Chapter 1 - Reactions

use capital letters $A, B, \ldots$ for names of chemical substances (large molecules such as proteins, or ions, etc) & corresp. lower-case $a, b, \ldots$ = concentrations

e.g. reaction: one unit of $C$ produced from one $A$ & one $B$:

$$A + B \xrightarrow{k} C$$

typical modeling assumption is (ideal) mass action:

formation rate of $C \propto$ (concentration $A$)(concentration $B$):

$$\dot{c} = \frac{dc}{dt} = k \cdot ab$$

and so $A$ and $B$ are being used-up at the same rate:

$$\dot{a} = \dot{b} = -k \cdot ab$$

collision theory; constant depends on energy needed to bind
(press to snap lego pieces), geometry of particles, etc

limitations: low numbers: e.g. 2-100 molecules in a cell

$\sim$ probabilistic models

saturation: other chemicals needed but in short supply

reversible bimolecular reaction:

$$A + B \underset{k_+}{\overset{k_-}{\rightleftharpoons}} C \quad \dot{c} = k_+ab - k_-c \quad (= -\dot{a} = -\dot{b})$$

so at steady state, and using $a + c \equiv \text{const} \equiv a_0$, will have:

$$c = \frac{k_+ab}{k_-} = a_0 \frac{b}{K_{eq} + b} \left( K_{eq} = \frac{k_-}{k_+} \text{ equilibrium const} \right)$$

(e.g. given $c(0) = 0$ and $a(0) = a_0$; and if also given $b(0) \equiv b + c$, then may solve (quadratic) for steady state)

enzymes: catalysts (proteins usually) facilitate reactions

(“substrate into product”); not changed themselves
e.g. put stress to help break a bond, or bring things together

Michaelis-Menten, 1913: basic mechanism two-step:

$$S + E \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} P + E \quad (C = \text{“complex”})$$

(ignoring reverse reaction – removal of $P$, or small rate)
full model of $S + E \xrightarrow{k_1 C} \xrightarrow{k_2} P + E$ is:

$$\dot{s} = k_{-1}c - k_1sc$$

$$\dot{c} = (k_{-1} + k_2)c - k_1sc$$

$$\dot{p} = k_2c$$

note $\dot{e} + \dot{c} \equiv 0$; so $c + e \equiv e_0$ total enzyme (bound or not) also, $p$ can be at first ignored (just integrate), so two ode’s

*quasi-steady-state approximation* is easier to deal with and explains observed “saturation” behavior ($\neq$ approx than original MM work, who assumed $\dot{s} = 0$)

*time-scale separation* is key to approximation – analyze separately what happens “slowly” vs “quickly”

next we’ll spend some time with this, since similar arguments will occur over and over

similarly, $y(t) =$

$$\frac{1}{2\varepsilon} \left( -\frac{1}{2} \left( A + \sqrt{1 + 4\varepsilon}A + 2B\varepsilon \right) e^{(\frac{-1+\sqrt{1+4\varepsilon}}{2\varepsilon})t} \frac{1}{\sqrt{1 + 4\varepsilon}} \right. $$

$$+ \frac{1}{2} \left( A - \sqrt{1 + 4\varepsilon}A + 2B\varepsilon \right) e^{(\frac{-1-\sqrt{1+4\varepsilon}}{2\varepsilon})t}$$

$$+ \frac{1}{2} \left( A - \sqrt{1 + 4\varepsilon}A + 2B\varepsilon \right) e^{(\frac{-1+\sqrt{1+4\varepsilon}}{2\varepsilon})t}$$

$$+ \frac{1}{2} \left( A - \sqrt{1 + 4\varepsilon}A + 2B\varepsilon \right) e^{(\frac{-1-\sqrt{1+4\varepsilon}}{2\varepsilon})t}$$

drop last two terms (dominated by first two for $t$ large) $\rightsquigarrow$

$$\frac{1}{2\varepsilon} \left( -\frac{1}{2} \left( A + \sqrt{1 + 4\varepsilon}A + 2B\varepsilon \right) e^{(\frac{-1+\sqrt{1+4\varepsilon}}{2\varepsilon})t} \frac{1}{\sqrt{1 + 4\varepsilon}} \right)$$

$$- \frac{1}{2} \left( A - \sqrt{1 + 4\varepsilon}A + 2B\varepsilon \right) e^{(\frac{-1-\sqrt{1+4\varepsilon}}{2\varepsilon})t} \frac{1}{\sqrt{1 + 4\varepsilon}}$$

last is $\approx 1$, and so $y(t) \approx Ae^t$, same as $x(t)$

(large $t$; this cannot be true for $t \approx 0$, since $y(0) = B$ !) easier way to see:

\[ \dot{x} = y \]
\[ \dot{y} = (1/\varepsilon)(x - y) \]

where $\varepsilon \approx 0$, with $x(0) = A$, $y(0) = B$

the solution (thanks to Maple) is given by

$$x(t) = \frac{1}{\sqrt{1 + 4\varepsilon}} e^{(\frac{-1+\sqrt{1+4\varepsilon}}{2\varepsilon})t} \frac{1}{\sqrt{1 + 4\varepsilon}}$$

$$- \frac{1}{\sqrt{1 + 4\varepsilon}} e^{(\frac{-1-\sqrt{1+4\varepsilon}}{2\varepsilon})t} \frac{1}{\sqrt{1 + 4\varepsilon}}$$

\( y(t) \) in next slide); so using expansions:

\[ -1 + \sqrt{1 + 4\varepsilon} = 1 - \varepsilon + O(\varepsilon^2) \]

\[ -1 - \sqrt{1 + 4\varepsilon} = -\varepsilon - 1 + 1 + \varepsilon + O(\varepsilon^2) \]

have for $t$ “not small” $e^{(\frac{-1+\sqrt{1+4\varepsilon}}{2\varepsilon})t} \approx e^t$, $e^{(\frac{-1-\sqrt{1+4\varepsilon}}{2\varepsilon})t} \approx 0$

$\rightsquigarrow x(t) \approx Ae^t$

\[ \dot{x} = y \]
\[ \dot{y} = (1/\varepsilon)(x - y) \]

where $\varepsilon \approx 0$, with $x(0) = A$, $y(0) = B$

now, as $\varepsilon \approx 0$, second ODE is “fast” compared to first, so view $x(t) \equiv a$ as constant there: $\dot{y} = (1/\varepsilon)(a - y)$

thus $y(t) \to a$ very fast, i.e. $y(t) \approx x(t)$ (“$y(t)$ tracks $x(t)$”)

from the point of view of $x$, time is passing slowly, and all it sees is $y(t) \approx x(t)$

so $x$’s eqn is $\dot{x} = x$, which has solution $x(0)e^t = Ae^t$

and so, $y(t) \approx x(t) \approx Ae^t$

*singular perturbation theory* studies this rigorously
but need to be careful!

\[ \dot{x} = y \]
\[ \dot{y} = (1/\varepsilon)(x - y) \]
said: “second equation fast compared to first, so assume \( x(t) \) is constant in second equation”

but what if \( y \) large?

e.g. if \( y(0) = B = \varepsilon^{-1} \gg 1 \), then \( \dot{x}(0) = y(0) = B \) is large, so \( x \) changes fast too; in fact, \( X(t) \approx Ae^t \), but \( \approx \)

\[ A + \sqrt{1 + 4\varepsilon A + 2Be^t} \approx \frac{A + \sqrt{1 + 4\varepsilon A + 2e^t}}{2\sqrt{1 + 4\varepsilon}} \approx (A + 1)e^t \]
e.g.: \( \varepsilon = 0.01 \), \( B = 100 \), \( A = 1 \), solution (to two decimals)
is \( X(t) = 1.97e^{0.99t} - 0.97e^{-100.99t} \) vs \( X(t) = e^{0.99t} \)

\[ v = \frac{ds}{dt} = \frac{1}{\varepsilon \frac{dx}{dt}} \] and \( \frac{dx}{d\tau} = \frac{1}{\varepsilon \frac{dx}{dt}} \) leads to eqs using \( \tau \) as time:

\[ v = \frac{d}{d\tau} = [(k_{-1} + k_1 s)x - k_1 s] \]

so setting \( \varepsilon = 0 \) (think of second equation converging fast to equilibrium, too fast to be “noticed” in the time scale \( \tau \)), obtain algebraic equality \( k_1 s - (k_1 s + k_2 + k_{-1})x = 0 \), i.e.

\[ x = \frac{s}{s + K_m}, \quad K_m = \frac{k_{-1} + k_2}{k_1} \]

so (substitute and simplify) \( \frac{ds}{d\tau} = -k_2 s/(s + K_m) \), so:

\[ \dot{s} = \varepsilon \frac{d}{d\tau} = -\frac{V_{\text{max}} s}{s + K_m} \quad (V_{\text{max}} = k_2 \varepsilon) \]

and, since \( \dot{p} = k_2 c = k_2 \varepsilon x = V_{\text{max}} x \),

\[ \dot{p} = \frac{V_{\text{max}} s}{s + K_m} \quad \text{Michaelis-Menten rate of product formation} \]

\[ \dot{p} = \frac{1}{\dot{p}} = \frac{s + K_m}{V_{\text{max}} s} = \frac{1}{V_{\text{max}}} + \frac{K_m}{V_{\text{max}}} \cdot \frac{1}{s} \] (linear \( 1/\dot{p} \) vs \( 1/s \))

“Lineweaver-Burk plot” to estimate params (regression)

back to \( S + E \xrightarrow{k_{-1}} C \xrightarrow{k_2} P + E \) (\( e = e_0 - c \) & ignore \( p \)):

\[ \dot{s} = k_{-1} c - k_1 s(e_0 - c) \]
\[ \dot{c} = k_1 s(e_0 - c) - (k_{-1} + k_2)c \]

enzymes typically at concentrations \( \ll \) substrates
so assume \( e(0) = e_0 = \varepsilon \ll 1 \), so also \( c = e_0 - e \) is small

but everything else (substrate concentration, kinetic const) is “\( O(1) \)” (not too small and not too large)
(see book for more careful nondimensional analysis)

write \( x = \frac{\varepsilon}{\varepsilon} \) and express eqns in terms of \( s, x \) (instead of \( c \))

so that everything but \( \varepsilon \) is \( O(1) \) (typical \( \varepsilon \approx 10^{-7} \) to \( 10^{-2} \))

\[ \dot{s} = \varepsilon [(k_{-1} + k_1 s)x - k_1 s] \]
\[ \dot{x} = k_1 s - (k_1 s + k_{-1} + k_2)x \quad \text{(use that } \dot{x} = \dot{c}/\varepsilon) \]

so to analyze what happens for \( t \text{ large} \), let \( \tau = \varepsilon t \)
e.g. view in hours \( \tau \) instead of seconds \( t \) when \( \varepsilon = 1/3600 \)

\[ V_{\text{max}} s \]
\[ s + K_m \]

slope at \( s=0 \) is \( V_{\text{max}}/K_m \), half of max rate reached at \( s=K_m \),
asymptotic value (max reaction rate) is \( V_{\text{max}} \)
(note: orig. M&M deriv (\( \dot{s} = 0 \)) gives \( k_{-1}/k_1 \) instead of \( K_m \))

this was all obtained for slow time scale; instead,

\[ \dot{s} = \varepsilon [(k_{-1} + k_1 s)x - k_1 s] \]
\[ \dot{x} = k_1 s - (k_1 s + k_{-1} + k_2)x \]

for original time scale and \( t \) small, as \( \varepsilon \approx 0, s(t) \approx s(0) \)
for \( t \) “not large”, so in this \textit{initial layer} near time \( t = 0 \),
\[ \dot{x} = k_1 s(0) - (k_1 s(0) + k_2 + k_{-1})x \] (linear ODE, can solve)
approx. vs exact.
Schnell & Mendoza, “Closed form solution for time dependent enzyme kinetics,” J Theor Biology 1997 (187):207-212. (That paper obtains a solution for $s(t)$ using “Lambert W function” (inverse of $y e^y = x$; separation of vars) The same result can be obtained by simply asking Maple to solve the equation (!).) Graph has time scaled to $(0, 1)$

Mechanisms for Enzyme Inhibition/Activation

cellular control built from feedforward and feedback loops
enzyme activation/inhibition modulates “gain” of processes
[but also: irreversible inhibitors: poisons (e.g. nerve gases)]

size of enzyme $\gg$ size of substrate
one or more binding sites for ligands - “lock and key” fit

competitive inhibition: occupies & prevent binding
alternative: bind at effector (“regulatory” “allosteric”) site
different from active site at which catalytic activity occurs

changes shape of protein - allosteric inhibition or activation

Merriam-Webster: allosteric: “all+steric”; steric: relating to or involving the arrangement of atoms in space; = “solid” in Greek

(pic from Rick Kahn, Emory U Biochem BAHS 501, 2001)
Conformation changes due to binding also important, e.g.:

Ca\(^{2+}\) binds (at two sites) to recoverin, inducing shape change

(recoverin is a protein that acts as a calcium sensor in retinal rod cells; it controls the lifetime of photoexcited rhodopsin by inhibiting rhodopsin kinase http://www.biochemj.org/)

Allosteric Inhibition

Allosteric activation

\(K_d\) for substrate: 10 \(\mu\)M

\(K_d\) for substrate: 0.30 \(\mu\)M
**Competitive Inhibition**

\[
S + E \xrightarrow{k_1} C_1 \xrightarrow{k_2} P + E \quad I + E \xrightarrow{k_3} C_2
\]

\(C_1\) is complex as before; but catalytic reaction cannot proceed if inhibitor \(I\) bound to active site (complex \(C_2\))

\[
\dot{s} = k_{-1}c_1 - k_1se \\
\dot{e} = (k_{-1} + k_2)c_1 + k_{-3}c_2 - k_1se - k_3ie \\
\dot{c}_1 = k_1se - (k_{-1} + k_2)c_1 \\
\dot{c}_2 = k_3ie - k_{-3}c_2 \\
\dot{i} = k_{-3}c_2 - k_3ie \\
\dot{p} = k_2c_1
\]

note \(c_1 + c_2 + e \equiv e_0\) total enzyme (bound or not)
and also \(i + c_2 \equiv \text{const}\), so eliminate \(e, i\)

as earlier, first ignore \(\dot{p}\), so three ode’s

quasi-steady-state: do \(c_i = \varepsilon x_i\), \(\tau = \varepsilon t\), set \(\varepsilon = 0 \ldots \infty\)

**Allosteric Inhibition**

\[
E \xrightarrow{k_{1s}} ES \xrightarrow{k_2} P + E
\]

\[
k_{3i} \quad k_{-3} \quad k_3i \quad k_{-3}
\]

\(E I \xrightarrow{k_{1s}} E IS\)

\(EI\) denotes complex of enzyme and inhibitor, etc

shorthand: “\(EI \xrightarrow{k_{1s}} E IS\)” really means \(EI + S \xrightarrow{k_1} E IS\), etc

assuming binding of \(S\) or \(I\) to \(E\) independent

but product can only be formed (\& released) if \(I\) not there

**Homework** (#2, p.30): do q-s-s approx to obtain a formula:

\[
\dot{p} = \frac{V_{\text{max}}}{1 + i/K_i} \cdot \frac{s^2 + as + b}{s^2 + cx + d}
\]

(for some \(a = a(i), \ldots\))

so max rate (large \(s\)) goes \(\downarrow\), compared w/competitive inh

intuition: \(i\) can bind, so max throughput affected

\[
S + E \xrightarrow{k_1} C_1 \xrightarrow{k_2} P + E \\
I + E \xrightarrow{k_3} C_2
\]

\[
c_1 = \frac{K_i s}{K_m i + K_i s + K_m K_i} \\
c_2 = \frac{K_m i + K_i s + K_m K_i}{K_m i + K_i s + K_m K_i}
\]

so, using \(\dot{p} = k_2c_1\), and again with \(V_{\text{max}} = k_2\varepsilon\)

\[
\dot{p} = \frac{V_{\text{max}} s}{s + K_m (1 + i/K_i)}
\]

so the rate of production of product \(\dot{p}(t)\)

is smaller than if there had been no inhibition,
given the same amount of substrate \(s(t)\)

(smaller for \(i \gg 1, k_3 \gg 1, k_3 \ll 1\))

but for \(s \approx \infty\) still same \(\dot{p} = V_{\text{max}}\)

(“so much \(s\) that \(i\) doesn’t get chance to bind \& block”)

**Cooperativity**

if multiple binding sites in enzyme, and

binding additional substrate molecules helped by previous

(classical example: oxygen/hemoglobin)

\[
S + E \xrightarrow{k_1} C_1 \xrightarrow{k_2} P + E \\
S + C_1 \xrightarrow{k_3} C_2 \xrightarrow{k_4} P + C_1
\]

(so product can be formed from either site)

\[
\begin{align*}
\dot{s} &= k_{-1}c_1 - k_1se + k_{-3}c_2 - k_3sc_1 \\
\dot{e} &= (k_{-1} + k_2)c_1 - k_1se \\
\dot{c}_1 &= k_1se - (k_{-1} + k_2)c_1 + (k_4 + k_{-3})c_2 - k_3sc_1 \\
\dot{c}_2 &= k_3sc_1 - (k_4 + k_{-3})c_2 \\
\dot{p} &= k_2c_1 + k_4c_2
\end{align*}
\]

note \(c_1 + c_2 + e \equiv e_0\) total enzyme (bound or not)

as earlier, first ignore \(\dot{p}\), so three ode’s

quasi-steady-state: do \(c_i = \varepsilon x_i\), \(\tau = \varepsilon t\), set \(\varepsilon = 0 \ldots \infty\)
$S + E \xrightarrow{k_1} C_1 \xrightarrow{k_2} P + E \quad S + C_1 \xrightarrow{k_3} C_2 \xrightarrow{k_4} P + C_1$

$C_1 = \frac{K_2 e_s}{K_1 K_2 + K_2 s + s^2}$

$C_2 = \frac{K_1 K_2 + K_2 s + s^2}{K_1 K_2 + K_2 s + s^2}$

$\Rightarrow \dot{p} = k_2 c_1 + k_4 c_2 = \frac{(k_2 K_2 + s) e_s}{K_1 K_2 + K_2 s + s^2}$

e.g.: independent identical binding: $k_1 = 2k_3, k_3 = 2k_1, k_4 = 2k_2$

$\dot{p} = 2 \frac{k_3 e_s}{K + s} \left( K = \frac{k_3}{k_1} \right)$

twice, as expected

more interesting: if $K_2 \ll 1$ and $1 \ll K_1$ (e.g. $k_3 \gg 1, k_1 \ll 1$)

$\dot{p} = \frac{V_{max} s^2}{K_m^2 + s^2}$

$\left( K_m = K_1 K_2, \ V_{max} = k_4 e_s \right)$

experimental example of cooperativity; fits to various Hill curves that arise due to allosteric effects (which change cooperativity)

from Ian J. MacRae et al., “Induction of Positive Cooperativity by Amino Acid Replacements within the C-terminal Domain of Penicillium chrysogenum ATP Sulfurylase,” J. Biol. Chem., Vol. 275, 36303-36310, 2000

(intracellular reaction in the incorporation of inorganic sulfate into organic molecules by sulfate assimilating organisms; the allosteric effector is “PAPS”)

velocity curves of C509S vs (a) MgATP and (b) MoO$_4^{2-}$

more generally:

$\dot{p} = \frac{V_{max} s^n}{K_m^n + s^n}$

$n = “Hill \ coefficient”$

$n$ may be fractional (different limits; non-independence, etc)

experimental determination of $V_{max}, n, K_m$: observe that

$n \ln s = n \ln K_m + \ln \left( \frac{\dot{p}}{V_{max} - \dot{p}} \right)$

so plot $\ln \left( \frac{\dot{p}}{V_{max} - \dot{p}} \right)$ vs $\ln s$, look at slope & intersects

E.g. of oscillations: glycolysis

adenosine triphosphate (ATP) = “energy currency” of cell obtained by phosphorylation (adding phosphate group HPO$_4^{2-}$) to adenosine biphosphate (ADP) or monophosphate (AMP)(+2)

energy stored in the covalent bonds between phosphates:

natural repulsion of negatives needs to be overcome

–think of compressing a spring and “clicking” it on position

hydrolysis: energy released: water cleaves bond ATP $\rightarrow$ ADP

glycolysis: process whereby metabolic energy (ATP) is produced via conversion of glucose (G) to pyruvate (PYR)

process entails multiple reactions, each of which is catalyzed by its own enzyme: “the glycolytic pathway”
glucose → two GAP molecules; net gain of two ATP’s

**Why?**

physiological significance unclear; suggested possibilities:
- circadian rhythms
- facilitate alternation between biochemical pathways
- increase efficiency of glycolysis itself
- drive pulsatile secretion of insulin in pancreas
- cause arrhythmia in cardiac cells

Golgobter: *alternatively, glycolytic oscillations may be an epiphenomenon, a necessary consequence of the regulatory properties of PFK and without functional significance*

negative feedback for regulation may produce oscillations - shower temperature control example; also: current work in control theory: “Bode integral formula”

### Oscillations

damped oscillations in glycolysis reported by Duysens and Amesz [1957]

sustained oscillations:

Fig. 2.2. Sustained oscillations in an extract of the yeast *Saccharomyces carlsbergensis* utilizing trehalose as the glycolytic substrate. The slow degradation of this substrate gives rise to regular oscillations that can be maintained for more than 100 cycles (Pye, 1971). The oscillations are recorded by measuring the fluorescence of the glycolytic intermediate, NADH.

simplified model (Sel’kov 68; mod: Goldbeter & Lefever 72)

step: phosphofructokinase (PFK) catalyzes conversion of fructose-6-phosphate (F6P) to fructose-1, 6-diphosphate (FDP)

will assume that PFK (enzyme) works as catalyst when in “active” form PFK* (bound with $\gamma$ molecules of ADP)

(in fact: there is allosteric inhibition of PFK by ATP, which is in turn removed by AMP, but since $2\text{ADP} \leftrightarrow \text{ATP}+\text{AMP}$, and AMP removes the ATP from the PFK allosteric site, same effect)

$\gamma\text{ADP}+\text{PFK} \rightleftharpoons \text{PFK}^*$

$\text{ATP}+\text{PFK}^* \rightleftharpoons C \overset{k_2}{\longrightarrow} \text{ADP}+\text{PFK}^*$

and also constant supply $\nu_1\text{ATP}$ and removal of ADP

conservation of total enzyme $\varepsilon \ll 1$, nondimensionalize, etc (in book, $E=\text{PFK}, ES_2^*=\text{PFK}^*, \ S_1=\text{ATP}, \ S_2=\text{ADP}, \ S_1ES_2^*=C$)
Applying the law of mass action to the Sel'kov kinetic scheme, we find five differential equations for the production of the five species $s_1 = [S_1], s_2 = [S_2], e = [E], s_3 = [ES]^2, s_4 = [ES]^3$:

\[
\begin{align*}
\frac{ds_1}{dt} &= s_1 - k_{11}s_1 + k_{12}s_2, \\
\frac{ds_2}{dt} &= k_{21}s_2 - k_{22}s_2 + k_{23}s_1 - v_2s_2, \\
\frac{ds_3}{dt} &= k_{32}s_2 + (k_{11} + k_{12})s_2 + k_{34}e - k_{32}s_1, \\
\frac{ds_4}{dt} &= k_{43}s_1 - (k_{31} + k_{32})s_2.
\end{align*}
\]

The fifth differential equation is not necessary, because the total available enzyme is conserved, $e + s_1 + s_2 = e_0$. Now we introduce dimensionless variables $\sigma_1 = \frac{s_1}{e_0}, \sigma_2 = \frac{s_2}{e_0}$, $\tau = \frac{t}{e_0}$, and find

\[
\begin{align*}
\frac{d\sigma_1}{d\tau} &= \nu - 1 + k_{12}\sigma_1 + k_{21}\sigma_2, \\
\frac{d\sigma_2}{d\tau} &= \alpha\left(1 - \sigma_1 - \sigma_2\right) + \frac{1}{2}k_{12}\sigma_1 - \frac{1}{2}k_{21}\sigma_2, \\
\frac{d\sigma_1}{d\tau} &= \sigma_1\sigma_2, \\
\frac{d\sigma_2}{d\tau} &= \sigma_2 - \sigma_1 - \sigma_2.
\end{align*}
\]

where $\nu = \frac{k_{12}s_1}{k_{11}s_1 + k_{12}s_2}, \alpha = \frac{k_{21}s_2}{k_{22}s_2 + k_{23}s_1}$.

The solution for (nondimensionalized) ATP and ADP concentrations, resp.:

\[
\begin{align*}
\dot{\sigma}_1 &= \nu - f(\sigma_1, \sigma_2) \quad (0 \leq \nu \leq 1), \\
\dot{\sigma}_2 &= \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2
\end{align*}
\]

where

\[
f(\sigma_1, \sigma_2) = \frac{\sigma_1 \sigma_2}{\sigma_1 + \sigma_2 + 1}
\]

see separate file: find nullclines and steady state linearize at steady-state; char eqn = $\lambda^2 - H + \text{positive}$ so stable if $H < 0$, unstable if $H > 0$

at $H = 0$ have imaginary roots; with a little more work: supercritical Hopf bifurcation (small periodic orbit)

$H(0) \equiv \eta(\gamma - 1) > 0$ provided $\gamma > 1$ & $H(1) = -\eta < 0$

so $\exists$ switch (periodic orbit for parameters $< \text{bifurcation}$) ($\nu$ small if e.g. $k_2$ large, so lots of ADP produced, or $\nu_1$ small (little ATP produced) – “positive feedback” effect larger

Goldbeter-Lefever model: better agreement with experiments: two bifurcation points. See Golbeter’s book for many examples!

Suggested problems:

- page 30, problem 1
- page 30, problem 2
- page 31, problem 4, parts (a) and (b)
- page 31, problem 5
- page 31, problem 7
- a bit harder(?): page 32, problem 10; also page 31, problem 6