

Testing Protocol for Multi-Compartment Transport Models

Soroush Safaei

CellML models are considered to be complex when there are more than one compartment in the model. The membranes between the compartments contain one or more protein channels. There also could be chemical reactions inside the compartments. In the following, different stages for testing the validity of such complex models have been explained:

Ground 0:

- Initialise all the variables to zero (1), close all the protein channels (2), deactivate all the inside reactions (3), and then run the model.

$$c_i = 0, \quad i = 1, \dots, 4 \quad (1)$$

$$T_j = 0, \quad j = 1, 2 \quad (2)$$

$$R_k = 0, \quad k = 1, 2 \quad (3)$$

- If the model does not run, check for any singularity or division by zero in the equations and identify them. Fix the problem in the code, so it would not happen again at any point during the simulation.
- Check all the variables for any leakage, they all should be constant and in the steady state condition. Also they should be all zero unless there is a mathematical explanation behind it (Figure 1).

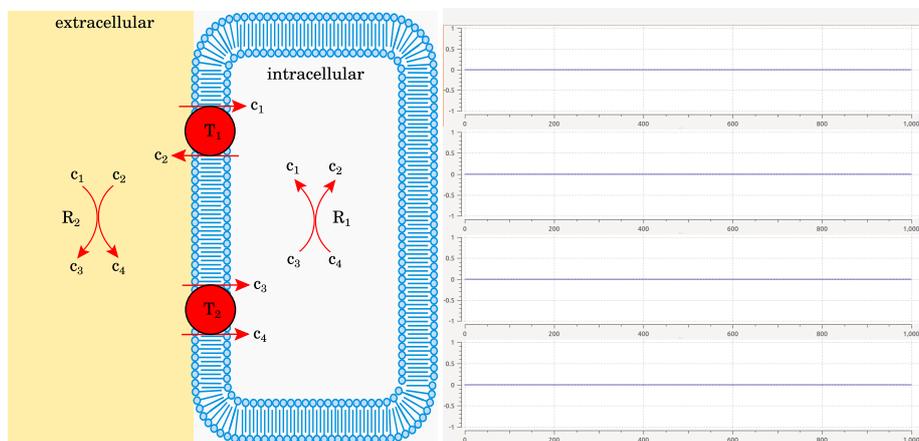


Figure 1: (left) A basic complex CellML model consisting of two compartments (extracellular and intracellular) and four substances (c_1 , c_2 , c_3 , c_4). (right) Concentrations of c_1 to c_4 in the extracellular environment during the first 1000 seconds of the simulation which are all zero.

Stage 1: Compartments, no reaction, no channel

- Initialise all the variables to their default values (4), close all the protein channels (5), deactivate all the inside reactions (6), and then run the model.

$$c_i = c(i), \quad i = 1, \dots, 4 \quad (4)$$

$$T_j = 0, \quad j = 1, 2 \quad (5)$$

$$R_k = 0, \quad k = 1, 2 \quad (6)$$

- Check all the variables for any leakage, they should be constant and in the steady state condition (Figure 2).

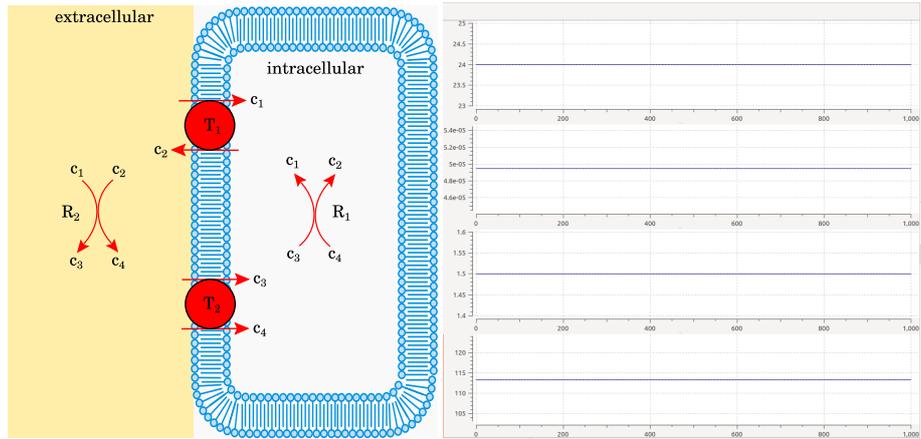


Figure 2: (left) A basic complex CellML model consisting of two compartments (extracellular and intracellular) and four substances (c_1 , c_2 , c_3 , c_4). (right) Concentrations of c_1 to c_4 in the extracellular environment during the first 1000 seconds of the simulation which remained constant.

Stage 2: Compartments with reactions, no channel

- Initialise all the variables to their default values (7), close all the protein channels (8), activate only one of the reactions at a time in each compartment (9), and then run the model.

$$c_i = c(i), \quad i = 1, \dots, 4 \quad (7)$$

$$T_j = 0, \quad j = 1, 2 \quad (8)$$

$$R_k = 1, \quad k = 1, 2 \quad (9)$$

- Check the flux direction for each reaction, make sure it is correct. Be consistent, set a standard for the model and document it in the model description (Figure 3).
- Check the variables in each compartment separately and investigate if they are behaving in the expected way. Check the reactions in each compartment to see if they reach the steady state condition (Figure 4).

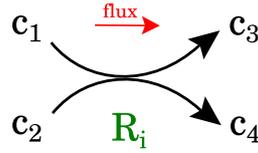


Figure 3: Flux direction for an inside reaction. It is always assumed to be positive from reactants side to products side.

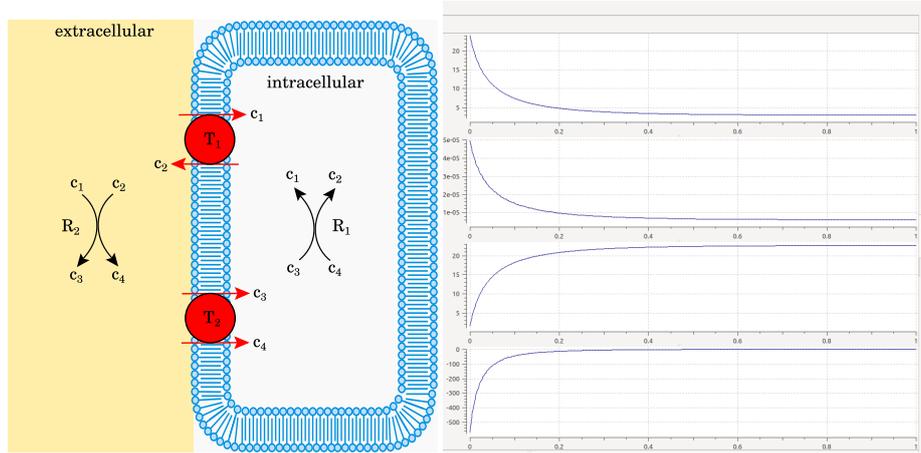


Figure 4: (left) A basic complex CellML model consisting of two compartments (extracellular and intracellular), four substances (c_1 , c_2 , c_3 , c_4) and two inside reactions (R_1 and R_2). (right) Concentrations of c_1 to c_3 and the reaction flux in the extracellular environment during the first second of the simulation which reached the steady state condition.

Stage 3: Compartments, no reaction, with one active channel

- Initialise all the variables to their default values (10), open only one of the protein channels between two compartments (11), deactivate all the inside reactions (12), and then run the model.

$$c_i = c(i), \quad i = 1, \dots, 4 \quad (10)$$

$$T_j = 1, \quad j = 1 \vee 2 \quad (11)$$

$$R_k = 0, \quad k = 1, 2 \quad (12)$$

- Check the flux direction for the channel, make sure it is correct. Be consistent, set a standard for the model and document it in the model description (Figure 5).

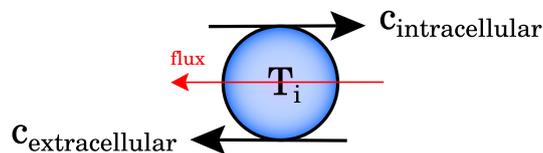


Figure 5: Flux direction for a protein channel. It is always assumed to be positive from intracellular environment to extracellular environment.

- Identify the intracellular and extracellular environments. As a standard, inside the cell is assumed to be the intracellular ground and moving away from the cell, the compartment closer to the cell consider as the intracellular relative to the further one (Figure 6).

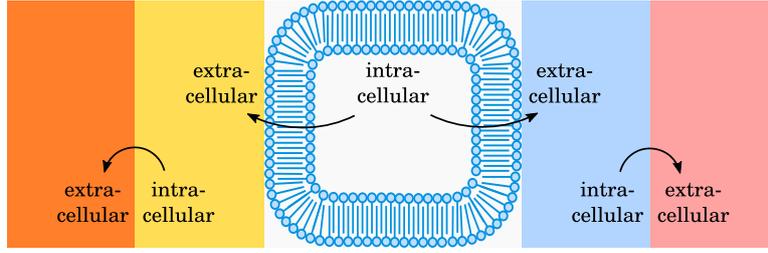


Figure 6: Relative extracellular and intracellular environments in a complex model with five compartments.

- Check the relative transport speed of each protein channel, categorise them as high-speed or low-speed. This can help in the future to identify the main protein channels and analyse the results. If the speed for two channels are significantly different, there may be some issues with the units. Make sure the units for input and output variables are consistent.
- Check the variables in each membrane separately. The variables related to the active protein channel should behave in the expected way, and all the other variables should stay constant and in the steady state condition (Figure 7).

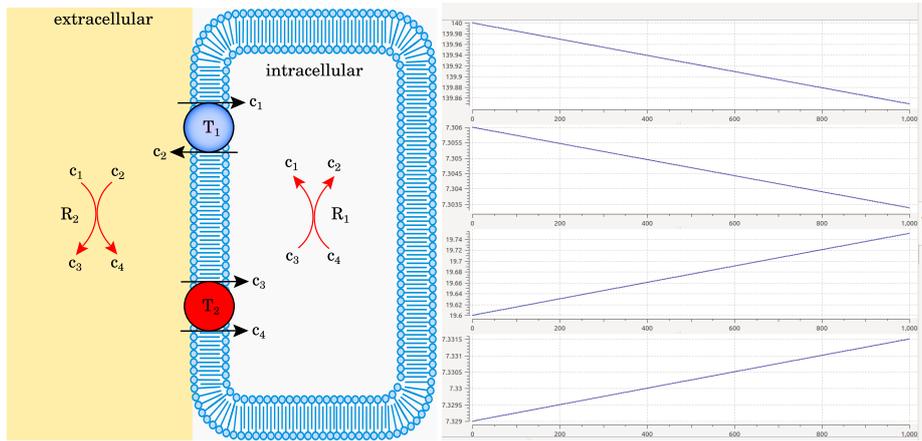


Figure 7: (left) A basic complex CellML model consisting of two compartments (extracellular and intracellular), four substances (c_1 , c_2 , c_3 , c_4) and one protein channel (T_1). (right) Concentrations of c_1 and c_2 in the extracellular and intracellular environments during the first 1000 seconds of the simulation.

Stage 4: Compartments with reactions and channels

- Initialise all the variables to their default values (13), open all the protein channels between two compartments (14), activate all the inside reactions (15), and then run the model.

$$c_i = c(i), \quad i = 1, \dots, 4 \quad (13)$$

$$T_j = 1, \quad j = 1, 2 \quad (14)$$

$$R_k = 1, \quad k = 1, 2 \quad (15)$$

- Check the variables in each membrane separately. The variables should behave in the expected way (Figure 8).

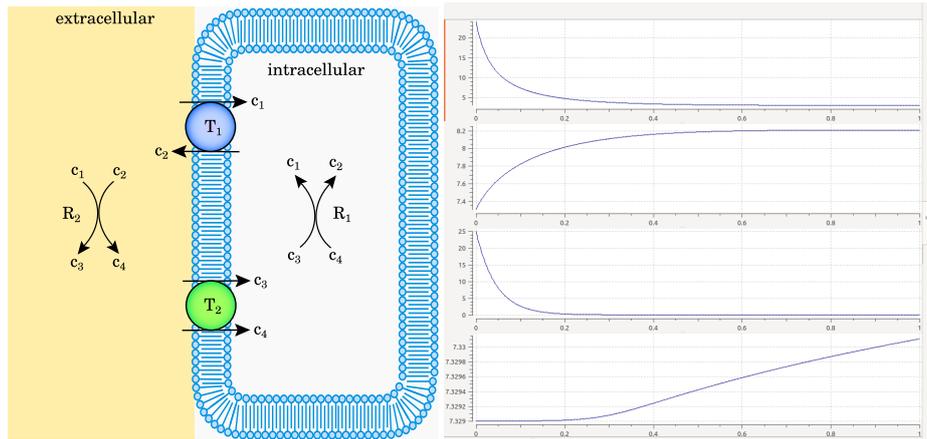


Figure 8: (left) A basic complex CellML model consisting of two compartments (extracellular and intracellular), four substances (c_1 , c_2 , c_3 , c_4), two protein channels (T_1 and T_2) and two inside reactions (R_1 and R_2). (right) Concentrations of c_3 and c_4 in the extracellular and intracellular environments during the first second of the simulation.

Stage 5: Domain Specific Protocols