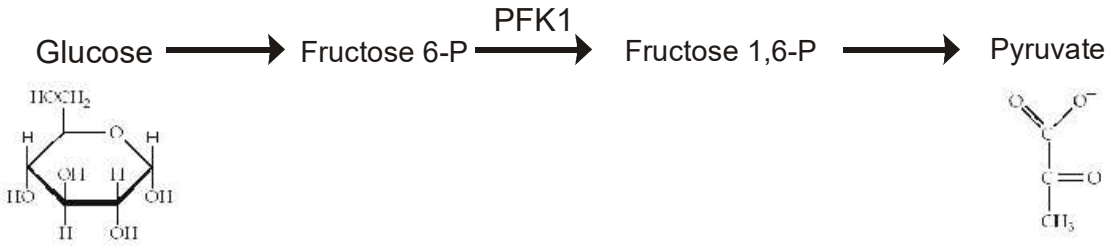
Quantitative Physiology I / Molecular and Cellular Systems, BMEN E4001x
Notes 06 – Numerical simulations
Keener & Sneyd, section 1.3 Glycolysis and Glycolytic oscillations
web-available Runge-Kutta and MATLAB resource

Sel'kov model



Under certain conditions, this system exhibits oscillations. K&S has a full description of the history and interactions. Earlier, we discussed that PFK1 is inhibited by ATP, and also acts on ATP. In this model, assume that ADP provides a positive regulation on PFK1; need to generate more ATP. Specifically, assume:

- ATP is a substrate and inhibitor to PFK1 (source of phos. for creating F-1,6-P)
- Inhibition is removed by AMP
- Steady state doesn't capture full behavior
- Oscillations have been observed in yeast models
- Sel'kov model as a simplified explanation
- Goal: find reaction behavior as a function of input ATP
- binding of a certain number of ADPs, γ, (correlated to AMP) activates PFK1
- In the following scenario,
  - PFK1=E, with further substitutions in the next section: $[ES_2^\gamma]=x_1$; $[S_1ES_2^\gamma]=x_2$
  - ATP=S_1, ADP=S_2,
  - γ= # of ADPs needed to activate PFK1
- scheme, given input rate v_1, (ON BOARD)

$$\gamma S_2 + E \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} ES_2^\gamma,$$

(activation of PFK1)

$$\xrightarrow{v_1} S_1,$$

$$S_1 + ES_2^\gamma \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} S_1ES_2^\gamma \xrightarrow{k_2} ES_2^\gamma + S_2,$$

$$S_2 \xrightarrow{v_2}.$$

(input of S_1, what is the rate S_2)

Gives the differential and conservation equations, using the normal substitutions (along with the one above)

$$\frac{ds_1}{dt} = v_1 - k_1 s_1 x_1 + k_{-1} x_2,$$
$$\frac{ds_2}{dt} = k_2 x_2 - k_3 s_2^{\gamma} e + k_{-3} x_1 - v_2 s_2,$$
$$\frac{dx_1}{dt} = -k_1 s_1 x_1 + (k_{-1} + k_2) x_2 + k_3 s_2^{\gamma} e - k_{-3} x_1,$$
$$\frac{dx_2}{dt} = k_1 s_1 x_1 - (k_{-1} + k_2) x_2.$$

$$e + x_1 + x_2 = e_0$$

Introduce the following non-dimensional variables (COPY KEY PARTS ONTO BOARD)

$$\sigma_1 = \frac{k_1 s_1}{k_2 + k_{-1}} \qquad \sigma_2 = \left(\frac{k_3}{k_{-3}}\right)^{1/\gamma} s_2 \qquad u_1 = \frac{x_1}{e_0} \qquad u_2 = \frac{x_2}{e_0} \qquad t = \frac{k_2 + k_{-1}}{e_0 k_1 k_2}\tau$$

along with the following derived parameters

$$\varepsilon = \frac{e_0 k_1 k_2}{(k_2 + k_{-1})^2} \text{;epsilon} \qquad \nu = \frac{v_1}{k_2 e_0} \text{;nu} \qquad \eta = \frac{v_2(k_2 + k_{-1})}{k_1 k_2 e_0} \text{;eta} \qquad \alpha = \frac{k_2 + k_{-1}}{k_1}\left(\frac{k_3}{k_{-3}}\right)^{1/\gamma} \text{;alpha}$$

the system becomes:

$$\frac{d\sigma_1}{d\tau} = \nu - \frac{k_2 + k_{-1}}{k_2} u_1 \sigma_1 + \frac{k_{-1}}{k_2} u_2,$$
$$\frac{d\sigma_2}{d\tau} = \alpha\left[u_2 - \frac{k_{-3}}{k_2}\sigma_2^{\gamma}(1 - u_1 - u_2) + \frac{k_{-3}}{k_2} u_1\right] - \eta\sigma_2,$$
$$\epsilon\frac{du_1}{d\tau} = u_2 - \sigma_1 u_1 + \frac{k_{-3}}{k_2 + k_{-1}}\left[\sigma_2^{\gamma}(1 - u_1 - u_2) - u_1\right],$$
$$\epsilon\frac{du_2}{d\tau} = \sigma_1 u_1 - u_2,$$

If we assume epsilon is small (following same argument as quasi steady-state, essentially), the lower two equations become:

$$u_1 = \frac{\sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1},$$
$$u_2 = \frac{\sigma_1 \sigma_2^\gamma}{\sigma_2^\gamma \sigma_1 + \sigma_2^\gamma + 1} = f(\sigma_1, \sigma_2),$$

which allows simplification of the two earlier equations

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2),$$
$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2.$$

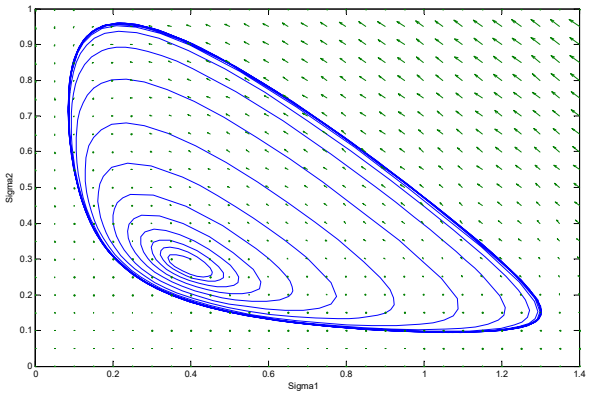
Following along the steady-state idea, we can set these differential equations to zero, and get the following STABLE SOLUTION

$$\sigma_1 = \frac{\nu\left(1+\sigma_2^\gamma\right)}{(1-\nu)\sigma_2^\gamma}$$
$$\sigma_2 = \frac{\alpha}{\eta}\nu$$

As an example, setting γ=2; ν=0.0285; η=0.1; α=1.0

Stable solution yields σ_1= 0.3905; σ_2= 0.285

But there are problems. In particular, this link between the two sigmas has no basis, such as a conservation equation. Make a vector plot of the two ODEs for the sigmas, and, indeed, if you solve the ODEs,



More notes:

- You can see on this graph the stability solution
- This stability is not, well, stable. That is, move from this point, you go to the attractors indicated by the curve.
- This path is highly dependent on parameters, including the balance of gamma, eta, nu, alpha. OUR GOAL HERE IS TO EXPLORE THIS BEHAVIOR NUMERICALLY. In solving ODEs, this usually means finding the dependent variables as a function of time, given necessary parameters and initial conditions.

For this, use the MATLAB program. (go to slides for very, very basic tutorial)

The ode45 method:

(help page from going to www.mathworks.com, entering ode45 in the search slot, then going to the first selection)

http://www.mathworks.com/access/helpdesk/help/techdoc/index.html?/access/helpdesk/help/techdoc/ref/ode113.html

See slides for Runge-kutta discussion, and we'll discuss the implications in class.