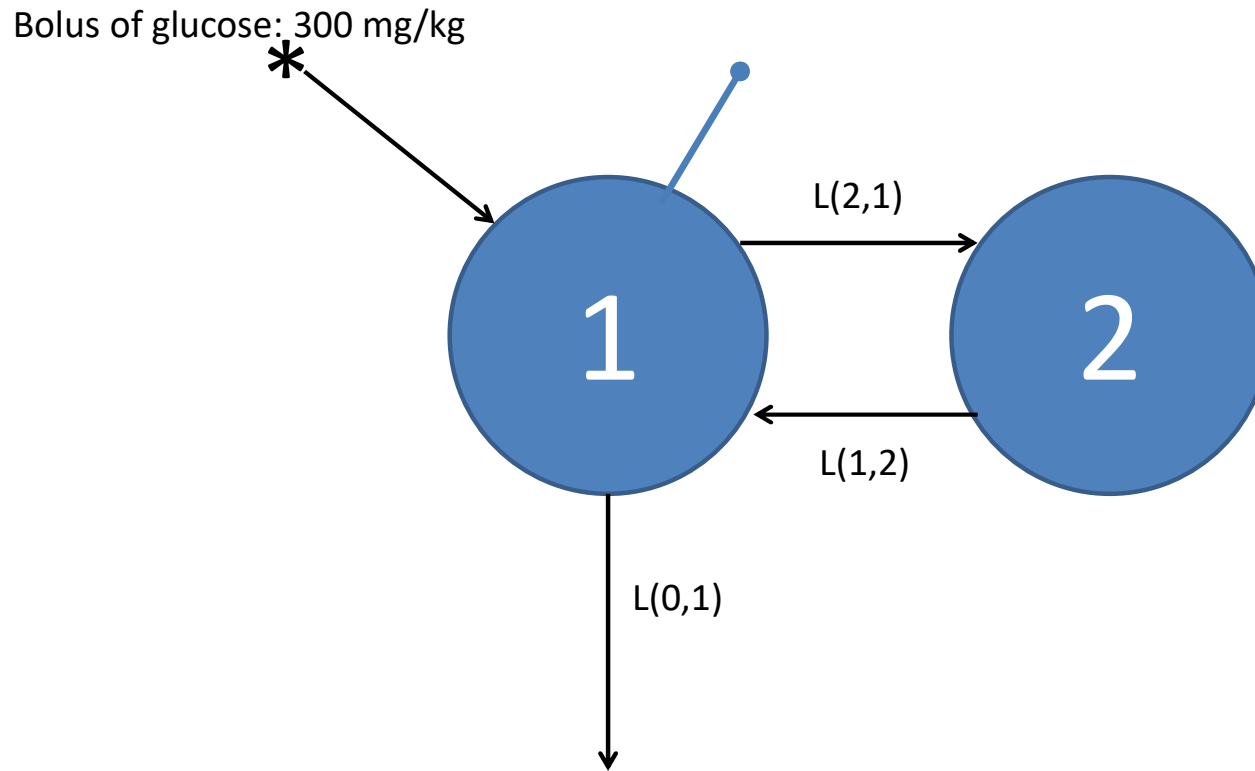


System of Ordinary Differential Equations (ODEs)

sdarko@upenn.edu

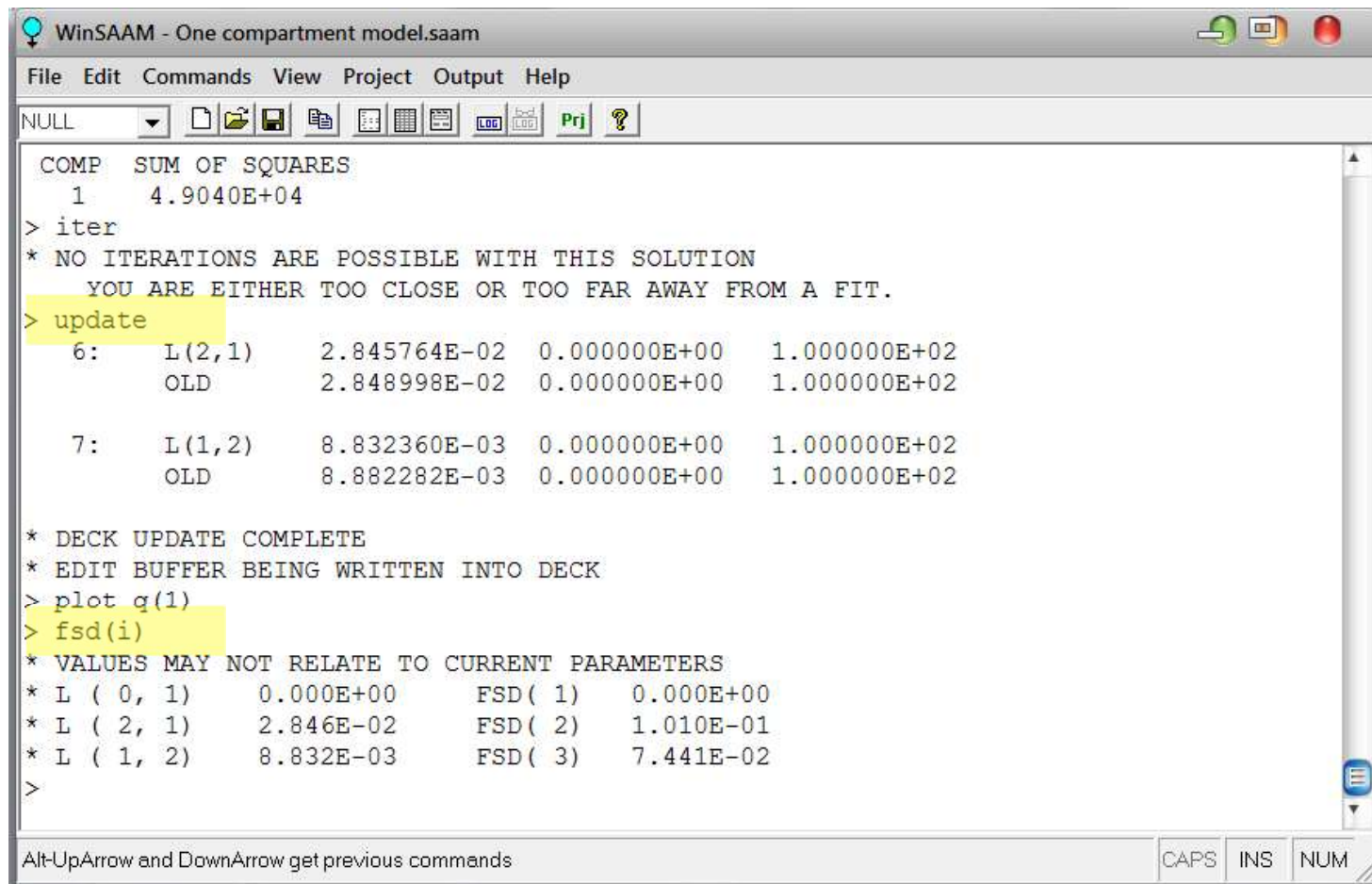
Two Compartment Model of Glucose Disposal During FSIGT Test



SAAM File

```
WS Working File Editor
File Edit View Help
[Icons: Save, Print, Copy, Paste, Undo, Redo, Help]
A SAAM31
C Insert Control lines 2,3,4 here as needed
H PAR
  IC(1) 250
  L(0,1) 0.000000E+00 0.000000E+00 1.000000E+02
  L(2,1) 2.845764E-02 0.000000E+00 1.000000E+02
  L(1,2) 8.832360E-03 0.000000E+00 1.000000E+02
H DAT
101 FSD=0.05
      0 82
      2 314
      3 290
      4 265
      5 249
      6 238
      8 214
     10 212
     12 199
     14 188
     16 174
     19 170
     22 155
```

How to Assess the Wellness of Parameter Estimates



```
WinSAAM - One compartment model.saam
File Edit Commands View Project Output Help
NULL
COMP  SUM OF SQUARES
  1    4.9040E+04
> iter
* NO ITERATIONS ARE POSSIBLE WITH THIS SOLUTION
  YOU ARE EITHER TOO CLOSE OR TOO FAR AWAY FROM A FIT.
> update
  6:   L(2,1)   2.845764E-02  0.000000E+00  1.000000E+02
      OLD      2.848998E-02  0.000000E+00  1.000000E+02

  7:   L(1,2)   8.832360E-03  0.000000E+00  1.000000E+02
      OLD      8.882282E-03  0.000000E+00  1.000000E+02

* DECK UPDATE COMPLETE
* EDIT BUFFER BEING WRITTEN INTO DECK
> plot q(1)
> fsd(i)
* VALUES MAY NOT RELATE TO CURRENT PARAMETERS
* L ( 0, 1)   0.000E+00   FSD( 1)  0.000E+00
* L ( 2, 1)   2.846E-02   FSD( 2)  1.010E-01
* L ( 1, 2)   8.832E-03   FSD( 3)  7.441E-02
>
```

Alt-UpArrow and DownArrow get previous commands CAPS INS NUM

What do ODEs Represent?

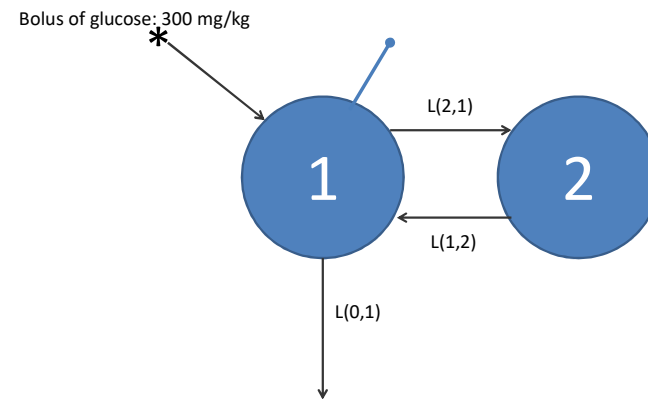
- Explain the concentration change of a compartment in infinitely small amount of time

Input of Compartment I from Comp. j

- $$\frac{dF_i}{dt} = \underbrace{-F_i * L(j, i)}_{\text{Output of Compartment i}} + \underbrace{F_j * L(i, j)}_{\text{Input of Compartment I from Comp. j}}$$

- $$\frac{dF_i}{dt} \equiv UF(i) \text{ in WinSAAM}$$

ODEs of Two Compartment Model



- System of Two ODEs

$$UF(1) = -L(0,1) * F(1) - L(2,1) * F(1) + L(1,2) * F(2)$$

$$UF(2) = L(2,1) * F(1) - L(1,2) * F(2)$$

ODEs of Two Compartment Model WinSAAM Implementation

```
WS Working File Editor
File Edit View Help
[Icons]
A SAAM31
C Insert Control lines 2,3,4 here as needed
H PAR
  IC(1) 250
c L(0,1) 0.000000E+00 0.000000E+00 1.000000E+02
  P(1) 0.02 0 100
C L(2,1) 2.795678E-02 0.000000E+00 1.000000E+02
  P(2) 2.795678E-03 0 100
c L(1,2) 8.607655E-03 0.000000E+00 1.000000E+02
  P(3) 8.607655E-04 0 100
H DAT
X UF(1)=-P(1)*F(1)-P(2)*F(1)+P(3)*F(2)
X UF(2)=P(2)*F(1)-P(3)*F(2)
101 FSD=0.4
  0 82
  2 314
  3 290
  4 265
  5 249
```

Switch Function

$$f(x) = \begin{cases} x \geq 0, & 1 \\ x \leq 60 & 0 \end{cases}$$



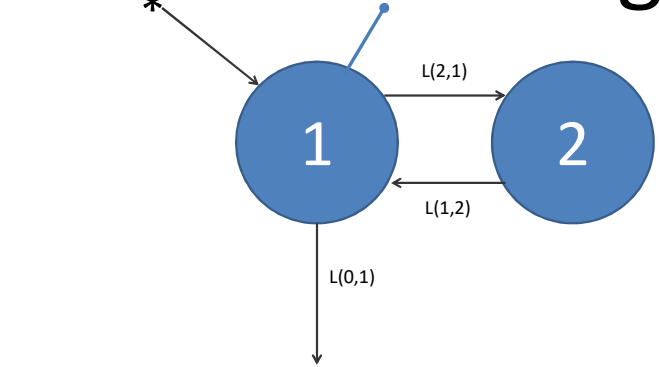
WinSAAM Implementation

```
H DAT
X UF(1)=-P(1)*F(1)*FF(3)-P(2)*F(1)+P(3)*F(2)
X UF(2)=P(2)*F(1) -P(3)*F(2)
X FF(3)=F(3)
103 Q0
      0      1
      60     0
```


WinSAAM Approach to Determine Eigenvalues & Eigenvector

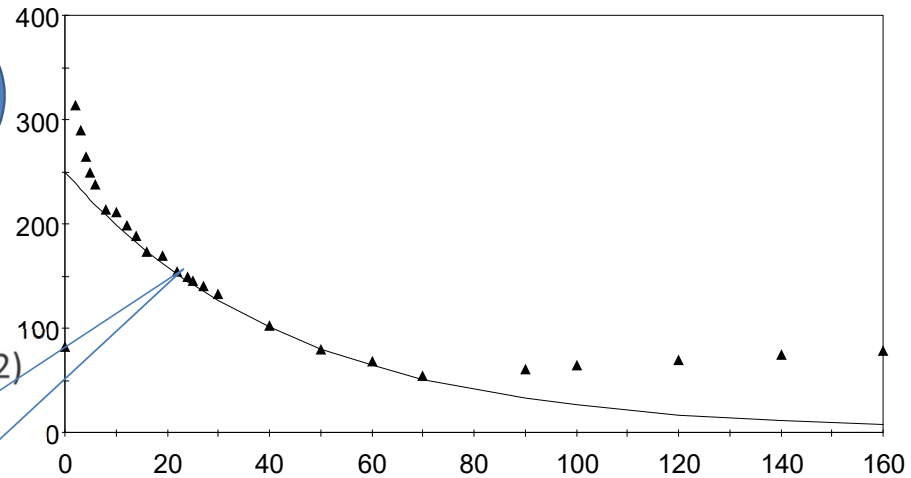
Integrating ODEs

Bolus of glucose: 300 mg/kg



$$UF(1) = -L(0,1) * F(1) - L(2,1) * F(1) + L(1,2) * F(2)$$

$$UF(2) = L(2,1) * F(1) - L(1,2) * F(2)$$



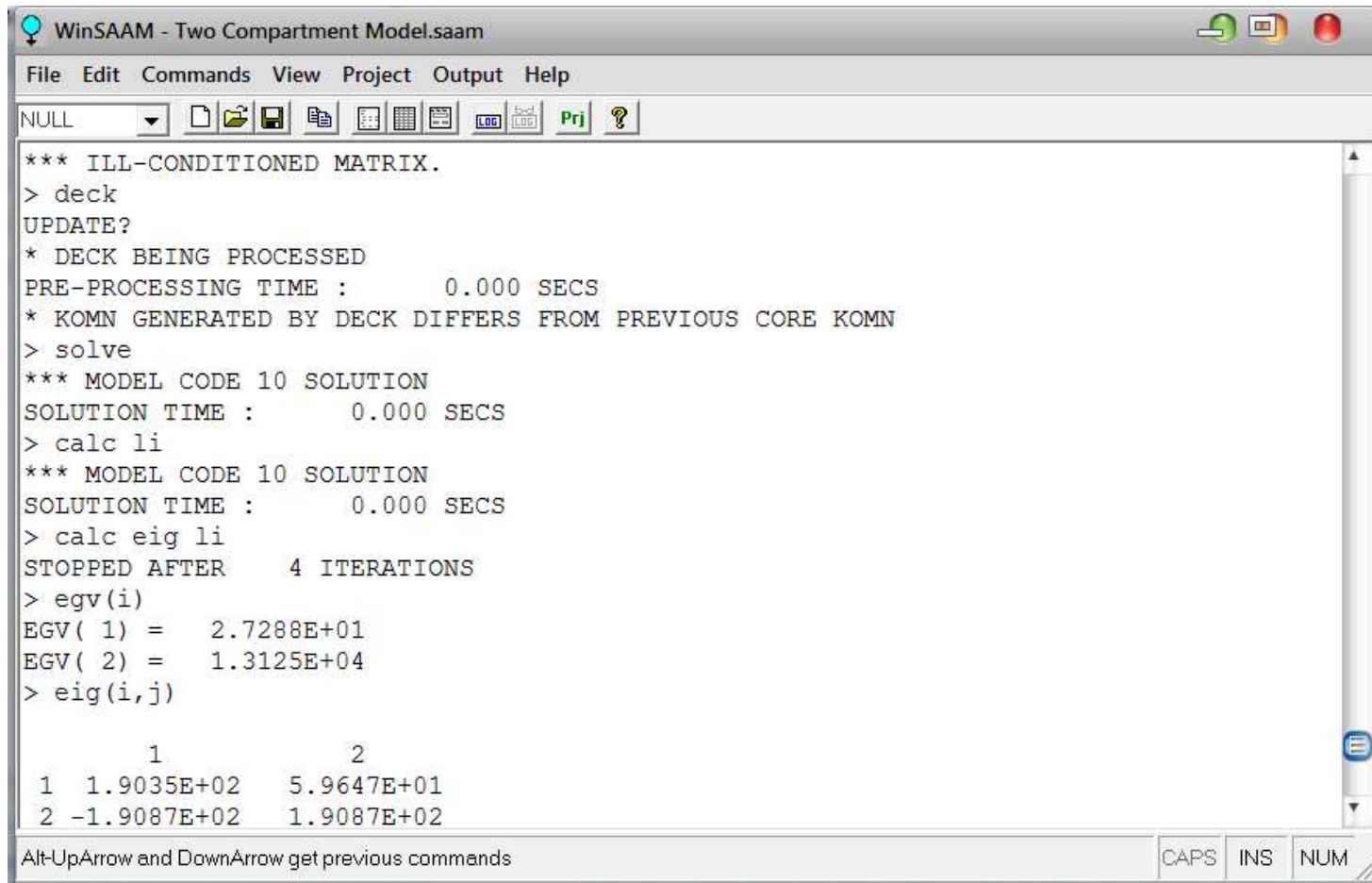
$$F_1(t) = C_{11} * \exp\left(\frac{-t}{\tau_1}\right) + C_{12} * \exp\left(\frac{-t}{\tau_2}\right)$$

$$F_2(t) = C_{21} * \exp\left(\frac{-t}{\tau_1}\right) + C_{22} * \exp\left(\frac{-t}{\tau_2}\right)$$

Back to Two-Compartment Model

```
A SAAM31
C Insert Control lines 2,3,4 here as needed
H PAR
  IC(1)      250
  L(0,2)     1.000000E-04  0.000000E+00  1.000000E+02
  L(2,1)     2.792092E-02  0.000000E+00  1.000000E+02
  L(1,2)     8.701256E-03  0.000000E+00  1.000000E+02
H DAT
101                                     FSD=0.05
      0                               82
      2                               314
      3                               290
      4                               265
      5                               249
      6                               238
      8                               214
```

Calculating Eigenvalues & Eigenvector in WinSAAM



The screenshot shows the WinSAAM software interface with the following text in the main window:

```
WinSAAM - Two Compartment Model.saam
File Edit Commands View Project Output Help
NULL
*** ILL-CONDITIONED MATRIX.
> deck
UPDATE?
* DECK BEING PROCESSED
PRE-PROCESSING TIME :      0.000 SECS
* KOMN GENERATED BY DECK DIFFERS FROM PREVIOUS CORE KOMN
> solve
*** MODEL CODE 10 SOLUTION
SOLUTION TIME :      0.000 SECS
> calc li
*** MODEL CODE 10 SOLUTION
SOLUTION TIME :      0.000 SECS
> calc eig li
STOPPED AFTER      4 ITERATIONS
> egv(i)
EGV( 1) =   2.7288E+01
EGV( 2) =   1.3125E+04
> eig(i,j)

      1      2
1  1.9035E+02  5.9647E+01
2 -1.9087E+02  1.9087E+02
```

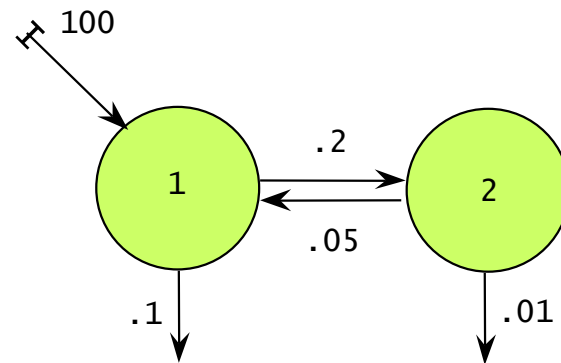
At the bottom of the window, there is a status bar with the text "Alt-UpArrow and DownArrow get previous commands" and three buttons labeled "CAPS", "INS", and "NUM".

Generating the Simulated Data

```
WS Working File Editor
File Edit View Help
[Icons]
A SAAM31
C Insert Control lines 2,3,4 here as needed
H PAR
  IC(1)      250
  L(0,2)     1.000000E-04  0.000000E+00  1.000000E+02
  L(2,1)     2.792092E-02  0.000000E+00  1.000000E+02
  L(1,2)     8.701256E-03  0.000000E+00  1.000000E+02
H DAT
x qo(11)=1.9035e+02*exp(-T/2.7288e+01)+
  5.9647e+01*exp(-T/1.3125e+04)
101                                     FSD=0.05
      0                               82
      2                               314
      3                               290
      4                               265
      5                               249
      6                               238
      8                               214
     10                               212
     12                               199
     ..                               ...
```

The analytic characterization of the system response

Consider the response of the below linear compartmental model to a bolus of 100 units in compartment 1



From (3) the response of this system is of the form

$$f = A.e^{at}$$

and this derives directly from (2)

$$f' = L.f$$

Our goal is to determine 'A', and 'a' from the values of 1) the elements of the 'L' matrix, and 2) the boundary conditions

$$L = \begin{pmatrix} -0.3 & 0.05 \\ 0.2 & -0.06 \end{pmatrix}$$

Boundary conditions: $f1|_0=100$, $f2|_0=0$,

In scalar form the system is mathematically representable as

$$\begin{aligned} f_1' &= -0.3.f_1 + 0.05.f_2 & f_1|_0 &= 100 \\ f_2' &= 0.2.f_1 - 0.06.f_2 & f_2|_0 &= 0 \end{aligned}$$

and the response as

$$\begin{aligned} f_1 &= c_1.\exp[-a_1.t] + c_2.\exp[-a_2.t] \\ f_2 &= c_3.\exp[-a_1.t] + c_4.\exp[-a_2.t] \end{aligned}$$

Note that both compartments have the same exponentials, but the level of each exponential in the response of each compartment differs

1. Eigenvalues

From (8)

$$\begin{vmatrix} -0.3-a & 0.05 \\ 0.2 & -0.06-a \end{vmatrix} = 0$$

or $a^2 + 0.36.a + 0.008 = 0$

or $a = -0.336, -0.024$, or $a_1 = -0.336, a_2 = -0.024$

Thus the exponential terms in the response for compartments 1 and 2 are

$e^{-0.336.t}$ and $e^{-0.024.t}$

2. Eigenvectors

We now require to find the non zero null space vectors of 'A' satisfying

$$L.A_j = a_j.A_j \quad \dots \quad (9)$$

or more generally

$$L.A = a.A \quad \dots \quad (9a)$$

i.e. $(L - I.a)A = 0 \quad \dots \quad (9b)$

Setting $a = a_1$ in (9b) where we denote A by $\begin{pmatrix} k_1 \\ k_2 \end{pmatrix}$ we obtain

$$\begin{aligned} 0.036 k_1 + 0.05 k_2 &= 0 \\ 0.200 k_1 + 0.276 k_2 &= 0 \end{aligned} \quad \dots \quad (10)$$

i.e. $k_1 = -1.38 k_2$, and setting $k_2 = -1$ gives $k_1 = 1.38$

Similarly setting $a = a_2$ in (9b) we obtain

$$\begin{aligned} -0.276 k_1 + 0.05 k_2 &= 0 \\ 0.200 k_1 - 0.036 k_2 &= 0 \end{aligned} \quad \dots \quad (11)$$

By similar methods for a_1 we obtain, for a_2 , $k_1 = 0.18 k_2$ whence, setting $k_2 = 1$ gives $k_1 = 0.18$

Thus our eigenvectors are: $\begin{pmatrix} 1.38 \\ -1.0 \end{pmatrix}$ and $\begin{pmatrix} 0.18 \\ 1.0 \end{pmatrix}$

3. The exponential model

If 'a' is a vector of distinct eigenvalues of the coefficient matrix 'L' of a first order homogeneous system and A_j are the corresponding eigenvectors with elements k_j , then the general solution of the system is given by:

$$f = c_1.A_1.exp(a_1.t) + c_2.A_2.exp(a_2.t) + c_3.A_3.exp(a_3.t) + \dots$$

The values of c_j are resolved from the initial (boundary) conditions

We thus have

$$\begin{aligned} f_1 &= 1.38.c_1.e^{-0.336.t} + 0.18.c_2.e^{-0.024.t} \\ f_2 &= -1.00.c_1.e^{-0.336.t} + 1.00.c_2.e^{-0.024.t} \end{aligned}$$

$$\text{Now } f(0) = \begin{pmatrix} f_1(0) \\ f_2(0) \end{pmatrix} = \begin{pmatrix} 100 \\ 0 \end{pmatrix}$$

We see that

$$1.38.c_1 + 0.28.c_2 = 100$$

$$c_1 = c_2$$

i.e. $c_1 = 64.1$

Thus

$$f_1 = 88.46 e^{-0.336t} + 11.54 e^{-0.024t}$$

$$f_2 = -64.10 e^{-0.336t} + 64.10 e^{-$$

0.024

Recapitulating:

The response of a linear system to a perturbation is describable as a sum of exponentials

The number of exponentials just equals the number of exchanging compartments in the model