# Love and differential equations:

# An introduction to modeling

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David M. Allen
Professor Emeritus
Department of Statistics
University of Kentucky

# What is a model?

## A model airplane

A model airplane operates, for the most part, on the same principles as an actual airplane.

## A lingerie model

Yasmeen Ghauri is a Victoria's Secret model.

## Definition of a model

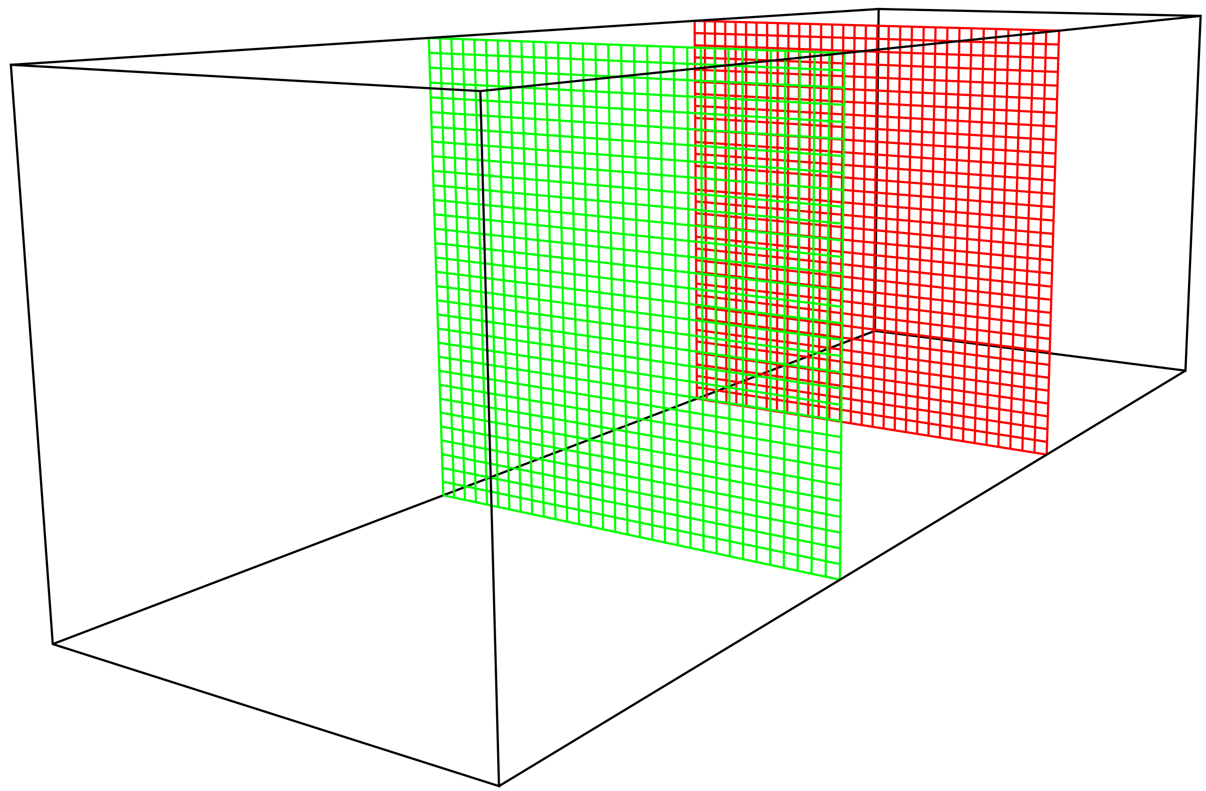
A model is a physical representation of a system we wish to study. We want to make the model as close to the real thing as our knowledge and resources will allow.

In drug and toxicology studies we are often interested in the metabolism of a substance by a human or an animal. Any model we might propose for one of these systems is going to be an oversimplification. Nevertheless, some models do an excellent job describing observations on these systems.

## Introduction to compartment models

- Models
- Kinetics
- Benefits of modeling
- Deterministic and stochastic models

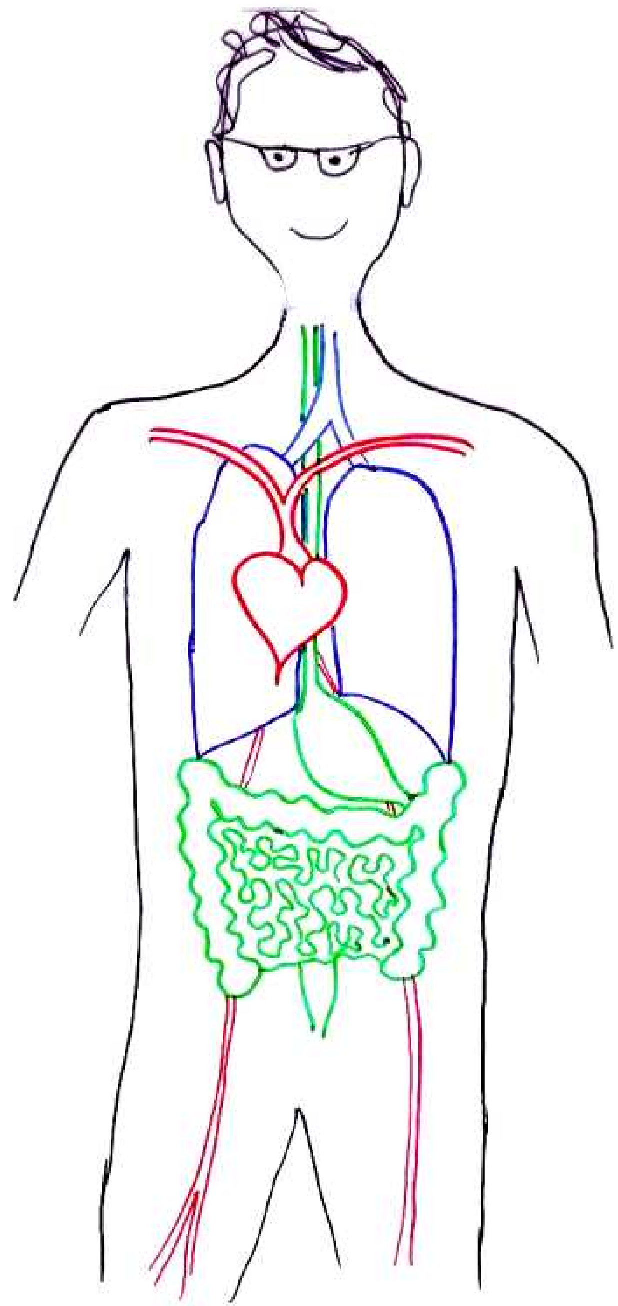
## Compartmental model



A fish tank separated into three compartments by membranes is an example of a compartment model. The tank is filled with a medium, and a substance is placed in the medium. We are interested in the movement of the substance from compartment to compartment.

## A more complicated system

Obviously, the fish tank model is a vast oversimplification of this system[a].



[a]Drawn by Diane Allen, now age 30, in about the eighth grade

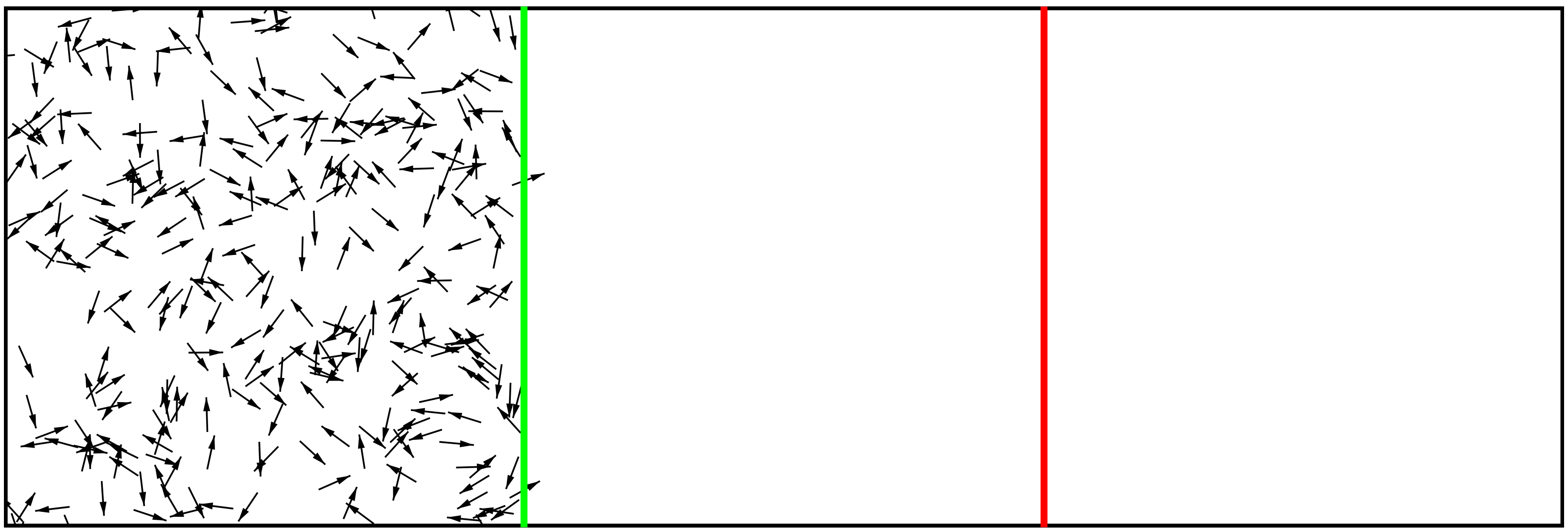
## Kinetics

**Kinetics:** a science that deals with the effects of forces upon the motions of material bodies or with changes in physical or chemical systems.

## Orders of kinetics

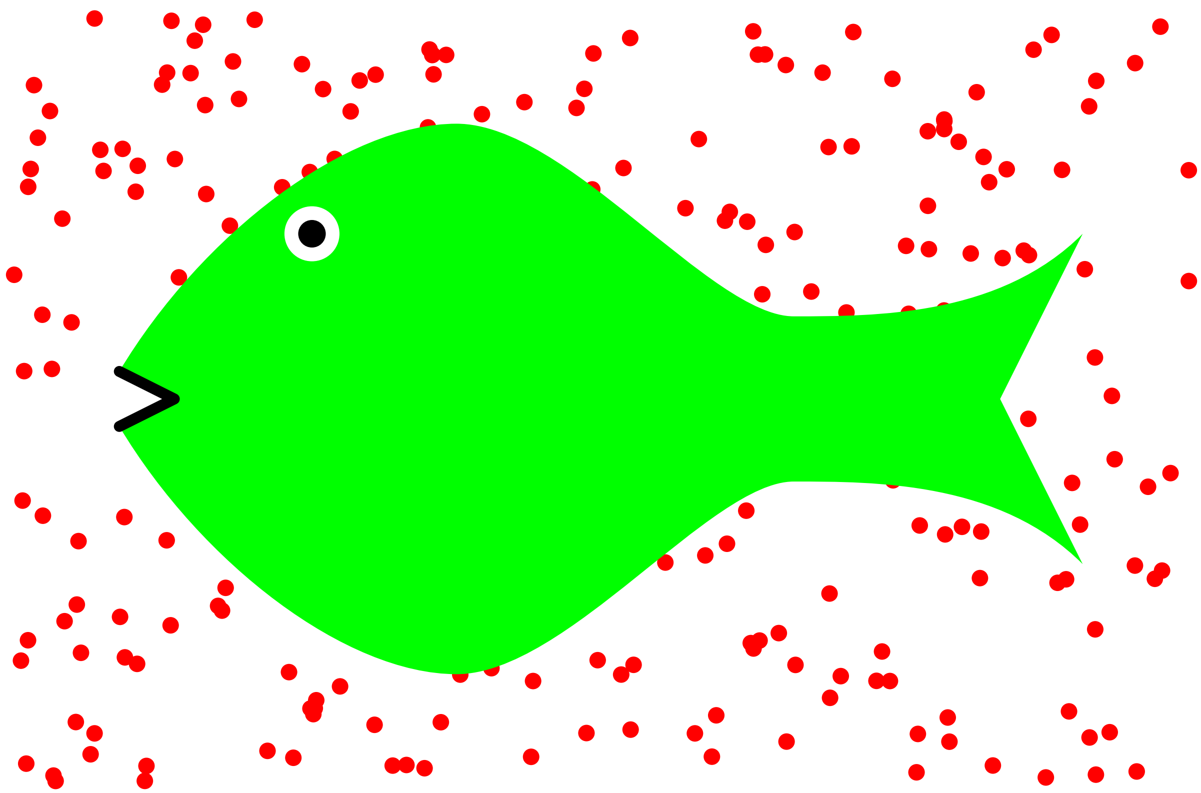
We have to make assumptions about the nature of the transfers from compartment to compartment. We now discuss zero and first order kinetics.

# First order kinetics



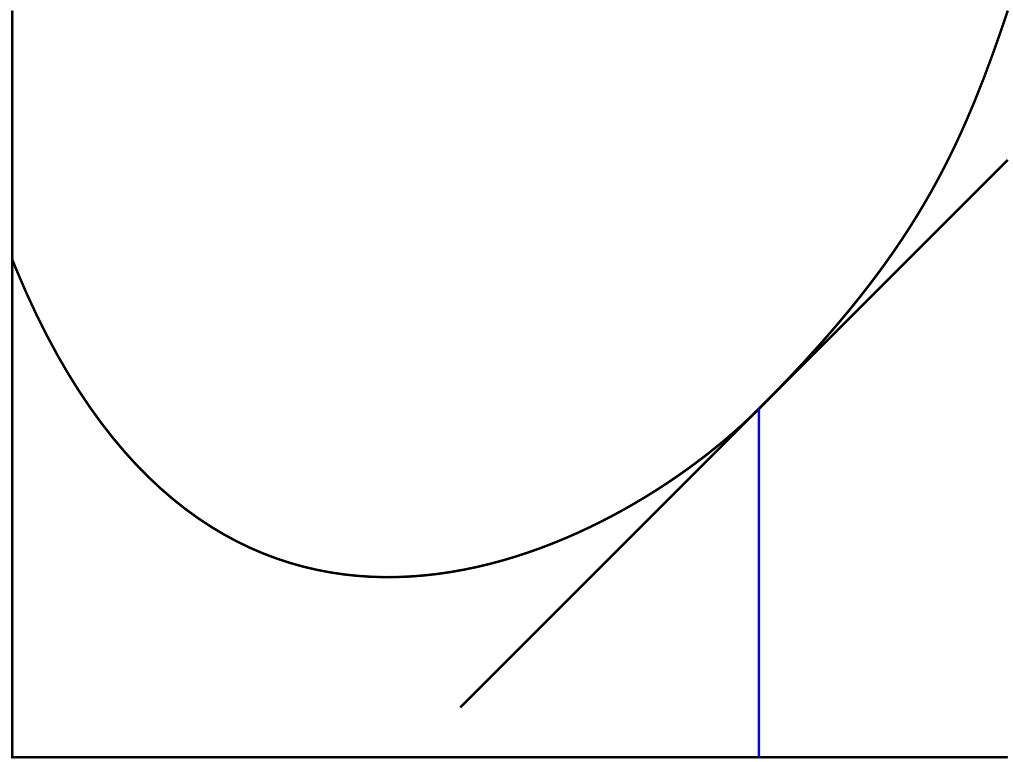
This figure depicts the side view of the fish tank. Suppose that, in any small interval of time, the number of molecules of the substance to move from compartment 1 to compartment 2 is approximately proportional to the number of molecules present. This is first order kinetics.

## Zero order kinetics



This figure depicts a fish swimming in water with mercury pollution. The uptake of mercury by the fish has no material effect on the amount of mercury in the water. The uptake of mercury is at a constant rate. This is zero order kinetics.

# The derivative of a function



The derivative of $X(t)$ with respect to $t$ is the change in $X(t)$ per unit change in $t$.

$$\dot{X}(t) = \frac{d}{dt}X(t) = \lim_{\Delta t \to 0} \frac{X(t+\Delta t) - X(t)}{\Delta t} = \frac{\text{rise}}{\text{run}}$$

## The order of a process in terms of a derivative

The order of a kinetic process is expressed in terms of the derivative of a function. Let $\theta$ be a rate constant. If

$$\dot{X}(t) = \theta$$

the process is zero order. If

$$\dot{X}(t) = \theta X(t)$$

the process is first order.

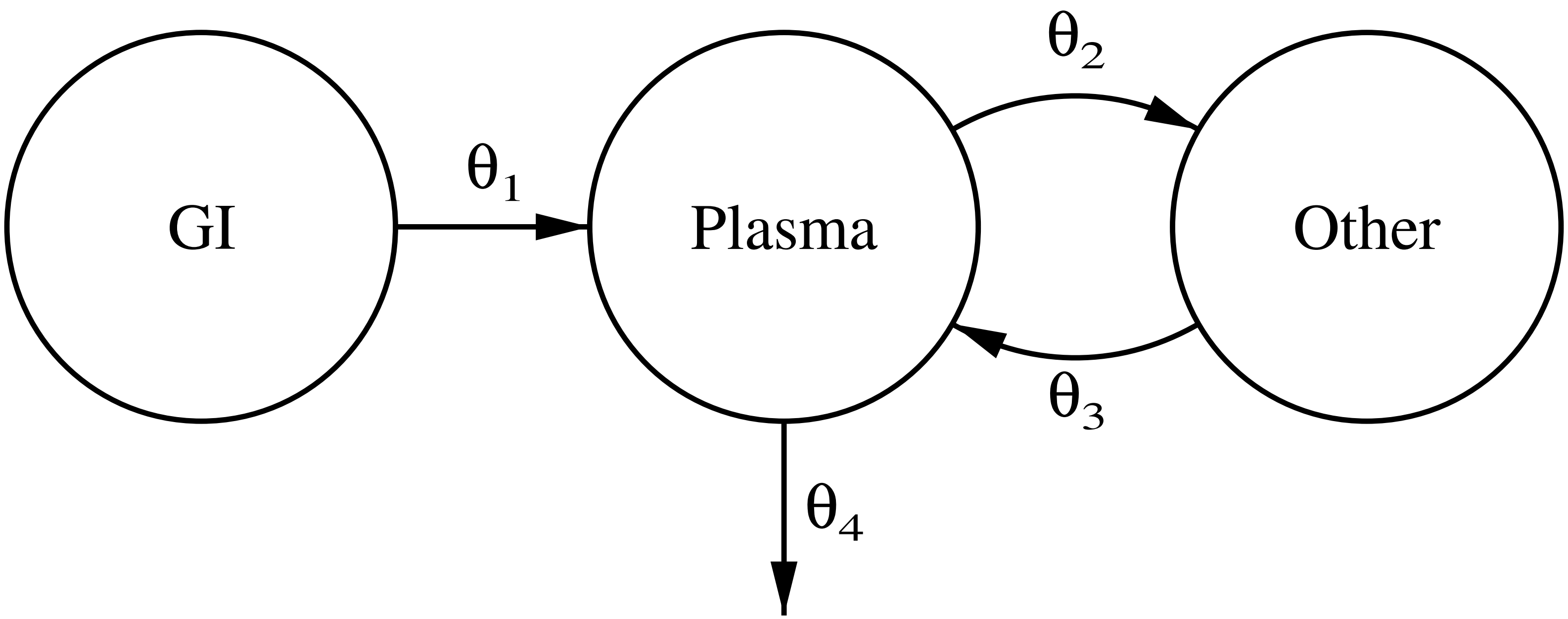
## Kinetic diagram

The first step of the modeling process is to create the kinetic diagram as follows:

- Determine what components of the system are to be represented by a compartment.
- Determine the possible transfers between compartments and adopt a symbol to represent the rate constant associated with each transfer.

## Pharmacokinetic model diagram

A frequently used pharmacokinetic model is



## Deterministic and stochastic models

There are two sets of premises commonly assumed for compartmental analysis. They share the kinetic diagram but differ in the mechanics of transfer between compartments. Traditionally we assume transfers are determined by a system of linear differential equations. Many believe it is more realistic to assume transfers are in accordance with a probabilistic mechanism. The two sets of premises are called *deterministic* and *stochastic models*, respectively.

## What can we learn from compartment models?

1. If we find a compartment model that describes our data well, we may have a plausible description of the mechanics underlying data generation.

## What can we learn? (continued)

2. Having found a plausible model that fits the data well, we can calculate many interesting things from the model:

- the uptake rate and steady state level of a heavy metal in animal tissue;
- the average time a drug stays at its site of action;
- the relative bioavailability of two drugs;
- the relationship between drug concentration in a compartment and symptom relief.

# Differential equations

The solution of systems of linear, first order, homogeneous, differential equations with constant coefficients is the main tool for deriving and fitting compartmental models to data.

# Derivatives and Integrals

In the following display, $c$ and $d$ are constants.

| $f(t)$ | $\frac{d}{dt}f(t)$ |
|---|---|
| $ct^d$ | $cdt^{d-1}$ |
| $\exp(ct)$ | $c\exp(ct)$ |
| $\exp(ct)X(t)$ | $\exp(ct)\left(\dot{X}(t)+cX(t)\right)$ |
| $\sin(ct)$ | $c\cos(ct)$ |
| $\cos(ct)$ | $-c\sin(ct)$ |
| $\int g(t)dt$ | $g(t)$ |

Read from left to right for derivatives and from right to left for integerals.

## Characteristic Polynomials

The characteristic polynomial of the 2 × 2 matrix

$$K = \begin{bmatrix} k_{11} & k_{12} \\ k_{21} & k_{22} \end{bmatrix}$$

is

$$\begin{vmatrix} k_{11} - \lambda & k_{12} \\ k_{21} & k_{22} - \lambda \end{vmatrix}.$$

Expanding the determinant gives

$$\lambda^2 - (k_{11} + k_{22})\lambda + k_{11}k_{22} - k_{12}k_{21}.$$

## Characteristic Equation

Setting the characteristic polynomial equal to zero gives the characteristic equation. The solutions to the characteristic equation are

$$\lambda = \frac{k_{11} + k_{22}}{2} \pm \sqrt{(k_{11} - k_{22})^2/4 + k_{21}k_{12}}.$$

The quantity under the radical is called the *discriminant*. The solutions to the characteristic equation are called the *characteristic roots* or *eigenvalues* of $K$.

## Solving 2 × 2 Systems

Let

$$c = (k_{11} - k_{22})^2/4 + k_{21}k_{12}$$

denote the discriminant of the characteristic equation. The solutions of

$$\begin{bmatrix} \dot{X}_1(t) \\ \dot{X}_2(t) \end{bmatrix} = \begin{bmatrix} k_{11} & k_{12} \\ k_{21} & k_{22} \end{bmatrix} \begin{bmatrix} X_1(t) \\ X_2(t) \end{bmatrix}$$

take a different form for each of the cases: $c > 0$, $c = 0$, and $c < 0$.

## Case $c > 0$

Without loss of generality, we can assume $k_{12} = 0$, and $k_{11} \neq k_{22}$. For illustration, we assume $X_1(0) = D$, and $X_2(0) = 0$.

Solving for $X_1(t)$

$$
\begin{aligned}
\dot{X}_1(t) &= k_{11} X_1(t) \\
\dot{X}_1(t) - k_{11} X_1(t) &= 0 \\
\exp(-k_{11}t)(\dot{X}_1(t) - k_{11} X_1(t)) &= 0 \\
\exp(-k_{11}t) X_1(t) &= d \\
X_1(t) &= d \exp(k_{11}t) \\
X_1(t) &= D \exp(k_{11}t)
\end{aligned}
$$

Solving for $X_2(t)$

$$\begin{aligned}
\dot{X}_2(t) &= Dk_{21}\exp(k_{11}t) + k_{22}X_2(t) \\
\exp(-k_{22}t)(\dot{X}_2(t) - k_{22}X_2(t)) &= Dk_{21}\exp((k_{11}-k_{22})t) \\
\exp(-k_{22}t)X_2(t) &= D\frac{k_{21}}{k_{11}-k_{22}}\exp((k_{11}-k_{22})t) + d \\
X_2(t) &= D\frac{k_{21}}{k_{11}-k_{22}}\exp(k_{11}t) + d\exp(k_{22}t) \\
X_2(t) &= D\frac{k_{21}}{k_{11}-k_{22}}(\exp(k_{11}t) - \exp(k_{22}t))
\end{aligned}$$

## **Case** $c = 0$

Without loss of generality, we can assume $k_{12} = 0$, and $k_{11} = k_{22}$.

For illustration, we assume $X_1(0) = D$, and $X_2(0) = 0$.

The solution for $X_1(t)$ is the same as for the previous case.

Solving for $X_2(t)$

$$
\begin{aligned}
\dot{X}_2(t) &= Dk_{21}\exp(k_{11}t) + k_{22}X_2(t) \\
\exp(-k_{22}t)(\dot{X}_2(t) - k_{22}X_2(t)) &= Dk_{21}\exp((k_{11}-k_{22})t) \\
\exp(-k_{22}t)(\dot{X}_2(t) - k_{22}X_2(t)) &= Dk_{21} \\
\exp(-k_{22}t)X_2(t) &= Dk_{21}t + d \\
X_2(t) &= (Dk_{21}t + d)\exp(k_{22}t) \\
X_2(t) &= Dk_{21}t\exp(k_{22}t)
\end{aligned}
$$

## **Case** $c < 0$

Let $m = (k_{11} + k_{22})/2$ and

$$M = \frac{1}{\sqrt{-c}} \begin{bmatrix} k_{11} - m & k_{12} \\ k_{21} & k_{22} - m \end{bmatrix}$$

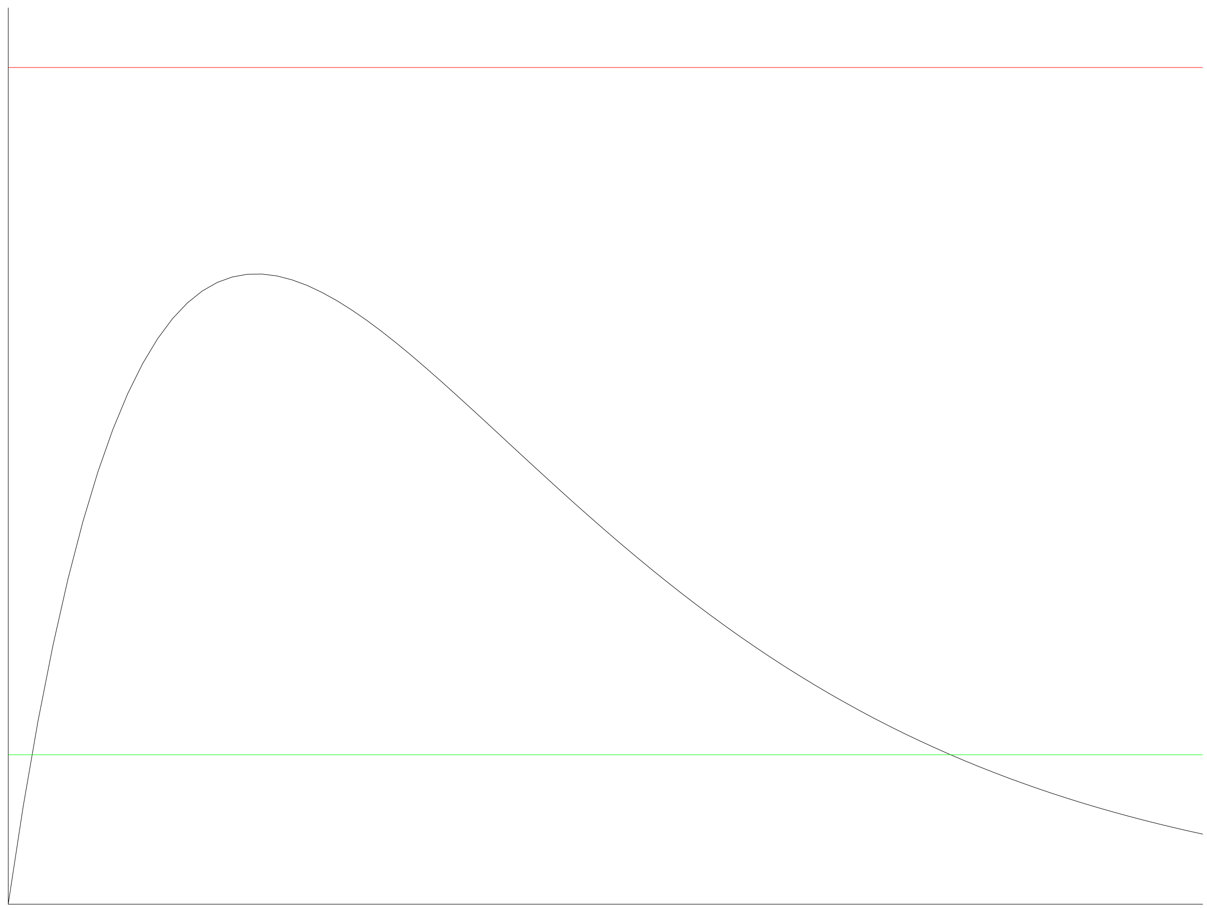
and $I$ is the identity matrix. The solutions are

$$\begin{bmatrix} X_1(t) \\ X_2(t) \end{bmatrix} = \big(\cos(\sqrt{-c}\,t)I + \sin(\sqrt{-c}\,t)M\big) \begin{bmatrix} X_1(0) \\ X_2(0) \end{bmatrix} \exp(mt).$$

## A pharmacokinetic example

The kinetics of drug absorption, distribution, and elimination is called pharmacokinetics. A knowledge of pharmacokinetics is needed to administer drugs optimally.

# Pharmacokinetic modeling

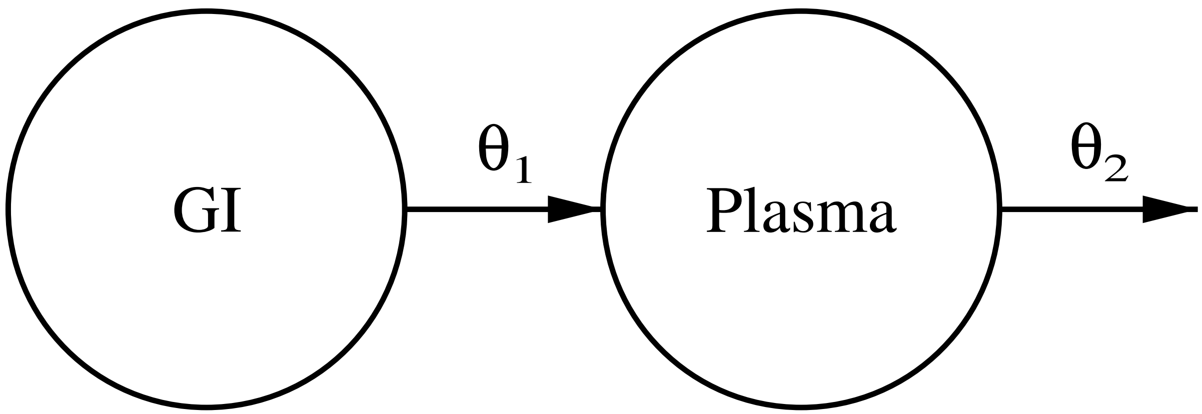


$$t \quad = \quad \text{time from administration of a drug}$$

$$X(t) \quad = \quad \text{amount of drug in tissue at time } t$$

## Modeling tetracycline metabolism

For Tetracycline given orally, what are the values of the rate constants, and what is the formula for the amount in the plasma?




Let $X_1(t)$ and $X_2(t)$ represent the respective amounts of tetracycline in the two compartments at time $t$. The equations associated with this diagram are

$$\begin{aligned}\dot{X}_1(t) &= -\theta_1 X_1(t)\\ \dot{X}_2(t) &= \theta_1 X_1(t) - \theta_2 X_2(t).\end{aligned}$$

## Matrix representation of equations

Let $\theta = \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix}$, $X(t) = \begin{bmatrix} X_1(t) \\ X_2(t) \end{bmatrix}$, $\dot{X}(t) = \begin{bmatrix} \dot{X}_1(t) \\ \dot{X}_2(t) \end{bmatrix}$, and $K = K(\theta) = \begin{bmatrix} -\theta_1 & 0 \\ \theta_1 & -\theta_2 \end{bmatrix}$. The matrix representation of the tetracycline equations is

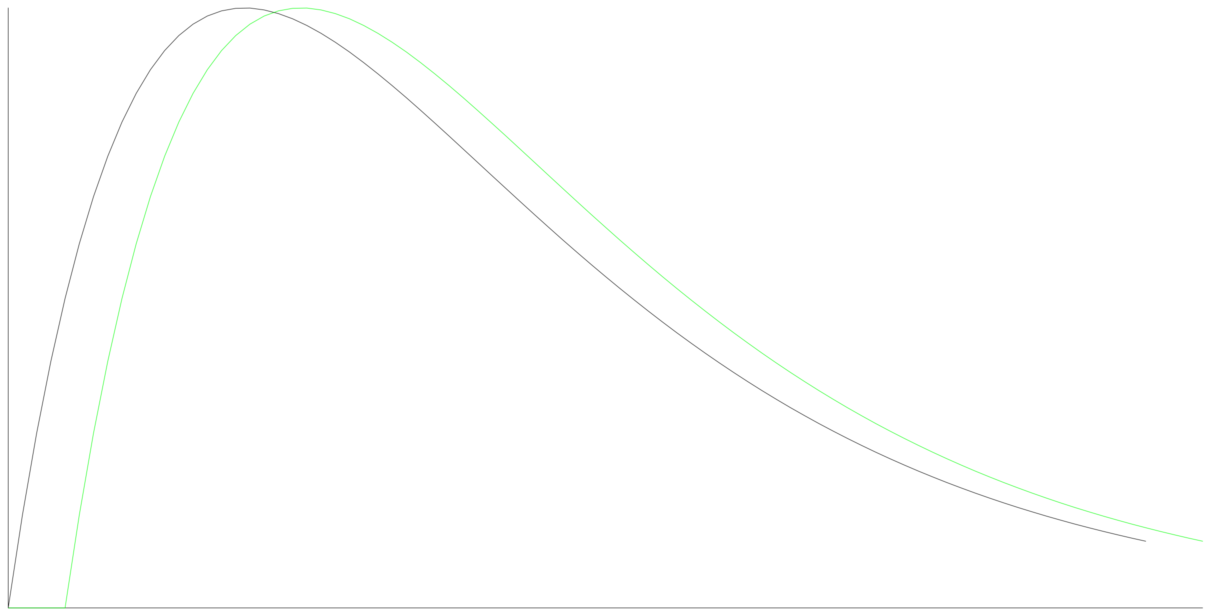
$$\dot{X}(t) = KX(t).$$

## The solution of the differential equations

We assume $\theta_1 \neq \theta_2$, $X_1(0) = D$, and $X_2(0) = 0$. Using results of derivation beginning on slide 25 we obtain:

$$\begin{aligned} X_1(t) &= D \exp(-\theta_1 t) \\ X_2(t) &= D \frac{\theta_1}{-\theta_1 + \theta_2} (\exp(-\theta_1 t) - \exp(-\theta_2 t)) \end{aligned}$$

# Lag times



Sometimes there is a time delay before the model takes effect. This delay is called a lag time, and we denote it by $\tau$. The response allowing for the possibility of a lag time is

$$X_2'(t) = \begin{cases} X_2(t-\tau) & \text{if } t > \tau \\ 0 & \text{otherwise} \end{cases}$$

## The data

We will fit the model to the data[a]:

| Time $t_i$ | Concentration $Y_i$ | Time $t_i$ | Concentration $Y_i$ |
|---|---|---|---|
| 1 | 0.7 | 2 | 1.2 |
| 3 | 1.4 | 4 | 1.4 |
| 6 | 1.1 | 8 | 0.8 |
| 10 | 0.6 | 12 | 0.5 |
| 16 | 0.3 | | |

[a] Wagner, 1967

## The observational model

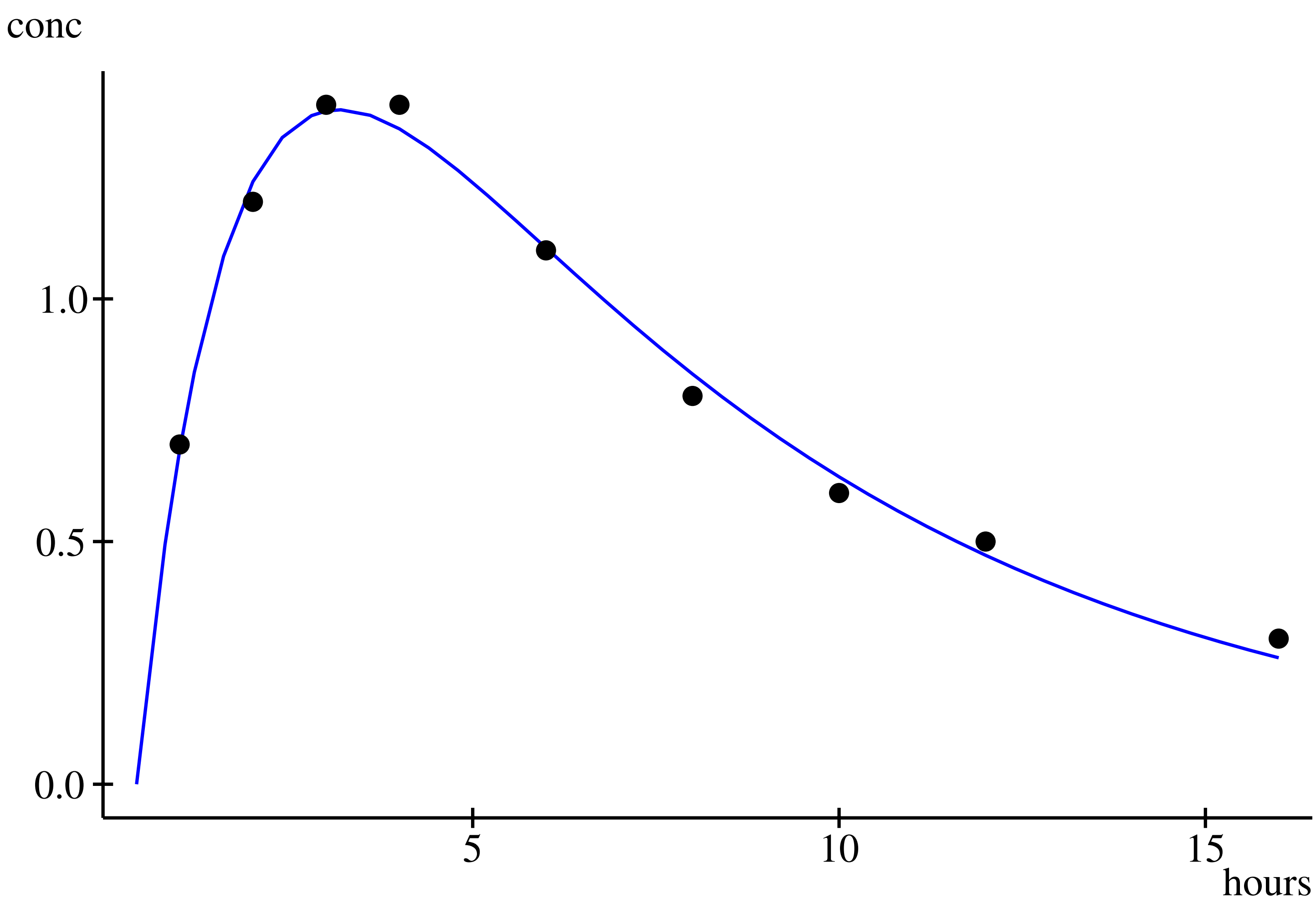
The observational model is

$$Y_i = X_2'(t_i) + \epsilon_i.$$

If the $\epsilon_i$ terms have equal variances and are uncorrelated, least squares is an efficient method of estimation. The parameter estimates are the values that minimize the least squares criteria:

$$\sum_{i=1}^{n} (Y_i - X_2'(t_i))^2.$$

# Fit the model to the data



## Results of model fitting

The estimate of $\tau$ is 0.4122. The estimated response for $t \geq 0.4122$ is

$$\begin{aligned} X_2'(t) &= +2.64969744 \exp(-0.1488026(t - 0.4122)) \\ &\quad -2.64969744 \exp(-0.7157319(t - 0.4122)) \end{aligned}$$

# Romeo and Juliet

This little story is by Strogatz[a]. I have added a bit about model fitting.

Juliet is in love with Romeo; but in our version of this story, Romeo is a fickle lover. The more Juliet loves him; the more he begins to dislike her. But when she loses interest, his feelings for her warm up. She, on the other hand, tends to echo him. Her love grows when he loves her, and it turns to hate when he hates her.

[a]Steven H. Strogatz, *Love Affairs and Differential Equations*, Mathematics Magazine, Vol. 61, No. 1, February 1988.

## A model

A simple model for their ill-fated romance is

$$\begin{aligned}\dot{X}_1(t) &= -\theta_1 X_2(t)\\ \dot{X}_2(t) &= \theta_2 X_1(t)\end{aligned}$$

where $X_1(t)$ = Romeo's love/hate for Juliet at time $t$, $X_2(t)$ = Juliet's love/hate for Romeo at time $t$, and $\theta_1 > 0$ and $\theta_2 > 0$ are "intensity" constants.

## The solution

The discriminant is $-\theta_1\theta_2$, a negative number. The solution is obtained by applying the formula derived starting on slide 29. The result is

$$\begin{bmatrix} X_1(t) \\ X_2(t) \end{bmatrix} = \left(\cos(\sqrt{\theta_1\theta_2}\, t)I + \sin(\sqrt{\theta_1\theta_2}\, t)M\right) \begin{bmatrix} X_1(0) \\ X_2(0) \end{bmatrix}$$

where

$$M = \begin{bmatrix} 0 & -\sqrt{\theta_1/\theta_2} \\ \sqrt{\theta_2/\theta_1} & 0 \end{bmatrix}.$$

## The data

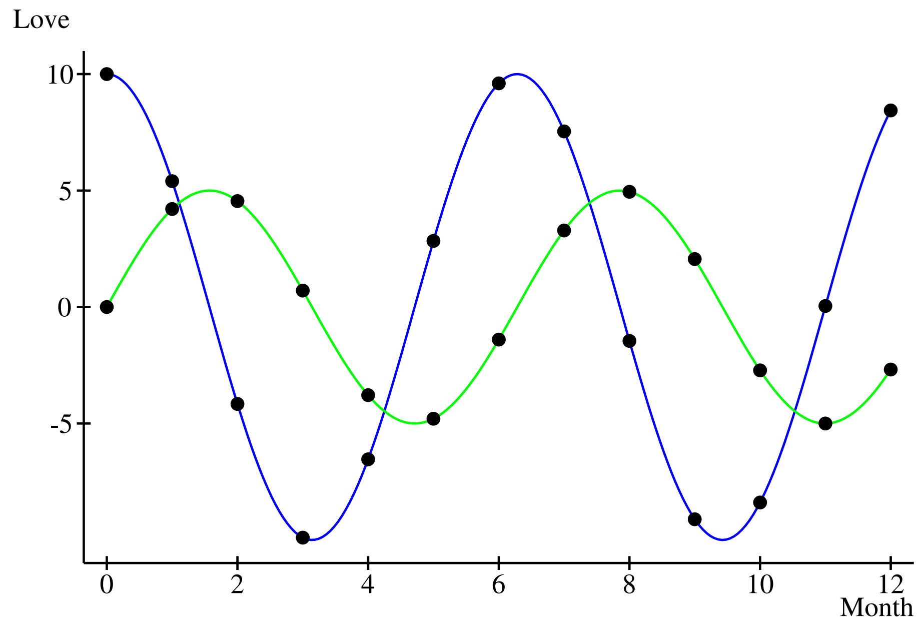
Juliet's nosey aunt looks in once a month to see how the relationship is going. The following are her observations:

| Month | Romeo | Juliet | Month | Romeo | Juliet |
|---|---|---|---|---|---|
| 0 | 10.0000 | 0.0000 | 1 | 5.4030 | 4.2074 |
| 2 | -4.1615 | 4.5465 | 3 | -9.8999 | 0.7056 |
| 4 | -6.5364 | -3.7840 | 5 | 2.8366 | -4.7946 |
| 6 | 9.6017 | -1.3971 | 7 | 7.5390 | 3.2849 |
| 8 | -1.4550 | 4.9468 | 9 | -9.1113 | 2.0606 |
| 10 | -8.3907 | -2.7201 | 11 | 0.0443 | -5.0000 |
| 12 | 8.4385 | -2.6829 | | | |

Positive numbers reflect love, and negative numbers reflect hate.

## The fitted response

$$X_1(t) = 10\cos(t)$$
$$X_2(t) = 5\sin(t)$$




"The sad outcome of their affair is, of course, a never ending cycle of love and hate; their governing equations are those of a simple harmonic oscillator. At least they manage to achieve simultaneous love one quarter of the time."