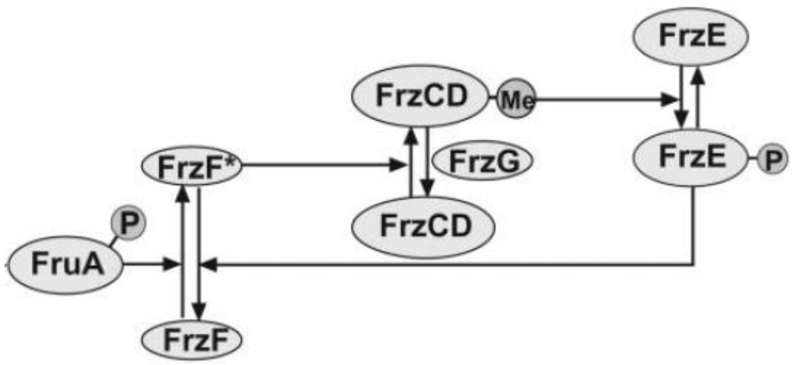
Project: Simulation of Biological Oscillations **Lab: Beer**

Background: Biological oscillators are important in many systems, including neuronal excitation, cardiomyocyte contraction, regulation of the cell cycle, and signalling that leads to complex social behavior in single celled organisms. The coordination of motion of many *Myxococcus xanthus* bacteria allows formation of fruiting bodies (or spores) and more efficient predation (http://www.youtube.com/watch?v=tstc6doiNCU). This coordination is established by signalling between individual bacteria via the Frz system of proteins which form a signal transduction cascade:



FruA responds to signals from nearby bacteria. FrzF becomes activated (FrzF*) by FruA. FrzF* in turn methylates FrzCD, and methylated FrzCD phosphorylates FrzE, which when phosphorylated deactivates FrzF. This system can be modeled by a set of rate equations for the concentrations of each protein in its active and inactive state [Igoshin et al 2004]:

The fraction of activated FrzF is given by: $f = [FrzF^*]/([FrzF^*]+[FrzF])$.

The fraction of methylated FrzCD is given by: $c = [FrzCDM]/([FrzCDM]+[FrzCD])$.

The fraction of phosphorylated FrzE is given by: $e = [FrzEP]/([FrzE]+[FrzEP])$.

The dynamical evolution of these fractions is given by:

$$\boxed{\begin{aligned} \frac{df}{dt} &= k_a(1-f) - k_d e f \\ \frac{dc}{dt} &= k_m(1-c) f - k_{dm} c \\ \frac{de}{dt} &= k_p(1-e)c - k_{dp} e \end{aligned}}\,,$$

where the rates are given by:

$$k_a = \frac{k_a^{\max}}{K_a + |1-f|} \quad k_d = \frac{k_d^{\max}}{K_d + f}$$

$$k_m = \frac{k_m^{\max}}{K_m + |1-c|} \quad k_{dm} = \frac{k_{dm}^{\max}}{K_{dm} + c}$$

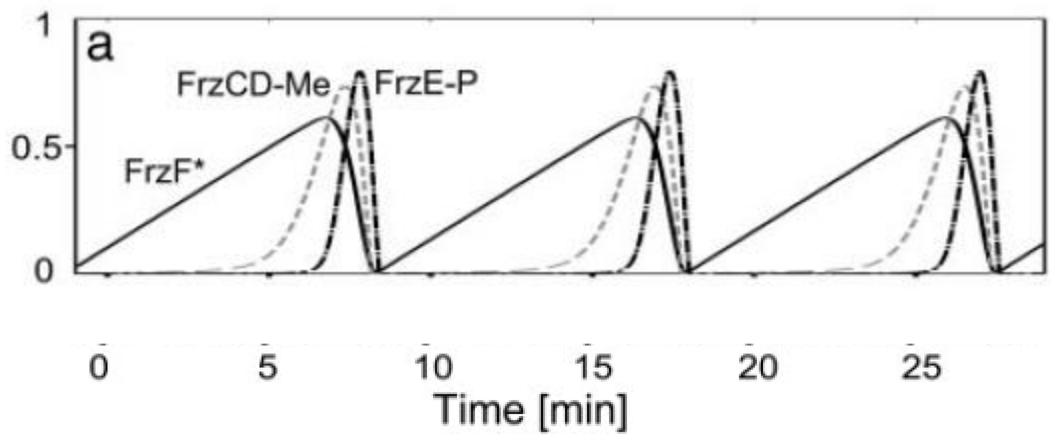
$$k_p = \frac{k_p^{\max}}{K_p + |1-e|} \quad k_{dp} = \frac{k_{dp}^{\max}}{K_{dp} + e}$$

with: $K_a = .01$, $K_d = K_m = K_{dm} = K_p = K_{dp} = .005$, $k_d^{\max} = 1$, $k_m^{\max} = k_p^{\max} = 4$, and $k_{dm}^{\max} = k_{dp}^{\max} = 2$.

Note: the absolute values are not in Igoshin et al 2004, but prevent numerical problems (the active fraction should never be greater than one).

Project:

1. Simulate this system in time. Using ode45 to simulate three first order ODEs is very similar to MATLAB Assignment 17, or you could use modified versions of the Python Runge-Kutta functions on p17 of Lecture 17, and plot the results in R. Reproduce the oscillations shown in Fig 1a of Igoshin et al. 2004 (below) using intial conditions $(f,c,e)=(0.01,0,0)$ and $k_a^{\max}=.08$. Also plot the behavior for $k_a^{\max}=0.8$.



2. Show that oscillations cease for larger $k_a^{\max}$, and find the critical $k_a^{\max}$ above which there are no oscillations. Support your conclusion by plotting the either the frequency or the period of oscillations vs. $k_a^{\max}$. You may approximate the period and/or frequency from graphing the solutions for different $k_a^{\max}$.

3. The critical $k_a^{\max}$ may depend on the other rate parameters in the model. Find the critical $k_a^{\max}$ when $k_d^{\max}$ is changed to $k_d^{\max}=2$. Support your conclusion by plotting either the frequency or the period of oscillations vs. $k_a^{\max}$. You may approximate the period and/or frequency from graphing the solutions for different $k_a^{\max}$.

Reference:

"A biochemical oscillator explains several aspects of Myxococcus xanthus behavior during development." Oleg A. Igoshin, Albert Goldbeter, Dale Kaiser, and George Oster, PNAS **101** 15760–15765 (2004).