Taming the BISEN?

(towards accurate metabolic models in CellML)

Mike Cooling

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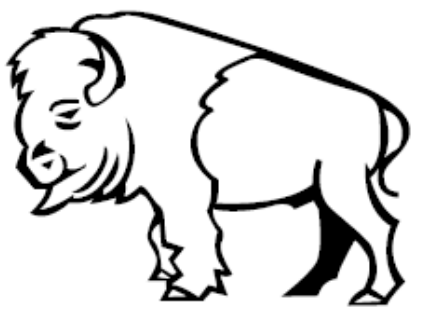
Metabolism

- Metabolism
  - Reactions that keep the cell healthy
  - Ubiquitous
  - Subject of study for some time: many known reactions
  - Sensitive to
    - pH
    - Temperature
    - Concentration of K^+, H^+ and Mg^{2+}
    - 'ionic strength' – [] dissolved in water
  - Accurate modelling should account for these…

Approach (Dan Beard et al.)

- "At the center of our biochemical systems modeling approach is an explicit accounting of the fact that biochemical reactants (e.g., ATP) exist in solution as a number of rapidly interconverting species (e.g., ATP_4, $HATP_3$, $MgATP_2$, and $KATP_3$)"
- Thermodynamic free energy calculations allow computation of " [reaction] apparent equilibrium constants at specified pH and metal ion concentrations."
- Useful as can
  - Scale kinetics by pH, temperature
  - Account for interconverting species
  - Constrain kinetics to thermodynamic data (which may be more precise)

BISEN: **Bi**ochemical **S**imulation **En**vironment



- Set of metabolic reactions
- For reactions, databases of
  - Thermodynamic data, for example:
    - Gibbs free energy of formation of reference species of reactants
    - Enthalpy of reference species
  - Kinetic data, for example:
    - First potassium ion dissociation constant
    - First magnesium ion dissociation constant
  - Other, for example:
    - Charge of references species
    - Number of protons in reference species

BISEN

- Modules
  - Mini models of a particular reaction e.g.

```
model E.ATPASE.0
    equations
        k1_ATPASE = unspecified;
        J = k1_ATPASE*(ATP - ADP*Pi/Keq);
```

  - Can have parameters (e.g. k1_ATPASE)
  - Can have multiple models for the same reaction, chosen by identifier

BISEN

- BSL (biochemical scripting language)

```
compartment cytoplasm 0.8425 0.4970
     ATPASE E.ATPASE.0
     CK E.CK.0

compartment matrix 0.6514 0.2106

transport cytoplasm matrix
     ANT T.ANT.1
EOF
```

$ATP + H_2O = ADP + Pi + H$

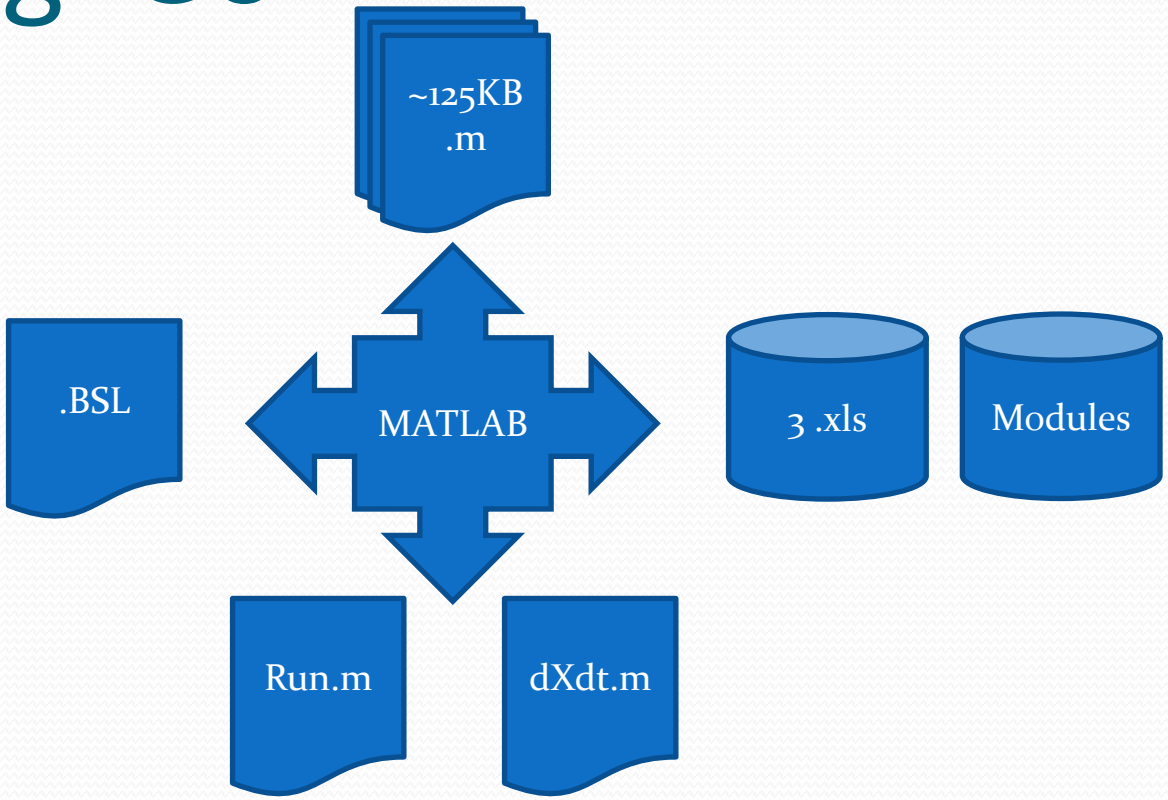
phosphocreatine + ADP + H = creatine + ATP

ATP(2) + ADP(1) = ATP(1) + ADP(2)

"Adenine nucleotide translocator (ANT), also known as the ADP/ATP translocator, exports ATP from the mitochondrial matrix and imports ADP into the matrix"

http://en.wikipedia.org/wiki/Adenine_nucleotide_translocator, 8th April 2014.

Pushing ‘Go’



- Run.m – set initial conditions (all species in all compartments, + ‘m’, ‘h’ & ‘k’), proton buffering, temperature, model parameters
- Builds ‘ODE’ file based on rules and data above
  - `[t,x] = ode23s(@dXdT,…);`

Some Results

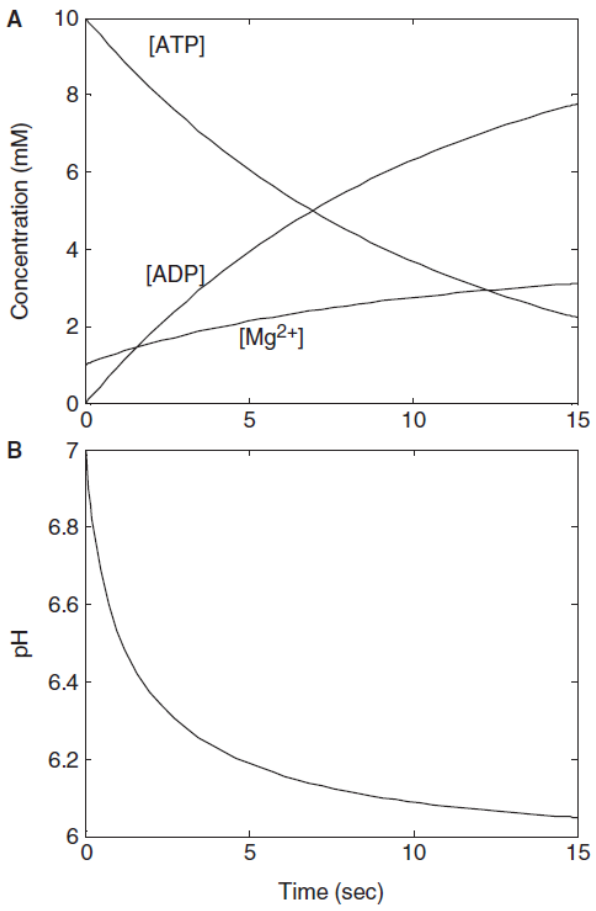


Fig. 1. Plots of [ATP], [ADP] and [Mg^{2+}] (**A**) and pH (**B**) versus time for the model of ATP hydrolysis of Example 1.

```
compartment A 1.0 1.0
  ATPASE E.ATPASE.0
EOF
```

- Can change temperature, pH etc.

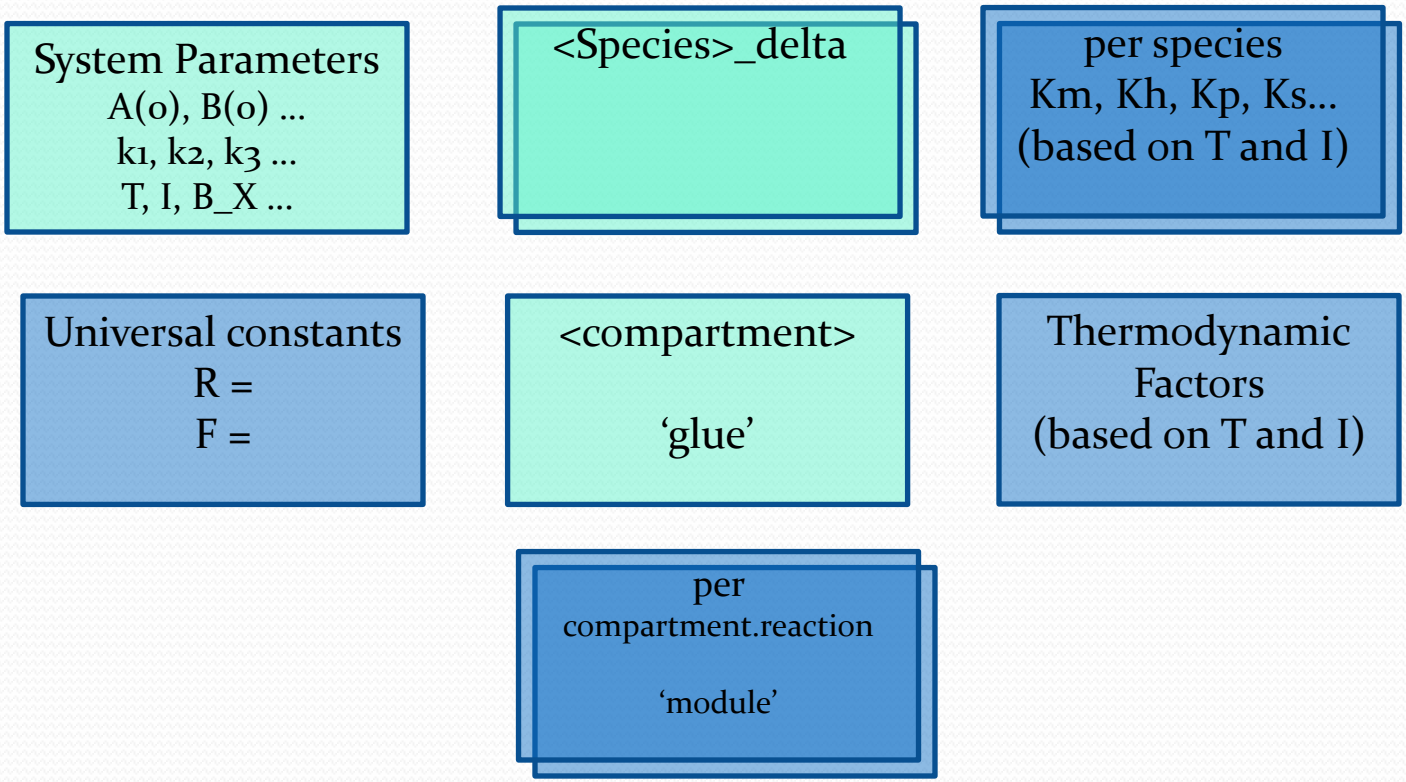
Vanlier et al. (2009) Bioinf. 25(6)

Interesting because

- Library of metabolic modules
- Sensitive to pH, temperature, ionic strength
- ODEs depend on what else is being modelled

- Can we replicate the functionality of BISEN in CellML?
  - (of course!)
  - Not just declarative CellML, but processing
    - Computer-assisted model composition

CellML version



Example Model

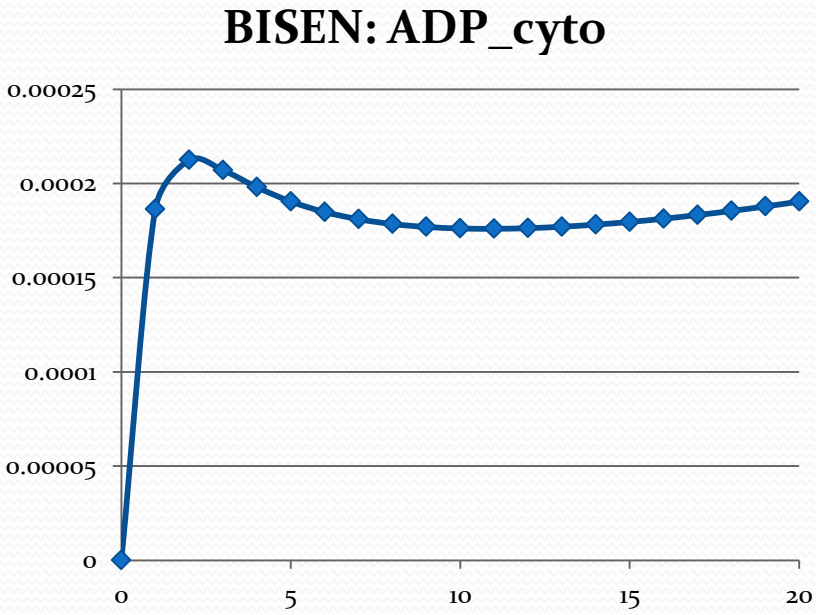
```
compartment cytoplasm 0.8425 0.4970
     ATPASE E.ATPASE.0
     CK E.CK.0

compartment matrix 0.6514 0.2106

transport cytoplasm matrix
     ANT T.ANT.1
EOF
```

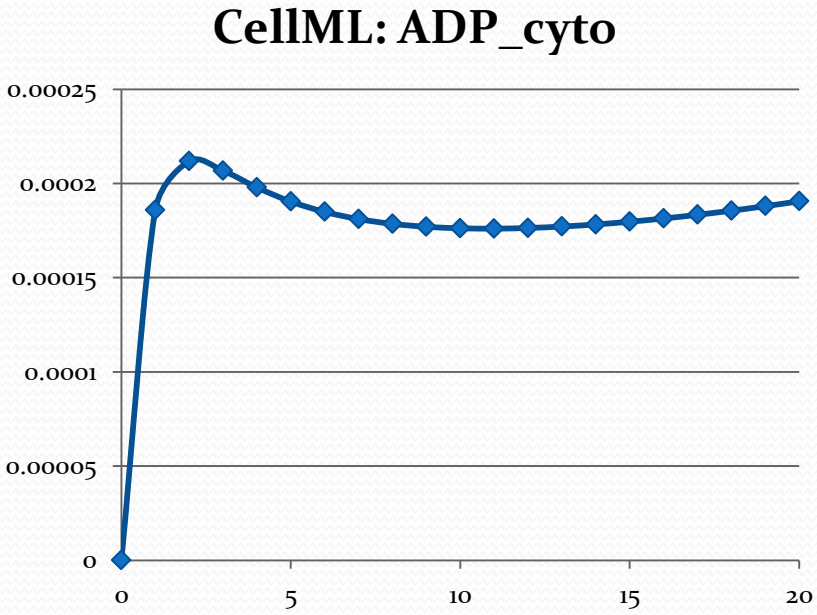
$ATP + H_2O = ADP + Pi + H$

phosphocreatine + ADP + H = creatine + ATP

ATP(2) + ADP(1) = ATP(1) + ADP(2)

Results Comparison - 1



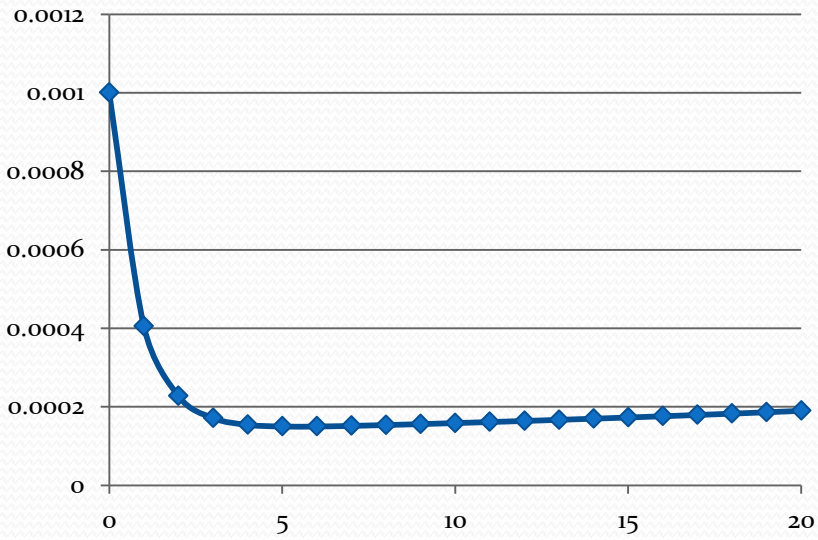


- 0.27% difference (from BISEN), to ~0.07 % difference

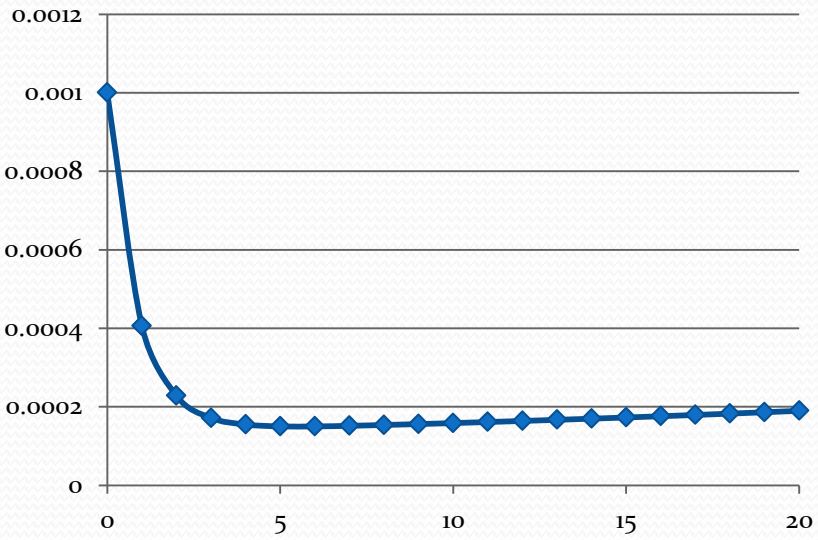
Results Comparison - 2

- Same system, changing Temp (+125 K), pH, & other i.c.s

BISEN: ADP_cyto



CellML: ADP_cyto



- 0.54% difference (from BISEN), to ~0.03 % difference

Next Steps

- Encode ‘dynamics’ and composition logic via
  - Semantic annotation +
  - Processes on top of the CellML API
- Some kind of interface
  - OpenCOR?
- Ensure easy expansion to more general rule-based systems
  - Systems with a great many cycles between closely related states e.g.
    - Proteins with multiple phosphorylation sites