Modelling the Michaelis-Menten System Using Bond Graph Technique

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1 Preamble

A bond graph is a representation of a system that includes both mass and energy transfers. It differs from most pharmacological representations that consider only mass.

The purpose of using this technique is to provide a system that is conserved on mass and energy. We measure mass in mole or molar units and in a closed system (not in equilibrium with the environment) require that the sum of all reactants and products remains constant, such that $\Sigma q = Q$, a constant. In chemical reactions we are also concerned with internal energy (U). If we measure the equilibrium energy of the reactants as the $\Delta U^o_{f_{reactants}}$ and the energy of the products as $\Delta U^o_{f_{products}}$ then conservation of energy in an isolated closed system (where the energy is not in equilibrium with the environment) requires $\Delta U^o_{f_{reactants}} + \Delta U^o_{f_{products}}$ to be constant.

2 The system

The Michaelis-Menten approximation of enzyme-catalysed reactions can be represented by:

$$q_1 + q_2 \underset{k^{-1}}{\overset{k^{+1}}{\rightleftharpoons}} q_3 \underset{k^{-2}}{\overset{k^{+2}}{\rightleftharpoons}} q_2 + q_4 \tag{1}$$

In this setting, q_1 is the reactant, q_2 is the enzyme which is conserved during the reaction, q_3 is the intermediate complex, and q_4 is the product. It is important to remember in this system that q_2 is the same species on both sides of this reaction and therefore is the sum of the enzyme as reactant and enzyme as product. Here q is defined in molar units.

The second-order rate constant on from q_1 and q_2 is k^{+1} (units: $mol^{-1}\, l^{-1}\, s^{-1}$) and the first-order rate constant off is k^{-1} (units: s^{-1}), similarly the first-order rate constant from q_3 is k^{+2} and the rate constant off is k^{-2}. Since formation of the product is generally irreversible then $k^{+2} \gg k^{-2}$.

A bond graph of this system will yield a schematic of the energy flow. The bond graphs is:

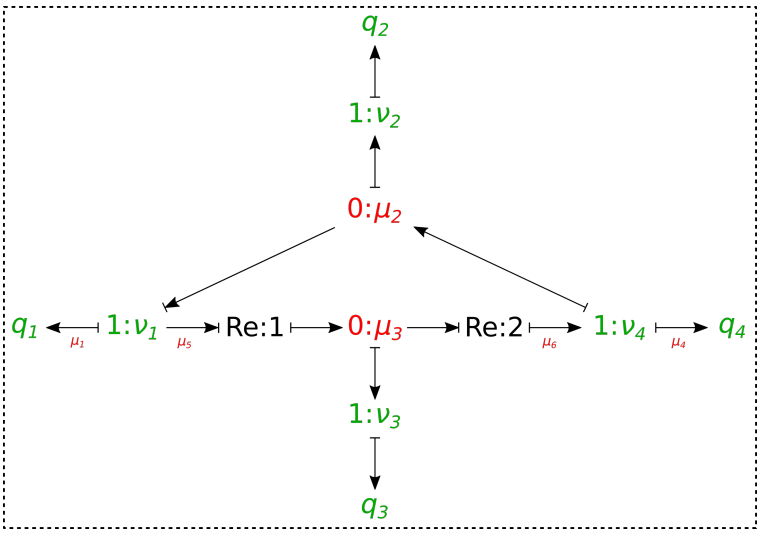

Figure 1: The bond graph representation of Michaelis-Menten closed system.

In Figure 1, the arrows represent the flow of energy. $Re1$ depicts reaction 1 and $Re2$ reaction 2, q has units of $mol\,l^{-1}$ and has the same meaning as in the usual reaction diagram, v are velocities of the change in substrate ($mol\,l^{-1}\,s^{-1}$), and μ the energy per mole ($J\,mol^{-1}\,l^{-1}$). A balanced system is balanced on v and μ.

The two energy points for conservation are μ_3 and μ_2 which correspond to the generation of q_3 and q_2 respectively. Note that the recycling of q_2 is shown here explicitly as this is required in this closed system.

The key to conserving both mass and energy is an attention to units. Here, q has units of $mol\,l^{-1}$ (molar concentration), v has units of $mol\,l^{-1}\,s^{-1}$ (this is also velocity as per MM equation), and μ has units of $J\,mol^{-1}\,l^{-1}$ (energy per molar concentration).

To achieve the purpose, for the system to be conserved for mass and energy, the system must be neutral for mass (in this case $mol\,l^{-1}$), that is Σq is constant, and energy ($J\,s^{-1}$), that is $\frac{\mathrm{d}J}{\mathrm{d}s} = \Sigma\mu \times v = -A$ and is constant (A is defined as affinity, when negative the reactants have affinity for each other). This is equivalent to Gibbs free energy at equilibrium for an isolated closed system. A negative value for Gibbs free energy means that a reaction will occur readily.

It is sufficient in the bond graph representation that only the four points μ_2, v_1, μ_3 and v_4 are conserved for energy and mass for the system to meet our goal.

3 The mass system

Given that the derivative of the moles of substance over time is velocity then $\dot{q} = v$, where $\dot{q} = \mathrm{d}q/\mathrm{d}t$. Therefore:

$$\begin{aligned} \dot{q}_1 &= -v_1, \\ \dot{q}_2 &= v_2, \\ \dot{q}_3 &= v_3, \\ \dot{q}_4 &= v_4. \end{aligned} \tag{2}$$

4 The energy system

Based on Gibbs free energy and at equilibrium, then the following energy per mol relationships are derived:

$$\begin{aligned} \mu_1 &= R.T.ln\left(K_1.q_1\right), \\ \mu_2 &= R.T.ln\left(K_2.q_2\right), \\ \mu_3 &= R.T.ln\left(K_3.q_3\right), \\ \mu_4 &= R.T.ln\left(K_4.q_4\right). \end{aligned} \tag{3}$$

Here, R is the gas constant (= 8.314 $J\,mol^{-1}\,°K^{-1}$), and T is the temperature in Kelvin (= 298 $°K$). Finally, K_x is an equilibrium constant and is defined as:

$$K_x = \left(\frac{1}{q_x}\right) e^{\left(\frac{\mu_x}{R.T}\right)}, \tag{4}$$

and therefore:

$$e^{\left(\frac{\mu_x}{R.T}\right)} = K_x q_x, \tag{5}$$

The derivation for Equation 3 is then:

$$\mu_1 = R.T.ln\left(K_1.q_1\right) = R.T.ln\left(e^{\left(\frac{\mu_1^0}{R.T}\right)} q_1\right). \tag{6}$$

5 Conservation of mass and energy

The velocities are conserved (and therefore mass is conserved) by the two species of interest relating to v_2 and v_3. In this model we consider the inward flow of energy and outward flow of energy. For example, we see that the inward velocity to v_2 is v_4 and outward velocity is v_1, therefore:

$$\begin{aligned} v_2 &= v_4 - v_1, \\ v_3 &= v_1 - v_4. \end{aligned} \tag{7}$$

Because the enzyme is reused in the reaction process then the bond graph represents a cycle and hence $v_2 = -v_3$.

The energy of the reactants going into the reaction is given by μ_1 (associated with the reactant) and μ_2 (associated with the enzyme). Hence the sum μ_5 is equivalent to $\Delta U^o_{f_{reactants}}$. Similarly the reaction energy of the products $\Delta U^o_{f_{products}}$ is expressed by μ_6 as per Equation 8.

$$\begin{aligned} \mu_5 &= \mu_1 + \mu_2, \\ \mu_6 &= \mu_2 + \mu_4. \end{aligned} \tag{8}$$

At this point we need to solve for μ_1, μ_2, μ_3, μ_4, v_1 and v_4 in order to assess the balance.

6 Dependence on molar concentration q

It turns out that both velocity and energy are related to molar concentration. We introduce κ as the reaction velocity with units of $mol\,l^{-1}\,s^{-1}$ and recalling that K is our equilibrium constant derived under mass law with units of $(mol\,l^{-1})^{-1}$. We see that K is actually the inverse of affinity and is equivalent to $(K^S_{eq})^{-1}$, which is the inverse of the equilibrium binding constant for substrate S in Langmuir's isotherm.

From Equations 2 and 3 and substituting K we can see that:

$$v_1 = \dot{q}_1 = \kappa_1 \left(e^{\left(\frac{\mu_5}{R.T}\right)} - e^{\left(\frac{\mu_3}{R.T}\right)} \right) = \kappa_1 \left(K_1 q_1 K_2 q_2 - K_3 q_3 \right), \tag{9}$$

$$v_4 = \dot{q}_4 = \kappa_2 \left(e^{\left(\frac{\mu_3}{R.T}\right)} - e^{\left(\frac{\mu_6}{R.T}\right)} \right) = \kappa_2 \left(K_3 q_3 - K_2 q_2 K_4 q_4 \right). \tag{10}$$

The link between the reaction rate constants and the thermodynamic parameters are provided by:

$$k^{+1} = \left(\frac{\kappa_1}{q_1 + q_2} \right) e^{\left(\frac{\mu_1 + \mu_2}{R.T}\right)} = \kappa_1 K_1 K_3, \tag{11}$$

$$k^{-1} = \left(\frac{\kappa_1}{q_3} \right) e^{\left(\frac{\mu_3}{R.T}\right)} = \kappa_1 K_3, \tag{12}$$

$$k^{+2} = \left(\frac{\kappa_2}{q_3} \right) e^{\left(\frac{\mu_3}{R.T}\right)} = \kappa_2 K_3, \tag{13}$$

$$k^{-2} = \left(\frac{\kappa_2}{q_2 + q_4} \right) e^{\left(\frac{\mu_2 + \mu_4}{R.T}\right)} = \kappa_2 K_2 K_4. \tag{14}$$

We see here that there is a special case solution where the rate constants are specifically drive by the energy transfer since $\mu_3 = f(k^{+2}, k^{-1})$, here $f()$ is a function.

7 The steady state Michaelis-Menten model

If we assume steady state, where $v_2 = 0$ (the change in abundance of enzyme is constant over time) and $v_3 = 0$ (the change in abundance of intermediate over time is zero), and we also consider that the return rate constant $k^{-2} = 0$ then we can define the standard Michaelis-Menten parameters; the equilibrium constant:

$$K_m = \frac{k^{-1} + k^{+2}}{k^{+1} + k^{-2}} = \frac{(\kappa_1 + \kappa_2)K_3}{\kappa_1 K_1 K_2}; \quad \text{units}: mol\,l^{-1} = \frac{mol\,l^{-1}\,s^{-1}.(mol\,l^{-1})^{-1}}{mol\,l^{-1}\,s^{-1}.(mol\,l^{-1})^{-2}} \tag{15}$$

And the maximum velocity:

$$V_{max} = \kappa_2 K_3 (q_2 + q_3); \quad \text{units}: mol\,l^{-1}\,s^{-1} = mol\,l^{-1}\,s^{-1}.(mol\,l^{-1})^{-1}.mol\,l^{-1} \tag{16}$$

Here the total abundance of enzyme is $q_2 + q_3$. For consistency the units are also solved to ensure mass and energy balance are retained.

8 The system parameters and laws

Constitutive parameters: $[\kappa, K]$
State variables: $[q]$
Conditional state variables*: $[\mu, \nu]$
Mass conservation laws: $\nu_2 = \nu_4 - \nu_1$, $\nu_3 = \nu_1 - \nu_4$
Energy conservation laws: $\mu_5 = \mu_1 + \mu_2$, $\mu_6 = \mu_2 + \mu_4$
Prior information: $[k^{-1}, k^{+1}, k^{-2}, k^{+2}]$
Constants: $[R, T]$

*Conditional state variables can be calculated from the state variables, *i.e.* ν is the time derivative of q and μ is proportional to $ln(q)$.

9 The open system

In order to create an open system from a closed system, the *chemostat* concept is introduced. When one species is fixed to have a constant concentration, a substrate with a fixed state is used as a chemostat. This applies an appropriate external flow to balance the internal flow of the species.

Assuming in Equation 1, q_1 and q_4 are used as chemostats then we have an open system for the enzyme catalysed reaction. Each chemostat imposes a chemical potential upon the system and inherits the flow on the corresponding junction.

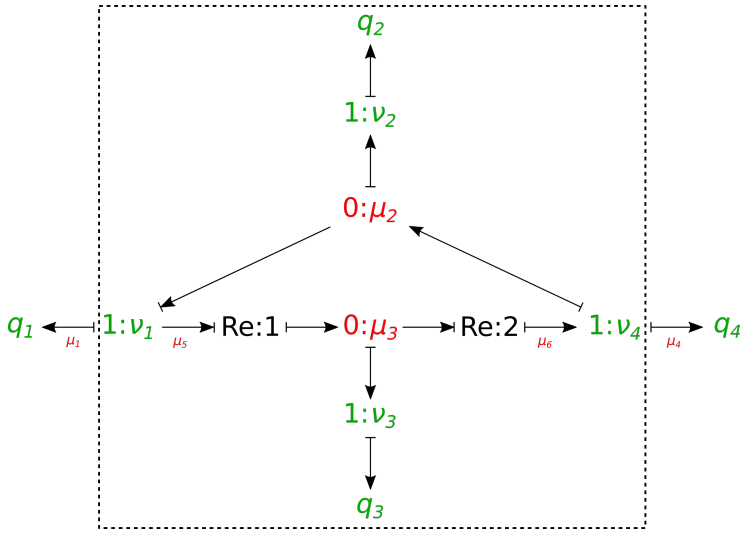

Figure 2: The bond graph representation of Michaelis-Menten open system.

In Figure 2, the dashed box represents a closed system with respect to q_2 and q_3. However, q_1 and q_4 correspond to large external pools with effectively fixed concentrations. The only modification that should be made to the closed system to represent an open system is:

$$
\begin{aligned}
\dot{q}_1 &= 0, \\
\dot{q}_2 &= v_2, \\
\dot{q}_3 &= v_3, \\
\dot{q}_4 &= 0.
\end{aligned}
\tag{17}
$$

The rest of the equations should remain as before.

9.1 Enzyme degradation

In this section, an enzyme degradation reaction $Re0$ is added and μ_0 is the zero-potential source.

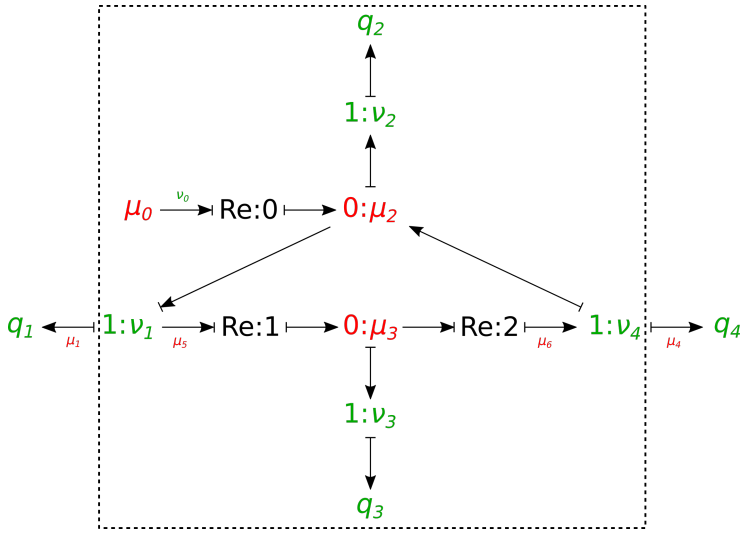

Figure 3: The bond graph representation of Michaelis-Menten open system with enzyme degradation.

Appendices

A OpenCOR output

The results from OpenCOR for both closed and open system are shown below:

B OpenCOR file

The CellML file from OpenCOR for both closed and open system is shown below:

```
def model MichaelisMenten as
    def comp state as
        var t: second;

        // State variables

        var q1: mole {init: 1.0e-0};
        var q2: mole {init: 1.0e-0};
        var q3: mole {init: 1.0e-6};
        var q4: mole {init: 1.0e-6};
        // var v0: mol_per_s; // activate for enzyme degradation
        var v1: mol_per_s;
        var v2: mol_per_s;
        var v3: mol_per_s;
```

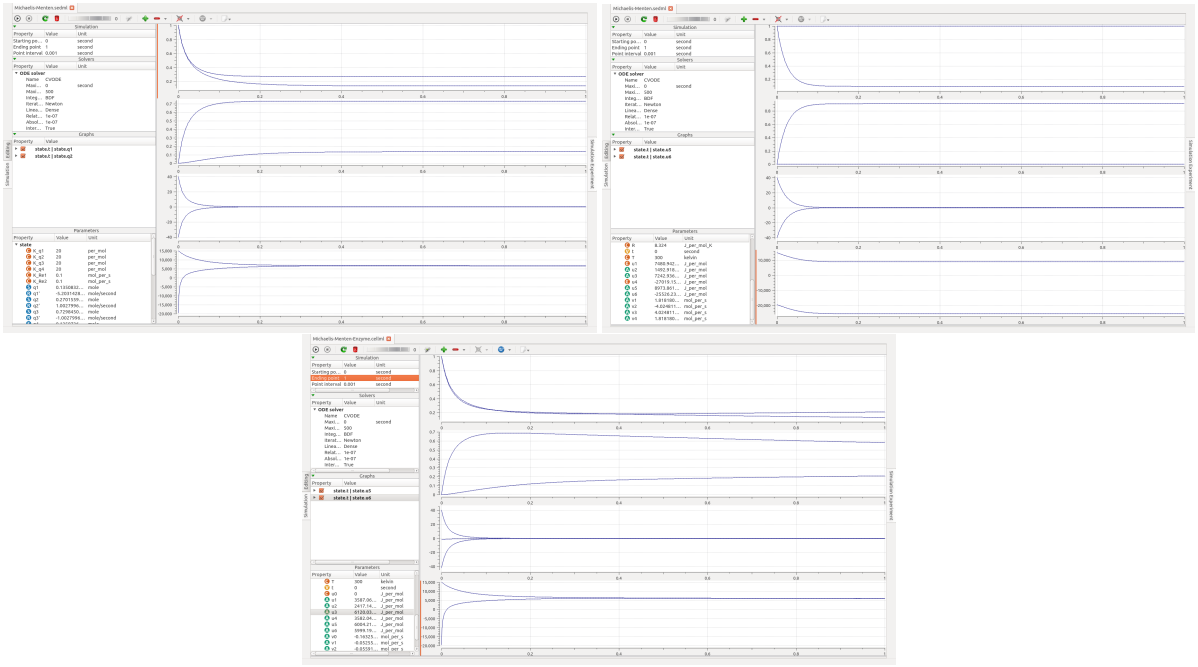

Figure 4: From top to bottom: q_1 & q_2 *vs* time, q_3 & q_4 *vs* time, v_2 & v_3 *vs* time, μ_5 & μ_6 *vs* time. left: closed system, right: open system.

```
var v4: mol_per_s;
var u1: J_per_mol;
var u2: J_per_mol;
var u3: J_per_mol;
var u4: J_per_mol;
var u5: J_per_mol;
var u6: J_per_mol;
// var u0: J_per_mol {init: 0.0}; // activate for enzyme degradation

// Constitutive parameters

var R: J_per_mol_K {init: 8.324};
var T: kelvin {init: 300};
var K_q1: per_mol {init: 20.0};
var K_q2: per_mol {init: 20.0};
var K_q3: per_mol {init: 20.0};
var K_q4: per_mol {init: 20.0};
var K_Re1: mol_per_s {init: 0.1};
var K_Re2: mol_per_s {init: 0.1};
// var K_Re0: mol_per_s {init: 0.1}; // activate for enzyme degradation

// Conservation laws

ode(q1, t) = -v1; // set to 0 for chemostat
ode(q2, t) = v2;
ode(q3, t) = v3;
ode(q4, t) = v4;  // set to 0 for chemostat
v2 = v4-v1;       // add +v0 for enzyme degradation
v3 = v1-v4;
u5 = u1+u2;
u6 = u2+u4;

// Constitutive relations
```

```
        u1 = R*T*ln(K_q1*q1);
        u2 = R*T*ln(K_q2*q2);
        u3 = R*T*ln(K_q3*q3);
        u4 = R*T*ln(K_q4*q4);
        v1 = K_Re1*(K_q1*q1*K_q2*q2-K_q3*q3);
        v4 = K_Re2*(K_q3*q3-K_q2*q2*K_q4*q4);
        // v0 = K_Re0*(exp(u0/(R*T))-K_q2*q2); // activate for enzyme degradation
    enddef;

    def unit per_mol as
        unit mole {expo: -1};
    enddef;

    def unit mol_per_s as
        unit mole;
        unit second {expo: -1};
    enddef;

    def unit J_per_mol as
        unit joule;
        unit mole {expo: -1};
    enddef;

    def unit J_per_mol_K as
        unit joule;
        unit mole {expo: -1};
        unit kelvin {expo: -1};
    enddef;
enddef;
```