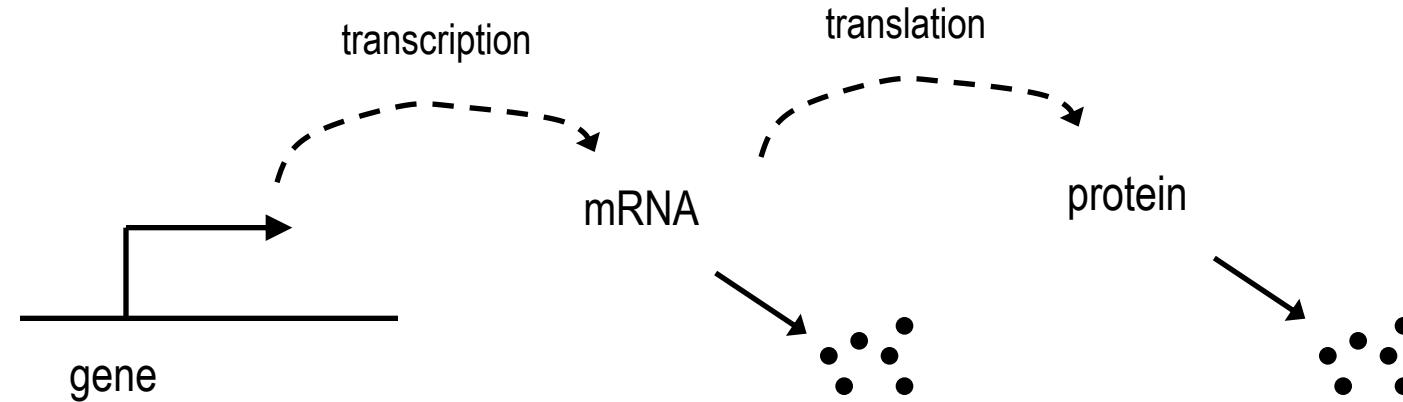
Allosteric inhibition:



Inhibitor I binds enzyme E and reduces its catalytic activity

Rate: $v = \frac{V_{max}s}{K_m + s(1 + I/k_i)}$

Genetic Circuits

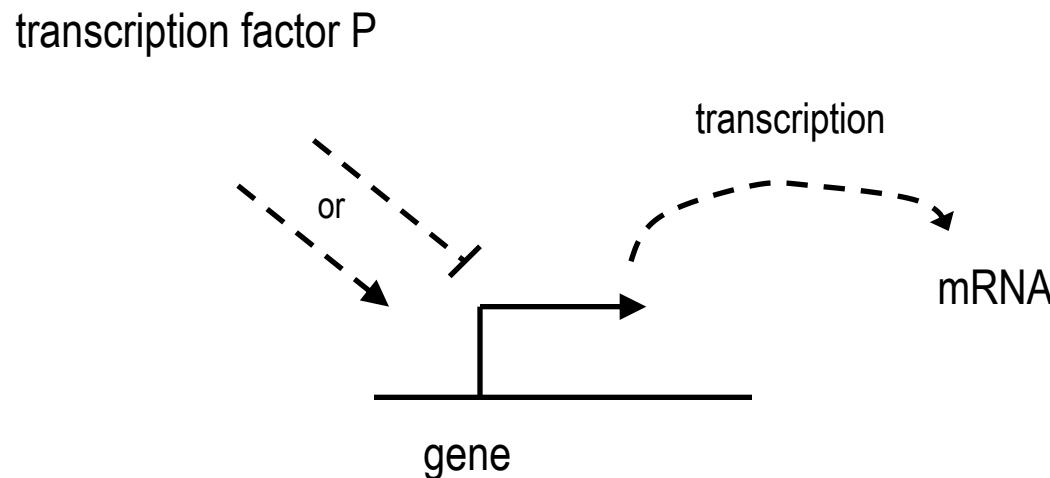


unregulated mRNA transcription: zeroth order

unregulated protein translation: first order in mRNA concentration

degradation/dilution: first order

Genetic Circuits



Regulated mRNA transcription: Hill type kinetics

Activation:

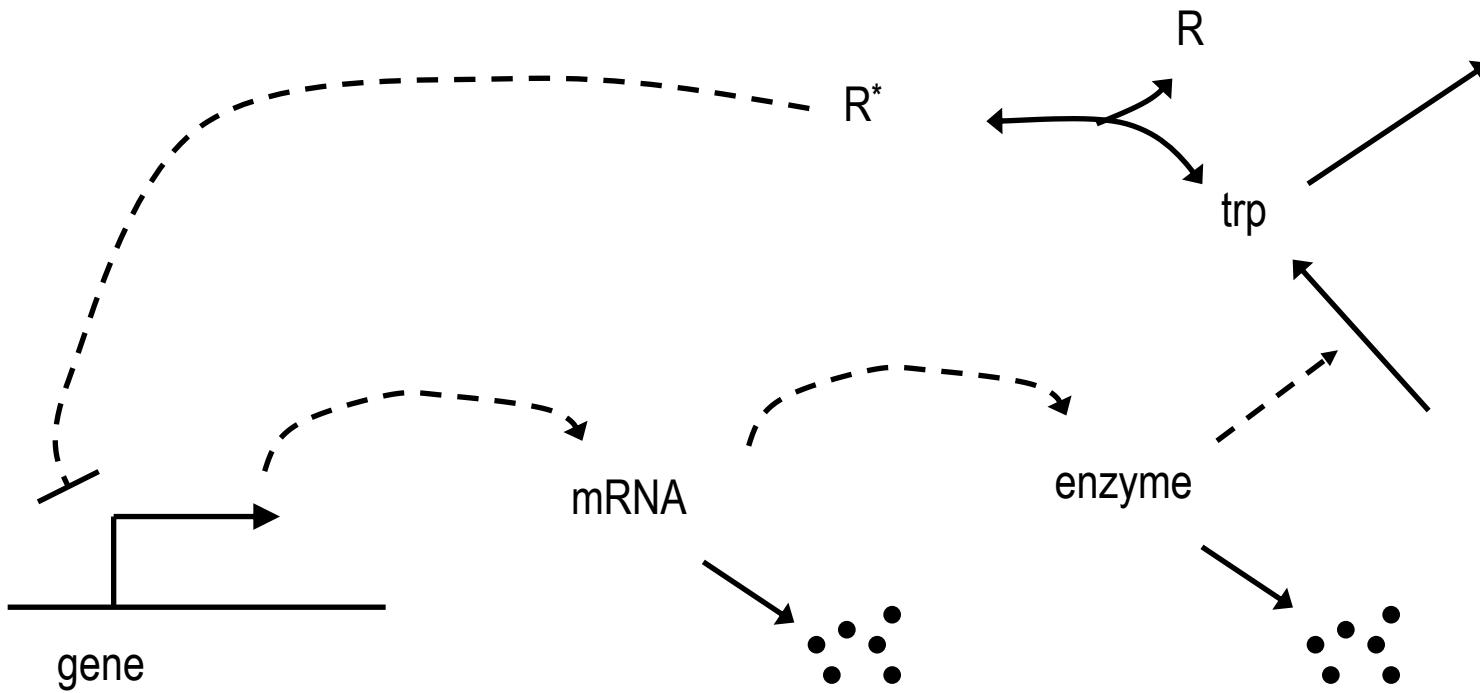
$$v = \alpha \frac{P^n}{K + P^n}$$

$n \approx$ multimerization of P

Inhibition:

$$v = \alpha \frac{1}{K + P^n}$$

Example: autoinhibitory gene circuit: trp operon



Species:

m (mRNA)

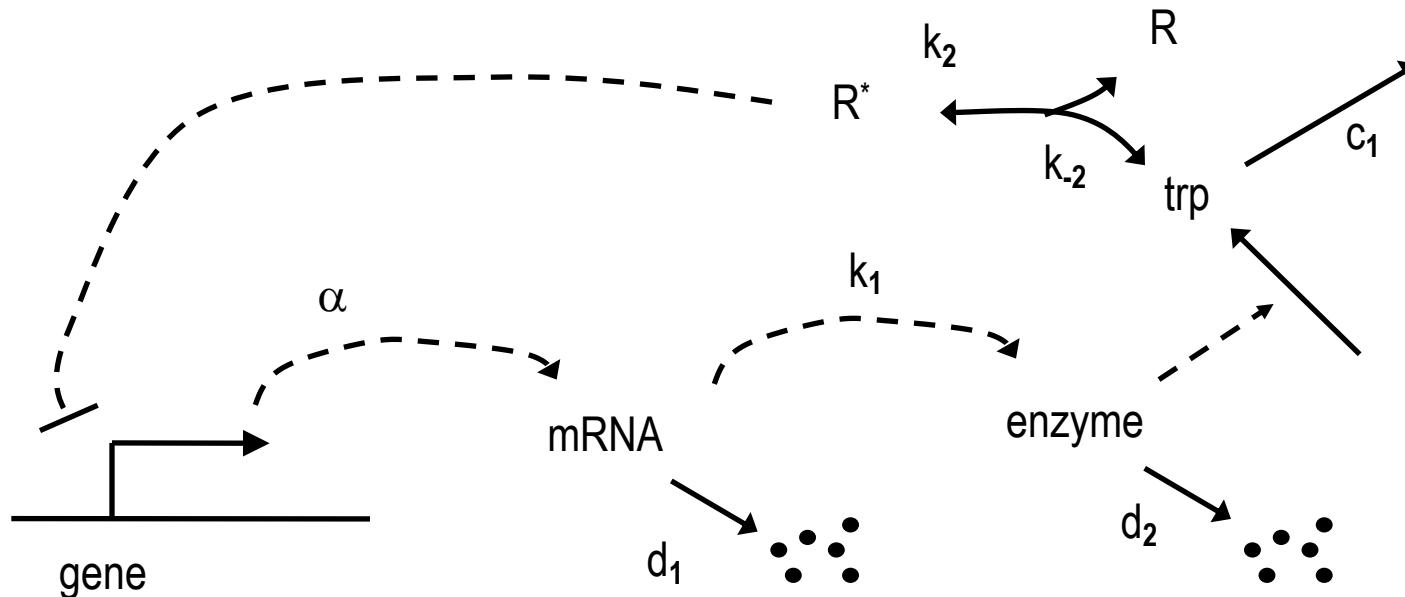
R (Repressor)

e (enzyme)

R* (Active Repressor)

T (trp)

Example: autoinhibitory gene circuit: trp operon



$$\frac{d}{dt}m(t) = \frac{\alpha}{1 + (R^*(t))^n} - d_1 m(t)$$

$$\frac{d}{dt}e(t) = k_1 m(t) - d_2 e(t)$$

$$\frac{d}{dt}T(t) = \frac{k_{cate}(t)X}{K_m + X} - c_1 T(t) - k_2 R(t)T(t) + k_{-2}R^*(t)$$

$$\frac{d}{dt}R(t) = -k_2 R(t)T(t) + k_{-2}R^*(t)$$

$$\frac{d}{dt}R^*(t) = k_2 R(t)T(t) - k_{-2}R^*(t)$$