MA 331

Differential Equations for the Life Sciences

Fall 2018

Lecture 10

Moving Beyond One Dimensional Models

The differential equation $\frac{dy}{dt} = g(t, y)$ describes how a single quantity changes over time

This is a **one dimensional model**

Most biological systems involve 2 or more quantities changing together, e.g. numbers of predators and their prey, biochemical reactants and their products, susceptibles, infectives and recovereds

Higher dimensional models, e.g.

$$\frac{dx}{dt} = f(t, x, y)$$
$$\frac{dy}{dt} = g(t, x, y)$$

Rate of change of *x* depends not only on value of *x*, but also value of *y*, etc

“coupled” equations

Sometimes label “species” with subscripts:

$$\frac{dx_1}{dt} = f_1(t, x_1, x_2)$$
$$\frac{dx_2}{dt} = f_2(t, x_1, x_2)$$

Prodrug Model

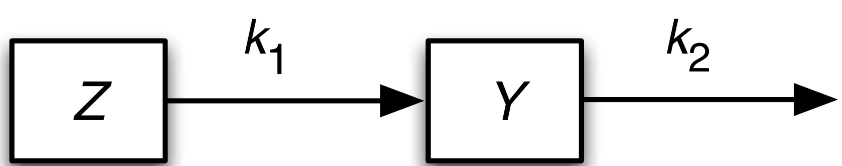
In many instances, a drug is administered by means of a **prodrug** rather than as the drug itself

Prodrug is metabolized into the drug: i.e. a precursor of the active product is administered

Why might you do this? The prodrug might be more easily absorbed through the GI tract: could give prodrug orally whereas drug might have to be injected, or given at a higher concentration

Can also help reduce non-target effects (e.g. imagine if the metabolic process only occurred in a particular organ)

Simplified schematic:



Prodrug, *z*, decays into drug, *y*, according to 1st order kinetics

1st order drug decay kinetics

$$\frac{dz}{dt} = -k_1 z$$
$$\frac{dy}{dt} = k_1 z - k_2 y$$

with initial conditions $z(0) = z_0$, $y(0) = 0$

Prodrug Model

$$\frac{dz}{dt} = -k_1 z$$

$$\frac{dy}{dt} = k_1 z - k_2 y$$

with initial conditions $z(0) = z_0$, $y(0) = 0$

We can make some progress in solving this model

Notice that the z equation doesn't involve y ("decoupled")

Furthermore, the z equation is just exponential decay, so has solution $z(t) = z_0 e^{-k_1 t}$

Substitute this expression for z into the y equation:

$$\frac{dy}{dt} = k_1 z_0 e^{-k_1 t} - k_2 y$$

How to solve this? It's not separable… but fortunately there is a method that will work…

First Order Linear Differential Equations

Another important class of differential equations that we can solve analytically:

$$\frac{dy}{dt} + a(t)y = b(t)$$

where *a*(*t*) and *b*(*t*) are functions of time (note: one or both could be constant)

To solve, first calculate $A(t) = \int a(t)\, dt$

(don't need a constant of integration here, even though we have an indefinite integral)

Then find *y*(*t*) by calculating

$$y(t) = e^{-A(t)}\left(\int e^{A(t)} b(t)\, dt + k\right)$$

k : constant of integration. Note: (1) it is needed at this step and (2) pay attention to its location

(Why does this method work and where does this formula come from? See the scanned notes if you are interested in the details.

But just to mention: the quantity $e^{A(t)}$ is known as an integrating factor, and the method is based on the product rule.)

First Order Linear Differential Equations

Example: solve $dy/dt = t + y$ Notice: not separable!

First step: have to rearrange to get it into the form $\dfrac{dy}{dt} + a(t)y = b(t)$

$dy/dt - y = t$

So: $a(t) = -1$ and $b(t) = t$

To solve, first calculate $A(t) = \int a(t)\, dt$

$$A(t) = \int -1\, dt = -t$$

(recipe says we don't need a constant of integration here, even though we have an indefinite integral)

Then find $y(t)$ by calculating

$$y(t) = e^{-A(t)}\left(\int e^{A(t)} b(t)\, dt + k\right)$$

$$y(t) = e^{-(-t)}\left(\int e^{-t} t\, dt + k\right) = e^{t}\left(\int t\, e^{-t}\, dt + k\right)$$

It turns out that $\int t\, e^{-t}\, dt = -(1+t)e^{-t}$, so $y(t) = e^{t}\left(-(1+t)e^{-t} + k\right)$

$$\boxed{y(t) = -1 - t + k\, e^{t}}$$

Prodrug Model

Returning to our prodrug example…

$$\frac{dy}{dt} = k_1 z_0 e^{-k_1 t} - k_2 y$$

Rearrange: $\frac{dy}{dt} + k_2 y = k_1 z_0 \exp\left(-k_1 t\right)$ so $a(t) = k_2$, $b(t) = k_1 z_0 \exp\left(-k_1 t\right)$

$$A(t) = \int a(t)\,dt = \int k_2 \, dt = k_2 t$$

$$y(t) = e^{-A(t)}\left(\int e^{A(t)} b(t)\,dt + k\right)$$

$$= e^{-k_2 t}\left(\int e^{k_2 t} k_1 z_0 e^{-k_1 t} \, dt + k\right)$$

$$= e^{-k_2 t}\left(k_1 z_0 \int e^{\{k_2 - k_1\}t} \, dt + k\right)$$

$$= e^{-k_2 t}\left(k_1 z_0 \frac{e^{\{k_2 - k_1\}t}}{k_2 - k_1} + k\right) \qquad = \frac{k_1 z_0}{k_2 - k_1} e^{-k_1 t} + k\, e^{-k_2 t}$$

Prodrug Model

$$y(t) = \frac{k_1 z_0}{k_2 - k_1} e^{-k_1 t} + k\, e^{-k_2 t}$$

Use initial condition, $y(0) = 0$ to fix value of k :

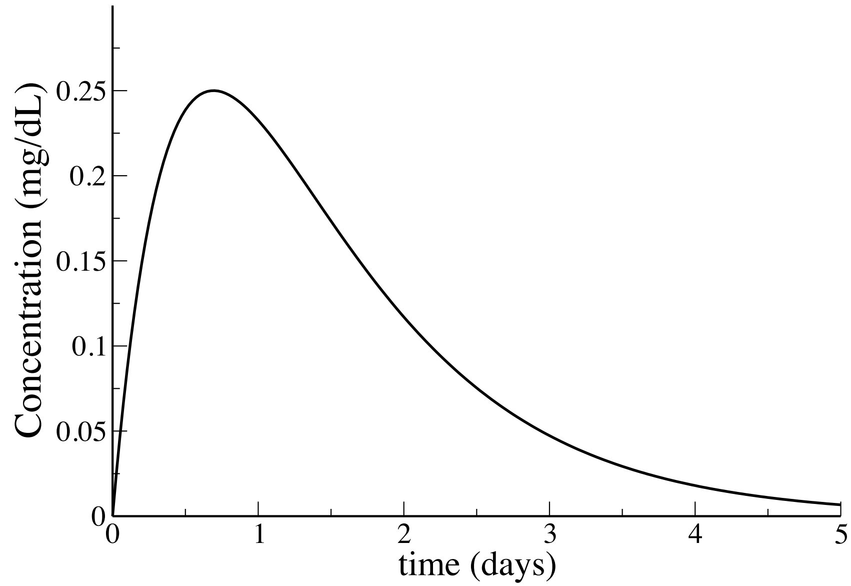
$$y(0) = \frac{k_1 z_0}{k_2 - k_1} + k \qquad \text{so} \quad k = -\frac{k_1 z_0}{k_2 - k_1}$$

$$\boxed{y(t) = \frac{k_1 z_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right)}$$

Prodrug Model

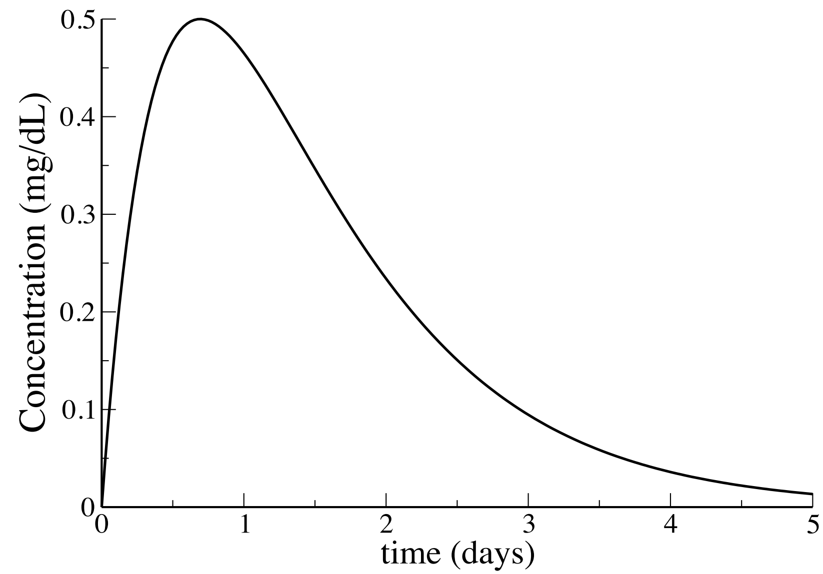
$$y(t) = \frac{k_1 z_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right)$$

Example: k_1 = 1 day^{-1}, k_2 = 2 day^{-1}



Example: k_1 = 2 day^{-1}, k_2 = 1 day^{-1}

Note scales on *y* axes



Prodrug Model

$$y(t) = \frac{k_1 z_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right)$$

Question: When does drug concentration, *y*, hit its maximum?

differentiate the solution formula:

$$\frac{dy}{dt} = \frac{k_1 z_0}{k_2 - k_1}\left(-k_1 e^{-k_1 t} + k_2 e^{-k_2 t}\right)$$

$$\frac{dy}{dt} = 0 \Rightarrow -k_1 e^{-k_1 t} + k_2 e^{-k_2 t} = 0$$

$$k_2 e^{-k_2 t} = k_1 e^{-k_1 t}$$

$$k_2 / k_1 = e^{-k_1 t} e^{k_2 t}$$

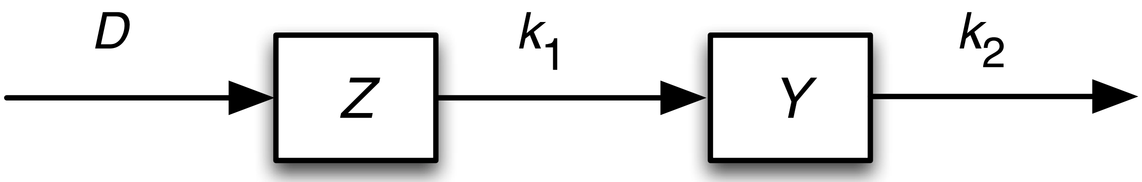
$$k_2 / k_1 = e^{\left(k_2 - k_1\right) t}$$

$$\ln\left(k_2 / k_1\right) = \left(k_2 - k_1\right) t$$

$$t = \frac{\ln\left(k_2\right) - \ln\left(k_1\right)}{k_2 - k_1}$$

Prodrug Model with IV infusion

How would things change if prodrug were continuously administered (e.g. via IV drip) at rate *D*, rather than as an initial dose?



$$\frac{dz}{dt} = D - k_1 z$$
$$\frac{dy}{dt} = k_1 z - k_2 y$$

with initial conditions $z(0) = 0$, $y(0) = 0$

As before, the *z* equation doesn't depend on *y*, so we can solve this separately

Furthermore, we have seen the *z* equation before. Can either solve by separation of variables, or look answer up (on formula sheet or notes from lecture 1)…

$$z(t) = \frac{D}{k_1}\left(1 - e^{-k_1 t}\right)$$

Prodrug Model with IV infusion

Substitute solution for *z* into *y* equation: $$\frac{dy}{dt} = k_1 \frac{D}{k_1}\left(1 - e^{-k_1 t}\right) - k_2 y$$

$$\frac{dy}{dt} = D\left(1 - e^{-k_1 t}\right) - k_2 y$$

Rearrange: $$\frac{dy}{dt} + k_2 y = D\left(1 - \exp\left(-k_1 t\right)\right) \quad \text{so} \quad a(t) = k_2 \;, \quad b(t) = D\left(1 - \exp\left(-k_1 t\right)\right)$$

$$A(t) = \int a(t)\,dt = \int k_2 \; dt = k_2 t$$

$$y(t) = e^{-A(t)}\left(\int e^{A(t)} b(t)\, dt + k\right)$$

$$= e^{-k_2 t}\left(\int e^{k_2 t} D\left(1 - e^{-k_1 t}\right) dt + k\right)$$

$$= e^{-k_2 t}\left(D \int \left(e^{k_2 t} - e^{\{k_2 - k_1\} t}\right) dt + k\right)$$

$$= e^{-k_2 t}\left(\frac{D e^{k_2 t}}{k_2} - \frac{D e^{\{k_2 - k_1\} t}}{k_2 - k_1} + k\right) \quad = \frac{D}{k_2} - \frac{D}{k_2 - k_1} e^{-k_1 t} + k\, e^{-k_2 t}$$

Prodrug Model with IV infusion

$$y(t) = \frac{D}{k_2} - \frac{D}{k_2 - k_1} e^{-k_1 t} + k\, e^{-k_2 t}$$

Use initial condition *y*(0) = 0:

$$y(0) = \frac{D}{k_2} - \frac{D}{k_2 - k_1} + k$$

Set equal to 0 and solve for *k*:

$$k = \frac{D}{k_2 - k_1} - \frac{D}{k_2}$$

$$y(t) = \frac{D}{k_2} - \frac{D}{k_2 - k_1} e^{-k_1 t} + \left(\frac{D}{k_2 - k_1} - \frac{D}{k_2} \right) e^{-k_2 t}$$

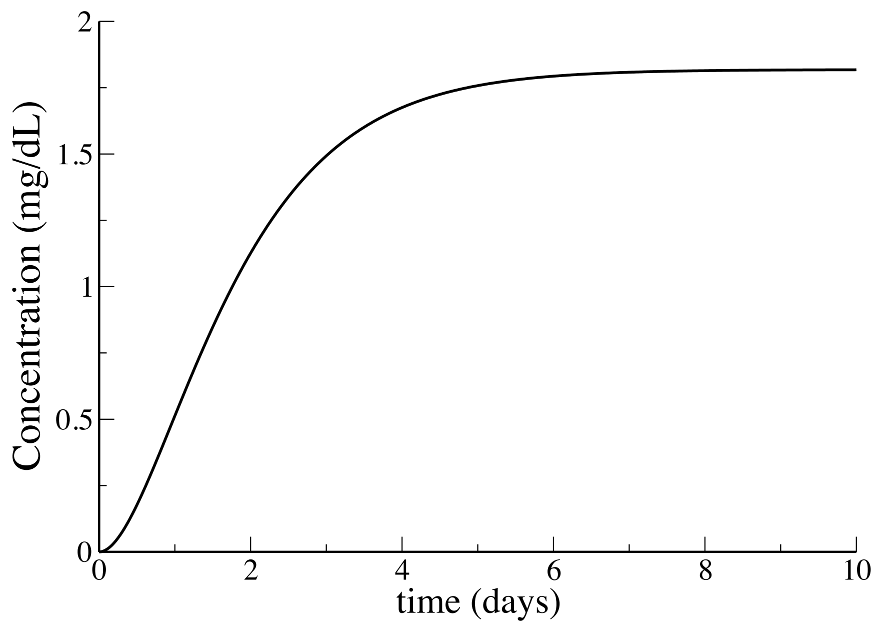
$$y(t) = \frac{D}{k_2}\left(1 - e^{-k_2 t}\right) + \frac{D}{k_2 - k_1}\left(e^{-k_2 t} - e^{-k_1 t}\right)$$

In the long run, *y* approaches D/k_2

Prodrug Model with IV infusion

$$y(t) = \frac{D}{k_2}\left(1 - e^{-k_2 t}\right) + \frac{D}{k_2 - k_1}\left(e^{-k_2 t} - e^{-k_1 t}\right)$$

Example: $D = 2$, $k_1 = 1$, $k_2 = 1.1$



Prodrug Model with IV infusion

Quite a lot of work to solve this model analytically… could we have found the long-term behavior more easily?

Look for equilibrium solution: for a 2D model, this requires that **both** $dy/dt=0$ **and** $dz/dt=0$

$$\frac{dz}{dt} = D - k_1 z$$

$$\frac{dy}{dt} = k_1 z - k_2 y$$

Setting $dz/dt=0$ quickly gives us that $z=D/k_1$

Substituting this into $dy/dt=0$ then gives us that $y=D/k_2$

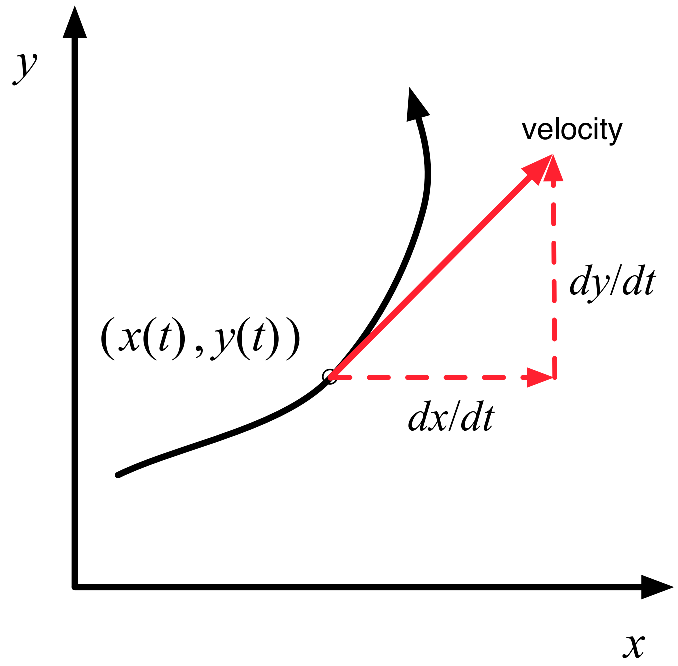
Moving Beyond One Dimensional Models

Now that we have more than one state variable, our phase space is no longer the line.

For a two dimensional model, we have the phase plane
(we will typically stick to 2D, because sketching things gets more difficult for 3+ dimensions)

$$\frac{dx}{dt} = f(t, x, y)$$

$$\frac{dy}{dt} = g(t, x, y)$$



We look at the point (*x*,*y*), and how this changes with time

Solution traces out a curve in the phase plane

Velocity vector at time *t* is tangent to solution curve at that point

Velocity vector has two components, one in *x* direction, one in *y* direction, given by *dx*/*dt* and *dy*/*dt*, respectively