System of Ordinary Differential Equations (ODEs)

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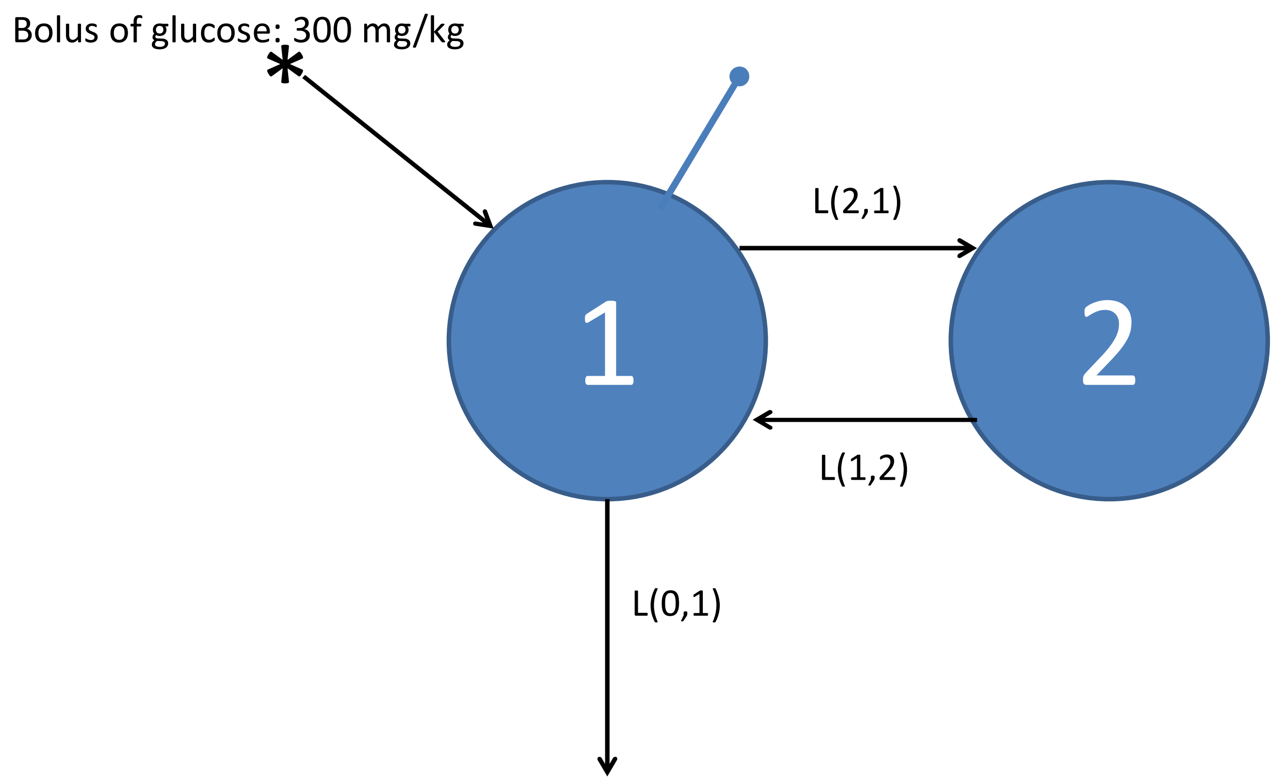
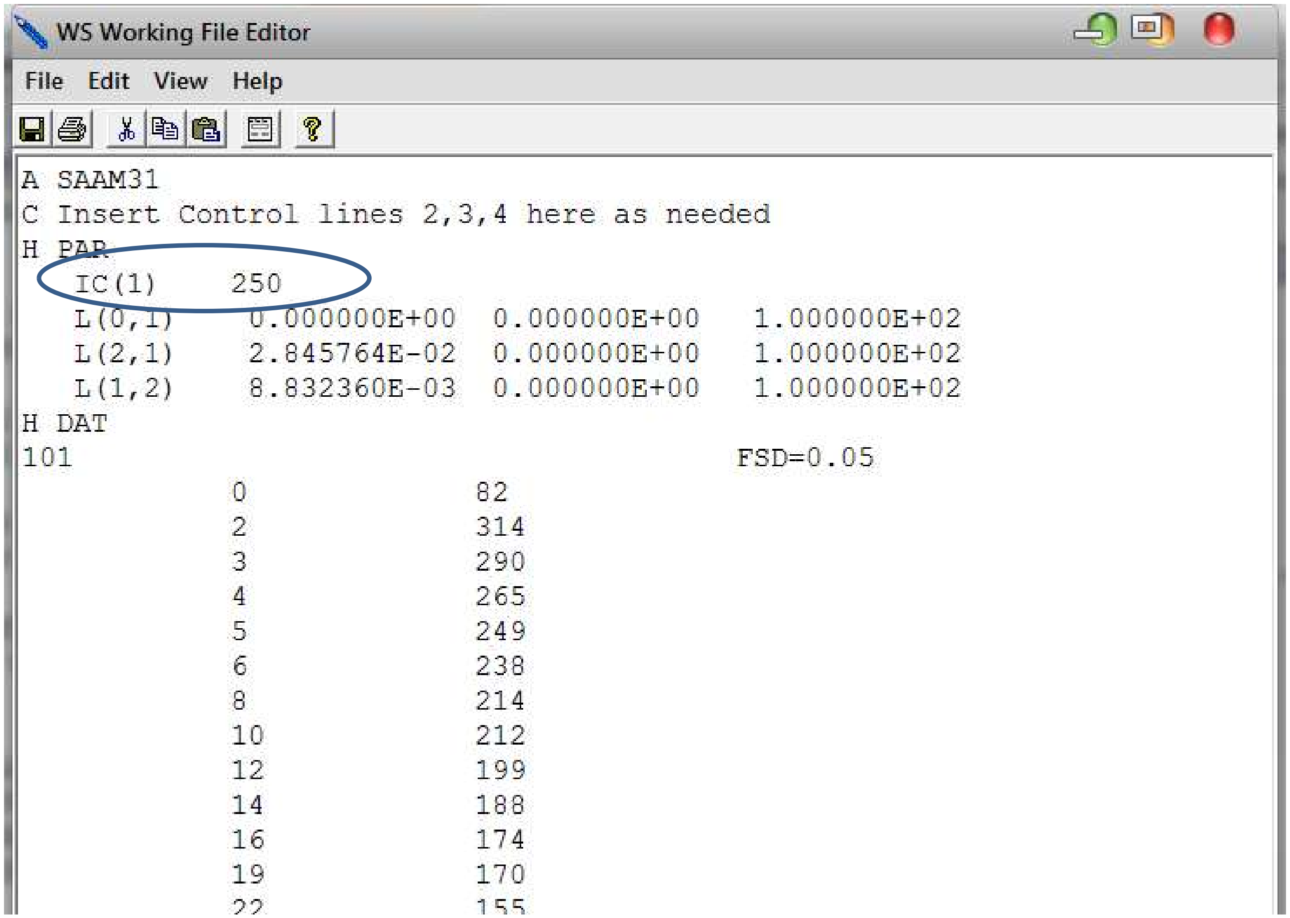
Two Compartment Model of Glucose Disposal During FSIGT Test

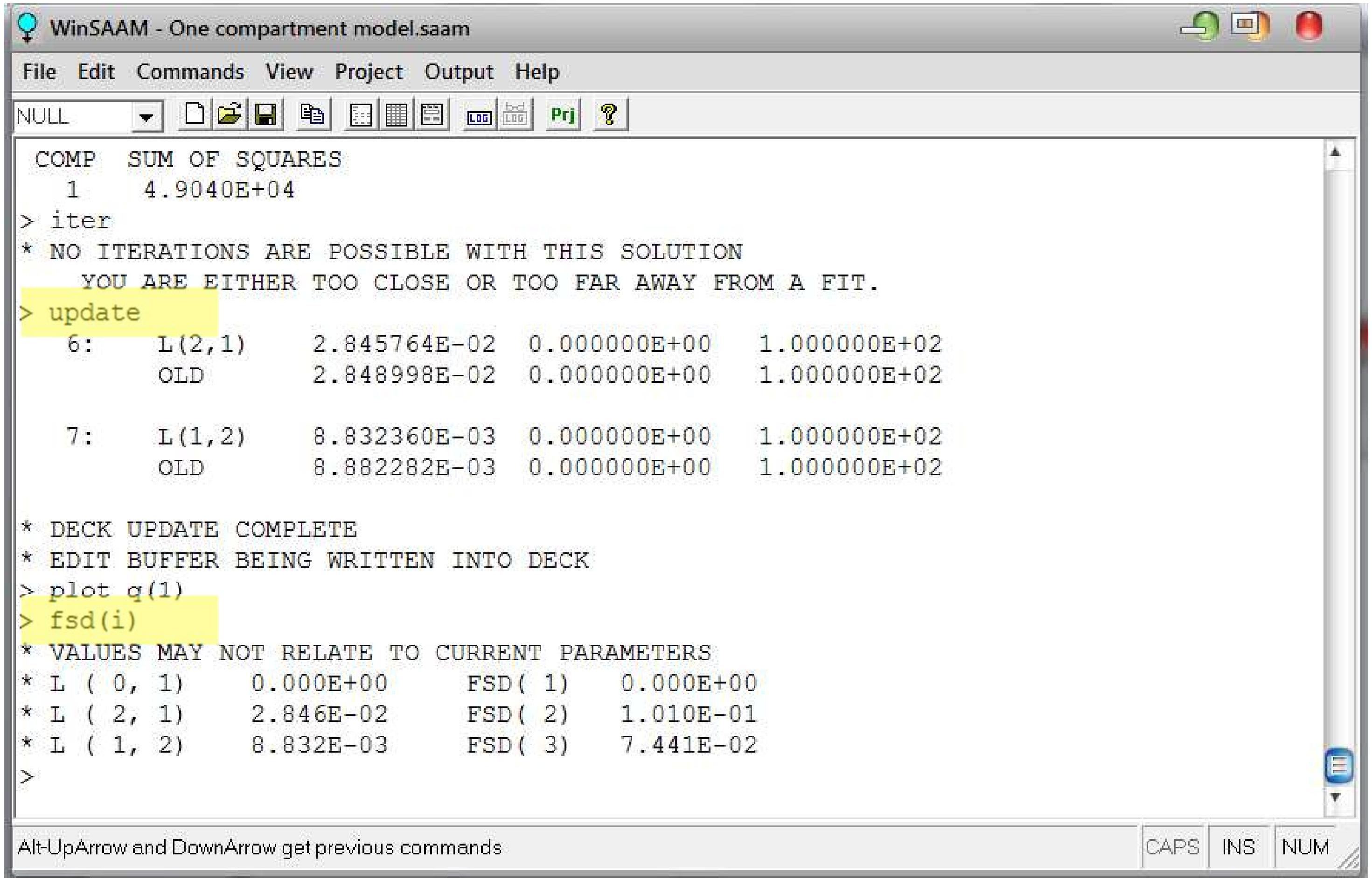


SAAM File




```
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



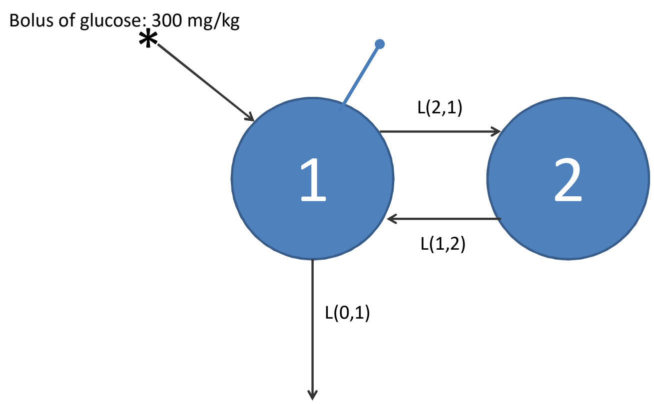
What do ODEs Represent?

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

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

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

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```
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

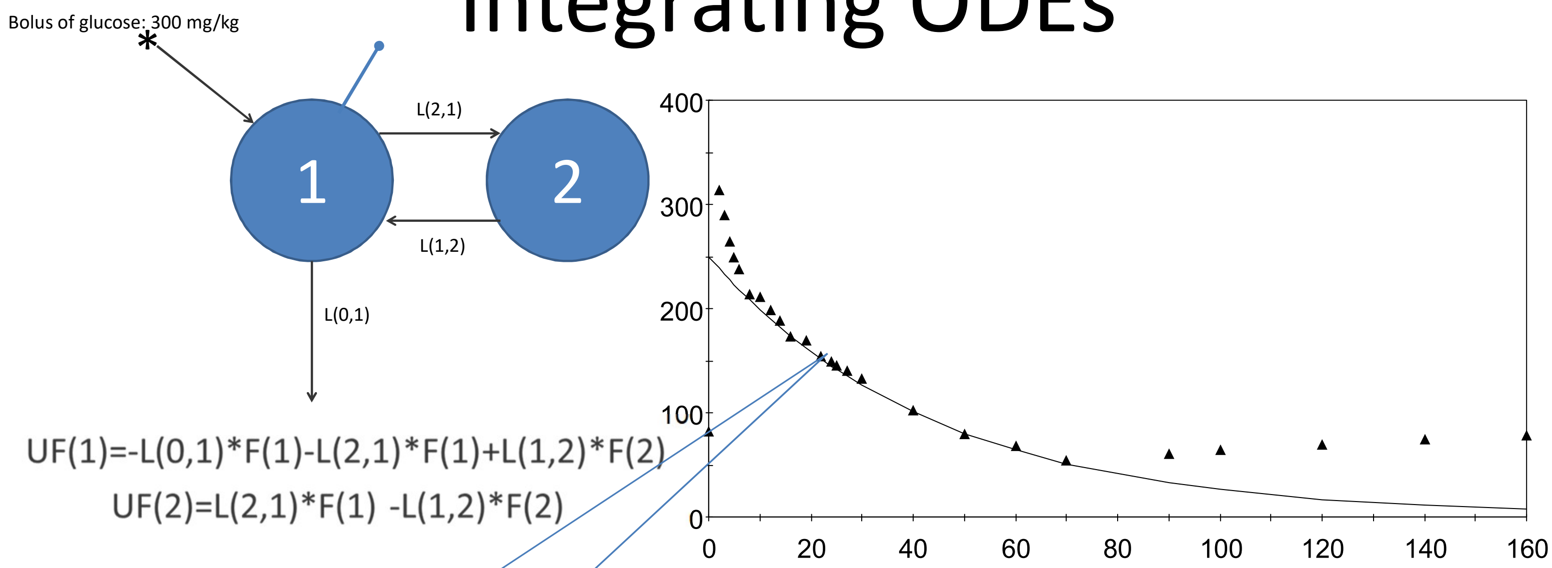
$$f(x) = \left\{ \frac{x \geq 0, \qquad\qquad 1}{x \leq 60 \qquad\qquad 0} \right\}$$

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 QO
            0              1
            60             0
```

WinSAAM Approach to Determine Eigenvalues & Eigenvector

Integrating ODEs



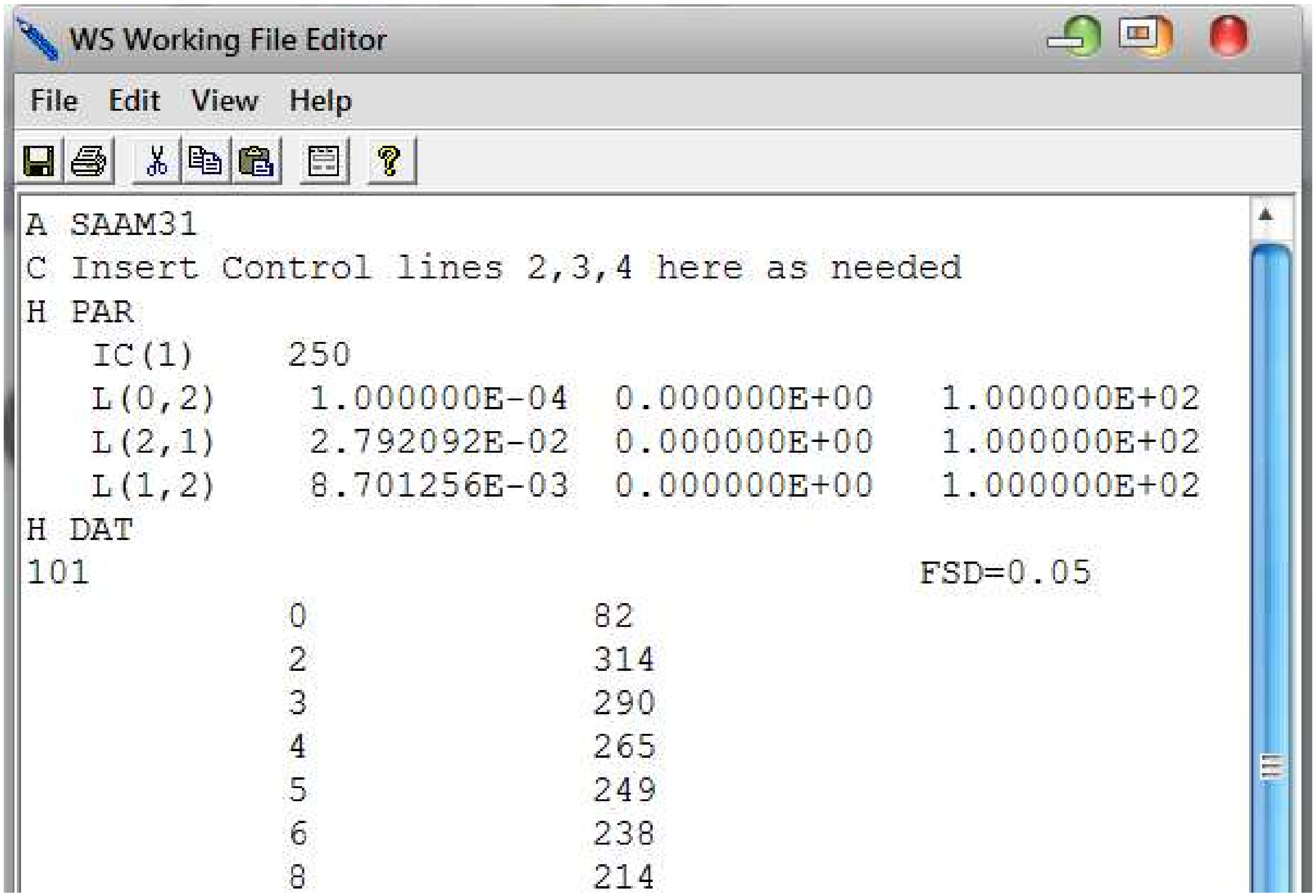
UF(1)=-L(0,1)*F(1)-L(2,1)*F(1)+L(1,2)*F(2)

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

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

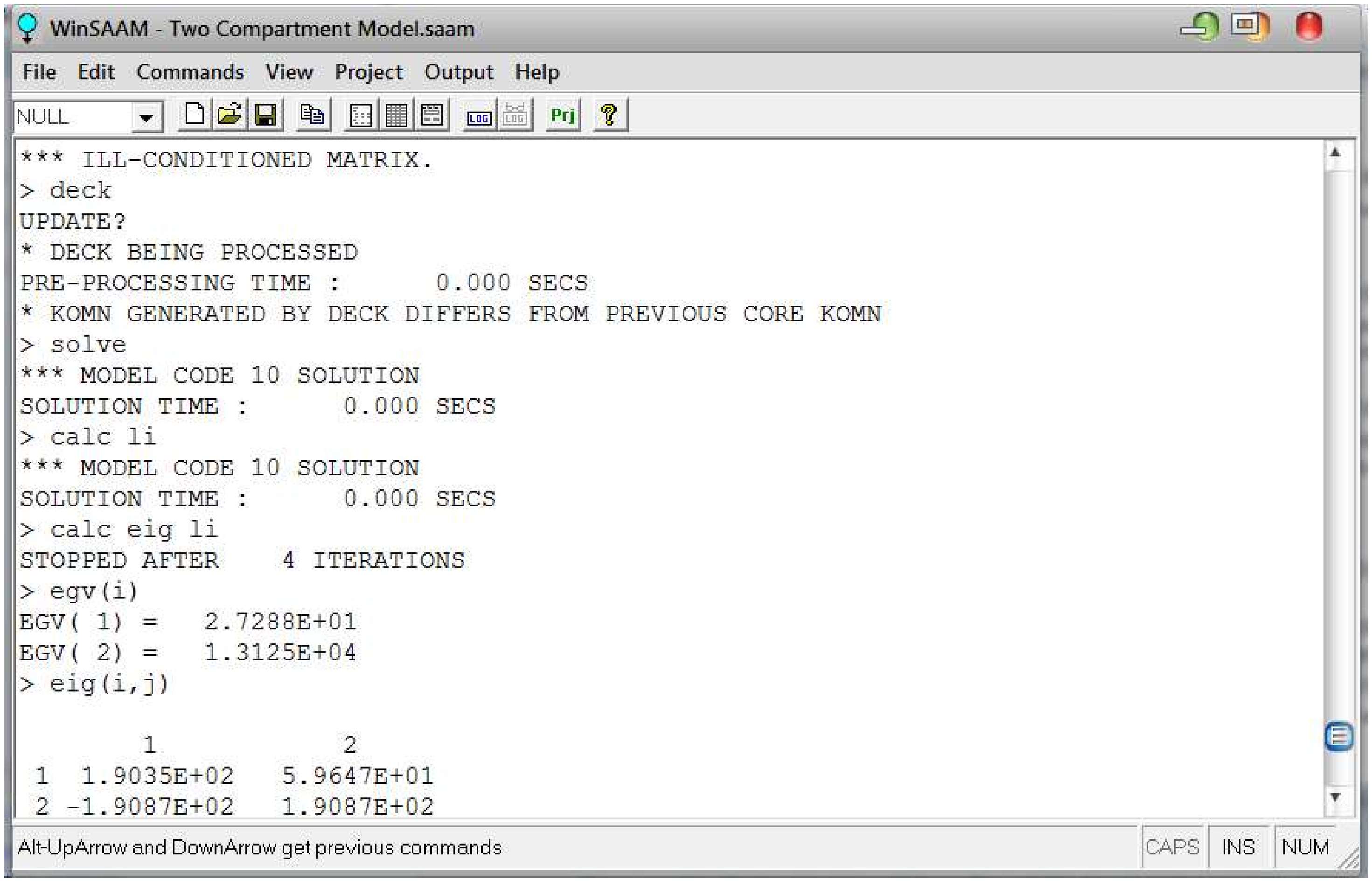
$$F_2(t) = C_{21} * \exp\left(\frac{-t}{\tau_1}\right) + C_{22} * \exp\left(\frac{-t}{\tau_2}\right)$$

Back to Two-Compartment Model

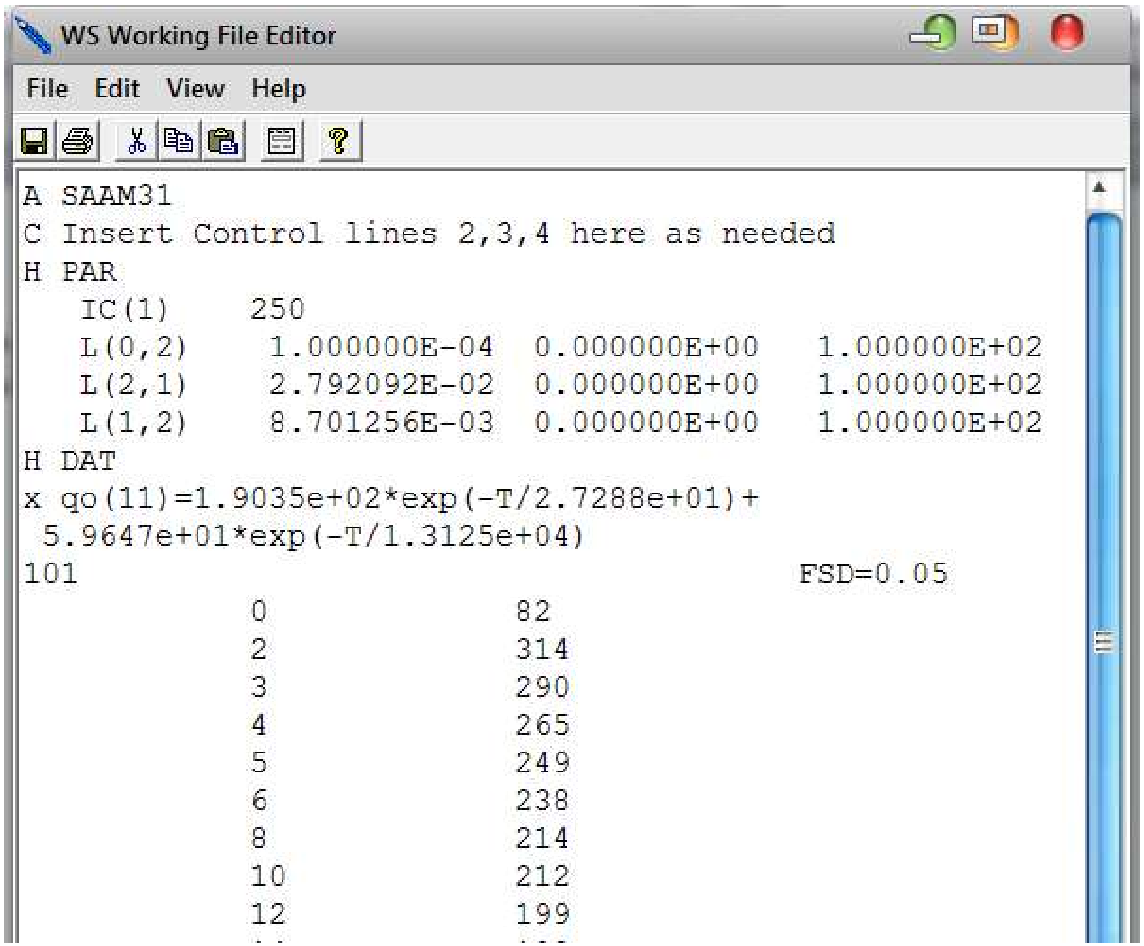



```
A SAAM31
C Insert Control lines 2,3,4 here as needed
H PAR
   IC(1)     250
   L(0,2)     1.000000E-04  0.000000E+00   1.000000E+02
   L(2,1)     2.792092E-02  0.000000E+00   1.000000E+02
   L(1,2)     8.701256E-03  0.000000E+00   1.000000E+02
H DAT
101                                          FSD=0.05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

Calculating Eigenvalues & Eigenvector in WinSAAM

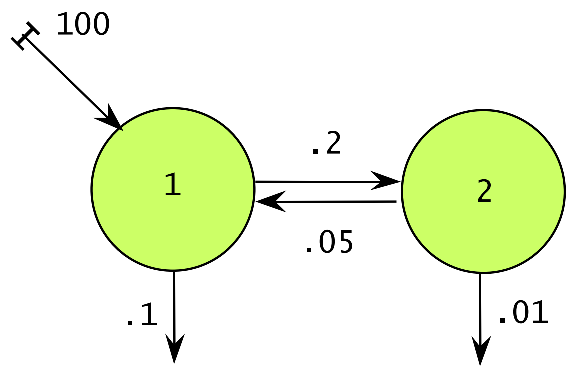


Generating the Simulated Data



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

$$f_1` = -0.3.f_1 + 0.05.f_2 \qquad f_1|_0 = 100$$
$$f_2` = 0.2.f_1 - 0.06.f_2 \qquad f_2|_0 = 0$$

and the response as

$$f_1 = c_1.\exp[-a_1.t] + c_2.\exp[-a_2.t]$$
$$f_2 = c_3.\exp[-a_1.t] + c_4.\exp[-a_2.t]$$

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

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

2. Eigenvectors

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

$$L.A_j = a_j.A_j \qquad \ldots.. \qquad (9)$$

or more generally

$$L.A = a.A \qquad \ldots.. \qquad (9a)$$

i.e. $\left(L - I.a\right) A = 0 \qquad \ldots.. \qquad (9b)$

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

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

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

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

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_i, then the general solution of the system is given by:

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

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

We thus have

$$f_1 = 1.38.c_1.e^{-0.336.t} + 0.18.c_2.e^{-0.024.t}$$
$$f_2 = -1.00.c_1.e^{-0.336.t} + 1.00.c_2.e^{-0.024.t}$$

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