**5.5 Membrane transporters**

The protein transporters that carry chemical species across a cell membrane fall into one of three basic types:

1. Neutral membrane transporters where, even though the chemical species being transferred can be charged ions, there is no *net* charge transferred. An example is the chloride ()/bicarbonate () exchanger AE1.
2. Electrogenic membrane transporters where there is net charge transfer, such as with the sodium-glucose cotransporter SGLT1.
3. ATPase-dependent transporters such as the sodium-potassium exchanger NKX, where both ions are being transported against their concentration gradients at a metabolic cost.

***SLC family***

The solute-carrier (SLC) group of membrane transport proteins carry nutrients and metabolites across cell membranes. They are associated with 400 genes that code for 65 protein families (many of which are therapeutic targets or involved in drug or drug metabolite transport).

***Example 5.5.1:* Neutral membrane transporters**

Figure 5.5.1(a) shows the bond graph model for AE1, which exchanges and across the membrane. There are 6 states for the transport enzyme and 6 reactions for the transitions between these states.

**1:**

**Figure 5.5.1** Schematic (left) and bond graph model (right) for AE1 exchange [10].

The enzyme has 6 confirmational states denoted by the two unbound states (**,** ) on the inner and outer sides of the membrane, respectively, the two states in which is bound (), and the two states in which is bound (). The rate of change of each of these states is obtained from the 6 corresponding 0:nodes:

:

:

:

:

:

:

Note that the total enzyme mass stays constant since the sum of these last 6 equations is zero.

From the remaining 0:nodes, the rate equations for the and ions in solution on either side of the membrane are:

:

:

:

:

These rate equations are represented in vector form by:

,

where contains the 10 state variables (the molar concentrations of and and their enzyme bound forms on either side of the membrane), contains the 6 reaction fluxes, and is the10 x 6 stoichiometric matrix (*S-matrix*) which captures the system connectivity.

The flows through each of the 6 reactions are specified in terms of the chemical potentials via the Marcelin-deDonder formula:

where the potentials for the enzyme state variables have been replaced by their Boltzmann definitions, and the remaining 4 potentials are given in terms of the enzyme and ion concentrations by:

Substituting these 4 potentials into the reaction flow equations above yields:

where the forward and reverse reaction rate constants and given in terms of the reaction and Boltzmann constitutive parameters by

Note that the Gibb’s free energy change for the overall system is given by .

Therefore

or

.

The reaction will proceed when , or when …

The above 10 ODEs and these 6 flow equations are formulated in CellML and solved in OpenCOR below for specified initial values of the 6 enzyme state variables and ion concentrations.

***Experimental measurement of model parameters***

The model equations derived above assume a system that is open to the environment. Experiments used to determine the model parameters will typically use a fully or partially closed system in which the total amount of all or some of the ligands does not change.

When the total amount of is fixed,

or

and hence

. (5.5.1)

When the total amount of is fixed,

or

and hence

. (5.5.2)

If N experiments are performed giving N sets of measured values of and, equation (5.5.1) can be solved for the 4 unknown rate constants , , , , and 4N unknown enzyme states **, , ,** (a different set for each of the N experiments).Similarly, for , , , .

Note that under steady state conditions when all fluxes are zero, the ratios of the forward to reverse reaction rate constants are determined by the molar concentrations of the state variables:

; ; ;

; ;

If the equilibrium molar concentrations of , , and are specified for a range of values, these 6 equations can be used to optimally fit the values and the molar concentrations of the enzyme state variables.

For , we denote and