Bond Graph Clinic: Part 4

The relationship between kinetic and bond graph models of biochemistry

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Motivation

“Is it possible to convert Model X into a bond graph?”

The current state of affairs

- Empirical models are generally unable to be represented as bond graphs
- Many biophysically detailed models fall into a grey area
- Biochemical systems with mass action are relatively well understood

Goals

- Look at some examples to revise deriving differential equations from bond graphs
- Relate kinetic parameters with bond graph parameters
- Discuss issues in converting kinetic parameters into bond graph parameters

  (and motivate the use of bond graphs for biochemical systems)

Example 1: Binary reaction

$$A \underset{k^-}{\overset{k^+}{\rightleftharpoons}} B$$

Example 1: Binary reaction

Constitutive equations

C:A

$$\mu_A = e_1 = RT \ln(K_A x_A) \quad (1)$$

$$\dot{x}_A = -f_1 \quad (2)$$

C:B

$$\mu_B = e_2 = RT \ln(K_B x_B) \quad (3)$$

$$\dot{x}_B = f_2 \quad (4)$$

Re:r1

$$v = f_1 = f_2 \quad (5)$$

$$v = \kappa(e^{A^f/RT} - e^{A^r/RT}) = \kappa(e^{e_1/RT} - e^{e_2/RT}) \quad (6)$$

Example 1: Binary reaction

Substitute (1) and (3) into (6):

$$v = \kappa(e^{RT\ln(K_A x_A)/RT} - e^{RT\ln(K_B x_B)/RT}) = \kappa K_A x_A - \kappa K_B x_B \qquad (7)$$

Substitute (7) into (2) and (4):

$$\dot{x}_A = -f_1 = -v = -\kappa K_A x_A + \kappa K_B x_B$$

$$\dot{x}_B = f_2 = v = \kappa K_A x_A - \kappa K_B x_B$$

This represents a mass action system, with

$$k^+ = \kappa K_A$$

$$k^- = \kappa K_B$$

Example 1: Binary reaction

Question: Given a set of kinetic parameters k^+ and k^-, can the bond graph constants be identified?

If we arbitrarily set the value of κ, the remaining bond graph constants are

$$K_A = k^+/\kappa$$

$$K_B = k^-/\kappa$$

If $k^+ = 2$, and $k^- = 4$, and we set $\kappa = 2$, then

$$K_A = 1, \qquad K_B = 2$$

If we instead set $\kappa = 1$, then

$$K_A = 2, \qquad K_B = 4$$

Non-uniqueness of bond graph parameters

Issue: While bond graph constants can be found for any given set of kinetic constants, the solution is non-unique.

Since all solutions result in identical kinetic parameters k^+ and k^-, the kinetics of the system are identical.

The reaction affinity is the same also:

$$A = A^f - A^r = \mu_A - \mu_B = RT \ln\left(\frac{K_A x_A}{K_B x_B}\right) = RT \ln\left(\frac{k^+ x_A}{k^- x_B}\right)$$

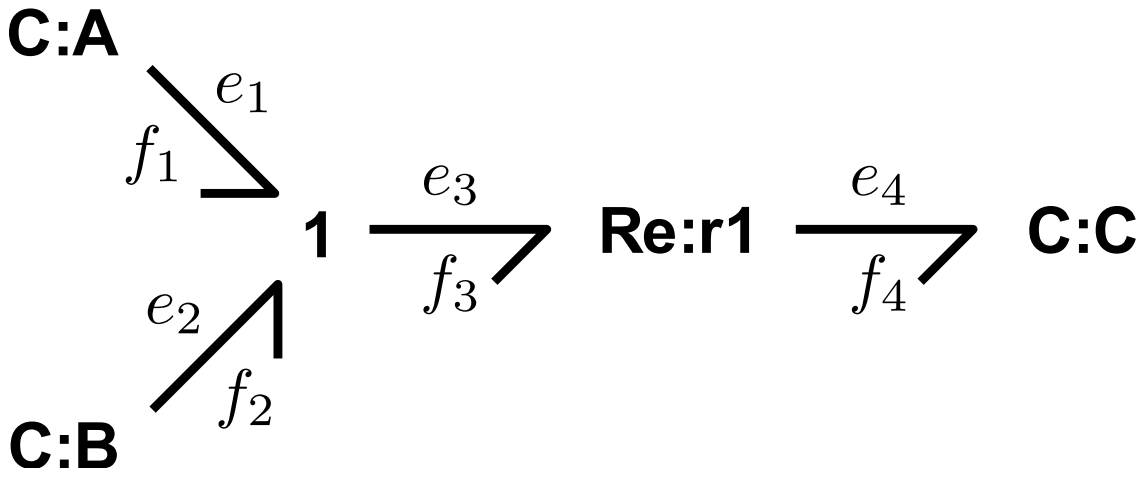
Where do models within the solution space differ?

The values of μ_A and μ_B are different

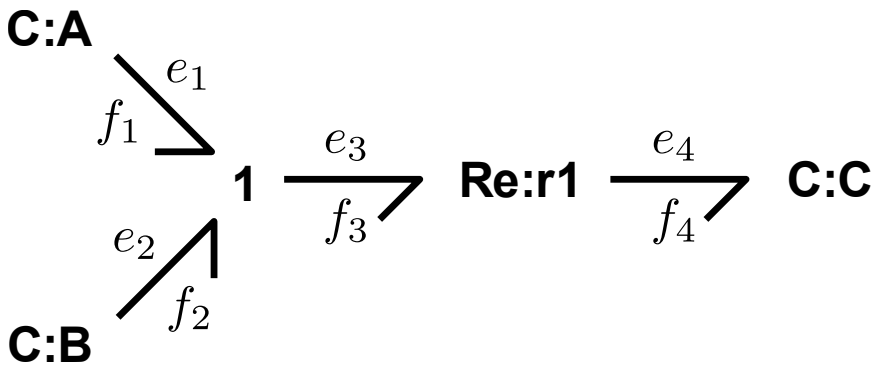
What kind of data is required to uniquely identify bond graph parameters?

Example 2: Branched reaction

$$A + B \underset{k^-}{\overset{k^+}{\rightleftharpoons}} C$$



Example 2: Branched reaction



Constitutive equations

C:A

$$\mu_A = e_1 = RT \ln(K_A x_A) \quad (1)$$

$$\dot{x}_A = -f_1 \quad (2)$$

C:B

$$\mu_B = e_2 = RT \ln(K_B x_B) \quad (3)$$

$$\dot{x}_B = -f_2 \quad (4)$$

C:C

$$\mu_C = e_4 = RT \ln(K_C x_C) \quad (5)$$

$$\dot{x}_C = f_4 \quad (6)$$

Re:r1

$$v = f_3 = f_4 \quad (7)$$

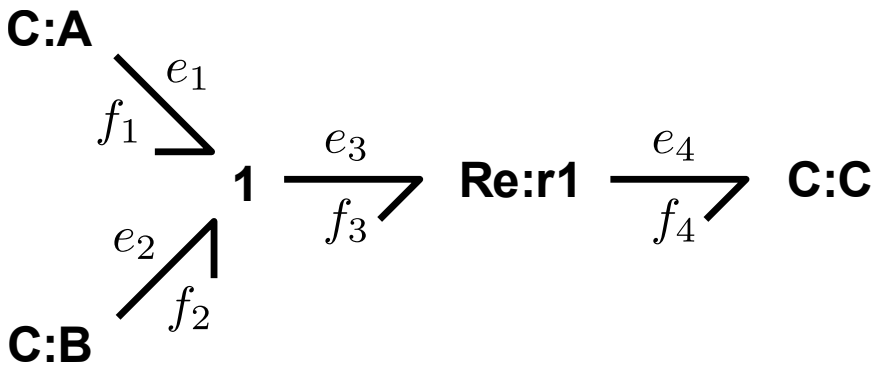
$$v = \kappa(e^{e_3/RT} - e^{e_4/RT}) \quad (8)$$

1

$$f_1 = f_2 = f_3 \quad (9)$$

$$e_1 + e_2 - e_3 = 0 \quad (10)$$

Example 2: Branched reaction



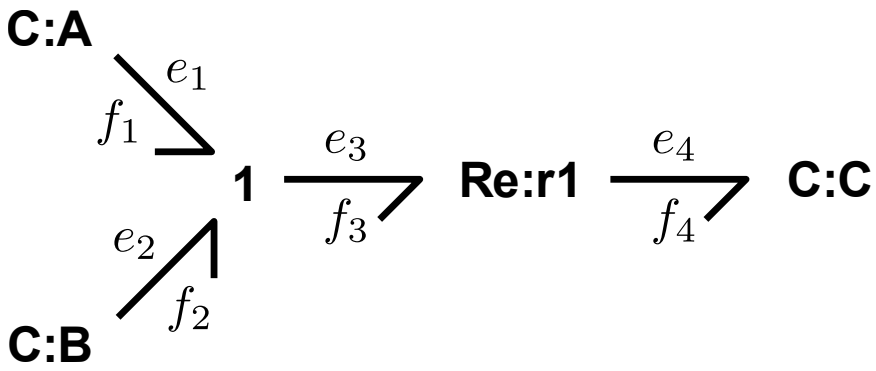
Substitute (1) and (3) into (9):

$$e_3 = e_1 + e_2 = RT\ln(K_A x_A) + RT\ln(K_B x_B) = RT\ln(K_A K_B x_A x_B) \quad (11)$$

Substitute (11) and (5) into (8):

$$v = \kappa(e^{RT\ln(K_A K_B x_A x_B)/RT} - e^{RT\ln(K_C x_C)/RT}) = \kappa K_A K_B x_A x_B - \kappa K_C x_C \quad (12)$$

Example 2: Branched reaction



Substitute (12) into (2), (4) and (6):

$$\dot{x}_A = -f_1 = -f_3 = -v = -\kappa K_A K_B x_A x_B + \kappa K_C x_C$$
$$\dot{x}_B = -f_2 = -f_3 = -v = -\kappa K_A K_B x_A x_B + \kappa K_C x_C$$
$$\dot{x}_C = f_4 = v = \kappa K_A K_B x_A x_B - \kappa K_C x_C$$

This represents a mass action system, with

$$k^+ = \kappa K_A K_B$$
$$k^- = \kappa K_C$$

Example 2: Branched reaction

Can bond graph parameters be identified for a set of given kinetic parameters k^+ and k^-?

If we arbitrarily set the value of κ and K_A, the remaining bond graph constants are

$$K_B = k^+/(\kappa K_A)$$

$$K_C = k^-/\kappa$$

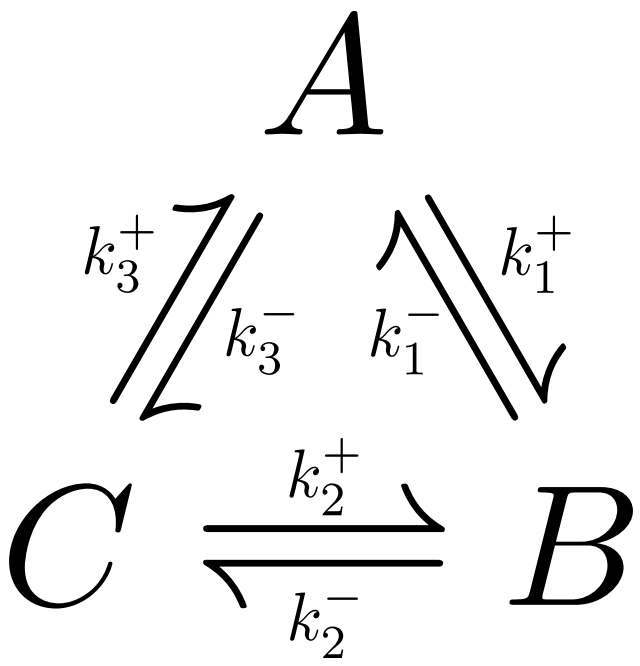
If $k^+ = 6$, and $k^- = 8$, and we set $\kappa = 2$ and $K_A = 3$, then

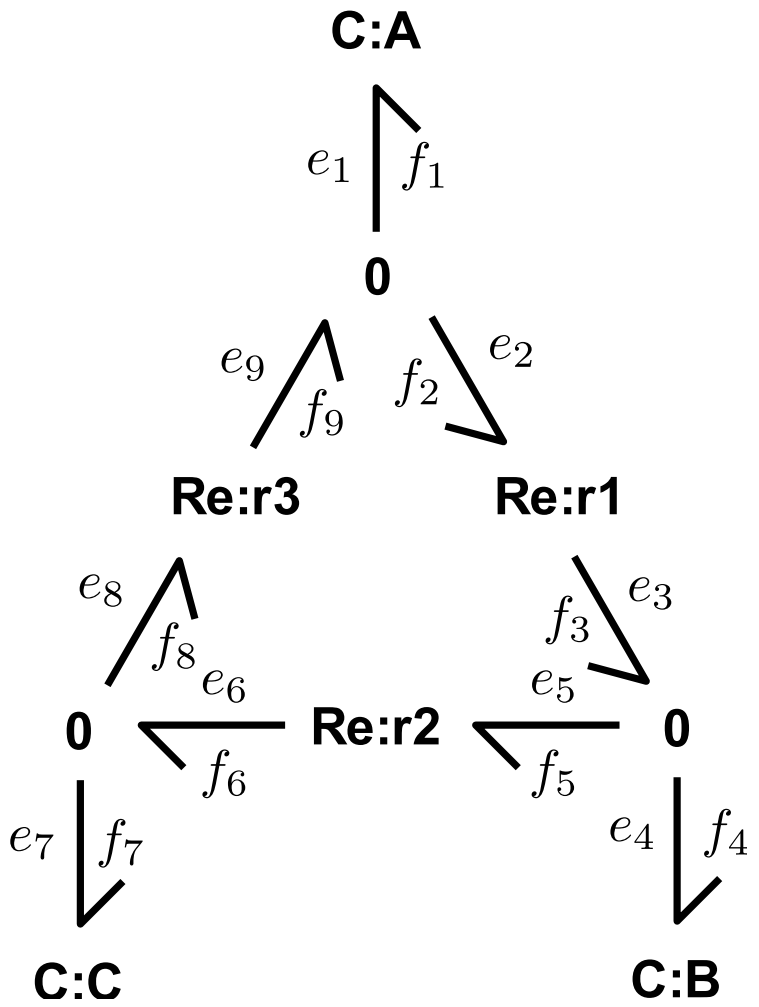
$$K_B = 1, \qquad K_C = 4$$

Like the first example, the solution is non-unique

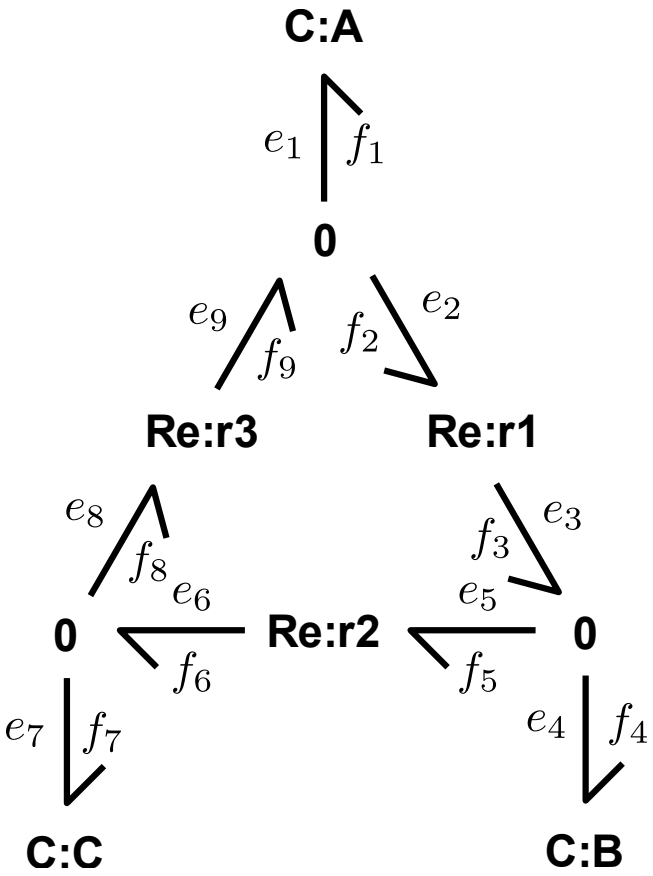
Exercise: Show that the choice of solution does not affect reaction affinity

Example 3: Biochemical cycle





Example 3: Biochemical cycle



C components

$$\mu_A = e_1 = RT\ln(K_A x_A)$$
$$\dot{x}_A = -f_1$$
$$\mu_B = e_4 = RT\ln(K_B x_B)$$
$$\dot{x}_B = -f_4$$
$$\mu_C = e_7 = RT\ln(K_C x_C)$$
$$\dot{x}_C = -f_7$$

Re components

$$v_1 = f_2 = f_3$$
$$v_1 = \kappa_1(e^{e_2/RT} - e^{e_3/RT})$$
$$v_2 = f_5 = f_6$$
$$v_2 = \kappa_2(e^{e_5/RT} - e^{e_6/RT})$$
$$v_3 = f_8 = f_9$$
$$v_3 = \kappa_3(e^{e_8/RT} - e^{e_9/RT})$$

0 junctions

$$e_1 = e_2 = e_9$$
$$-f_1 - f_2 + f_9 = 0$$
$$e_3 = e_4 = e_5$$
$$f_3 - f_4 - f_5 = 0$$
$$e_6 = e_7 = e_8$$
$$f_6 - f_7 - f_8 = 0$$

Example 3: Biochemical cycle

Substitute the equations for the C components into the equations of the Re components to find the reaction rates

$$v_1 = \kappa_1(e^{e_1/RT} - e^{e_4/RT}) = \kappa_1(e^{\mu_A/RT} - e^{\mu_B/RT}) = \kappa_1 K_A x_A - \kappa_1 K_B x_B$$
$$v_2 = \kappa_2(e^{e_4/RT} - e^{e_7/RT}) = \kappa_2(e^{\mu_B/RT} - e^{\mu_C/RT}) = \kappa_2 K_B x_B - \kappa_2 K_C x_C$$
$$v_3 = \kappa_3(e^{e_7/RT} - e^{e_1/RT}) = \kappa_3(e^{\mu_C/RT} - e^{\mu_A/RT}) = \kappa_3 K_C x_C - \kappa_3 K_A x_A$$

Use the flow relationships in the 0 junctions to find the rates of change for each species

$$\dot{x}_A = f_1 = f_9 - f_2 = v_3 - v_1$$
$$\dot{x}_B = f_4 = f_3 - f_5 = v_1 - v_2$$
$$\dot{x}_C = f_7 = f_6 - f_8 = v_2 - v_3$$

Example 3: Biochemical cycle

The bond graph model represents a mass action system with

$$k_1^+ = \kappa_1 K_A \qquad k_1^- = \kappa_1 K_B$$
$$k_2^+ = \kappa_2 K_B \qquad k_2^- = \kappa_2 K_C$$
$$k_3^+ = \kappa_3 K_C \qquad k_3^- = \kappa_3 K_A$$

If the above equations are satisfied, there is a constraint on the kinetic constants:

$$\frac{k_1^+ k_2^+ k_3^+}{k_1^- k_2^- k_3^-} = \frac{\kappa_1 K_A \kappa_2 K_B \kappa_3 K_C}{\kappa_1 K_B \kappa_2 K_C \kappa_3 K_A} = 1$$

Example 3: Biochemical cycle

Can bond graph parameters be found for the kinetic constants below?

$$k_1^+ = 4, \quad k_2^+ = 2, \quad k_3^+ = 1, \quad k_1^- = 2, \quad k_2^- = 2, \quad k_3^- = 2$$

These parameters satisfy the constraint on the previous slide, so we can ignore one of the equations ($k_3^- = \kappa_3 K_A$)

If we arbitrarily set $K_A = 2$, then

$$\kappa_1 = k_1^+ / K_A = 2, \quad K_B = k_1^- / \kappa_1 = 1, \quad \kappa_2 = k_2^+ / K_B = 2$$
$$K_C = k_2^- / \kappa_2 = 1, \quad \kappa_3 = k_3^+ / K_C = 1$$

The solution is non-unique, as different sets of parameters can be found by setting K_A to a different value

Example 3: Biochemical cycle

What if we are given the following parameters?

$$k_1^+ = 2, \quad k_2^+ = 2, \quad k_3^+ = 2, \quad k_1^- = 1, \quad k_2^- = 1, \quad k_3^- = 1$$

Issue: Bond graph parameters cannot be found, as

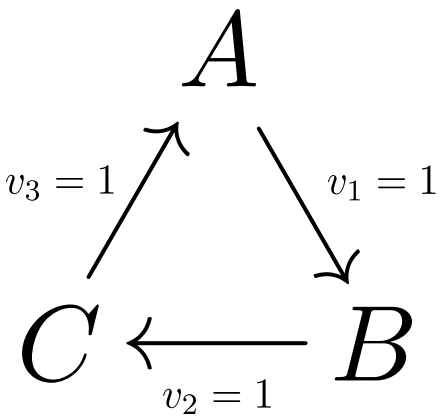
$$\frac{k_1^+ k_2^+ k_3^+}{k_1^- k_2^- k_3^-} = 8 \neq 1$$

Is there an issue with this set of kinetic parameters?

Detailed balance constraints

If we set $x_A = x_B = x_C = 1$, then

$$v_1 = k_1^+ x_A - k_1^- x_B = 1$$
$$v_2 = k_2^+ x_B - k_2^- x_C = 1$$
$$v_3 = k_3^+ x_C - k_3^- x_A = 1$$



The cycle is thermodynamically infeasible

Detailed balance constraints

$$\frac{k_1^+ k_2^+ k_3^+}{k_1^- k_2^- k_3^-} = 1$$

is a detailed balance constraint

- When cycles exist within a biochemical reaction network, thermodynamic constraints exist between kinetic parameters
- Detailed balance is used to constrain kinetic parameters to avoid thermodynamically infeasible cycles
- Because bond graphs are thermodynamically consistent, they only allow kinetic parameters satisfying detailed balance to be converted into bond graph parameters

Summary

- The bond graph components in the biochemical domain give rise to mass action equations
- The bond graph parameters define a unique set of kinetic parameters. However, finding bond graph parameters from a set of kinetic parameters is trickier.
- There is generally a non-unique set of bond graph parameters corresponding to a single set of kinetic parameters
- Bond graph parameters can be found only for thermodynamically consistent sets of kinetic parameters.