

MCB 135 Lecture 5

Introduction to modeling and common simplifying assumptions

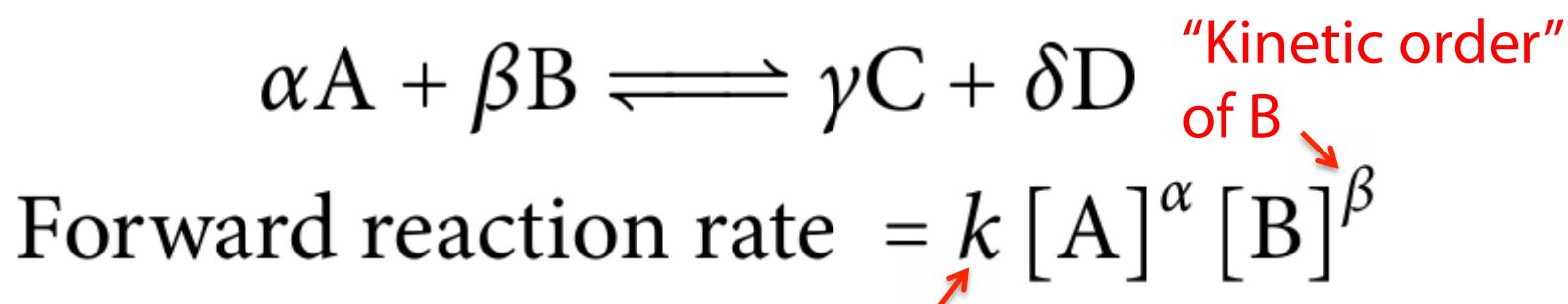
Logistical issues

- Selecting a paper discussion time
- Problem Set 1 has been posted and is due at 2:30 PM on Monday, February 9 (note time error in previous lecture slides)
- Getting help with the first problem set
- Lecture videos through Monday now online
 - For a link to the lecture 2 file, click on Modules -> Lecture 2

Recap: Lessons from gene regulation

- Cannot treat all changes as instantaneous and all concentrations as booleans.
 - Need to study the dynamics of (quasi)continuous concentration changes
- Gene regulation, like many biological processes, takes place through chemical reactions
 - The Law of Mass Action explains chemical reaction rates

Recap: Law of Mass Action



Mass action rate constant (usually written above the reaction arrow)

Applies to elementary reactions, not composite reactions

- The slowest “rate-limiting” elementary reaction effectively sets the composite reaction rate

Catalysts like enzymes work via composite reactions

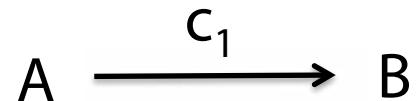
- On Friday, we will learn to deal with them using Michaelis-Menten kinetics

How do we apply the Law of Mass Action
to study system dynamics?

Today's Outline

- Differential equation models for reaction networks
 - Constraints from conservation
- Reducing complexity using separation of timescales
 - Effective constancy assumptions
 - Rapid equilibrium assumptions
 - Quasi-steady-state assumptions
- Visualizing system dynamics
 - Numerical integration techniques
 - MATLAB demo

Example: Radioactive decay



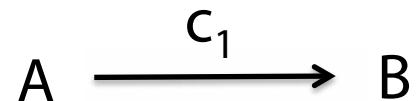
Reaction rate: $c_1[A]$

Rate of change in [A]: $d[A]/dt = -c_1[A]$

Rate of change in [B]: $d[B]/dt = c_1[A]$

Can we find an analytical solution?

Example: Radioactive decay



$$\frac{dA}{dt} = -c_1 A \implies \frac{\frac{dA}{dt}}{A} = -c_1$$

$$\int \frac{\frac{dA}{dt} dt}{A} = \int \frac{1}{A} dA = \int -c_1 dt$$

$$\ln A = -c_1 t + c_2$$

$$A = e^{-c_1 t + c_2} = e^{-c_1} e^{c_2} = c_3 e^{-c_1 t}$$

Example: Radioactive decay

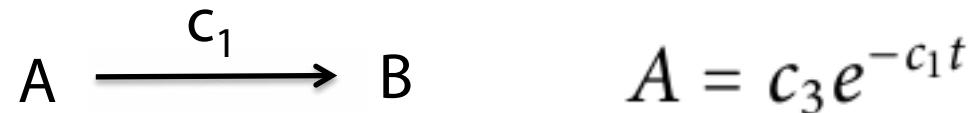


What is the physical interpretation of c_3 ?

At time zero: $A(0) = c_3 e^0 = c_3$

- In other words, c_3 is just the initial concentration of A.

Example: Radioactive decay



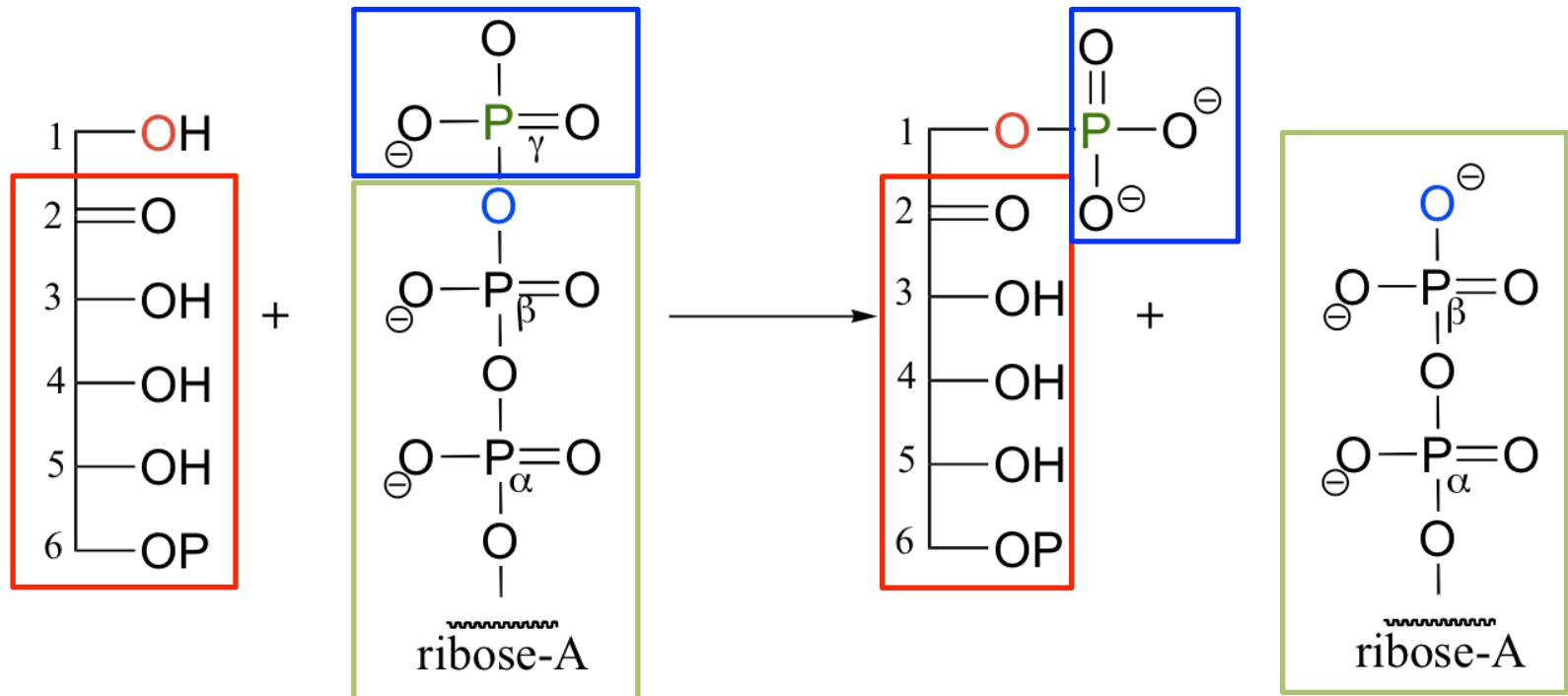
We have an expression for A: how do we get an expression for B?

One option: plug in and integrate

$$\text{Rate of change in [B]: } \frac{d[B]}{dt} = c_1[A]$$

The easier way: exploiting *moiety conservation*

Moiety conservation restricts how concentrations change together



fructose 6-phosphate ATP

$$[F6P] + [ATP] = \text{constant}$$

fructose 1,6-bisphosphate ADP

$$[ATP] + [F1,6BP] = \text{constant}$$

$$[ATP] + [ADP] = \text{constant}$$

Example: Radioactive decay



We have an expression for A: how do we get an expression for B?

The Easy Way (exploiting *moiety conservation*):

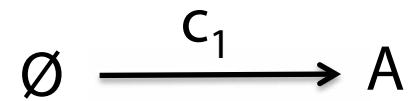
- A and B share something in common called a *moiety*.
 - Physical interpretation: the moiety is the atom A, minus whatever gets emitted during the decay.)
- None of the moiety enters or exits the system, so:
 - $[A] + [B] = c_4$
 - $[B] = c_4 - [A] = c_4 - c_3 e^{-c_1 t}$

Living things are often leaky

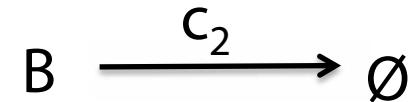


Two types of “pseudoreactions:”

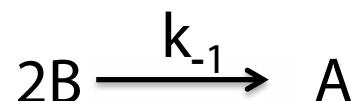
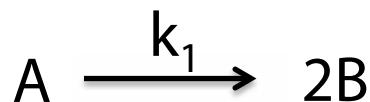
Generation or addition to
the system:



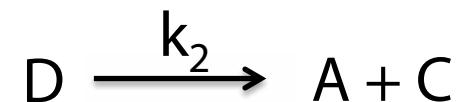
Removal, degradation, or
dilution:



Example: A more complicated chemical reaction network

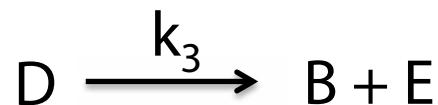


(homodimerization
and reseparation)

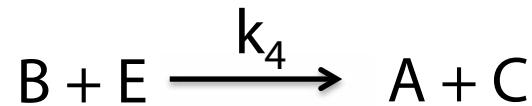


(heterodimerization
and reseparation)

Irreversible disintegration

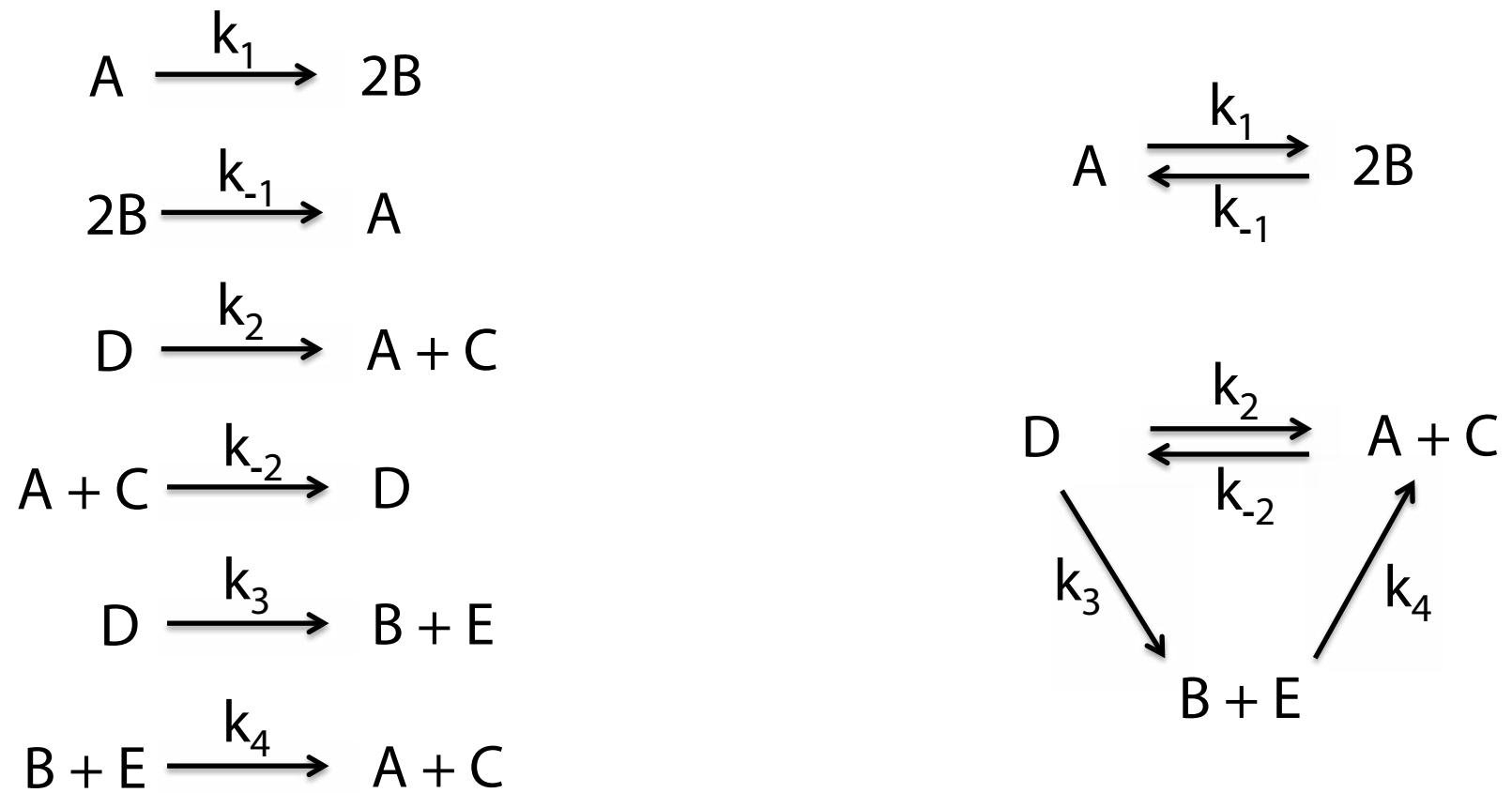


Irreversible conversion



Example from Gunawardena 2003

Example: A more complicated chemical reaction network

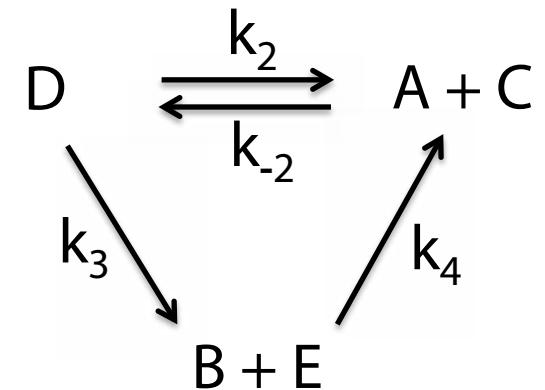
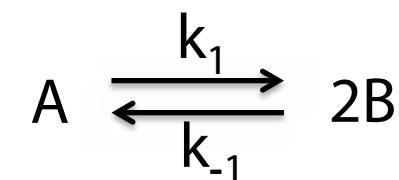


Example: A more complicated chemical reaction network

Find two moieties in this system.
Determine their conservation relations.

$$2[A] + 2[D] + [B] + [E] = \text{constant}$$

$$[D] + [C] + [E] = \text{constant}$$



Example: A more complicated chemical reaction network

$$\frac{dE}{dt} = \text{Rate of formation - Rate of breakdown}$$

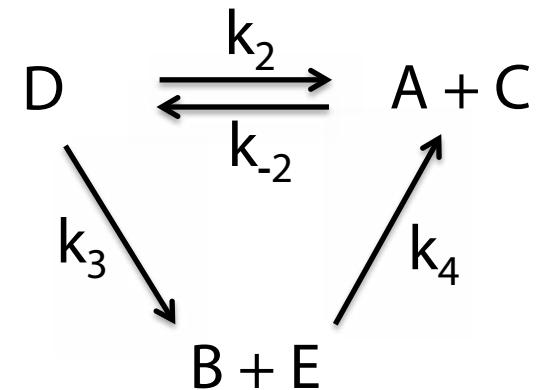
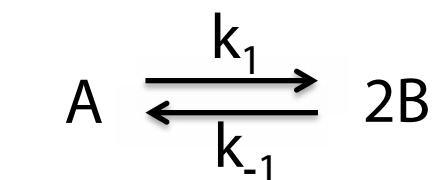
$$= k_3D - k_4BE$$

$$\frac{dC}{dt} = k_2D + k_4BE - k_{-2}AC$$

$$\frac{dA}{dt} = k_{-1}B^2 + k_2D + k_4BE - k_1A - k_{-2}AC$$

$$\frac{dB}{dt} = 2k_1A + k_3D - 2k_{-1}B^2 - k_4BE$$

$$\frac{dD}{dt} = k_{-2}AC - k_3D - k_2D$$



Example: A more complicated chemical reaction network

This system of ODEs:

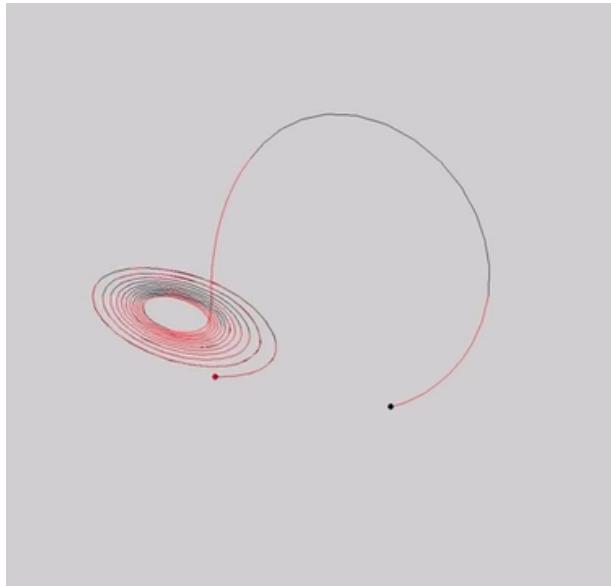
- Is non-linear

$$\begin{aligned}\frac{dA}{dt} &= k_{-1}B^2 + k_2D + k_4BE - k_1A - k_{-2}AC \\ \frac{dB}{dt} &= 2k_1A + k_3D - 2k_{-1}B^2 - k_4BE \\ \frac{dC}{dt} &= k_2D + k_4BE - k_{-2}AC \\ \frac{dD}{dt} &= k_{-2}AC - k_3D - k_2D \\ \frac{dE}{dt} &= k_3D - k_4BE\end{aligned}$$

Example: A more complicated chemical reaction network

This system of ODEs:

- Is non-linear
- Has five species



The Lorenz attractor

$$\begin{aligned}\frac{dA}{dt} &= k_{-1}B^2 + k_2D + k_4BE - k_1A - k_{-2}AC \\ \frac{dB}{dt} &= 2k_1A + k_3D - 2k_{-1}B^2 - k_4BE \\ \frac{dC}{dt} &= k_2D + k_4BE - k_{-2}AC \\ \frac{dD}{dt} &= k_{-2}AC - k_3D - k_2D \\ \frac{dE}{dt} &= k_3D - k_4BE\end{aligned}$$

Example: A more complicated chemical reaction network

This system of ODEs:

- Is non-linear
- Has five species
- Has six parameters (the mass action rate constants)

$$\begin{aligned}\frac{dA}{dt} &= k_{-1}B^2 + k_2D + k_4BE - k_1A - k_{-2}AC \\ \frac{dB}{dt} &= 2k_1A + k_3D - 2k_{-1}B^2 - k_4BE \\ \frac{dC}{dt} &= k_2D + k_4BE - k_{-2}AC \\ \frac{dD}{dt} &= k_{-2}AC - k_3D - k_2D \\ \frac{dE}{dt} &= k_3D - k_4BE\end{aligned}$$

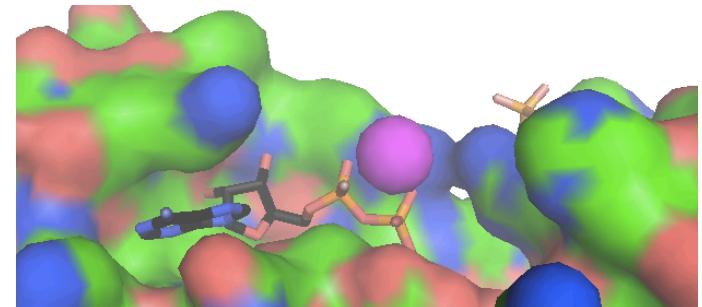
How can we simplify
chemical reaction networks?

Exploit separation of timescales

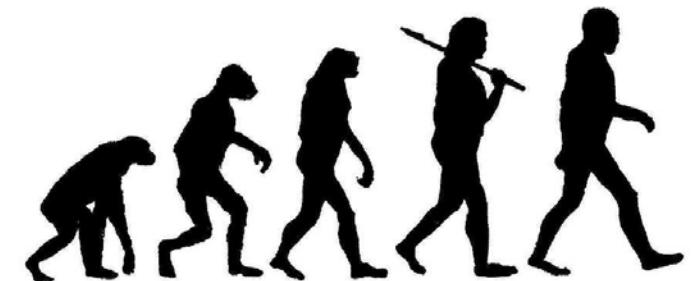
We choose a timescale of interest:

- Anything that changes more rapidly, we assume has already reached steady-state.
- Anything that changes more slowly, we approximate as constant.

Too fast



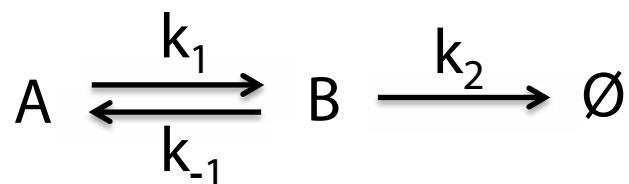
Too slow



Just right



Assume fast processes have reached equilibrium



$$k_1, k_{-1} \gg k_2$$

We can simplify the system down to “one species”:

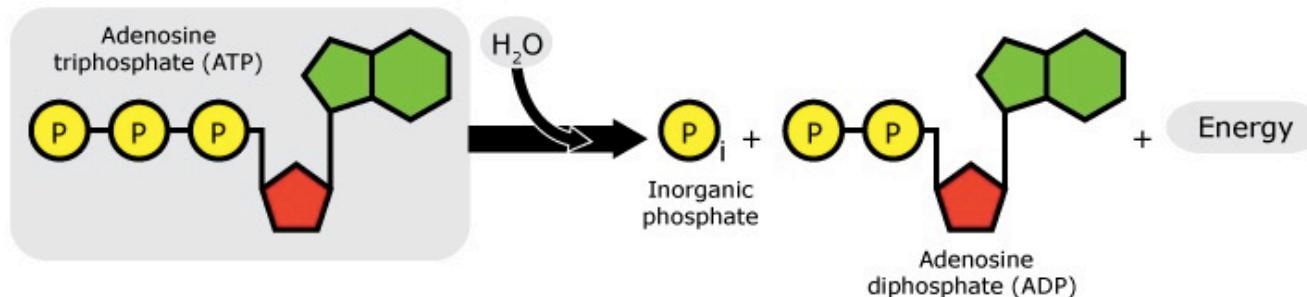
$$[C] = [A] + [B]$$

A and B are in *rapid equilibrium*:

$$k_1[A] = k_{-1}[B] \implies \frac{k_1}{k_{-1}} = \frac{[B]}{[A]}$$

Eliminate molecular species whose concentrations are effectively constant

Homeostasis buffers the concentrations of critical molecules, e.g. the ATP:ADP ratio



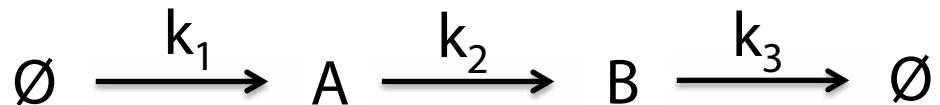
e.g., a reaction rate = $k_1[ATP][E] \approx k_1'[E]$, where $k_1' = k_1[ATP]_{s-s}$

We can also ignore changes that are small relative to absolute concentration (at least initially):

e.g., a reaction rate = $k_1[A][B] \approx k_1'[A]$, if [B] is fairly constant

These are called “pseudo-first-order” reactions

Alternatively, assume a species' concentration is at steady-state



Assume $[A]$ is at steady-state.

$$\frac{d[A]}{dt} = k_1 - k_2 [A] = 0$$

$$\implies [A] = \frac{k_1}{k_2}$$

$$\begin{aligned}\frac{d[B]}{dt} &= k_2 [A] - k_3 [B] \\ &= k_1 - k_3 [B]\end{aligned}$$

As they come up in the course, we'll discuss two other methods:

- Nondimensionalization (reduces parameter number)
- Linearization (clarifies behavior near points of interest)

Visualizing changes with time

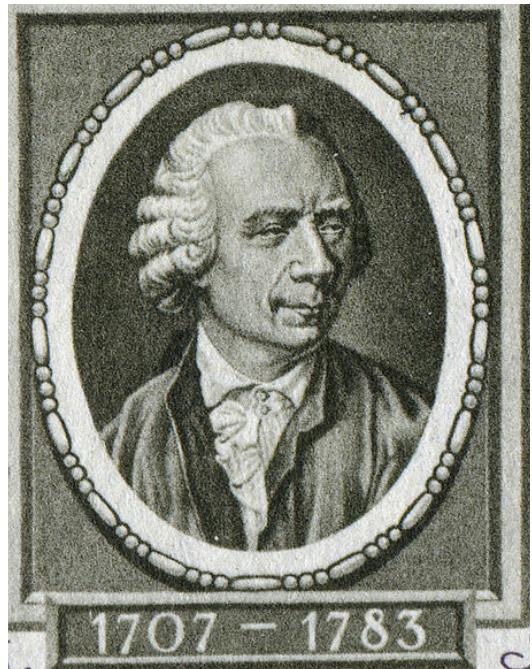
How to plot $y(t)$, when you only have:

- An initial condition, $y(t_0) = y_0$

- An ODE, $\frac{dy}{dt} = f(t, y)$



Often there may be no dependence of f on the time t (the laws of mass action aren't time-dependent)

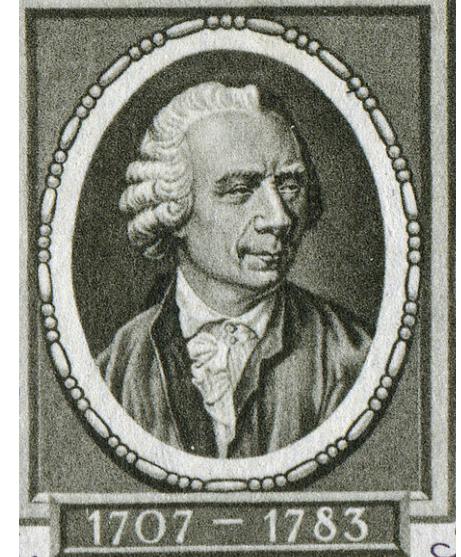


Good enough (?) numerical
integration of ODEs

Euler's method

Want to plot $y(t)$, but only have:

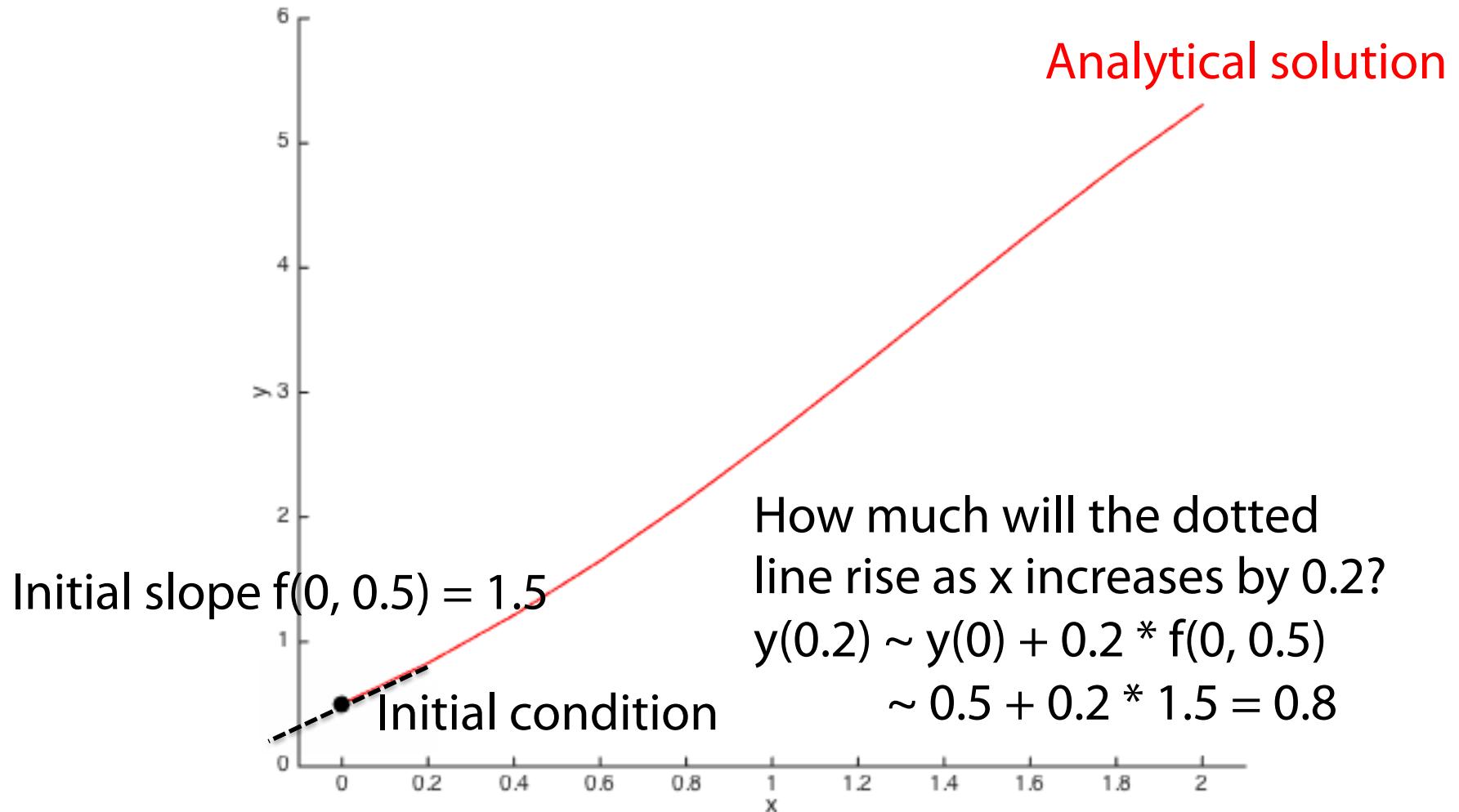
- An initial condition, $y(t_0) = y_0$
- An ODE, $\frac{dy}{dt} = f(t, y)$



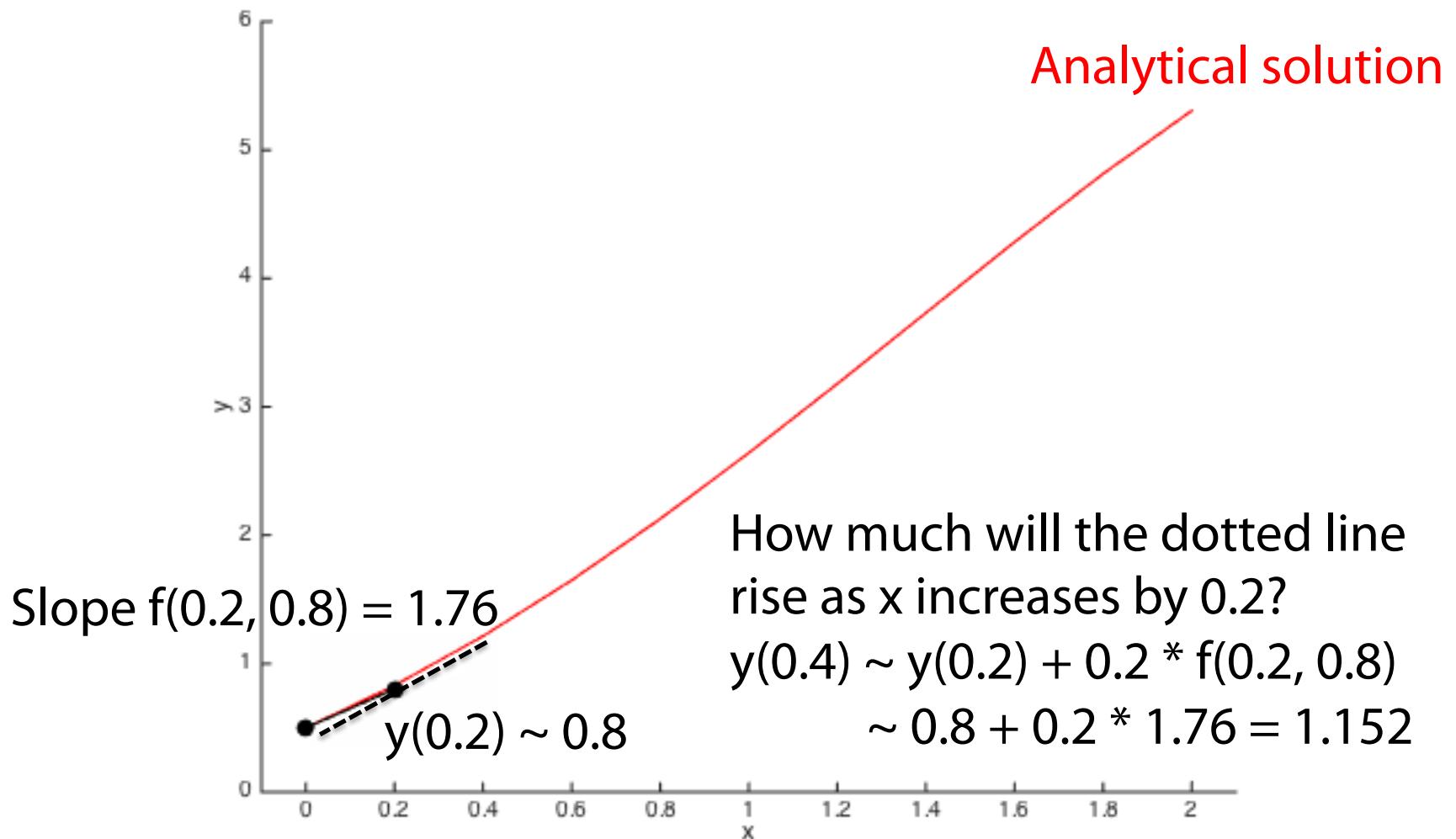
Start from initial condition and take a small step based on the slope there.

Take another small step based on the slope at that point...and so forth.

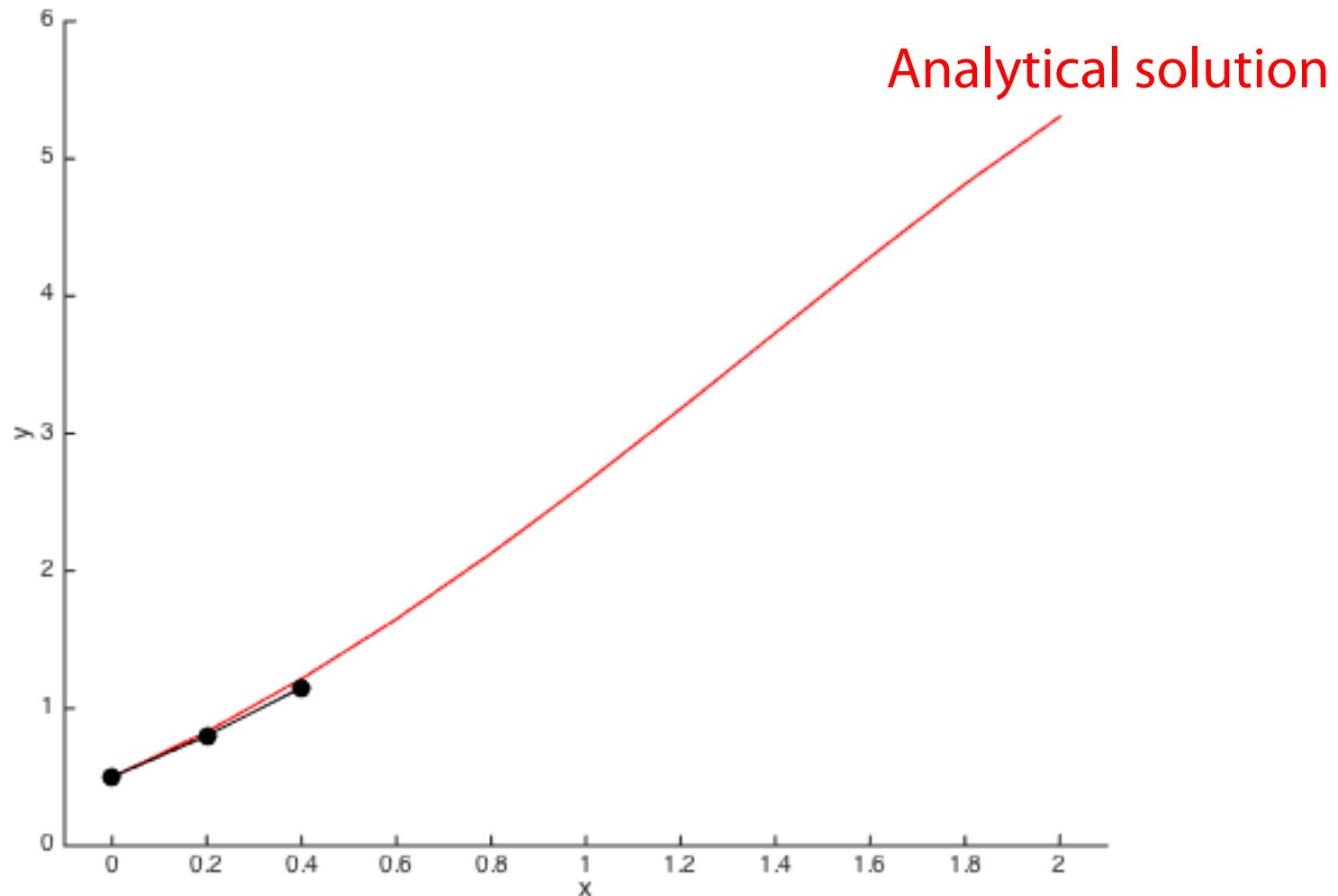
Example: $\frac{dy}{dx} = f(x, y) = y - x^2 + 1, \quad y(0) = 0.5$



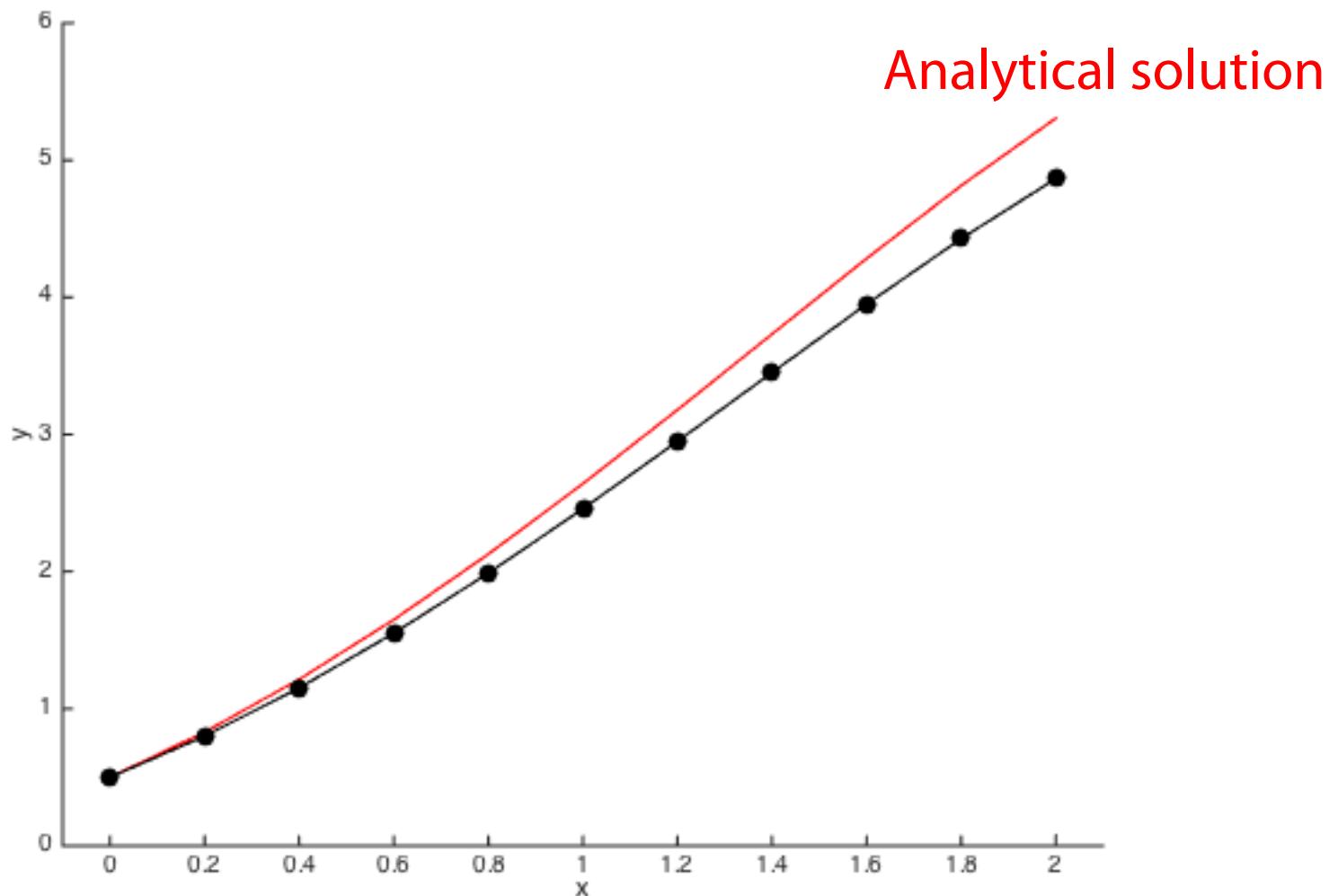
Example: $\frac{dy}{dx} = f(x, y) = y - x^2 + 1, \quad y(0) = 0.5$



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Example: $\frac{dy}{dx} = f(x, y) = y - x^2 + 1,$ $y(0) = 0.5$



Algorithm for Euler's method

$$\frac{dy}{dt} = f(t, y) \quad \text{is our ODE}$$

$$y(t_0) = y_0 \quad \text{is our initial condition}$$

$$t_k = t_0 + k\Delta t \quad \text{are our "mesh points"}$$

$$\begin{aligned} y_k &= y_{k-1} + \Delta t \cdot f(t_{k-1}, y_{k-1}) \\ &\approx y(t_k) \end{aligned}$$

Let's apply this to a simple production
and decay example



$$\frac{dA}{dt} = k_0 - k_1 A = f(t, A)$$

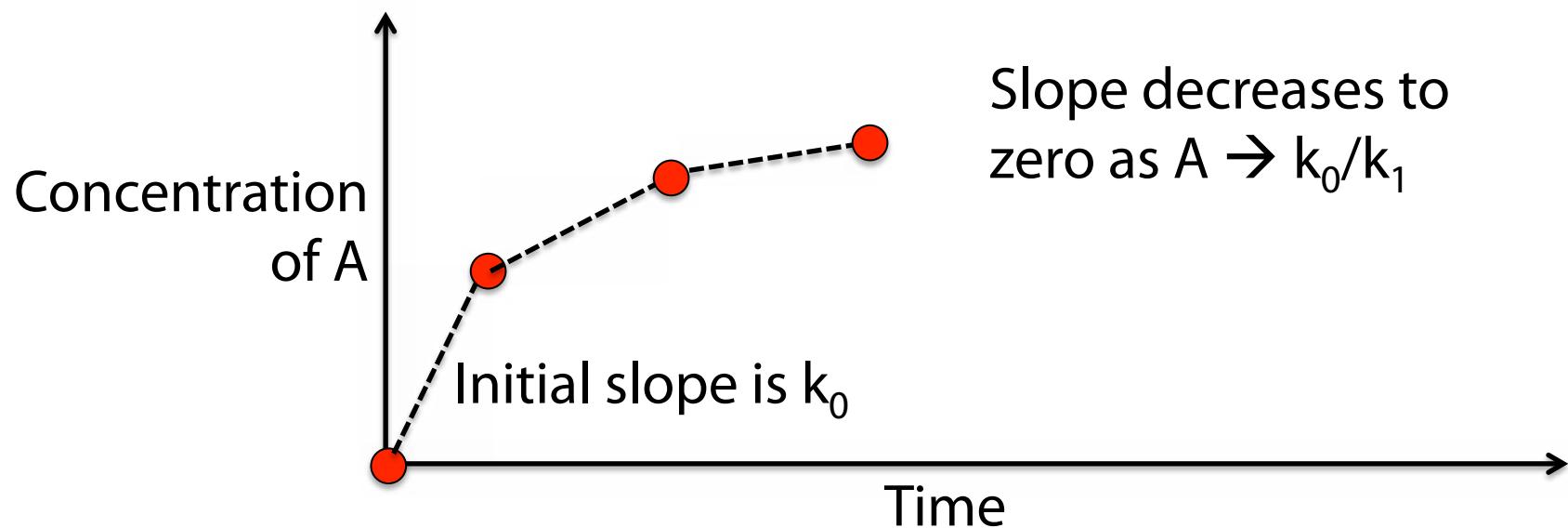
$$t_k = t_0 + k\Delta t$$

Let's apply this to a simple production and decay example



$$\frac{dA}{dt} = k_0 - k_1 A = f(t, A)$$

$$A(t = 0) = A_0 = 0$$



What if our system has more than one molecular species?

$$\begin{aligned}\frac{dx}{dt} &= f(t, x, y) & \frac{dy}{dt} &= g(t, x, y) \\ x(t_0) &= x_0 & y(t_0) &= y_0\end{aligned}$$

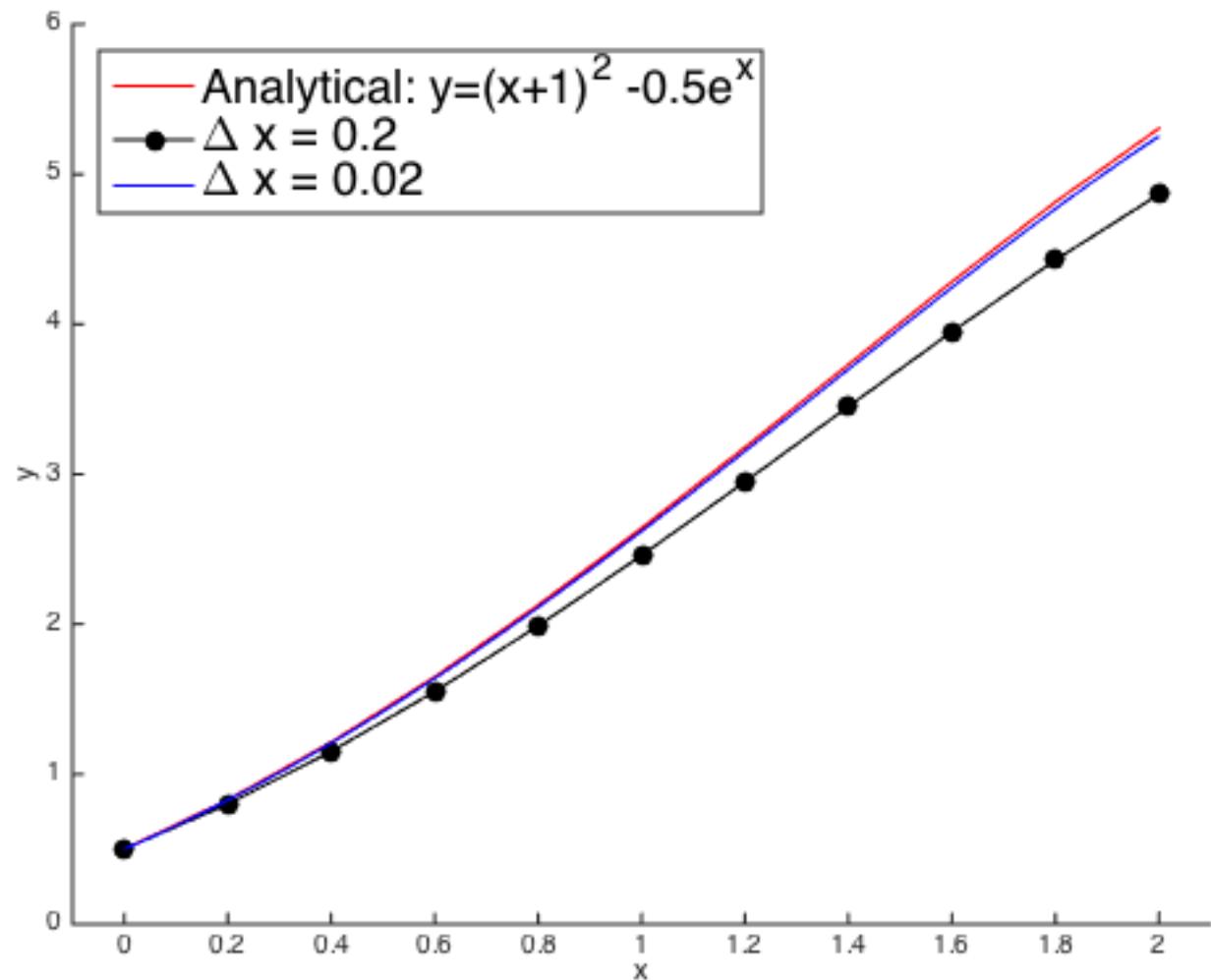
$$x_k = x_{k-1} + \Delta t \cdot f(t_{k-1}, x_{k-1}, y_{k-1})$$

$$\approx x(t_k)$$

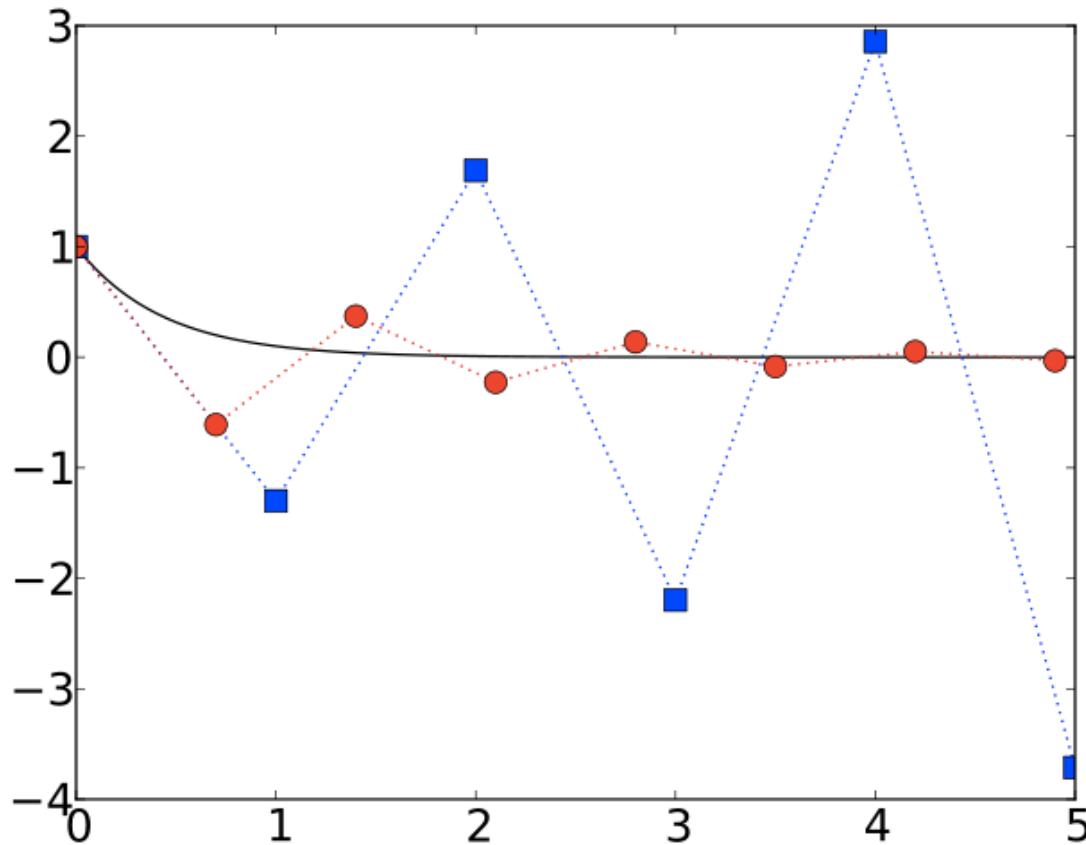
$$y_k = y_{k-1} + \Delta t \cdot g(t_{k-1}, x_{k-1}, y_{k-1})$$

$$\approx y(t_k)$$

Smaller step sizes give more accurate results



Oscillations and instability can result from overly large step sizes



$$\frac{dy}{dx} = -2.3y \quad y(0) = 1$$

Analytical solution

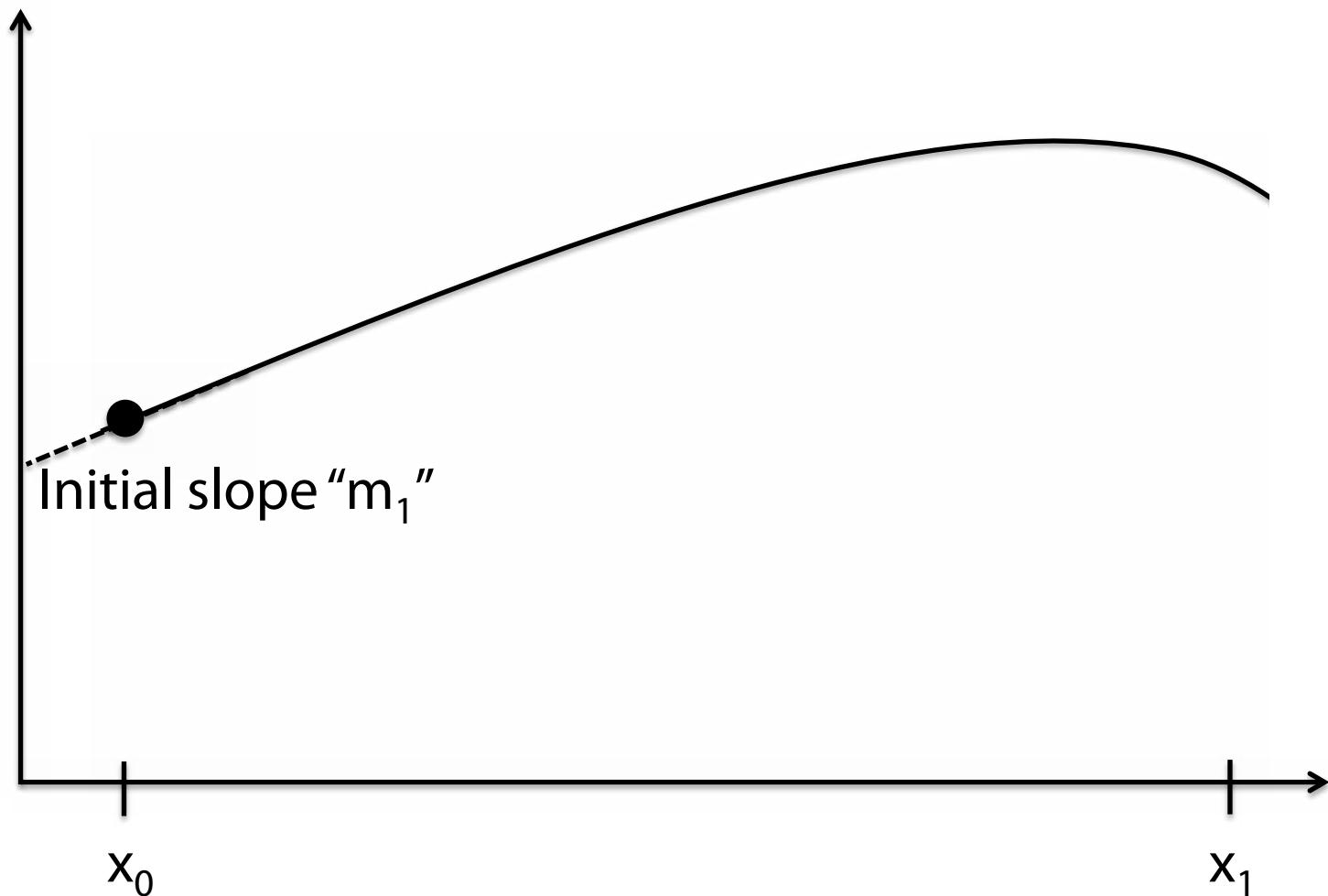
$\Delta x = 1$

$\Delta x = 0.7$

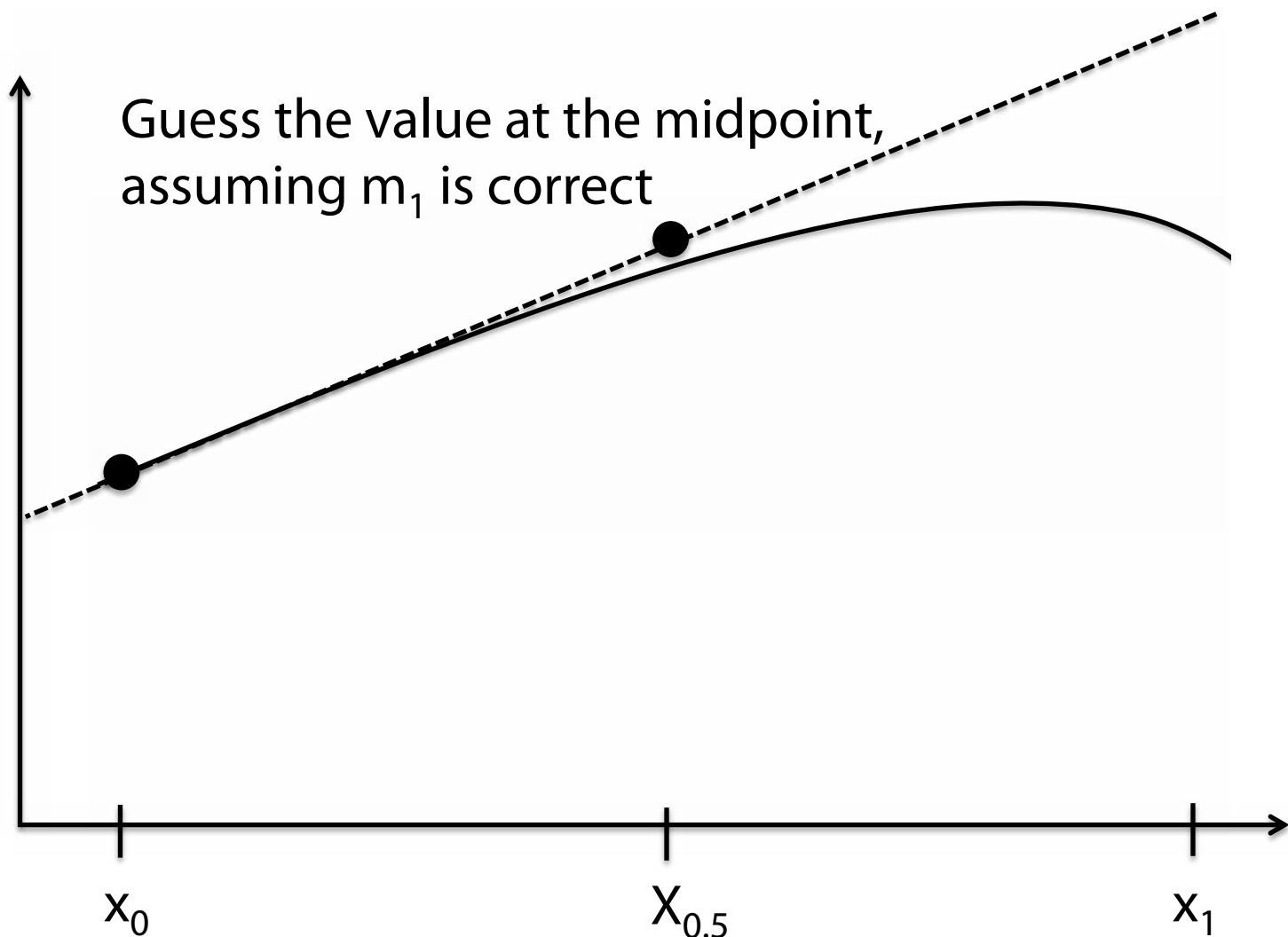
An improvement on Euler's method:
estimating the slope at multiple places
within each interval

The Runge-Kutta methods [e.g. `ode45()`
in MATLAB] do this

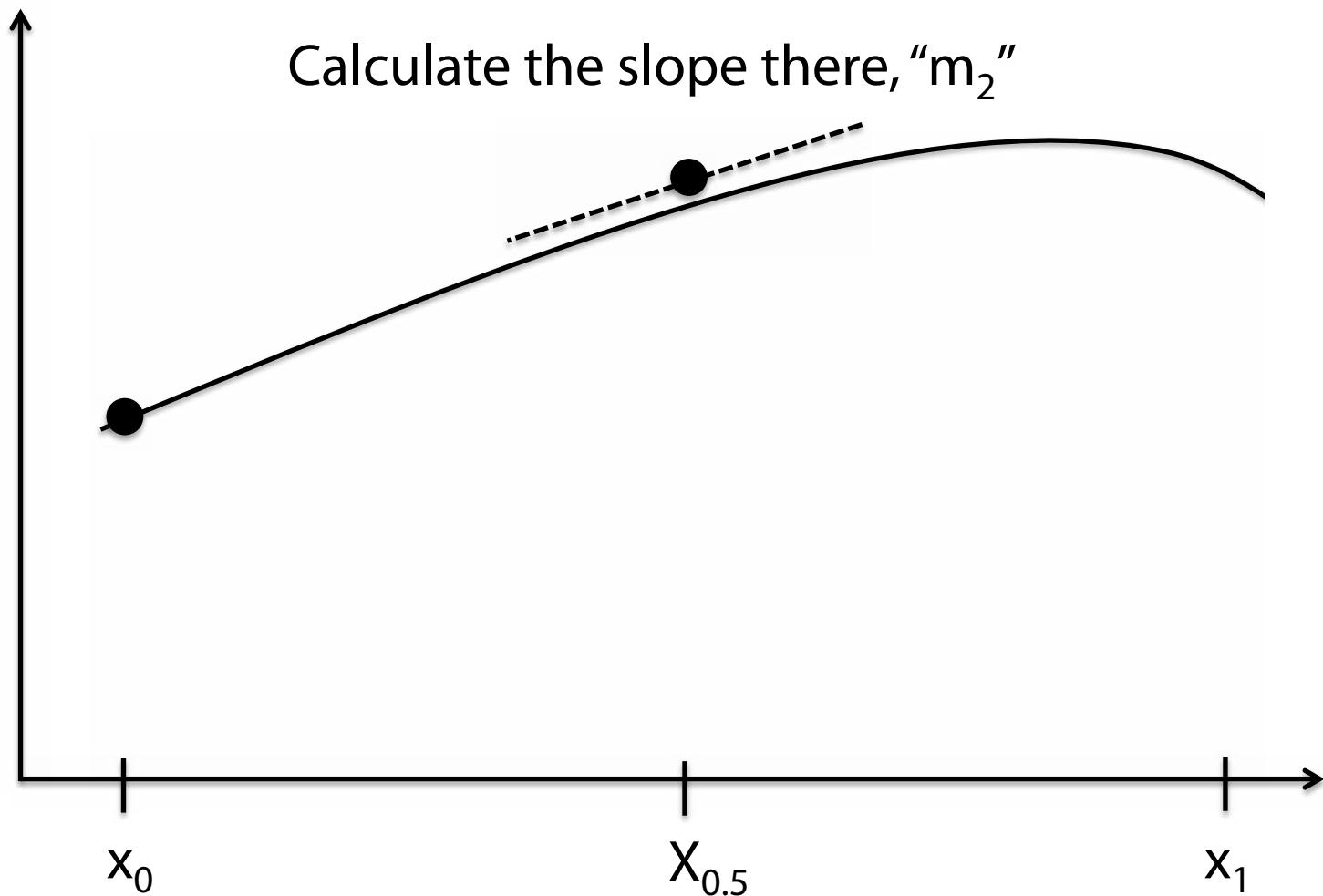
Runge-Kutta in action



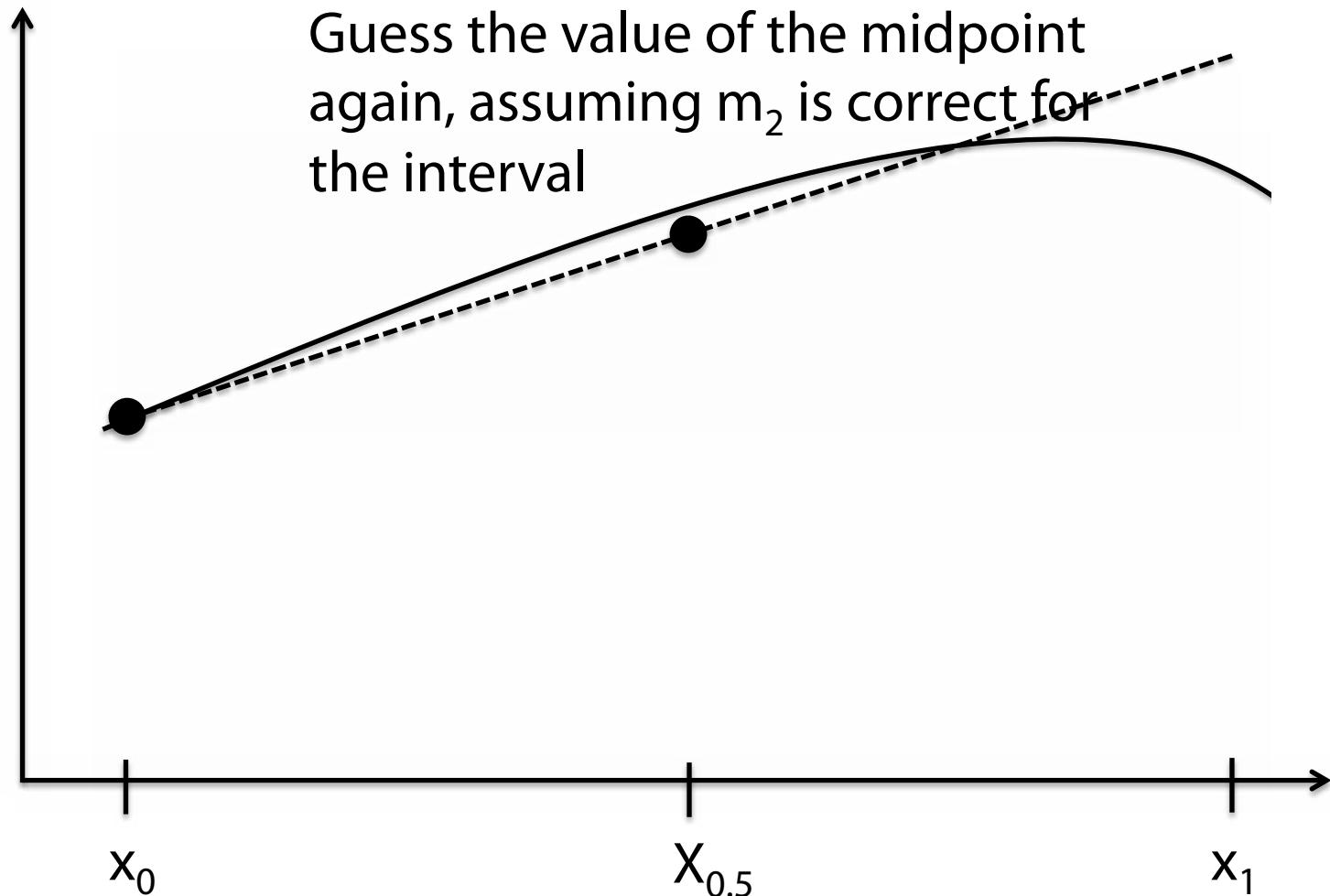
Runge-Kutta in action



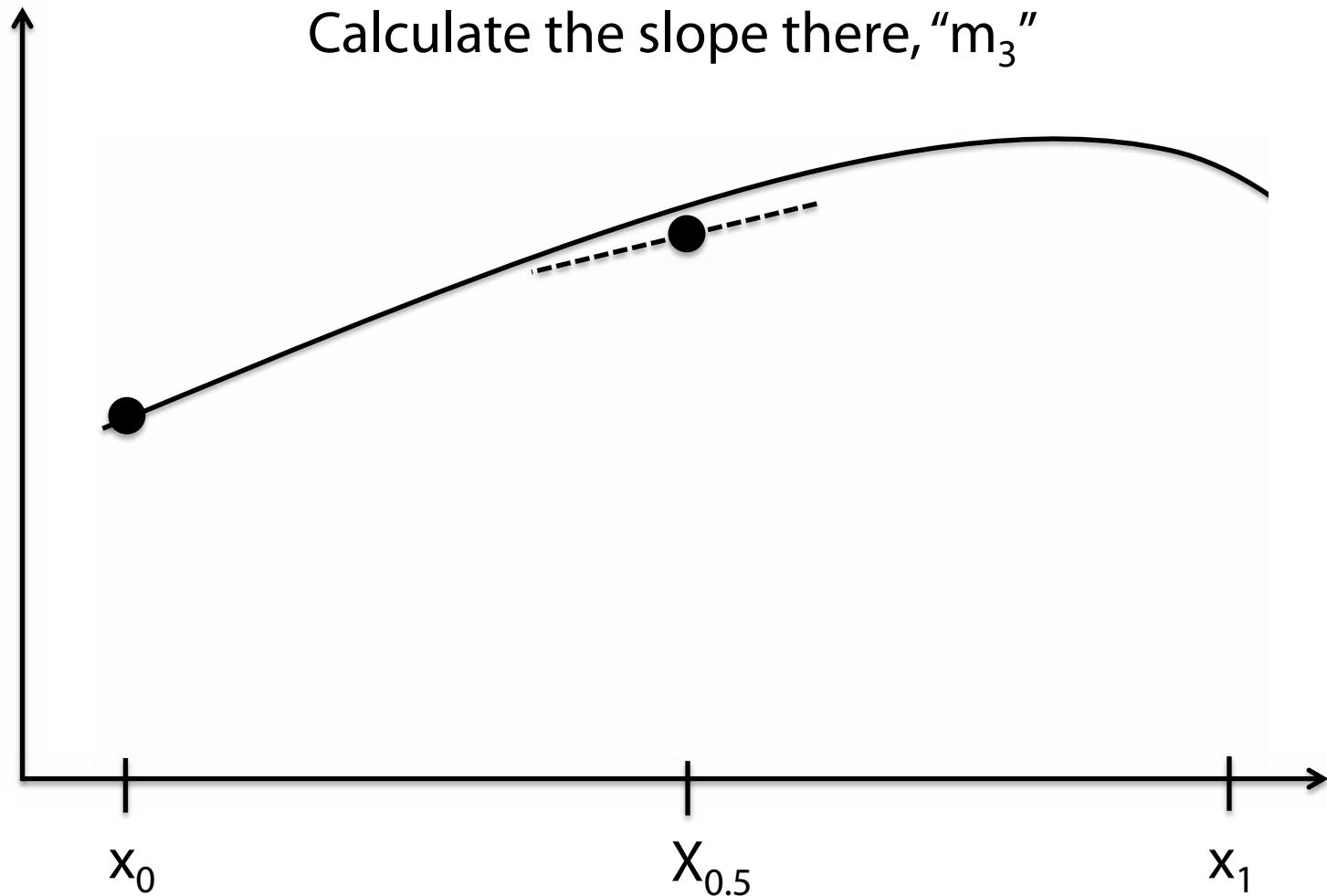
Runge-Kutta in action



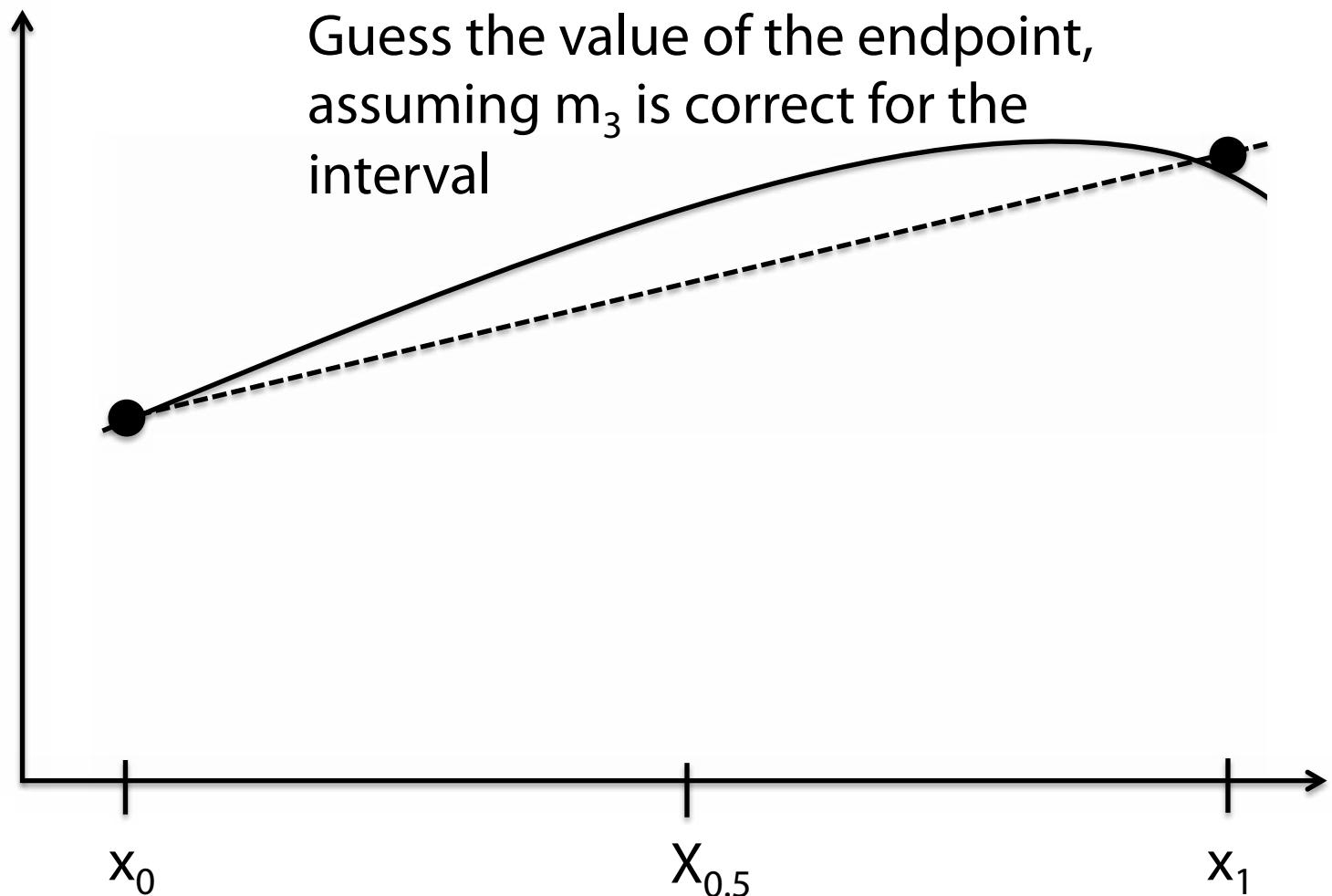
Runge-Kutta in action



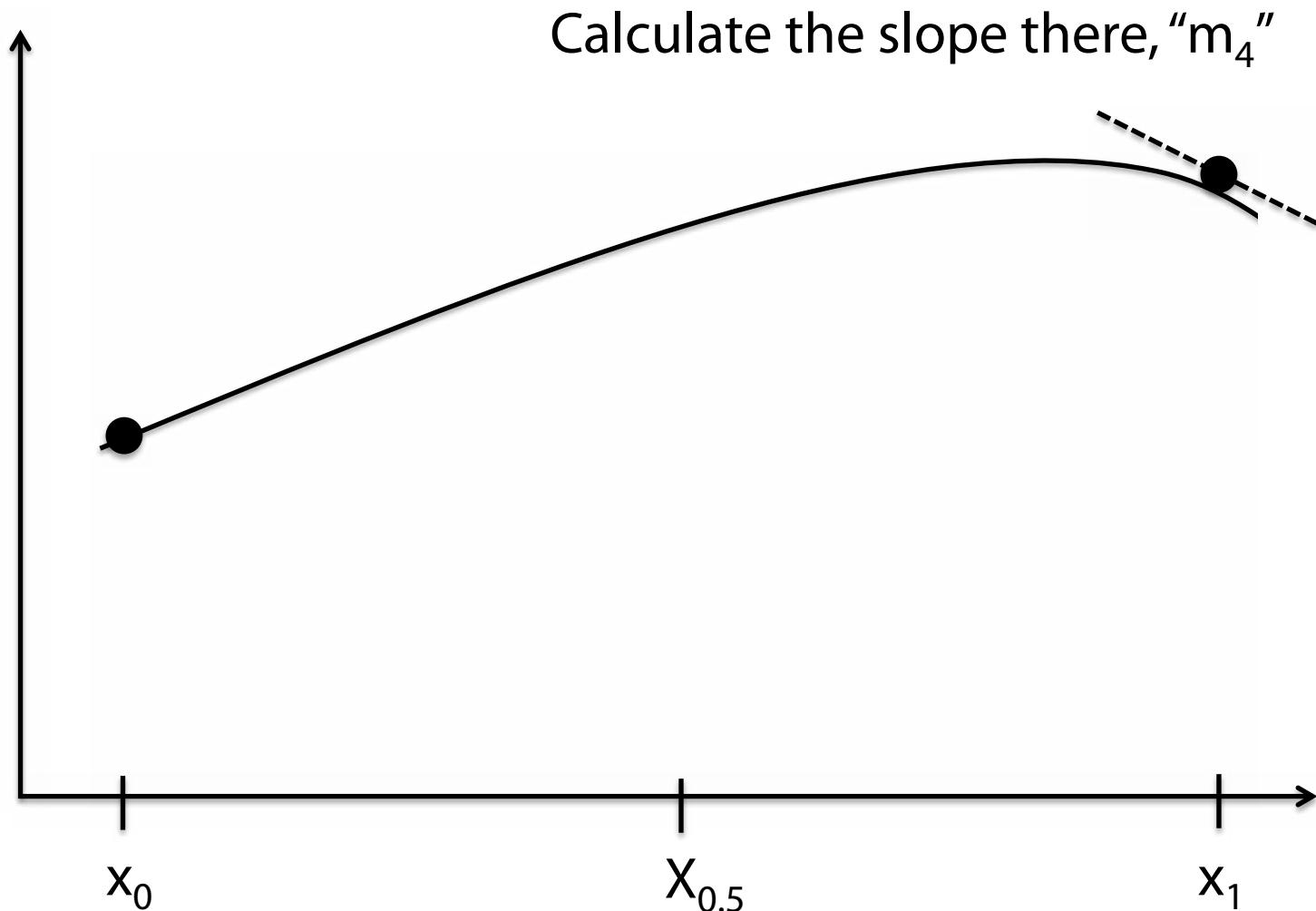
Runge-Kutta in action



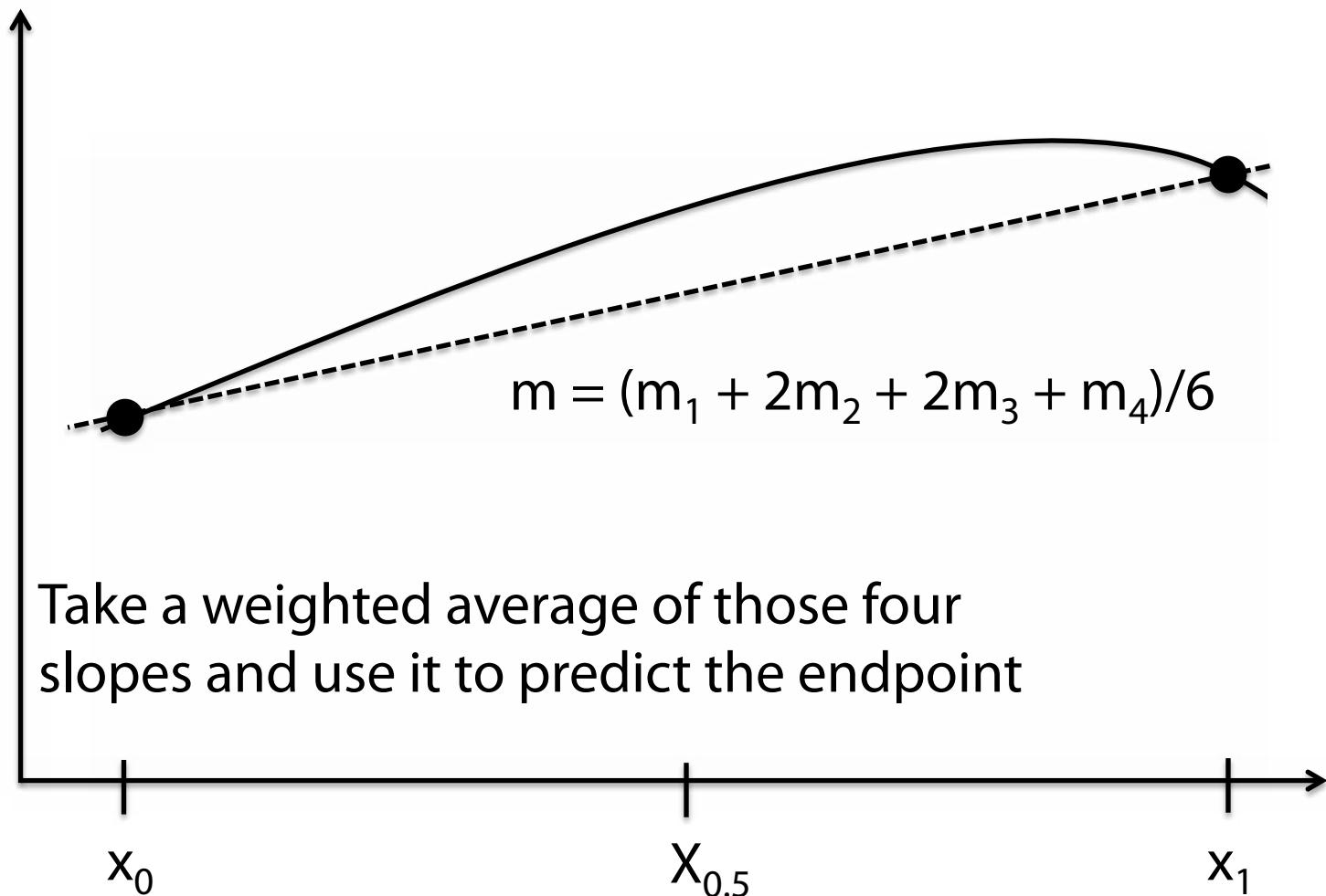
Runge-Kutta in action



Runge-Kutta in action



Runge-Kutta in action



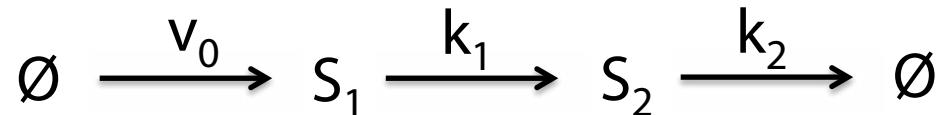
Using the Runge-Kutta method in MATLAB

- Define a function that returns the instantaneous rate of change for each variable
- Call the `ode45()` function with:
 - The name of your function, e.g. `@myfunction`
 - The time range that interests you
 - The initial concentrations of all molecular species

Demo in MATLAB (tutorial in Ingalls, appendix C)

Also ported to Python, see course website

MATLAB Demo



$$\frac{dS_1}{dt} = v_0 - k_1 S_1$$

Initial conditions: $S_1(0) = 1 \text{ } \mu\text{M}$, $S_2(0) = 0 \text{ } \mu\text{M}$

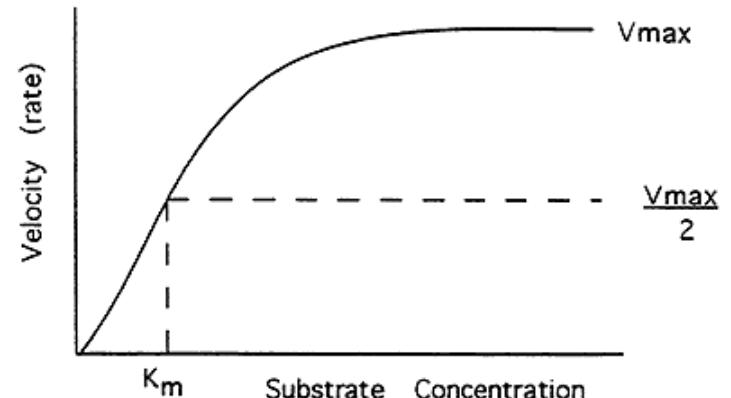
Parameter values: $v_0 = 5 \text{ } \mu\text{M min}^{-1}$

$$k_1 = 3 \text{ } \text{min}^{-1}$$

$$k_2 = 2 \text{ } \text{min}^{-1}$$

Goal: plot concentrations over the first five minutes.

Next time:



Enzyme kinetics