Drug Dynamics: Changing Concentration of a Drug

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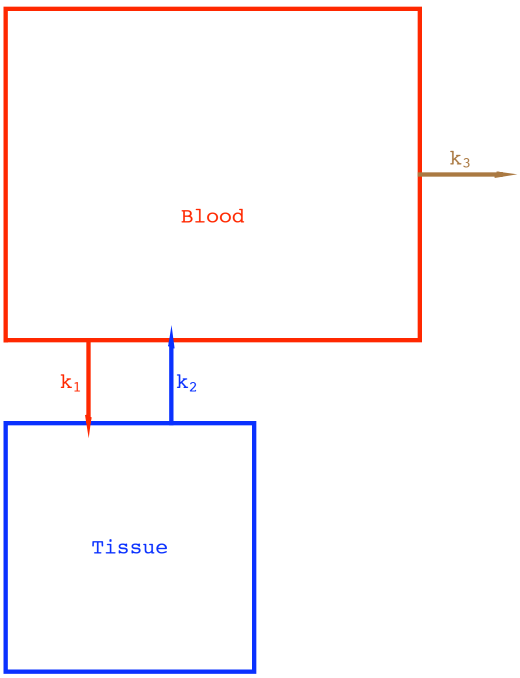
Introduction

- **Two compartments drug model.**
- **When concentration is higher.**
- **Eliminated from the blood.**
- **Single drug injection.**



Part1: Derivation of the Model

Variables & Parameters

Main Variables

a_B=a_B[t]= amount of drug in the blood as a function of time

c_B = c_B[t]= concentration of drug in the blood as a function of time, $c_B=\frac{a_B[t]}{v_B}$

a_T=a_T[t]= amount of drug in the tissue as a function of time

c_T=c_T[t] = concentration of drug in the tissue as a function of time, $c_T=\frac{a_t[t]}{v_T}$

Drug and Patient- specific Parameters

k_1= rate constant determining flow out of the blood compartment (due to difference in concentration)

k_3= kidney elimination

v_B= volume of blood

v_T= volume of the tissue

k_2= rate constant determining flow into the tissue compartment

The formula for $k_2 = k_1 \frac{v_B}{v_T}$ is a key in setting up the equations that describe the rates of change of the two concentrations ***

Amount vs. Concentration: equal amounts means $k_2 = k_1 \frac{v_B}{v_T}$

Equations of Change

$$\frac{dc_B}{dt} = (-k_1 + k_3)\ c_B + k_1\ c_T$$

$$\frac{dc_T}{dt} = k_2\ c_B - k_2\ c_T$$

Part2: Solving the Model

Recap the Models

$\frac{dc_B}{dt}$= -(k_1+k_3) c_B+$k_1 c_T$

$\frac{dc_T}{dt}$= $k_2 c_B$-$k_2 c_T$

Writing the Differential Equation in Matrix Form

$\frac{dC}{dt}=\begin{pmatrix} -k_1 - k_3 & k_1 \\ k_2 & -k_2 \end{pmatrix}\begin{pmatrix} c_B \\ c_T \end{pmatrix}$ = K C , Where K is the coefficient matrix.

Eigenvalues and Eigenvectors

Defination Eigenvalues and Eigenvectors

$$K\ V = \lambda\ V$$

Where h is the eigenvalue and V is its associated eigenvector.

Eigenvalues

$\det\begin{pmatrix} -k_1 - k_3 - \lambda & k_1 \\ k_2 & -k_2 - \lambda \end{pmatrix}= \lambda^2+(k_1+k_2+k_3)\lambda+k_2 k_3=0.$

$$\lambda_1=\frac{-(k_1+k_2+k_3)-\sqrt{(k_1+k_2+k_3)^2-4\,k_2\,k_3}}{2}$$

$$\lambda_2=\frac{-(k_1+k_2+k_3)+\sqrt{(k_1+k_2+k_3)^2-4\,k_2\,k_3}}{2}$$

Eigenvectors

$$K\ V = \lambda\ V$$

When $\lambda = -h_1= \frac{-(k_1+k_2+k_3)-\sqrt{(k_1+k_2+k_3)^2-4\,k_2\,k_3}}{2}$

$$V_1 = \begin{pmatrix} \frac{k_2-k_1-k_3-\sqrt{(k_1+k_2+k_3)^2-4\,k_2\,k_3}}{k_2} \\ 1 \end{pmatrix}$$

When $\lambda = -h_2= \frac{-(k_1+k_2+k_3)+\sqrt{(k_1+k_2+k_3)^2-4\,k_2\,k_3}}{2}$

$$V2 = \begin{pmatrix} \frac{k_2 - k_1 - k_3 + \sqrt{(k_1 + k_2 + k_3)^2 - 4 k_2 k_3}}{k_2} \\ 1 \end{pmatrix}$$

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Solving Differential equation

■ Solution Associated with h_1 and V_1

Suppose that $c_1 = \alpha(t) V_1$ is a solution that statifies $\frac{dc}{dt} = KC$.

Where $\alpha(t)$ is a scalar based on time.

$\frac{dc_1}{dt} = Kc_1$

$Kc_1 = K \alpha(t) V_1 = \alpha(t)(-h_1) V_1$

$\frac{dc_1}{dt} = \alpha'(t) V_1$

From the two equalities mentioned above, we obtained
$\alpha(t)(-h_1) V_1 = \frac{d(\alpha(t))}{dt} V_1$

Two scalars have to equal to each other
$\alpha(t)(-h_1) = \frac{d(\alpha(t))}{dt}$

Solve the simple differential equation and we get the answer
$\alpha(t) = \beta_1 e^{-h_1 t}$

When t=0, $\alpha(0) = \beta_1$, therefore β_1 depends on the initial condition.

This is one of the solutions of the differential equations.
$c_1 = \beta_1 e^{-h_1 t} V_1$

■ Solution Associated with h_2 and V_2

Suppose that $c_2 = \gamma(t) V_2$ is a solution that statifies $\frac{dc}{dt} = KC$.

Where $\gamma(t)$ is a scalar based on time.

Similar calculation could be used to find that

$\gamma(t) = \beta_2 e^{-h_2 t}$

When t=0, $\gamma(0) = \beta_2$, therefore β_2 depends on the initial condition.

We get the final solution
$c_2 = \beta_2 e^{-h_2 t} V_2$

■ Solution Space of c_1 and c_2

By the principal of superposition, we know that if c_1 and c_2 are both solutions to the system of equations $\frac{dc}{dt} = KC$ then $ac_1 + bc_2$ is also a solution for all a and b in real number.

Distinct eigenvalues give distinct eigenvectors, which means the eigenvectors will be linearly indipendent.

Solutions

General form of Solution

All solutions has the general form of

$C = \beta_1 e^{-h_1 t} V_1 + \beta_2 e^{-h_2 t} V_2$

$\begin{pmatrix} c_B \\ c_T \end{pmatrix} = \beta_1 e^{-h_1 t} \begin{pmatrix} V_{11} \\ V_{12} \end{pmatrix} + \beta_2 e^{-h_2 t} \begin{pmatrix} V_{21} \\ V_{22} \end{pmatrix}$

or in the system of equation form.

$c_B = \beta_1 e^{-\mathrm{h1t}} V_{11} + \beta_2 e^{-\mathrm{h2t}} V_{21}$

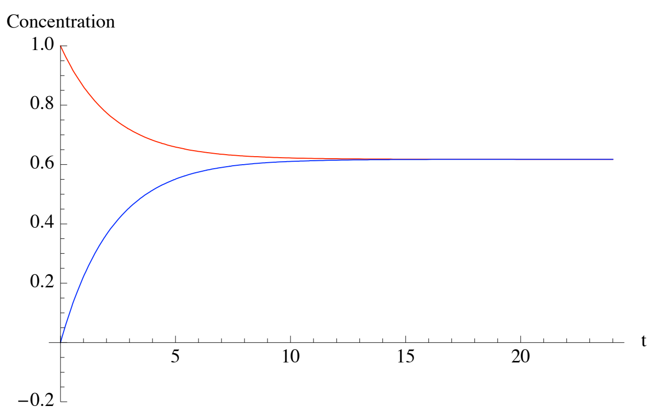
$c_T = \beta_1 e^{-\mathrm{h1t}} V_{12} + \beta_2 e^{-\mathrm{h2t}} V_{22}$

Solution without a Kidney

vB	vT	k_1	k_3	c_{Ti}	c_{Bi}	k_2
2.1	1.3	0.17	0	1	0	k_1 vB / vT

$cB[t] \to 0.62 + 0.38\, e^{-0.44\, t}$

$cT[t] \to 0.62 - 0.62\, e^{-0.44\, t}$



This is how the solutions of a patient's without kidney behave.

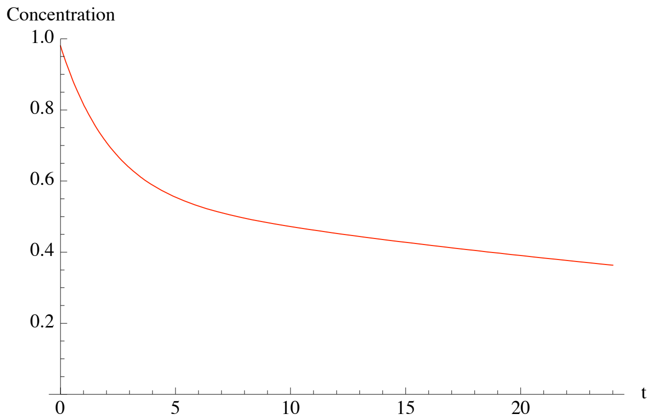
Part3: Behavior of the Solutions

```
cB[t_] = b1 ⅇ^(-h1 t) + b2 ⅇ^(-h2 t)
cT[t_] = -b3 ⅇ^(-h1 t) + b3 ⅇ^(-h2 t)
```

$0.42\, e^{-0.456571\, t} + 0.56\, e^{-0.0180442\, t}$

$-0.63\, e^{-0.456571\, t} + 0.63\, e^{-0.0180442\, t}$

```
Plot[{cB[t]}, {t, 0, 24}, PlotRange → {0, 1},
 PlotStyle → {Red}, AxesLabel → {"t", "Concentration"}]
```



$h1=\frac{(k1+k2+k3)+\sqrt{(k1+k2+k3)^2-4\,k2k3}}{2}$

$h2=\frac{(k1+k2+k3)-\sqrt{(k1+k2+k3)^2-4\,k2k3}}{2}$

cB[t_] = b1 ⅇ$^{-h1\, t}$ + b2 ⅇ$^{-h2\, t}$

If k_1,k_2,k_3 is positive then $k_1+k_2+k_3>0$. $h_1=(k_1+k_2+k_3)^{\ 2}$-$4k_2k_3>0 \rightarrow (h_1)^{\ 1/2}$

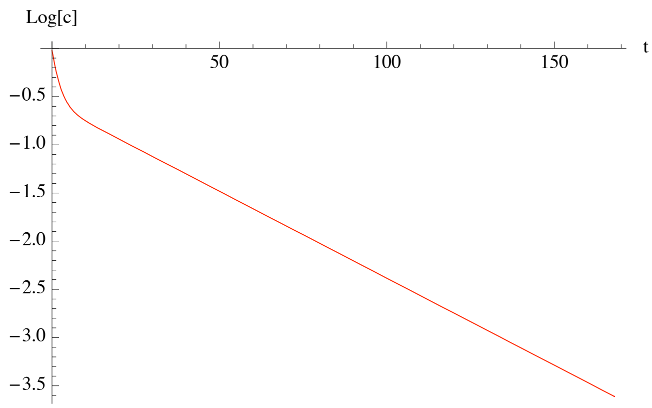
So $(k_1+k_2+k_3)^{\ 2} > (k_1+k_2+k_3)^{\ 2}$-$4k_2k_3>0$.

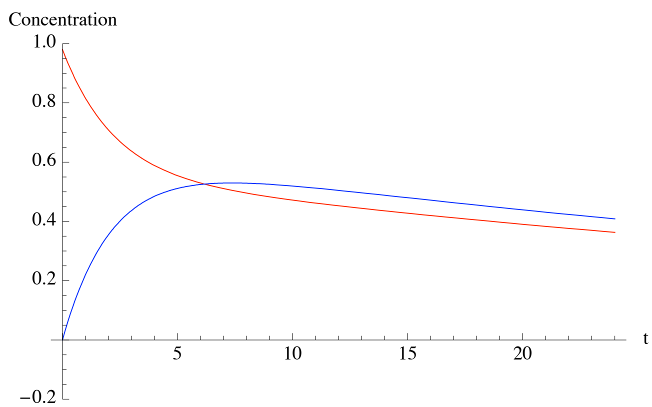
$k_1+k_2+k_3 > \sqrt{(k_1+k_2+k_3)^2 - 4\, k_2\, k_3}$

$h_2>0 \rightarrow (k_1+k_2+k_3)$ -$\sqrt{(k_1+k_2+k_3)^2 - 4\, k_2\, k_3}$

$((k_1+k_2+k_3)+\sqrt{(k_1+k_2+k_3)^2 - 4\, k_2\, k_3}\ )/2\ >\ ((k_1+k_2+k_3)$-$\sqrt{(k_1+k_2+k_3)^2 - 4\, k_2\, k_3}\ )/2$

```
Plot[{Log[cB[t]]}, {t, 0, 24*7}, PlotStyle→{Red}, AxesLabel→{"t", "Log[c]"}]
```



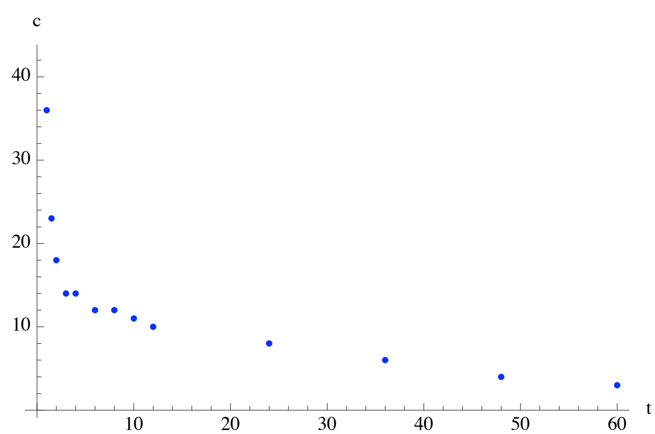


Part 4: Comparison with a Real Patient

Introduction

- **Warfarin (also under other brand names of Coumadin (commonly used), Jantoven, Marevan, and Waran) is an anticogulant medication that is administered orally, very rarely, by injection. Warfarin can be also defined as a blood thinner.**
- **The drug concentration of patient must stay at a constant level of effectiveness. Blood test are administered frequently to test levels of concentration.**
- **We measure the drug concentration in the tissues and blood of a patient to see the lowest point when it uneffective and its highest when the drug is dangerous.**

Warfarin Data:



This graphs displays the drug concentration versus time where the concentration was checked starting at the initial dosage every halff hour in a sixty hour period.

The Semilog Plot of Blood Concentrations

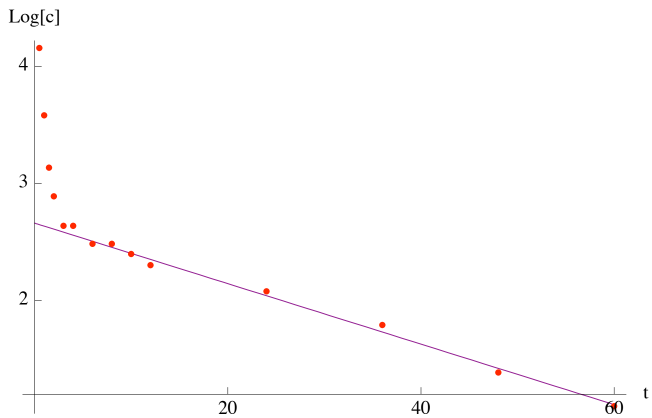
```
logData = Transpose[{times,logCons}]
```

```
{{0.5, 4.15888}, {1, 3.58352}, {1.5, 3.13549}, {2, 2.89037},
 {3, 2.63906}, {4, 2.63906}, {6, 2.48491}, {8, 2.48491}, {10, 2.3979},
 {12, 2.30259}, {24, 2.07944}, {36, 1.79176}, {48, 1.38629}, {60, 1.09861}}
```

The Log-Linear Tail

Five Points

After looking closely at the graphs tested then the deciding factor is which one suffices being linear. While graphing these graphs the changes where not to much of a difference. It was not much change in the line to be the best fitted. The winner was graph of five points were the last 5 points was taken to have the best fit.

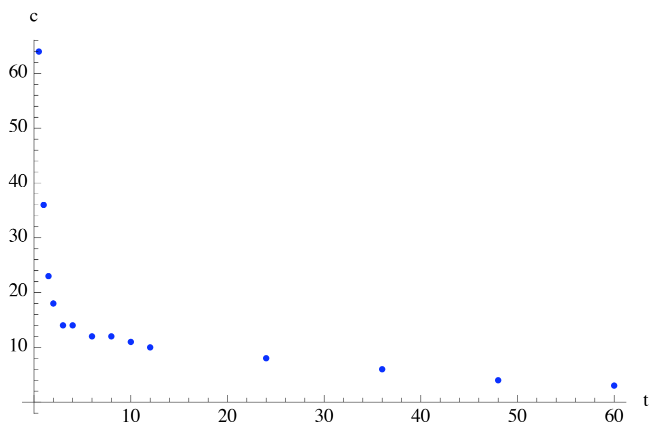


2.66207 - 0.0258424 t

■ Removing the Tail to find the Head

```
h2 = 0.02584;
b2 = Exp[2.662];
remainders = concens - b2 Exp[-h2 times]
```

```
b1 = Exp[4.71];
h1 = 1.63;
cA[t_] := b1 Exp[-h1 t] + b2 Exp[-h2 t];
curvePlot = Plot[cA[t],{t,0,60},AxesLabel->{"t","c"},PlotStyle->Purple,PlotRange->All];
Show[curvePlot,dataPlot,Prolog->AbsolutePointSize[4],PlotRange->All]
cA[t]
```



$111.052\, e^{-1.63\, t} + b2\, e^{-h2\, t}$

b1 = $e^{4.715280528508673}$

111.64

h1 = 1.661442291806

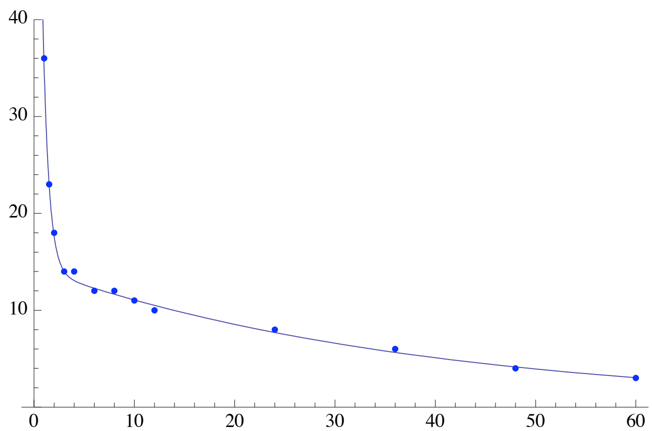
1.66144

cB[t]

$111.64\, e^{-1.66144\, t} + 14.3259\, e^{-0.0258424\, t}$

■ Final Fit

```
Show[Graph1, dataPlot]
```



Now that b_1, h_1,b_2, and ,$h_2$has been found gives us now the opportunity to solve all the other variables to give us the general equation by solving k_1,k_2, and k_3 in terms of $h_1$and $h_2$of the physical parameters of the patient. First, it was proven that $h_1 h_2$=$k_2 k_3$ and h_1 +h_2==k_1+k_2+k_3 which are both true. Knowing this helps to solve for k_1 and that it was already given that k_2==k_1 $\frac{v_B}{v_T}$and k_3==$\frac{h_1 h_2}{k_2}$ (hence : h₁ h₂==$k_2 k_3$),vB = 100/cA[0] andvT = k1 vB/k2.

Physical Parmeters of a Patient:

$$h_1 = \frac{1}{2} [(k_1 + k_2 + k_3) + \sqrt{(k_1 + k_2 + k_3)^2 - 4 k_2 k_3}]$$

$$h_2=\frac{1}{2}[(k_1+k_2+k_3)-\sqrt{(k_1 + k_2 + k_3)^2 - 4 k_2 k_3}]$$

Solve k_1,k_2, and k_3 in terms of h_1 and h_2, given that k_2=$k_1 \frac{V_B}{V_T}$ and k_3=$\frac{h_1 h_2}{k_2}$($h_1 h_2$=k_2 k_3)

$$k_1 = \frac{-(h_1{}^2+h_1 h_2)\pm\sqrt{(h_1{}^2+h_1 h_2)^2-4\left(-h_1-h_1 \frac{V_B}{V_T}\right)\left(-h_1{}^2 \frac{V_B}{V_T}\right)}}{2\left(-h_1-h_1 \frac{V_B}{V_T}\right)}$$

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THE END

THANK YOU!!!!