BIOE 498 / BIOE 599: Computational Systems Biology for Medical Applications

CSE 599V: Advancing Biomedical Models

Lecture 6: Model Solutions & System Response

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**BioEngineering

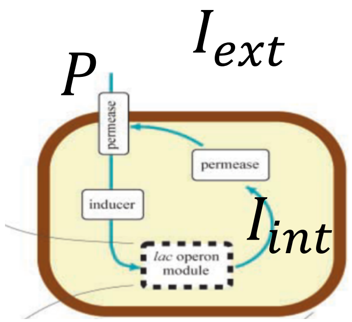
Model Solvers

- Motivating example – lac operon
- Alternative methods
- Software
- In class exercise

Motivation: Model of the lac Operon

$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int}$$

$$\frac{dP}{dt} = cI_{int} - eP$$



I_{ext} = concentration of external inducer (lactose)
I_{int} = concentration of internal inducer
P = concentration of permease

Given values of $I_{ext}, I_{int}(0), P(0)$, parameters a, b, c, e
Find $I_{int}(t), P(t)$

Initial Value Problem (IVP)

Given

- *N* ordinary differential equations in *N* variables
- Values for the *N* variables at time 0

Find

- Values of the *N* variables over time

Notation

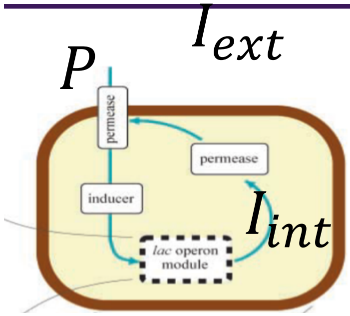
x_n is the value of the *n*-th variable at time *t*

$\frac{dx_n}{dt}$ is the derivate of the *n*-th variable w.r.t. time

$f_n(\cdot)$ is an analytic function (infinitely differentiable)

$$\frac{dx_n}{dt} = f_n(x_1, \cdots, x_N)$$

IVP for lac Operon Model



$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int} \qquad \frac{dP}{dt} = cI_{int} - eP$$

- What is N?

  2

- What is f_n for $\frac{dI_{int}}{dt}$?

  $$a(I_{ext} - I_{int})P - bI_{int}$$

- What are reasonable initial values for I_{int}, P?
  - Something small, but not 0.

Euler Algorithm for IVP

Given: Differential equations and initial values for *n* variables

$$\frac{dx_n(t)}{dt} = f_n\big(x_1(t), \cdots, x_N(t)\big),\ x_n(0)$$

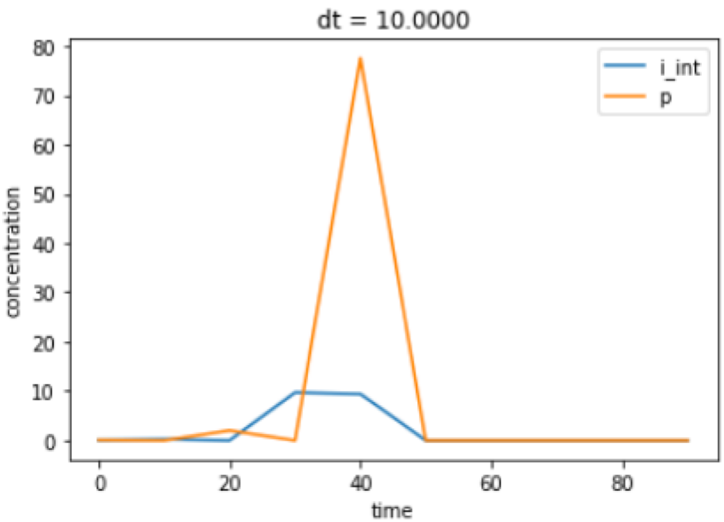
Find Values of variables at time T

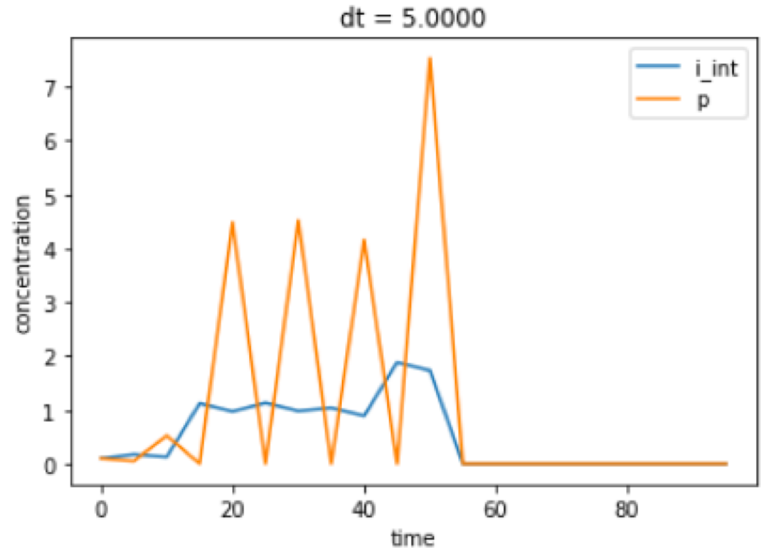
$$x_n(T)$$

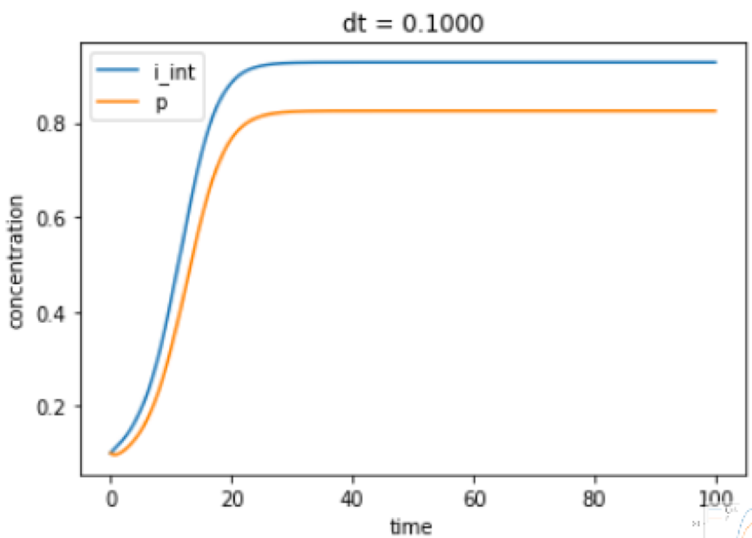
Key consideration:How big is dt

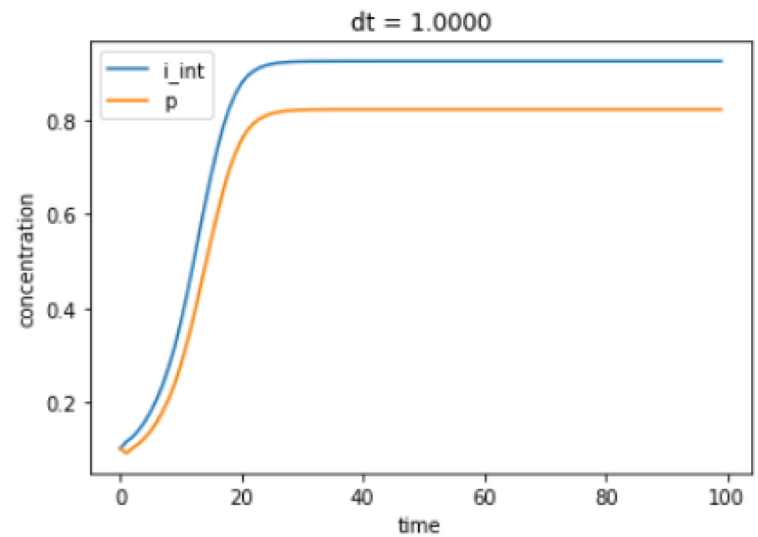
1. For t = 0..T-1
   1. For n = 0..N
      1. delta $= f_n\big(x_1(t), \cdots, x_n(t)\big)dt$
      2. $x_n(t+1) \ = \ x_n(t) + \text{delta}$

Euler for lac Operon Model









Requirement for a Numerical Solution

- The function is "smooth enough"
  - Two ways of expressing "smooth enough"
    - Lipschitz continuity
    - Smooth and uniformly monotone decreasing
- If smooth enough, then
  - a solution will exist and be unique
  - we will be able to approximate it accurately with a wide variety of method

Euler's method is only first-order accurate (O(*dt*)).

Variants of Euler's Method

- If we use

$$y'(t) = \frac{y(t) - y(t-h)}{h} - \frac{1}{2} h y''(\theta),$$

O(h)

$$h = dt$$

then we get the backward Euler method

Method 1

$$y_{n+1} = y_n + hf(t_{n+1}, y_{n+1}) :$$

- If we use

$$y'(t) = \frac{y(t+h) - y(t-h)}{2h} - \frac{1}{6} h^2 y'''(\theta_{t,h}),$$

O(h^2)

then we get the midpoint method

Method 2

$$y_{n+1} = y_{n-1} + 2hf(t_n, y_n).$$

6.5 Single-step Method: Runge-Kutta

- The Runge-Kutta family of methods is one of the most popular families of accurate solvers for initial value problems.

Recall the usual predictor-corrector formulation of the trapezoid method:

$$\begin{aligned}\bar{y}_{n+1} &= y_n + hf(t_n, y_n)\\ y_{n+1} &= y_n + \frac{1}{2}h\left[f(t_{n+1}, \underline{\bar{y}_{n+1}}) + f(t_n, y_n)\right].\end{aligned}$$

We can directly substitute the predictor into the corrector to write this as a single recursion:

$$y_{n+1} = y_n + \frac{1}{2}h\left[f(t_{n+1}, \underline{y_n + hf(t_n, y_n)}) + f(t_n, y_n)\right]. \tag{6.44}$$

Variants of Euler's Method

- By integrating the differential equation:

$$y(t+h) = y(t) + \int_t^{t+h} f(s,y(s))\,ds. \qquad (6.23)$$

and apply the trapezoid rule to (6.23) to get

$$y(t+h) = y(t) + \frac{1}{2}h[f(t+h,y(t+h)) + f(t,y(t))] - \underbrace{\frac{1}{12}h^3 y'''(\theta_{t,h})}_{O(h^3)},$$

where $\theta_{t,h} \in [t, t+h]$, and we remind the reader that

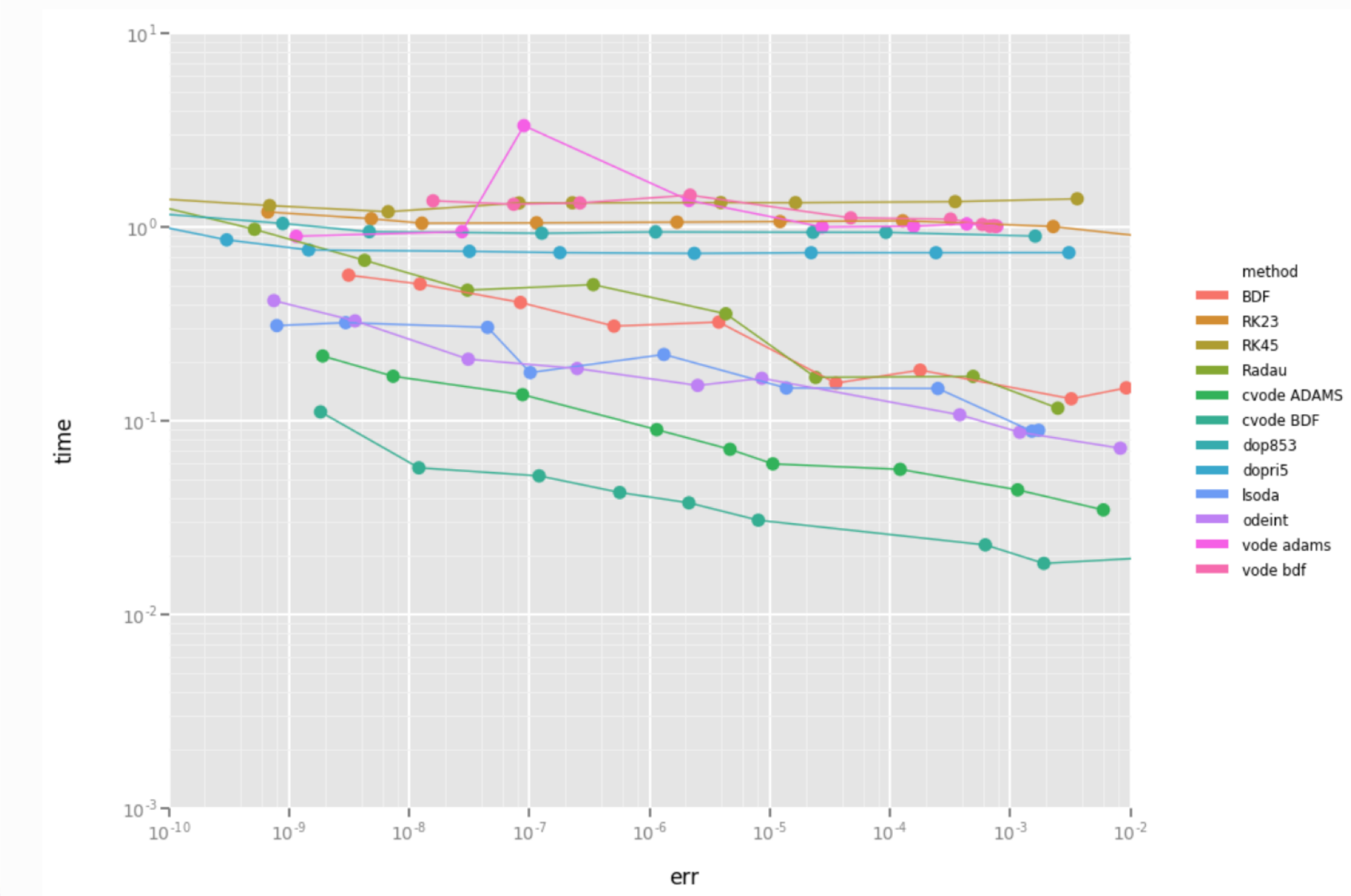
$$\underline{f(t,y(t)) = y'(t)} \quad \Rightarrow \quad \frac{d^2}{dt^2} f(t,y(t)) = y'''(t).$$

Thus

Method 5

$$y_{n+1} = y_n + \frac{1}{2}h\left(f(t_{n+1},y_{n+1}) + f(t_n,y_n)\right). \qquad (6.25)$$

Performance of Python Solvers



MATLAB Solver

The ode45 solver implements a variable step size Runge-Kutta method by using the Dormand-Prince method. The basic syntax for ode45 is:

```
[t,y] = ode45(@myModel, [t0, tend], yo, [], p);
```

where

myModel is the function containing the differential equations.

t0, tend are the initial and final values for the independent variable, t.

yo is a vector of initial conditions.

p is the set of parameters for the model, and can be any size.

```
function dy = myModel(t, y, p)
dy = zeros (2,1);
vo = p(1);
k1 = p(2);
k2 = p(3);
dy(1) = vo - k1*y(1);
dy(2) = k1*y(1) - k2*y(2);
```

```
p = [10, 0.5, 0.35]
y0 = [0, 0]
[t, y] = ode45 (@myModel, [0, 20], y0, [], p)
```

Python Solver

```
import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import odeint

vo = 10
k1 = 0.5
k2 = 0.35

# Declare the model
def myModel(y, t):

   dy0 = vo - k1*y[0]
   dy1 = k1*y[0] - k2*y[1]
   return [dy0, dy1]

time = linspace(0.0, 20.0, 100)
yinit = array([0.0, 0.0])
y = odeint (myModel, yinit, time)
```

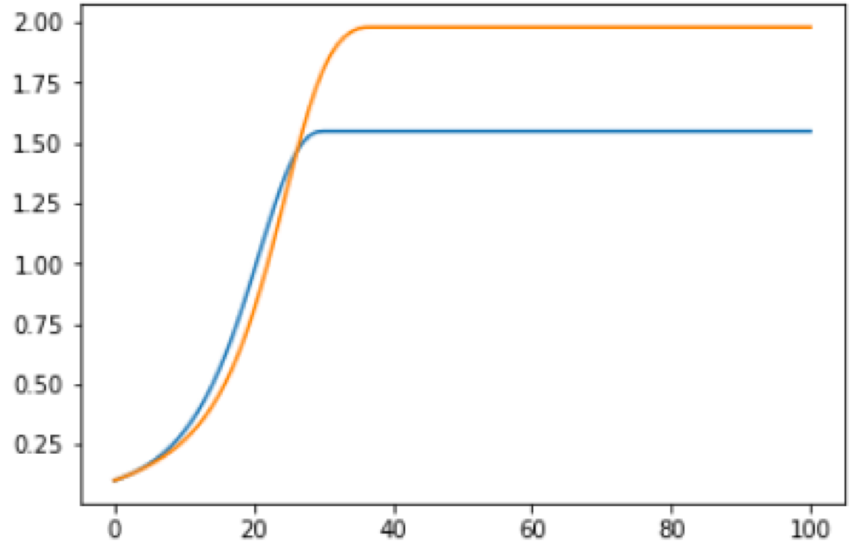
In Class Exercise

Numerically Evaluate lac Operon Model

$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int} \qquad \frac{dP}{dt} = cI_{int} - eP$$

$\mathrm{a = 0.5;\ b = 0.03;\ c = 0.8;\ d = 0.9;\ I_{ext} = 1.0}$

$\mathrm{I_{int}(0) = 0.1;\ P(0) = 0.1}$



Finding Fixed Points – Steady State

Solve for variable values when derivatives are 0.

lac operon model

$$\frac{dI_{int}}{dt} = a(I_{ext} - I_{int})P - bI_{int}$$

$$\frac{dP}{dt} = cI_{int} - eP$$

$$0 = a(I_{ext} - I_{int})P - bI_{int}$$

$$0 = cI_{int} - eP$$

Solving:

$$I_{int} = I_{ext} - \frac{be}{ac}$$

$$P = \frac{c}{e} I_{int}$$

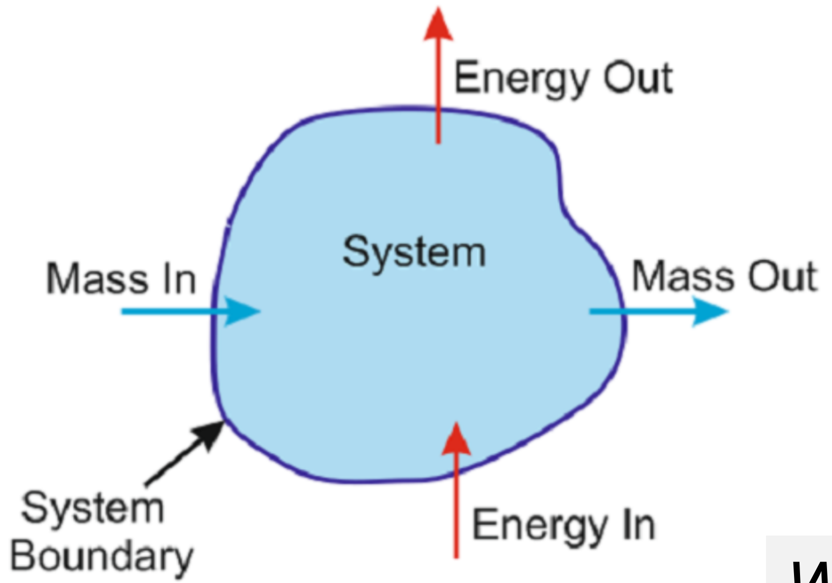
For the values used:

$$I_{int} \approx I_{ext} \qquad P \approx 2I_{ext}$$

System Responses

- Thermodynamics in brief
- Reversible system in equilibrium
- Open system in steady state
- Solutions in Tellurium

Thermodynamics: Key Definitions

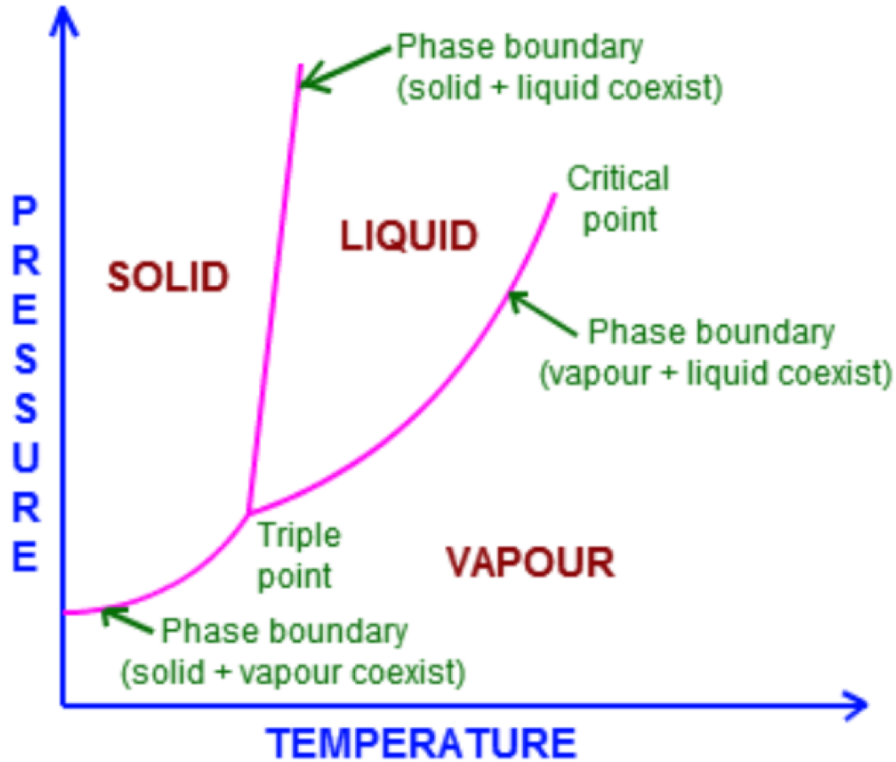


What type of system is a cell?

System Types

	No Mass Flow	Mass Flow
No Energy Flow	Isolated	X
Energy Flow	Closed	Open

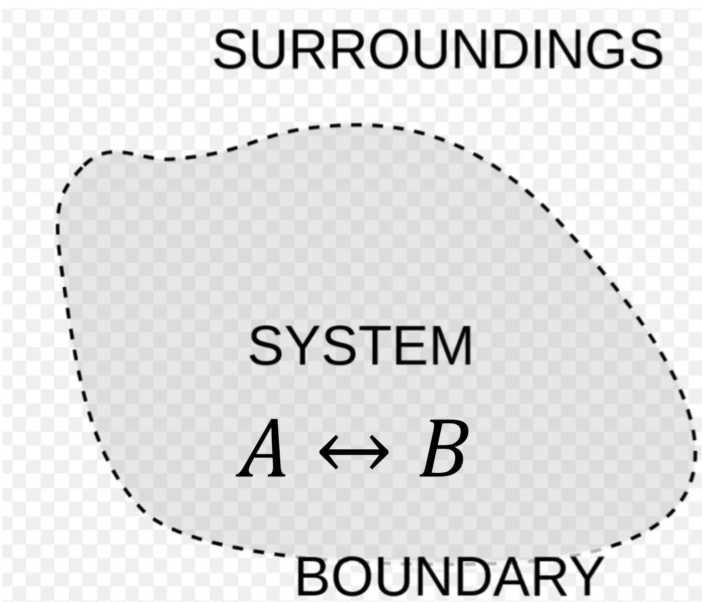
Thermodynamic Equilibrium



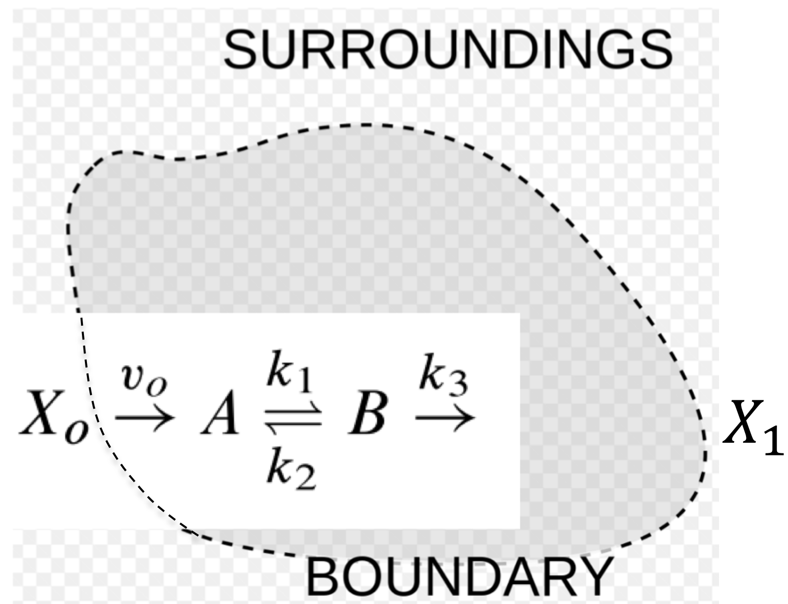
A system is in thermodynamic equilibrium if no simple process lowers its energy.

Chemical Systems

A chemical system is in **equilibrium** if no reaction lowers its energy and hence no net reaction take place.



An chemical system is in **steady state** if no concentrations are changing as time goes to infinity.



Equilibrium and Steady State

A chemical system is in **equilibrium** if no reaction lowers its energy and hence no net reaction take place.

An chemical system is in **steady state** if no concentrations are changing as time goes to infinity.

- Equilibrium implies steady state.
  - No reactions and so no change in concentrations
- Steady state does NOT imply equilibrium
  - Reactions may still happen

Computing Species Concentrations

- Solve simple differential equations for chemical systems
- Given an initial amount of A, A_0, find A, B over time.

$$A \rightarrow B$$

- Equations

$$\frac{dA}{dt} = -kA \qquad \frac{dB}{dt} = kA$$

Solution by Separation of Variables

$A \rightarrow B$

$$\frac{dA}{A} = -kdt$$

$$\int \frac{dA}{A} = -\int kdt$$

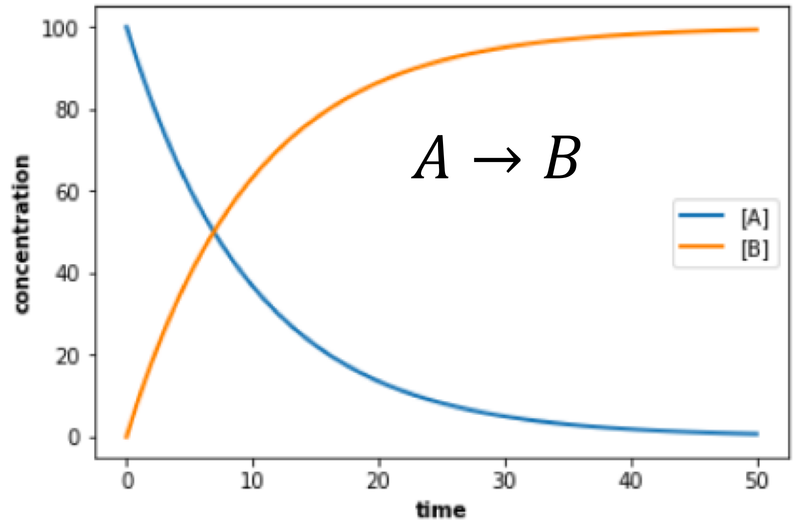
$$\ln(A) = -kt + C$$

So, $A = C'e^{-kt}$, where $C' = e^{C}$

We find C' by observing that $A(0) = A_0 = C'e^{-(k)(0)} = C'$

Result: $A = A_0 e^{-kt}$

Interpreting the Solution

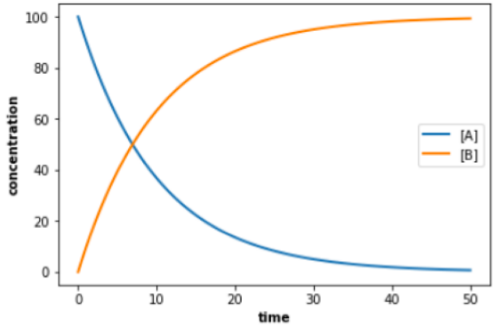


$A = A_0 e^{-kt}$

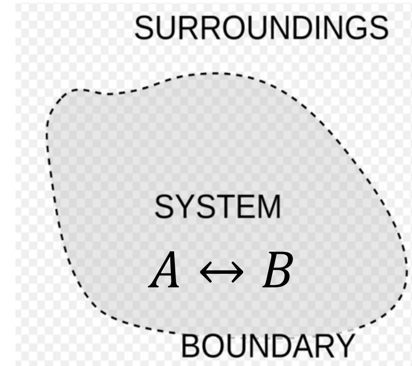
- What is *A* at time 0?
- How much *A* is there at steady state, $t \rightarrow \infty$?
- How much *B* is there at steady state?
- If we know $A(t)$, how do we find $B(t)$?

Solving in Tellurium

```
te.setDefaultPlottingEngine('matplotlib')
model = """
   model test
      species A, B;
      A = 100.0;
      B = 0.0;
      J1: A -> B; k1*A;
      k1 = 0.1;
   end"""
r = te.loada(model)
r.simulate(0, 50, 100)
r.plot(xtitle="time", ytitle="concentration")
```



Reversible Reaction, Closed System



Given $A(0) = A_0, B(0) = B_0$

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

Note that $B = B_0 + A_0 - A$

$$\frac{dA}{dt} = -k_1 A + k_2(B_0 + A_0 - A) = -(k_1 + k_2)A + k_2(A_0 + B_0)$$

Solving the differential equation:

Homogeneous eqn (function of A): $\frac{dA}{dt} = -(k_1 + k_2)A \equiv A(t) = C'e^{-(k_1+k_2)t}$

Particular soln (soln for the constant $k_2(A_0+B_0)$) : Set $A = c$.

Solve $\frac{dc}{dt} = -(k_1 + k_2)c + k_2(A_0+B_0)$. So, $c = \frac{k_2}{k_1+k_2}(A_0 + B_0)$

Full soln (homogeneous + particular): $A(t) = \frac{k_2}{k_1+k_2}(A_0 + B_0) + C'e^{-(k_1+k_2)t}$

Find C' using initial value: $A(0) = A_0 = \frac{k_2}{k_1+k_2}(A_0 + B_0) + C' \qquad C' = \frac{k_1 A_0 - k_2 B_0}{k_1+k_2}$

Result (Use C'): $A(t) = \frac{k_2}{k_1+k_2}(A_0 + B_0) + \frac{k_1 A_0 - k_2 B_0}{k_1+k_2} e^{-(k_1+k_2)t}$

A Closer Look at the Solution to $\boldsymbol{A \leftrightarrow B}$

$$A(t) = \frac{k_2}{k_1 + k_2}(A_0 + B_0) + \frac{k_1 A_0 - k_2 B_0}{k_1 + k_2} e^{-(k_1+k_2)t}$$

- What is the steady, $A(\infty)$? What is the transient?
- What is the initial reaction velocity $v_{initial} = \frac{dA}{dt}|_{t=0}$?

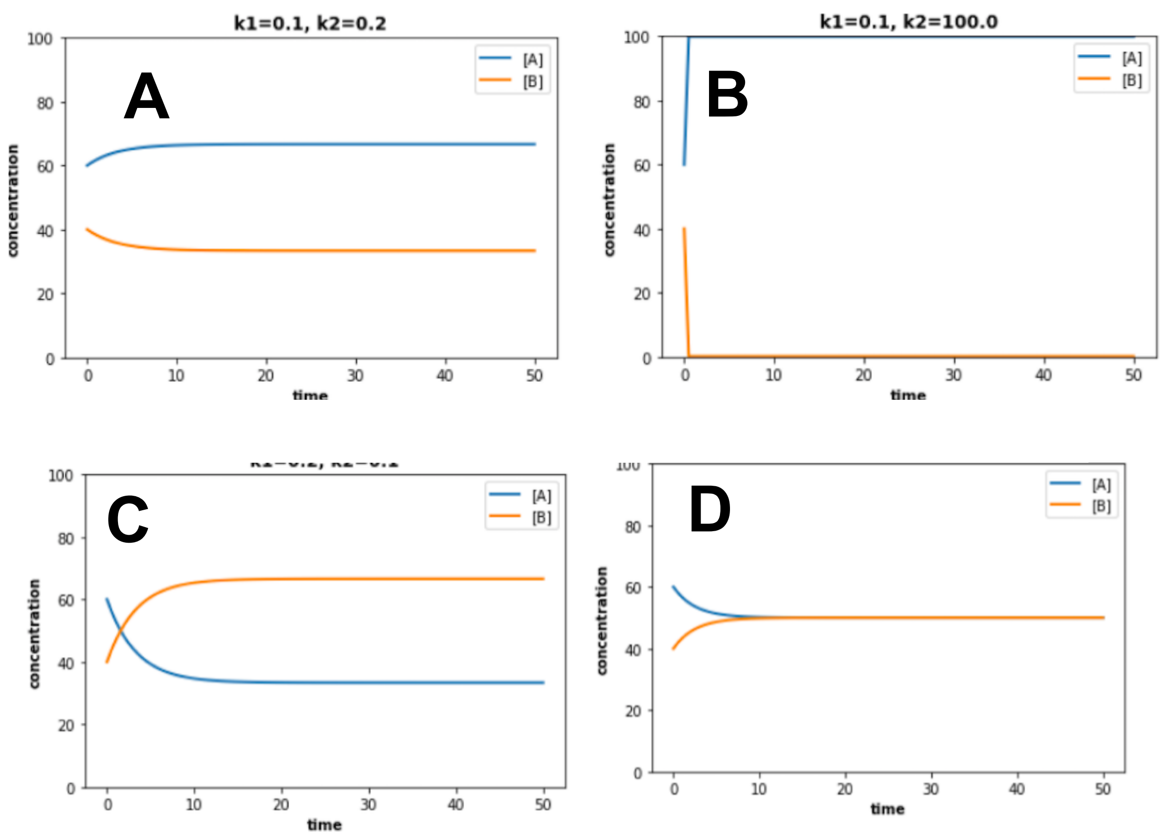
$$v_{initial} = k_1 A_0 - k_2 B_0$$

- What is $B(t)$?

$$B(t) = A_0 + B_0 - A(t)$$
$$= \frac{k_1}{k_1 + k_2}(A_0 + B_0) + \frac{-k_1 A_0 + k_2 B_0}{k_1 + k_2} e^{-(k_1+k_2)t}$$

$A \leftrightarrow B$

$$A(t) = \frac{k_2}{k_1 + k_2}(A_0 + B_0) + \frac{k_1 A_0 - k_2 B_0}{k_1 + k_2} e^{-(k_1+k_2)t}$$



Questions:

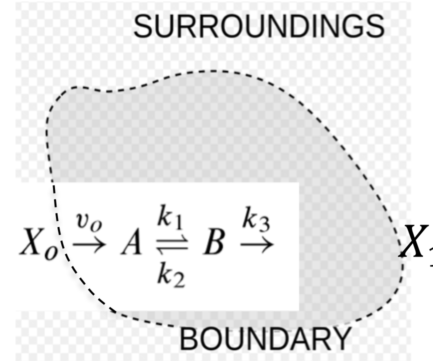
1. What are A_0, B_0?
2. Where is $k_1 > k_2$?
3. What is A_{EQ}?

Solution In Tellurium

```
model test
    species A, B;
    A = 60.0;
    B = 40.0;
    J1: A -> B; k1*A;
    J2: B -> A; k2*B;
    k1 = 0.1;
    k2 = 0.2
end
```

Try it!

Reversible Reaction, Open System



$$A(t) = v_o \frac{1 - e^{-k_1 t}}{k_1}$$

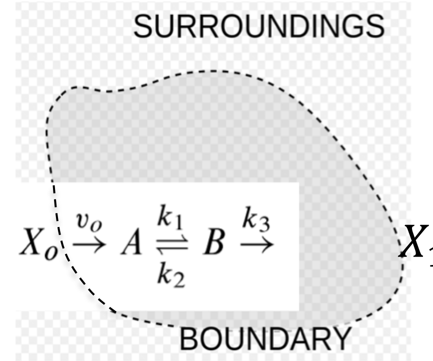
$$B(t) = v_o \frac{k_1 \left(1 - e^{-k_3 t}\right) + k_3 \left(e^{-k_1 t} - 1\right)}{k_3 \left(k_1 - k_3\right)}$$

(7.3)

(from text book)

- What is $A(0), B(0)$?
- What is $A(\infty), B(\infty)$?
- What is $\frac{dA}{dt}|_{t\to\infty}$?

Class Exercise



Write a Tellurium simulation for the above system

A0 = 40; B0 = 60;

k1 = 0.1; k2 = 0.2; k3 = 0.1 vin = 1

Questions

- What are the steady state values of A, B?
- At what time is A = B?
- How do the above change if k1=0.2, k2=0.1?

What You Should Know

- Numerical solutions to differential equations
  - Euler algorithm, how improve efficiency
  - How use python solver
- System response
  - Thermodynamics system types: isolated, closed, open
  - Transient and steady state responses
  - Steady state vs. equilibrium
  - Solutions in Tellurium