Modeling the heat shock response of alpha-amylase in barley aleurone cells

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Outline

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Heat Shock

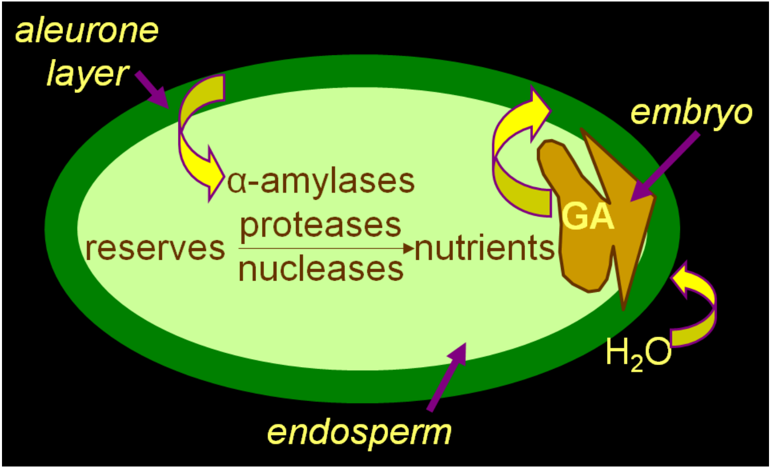
How does heat shock affect the production and effectiveness of digestive proteins in barley?

Heat shock occurs when temperatures rise above the range where cells are able to function optimally.

It causes slowed production and misfolding of proteins, which causes developmental and physiological problems in plants and animals.

Barley Aleurone Model

Heat shock suppresses α-amylase synthesis...



...which in turn prevents germination.

Motivation

- Practical applications: Understanding how plants react to high temperature stress, and what the process of protein synthesis looks like under those conditions will be critical to address environmental changes imposed by climate change.

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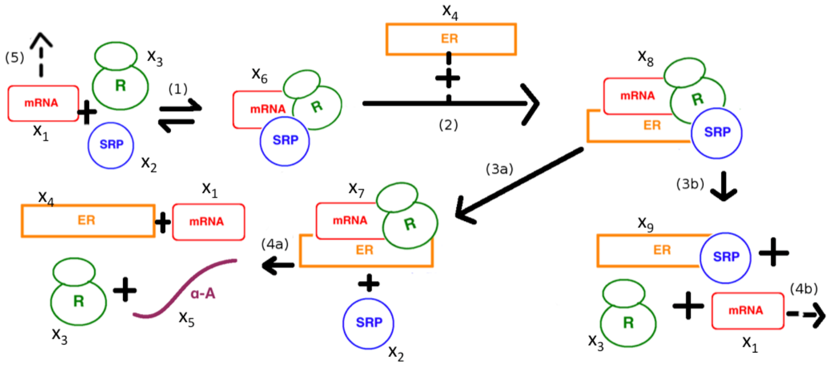
- Practical applications: Understanding how plants react to high temperature stress, and what the process of protein synthesis looks like under those conditions will be critical to address environmental changes imposed by climate change.
- This project has allowed me to experience one way that mathematics can play a crucial and practical role in solving real-world problems.

How Math is Used in Biology

Use systems of differential equations to model biological processes.

Use Matlab to numerically solve these systems and be able to predict how plants will react to certain stimuli.

α-amylase Synthesis Reactions



Creating a System of Equations

Principle of Mass Action:
The rate of each reaction is proportional to the concentration of reactants.

$$R_1: \; A + B \rightarrow C,$$

$$\frac{dA}{dt} = \frac{dB}{dt} = -k\, A(t)\, B(t), \qquad \frac{dC}{dt} = k\, A(t)\, B(t).$$

For a reversible reaction

$$R_2: \; A + B \leftrightarrows C,$$

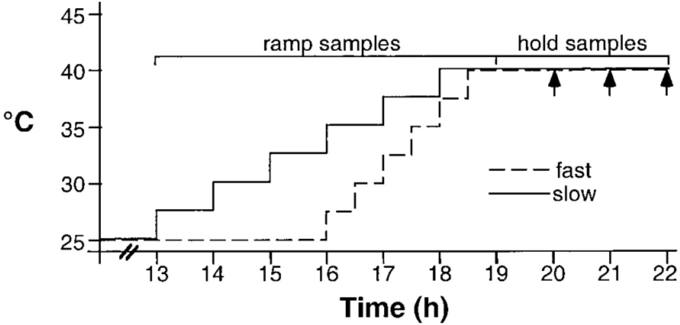
the rate is $f_2(t) = k_1\, A(t)\, B(t) - k_2\, C(t)$, for some constants $k_1,\, k_2 \geq 0$. The differential equations are written in a similar way:

$$\frac{dA}{dt} = \frac{dB}{dt} = -f_2(t), \qquad \frac{dC}{dt} = f_2(t). \qquad (*)$$

For the rate of each reactant, sum all terms that contain reactant.

3 Temperature Schemes

Plunge, Slow Ramp, Fast Ramp



Fitting Functions

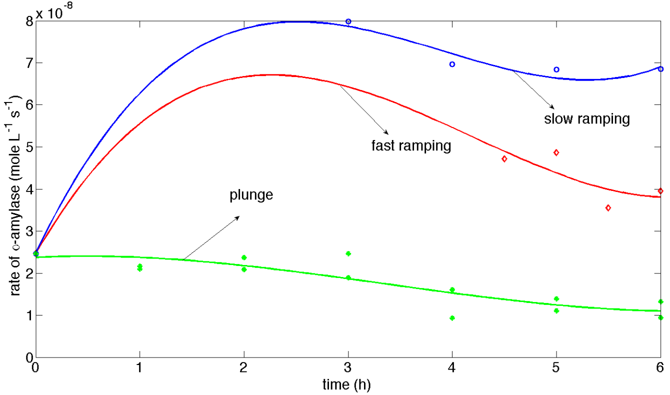
Matlab:

- Input data points and ask Matlab to find a least-squares function that best approximates the points.
- Began with a cubic polynomial function. Switched to piecewise linear function to get a more accurate estimate due to the lack of data.

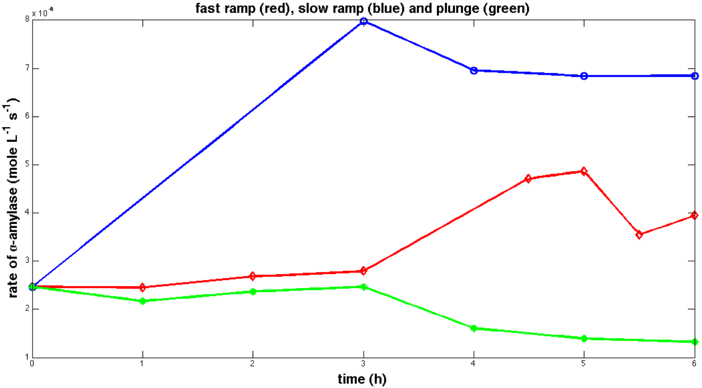
```
function dxdt = alphap3(t,x,flag,k)

dxdt = zeros(size(x));


%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% alpha-amylase
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%pars = find_FTp3();
%F =  polyval(pars,t);


[tt,FTt] = find_FTp3();
F = interp1(tt,FTt,t);
```

Original Fitting Functions

Fit $F(T(t))$ function to data that takes temperature into account. Temperature is also a function of time, so indirectly, F is also a function of time.



Revised Fitting Functions



System of Differential Equations

$$\frac{dx_1}{dt} = -k_1 x_1 x_2 x_3 + l_1 x_6 + k_4 x_7 + k_5 x_8 - l_2 x_1 - l_3 x_1 \quad (1)$$

$$\frac{dx_2}{dt} = -k_1 x_1 x_2 x_3 + l_1 x_6 + k_3 x_8 \quad (2)$$

$$\frac{dx_3}{dt} = -k_1 x_1 x_2 x_3 + l_1 x_6 + k_4 x_7 + k_5 x_8 \quad (3)$$

$$\frac{dx_4}{dt} = -k_2 x_6 x_4 + k_4 x_7 \quad (4)$$

$$\frac{dx_5}{dt} = k_4 x_7 \quad (5)$$

$$\frac{dx_6}{dt} = -l_1 x_6 + k_1 x_1 x_2 x_3 - k_2 x_6 x_4 \quad (6)$$

$$\frac{dx_7}{dt} = k_3 x_8 - k_4 x_7 \quad (7)$$

$$\frac{dx_8}{dt} = k_2 x_6 x_4 - k_3 x_8 - k_5 x_8 + F(T(t)), \text{where } T \text{ is temperature,} \quad (8)$$

$$\frac{dx_9}{dt} = k_5 x_8 \quad (9)$$

Solving Systems of ODEs

Given a system of ODEs, we can find a solution either numerically or analytically. When systems are large and complex, numerical methods must be used to obtain approximate solutions to the systems since the analytical techniques are not powerful enough.

Runge-Kutta 4 (RK4): a 4-step numerical method used in Matlab ode45 to solve a system of ODEs.

Runge-Kutta 4

Begin with an initial value problem:

$$\mathbf{y}' = \mathbf{f}(t, \mathbf{y}), \qquad \mathbf{y}(t_o) = \mathbf{y}_o$$

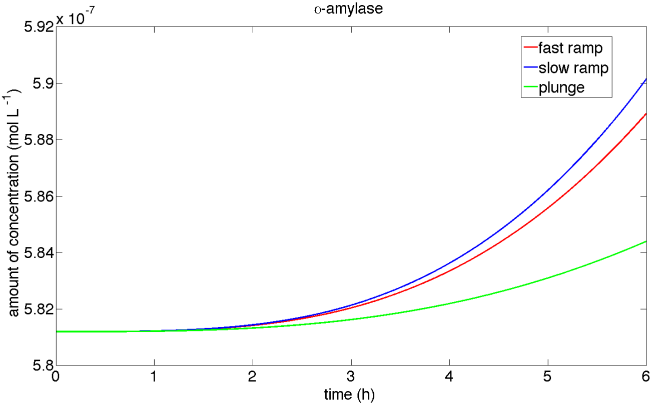
The RK4 method is:

$$\begin{aligned}
\mathbf{y}_{n+1} &= \mathbf{y}_n + \tfrac{1}{6}(\mathbf{k}_1 + 2\mathbf{k}_2 + 2\mathbf{k}_3 + \mathbf{k}_4), \\
t_{n+1} &= t_n + h, \\
\mathbf{k}_1 &= h\mathbf{f}(t_n, \mathbf{y}_n), \\
\mathbf{k}_2 &= h\mathbf{f}(t_n + \tfrac{1}{2}h, \mathbf{y}_n + \tfrac{1}{2}\mathbf{k}_1), \\
\mathbf{k}_3 &= h\mathbf{f}(t_n + \tfrac{1}{2}h, \mathbf{y}_n + \tfrac{1}{2}\mathbf{k}_2), \\
\mathbf{k}_4 &= h\mathbf{f}(t_n + h, \mathbf{y}_n + \mathbf{k}_3),
\end{aligned}$$

where h is the time step and $\mathbf{y}_{n+1}$ is an approximation of $\mathbf{y}(t_{n+1})$.

The RK4 method has an error of order h^5 per step, and a total error of order h^4.

Simulated Concentrations of α-amylase



α-amylase is most severely affected by the plunge temperature scheme. In the slow ramp experiment, the BAL cells have enough time to adapt so that amylase synthesis is not as drastically decreased.

Goals

- Introduce a membrane fluidity variable into model.

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- Introduce a membrane fluidity variable into model.
- Use Matlab to numerically solve a refined system of ODEs.

Fluidity

How does fluidity influence synthesis of α-amylase?

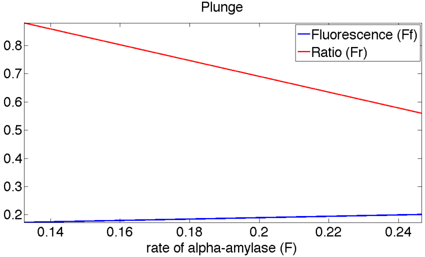
Two measures of fluidity

- Fatty acid ratio
- Fluorescence polarization

Fitting functions for fluidity

Temp. (C)	Fluorescence	α-a	Ratio
25	.201	.2466	.52
40	.173	.1324	.8

Fluidity: Ff = (.173-.201)/(.1324-.2466)*(F-.2466)+.201;
Ratio: Fr = ((.8-.52)/(.1324-.2466)*(F-.2466)+.52;



Refined System of Differential Equations

$$\frac{dx_1}{dt} = -k_1 x_1 x_2 x_3 + l_1 x_6 + k_4 x_7 + k_5 x_8 - l_2 x_1 - l_3 x_1$$

$$\frac{dx_2}{dt} = -k_1 x_1 x_2 x_3 + l_1 x_6 + k_3 x_8$$

$$\frac{dx_3}{dt} = -k_1 x_1 x_2 x_3 + l_1 x_6 + k_4 x_7 + k_5 x_8$$

$$\frac{dx_4}{dt} = -k_2 x_6 x_4 + k_4 x_7$$

$$\frac{dx_5}{dt} = k_4 x_7$$

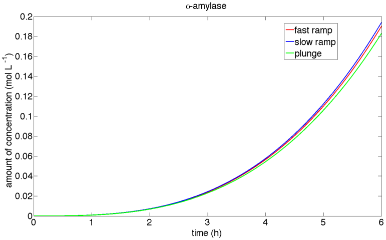
$$\frac{dx_6}{dt} = -l_1 x_6 + k_1 x_1 x_2 x_3 - k_2 x_6 x_4$$

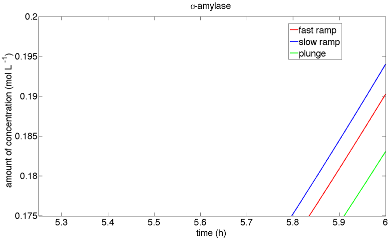
$$\frac{dx_7}{dt} = k_3 x_8 - k_4 x_7$$

$$\frac{dx_8}{dt} = k_2 x_6 x_4 - k_3 x_8 - k_5 x_8 + F(T) + Fr(T) + Ff(T), \text{where } T \text{ is temperature,}$$

$$\frac{dx_9}{dt} = k_5 x_8$$

Revised Total Concentrations





The revised solutions to the system of ODEs gives us one more characteristic that lines up with the literature. The total concentration for the fast ramp at 6 hours should be about 2/3 of the way up from the plunge to the slow ramp.

Results

Understood the formula of the underlying method (RK4) when using ode45 to solve a system numerically.

Obtained graphs and results that allow us to predict how α-amylase will react to heat shock, based on other conditions.

Continuing

- Want to understand the derivation of the formula and error analysis of RK4.

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- Standardize data.

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- Want to understand the derivation of the formula and error analysis of RK4.
- Standardize data.
- Write a paper to be published in a Biomath journal.

References

- K. K. Grindstaff, L. A. Fielding, and M. R. Brodl; *Effect of gibberellin and heat shock on the lipid composition of endoplasmic reticulum in barley aleurone layers,* Journal of Plant Physiology, 1996.
- Zuzanna Szymanska and Maciej Zylicz; *Mathematical modeling of heat shock protein synthesis in response to temperature change,* Journal of Theoretical Biology, 2009.

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