Oscillations in Michaelis-Menten Systems

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Background

A simple example of genetic oscillation

- Gene makes compound (transcription factor)
- Transcription factor binds to promoter
- Circadian Clocks

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Mass Action Kinetics

- Write chemical reaction network as a system of differential equations

Michaelis-Menten (MM) Approximation for Biochemical Systems

- Assume low concentration of intermediates
- Allows for elimination of variables, reducing differential equations from mass action
- Michaelis-Menten approximation has oscillations implies original has oscillations

Michaelis-Menten System (Dual Futile Cycle)

Phosphorylation $\quad S_0 + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S_0E \xrightarrow{k_3} S_1 + E \underset{k_5}{\overset{k_4}{\rightleftharpoons}} S_1E \xrightarrow{k_6} S_2 + E$

Dephosphorylation $\quad S_2 + F \underset{l_2}{\overset{l_1}{\rightleftharpoons}} S_2F \xrightarrow{l_3} S_1 + F \underset{l_5}{\overset{l_4}{\rightleftharpoons}} S_1F \xrightarrow{l_6} S_0 + F$

- Oscillatory behavior is unknown.
- Wang and Sontag (2008) showed Michaelis-Menten approximation has **no** oscillations
- Bozeman and Morales (REU 2016) showed Michaelis-Menten approximation has no oscillations with more elementary techniques

Processive vs Distributive

Distributive:

$$S_0 + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S_0E \xrightarrow{k_3} S_1 + E \underset{k_5}{\overset{k_4}{\rightleftharpoons}} S_1E \xrightarrow{k_6} S_2 + E$$

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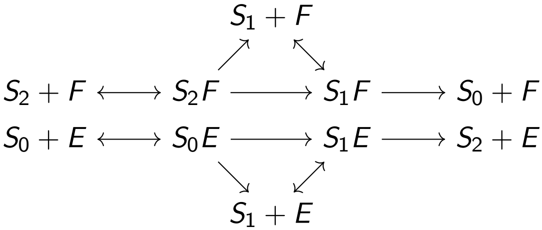
Processive:

$$S_0 + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S_0E \xrightarrow{k_7} S_1E \xrightarrow{k_6} S_2 + E$$

$$S_2 + F \underset{l_2}{\overset{l_1}{\rightleftharpoons}} S_2F \xrightarrow{l_7} S_1F \xrightarrow{l_6} S_0 + F$$

This Year's Project



- Does it have oscillations?
- Does its Michaelis-Menten approximation have oscillations?

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$$\frac{d[S_0E]}{dt} = k_1[S_0][E] - k_2[S_0E]$$

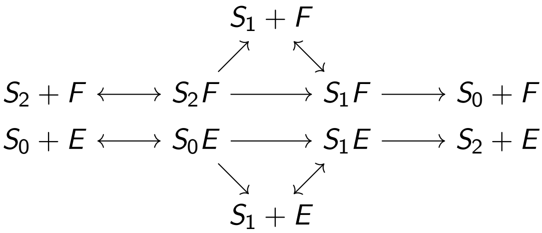
Corresponding ODEs

$$\frac{d[S_0]}{dt} = l_6[S_1F] - k_1[S_0][E] + k_2[S_0E]$$
$$\frac{d[S_2]}{dt} = k_6[S_1E] - l_1[S_2][F] + l_2[S_2F]$$
$$\frac{d[S_1]}{dt} = k_3[S_0E] - k_4[S_1][E] + k_5[S_1E] + l_3[S_2F] + l_5[S_1F] - l_4[S_1][F]$$
$$\frac{d[E]}{dt} = (k_2 + k_3)[S_0E] + (k_5 + k_6)[S_1E] - k_1[S_0][E] - k_4[S_1][E]$$
$$\frac{d[F]}{dt} = (l_2 + l_3)[S_2F] + (l_5 + l_6)[S_1F] - l_1[S_2][F] - l_4[S_1][F]$$
$$\frac{d[S_0E]}{dt} = k_1[S_0][E] - (k_2 + k_3)[S_0E] - k_7[S_0E]$$
$$\frac{d[S_1E]}{dt} = k_4[S_1][E] - (k_5 + k_6)[S_1E] + k_7[S_0E]$$
$$\frac{d[S_2F]}{dt} = l_1[S_2][F] - (l_2 + l_3)[S_2F] - l_7[S_2F]$$
$$\frac{d[S_1F]}{dt} = l_4[S_1][F] - (l_5 + l_6)[S_1F] + l_7[S_2F]$$

Michaelis-Menten Approximation of ODEs: Conservation Equations

Conservation equations refer to conservation of mass.

$$
\begin{aligned}
S_T &= [S_0] + [S_1] + [S_2] + [S_0E] + [S_1E] + [S_2F] + [S_1F] \\
E_T &= [E] + [S_0E] + [S_1E] \\
F_T &= [F] + [S_2F] + [S_1F]
\end{aligned}
$$



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F_T &= [F] + [S_2F] + [S_1F]
\end{aligned}
$$

$$
\begin{aligned}
\frac{d[E]}{dt} &= (k_2 + k_3)[S_0E] + (k_5 + k_6)[S_1E] - k_1[S_0][E] - k_4[S_1][E] \\
\frac{d[S_0E]}{dt} &= k_1[S_0][E] - (k_2 + k_3)[S_0E] - k_7[S_0E] \\
\frac{d[S_1E]}{dt} &= k_4[S_1][E] - (k_5 + k_6)[S_1E] + k_7[S_0E]
\end{aligned}
$$

Michaelis-Menten Approximation of ODEs: Assumption

We assume enzyme concentrations are small:

$$
\begin{aligned}
E_T &= \varepsilon \widetilde{E_T}, \\
F_T &= \varepsilon \widetilde{F_T}, \\
[E] &= \varepsilon [\widetilde{E}], \\
[F] &= \varepsilon [\widetilde{F}], \\
[S_0 E] &= \varepsilon [\widetilde{S_0 E}], \\
[S_1 E] &= \varepsilon [\widetilde{S_1 E}], \\
[S_2 F] &= \varepsilon [\widetilde{S_2 F}], \\
[S_1 F] &= \varepsilon [\widetilde{S_1 F}], \\
\tau &= \varepsilon t
\end{aligned}
$$

Michaelis-Menten Approximation of ODEs: Plug in

$$\frac{d[S_0]}{d\tau} = l_6[\widetilde{S_1F}] - k_1[S_0][\widetilde{E}] + k_2[\widetilde{S_0E}]$$

$$\frac{d[S_2]}{d\tau} = k_6[\widetilde{S_1E}] - l_1[S_2][\widetilde{F}] + l_2[\widetilde{S_2F}]$$

X $$\frac{d[S_1]}{dt} = k_3[S_0E] - k_4[S_1][E] + k_5[S_1E] + l_3[S_2F] + l_5[S_1F] - l_4[S_1][F]$$

X $$\frac{d[E]}{dt} = (k_2 + k_3)[S_0E] + (k_5 + k_6)[S_1E] - k_1[S_0][E] - k_4[S_1][E]$$

X $$\frac{d[F]}{dt} = (l_2 + l_3)[S_2F] + (l_5 + l_6)[S_1F] - l_1[S_2][F] - l_4[S_1][F]$$

$$\varepsilon\frac{d[\widetilde{S_0E}]}{d\tau} = k_1[S_0][\widetilde{E}] - (k_2 + k_3)[\widetilde{S_0E}] - k_7[\widetilde{S_0E}]$$

$$\varepsilon\frac{d[\widetilde{S_1E}]}{d\tau} = k_4[S_1][\widetilde{E}] - (k_5 + k_6)[\widetilde{S_1E}] + k_7[\widetilde{S_0E}]$$

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Michaelis-Menten Approximation of ODEs

$$\frac{d[S_0]}{d\tau} = \frac{(a_1[S_1] + a_2[S_2])[\widetilde{F_T}]}{1 + c_2[S_1] + d_2[S_2]} - \frac{a_3[S_0][\widetilde{E_T}]}{1 + b_1[S_0] + c_1[S_1]}$$

$$\frac{d[S_2]}{d\tau} = \frac{(a_4[S_1] + a_5[S_0])[\widetilde{E_T}]}{1 + b_1[S_0] + c_1[S_1]} - \frac{a_6[S_2][\widetilde{F_T}]}{1 + c_2[S_1] + d_2[S_2]}$$

$$[S_1] = S_T - [S_0] - [S_2]$$

$$b_1 = \frac{k_1(k_5 + k_6 + k_7)}{(k_2 + k_3 + k_7)(k_5 + k_6)}$$

$$c_1 = \frac{k_4}{k_5 + k_6}$$

$$a_1 = \frac{l_4 l_6}{l_5 + l_6}$$

$$a_2 = \frac{l_1 l_6 l_7}{(l_2 + l_3 + l_7)(l_5 + l_6)}$$

$$a_3 = \frac{k_1(k_3 + k_7)}{(k_2 + k_3 + k_7)}$$

$$d_1 = \frac{l_1(l_5 + l_6 + l_7)}{(l_2 + l_3 + l_7)(l_5 + l_6)}$$

$$c_2 = \frac{l_4}{l_5 + l_6}$$

$$a_4 = \frac{k_4 k_6}{k_5 + k_6}$$

$$a_5 = \frac{k_1 k_6 k_7}{(k_2 + k_3 + k_7)(k_5 + k_6)}$$

$$a_6 = \frac{l_1(l_3 + l_7)}{(l_2 + l_3 + l_7)}$$

Dulac's Criterion

$$f([S_0],[S_2]) = \frac{d[S_0]}{d\tau} = \frac{(a_1[S_1] + a_2[S_2])[\widetilde{F_T}]}{1 + c_2[S_1] + d_2[S_2]} - \frac{a_3[S_0][\widetilde{E_T}]}{1 + b_1[S_0] + c_1[S_1]}$$

$$g([S_0],[S_2]) = \frac{d[S_2]}{d\tau} = \frac{(a_4[S_1] + a_5[S_0])[\widetilde{E_T}]}{1 + b_1[S_0] + c_1[S_1]} - \frac{a_6[S_2][\widetilde{F_T}]}{1 + c_2[S_1] + d_2[S_2]}$$

Theorem (Dulac)

If the sign of

$$\frac{df}{d[S_0]} + \frac{dg}{d[S_2]}$$

does not change across a simply connected domain in $\mathbb{R}^2$*, the system does not exhibit oscillations in the domain.*

Results

Theorem (T.)

In order for the reduced system to exhibit oscillations, one of the following must be true:

$$(a_5 c_1 - a_4 b_1 - a_3 c_1) S_T \geq a_3 + a_4$$

$$(a_2 c_2 - a_1 d_1 - a_6 c_2) S_T \geq a_1 + a_6$$

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Corollary

The MM approximation of the distributive model does not have oscillations, as shown earlier by Bozeman & Morales (2016) and Wang & Sontag (2008).

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Corollary

The MM approximation of the mixed-mechanism model does not have oscillations.

$$S_0 + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S_0 E \xrightarrow{k_3} S_1 + E \underset{k_5}{\overset{k_4}{\rightleftharpoons}} S_1 E \xrightarrow{k_6} S_2 + E$$

$$S_2 + F \underset{l_2}{\overset{l_1}{\rightleftharpoons}} S_2 F \xrightarrow{l_7} S_1 F \xrightarrow{l_6} S_0 + F$$

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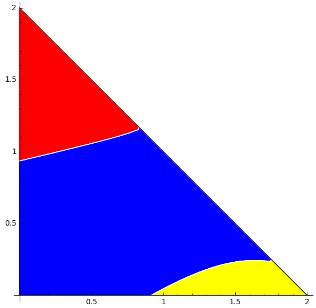

Blue	↗
Red	↘
Yellow	↖
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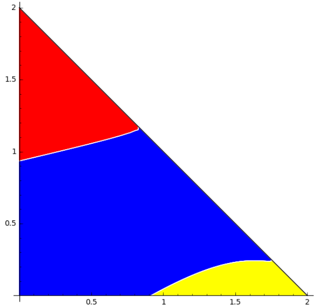

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Possible proof from Wang & Sontag's approach (monotone systems theory)

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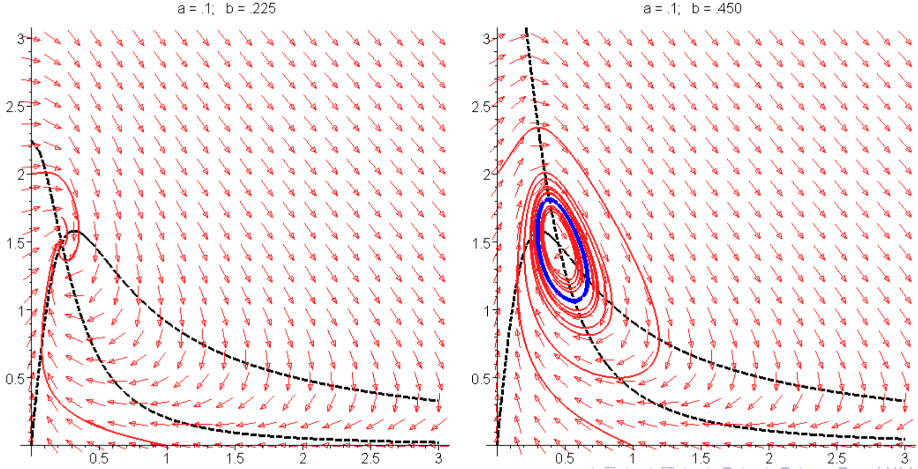
Hopf Bifurcations:

- Equilibrium changes stability type when parameters are changed
- Implies existence of oscillations generally
- Routh-Hurwitz Criterion gives necessary conditions for Hopf bifurcation

Future Directions: Does MM approx ever oscillate?

Ex: Selkov model

$$\frac{dx}{dt} = -x + ay + x^2 y$$
$$\frac{dy}{dt} = b - ay - x^2 y$$



Future Directions: Issues with MM Approximation

Networks	Can Oscillate	MM Approx Can Oscillate
Distributive	Unknown	No
Processive	No	No
Mixed-Mechanism	Yes	No

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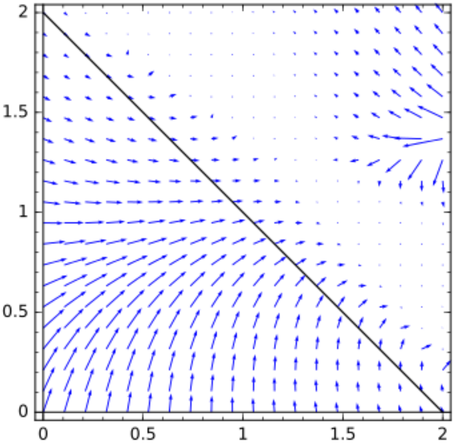

Conservation law $S_T \geq S_0 + S_2$ is violated.

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- Future Directions
  - Monotone Systems Theory if you think no oscillations
  - Hopf Bifurcations if you think there are oscillations
  - When does Michaelis-Menten Approximation preserve oscillations?

Thanks for Listening!

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