

Understanding the Comp2FlowExchange Model

This is a two compartment model with flow. A flow, F_p , carries an inflow concentration, C_{in} , into a plasma compartment with volume V_p . The substance is instantaneously well mixed. The material undergoes a passive exchange with an interstitial fluid (ISF) space with volume V_{isf} . No reactions occur in this system.

For a constant concentration of inflowing material the analytic solution $C_p=C_{in}$ and $C_{isf}=C_{in}$ if P_{sc} is positive.

Various methods for checking the calculations in a model are illustrated: (1) comparison with an analytic solution for constant inflow, (2) two methods of calculating the amount of material in a compartment with flow, (3) comparison of the running integrals of inflow and outflow concentrations, and (4) calculation of the system transit time of a compartment model with flow by two different methods.

The flow rates for inflow and outflow are equal and the plasma compartment volume remains a constant. The governing ordinary differential equation for the concentrations are given as

$$dC_p/dt = (F_p/V_p) \cdot (C_{in} - C_p) + (P_{sc}/V_p) \cdot (C_{isf} - C_p) \text{ and}$$

$$dC_{isf}/dt = (P_{sc}/V_p) \cdot (C_p - C_{isf})$$

with initial conditions

$$C_p(0) = C_{p0} \text{ and } C_{isf}(0) = C_{isf0} . .$$

Various checks can be done on the model. If an closed analytic solution exists, it can be compared with the numeric result. The Comp2FlowExchange model has a simple closed analytic solution for constant inflow concentration:

$$C_p(t) = C_{in} \text{ and } C_{isf}(t) = C_{in} .$$

The quantity of material that enters the compartment can be calculated in two different ways:

$$Q(t) = V_p \cdot C_p(t) + V_{isf} \cdot C_{isf}(t)$$

and also as

$$Q_{integral}(t) = \int_0^t F_p \cdot (C_{in}(t') - C_{out}(t')) dt' .$$

Checks can be done on the model inflow and outflow concentrations. After a long time, the integrals of C_{in} and C_{out} with respect to time, known as Area_in and Area_out, must become equal (input quantity=output quantity).

Another check performed is transit time. The transit time of an curve is defined by the integral of its first moment divided by its zeroth moment (the area). Transit time is known as \bar{t} , usually pronounced as "Teebar", but spelled as "Tbar".

$$\bar{t} = \frac{\int_0^{\infty} C(t) \cdot t \, dt}{\int_0^{\infty} C(t) \, dt} .$$

Tbar can also be given as a function of time, in which case

$$\bar{t}(t) = \frac{\int_0^t C(t') \cdot t' \, dt'}{\int_0^t C(t') \, dt'} .$$

In this model the areas and transit times are given as functions of time. Elsewhere, they are given as the values after long time. The transit time of the system is given as

$$t_{sys}^- = t_{out}^- - t_{in}^- .$$

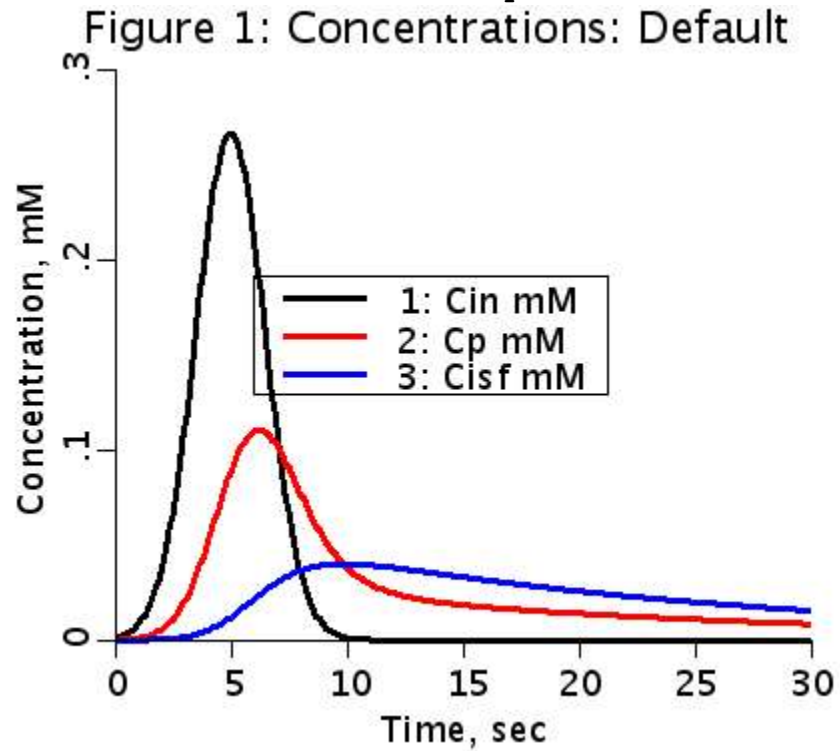
Tbar_sys is also given as

$$t_{sys}^- = (V_p) / F_p \text{ if } PS_c = 0 \text{ and}$$

$$t_{sys}^- = (V_p + V_{isf}) / F_p \text{ if } PS_c > 0.$$

Figures and Explanations

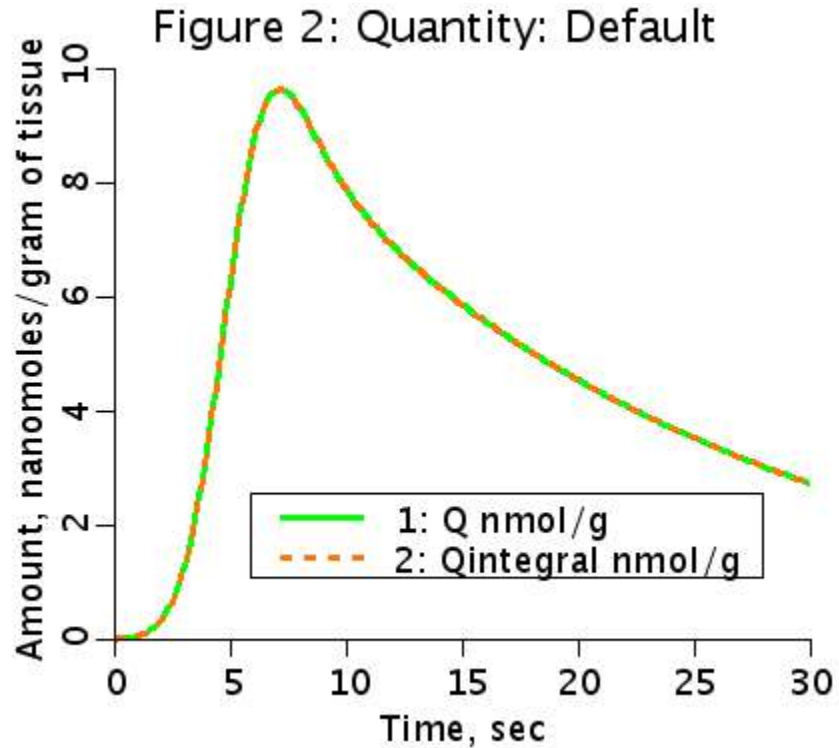
Figure 1: Concentrations: Default parameter set



This is a plot of the inflow concentration (black line), outflow concentration (red line), and the concentration in the interstitial fluid space (ISF) (blue line) as a function of time.

Question 1. What event coincides with the peak of the curve of the ISF concentration.

Figure 2: Quantity: Default parameter set



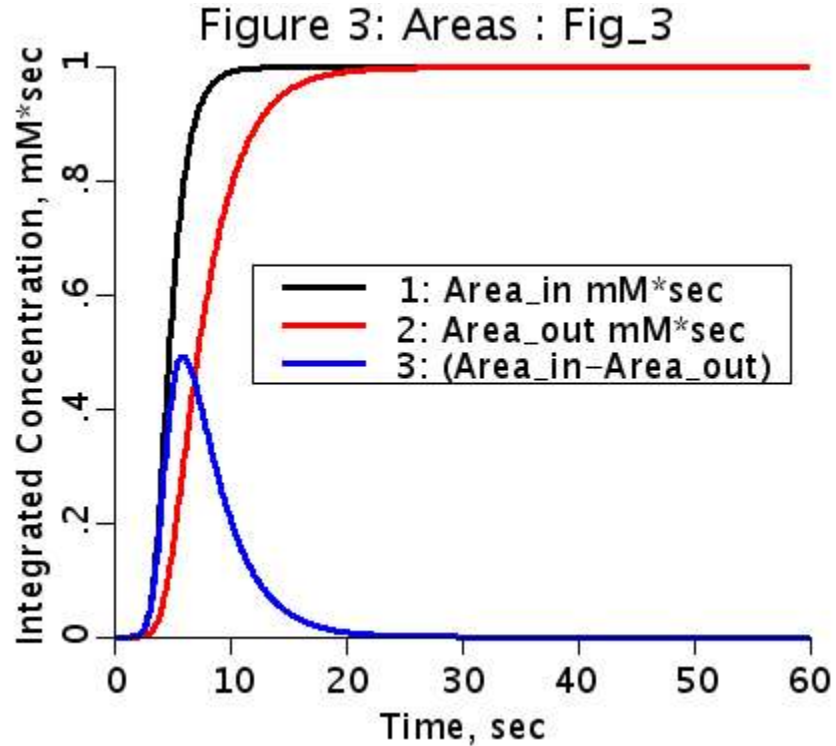
Quantity of material in the two compartments as a function of time is calculated by two different methods:

$$Q(t) = V_p \cdot C_p(t) + V_{isf} \cdot C_{isf}(t), \text{ and}$$

$$Q_{integral}(t) = \int_0^t F_p \cdot (C_{in}(t') - C_{out}(t')) dt'$$

and give the same result.

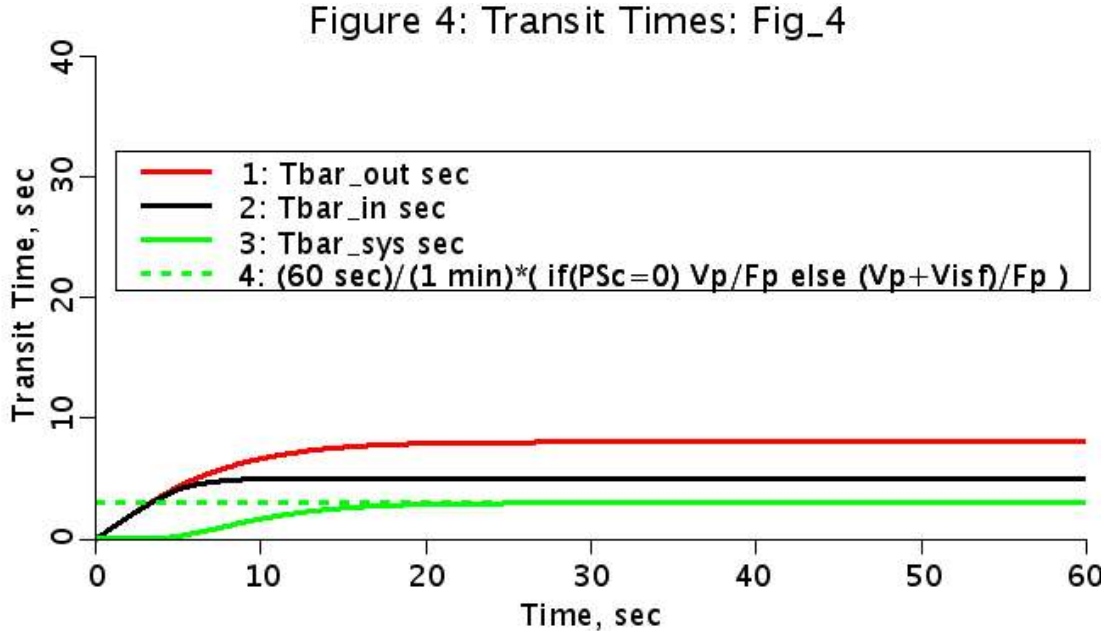
Figure 3: Areas: Fig_3 parameter set



PSc was set to zero and t.max to 60. The integrated inflow (black) and outflow (red) concentrations are plotted as functions of time. The difference is plotted in blue and is equal to the Quantity of material in the system divided by F_p .

Run loops to see how a positive value of PSc makes a large change in the Area-out. It rises much more slowly.

Figure 4: Transit Times: Fig_4 parameter set



PSc was set to zero and t.max was set to 60 seconds. The transit time of the inflow concentration is 5 seconds, outflow concentration 8 seconds, and system transit time is 3 seconds = V_p/F_p (expressed in seconds).

Set PSc to 1, t.max to 300, and run again. What happened to the output transit time, Tbar_out?

Set PSc to 0.001 and run again. Explain what has happened. Explain the difference between the estimated Tbar_sys (dashed green line) and the apparent value of Tbar_sys (green solid line.) Look at the area plots in Figure 3 on a log scale. Although Area_out at 300 seconds is 99.9% of Area_in, not enough time has elapsed to make the calculation based on integrating concentration curves accurate.

Set t.delta = 10, and t.max = 100,000 and run again. This should help explain the values of the previous run with Psc=0.001 and t.max=300.

Figure 5: Optimization: Fig_5 parameter set

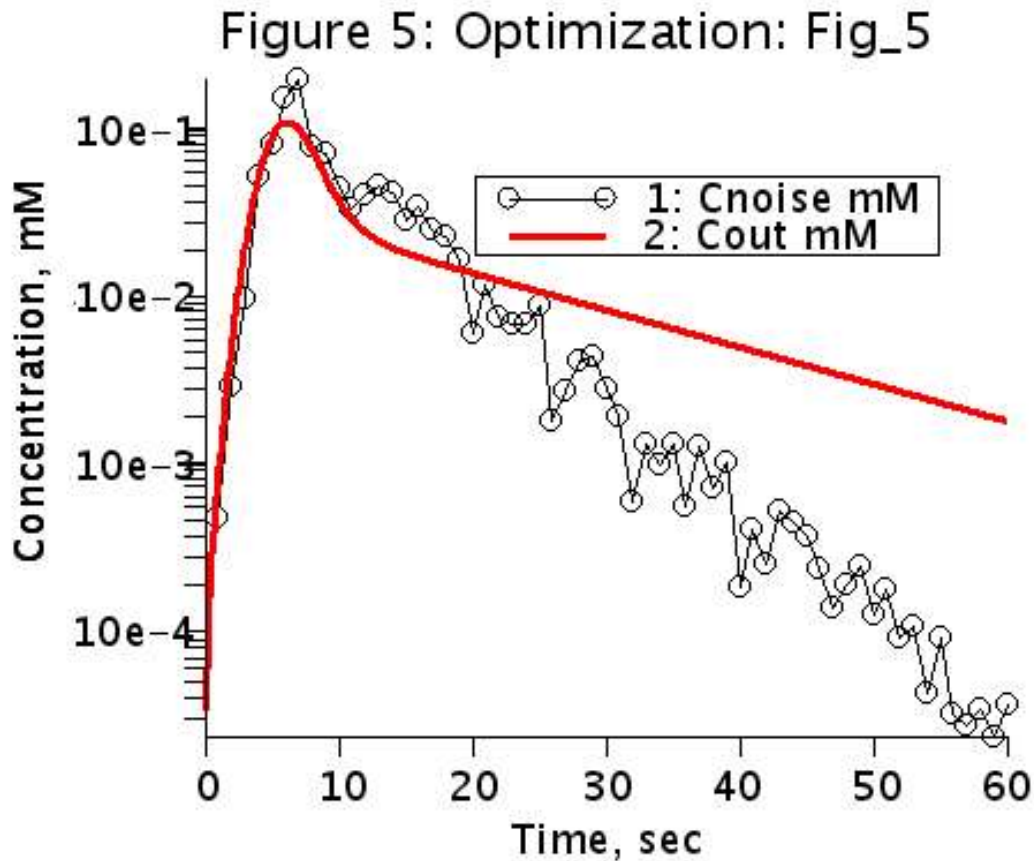


Figure 5 illustrates fitting a model to noisy data. The data was generated by

```
Cnoise=Cout*(1+.4*randomg()), using seed 2929,
```

with $F=2.3$ ml/(g*min), $PSc=4$ ml/(g*min), $t.\text{delta} = 1$ sec; and the input function being the Gaussian probability density function in the function generator with $\text{area}=1$, $t\text{Mean}=5$, and $RD=0.3$. The data was stored in `data_1`.

Assume the flow, F_p , and the exchange rate, PSc , are unknown and optimize on both. Could both flow and the exchange rate be calculated from this experiment? Note that the RMS error is 0.0126. (The RMS error is in the Optimization Report--use button in Optimization GUI.)

Now fix F_p to 2.3 ml/(g*min) (Uncheck the box for this parameter after you have changed it.) Optimize on PSc . The fit appears better even though the RMS error is slightly higher, 0.0131.

Now optimize on both parameters again from this starting point. The fit is substantially worse, but the RMS error is the lowest so far.

What is necessary is to weight the data so that the smallest values are as significant as the largest values. In the Pwgt (point weight) box, replace the 1 with

```
if(Cout>0) 1/Cout else 0
```

This weighting effectively fits the data in the logarithm space.

Answer (1): When the plasma concentration equals the ISF concentration, the ISF concentration is at its maximum.