BondGraphTools: Modelling Network Bioenergetics

https://github.com/peter-cudmore/

Peter Cudmore

Modelling Biochemical Systems

Network Energetics

BondGraphTools

Conclusion

An Example Biochemical Systems.

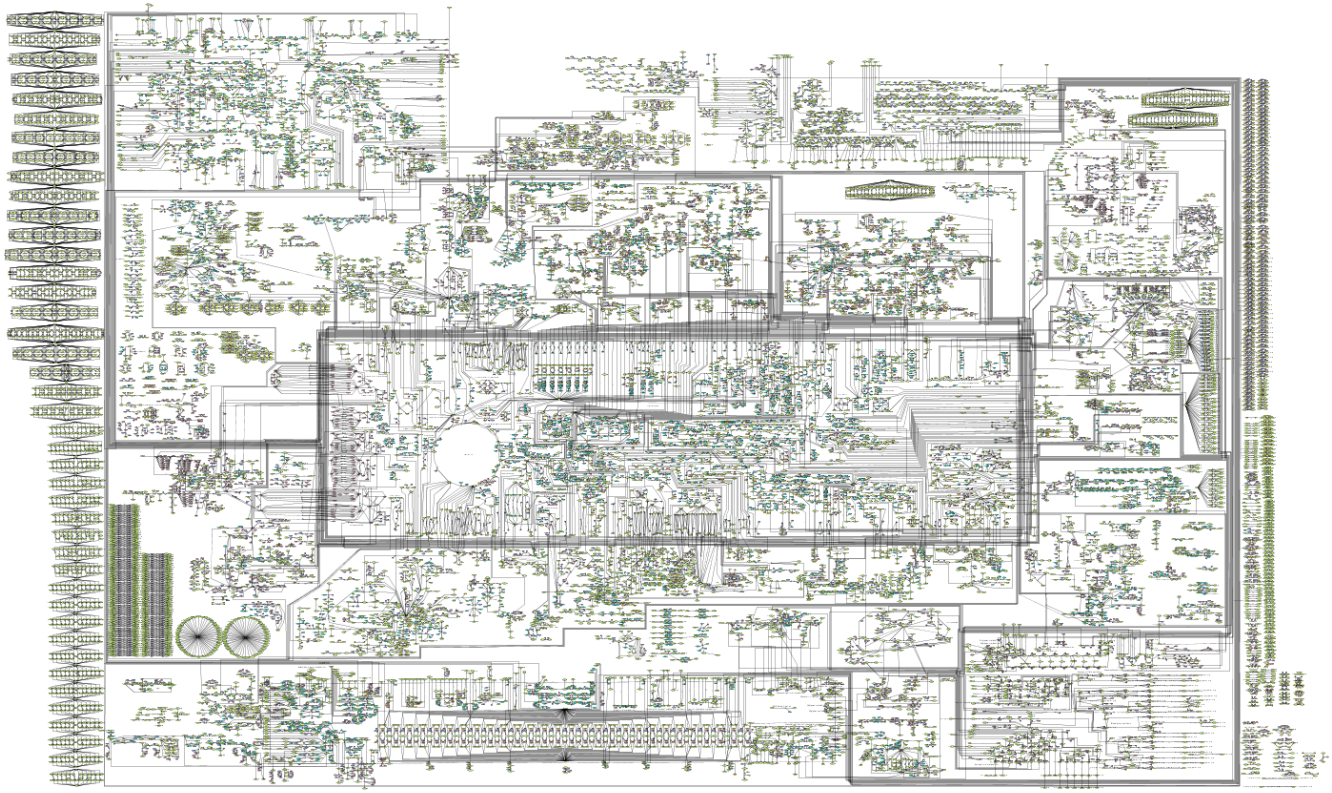

Figure: Map of the Human Metabolome [1]

[1] Wishart et al., "HMDB: the Human Metabolome Database", (2007).

Biochemical systems are complex.

We want to:

- Predict how particular *nonequilibrium* states depend upon system parameters and network topology.
- Track how these states vary with parameter changes.
- Design and implement synthetic control devices.

We require models that can be used to engineer biological systems!

Problems At Scale.

Issues that can occur when attempting to ‘scale-up’ existing approaches:

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Issues that can occur when attempting to 'scale-up' existing approaches:

- *Models may not generalise*.

Models may not capture the environment, and hence fail to predict how a process behaves in different circumstance. For example; *in vitro* vs *in vivo*.

Problems At Scale.

Issues that can occur when attempting to 'scale-up' existing approaches:

- *Models may not generalise*.
- *Models may not integrate*.

Models may fail to correctly describe shared physical quantities, such as two different processes known to sharing the same enzyme, and hence incorrectly infer modularity.

Problems At Scale.

Issues that can occur when attempting to 'scale-up' existing approaches:

- *Models may not generalise*.
- *Models may not integrate*.
- *Models may not be parametrisable*.

Even if there did exist a sufficient amount of observational data, certain parameters may not be inferable, let alone observable.

Problem: Non-physical models

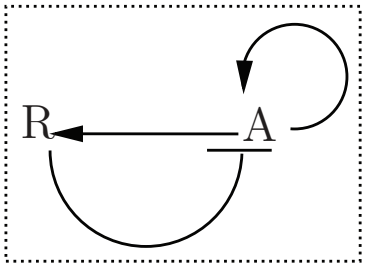
The Michaelis-Menten 'law' for enzyme dynamics:

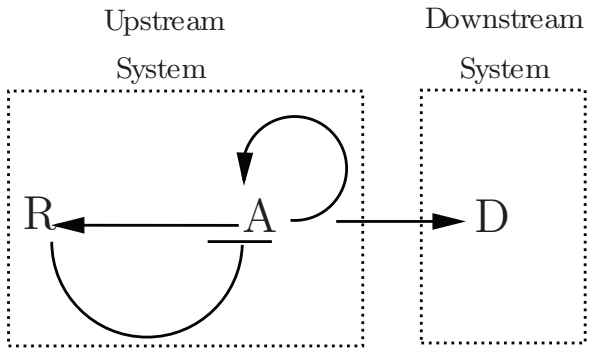
$$\mathrm{E} + \mathrm{S} \rightleftharpoons \mathrm{ES} \longrightarrow \mathrm{E} + \mathrm{P} \qquad \frac{\mathrm{d}[P]}{\mathrm{d}t} = -\frac{\mathrm{d}[S]}{\mathrm{d}t} = \frac{V_{\mathrm{max}}[S]}{[S] + K_m}$$

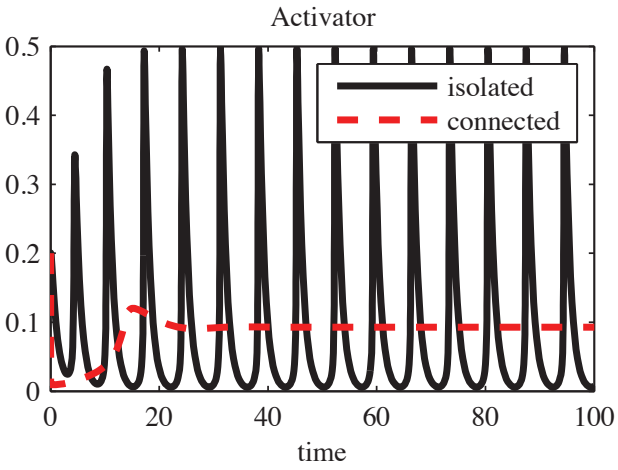
> *...in model building [the Michaelis-Menten approximation] is often invoked without regard to the underlying assumptions.* [2]

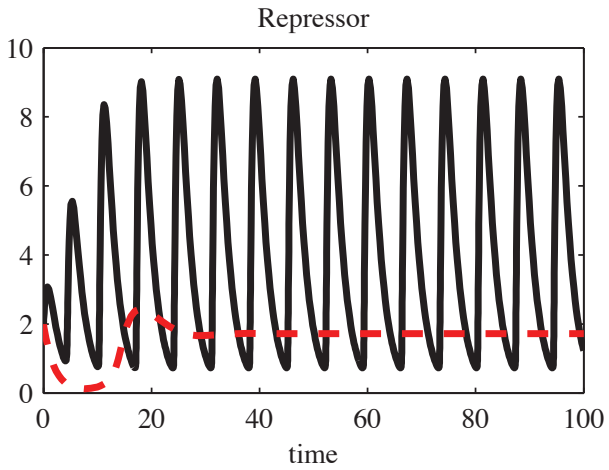
[2] Keener and Sneyd, *Mathematical Physiology*, (2009).

Problem: Retroactivity [3]









[3] Del Vecchio, "A control theoretic framework for modular analysis and design of biomolecular networks", (2013).

Problem: 'Sloppy' Parameters

> *'Sloppy' is the term used to describe a class of complex models exhibiting large parameter uncertainty when fit to data.* [4]

For example, fitting decaying observations $y(t)$ to

$$y(t;\theta) = \sum_{\mu} \exp(-\theta_\mu t)$$

Each parameter θ_μ is almost completely undetermined.
Data **constrains** *parameters!*

[4] Transtrum et al., "Perspective: Sloppiness and emergent theories in physics, biology, and beyond", (2015).

Problems At Scale.

Question: How do we address the fact that

- *models may not generalise*,
- *models may not integrate*,
- *models may not be parametrisable*.

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Answer (or at least, one approach): *Network Energetics*.

The Fundamental Law: Conservation of Energy

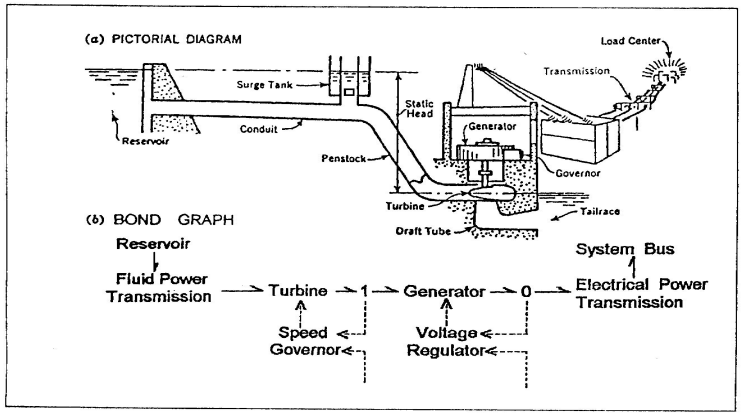
> *There is a fact, or if you wish, a law, governing all natural phenomena that are known to date. There is no known exception to this law—it is exact so far as we know. The law is called the conservation of energy.*

- Richard Feynman, 1963 [5] .

[5] Feynman, Leighton, and Sands, *The Feynman Lectures on Physics*, (1963).

Bond Graphs

Bond Graphs [6] are a graphical representation of how energy networks distribute power through a physical system.



Hydroelectric plant.

- Energy is currency
- Discrete subsystems
- Power flows via ports

Network thermodynamics [7] and *port Hamiltonians* [8] followed.

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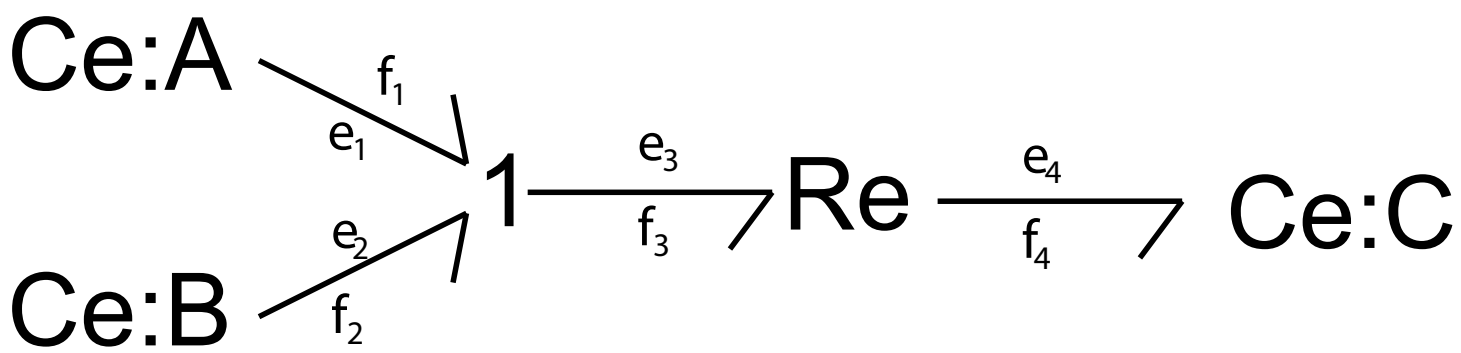
[6] Paynter, *The Gestation and Birth of Bond Graphs*, (2000).

[7] Oster, Perelson, and Katchalsy, "Network Thermodynamics", (1971).

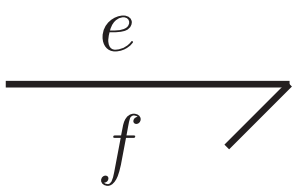
[8] van der Schaft and Jeltsema, *Port-Hamiltonian Systems Theory: An Introductory Overview*, (2014).

Bond Graph of $A + B \rightleftharpoons C$



- 'Ce' nodes *store energy* (via concentration)
- The 'Re' node *dissipate energy*
- The '1' node is a conservation law. (Conservation of flow)
- e is 'pressure'-like (similarly force or voltage).
- f is 'flow'-like (similarly velocity, or current).
- $P_i = e_i \times f_i$ is the instantaneous power $P_i = \frac{\mathrm{d}}{\mathrm{d}t}\text{energy}_i$

Chemical Subsystems Store Energy



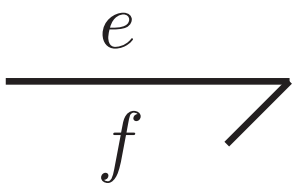
$$e = \mu^{\oslash}(R, T) + RT \ln\left(\frac{n}{c^{\oslash} V}\right),$$

$$f = \dot{n}.$$

This is just a network reformulation of the Gibbs free energy $\mathrm{d}G = V\,\mathrm{d}p - S\,\mathrm{d}T + \mu\,\mathrm{d}n$ for

- constant pressure $p = R$
- constant temperature T
- constant volume V
- Reference concentration $c^{\oslash}$ and chemical potential $\mu^{\oslash}$

Chemical Subsystems Store Energy



$$e = \mu^{\oslash}(R, T) + RT \ln\left(\frac{n}{c^{\oslash} V}\right),$$
$$f = \dot{n}.$$

$\mu^{\oslash}$ has controlled dependence on the environment.

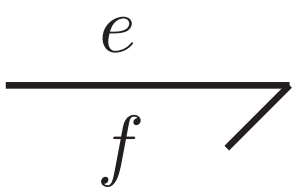
Chemical Subsystems Store Energy

$$e = \mu^{\oslash}(R, T) + RT \ln\left(\frac{n}{c^{\oslash} V}\right),$$

$$f = \dot{n}.$$

$\mu^{\oslash}$ can be estimated and (occasionally) measured.

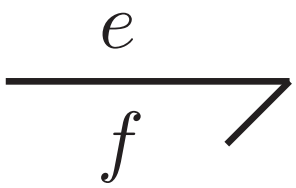
Chemical Subsystems Store Energy



$$e = \mu^{\oslash}(R, T) + RT \ln\left(\frac{n}{c^{\oslash} V}\right),$$
$$f = \dot{n}.$$

$\mu^{\oslash}$ is taken as a derived physical quantity of that molecule.

Chemical Subsystems Store Energy



$$e = \mu^{\oslash}(R, T) + RT \ln\left(\frac{n}{c^{\oslash} V}\right),$$

$$f = \dot{n}.$$

$\mu^{\oslash}$ is supposed to generalise across experimental conditions.

Chemical Reactions Dissipate Energy

$$f_1 = \kappa \left[e^{e_1/RT} - e^{e_2/RT} \right],$$
$$0 = f_1 + f_2.$$

This is a network reformulation of the Marcelin de-Donder formula, which relates reaction affinities e_1, e_2 to the flow $f_1 = -f_2$.

Chemical Reactions Dissipate Energy

$$f_1 = \kappa \left[e^{e_1/RT} - e^{e_2/RT} \right],$$
$$0 = f_1 + f_2.$$

κ is a constant relating time and extent of reaction

Chemical Reactions Dissipate Energy

$$f_1 = \kappa \left[e^{e_1/RT} - e^{e_2/RT} \right],$$
$$0 = f_1 + f_2.$$

κ is not generally measurable!

Chemical Reactions Dissipate Energy

$$f_1 = \kappa \left[e^{e_1/RT} - e^{e_2/RT} \right],$$
$$0 = f_1 + f_2.$$

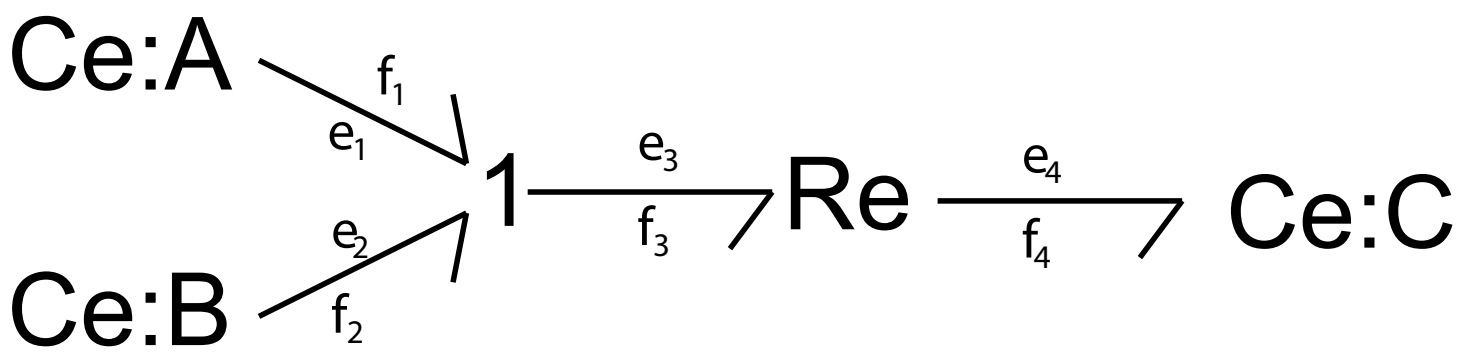
κ is constant for simple reactions

Chemical Reactions Dissipate Energy

$$f_1 = \kappa \left[e^{e_1/RT} - e^{e_2/RT} \right],$$
$$0 = f_1 + f_2.$$

κ can be a function for more complex models.
For example; $\kappa = (\alpha + \beta \exp(e_1))^{-1}$ can produce a Hill equation.

Bond Graph of $A + B \rightleftharpoons C$



If we define $k_i = \frac{1}{Vc_i^{\oslash}} \exp(\mu_i^{\oslash}/RT)$; evaluating the model

$$f_i = \dot{C} = -\dot{A} = -\dot{B} = \kappa\left(k_A k_B AB - k_C C\right) = k_+ AB - k_C C$$

with

$$k_+ = \kappa k_A k_b, \quad k_- = \kappa k_C, \qquad k_{\mathrm{Eq}} = k_A k_B / k_C.$$

How does Network Energetics help?

- Based on well established physics.
- Processes and parameters are tied to physical properties.
- Power connections by definition capture 'loading effects'.
- Parameters can be fitted across many experiments.

This gives us a framework to predict, engineer and refine *reusable* models of processes.

Trade offs

Bond Graphs/Network Energetics:

- is more complicated than doing it by hand
  but it can be done algorithmically.

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- is more 'abstract' than some other modelling techniques
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Bond Graphs/Network Energetics:

- is more complicated than doing it by hand
  but it can be done algorithmically.
- is more 'abstract' than some other modelling techniques
  but it can handle multi-physics.
- fitting a particular experiment even more difficult
  but parameters can be tabulated.

BondGraphTools

BondGraphTools

- is a Python library for network energetics model building,
- has addons specifically for biological processes,
- is designed to be used alongside and in conjunction with scipy,
- is symbolic yet has simulation tools

For more information on BondGraphTools visit
`bondgraphtools.readthedocs.io`

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- Domitilla Del Vecchio. "A control theoretic framework for modular analysis and design of biomolecular networks". In: *Annual Reviews in Control* 37.2 (2013), pp. 333–345.
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Arjan van der Schaft and Dimitri Jeltsema. *Port-Hamiltonian Systems Theory: An Introductory Overview*. Vol. 1. 2. 2014, pp. 173–378.


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