Computer modeling of cellular processes

Glycolysis: a few reactions

By

Raquell M. Holmes, Ph.D.

Boston University

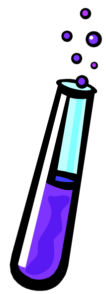
Dynamics:
Answering different questions

- If glucose concentration is 300 mM outside of the cell,
  - How quickly is glucose converted to glucose 6-phosphate?
  - How does the concentration of glucose 6 phosphate change over time?

Yeast Glycolysis

suspended

Liquid, flasks, temp, ph

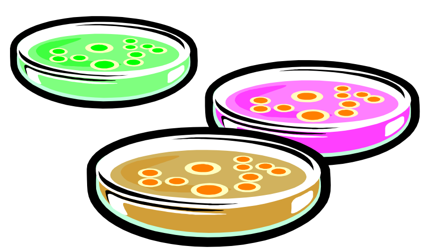


Experiment:
Sample media or characterize
cell content over time

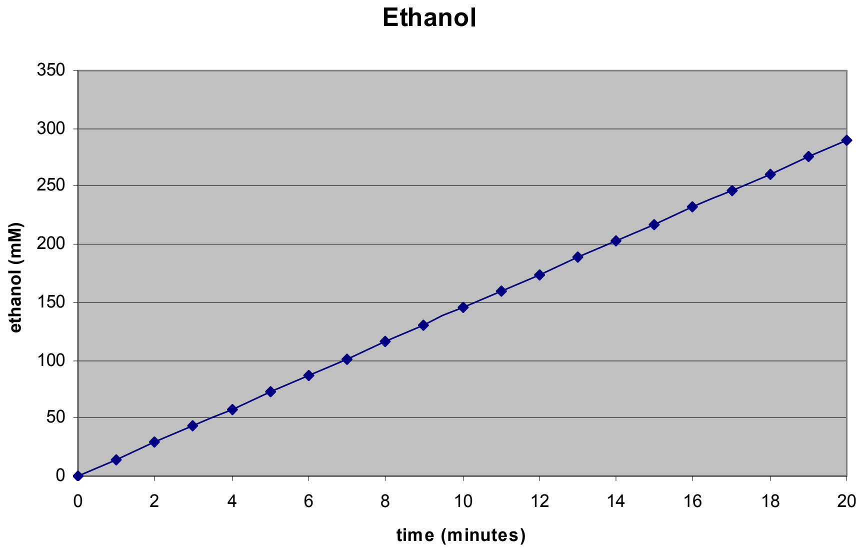
Repeat under different conditions

immobile

Agar, temp, ph



Results may look like



Computer Modeling

- Method for analyzing what we know about a biological process

- Used to describe mechanisms behind changes

- Determines what can be seen or predicted

Walking through a Computational Model

- Concept Map
- Factors and relationships between factors
- Describe relationships mathematically

- Solve equations: using computer tools
- View and interpret results

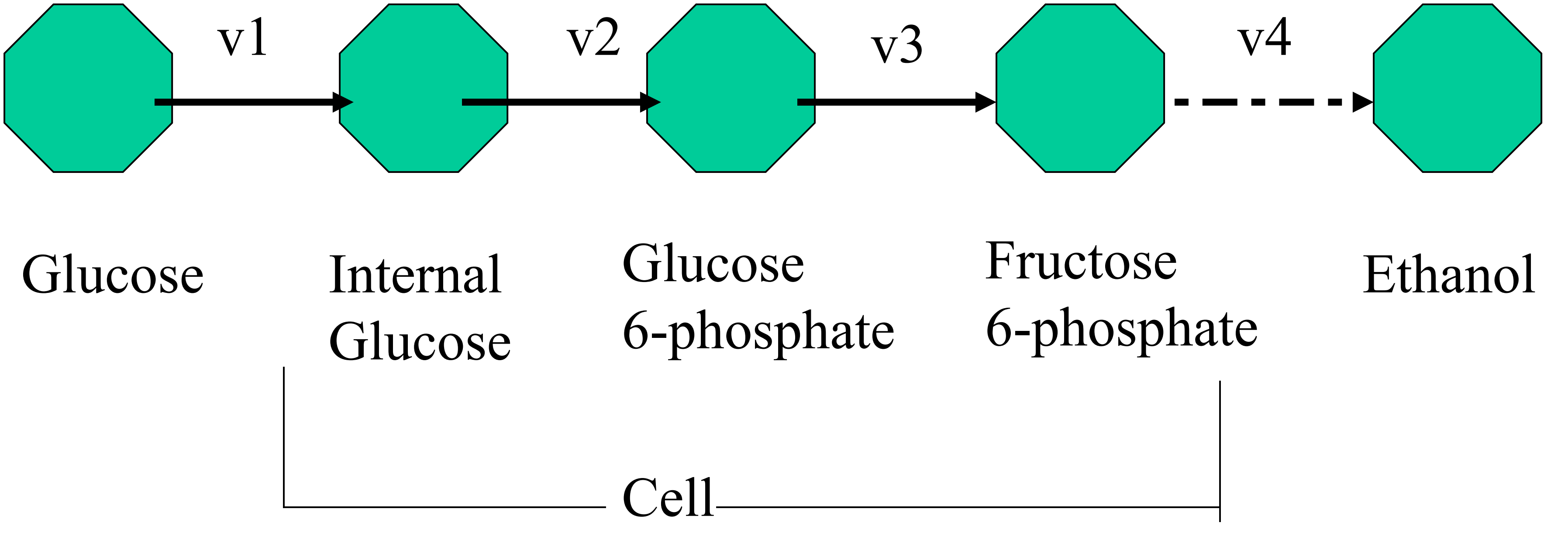
Designing a dynamic experiment

- What components are involved?
  - Glucose, glucose 6 phosphate, fructose 6 phosphate…

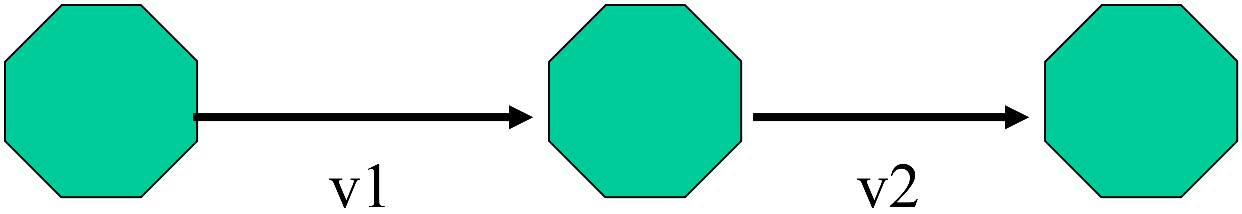
- What chemical reactions involved?
  - Transport, chemical conversions…

Glycolysis: Concept Map

Often drawings, schematics or chemical reactions



Examples of relationships



Internal Glucose

Glucose 6-phosphate

Fructose 6-phosphate

[Glucose 6-phosphate] is determined by increase from Glucose conversion and decrease by conversion to Fructose 6-phosphate

Amount of glucose 6 phosphate= amount produced- amount converted

Designing a dynamic experiment

- Describing relationship mathematically

Relationship in terms of rates of change

The rate of change of Glucose-6-phosphate (S_2) is the rate of Glucose conversion (v1) minus the rate of conversion (v2) to Fructose-6-phosphate.

$$\frac{dS_2}{dt} = v_1 - v_2$$

Designing a dynamic experiment

- Describing relationship mathematically

- What rate laws are known to describe the enzymatic reaction?
  - Types of rate laws/kinetic models
    - Constant, mass action, michaelis menten…

Simplify

- Glucose transport (v1)
- Facilitated diffusion

$$v = V^{+} \frac{\dfrac{Glc_{out} - Glc_{in}}{K_{Glc}}}{1 + \dfrac{Glc_{out}}{K_{Glc}} + \dfrac{Glc_{in}}{K_{Glc}} + K_{i} \dfrac{Glc_{out} Glc_{in}}{K_{Glc}}}$$

Rate Equations

Substrates

- Glucose: S_1
- Glucose-

6-phosphate: S_2

Rate constants

- Enzyme1: k_1
- Enzyme2: k_2

•Mass action kinetics are used here to describe the enzymatic reactions.

$$v_1 = k_1 S_1$$

$$v_2 = k_2 S_2$$

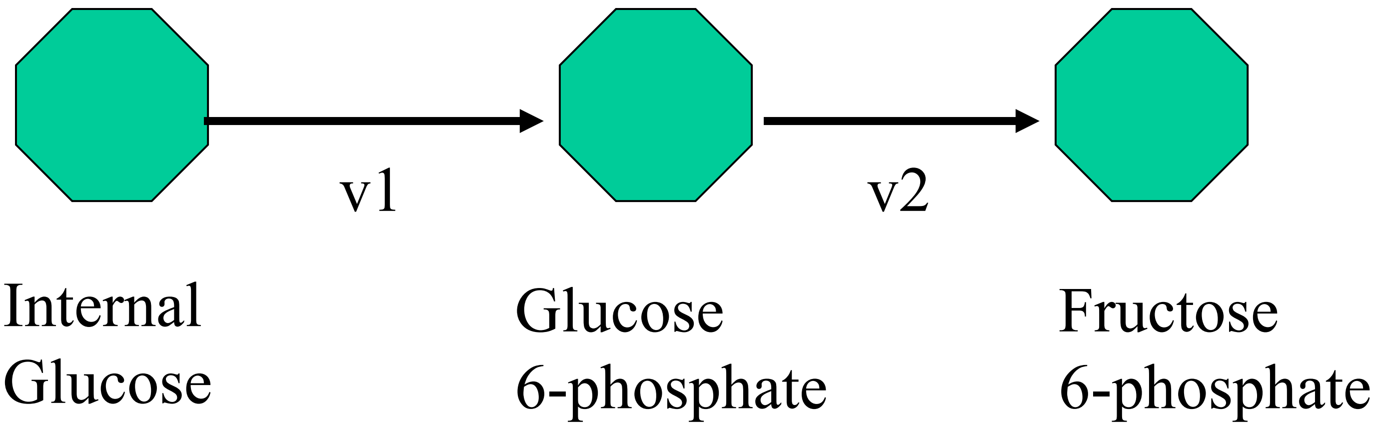
•This is a simplification of the enzyme kinetics for this example.

Initial conditions

- Concentrations of components
  - External glucose (i.e. 300mM)

- Enzymatic rates
  - Rate constant k (i.e. 50mM/min)
  - Michaelis-Menten constants, Hill Coefficients

The model



Ordinary differential equation

$$\frac{dS_2}{dt} = v_1 - v_2$$

Rate equations

$$v_1 = k_1 S_1$$

$$v_2 = k_2 S_2$$

Initial conditions

S1=300mM
k1=55mM/min
k2=9.8mM/min

Walking through a Computational Model

- Concept Map
- Factors and relationships between factors
- Describe relationships mathematically

- Solve equations: using computer tools
- View and interpret results

Some Available Tools

General

1. Stella
   - Install
   - Mac or PC
2. Excel
   - Install
   - Mac or PC

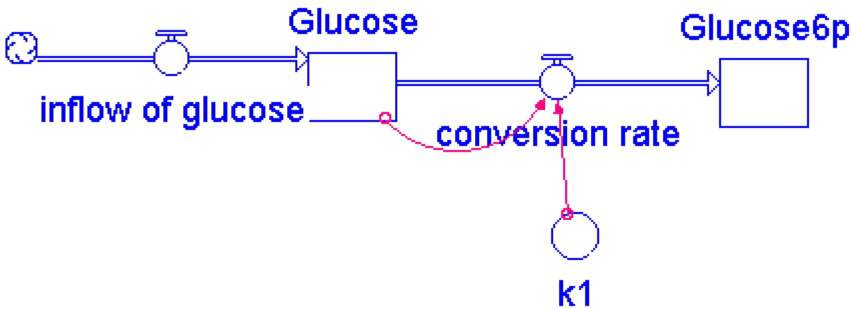
Customized

3. GEPASI
   - Install
   - Mac or PC
4. Virtual Cell
   - Browser: Java
   - Mac or PC

1. Concept mapping and system dynamics (changes over time).
2. Discrete events, algebraic equations
3. Biochemical kinetics and kinetic analyses.
4. Icon mapping, dynamics and space

Stella

Concept Map



Rules as math

```
{ RUNTIME EQUATIONS }
Glucose(t) = Glucose(t - dt) + (inflow_of_glucose_ - conversion_rate) * dt

Glucose6p(t) = Glucose6p(t - dt) + (conversion_rate) * dt

conversion_rate = k1*Glucose
```

Initial Conditions

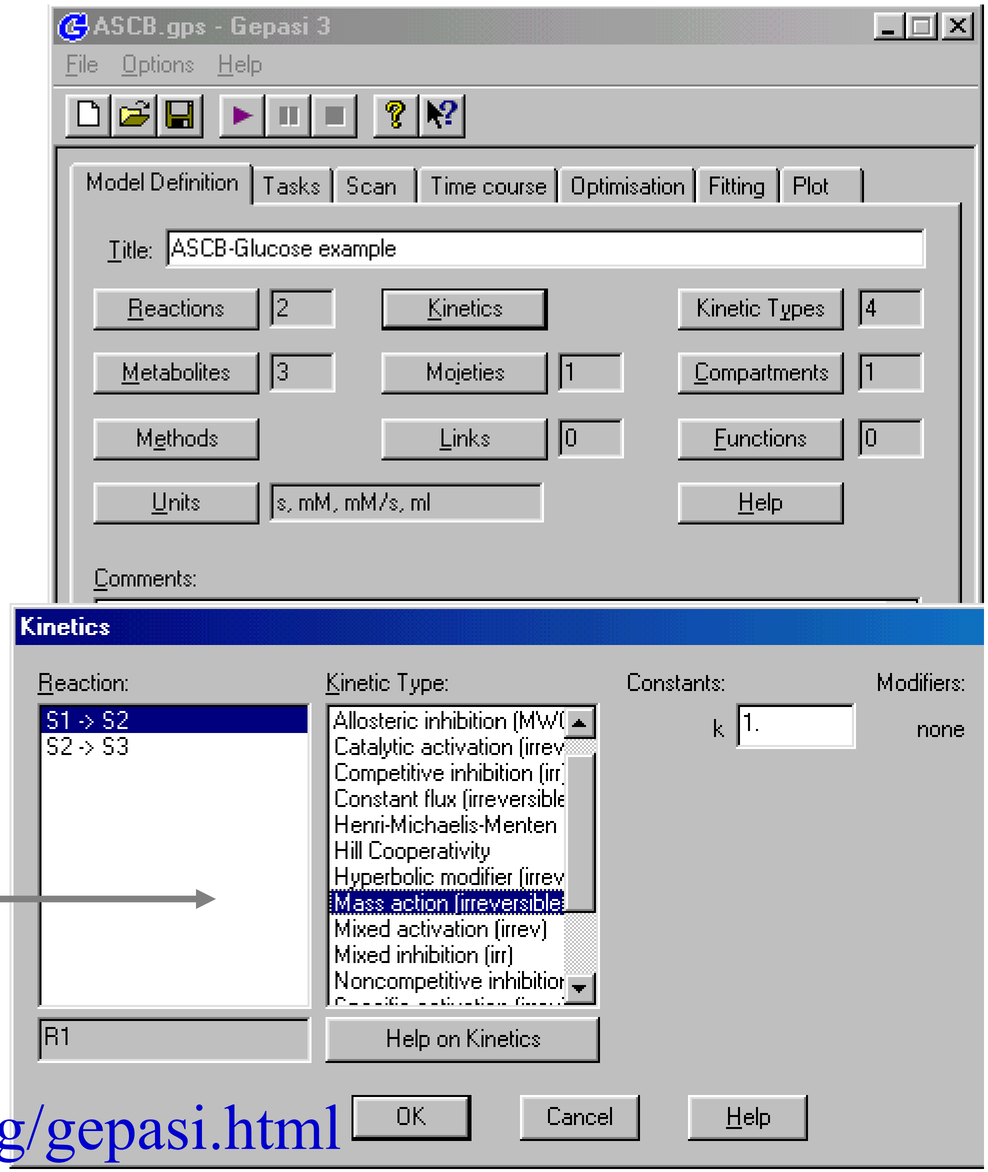
```
{ INITIALIZATION EQUATIONS }
k1 = 55{1/mM*1/min}
INIT Glucose = 0

inflow_of_glucose_ = 50{mM*1/min}
conversion_rate = k1*Glucose
INIT Glucose6p = 0
```

GEPASI

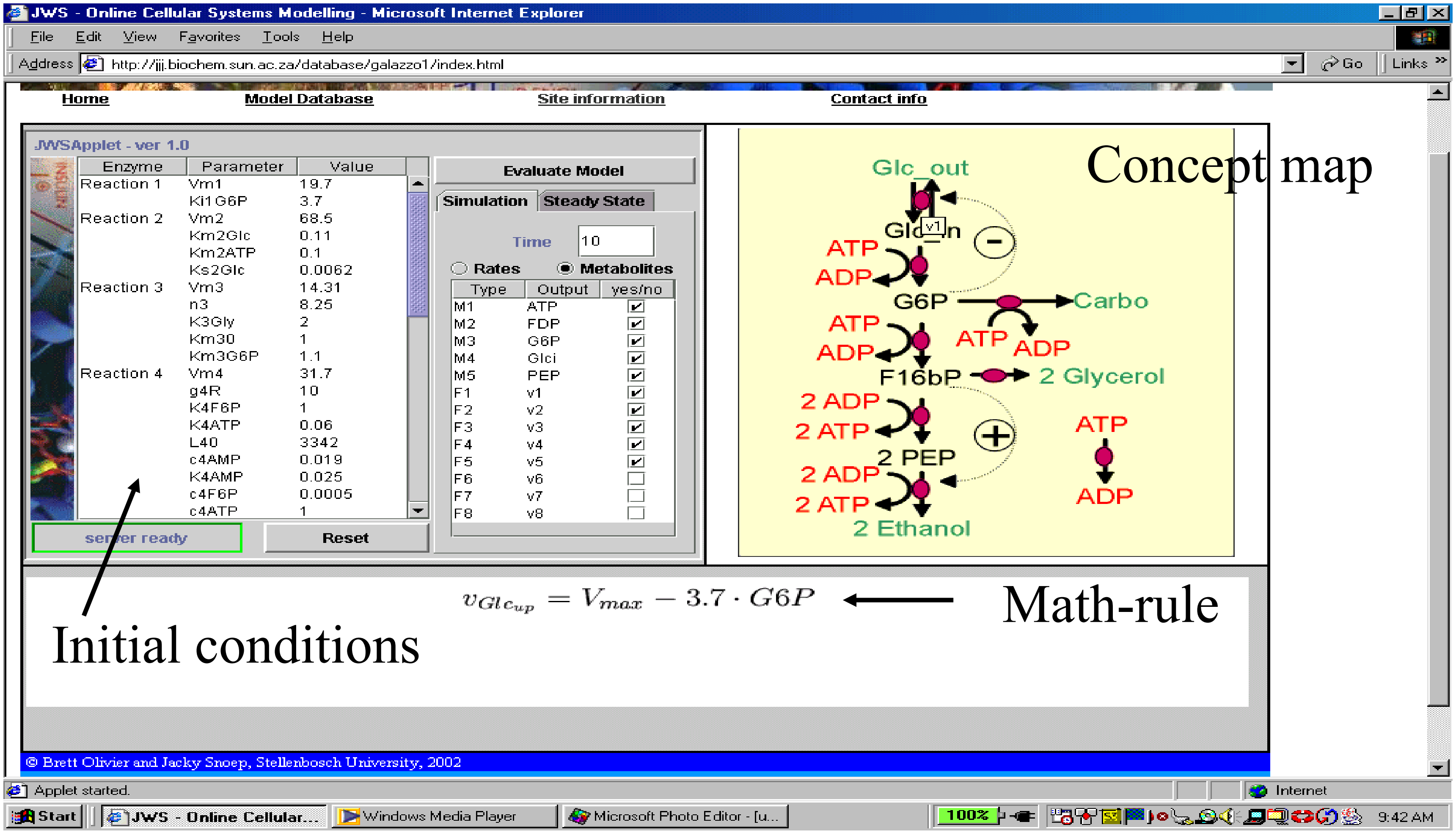
Chemical Equations

Math



http://www.gepasi.org/gepasi.html

Online Glycolysis models



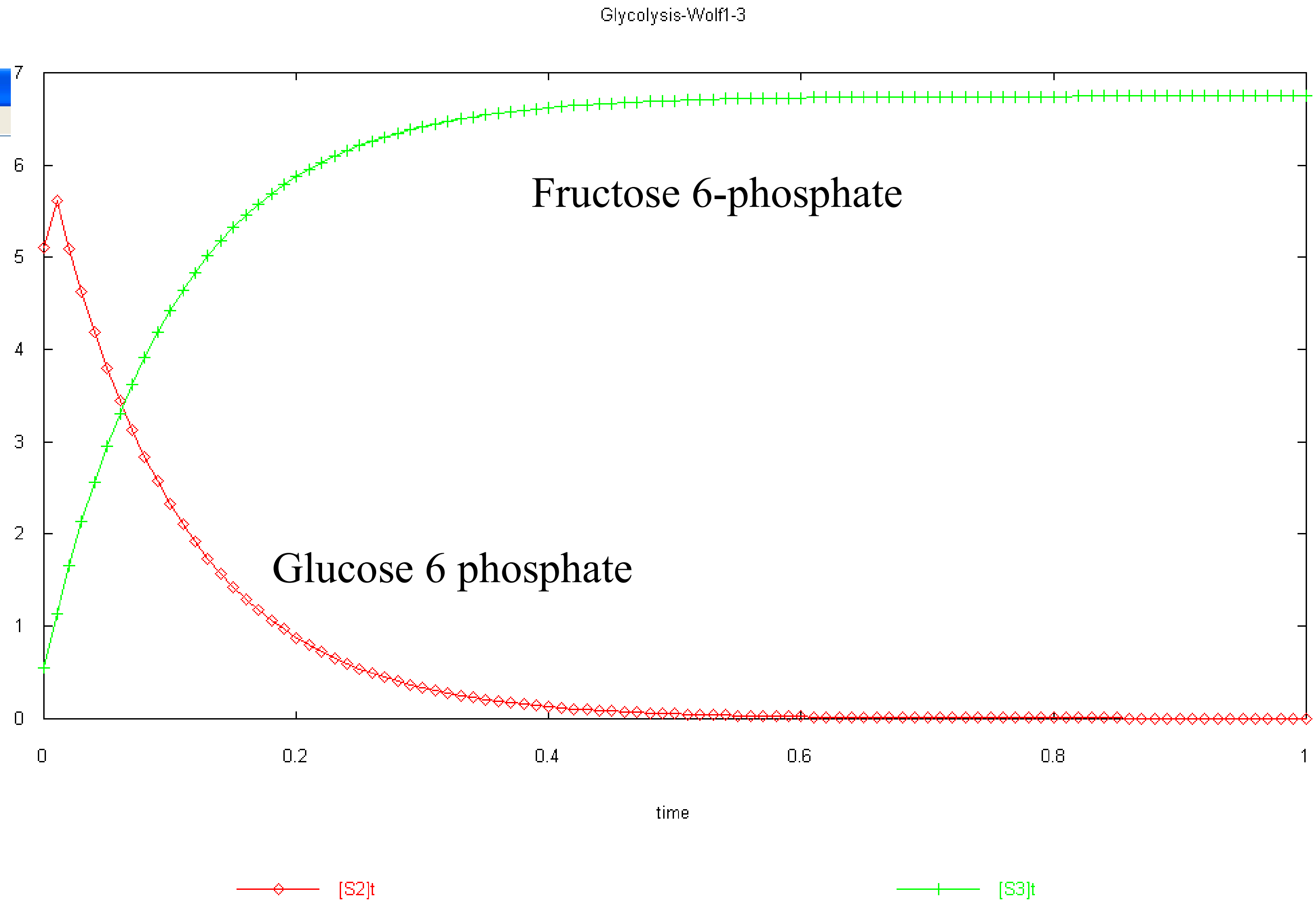
http://jjj.biochem.sun.ac.za/database/

Results

glycolysis-wolf1-3Numbers - Notepad

File Edit Format View Help

3.0000e+002	5.1000e+000	5.5000e-001
2.9941e+002	5.6169e+000	1.1281e+000
2.9991e+002	5.0925e+000	1.6525e+000
3.0041e+002	4.6172e+000	2.1278e+000
3.0091e+002	4.1862e+000	2.5588e+000
3.0141e+002	3.7954e+000	2.9496e+000
3.0191e+002	3.4411e+000	3.3039e+000
3.0240e+002	3.1199e+000	3.6251e+000
3.0290e+002	2.8286e+000	3.9164e+000
3.0341e+002	2.5646e+000	4.1804e+000
3.0391e+002	2.3252e+000	4.4198e+000
3.0441e+002	2.1082e+000	4.6368e+000
3.0490e+002	1.9114e+000	4.8336e+000
3.0540e+002	1.7329e+000	5.0121e+000
3.0590e+002	1.5712e+000	5.1738e+000
3.0640e+002	1.4245e+000	5.3205e+000
3.0690e+002	1.2915e+000	5.4535e+000
3.0740e+002	1.1710e+000	5.5740e+000
3.0790e+002	1.0617e+000	5.6833e+000
3.0840e+002	9.6255e-001	5.7825e+000
3.0890e+002	8.7269e-001	5.8723e+000
3.0940e+002	7.9123e-001	5.9538e+000
3.0990e+002	7.1737e-001	6.0276e+000
3.1040e+002	6.5040e-001	6.0946e+000
3.1090e+002	5.8968e-001	6.1553e+000
3.1140e+002	5.3464e-001	6.2104e+000
3.1190e+002	4.8473e-001	6.2603e+000
3.1240e+002	4.3948e-001	6.3055e+000
3.1290e+002	3.9846e-001	6.3465e+000
3.1340e+002	3.6126e-001	6.3837e+000
3.1390e+002	3.2753e-001	6.4175e+000
3.1440e+002	2.9696e-001	6.4480e+000
3.1490e+002	2.6924e-001	6.4758e+000
3.1540e+002	2.4410e-001	6.5009e+000
3.1590e+002	2.2132e-001	6.5237e+000
3.1640e+002	2.0066e-001	6.5443e+000
3.1690e+002	1.8192e-001	6.5631e+000
3.1740e+002	1.6494e-001	6.5801e+000
3.1790e+002	1.4954e-001	6.5955e+000
3.1840e+002	1.3558e-001	6.6094e+000
3.1890e+002	1.2293e-001	6.6221e+000



Conclusions…

- Model based discoveries in glycolysis::
  - Oscillations in concentrations of some but not all metabolites.
  - Control of process distributed throughout pathway
  - Development of theoretical models

- Method integrates knowledge of pathway factors to examine pathway behaviors.

Examples of other models

Calcium dynamics: Wave patterns in neuronal cells

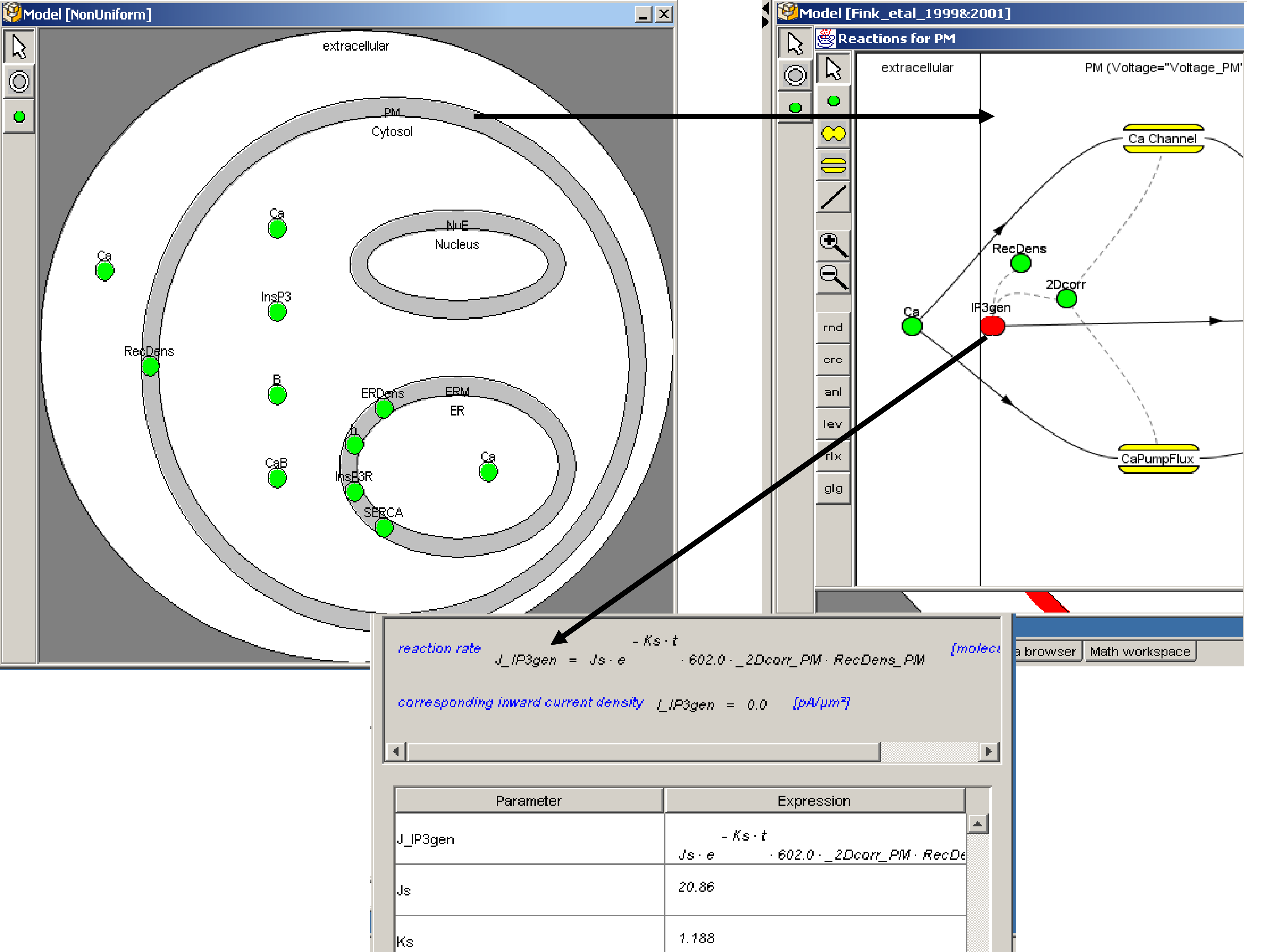
Virtual Cell

Receptor signaling: IgE triggering mast cells

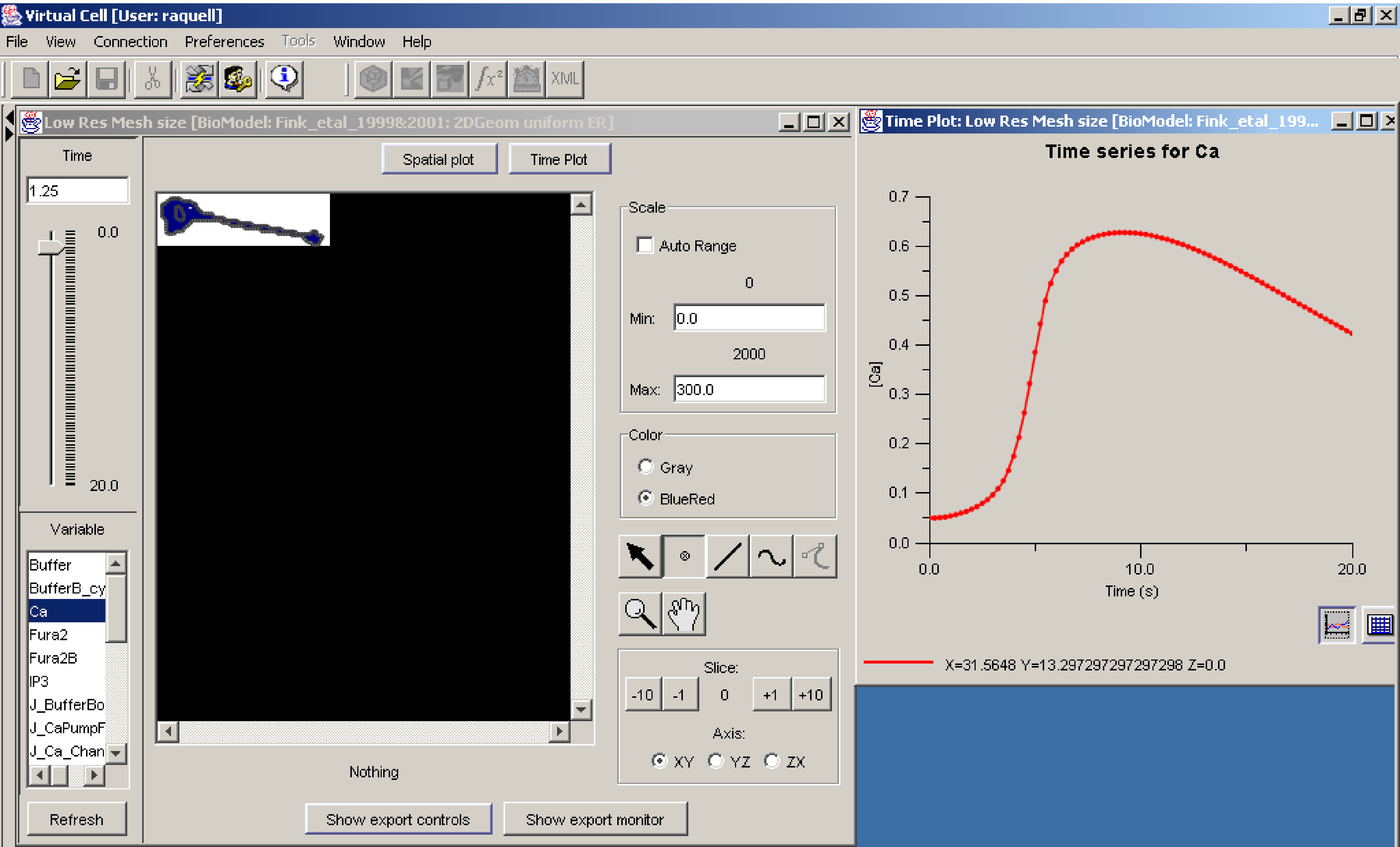
Personal computer codes

Cell cycle regulation: length of wee 1 mutant cell divisions

Matlab, Mathematica, personal computer codes


Model [NonUniform]
extracellular
PM
Cytosol
Ca
Ca
InsP3
RecDens
B
CaB
NuE
Nucleus
ERDens
ERM
ER
InsP3R
SERCA
Ca
Model [Fink_etal_1999&2001]
Reactions for PM
extracellular
PM (Voltage="Voltage_PM"
Ca Channel
RecDens
2Dcorr
IP3gen
Ca
CaPumpFlux
rnd
crc
anl
lev
rlx
glg
reaction rate
J_IP3gen = Js · e^(- Ks · t) · 602.0 · _2Dcorr_PM · RecDens_PM
corresponding inward current density
I_IP3gen = 0.0
[pA/μm²]
a browser
Math workspace
Parameter
Expression
J_IP3gen
Js · e^(- Ks · t) · 602.0 · _2Dcorr_PM · RecDe
Js
20.86
Ks
1.188

Calcium dynamics in neuroblastoma cells



Modeling

- Requires formalizing assumptions
  - Rate equations
  - Inclusion or exclusion from model
- Worst case scenario
  - See what you believe
- Best case scenario
  - See something unexplainable
  - Create new laboratory experiments