Math 609:
Mathematical Methods for Systems Biology
Guest Lecture

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Tuesday, May 6, 2014
1. Basic Enzyme Model
   - Set-up
   - Properties
   - Numerical Simulation
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2 Futile Cycle (Single Equilibrium)
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Basic Michaelis-Menten Enzyme Model is

\[
S + E \overset{k_1^+}{\underset{k_1^-}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} P + E
\]

where

1. \(S\) is a \textbf{substrate} (e.g. unphosphorylated protein)
2. \(E\) is an \textbf{enzyme}
3. \(C\) is an \textbf{intermediate compound} (really, \(C = SE\))
4. \(P\) is a \textbf{product} (e.g. phosphorylated protein)
5. \(k_1^+\), \(k_1^-\), and \(k_2\) are (positive) \textbf{rate constants}
Dynamics \textbf{(mass-action model)} given by:

\begin{align*}
\dot{s} &= -k_1^+ s \cdot e + k_1^- c \\
\dot{e} &= -k_1^+ s \cdot e + (k_1^- + k_2)c \\
\dot{c} &= k_1^+ s \cdot e - (k_1^- + k_2)c \\
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\end{align*}
\]

where \(s = [S]\), \(e = [E]\), \(c = [C]\), and \(p = [P]\).

**Distressing observation**: system is 4-dimensional and has undetermined parameters. :-(
What properties can we use to analyse this model?
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There are two conservation laws:

1. \[ \dot{s} + \dot{c} + \dot{p} = 0 \implies s(t) + c(t) + p(t) = \text{constant}. \]
2. \[ \dot{e} + \dot{c} = 0 \implies e(t) + c(t) = \text{constant}. \]
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Relevant dynamics are on 2-dimensional subspace of the original 4-dimensional space. (Variable substitution.)
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Quasi-steady state approximation may further reduce system to 1-dimensional space. (But with some loss of information.)
Alternative view on conservation relations...
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Each reaction gives a **reaction vector**—a net push of each reaction in the state space of the concentrations.
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For this example, we have

<table>
<thead>
<tr>
<th></th>
<th>$S + E \rightarrow C$</th>
<th>$C \rightarrow S + E$</th>
<th>$C \rightarrow P + E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S$</td>
<td>$[-1]$</td>
<td>$[1]$</td>
<td>$[0]$</td>
</tr>
<tr>
<td>$E$</td>
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These vectors span a 2-dimensional subspace of the concentration space called the **stoichiometric subspace** (notationally, $S$).
Divides state space into **stoichiometric compatibility classes** \( x_0 + S \) (different example pictured below):
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Roughly, more “stuff” gives a higher compatibility class (since “stuff” is usually conserved)
Without simplification, what is the long-term behavior of the system?
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Network structure (and intuition) dictates that $S$ is converted into $P$ (in some limiting way).
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**Network structure** (and intuition) dictates that $S$ is converted into $P$ (in some limiting way).

**Mathematically**, we have that

\[
\dot{s} + \dot{c} = -k_2 c < 0 \\
\dot{p} = k_2 c > 0.
\]

That is, we lose $S$ and $C$ to $P$ as time passes.
Figure: Numerical simulation of simple Enzyme model
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Consider now the **Goldbeter-Koshland model** (also called the futile cycle):

\[
S + E \overset{k_1^+}{\underset{k_1^-}{\rightleftharpoons}} C_1 \overset{k_2}{\rightarrow} P + E
\]

\[
P + F \overset{k_3^+}{\underset{k_3^-}{\rightleftharpoons}} C_2 \overset{k_4}{\rightarrow} S + F
\]
Consider now the **Goldbeter-Koshland model** (also called the **futile cycle**):

\[
S + E \xrightleftharpoons[k^-_1]{k^+_1} C_1 \xrightarrow[k_2]{k^+_2} P + E \\
P + F \xrightleftharpoons[k^-_3]{k^+_3} C_2 \xrightarrow[k_4]{k^-_4} S + F
\]

Notice that **different enzymes** catalyze the forward and backward directions!
Dynamics (mass-action model) given by:

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\begin{align*}
\dot{s} &= -k_1^+ s \cdot e + k_1^- c_1 + k_4 c_2 \\
\dot{e} &= -k_1^+ s \cdot e + (k_1^- + k_2) c_1 \\
\dot{c}_1 &= k_1^+ s \cdot e - (k_1^- + k_2) c_1 \\
\dot{p} &= k_2 c_1 - k_3^+ p \cdot f + k_3^- c_2 \\
\dot{f} &= -k_3^+ p \cdot f + (k_3^- + k_4) c_2 \\
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\end{align*}
\]

6-dimensional system with 6 undetermined parameters. Ack!
How can we **simplify** this model?
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Three **conservation laws**:

1. \( \dot{s} + \dot{c}_1 + \dot{c}_2 + \dot{p} = 0 \)  
   \[ \Rightarrow s(t) + c_1(t) + c_2(t) + p(t) = \text{constant}. \]

2. \( \dot{e} + \dot{c}_1 = 0 \)  
   \[ \Rightarrow e(t) + c_1(t) = \text{constant}. \]

3. \( \dot{f} + \dot{c}_2 = 0 \)  
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Reduces system to **3-dimensional system**.
How can we *simplify* this model?

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First component: \( S \rightarrow P \)
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\( \implies \) **Dynamic balance** should be struck!
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Questions:

1. Is this point of balance **unique**?
2. Is this point **attracting**?
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$\implies$ **Dynamic balance** should be struck!

Questions:

1. Is this point of balance unique? (Yes! [1], 2008)
2. Is this point attracting? (Yes! [1], 2008)
Figure: Two simulations of futile cycle with different initial conditions (same parameter values). Notice different transient behavior but same eventual long-term behavior.
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Generalize the model again! **(2-site phosphorylation chain):**

\[
S_0 + E \xrightleftharpoons[k_1^-]{k_1^+} C_1 \xrightarrow{k_2} S_1 + E \xrightleftharpoons[k_3^-]{k_3^+} C_2 \xrightarrow{k_4} S_2 + E
\]

\[
S_2 + F \xrightleftharpoons[k_5^-]{k_5^+} C_3 \xrightarrow{k_6} S_1 + F \xrightleftharpoons[k_7^-]{k_7^+} C_4 \xrightarrow{k_8} S_0 + F
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Imagine $S_0, S_1, S_2$ are phosphorylated substrates, $E$ is a kinase (adds phosphate group), $F$ is a phosphatase (removes phosphate group). 9 species, 12 parameters, 3 conservation laws $\Rightarrow$ large system even after simplification!
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\[ \implies \text{Dynamic balance struck?} \]

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More complicated than it appears...
For most parameter values, system \textbf{settles} to a dynamic equilibrium regardless of initial conditions.
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In general, the long-term behavior depends on:

1. The **parameter values** $k_i$, $i = 1, \ldots, r$;
2. The **initial condition** $x_0$; and
3. The **stoichiometric compatibility class** ($\text{spaces } x_0 + S$).
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In fact, there are parameter values and stoichiometric compatibility classes such that there are three equilibria, two of which are stable!
Figure: Two simulations of 2-site phosphorylation chain with two different initial conditions (same parameter values). Notice that the long-term behavior is significantly different! (Note: Only $S_0$, $S_1$, and $S_2$ shown.)

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Guest Lecture


General *n-site phosphorylation chain* known to exhibit multistationarity for all $n \geq 2$ (maximum bounded between $n$ and $2n - 1$ steady states) (Wang *et al.* [4] (2008).


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Multistationarity (i.e. existence of two asymptotically stable fixed points) still an active area of research.
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General, **no model reduction / simplification.** (Scary!)
Selected Bibliography


