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# Bond Graph Clinic: Part 3
## Biomolecular Systems

Peter Cudmore

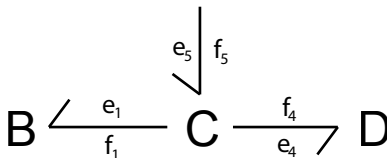Systems Biology Lab, The University of Melbourne

April 19, 2018

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Previously...

# Network models of energetic systems



Bond Graphs capture:

▶ Energy transferred between $B, C, D$ without loss via bonds.

▶ Power transfer represented by conjugate variables $P_i = e_i f_i$.

▶ Subsystem dynamics via constitutive relations $\Phi_B(e, f) = 0$

We've also looked at some examples.

# A Mathematicians Model of a Chemical System

A naive description of molecular systems is as follows:

1. A set of distinct quanta (molecules, complexes, atoms and free electrons) $A, B, \ldots$ move stochastically through a volume.

2. When $A, B$ are sufficiently close they may bind to form complex $C$.

3. After some time $\tau$, $C$ may disassociate into a number of quanta $E, \ldots$.

All basic reaction types (synthesis, decomposition and replacement) can be represented in this way.

Clearly this is an example of a *reaction-diffusion* process.

# This Clinic

Today we shall consider *reactions*.

Next clinic will consider *diffusion*.

# Spatial Assumptions

Consider chemical reactions inside some vessel of fixed volume.
We assume that the chemical solution is well mixed, ie:

- ▶ The solution is actively stirred or,
- ▶ the diffusion rate across the volume is orders of magnitude faster than the fastest reaction rate.

This basically means we can work with average concentration, and ignore spatial effects inside the vessel.

Later, we will couple many vessels together to represent diffusion.

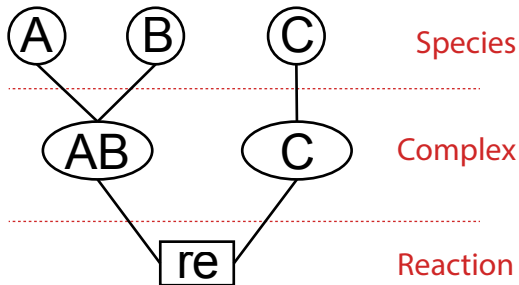Introduction
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Chemical Reaction Networks

# Chemical Reaction Network: Petri Net



Figure: Petri net of $A + B \rightleftharpoons C$

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Chemical Reaction Networks

# Chemical Reaction Network: Bond Graph
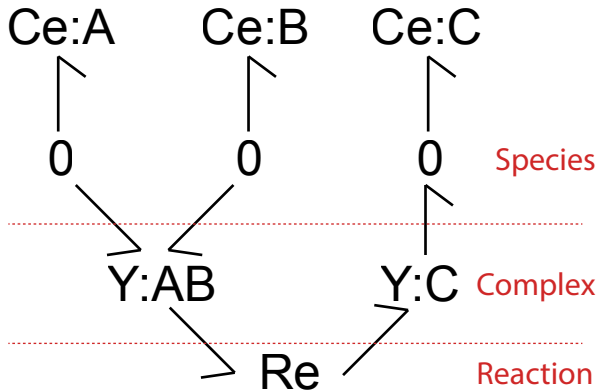


Figure: Bond Graph of $A + B \rightleftharpoons C$

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Chemical Reaction Networks

# Thermodynamic Assumptions

Consider chemical reactions inside some vessel of fixed volume. We assume that the solution is *isobaric* and *isothermic*. These assumptions allow us to define the chemical potential

$$\mu_A = \mu_A^{\oslash} + RT \ln \frac{x_A}{V_m}$$

- ▶ $R = N_A k_b \approx 8.314$ is the gas constant in $J\,K^{-1}\,mol^{-1}$
- ▶ $T \approx 300$ is temperature (in K)
- ▶ $\mu_A^{\oslash}$ is the chemical potential of a pure solution of $A$ in J
- ▶ $x_A$ the amount of species $A$ in mol.
- ▶ $V_m$ is volume of the solution in mol

This follows from the *Ideal Gas Law* and the *Fundamental Equation of Thermodynamics*.

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Chemical Reaction Networks

# Thermodynamic Assumptions

Consider chemical reactions inside some vessel of fixed volume. We assume that the solution is *isobaric* and *isothermic*. These assumptions allow us to define the chemical potential

$$\mu_A = \mu_A^\varnothing + RT \ln \frac{x_A}{V_m}$$

$$\text{Energy} = x_A \cdot \mu_A \mathsf{J}$$

$$\text{Power} = \dot{x}_A \cdot \mu_A \ \mathsf{J\,s}^{-1}$$

$\mu_A$ is *effort* or force-like

$\dot{x}_A$ is the *flow* or flux-like.

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# Thermodynamic Assumptions

Consider chemical reactions inside some vessel of fixed volume.
We assume that the solution is *isobaric* and *isothermic*. These
assumptions allow us to define the chemical potential

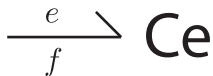$$\mu_A = \mu_A^{\varnothing} + RT \ln \frac{x_A}{V_m}$$

Recall $x_A$ is the molar amount of species $A$.

Question:
What happens to $\mu_A$ when $x_A \to 0$ but $V_m$ is constant?
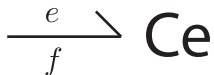When might this occur and is this physical?

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# Ce Constitutive Relation



$$\xrightarrow[f]{e} \quad Ce$$

Constitutive Relation for a Chemical Species:

$$\Phi_{Ce}(e, f) = e - \beta \ln kq = 0$$

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# Ce Constitutive Relation

$$\xrightarrow[f]{e} \quad \text{Ce}$$

Constitutive Relation for a Chemical Species:

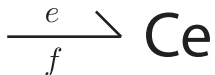$$\Phi_{Ce}(e, f) = e - \beta \ln kq = 0$$

This follow from substituting the parameters

$$k = \exp(\mu_A^\oslash / RT) / V_m, \qquad \beta = RT$$

and the state variables $\mu_A = e$, $\dot{x}_A = f$ and $x_A = q = q_0 + \int_0^t f \, dt$ into

$$\mu_A = \mu_A^\oslash + RT \ln \frac{x_A}{V_m}.$$

# Ce Constitutive Relation

$$\xrightarrow[\;f\;]{\;e\;} \quad \text{Ce}$$

Constitutive Relation for a Chemical Species:

$$\Phi_{Ce}(e, f) = e - \beta \ln kq = 0$$

$$\beta = RT, \qquad k = \exp(\mu_A^{\oslash}/\beta)/V_m$$

*It will often be convenient for us to take $\beta = 1$*

# Chemical Kinetics

Reactions proceed according to the *Marcelin-de Donder* formula

$$v = \kappa \left( \mathrm{e}^{A^f/RT} - \mathrm{e}^{A^r/RT} \right)$$

Here:

- ▶ $v$ is the reaction velocity or molar flow
- ▶ $A^f, A^r$ are the forward and reverse chemical affinities
- ▶ $\kappa$ is the reaction rate constant.
- ▶ $R, T$ is the gas constant and temperature respectively.

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# Chemical Kinetics

Reactions proceed according to the *Marcelin-de Donder* formula

$$v = \kappa \left( e^{A^f/RT} - e^{A^r/RT} \right)$$

The mass flow in is $v$, hence the mass flow out is $-v$.

So

$$f_1 = v, \qquad f_2 = -v$$

are natural *flow* variables.

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# Chemical Kinetics

Reactions proceed according to the *Marcelin-de Donder* formula

$$v = \kappa \left( e^{A^f/RT} - e^{A^r/RT} \right)$$

For a chemical reaction $\nu_A^f A + \nu_B^f B + \ldots \rightleftharpoons \nu_A^f A + \nu_B^f B + \ldots$ with forward and reverse stoichiometric coefficients $\nu^f$ and $\nu^r$.

The forward (and similarly reverse) affinity is defined as

$$A^f = \nu_A^f \mu_A + \nu_B^f \mu_B + \ldots$$

So the natural effort variables are

$$e_1 = A^f, \qquad e_2 = A^r.$$

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# Re Constitutive Relation

$$\xrightarrow{\quad e_1 \quad \diagdown} \underset{\kappa}{\mathsf{Re}} \underset{\diagdown \quad f_2}{\xleftarrow{\quad e_2 \quad}}$$

Constitutive Relation for a reaction component:

$$\Phi_{Re}(\mathbf{e}, \mathbf{f}) = \begin{pmatrix} \kappa[\exp(e_1/\beta) - \exp(e_2/\beta)] - f_1 \\ f_1 + f_2 \end{pmatrix} = 0$$

Where again $\beta = RT$ is often taken as $\beta = 1$.

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# Re Constitutive Relation

$$\xrightarrow{\quad e_1 \quad}_{\displaystyle f_1} \searrow \underset{\kappa}{\text{Re}} \underset{\displaystyle f_2}{\overset{\displaystyle e_2}{\longleftarrow}} \searrow$$

Constitutive Relation for a reaction component:

$$\Phi_{Re}(\mathbf{e}, \mathbf{f}) = \begin{pmatrix} \kappa[\exp(e_1/\beta) - \exp(e_2/\beta)] - f_1 \\ f_1 + f_2 \end{pmatrix} = 0$$

This follows directly from the Marcelin-de Donder formula.

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# Putting it together

$$\text{Ce:A} \xrightarrow[f_1]{e_1} \text{Re} \xrightarrow[f_2]{e_2} \text{Ce:B}$$

The above bond graph describes the reaction $A \rightleftharpoons B$.

$$\Phi_{Ce:A} = e_1 - \ln k_A \left[ q_A(0) + \int (-f_1) \, dt \right] \quad (1)$$

$$\Phi_{Ce:B} = e_2 - \ln k_B \left[ q_B(0) + \int f_2 \, dt \right] \quad (2)$$

$$\Phi_{Re}(\mathbf{e}, \mathbf{f}) = \begin{pmatrix} \kappa \left[ e^{e_1} - e^{e_2} \right] - f_1 \\ f_1 + (-f_2) \end{pmatrix} \quad (3)$$

Recall that $q(t) = q_0 + \int_0^t f(t) \, dt$. So define

$$\dot{x}_A = \dot{q}_1 = -f_1 \qquad \Longrightarrow \qquad q_1 = q_A(0) - \int_0^t f_1 \, dt \qquad \Longrightarrow \qquad e^{e_1} = k_A q_1,$$

$$\dot{x}_B = \dot{q}_2 = f_2 \qquad \Longrightarrow \qquad q_2 = q_B(0) + \int_0^t f_2 \, dt \qquad \Longrightarrow \qquad e^{e_2} = k_B q_2.$$

The second line of (3) gives $f_1 = f_2$ which implies $-\dot{q}_1 = \dot{q}_2$, and the first gives the result

$$\dot{q}_1 = -\kappa \left( k_A q_1 - k_B q_2 \right) = k_- q_2 - k_+ q_1 \quad \text{where} \quad k_+ = \kappa k_A, \ k_- = \kappa k_B.$$

## Complexes

The reaction $A + B \rightleftharpoons C$ can be though of

1. $A$ and $B$ collide forming a complex $AB$.
2. $AB$ reacts to form $C$.

Clearly, the flow of $A$ and the flow of $B$ into this reaction are equal.

Hence, we *should* be able to represent the $AB$ complex as a equal flow junction, and allow the reaction to drive what that flow is.

**Just using the usual common flow 1 junction wont work!**

*Question: Why?*

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# Naive example: $A + B \rightleftharpoons B$
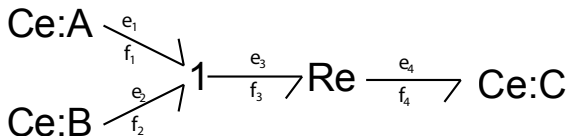


$$\Phi_{Ce:A} = e_1 - \ln k_A(q_1), \quad (4)$$
$$\Phi_{Ce:B} = e_2 - \ln k_B(q_2), \quad (5)$$
$$\Phi_{Ce:B} = e_2 - \ln k_C(q_3) \quad (6)$$

$$\Phi_{Re} = \begin{pmatrix} \kappa \left[ e^{e_3} - e^{e_4} \right] - f_3 \\ f_3 + (-f_4) \end{pmatrix}, \quad (7)$$

$$\Phi_1(\mathbf{e}, \mathbf{f}) = \begin{pmatrix} e_1 + e_2 + e_3 \\ f_1 - (-f_3) \\ f_2 - (-f_3) \end{pmatrix}, \quad (8)$$

From the first equation of (8) we have

$$e_3 = -(e_1 + e_2) \implies f_3 = \kappa \left( e^{-e_1 - e_2} - e^{e_4} \right) = \kappa \left( \frac{1}{k_A k_B q_1 q_2} + k_C q_3 \right)$$

Which is clearly wrong as we should not be able to get inverse powers!

# What when wrong

We're actually coupling two slightly different thermodynamic domains;

▶ *chemical potential energy* (that is, the stored in a heterogeneous solution)

▶ *chemical reaction affinity* (the energy stored in a complex).

These overlap only when the species IS the complex; hence why it works for the reaction $A \rightleftharpoons B$.

What we need is a mapping between species space and complex space.

## Stoichiometry
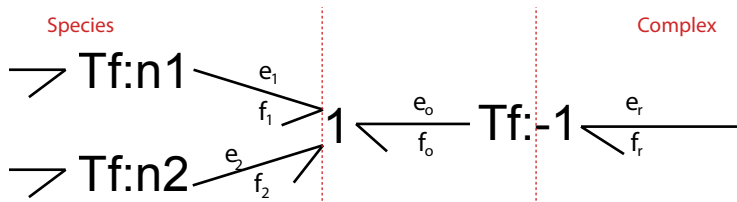


Oster *et. al.* [1] represented reaction stoichiometry using the above bond graph.

Here $n1$ and $n2$ are the number of molecules of species 1 and 2 consumed by the reaction.

Recall that $\Phi_{TF:\rho}(e_j, f_j, e_k, f_k) = 0 \implies e_k = \rho e_j, \qquad f_k = \rho^{-1} f_j$ and hence

$$e_r = -e_o, \qquad e_1 = n_1 \mu_1, \qquad e_2 = n_2 \mu_2.$$

Since $e_1 + e_2 + e_o = 0$ it follows that the reaction affinity is

# Gawthrop's Reduction
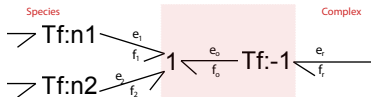


Gawthrop [2] replace the shaded box with the
*biochemical 1 junction* defined by
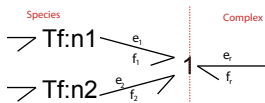


$$\Phi_1 = \begin{pmatrix} e_o - (e_1 + e_2) \\ f_o - f_1 \\ f_o - f_2 \end{pmatrix} = 0 \implies f_r = -f_1 = -f_2, \quad e_r = e_1 + e_2$$

# An alternative
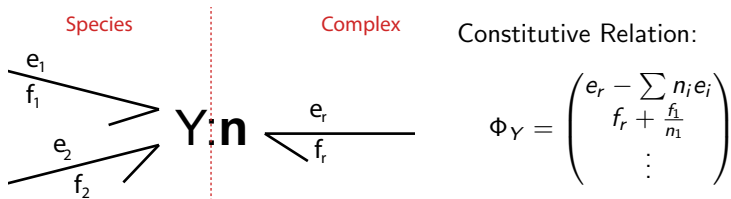
An alternative would be to replace
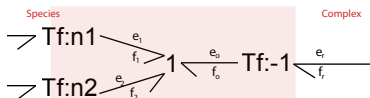


with
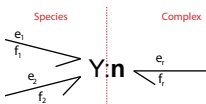


Where **n** is the forward or reverse (truncated) stoichiometric vector which in this case $\mathbf{n} = (n_1, n_2)$.

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Through Junction

# Through Junction



Constitutive Relation:

$$\Phi_Y = \begin{pmatrix} e_r - \sum n_i e_i \\ f_r + \frac{f_1}{n_1} \\ \vdots \end{pmatrix}$$

Y is power conserving. Multiplying the top line by $f_r$ gives

$$0 = e_r f_r - f_r \sum e_i n_i = e_r f_r - \sum e_i (n_i f_r)$$

Since $n_i f_r = -f_i$, the result follows from

$$0 = e_r f_r - \sum e_i (n_i f_r) = e_r f_r + \sum e_i f_i.$$

This is no surprise as Y is built from conserving components.

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Through Junction

# Through Junction



Species      Complex      Constitutive Relation:

$$\Phi_Y = \begin{pmatrix} e_r - \sum n_i e_i \\ f_r + \frac{f_1}{n_1} \\ \vdots \end{pmatrix}$$
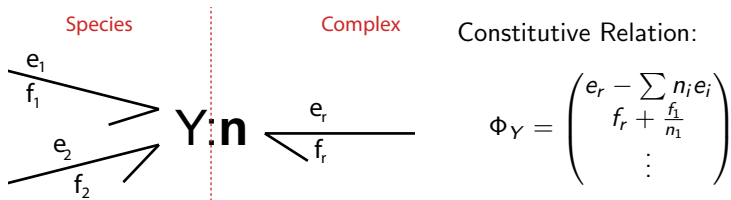
The through junction Y

- ▶ is power conserving,
- ▶ is unambiguous,
- ▶ is symbolically consistent,
- ▶ maps cleanly on existing C.R.N. theory.

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Through Junction

# $A + B \rightleftharpoons C$: redux.
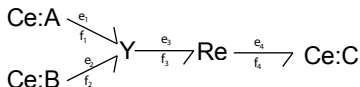


Figure: Bond Graph of $A + B \rightleftharpoons C$

$$\Phi_{Ce:A} = e_1 - \ln k_A(q_1), \qquad (9)$$
$$\Phi_{Ce:B} = e_2 - \ln k_B(q_2), \qquad (10)$$
$$\Phi_{Ce:B} = e_2 - \ln k_C(q_3) \qquad (11)$$

$$\Phi_{Re} = \begin{pmatrix} \kappa \left[ e^{e_3} - e^{e_4} \right] - f_3 \\ f_3 + (-f_4) \end{pmatrix}, \qquad (12)$$

$$\Phi_Y = \begin{pmatrix} e_3 - e_1 - e_2 \\ (-f_3) + f_1 \\ (-f_3) + f_2 \end{pmatrix} \qquad (13)$$

Clearly

$$e_3 = e_1 + e_2 \implies \exp(e_3) = \exp(\ln k_A q_1 + \ln k_B q_2) = k_A k_B q_1 q_2.$$

Since $f_4 = \dot{q}_4$, it follows from (12) that

$$\dot{q}_4 = \kappa k_A k_B q_1 q_2 - \kappa k_C q_4 = k_+ q_1 q_2 - k_- q_4.$$

From (12) and (13) we have $\dot{q}_4 = f_4 = f_3 = f_2 = f_1$.

Combining this with $f_1 = -\dot{q}_1$ and $f_2 = -\dot{q}_2$ completes the picture.

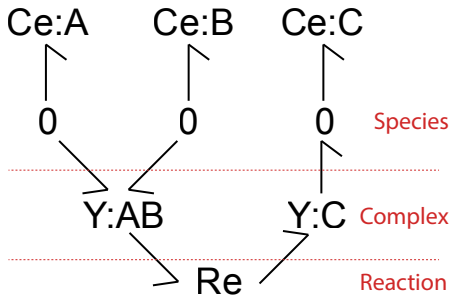# $A + B \rightleftharpoons C$: final form!



Figure: Bond Graph of $A + B \rightleftharpoons C$

In the above figure we have added standard 0 junctions. While this is
redundant in this above reaction, it allows us to use the same species for
many reactions. Also, note that Y:C is the identity (*prove it!*) and may
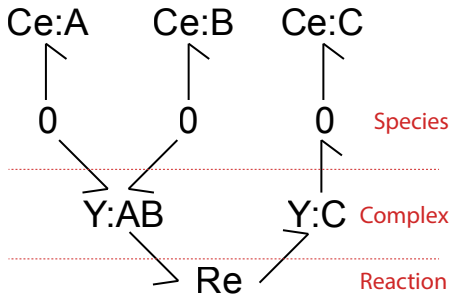be omitted.

# In Review



Figure: Bond Graph of $A + B \rightleftharpoons C$

The Ce is a one port component representing a store of a particular chemical species and has a constitutive relation that captures the usual definition of *chemical potential energy*.
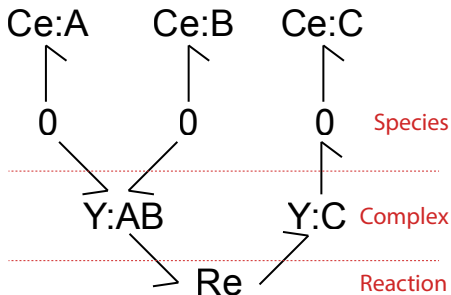
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Figure: Bond Graph of $A + B \rightleftharpoons C$

The zero junctions allow species A B and C to be share across reactions other than the one modelled in this graph.
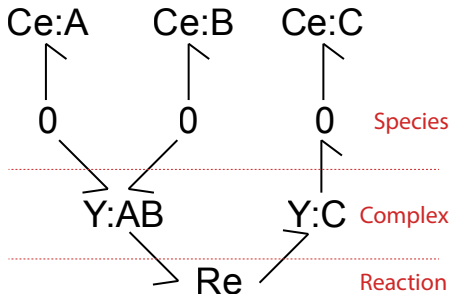
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Figure: Bond Graph of $A + B \rightleftharpoons C$

The Y component is a power conserving through junction, which captures the forward (in the case of Y:AB) and reverse stoichiometry of this reaction.

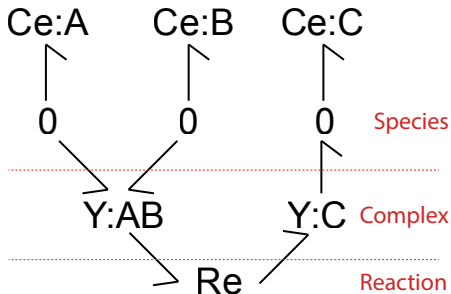| Introduction | Chemical Reactions | Stoichiometry | Conclusion | References |
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# In Review



Figure: Bond Graph of $A + B \rightleftharpoons C$

The Re component models how the complex $A + B$ transmutes into $C$.
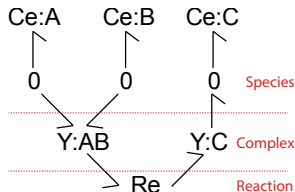The reaction proceeds according to the *Marcelin-de Donder* formula.

# Try for yourself

Try drawing bond graphs of these common reactions:

- $A + B \rightleftharpoons D + C$
- $A + B \rightleftharpoons B + C$
- $E + S \rightleftharpoons ES \rightleftharpoons E + P$

$$\Phi_{Ce}(e, f) = e - \ln k(q),$$

$$\Phi_{Re}(e_f, f_f, e_r, f_r) = \begin{pmatrix} \kappa \left[ e^{e_f} - e^{e_r} \right] - f_f \\ f_f + f_r \end{pmatrix}$$

$$\Phi_Y(e_0, f_0, e_1, f_1, \ldots) = \begin{pmatrix} e_0 - \sum n_i e_i \\ f_0 + f_i / n_i \\ \vdots \end{pmatrix}$$

# References

Oster, G. F.; Perelson, A. S.; Katchalsky, A. *Quarterly Reviews of Biophysics* **1973**, *6*, 1–134.

Gawthrop, P. J.; Crampin, E. J. *Proceedings. Mathematical, Physical, and Engineering Sciences / The Royal Society* **2014**, *470*, 20140459.