Math Systems Biology
Slides to accompany lecture notes

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Outline

Modeling, Growth, Number of Parameters
Steady States and Linearized Stability Analysis
More Modeling Examples
Geometric Analysis: Vector Fields, Phase Planes
Epidemiology: SIRS Model
Chemical Kinetics
Enzymatic Reactions, QSS
Other enzyme actions, cooperativity, sigmoidal responses
Multi-Stability
Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
Exponential Growth: Modeling

\[ N(t) = \text{population of (e.g.) microorganism in culture, at time } t \]

\[ g(N(t), h) := N(t + h) - N(t) \]

expand

\[ g(N, h) = a + bN + ch + eN^2 + fh^2 + KNh + \text{terms of higher order} \]

since \( g(0, h) \equiv 0 \) and \( g(N, 0) \equiv 0 \):

\[ g(N, h) = KNh + \text{terms of higher order} \]

hence, for \( h \) and \( N \) small:

\[ N(t + h) = N(t) + KN(t)h \]

not true for large \( h \) ("compounding" effects)
may or may not be true for large \( N \)
explore mathematical consequences and generate predictions to be experimentally validated... iterate modeling...
Exponential Growth: Math

\[ KN(t)h = N(t + h) - N(t) \Rightarrow KN(t) = \frac{1}{h} \left( N(t + h) - N(t) \right) \]

taking \( h \to 0: \]

\[ \frac{dN}{dt} = KN \]

solve by separation of variables:

\[ \frac{dN}{N} = Kdt \Rightarrow \int \frac{dN}{N} = \int K \, dt \Rightarrow \ln N = Kt + c \]

so:

\[ N(t) = N_0 e^{Kt} \] (exponential growth: Malthus, 1798)

e.g. bacterial population, so long as enough nutrient available
suppose populations $N > B$ not sustainable, i.e.: $dN/dt < 0$ whenever $N = N(t) > B$:

$(B = \text{carrying capacity of the environment})$

reasonable to pick simplest such function, a parabola:

\[
\frac{dN}{dt} = rN \left(1 - \frac{N}{B}\right) \quad \text{(for some constant } r > 0)\]

or alternatively (less arbitrary!):
Justification of logistic growth via substrate consumption

if growth rate “$K$” depends on availability of a nutrient:

$K = K(C) = K(0) + \kappa C + o(C) \approx \kappa C \quad \text{(using that } K(0) = 0)$

$C = C(t) =$ amount of nutrient, depleted $\propto$ population change:

$$\frac{dC}{dt} = -\alpha \frac{dN}{dt} = -\alpha KN$$

(ignores nutrient depletion due to growth; better $N(t) =$ biomass)

$$\frac{d}{dt}(C + \alpha N) = \frac{dC}{dt} + \alpha \frac{dN}{dt} = -\alpha KN + \alpha KN = 0$$

$\Rightarrow \quad C(t) + \alpha N(t) \equiv C_0 \quad \text{(example of “conservation law”)}$

$\therefore K = \kappa C = \kappa(C_0 - \alpha N) \Rightarrow \text{again, } \frac{dN}{dt} = \kappa \left( C_0 - \alpha N \right) N$
Logistic Equation: Math

\[
\frac{dN}{dt} = rN \left(1 - \frac{N}{B}\right) = r \frac{N(B - N)}{B}
\]

by separation of vars:

\[
\int \frac{B \, dN}{N(B - N)} = \int r \, dt
\]

and compute integral using partial fractions:

\[
\int \left( \frac{1}{N} + \frac{1}{B - N} \right) \, dN = \int r \, dt \Rightarrow \ln \left( \frac{N}{B - N} \right) = rt + c
\]

\[
\Rightarrow \frac{N}{B - N} = \tilde{c} e^{rt} \quad \Rightarrow \quad N(t) = \frac{\tilde{c}B}{\tilde{c} + e^{-rt}} \quad \Rightarrow \quad \tilde{c} = \frac{N_0}{(B - N_0)}
\]

\[
N(t) = \frac{N_0 B}{N_0 + (B - N_0)e^{-rt}}
\]
G.F. Gause carried out experiments in 1934, involving Paramecium caudatum and Paramecium aurelia, which show clearly logistic growth:

(\# \text{ individuals and volume of P. caudatum and P. aurelia, cultivated separately, medium changed daily, 25 days.})
we solved and graphed for special values of parameters $C_0, \kappa, \alpha$:

$$\frac{dN}{dt} = \kappa (C_0 - \alpha N) N$$

does qualitative behavior of sols depend upon numbers $C_0, \kappa, \alpha$?

first of all, notice could collect terms:

$$\frac{dN}{dt} = ((\kappa C_0) - (\kappa \alpha)N) N = \left(\tilde{C}_0 - \tilde{\alpha}N\right)N$$

so might as well suppose $\kappa = 1$ (but change $\alpha, C_0$)

but can do much better, eliminating all params!: 
Outline of method

suppose $N(t)$ is any solution of

$$\frac{dN}{dt} = f(t, N(t))$$

(allow even explicit dependence of $f$ on $t$)

introduce a new function $N^*$

that depends on new time variable $t^*$:

$$N^*(t^*) := \frac{1}{\hat{N}} N(t^* \hat{t})$$

where $\hat{N}$ and $\hat{t}$ are two constants to be picked
so equations end up having fewer parameters

chain rule:

$$\frac{dN^*}{dt^*}(t^*) = \frac{\hat{t}}{\hat{N}} \frac{dN}{dt}(t^* \hat{t}) = \frac{\hat{t}}{\hat{N}} f(t^* \hat{t}, N(t^* \hat{t}))$$

(“$dN/dt(t^* \hat{t})$” is just “$N'(t^* \hat{t})$”; “$t$” is dummy variable)
Outline of method, ctd’

\[
\frac{dN^*}{dt^*}(t^*) = \frac{\hat{t}}{\hat{N}} \frac{dN}{dt}(t^*\hat{t}) = \frac{\hat{t}}{\hat{N}} f(t^*\hat{t}, N(t^*\hat{t}))
\]

but we get the same result if we just write formally:

\[
\begin{align*}
\text{“} \quad \frac{dN}{dt} &= \frac{d(N^* \hat{N})}{d(t^*\hat{t})} = \frac{\hat{N}}{\hat{t}} \frac{dN^*}{dt^*} \text{”}
\end{align*}
\]

general strategy:

- write each variable (in this example, \(N\) and \(t\)) as product of a new variable and a still-to-be-determined constant
- substitute into the equations, simplify, and collect terms
- finally, pick values for constants so that the equations have as few remaining parameters as possible

procedure can be done in many ways, so different solutions!
Method applied to above example

start by writing: \( N = N^* \hat{N} \) and \( t = t^* \hat{t} \)

where stars = new variables, and hatted constants to be chosen purely formally, substitute these into ODE:

\[
\frac{d \left( N^* \hat{N} \right)}{d \left( t^* \hat{t} \right)} = \kappa \left( C_0 - \alpha N^* \hat{N} \right) N^* \hat{N}
\]

\[
\Rightarrow \quad \hat{N} \frac{dN^*}{\hat{t} \ dt^*} = \kappa \left( C_0 - \alpha N^* \hat{N} \right) N^* \hat{N}
\]

\[
\Rightarrow \quad \frac{dN^*}{dt^*} = \kappa \hat{t} \alpha \hat{N} \left( \frac{C_0}{\alpha \hat{N}} - N^* \right) N^*
\]

we’d like to make: \( \frac{C_0}{\alpha \hat{N}} = 1 \) and \( \kappa \hat{t} \alpha \hat{N} = 1 \); can be done!!

just pick: \( \hat{N} := \frac{C_0}{\alpha} \) and \( \hat{t} = \frac{1}{\kappa \alpha \hat{N}} \), that is: \( \hat{t} := \frac{1}{\kappa C_0} \)

\[
\sim \quad \frac{dN^*}{dt^*} = \left( 1 - N^* \right) N^* \quad \text{or, drop stars, write} \quad \frac{dN}{dt} = \left( 1 - N \right) N
\]
But remember new “$N, t$” are rescaled versions of old ones!

recall “$\hat{N} \hat{N}^*$” is short for $N(t) = \hat{N} \hat{N}^*(t^*)$ and $t = t^* \hat{t}$, so

$$N(t) = \hat{N} \hat{N}^* \left( \frac{t}{\hat{t}} \right)$$

formula allows us to recover solution $N(t)$ of original problem from solution to the problem in the $N^*, t^*$ coordinates so may:

1. solve the equation
   \[
   \frac{dN}{dt} = (1 - N) N
   \]
2. plot its solution
3. interpret plot in original vars as “stretching” of plot in new vars concretely, in our example:

$$N(t) = \frac{C_0}{\alpha} \hat{N}^* (\kappa C_0 t)$$

think of $N^*, t^*$ as quantity & time in new units of measurement procedure related to “nondimensionalization” of equations
A More Interesting Example: the Chemostat

\[ V = \text{constant volume of solution in culture chamber} \]
\[ F = \text{(constant and equal) flows in vol/sec, e.g. } m^3/s \]
\[ N(t) = \text{bacterial concentration in mass/vol, e.g. } g/m^3 \]
\[ C_0, C(t) = \text{nutrient concentrations in mass/vol (} C_0 \text{ constant)} \]

chamber well-mixed ("continuously stirred tank reactor (CSTR)")
Modeling assumptions

same as in second derivation of logistic growth:

- growth of biomass in each unit of volume proportional to population (and to interval length), and depends on amount of nutrient in that volume:

\[ N(t + \Delta t) - N(t) \text{ due to growth} = K(C(t)) N(t) \Delta t \]

(function \( K(C) \) discussed below)

- consumption of nutrient per unit volume proportional to increase of bacterial population:

\[ C(t + \Delta t) - C(t) \text{ due to consumption} = - \alpha \left[ N(t + \Delta t) - N(t) \right] \]
total biomass: \( N(t) V \)
total nutrient in culture chamber: \( C(t) V \)

*biomass change in interval \( \Delta t \) due to growth:*

\[
N(t+\Delta t) V - N(t) V = [N(t+\Delta t) - N(t)] V = K(C(t)) N(t) \Delta t V
\]

so contribution to \( d(NV)/dt \) is “\(+K(C)NV\)”

*bacterial mass in effluent:*
in a small interval \( \Delta t \), the volume out is: \( F \cdot \Delta t \left( \frac{m^3}{s} \right) = m^3 \)

so, since concentration is \( N(t) \) g/m\(^3\), mass out is: \( N(t) \cdot F \cdot \Delta t \) g

∴ contribution to \( d(NV)/dt \) is “\(-N(t)F\)”

*for \( d(CV)/dt \) equation:*

have three terms:

\(-\alpha K(C)NV \) (depletion), \(-C(t)F \) (outflow), and \(+C_0 F \) (inflow)
get system of ODE’s for $N, C$:

\[
\frac{d(NV)}{dt} = K(C)NV - NF \\
\frac{d(CV)}{dt} = -\alpha K(C)NV - CF + C_0F.
\]

or better, divide by $V$ (constant):

\[
\frac{dN}{dt} = K(C)N - NF/V \\
\frac{dC}{dt} = -\alpha K(C)N - CF/V + C_0F/V
\]
\[ K(C) = \frac{k_{\text{max}} C}{k_n + C} \]

or, in another very usual notation:

\[ \frac{V_{\text{max}} C}{K_m + C} \]

linear growth for small nutrient concentrations:

\[ K(C) \approx K(0) + K'(0)C = \frac{V_{\text{max}} C}{K_m} \]

but saturates at \( V_{\text{max}} \) as \( C \to \infty \)

(more nutrient \( \Rightarrow \) more growth, up to limits; “buffet dinner”)
Remark: “Lineweaver-Burk plot” to estimate parameters estimating of $K_m$ and $V_{\text{max}}$ from experimentally measured $K(C_i)$’s: observe:

$$\frac{1}{K(C)} = \frac{K_m + C}{V_{\text{max}} C} = \frac{1}{V_{\text{max}}} + \frac{K_m}{V_{\text{max}}} \cdot \frac{1}{C}$$

so $1/K(C)$ is a linear function of $1/C$!

so, just plot $1/K(C)$ against $1/C$ and fit line (linear regression):
write $C = C^* \hat{C}$, $N = N^* \hat{N}$, $t = t^* \hat{t}$ and substitute:

$$\begin{align*}
\frac{d(N^* \hat{N})}{d(t^* \hat{t})} &= \frac{k_{\text{max}}(C^* \hat{C})}{k_n + (C^* \hat{C})} (N^* \hat{N}) - (F/V)(N^* \hat{N}) \\
\frac{d(C^* \hat{C})}{d(t^* \hat{t})} &= -\alpha \frac{k_{\text{max}}(C^* \hat{C})}{k_n + (C^* \hat{C})} (N^* \hat{N}) - (F/V)C^* \hat{C} + (F/V)C_0 \\
\frac{dN^*}{dt^*} &= \frac{\hat{t} k_{\text{max}} C^* \hat{C}}{k_n + C^* \hat{C}} N^* - \frac{\hat{t}F}{V} N^* \\
\frac{dC^*}{dt^*} &= -\alpha \frac{\hat{t} k_{\text{max}} C^* \hat{N}}{k_n + C^* \hat{C}} N^* \hat{N} - \frac{\hat{t}F}{V} C^* + \frac{\hat{t}F}{\hat{C} V} C_0 
\end{align*}$$

or:

$$\begin{align*}
\frac{dN^*}{dt^*} &= (\hat{t} k_{\text{max}}) \frac{C^*}{k_n/\hat{C} + C^*} N^* - \frac{\hat{t}F}{V} N^* \\
\frac{dC^*}{dt^*} &= -\left(\frac{\alpha \hat{t} k_{\text{max}} \hat{N}}{\hat{C}}\right) \frac{C^*}{k_n/\hat{C} + C^*} N^* - \frac{\hat{t}F}{V} C^* + \frac{\hat{t}F}{\hat{C} V} C_0
\end{align*}$$
Now pick constants to simplify

let’s try to make \( k_n/\hat{C} = 1 \), \( \frac{\hat{t}F}{V} = 1 \), and \( \frac{\alpha \hat{t} k_{\text{max}} \hat{N}}{\hat{C}} = 1 \)
can indeed be done, if we define:
\[
\hat{C} := k_n, \quad \hat{t} := \frac{V}{F}, \quad \text{and} \quad \hat{N} := \frac{\hat{C}}{\alpha \hat{t} k_{\text{max}}} = \frac{k_n}{\alpha \hat{t} k_{\text{max}}} = \frac{k_n F}{\alpha V k_{\text{max}}}
\]

\[
\frac{dN^*}{dt^*} \sim \left( \frac{V k_{\text{max}}}{F} \right) \frac{C^*}{1 + C^*} N^* - N^*
\]
\[
\frac{dC^*}{dt^*} = -\frac{C^*}{1 + C^*} N^* - C^* + \frac{C_0}{k_n}
\]

drop stars and introduce new constants \( \alpha_1 = \left( \frac{V k_{\text{max}}}{F} \right) \), \( \alpha_2 = \frac{C_0}{k_n} \):
\[
\frac{dN}{dt} = \alpha_1 \frac{C}{1 + C} N - N
\]
\[
\frac{dC}{dt} = -\frac{C}{1 + C} N - C + \alpha_2
\]
study how behavior of chemostat depends on these two parameters (bifurcation analysis w/ $\alpha_1, \alpha_2$ as parameters)

once finished, must translate back into original vars and params:

$$N(t) = \hat{N} N^* \left( \frac{t}{\hat{t}} \right) = \frac{k_n F}{\alpha V k_{\text{max}}} N^* \left( \frac{F}{V} t \right)$$

$$C(t) = \hat{C} C^* \left( \frac{t}{\hat{t}} \right) = k_n C^* \left( \frac{F}{V} t \right)$$
since $k_{\text{max}}$ is a rate (obtained at saturation), it has units $\text{time}^{-1}$
thus, $\alpha_1$ is “dimensionless”

similarly, $k_n$ has units of concentration (since it is being added to $C$, and in fact for $C = k_n$ we obtain half of the max rate $k_{\text{max}}$)
so also $\alpha_2$ is dimensionless

dimensionless constants are a nice thing to have,
since then we can talk about their being “small” or “large”

(what does it mean to say that a person of height 2 is tall? 2 cm? 2in? 2 feet? 2 meters?)
Signs of interactions among variables

classify systems according to signs of interactions between variables

in general, but here for simplicity just two components \( x \) and \( y \)

\[
\frac{dx}{dt} = f(x, y) \\
\frac{dy}{dt} = g(x, y)
\]

could be concentrations of intracellular chemicals (proteins, . . . ) in ecology, numbers of individuals of a pair of species, etc . . . we will suppose signs of partial derivatives

\[
\frac{\partial f}{\partial y}(x, y) \quad \text{and} \quad \frac{\partial g}{\partial x}(x, y)
\]

are always \( \geq 0 \) or always \( \leq 0 \) at all \((x, y)\) of interest (e.g. \( \geq 0 \))

we do not study cases where partial derivative can change sign, as \( g(x, y) = (x - x^2)y \)

\((x = \text{nutrient needed for growth of } y, \text{toxic if overdose})\).
two nodes $X$ and $Y$, and:

- draw positive arrow $X \rightarrow Y$ if $\frac{\partial g}{\partial x}(x, y) > 0$
- blunt arrow $X \nmid Y$ (or negative $X \longrightarrow Y$) if $\frac{\partial g}{\partial x}(x, y) < 0$
- similarly backward; no arrow if partial derivative $\equiv 0$

often no need to take derivatives, e.g.:

$$f(x, y) = e^{\frac{1+x}{x^2y+e^{y}+y^2}}$$

clearly increasing $y$ makes $f$ decrease, so $Y \nmid X$
if partial derivatives are everywhere nonzero (and have constant sign),
there are three types of interactions:
Mutualism (cooperativity)

variables have positive ("activation") effects on each other’s growth rates

positive change in $A$ results in a positive change in the growth of $B$ and vice-versa

these interactions create a positive feedback on both variables

these configurations are associated to signal amplification and production of switch-like biochemical responses
Competition or mutual inhibition

variables have negative ("repression") effects on each other’s growth rates

positive change in \( A \) results in repression of growth of \( B \), and repression of \( B \) in turn enhances the growth of \( A \)

these interactions also create a positive feedback on both variables

these configurations allow systems to exhibit multiple discrete, alternative stable steady-states, thus providing a mechanism for memory

they also help in allowing sharp ("binary") responses to inputs and are important in cell decision-making (apoptosis, division, ... )
Activation-inhibition or predator-prey variables have opposite effects on each other’s growth rates, a negative feedback is created. Activation-inhibition configurations necessary for generation of periodic behaviors such as circadian rhythms or cell cycle oscillations and for tight regulation (homeostasis) of physiological variables.
cooperative systems are examples of “monotone systems”
simple example of nice theory for monotone systems:

*Theorem: there cannot be any periodic orbit in such a system*

Proof by contradiction: suppose $\exists$ counterclockwise periodic orbit

pick two points in this orbit with $\xi = x(t_0) = x(t_1), y(t_0) < y(t_1)$
as $y(t_1) > y(t_0)$, and activating, $f(\xi, y(t_1)) \geq f(\xi, y(t_0))$
so $\dot{x}(t_1) \geq \dot{x}(t_0) > 0$, contradicting $\dot{x}(t_1) < 0$!
so $\not\exists$ counterclockwise-oriented curve; same to rule out clockwise
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**Steady States and Linearized Stability Analysis**

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Epidemiology: SIRS Model

Chemical Kinetics

Enzymatic Reactions, QSS

Other enzyme actions, cooperativity, sigmoidal responses

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Geometric analysis for systems of ODE's

write eqs in vector form:

\[
\frac{dX}{dt} = F(X) \quad \text{(where } F \text{ is a vector function and } X \text{ is a vector)}
\]

vector \( X = X(t) \) has some number \( n \) of components, each of which is a function of time
write components as \( x_i \) (\( i = 1, 2, 3, \ldots, n \)), or when \( n = 2 \) or \( n = 3 \) as \( x, y \) or \( x, y, z \)
or use notations related to problem being studied, like \((N, C)\)
e.g. chemostat

\[
\frac{dX}{dt} = F(X) = \left( \begin{array}{c}
f(N, C) \\
g(N, C)
\end{array} \right)
\]

with

\[
f(N, C) = \alpha_1 \frac{C}{1 + C} N - N
\]

\[
g(N, C) = -\frac{C}{1 + C} N - C + \alpha_2.
\]
**Definition:** A *steady state* or *equilibrium* is any root of the algebraic equation

\[ F(\bar{X}) = 0 \]

(Warning: “equilibrium” in math is synonym for steady state, different from physics)

**Meaning of equilibria:**
If \( \bar{X} \) equilibrium, then constant vector \( X(t) \equiv \bar{X} \) is a solution of the system of ODE’s, because a constant has zero derivative: \( d\bar{X}/dt = 0 \), and since \( F(\bar{X}) = 0 \) by definition of equilibrium, we have that \( d\bar{X}/dt = F(\bar{X}) \)

Conversely, if a constant vector \( X(t) \equiv \bar{X} \) is a solution of \( dX(t)/dt = F(X(t)) \), then, since \( (d/dt)(X(t)) \equiv 0 \), also then \( F(\bar{X}) = 0 \) and therefore \( \bar{X} \) is an equilibrium.

So, an equilibrium is a point where the solution stays forever.

An equilibrium may be stable or unstable (pencil perfectly balanced on upright position).
Example: steady states for chemostat

\[
\begin{align*}
\alpha_1 \frac{C}{1+C} N - N & = 0 \\
- \frac{C}{1+C} N - C + \alpha_2 & = 0.
\end{align*}
\]

trick which often works for chemical and population problems, factor:

\[
\left( \alpha_1 \frac{C}{1+C} - 1 \right) N = 0
\]

so, for an equilibrium \( \bar{X} = (\bar{N}, \bar{C}) \):

either \( \bar{N} = 0 \) or \( \alpha_1 \frac{\bar{C}}{1 + \bar{C}} = 1 \)

consider each of these two possibilities separately:
Steady states, ctd

in first case, \( \bar{N} = 0 \); so substitute into:

\[
- \frac{\bar{C}}{1 + \bar{C}} \bar{N} - \bar{C} + \alpha_2 = -\bar{C} + \alpha_2 = 0
\]

conclude that \( \bar{X} = (0, \alpha_2) \)

no bacteria alive, and nutrient concentration is \( C^* = \alpha_2 = C_0/k_n \)

(i.e., \( C = k_n C^* = C_0 \))

in second case, \( \bar{C} = \frac{1}{\alpha_1 - 1} \), so second equation gives

\[
\bar{N} = \alpha_1 \left( \alpha_2 - \frac{1}{\alpha_1 - 1} \right) \text{ (check!)}
\]

so we found two equilibria:

\[
\bar{X}_1 = (0, \alpha_2) \quad \text{and} \quad \bar{X}_2 = \left( \alpha_1 \left( \alpha_2 - \frac{1}{\alpha_1 - 1} \right), \frac{1}{\alpha_1 - 1} \right)
\]

but an equilibrium is physically meaningful only if \( \bar{C} \geq 0 \) and \( \bar{N} \geq 0 \)

negative populations or concentrations, while mathematically valid, do not represent physical solutions
first steady state always well-defined in this sense but $X_2$ well-defined and makes physical sense only if:

$$\alpha_1 > 1 \quad \text{and} \quad \alpha_2 > \frac{1}{\alpha_1 - 1}$$

or equivalently:

$$\alpha_1 > 1 \quad \text{and} \quad \alpha_2(\alpha_1 - 1) > 1.$$ 

reducing parameters to just two ($\alpha_1$ and $\alpha_2$) allowed us to obtain this very elegant and compact condition but $\alpha_1, \alpha_2$ only introduced for mathematical convenience, not part of the original problem as $\hat{t} := \frac{V}{F}$, $\alpha_1 = \hat{t} k_{\text{max}} = \frac{V}{F} k_{\text{max}}$ and $\alpha_2 = \frac{\hat{t} F}{C V} C_0 = \frac{C_0}{C} = \frac{C_0}{k_n}$, conditions are:

$$k_{\text{max}} > \frac{F}{V} \quad \text{and} \quad C_0 > \frac{k_n}{\frac{V}{F} k_{\text{max}} - 1}.$$ 

first condition says roughly that maximal possible bacterial reproductive rate is larger than the tank emptying rate
analyze behavior of sols of \( \frac{dX}{dt} = F(X) \) near a steady state \( \bar{X} \):

equation for \( \hat{X} = X - \bar{X} = \text{displacement (translation)} \) relative to \( \bar{X} \)

\[
\frac{d\hat{X}}{dt} = \frac{dX}{dt} - \frac{d\bar{X}}{dt} = \frac{dX}{dt} - 0 = \frac{dX}{dt} = F(\hat{X} + \bar{X})
\]

\[
= F(\bar{X}) + F'(\bar{X})\hat{X} + o(\hat{X}) \approx A\hat{X}
\]

where \( A = F'(\bar{X}) = \text{Jacobian of } F \text{ evaluated at } \bar{X} \)

"A" depends on the particular \( \bar{X} \)

small displacements \( X \approx \bar{X} \leftrightarrow \text{small } \hat{X} \)

write just \( \frac{dX}{dt} = AX \), but remember \( X = \text{displacement from } \bar{X} \)!
Example: linearizations of chemostat

\[
\frac{d}{dt} \begin{pmatrix} N \\ C \end{pmatrix} = F(N, C) = \begin{pmatrix} \frac{\alpha_1 C}{1+C} N - N \\ -\frac{C}{1+C} N - C + \alpha_2 \end{pmatrix}
\]

so that, at any point \((N, C)\) the Jacobian \(A = F'\) of \(F\) is:

\[
\begin{pmatrix}
\alpha_1 \frac{C}{1+C} - 1 & \frac{\alpha_1 N}{(1+C)^2} \\
-\frac{C}{1+C} & -\frac{N}{(1+C)^2} - 1
\end{pmatrix}
\]

so at the point \(\bar{X}_2\), where \(\bar{C} = \frac{1}{\alpha_1-1}\), \(\bar{N} = \frac{\alpha_1(\alpha_1\alpha_2-\alpha_2-1)}{\alpha_1-1}\):

\[
\begin{pmatrix}
0 & \beta (\alpha_1 - 1) \\
-\frac{1}{\alpha_1} & \frac{\beta (\alpha_1 - 1) + \alpha_1}{\alpha_1}
\end{pmatrix}
\]

\([\beta = \alpha_2(\alpha_1 - 1) - 1]\)

**Hartman-Grobman Theorem:**

sols of \(\frac{dX}{dt} = F(X)\) look like those of \(\frac{dX}{dt} = AX\)
up to a local homeomorphism
(assuming hyperbolicity; false in general)
general solution of $\frac{dX}{dt} = AX$ is $e^{tA}X(0)$

where $e^B$ def by power series expansion: $I + B + (1/2)B^2 + \ldots$

but usually computed using similarities, leading to general solution:

$$X(t) = \sum_{i=1}^{n} c_i e^{\lambda_i t} v_i \quad Av_i = \lambda_i v_i \quad \text{eigenpairs}$$

assuming simple eigens (else, $c_i t^k e^{\lambda_i t} v_i$)

OK for complex too, using Euler:

$$e^{\lambda t} = e^{at+i bt} = e^{at} (\cos bt + i \sin bt)$$

intuition: if $X(t) = e^{\lambda t} v$ is solution, then

$$\lambda e^{\lambda t} v = \frac{dX}{dt} = e^{\lambda t} v$$

so (divide by $e^{\lambda t}$) also $Av = \lambda v$

note terms can only approach zero as $t \rightarrow +\infty$ if $\Re \lambda < 0$

complex: use $|e^{\lambda t}| = e^{at} \sqrt{(\cos bt)^2 + (\sin bt)^2} = e^{at}$
Review of (local) stability

equil $\bar{X}$ of $dX/dt = F(X)$ (locally asymptotically) stable if:

1. all solutions that start near $\bar{X}$ stay near
2. have $X(t) \to \bar{X}$ as $t \to \infty$ for all sols starting near $\bar{X}$

for linear, $2 \Rightarrow 1$ (but not in general, e.g., homoclinics) and:

asy.stability $\iff$ the real parts of all eigenvalues of $A$ are negative

linearization OK $\Rightarrow$ local a.s.

hyperbolic case (no eigens with $\Re = 0$): also converse OK

in general, if $A$ has some eigen with $\Re > 0$, then
for $dX/dt = F(X)$ $\exists$ sols that start near $\bar{X}$ but move away from $\bar{X}$.

if $A$ has eigens with $\Re = 0$: Center Manifold Theory
Local vs global stability

linearization \( \frac{dX}{dt} = AX \) at a steady state \( \bar{X} \)
says nothing about global stability

e.g. for both \( \frac{dx}{dt} = -x - x^3 \) and \( \frac{dx}{dt} = -x + x^2 \):

linearization at \( x = 0 \) is just \( \frac{dx}{dt} = -x \), which is stable

in first case, all solutions of nonlinear system also converge to zero

but in second case, false; e.g. starting at a state \( x(0) > 1 \),
solutions diverge to \( +\infty \) as \( t \to \infty \)
for $n = 2$, no need to compute eigenvalues:

| stability is equivalent to: $\text{trace } A < 0$ and $\text{det } A > 0$ |

recall: $\text{trace } A = a_{11} + a_{22} = \lambda_1 + \lambda_2$

$\text{det } A = a_{11}a_{22} - a_{12}a_{21} = \lambda_1\lambda_2$

if eigens real, then $\lambda_1\lambda_2 > 0 \Rightarrow$ same sign, so first cond says $< 0$

if eigens complex, $\lambda_1\lambda_2 = |\lambda|^2 \geq 0$ always, but $\lambda_1 + \lambda_2 = 2\Re\lambda$

for $n > 2$, can also check stability without computing eigenvalues: *Routh-Hurwitz criteria*  

(necessary, but not sufficient, that coefs of char poly positive)
assume that the positive equilibrium \( \bar{X}_2 \) exists:

\[
\alpha_1 > 1 \quad \text{and} \quad \beta = \alpha_2(\alpha_1 - 1) - 1 > 0
\]

Jacobian:

\[
A = F'(\bar{X}_2) = \begin{bmatrix}
0 & \frac{\beta (\alpha_1 - 1)}{\alpha_1} \\
-\frac{1}{\alpha_1} & -\frac{\beta (\alpha_1 - 1) + \alpha_1}{\alpha_1}
\end{bmatrix}
\]

trace negative (\( \beta > 0, \alpha_1 - 1 > 0, \alpha_1 > 0 \)), and determinant positive:

\[
\alpha_1 - 1 > 0 \quad \text{and} \quad \beta > 0 \quad \Rightarrow \quad \frac{\beta (\alpha_1 - 1)}{\alpha_1} > 0
\]

so conclude (local) stability of the positive equilibrium

if initial concentration \( X(0) \approx \bar{X}_2 \), then \( X(t) \to \bar{X}_2 \) as \( t \to \infty \)

(later see global convergence holds as well)
Chemostat: local stability of boundary equilibrium

\[ A = F'(\bar{X}_1) = \begin{pmatrix} \alpha_1 \frac{C}{1+C} - 1 & \frac{\alpha_1 N}{(1+C)^2} \\ -\frac{C}{1+C} & -\frac{N}{(1+C)^2} - 1 \end{pmatrix} \bigg|_{N=0, C=\alpha_2} \]

\[ = \begin{pmatrix} \alpha_1 \frac{\alpha_2}{1+\alpha_2} - 1 & 0 \\ -\frac{\alpha_2}{1+\alpha_2} & -1 \end{pmatrix} \]

so unstable because \( \text{det} < 0: \)

\[ 1-\alpha_1 \frac{\alpha_2}{1+\alpha_2} = \frac{1+\alpha_2 - \alpha_1 \alpha_2}{1+\alpha_2} = \frac{1+\alpha_2(1-\alpha_1)}{1+\alpha_2} = -\frac{\beta}{1+\alpha_2} < 0 \]

(turns out \( \bar{X}_1 \) is a saddle; small perturbations, where \( N(0) > 0 \), will lead away from \( \bar{X}_1 \): if even a small amount of bacteria is initially present, growth will occur)
Outline

Modeling, Growth, Number of Parameters
Steady States and Linearized Stability Analysis
More Modeling Examples
Geometric Analysis: Vector Fields, Phase Planes
Epidemiology: SIRS Model
Chemical Kinetics
Enzymatic Reactions, QSS
Other enzyme actions, cooperativity, sigmoidal responses
Multi-Stability
Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
drug (chemotherapy agent) in blood & cells in an organ

\[ V = \text{volume of blood} \]
\[ F_{\text{in}}, F_{\text{out}} = \text{blood flows} \]
\[ N(t) = \text{biomass exposed to drug} \]
\[ C_0, C(t) = \text{drug concentrations} \]

IV model; other models: \( C_0(t) \)

assume “well-mixed” — in more realistic models drug affects e.g. outside layers of tumor
key differences with the chemostat are:

▶ underlying reproduction rate
▶ but drug has an effect on the growth: “kill rate” $K(C)$
▶ outflow contains only (unused) drug, and not any cells

assuming that cells reproduce exponentially and drug consumed at rate proportional to kill rate $K(C)N$:

\[
\frac{dN}{dt} = -K(C)N + kN
\]

\[
\frac{dC}{dt} = -\alpha K(C)N - \frac{CF_{out}}{V} + \frac{C_0F_{in}}{V}
\]
Other kill/growth models (not chemostat, for simplicity)

Gompertz law (originates in actuarial science): assume

\[
\frac{dN}{dt} = CN \quad \text{[or \,} -CN]\]
\[
\frac{dC}{dt} = -\alpha C
\]

assuming growth rate goes down exponentially
hard to reach core; increasing \# resting cells; embryonic growth

\[C = ae^{-\alpha t}, \quad (d/dt) \ln N = ae^{-\alpha t}, \text{ so } \int_0^T:\]
\[\Rightarrow \ln(N(t)/N(0)) = \frac{a}{\alpha} - \frac{a}{\alpha}e^{-\alpha t}, \text{ and so}
N(t) = N(0)e^c(1-e^{-\alpha t})\]

P.W. Sullivan and S.E. Salmon.
Kinetics of tumor growth and regression in IgG multiple myeloma.
very common in pharmacology: \( \neq \) behaviors in different tissues

simplest case: two compartments, e.g. organ and circulating blood

model two-compartment case (general case is similar)
Set up of equations

\(x_1, x_2 = \text{concentrations (mass/vol) of a substance (drug, hormone, metabolite, protein, ...)}\) in compartments

\(m_1, m_2 = \text{masses}\)

\(F_{ij} = \text{flow (vol/sec) from compartment } i \text{ to compartment } j\)

in comp. \(i\), fraction \(d_i \Delta t\) of mass degrades (or consumed) in \(\Delta t\)

if also external source: \(u_1 = \text{inflow (mass/sec) into compartment 1}\)

\(m_1(t + \Delta t) - m_1(t) = -F_{12}x_1\Delta t + F_{21}x_2\Delta t - d_1m_1\Delta t + u_1\Delta t.\)

E.g. mass flowing 1 \(\rightarrow\) 2:

flow \(\times\) concentration in 1 \(\times\) time = \(\frac{\text{vol}}{\text{time}} \times \frac{\text{mass}}{\text{vol}} \times \text{time}\)

also equation for \(m_2\); divide by \(\Delta t\) and take limit as \(\tau \rightarrow 0\):
Final form of equations:

system of two linear differential equations:

\[
\frac{dm_1}{dt} = -\frac{F_{12}m_1}{V_1} + \frac{F_{21}m_2}{V_2} - d_1m_1 + u_1 \\
\frac{dm_2}{dt} = \frac{F_{12}m_1}{V_1} - \frac{F_{21}m_2}{V_2} - d_2m_2 + u_2
\]

\((x_i = m_i/V_i)\)

for the concentrations \(x_i = m_i/V_i\):

\[
\frac{dx_1}{dt} = -\frac{F_{12}}{V_1}x_1 + \frac{F_{21}}{V_1}x_2 - d_1x_1 + \frac{u_1}{V_1} \\
\frac{dx_2}{dt} = \frac{F_{12}}{V_2}x_1 - \frac{F_{21}}{V_2}x_2 - d_2x_2 + \frac{u_2}{V_2}
\]
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Enzymatic Reactions, QSS
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Bifurcations
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Neurons
view $\frac{dX}{dt} = F(X)$ as “flow” in $\mathbb{R}^n$: 

at each position $X$, $F(X) =$ vector showing direction (and speed) 

(“go with the flow” or “follow directions”) 

we draw pictures in 2d, but geometric interpretation always valid 

“zooming in” at steady states $\sim$ look at linearization $F(X) \approx AX$ 

where $A =$ Jacobian $F'(\bar{X})$ evaluated at this equilibrium 

(zooming into NON-equilibria boring: “flow box theorem”!)
1. both $\lambda_1, \lambda_2$ negative: sink (stable node)
   all trajectories approach origin, tangent to direction of eigenvectors corresponding to eigenvalue closest to zero

2. both $\lambda_1, \lambda_2$ are positive: source (unstable node)
   all trajectories go away from origin, tangent to direction of eigenvectors corresponding to eigenvalue closest to zero

3. $\lambda_1, \lambda_2$ have opposite signs: saddle
Review: linear phase planes, complex eigenvalues

\[ \lambda_i = a \pm ib \ (b \neq 0) : \]

1. \( a = 0 \): center
   solutions look like ellipses (or circles)
   to decide if clockwise or counterclockwise, just check one point
   \( x(t) \) and \( y(t) \) oscillatory

2. \( a < 0 \): spiral sink (stable spiral)
   trajectories go toward the origin while spiraling around it,
   and direction can be figured out as above;
   \( x(t) \) and \( y(t) \) damped oscillations

3. \( a > 0 \): spiral source (unstable spiral)
   trajectories go away from the origin while spiraling around it,
   and direction can be figured out as above;
   \( x(t) \) and \( y(t) \) unstable oscillations
Trace/Determinant Plane
Type of equilibria in chemostat

assuming $\alpha_1 > 1$ and $\alpha_2(\alpha_1 - 1) - 1 > 0$, so $\exists \bar{X}_2 > 0$

recall Jacobian at $\bar{X}_2 = \left( \alpha_1 \left( \alpha_2 - \frac{1}{\alpha_1 - 1} \right), \frac{1}{\alpha_1 - 1} \right)$:

$$A = F'(\bar{X}_2) = \begin{bmatrix} 0 & \frac{\beta(\alpha_1 - 1)}{\alpha_1} \\ -1 & -\frac{\beta(\alpha_1 - 1) + \alpha_1}{\alpha_1} \end{bmatrix}$$

where $\beta = \alpha_2(\alpha_1 - 1) - 1$

$$\text{tr}(A) = -1 - \Delta, \quad \text{where} \quad \Delta = \text{det}(A) = \frac{\beta(\alpha_1 - 1)}{\alpha_1} > 0$$

and therefore $\text{tr}^2 - 4\text{det} = 1 + 2\Delta + \Delta^2 - 4\Delta = (1 - \Delta)^2 > 0$,

so $\bar{X}_2$ is a stable node (assuming $\Delta \neq 1$)

if $\Delta = 1$, repeated real eigenvalues; ignore that very special case

homework: $\bar{X}_1$ is a saddle
linearization helps understand the “local” picture of flows (at hyperbolic points, to be precise)

far harder to obtain global information

how do the pictures fit together? (“connecting the dots”)

one useful technique (at least in 2d): nullclines

$x_i$-nullcline is defined as set where $\frac{dx_i}{dt} = 0$

may be the union of several curves and lines, or just one such curve

intersections of nullclines are the steady states
Nullclines for chemostat: $N$

$$F(X) = \left(\frac{f(N, C)}{g(N, C)}\right)$$

\[
\begin{align*}
  f(N, C) & = \alpha_1 \frac{C}{1 + C} N - N \\
  g(N, C) & = -\frac{C}{1 + C} N - C + \alpha_2
\end{align*}
\]

$N$-nullcline: $\alpha_1 \frac{C}{1 + C} N - N = 0$

since can factor as $N(\alpha_1 \frac{C}{1 + C} - 1) = 0$,
the $N$-nullcline is the union of a horizontal and a vertical line:

$$C = \frac{1}{\alpha_1 - 1} \quad \text{and} \quad N = 0$$

on this set, the arrows are vertical, because $dN/dt = 0$
(no movement in $N$ direction)
Nullclines for chemostat: $C$

$C$-nullcline obtained by setting $-\frac{C}{1+C} N - C + \alpha_2 = 0$

can describe a curve in any way, but in this case, simpler to solve $N = N(C)$ than $C = C(N)$:

$$N = (\alpha_2 - C) \frac{1+C}{C} = -1 - C + \frac{\alpha_2}{C} + \alpha_2.$$

_on this set, arrows are horizontal, since $dC/dt = 0$ (no movement in $C$ direction)_

note that $N(\alpha_2) = 0$ and $N(C)$ is a decreasing function of $C$ such that $\rightarrow +\infty$ as $C \searrow 0$, so obtain $C = C(N)$ by flipping along the main diagonal (dotted and dashed curves in graph)
assuming $\alpha_1 > 1$ and $\alpha_2 > 1/(\alpha_1 - 1)$
(so positive steady-state exists),
we have the two intersections:

$(0, \alpha_2)$ (saddle) and $\left(\alpha_1 \left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right), \frac{1}{\alpha_1 - 1}\right)$ (stable node)

which direction do horiz/vert arrows point (left, right, . . .)?
Directions of flow on \( N \)-nullcline

on line \( N = 0 \):

\[
\frac{dC}{dt} = -\frac{C}{1 + C} N - C + \alpha_2 = -C + \alpha_2 \begin{cases} > 0 & \text{if } C < \alpha_2 \\ < 0 & \text{if } C > \alpha_2 \end{cases}
\]

so arrows point up if \( C < \alpha_2 \) and down otherwise

on line \( C = \frac{1}{\alpha_1 - 1} \):

\[
\frac{dC}{dt} = - \frac{C}{1 + C} N - C + \alpha_2 = \alpha_2 - \frac{1}{\alpha_1 - 1} - \frac{N}{\alpha_1} \begin{cases} > 0 & \text{if } N < \alpha_1 \left( \alpha_2 - \frac{1}{\alpha_1 - 1} \right) \\ < 0 & \text{if } N > \alpha_1 \left( \alpha_2 - \frac{1}{\alpha_1 - 1} \right) \end{cases}
\]

so arrows point up if \( N < \alpha_1 \left( \alpha_2 - \frac{1}{\alpha_1 - 1} \right) \) and down otherwise
Directions of flow on C-nullcline

\[
\frac{dN}{dt} = N \left( \alpha_1 \frac{C}{1 + C} - 1 \right) \begin{cases} 
> 0 & \text{if } C > \frac{1}{\alpha_1 - 1} \\
< 0 & \text{if } C < \frac{1}{\alpha_1 - 1}
\end{cases}
\]

(as \( N \geq 0 \), sign of expression same as sign of \( \alpha_1 \frac{C}{1 + C} - 1 \))

so:
key observation: arrows *can only* reverse direction crossing a nullcline

e.g.: if $\frac{dx_1}{dt} > 0$ at A and $< 0$ at B, then A and B must be on “opposite sides” of $x_1$ nullcline:

proof: trace any path $A \sim B$ (not necessarily solution of system); as derivative $\frac{dx_1}{dt}$ at points in the path varies continuously (assuming vector field continuous), by IVT $\exists$ point in path where $\frac{dx_1}{dt} = 0$

so: the orientations of arrows remain the same on the connected components of complement of union of nullclines
Directions of flow elsewhere: chemostat

4 regions, as shown in the figure
in region 1, $\frac{dN}{dt} > 0$ and $\frac{dC}{dt} < 0$ (look at boundaries)
so the flow is “Southeast” (↘) in that region
similarly for the other three regions

arrows are just “icons” but numerical slopes will vary
(e.g. near the nullclines, arrows $\approx$ horizontal or vertical)
assuming parameters s.t. positive steady state $\bar{X}_2$ exists

already know trajectories starting near $\bar{X}_2$ converge to it (local stability)

and most trajectories starting near $\bar{X}_1$ go away from it (instability)

next, sketch a proof that, in fact, every trajectory converges to $\bar{X}_2$ (only exception: trajectories that start with $N(0) = 0$)

“global attraction” result: $\forall$ initial conditions, the chemostat will settle into the steady state $\bar{X}_2$
consider line:

\[(L) \quad N + \alpha_1 C - \alpha_1 \alpha_2 = 0\]

through points \(\bar{X}_1 = (0, \alpha_2)\) and \(\bar{X}_2 = (\alpha_1 \left( \alpha_2 - \frac{1}{\alpha_1 - 1} \right) , \frac{1}{\alpha_1 - 1})\)

note \((\alpha_1 \alpha_2, 0)\) is also in this line
claim: $L$ is invariant: solutions that start in $L$ remain in $L$

even more interesting, all trajectories converge to $L$
(except those that start with $N(0) = 0$)

for any trajectory, consider the following function:

$$z(t) = N(t) + \alpha_1 C(t) - \alpha_1 \alpha_2$$

and observe that:

$$z' = N' + \alpha_1 C' = \alpha_1 \frac{C}{1 + C} N - N + \alpha_1 \left( - \frac{C}{1 + C} N - C + \alpha_2 \right) = -z$$

which implies that $z(t) = z(0)e^{-t}$

therefore, $z(t) = 0$ for all $t > 0$, if $z(0) = 0$ (invariance),

and in general $z(t) \to 0$ as $t \to +\infty$ (solutions approach $L$)

moreover, points in the line $N + \alpha_1 C - \alpha_1 \alpha_2 = m$ are close to points in $L$ if $m$ is near zero
as $L$ invariant, and no steady states in $L$ except $\tilde{X}_1$ and $\tilde{X}_2$,
the open segment from $\tilde{X}_1$ to $\tilde{X}_2$ is a trajectory that “connects”
unstable state $\tilde{X}_1$ to stable state $\tilde{X}_2$ (*heteroclinic connection*)

we know all trajectories approach $L$, and cannot cross $L$
(uniqueness of sols)

suppose a trajectory starts, and hence remains, on top of $L$
(analogous argument if remains under $L$)
and has $N(0) > 0$

since trajectory approaches $L$, and must stay in the first quadrant
it must either converge to $\tilde{X}_2$ “from the NW”
or it will eventually enter region with the “NW arrow”
at which point it must have turned and start moving towards $\tilde{X}_2$

in summary, every trajectory converges!
Worked example: global behavior of chemostat, end
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modeling of infectious diseases: mathematical epidemiology
impact of vaccination strategies; control or eradication of diseases.

Kermack and McKendrick 1927: SIR and SIRS models
susceptibles / infected / removed (e.g. stay at home; or immune)

here only simplest ODE model
no age structure, geographical distribution

more sophisticated models:
  ▶ compartmental systems (age groups)
  ▶ PDE’s for ages and/or locations; etc
  ▶ vital dynamics
A key modeling assumption

transmission of disease only if susceptible and infective come close to each other (direct contact, sneezing, etc.) may only get infected if infective within a certain radius

for each infective individual, probability $p = \beta \Delta t$ he will happen to pass through this region in $[t, t + \Delta t]$

$\beta$ depends on size of region, how fast infectives moving, etc.

(if traveling at fixed speed, twice length of time $\Rightarrow$ double chance passing by this region)
we take $\Delta t \ll 0$, so also $p \ll 0$

prob this particular infective will not enter region: $1 - p$
assuming independence, prob no infective enters: $(1 - p)^I$
so prob some infective comes close to our susceptible:

\[ 1 - (1 - p)^I \approx 1 - (1 - pl + \binom{I}{2} p^2 + \ldots) \approx pl \quad \text{(since } p \ll 1) \]

so this particular susceptible has a prob \( pl \) of being infected since there are \( S \) of them, that the total number infected \( S \times pl \)

conclude \# new infections:

\[ I(t + \Delta t) - I(t) = pSI = \beta SI \Delta t \]

next divide by \( \Delta t \), take limits, ⇒ have a term \( \beta SI \) in \( \frac{dI}{dt} \)

similarly, term \( -\beta SI \) in \( \frac{dS}{dt} \)

basically same as mass action kinetics for chemical reactions: collisions among particles, dependent on temp (speed), shapes, etc.
Completing the model

also: fraction of I’s removed per unit of time; flow of R back into S

\( \frac{dS}{dt} = -\beta SI + \gamma R \)
\( \frac{dI}{dt} = \beta SI - \nu I \)
\( \frac{dR}{dt} = \nu I - \gamma R \)

variations: vital dynamics (birth/death rates); vaccines; etc
total population size $N = S(t) + I(t) + R(t)$ constant ($dN/dt = 0$)

conservation law; eliminate one equation, e.g. $R = N - S - I$

$\leadsto$ two dimensional system:

\[
\begin{align*}
\frac{dS}{dt} & = -\beta SI + \gamma(N - S - I) \\
\frac{dI}{dt} & = \beta SI - \nu I
\end{align*}
\]
$I$-nullcline: union of lines $I = 0$ and $S = \nu/\beta$

$S$-nullcline: curve $I = \frac{\gamma (N-S)}{S\beta + \gamma}$

steady states:

$$\bar{X}_1 = (N, 0) \text{ and } \bar{X}_2 = \left( \frac{\nu}{\beta}, \frac{\gamma (N - \frac{\nu}{\beta})}{\nu + \gamma} \right)$$

where $\bar{X}_2$ only makes physical sense if:

**“σ” or “$R_0$”** = $N\beta/\nu > 1$
Behavior depends critically on $R_0$

\[ R_0 := N\beta/\nu \]

may be interpreted as expected \# new infections per each sick person when $> 1$, infection persists, else it goes away (eventually!)

some estimated values of $R_0$ (Wikipedia Oct 2014):

<table>
<thead>
<tr>
<th>Disease</th>
<th>Transmission</th>
<th>$R_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>Airborne</td>
<td>12–18</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Airborne droplet</td>
<td>12–17</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>Saliva</td>
<td>6–7</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Airborne droplet</td>
<td>5–7</td>
</tr>
<tr>
<td>Polio</td>
<td>Fecal-oral route</td>
<td>5–7</td>
</tr>
<tr>
<td>Rubella</td>
<td>Airborne droplet</td>
<td>5–7</td>
</tr>
<tr>
<td>Mumps</td>
<td>Airborne droplet</td>
<td>4–7</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Sexual contact</td>
<td>2–5</td>
</tr>
<tr>
<td>SARS</td>
<td>Airborne droplet</td>
<td>2–5[2]</td>
</tr>
<tr>
<td>Influenza</td>
<td>Airborne droplet</td>
<td>2–3[3]</td>
</tr>
<tr>
<td>(1918 pandemic strain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ebola</td>
<td>Bodily fluids</td>
<td>1–2[4]</td>
</tr>
<tr>
<td>(2014 Ebola outbreak)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example of nullclines

$N = 2$, $\beta = 1$, $\nu = 1$, and $\gamma = 1$

$I$-nullcline is union of $I = 0$ and $S = 1$

$S$-nullcline is $I = \frac{(2-S)}{S+1}$,

equilibria are at $(2, 0)$ and $(1, 1/2)$
Linearization

\[
\text{Jacobian} = \begin{bmatrix}
  -I\beta - \gamma & -S\beta - \gamma \\
  I\beta & S\beta - \nu
\end{bmatrix}
\]

so the trace and determinant at \( \bar{X}_1 = (N, 0) \) are, respectively:

\[
\text{trace} = -\gamma + N\beta - \nu \quad \text{det} = -\gamma(N\beta - \nu)
\]

(still assuming \( R_0 = N\beta/\nu > 1 \) \( \det < 0 \Rightarrow \) saddle
\[
\bar{X}_2: \text{trace} = -I\beta - \gamma < 0 \quad \text{and det} = I\beta(\nu + \gamma) > 0 \Rightarrow \text{stable}
\]

for close enough initial conditions, assuming \( R_0 > 1 \):

\[
\# \text{ infected individuals} \rightarrow I_{\text{steady state}} = \frac{\gamma(N - \frac{\nu}{\beta})}{\nu + \gamma}
\]

**Homework problem:** (take \( \beta = \nu = \gamma = 1 \)) for what values of \( N \) does one have stable spirals and for what values does one get stable nodes, for \( \bar{X}_2 \)?
Intuitive interpretation of $R_0$

“thought experiment”: isolate group of $P$ infecteds, and allow them to recover since no susceptibles in imagined experiment, $S(t) \equiv 0$, so \[ \frac{dl}{dt} = -\nu l, \text{ so } l(t) = Pe^{-\nu t} \]
suppose $i$th individual is infected for a total of $d_i$ days

<table>
<thead>
<tr>
<th>cal. days→</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>$\ldots$</th>
<th>$d_1$</th>
<th>$\infty$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ind. 1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>$d_1$</td>
</tr>
<tr>
<td>Ind. 2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>$d_2$</td>
</tr>
<tr>
<td>Ind. 3</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>$d_3$</td>
</tr>
<tr>
<td>$\ldots$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ind. $P$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>$d_P$</td>
</tr>
</tbody>
</table>

= $l_0$ = $l_1$ = $l_2$ \ldots

clear that $d_1 + d_2 + \ldots = l_0 + l_1 + l_2 + \ldots$
(count on integer days, or hours, or some other discrete time unit)
so average number of days that individuals infected:

\[ \frac{1}{P} \sum d_i = \frac{1}{P} \sum l_i \approx \frac{1}{P} \int_0^\infty l(t) \, dt = \int_0^\infty e^{-\nu t} \, dt = \frac{1}{\nu} \]

[stochastic model: exponential r.v. for diseased time]

back to the original model: \( I(\Delta t) - I(0) \approx \beta S(0)I(0)\Delta t \)

so, starting from \( I(0) \), on time interval \( \Delta t = 1/\nu \) (average time of infection)

end up number of new infectives =

\[ \beta (N - I(0))I(0)/\nu \approx \beta NI(0)/\nu \quad \text{(assuming that } I(0) \ll N) \]

on the average, each individual infects \( (\beta NI(0)/\nu)/I(0) = R_0 \) ones

(assuming \( \nu \) is large, so that \( \Delta t \) is small)

so \( R_0 \sim \text{expected number infected by a single individual} \)
Nullcline analysis (taking $N = 2$, $\beta = 1$, $\nu = 1$, and $\gamma = 1$)

\[
\frac{dS}{dt} = -SI + 2 - S - I \\
\frac{dI}{dt} = SI - I
\]

equilibria at $(2, 0)$ and $(1, 1/2)$
$I$-nullcline = union of $I=0$ and $S=1$
on $I = 0$, $dS/dt = 2 - S$
and on $S = 1$, $dS/dt = 1 - 2I$
tells if arrows right or left
on $S$-nullcline $I = \frac{(2-S)}{S+1}$:
\[
\frac{dI}{dt} = \frac{(S - 1)(2 - S)}{S + 1}
\]
so arrows down if $S < 1$; up if $S \in (1, 2)$
Computer-generated phase-planes

physically, only initial conditions with \( I + S \leq 2 \) make sense!

right plot: modify so \( \nu = 3 \) (hence \( R_0 < 1 \))

first case: global asympt. stability (provided \( I(0) > 0 \))

second case: only one equilibrium, b/c vertical component of \( I \)-nullcline at \( S = 3/1 = 3 \), so does not intersect other nullcline

*no interior equilibrium good in this case: disease eradicated!*
Example simulation ($\beta = .003, \nu = 1, \gamma = 0.5$)

SIRS Model

start with $I=1, S=999, R=0$
solution tends to $S=333, I=222, R=445$
and stays there
Example simulation (same parameters, different initial)

SIRS Model

start with I=400, S=600, R=0
solution tends to S=333, I=222, R=445
and stays there
immunizations reduce $N$
if $N$ small, “$R_0 = N\beta/\nu > 1$” fails, so no positive steady states exist

permanently remove proportion $p$ of individuals from the population
$N \sim pN$

so vaccinating just $p > 1 - \frac{1}{R_0}$ individuals gives $(1 - p)R_0 < 1$, and hence suffices to eradicate a disease!
A Variation: STD’s

Suppose a virus can only be passed on by heterosexual sex, one must consider two separate populations, male and female.

\( S \) = susceptible males, \( S \) = susceptible females

Similarly for \( I \) and \( R \)

\[
\begin{align*}
\frac{dS}{dt} &= -\bar{\beta}SI + \bar{\gamma}R \\
\frac{dI}{dt} &= \bar{\beta}SI - \bar{\nu}I \\
\frac{dR}{dt} &= \bar{\nu}I - \bar{\gamma}R \\
\frac{dS}{dt} &= -\beta S\bar{I} + \gamma R \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I \\
\frac{dR}{dt} &= \nu I - \gamma R.
\end{align*}
\]
difficult to study, but for some STD's (especially asymptomatic) no “removeds’, and infecteds get back into susceptible population:

\[
\begin{align*}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{S}\bar{I} + \bar{\nu}\bar{I} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{S}\bar{I} - \bar{\nu}\bar{I} \\
\frac{dS}{dt} &= -\beta S\bar{I} + \nu I \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I.
\end{align*}
\]

conservation: \( \bar{N} = \bar{S}(t) + \bar{I}(t) \) and \( N = S(t) + I(t) \) (total #’s) so reduce to two ODE’s:

\[
\begin{align*}
\frac{d\bar{I}}{dt} &= \bar{\beta}(\bar{N} - \bar{I})I - \bar{\nu}\bar{I} \\
\frac{dI}{dt} &= \beta(N - I)\bar{I} - \nu I.
\end{align*}
\]
prove that there are two equilibria, \( I = \bar{I} = 0 \) and, provided that

\[
R_0 \bar{R}_0 = \left( \frac{N\beta}{\nu} \right) \left( \frac{\bar{N}\bar{\beta}}{\bar{\nu}} \right) > 1
\]

and

\[
I = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\nu/\beta + \bar{N}}
\]

\[
\bar{I} = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\bar{\nu}/\bar{\beta} + N}
\]

Furthermore, prove first equilibrium is unstable and second stable.

What vaccination strategies could be used to eradicate the disease?
A variation, “SIR”: no recovery from $R$ to $S$

$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \nu I$$
$$\frac{dR}{dt} = \nu I$$

interesting behavior
(analyze as a homework problem!)
why does $I(t)$ peak, then go down?
why is there a residual $S$?
a simulation ($\beta = .003$, $\nu = 1$):

![Graph showing the dynamics of the SIR model with no recovery from $R$ to $S$. The graph illustrates the changes in $S$, $I$, and $R$ over time.]
A variation: “SEIR” model

SIR model has no latent stage, so inappropriate for certain diseases
add “incubation period” as intermediate Susceptible $\rightarrow$ Infected
this leads to the “SEIR” model with:
“Susceptible”, “Exposed”, “Infected”, and “Removed” stages
differential equations for SEIR model:

\[
\begin{align*}
\frac{dS}{dt} &= -\beta I(t)S(t) \\
\frac{dE}{dt} &= \beta I(t)S(t) - \varepsilon E(t) \\
\frac{dl}{dt} &= \varepsilon E(t) - \nu l(t) \\
\frac{dR}{dt} &= \nu l(t)
\end{align*}
\]

$\nu$ and $\varepsilon$ interpreted as inverses of infection and incubation periods
Example of SEIR model

eexample: flu pandemic, Istanbul 2009-2010

June 2009: World Health Organization declared A/H1N1 a pandemic

from:

“A susceptible-exposed-infected-removed (SEIR) model for the 2009-2010 A/H1N1 epidemic in Istanbul”

by Funda Samanlioglu, Ayse Humeyra Bilge, Onder Ergonul (arXiv 1205.2497)
Data fit to model is quite reasonable using data from major Istanbul hospitals: medical reports, dates of hospitalization and recovery or death
parameters in the model are $I_0$, $\nu$, $\varepsilon$ and $\beta$

where $I_0$ is the percentage of people infected initially

assuming for fitting:

- number of fatalities proportional to # removed individuals
- number of hospitalizations proportional to # infections

parameters found for best fit to model:

$\nu = 0.09$, $I_0 = 10^{-7.4}$, $\varepsilon = 0.32$, $\beta = 0.585$

(mean-squared error:
10% and 2.6% to infections and fatalities respectively)
Outline

Modeling, Growth, Number of Parameters
Steady States and Linearized Stability Analysis
More Modeling Examples
Geometric Analysis: Vector Fields, Phase Planes
Epidemiology: SIRS Model

**Chemical Kinetics**

Enzymatic Reactions, QSS
Other enzyme actions, cooperativity, sigmoidal responses
Multi-Stability
Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
elementary reactions (in gas or liquid) due to collisions of particles (molecules, atoms)

particle velocity depends on temperature (higher temp ⇒ faster)

*collision theory* ∼ *law of mass action*:

*reaction rates (at constant temperature) are proportional to products of concentrations*

proportionality factor (*rate constant*) accounts for temperature,

probabilities of the right collision if molecules are near each other (collisions must happen in “right way” and with enough energy for bonds to break)

e tc.
Example

(http://www.chemguide.co.uk/physical/basicrates/introduction.html) ethene (CH\(_2\)=CH\(_2\)) and hydrogen chloride (HCl) \(\rightarrow\) chloroethane double bond between two carbons converted into single bond, a hydrogen atom gets attached to one of the carbons, and a chlorine atom to the other. The reaction can only work if the hydrogen end of the H-Cl bond approaches the carbon-carbon double bond. Any other collision between the two molecules doesn’t produce the product, since the two simply bounce off each other.
Limitations of ODE model to be derived

may not be valid if:

▶ medium not “well mixed”
▶ concentrations small (probabilistic model)
▶ catalyst required

analog: in cafeteria: \( A + B \rightarrow C \), \( A = \# \) students, \( B = \) food on counters, \( C = \) students with full tray walking away from counter

if each student may at random times pick food,
twice number of students \( \Rightarrow \) twice walking away per time unit
but, if server must hand out food (“catalyst”),
then \( \exists \) max rate at which students will leave counter,

rate determined by speed cafeteria worker can serve each student
doubling \( \# \) students \( \not\Rightarrow \) twice walk away with food per time unit
(later study some catalytic reactions)
capital $A, B, \ldots = \text{names of substances (molecules, ions, etc)}$

lower-case $a, b, \ldots = \text{concentrations (more usual: } [A], \text{etc)}$

systematic approach later, but first intuitively:

just use the mass-action principle for each; then add up effects
Single reactant

simplest “reaction”: zeroth order, formation: \( 0 \xrightarrow{k} X \)

\[ \frac{dx}{dt} = k \]

first-order, one reactant, degrade/decay/inactivate/dilute, rate of the reaction is proportional to concentration \( X \xrightarrow{k} 0 \)

\[ \frac{dx}{dt} = -kx \]

transformation \( X \xrightarrow{k} Y \) gives:

\[ \frac{dx}{dt} = -kx \]
\[ \frac{dy}{dt} = kx \]

dissociation reaction \( Z \xrightarrow{k} X + Y \) gives:

\[ \frac{dx}{dt} = kz \]
\[ \frac{dy}{dt} = kz \]
\[ \frac{dz}{dt} = -kz \]
Bimolecular reactions

\[ X + Y \xrightarrow{k_+} Z \] gives:

\[
\begin{align*}
\frac{dx}{dt} &= -k_+xy \\
\frac{dy}{dt} &= -k_+xy \\
\frac{dz}{dt} &= k_+xy
\end{align*}
\]

if reverse reaction \( Z \xleftarrow{k_-} X + Y \) also takes place:

\[
\begin{align*}
\frac{dx}{dt} &= -k_+xy + k_-z \\
\frac{dy}{dt} &= -k_+xy + k_-z \\
\frac{dz}{dt} &= k_+xy - k_-z
\end{align*}
\]

another way to symbolize that both \( X + Y \xrightarrow{k_+} Z \) and \( Z \xleftarrow{k_-} X + Y \):

\[
X + Y \xleftrightarrow[k_+]{k_-} Z.
\]
reversible bimolecular reaction that we just saw:

\[
\begin{align*}
\frac{dx}{dt} &= -k_+ xy + k_- z \\
\frac{dy}{dt} &= -k_+ xy + k_- z \\
\frac{dz}{dt} &= k_+ xy - k_- z
\end{align*}
\]

as \( d(x + z)/dt \equiv 0 \) and \( d(y + z)/dt \equiv 0 \): for every solution, there are constants \( x_0 \) and \( y_0 \) such that \( x + z \equiv x_0 \) and \( y + z \equiv y_0 \)

if these constants known (from initial conditions)

only need to study scalar first-order ODE:

\[
\frac{dz}{dt} = k_+(x_0 - z)(y_0 - z) - k_- z
\]

on \( 0 \leq z \leq \min\{x_0, y_0\} \) (equivalent to asking \( x, y, z \geq 0 \))

intersect \( u = k_- z \) \& parabola \( u = k_+(x_0 - z)(y_0 - z) \Rightarrow \) GAS state

once \( z(t) \) solved for, find \( x(t) = x_0 - z(t) \) and \( y(t) = y_0 - z(t) \)
formalism allows to easily write up ODE from diagrams like

$$2H + O \leftrightarrow H_2O$$

generally, collection of chemical reactions involving $n_s$ “species”:

$$S_i, \ i \in \{1, 2, \ldots n_s\}$$

may be ions, atoms, molecules; just say “molecules” for simplicity

e.g. above represents two reactions that involve $n_s = 3$ species:

$$S_1 = H, \ S_2 = O, \ S_3 = H_2O$$

(one going forward and one going backward)
Chemical reaction networks ("CRN")

collection of chemical reactions \( \mathcal{R}_j, j \in \{1, 2, \ldots, n_r\} \):

\[
\mathcal{R}_j : \sum_{i=1}^{n_s} \alpha_{ij} S_i \rightarrow \sum_{i=1}^{n_s} \beta_{ij} S_i
\]

\( \alpha_{ij} \)'s, \( \beta_{ij} \)'s nonnegative integers: stoichiometry coefficients

reactants = species with coefficients \( \neq 0 \) on LHS
products = on RHS
(zero coefficients not shown in diagrams)

\( \alpha_{11} \) molecules of species \( S_1 \) combine w/ \( \alpha_{21} \) molecules of species \( S_2 \)
to produce \( \beta_{11} \) molecules of species \( S_1 \), \( \beta_{21} \) molecules of species \( S_2 \),
etc.
e.g.

\[ R_1 : \ 2H + O \rightarrow H_2O \]
\[ R_2 : \ H_2O \rightarrow \ 2H + O. \]

\[ \alpha_{11} = 2, \ \alpha_{21} = 1, \ \alpha_{31} = 0, \ \beta_{11} = 0, \ \beta_{21} = 0, \ \beta_{31} = 1 \]

and

\[ \alpha_{12} = 0, \ \alpha_{22} = 0, \ \alpha_{32} = 1, \ \beta_{12} = 2, \ \beta_{22} = 1, \ \beta_{32} = 0 \]
Stoichiometry matrix

\[ n_s \times n_r \text{ matrix } \Gamma = \Gamma_{ij}: \]

\[ \Gamma_{ij} = \beta_{ij} - \alpha_{ij}, \quad i = 1, \ldots, n_s, \quad j = 1, \ldots, n_r \]

\( \Gamma \) has as many columns as there are reactions

columns show for each species (ordered according to index \( i \))
net “produced−consumed”

e.g. for \( \text{H}_2\text{O} \):

\[
\Gamma = \begin{pmatrix}
-2 & 2 \\
-1 & 1 \\
1 & -1 \\
\end{pmatrix}
\]

remark: \( A \to 0 \) allowed (all \( \beta \)'s = 0)
Dynamics

give the evolution of the vector:

\[
S(t) = \begin{pmatrix}
[S_1(t)] \\
[S_2(t)] \\
\vdots \\
[S_{ns}(t)]
\end{pmatrix}
\]

where \([S_i(t)] = \text{concentration of the species } S_i \text{ at time } t\)

drop the brackets and write \(S_i\) (or lower case) for the concentration

observe only nonnegative concentrations make physical sense

graphical information given by reaction diagrams reflected in \(\Gamma\)

need formula for rates of individual reactions \(R_i(S)\)
most common assumption is *mass-action kinetics*:

\[
R_j(S) = k_j \prod_{i=1}^{n_s} S_i^{\alpha_{ij}} \text{ for all } i = 1, \ldots, n_r
\]

reaction rate prop to products of concentrations of reactants
higher exponents when more than one molecule is needed
\(k_j\)'s = “reaction constants” labels of arrows in diagrams
vector of reactions:

\[
R(S) := \begin{pmatrix}
R_1(S) \\
R_2(S) \\
\vdots \\
R_{nr}(S)
\end{pmatrix}
\]

then ODE system is:

\[
\frac{dS}{dt} = \Gamma R(S).
\]
Example: futile cycle

\[
E + P \xrightleftharpoons[k_{-1}]{k_1} C \xrightarrow{k_2} E + Q, \quad F + Q \xrightleftharpoons[k_{-3}]{k_3} D \xrightarrow{k_4} F + P
\]

- e.g. activation of protein substrate \( P \) by enzyme \( E \);
- \( C \) = intermediate complex
- dissociates into the original components or into product (activated protein) \( Q \) and enzyme
- second reaction transforms \( Q \) back into \( P \), catalyzed by another enzyme (a phosphatase denoted by \( F \))

\[
S = \begin{pmatrix} P \\ Q \\ E \\ F \\ C \\ D \end{pmatrix}, \quad \Gamma = \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 & 1 & 0 \\ -1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 & 1 \\ 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 \end{pmatrix}, \quad R(S) = \begin{pmatrix} k_1 E P \\ k_{-1} C \\ k_2 C \\ k_3 F Q \\ k_{-3} D \\ k_4 D \end{pmatrix}
\]

write equations from these
a row vector \( c \) such that \( c\Gamma = 0 \) is a *conservation law*:

\[
\frac{d(cS)}{dt} = c \frac{dS}{dt} = c \Gamma R(S) = 0 \quad \text{for all } t, \text{ i.e.}
\]

\[
c \ S(t) = \text{constant}
\]

along all solutions ("first integral" of the motion)

set is linear subspace (of vector space of size \( n_s \) row vectors)
in previous example:

\[
P(t) + Q(t) + C(t) + D(t) \equiv \text{constant}
\]

because \((1, 1, 0, 0, 1, 1)\Gamma = 0\)

also two more linearly independent conservation laws:

namely \((0, 0, 1, 0, 1, 0)\) and \((0, 0, 0, 1, 0, 1)\), so also

\[
E(t) + C(t) \quad \text{and} \quad F(t) + D(t) \quad \text{constant along trajectories}
\]

since \( \Gamma \) has rank 3 (easy to check) and has 6 rows,

its left-nullspace has dimension three;

so basis of conservation laws given by the three found
above example symbolized by:

\[
E + S_0 \leftrightarrow ES_0 \rightarrow E + S_1 \leftrightarrow ES_1 \rightarrow E + S_2 \\
F + S_2 \leftrightarrow FS_2 \rightarrow F + S_1 \leftrightarrow FS_1 \rightarrow F + S_0
\]

‘\(ES_0=\)’ complex consisting of \(E\) bound to \(S_0\), etc
attach constants to all arrows, write ODE’s, show dim conservation laws is 3
Modeling, Growth, Number of Parameters
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More Modeling Examples
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Chemical Kinetics
**Enzymatic Reactions, QSS**
Other enzyme actions, cooperativity, sigmoidal responses
Multi-Stability
Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
catalysts facilitate reactions, converting substrates into products, while remaining basically unchanged.

think of “pliers” that place appropriate stress to help break bonds.

bring substrates together or place a chemical group on substrate.

enzymes are proteins that act as catalysts.

enzymatic reactions are one of main ways for information flow.
very important type of enzymatic reaction: *phosphorylation*: an enzyme X (a *kinase*) transfers a phosphate group (PO$_4$) from a “donor” molecule such as ATP to another protein Y, which becomes “activated” (increased energy).

Y then influences other components (perhaps itself as kinase).

proteins do not stay activated forever: (enzyme) *phosphatases* take away phosphate group so signaling is “turned off” and ready to detect new signals.
Adenosine triphosphate nucleotide is "energy currency" usually recycled in mitochondria where it is "recharged" into ATP [chloroplasts in plants; cell wall or cytosol (glycolysis), in prokaryotes] human cells contain \( \approx \) one billion ATP molecules, only sufficient for a few minutes
outside chemical and electrical signals sensed by receptors which relay info to inside cell

receptors may be viewed as enzymes: “substrate” is extracellular ligand (usually small molecule, e.g. hormone or a growth factor) and “product” is new conformation, or a small molecule (second messenger) released in response to ligand binding

this triggers signaling through a series of chemical reactions
e.f. from Hananan & Weinberg: schematics of the wiring diagram of circuitry (mammalian cells) for growth, differentiation, and apoptosis in red, some genes functionally altered in cancer cells.
More on Receptors

most receptors designed to recognize a specific type of ligand

receptors usually made up of several parts:

- extracellular domain (part of protein), where ligands bind
- transmembrane domain “anchors” receptor to cell membrane
- cytoplasmic domain initiates reactions inside cell in response to signals
special class of receptors, common target of pharmaceutical drugs: G-protein-coupled receptors (GPCR’s)

when conformation changes in response to ligand binding event activate “G”-proteins using guanine (tri/di)phosphate (GTP/GDP)

made up of subunits $G_\alpha$, $G_\beta$, $G_\gamma$

involved in detection of metabolites, odorants, hormones, neurotransmitters, light (rhodopsin, a visual pigment)
Basic differential equations for enzyme kinetics

basic elementary reaction:

\[ S + E \xrightleftharpoons[k_{-1}]{k_1} C \xrightarrow{k_2} P + E \]

so eqs for concentrations of substrate, (free) enzyme, complex (enzyme with substrate together), and product:

\[
\begin{align*}
\frac{ds}{dt} &= k_{-1}c - k_1se \\
\frac{de}{dt} &= (k_{-1} + k_2)c - k_1se \\
\frac{dc}{dt} &= k_1se - (k_{-1} + k_2)c \\
\frac{dp}{dt} &= k_2c
\end{align*}
\]

which is a 4-dimensional system
Some simplifications of basic enzyme ODE’s

last equation (product formation) doesn’t feed back into first three
so ignore it now; later, after solving for \( c(t) \), integrate and get \( p(t) \)

moreover, since \( \frac{de}{dt} + \frac{dc}{dt} \equiv 0 \), we also know that \( e + c \) is constant
write “\( e_0 \)” for this sum:

\[
e(t) + c(t) = e_0
\]

often \( c(0) = 0 \), so \( e_0 = e(0) \) = initial concentration of free enzyme
eliminate \( e \) from the equations:

\[
\begin{align*}
\frac{ds}{dt} &= k_{-1} c - k_1 s(e_0 - c) \\
\frac{dc}{dt} &= k_1 s(e_0 - c) - (k_{-1} + k_2)c
\end{align*}
\]

now down to two dimensions, so can use phase planes etc
Michaelis and Menten approximation

Leonor Michaelis and Maud Leonora Menten, 1913:

reduce the problem even further by “equilibrium approximation”: 
\[ k_{-1} c(t) - k_1 s(t) e(t) = 0 \] (assumes first reaction is in equilibrium)

hard to justify

Briggs/Haldane (1925) approach: different approximation, but final form of production rate is algebraically same (though parms have \(\neq\) interpretation in terms of reactions)

- useful when “connecting” many enzymatic reactions, overall reduction in complexity
- often hard to measure kinetic constants \((k_1, \text{etc})\) but easier to estimate parms of reduced model
Quasi-Steady State and Michaelis-Menten Reactions

\begin{align*}
\frac{ds}{dt} &= k_{-1}c - k_1s(e_0 - c) \\
\frac{dc}{dt} &= k_1s(e_0 - c) - (k_{-1} + k_2)c = k_1 \left[ se_0 - (K_m + s)c \right]
\end{align*}

where \( K_m = \frac{k_{-1} + k_2}{k_1} \)

MM approximation: set \( \frac{dc}{dt} = 0 \)

biochemical justification:

after transient period during which the free enzymes “fill up,”
amount complexed stays more or less constant

solve algebraic equation:

\[ se_0 - (K_m + s)c = 0 \quad \leadsto \quad c = \frac{se_0}{K_m + s} \]
so production rate:

\[
\frac{dp}{dt} = k_2 \; c = \frac{V_{\text{max}} \cdot s}{K_m + s}
\]

and substituting into \( s \) equation:

\[
\frac{ds}{dt} = k_{-1} \frac{s \cdot e_0}{K_m + s} - k_1 \; s \left( e_0 - \frac{s \cdot e_0}{K_m + s} \right) = -\frac{V_{\text{max}} \cdot s}{K_m + s}
\]

where \( V_{\text{max}} = k_2 \cdot e_0 \)

to show role of enzyme as “input”, write as:

\[
\frac{ds}{dt} = -e_0 \frac{k_2 \; s}{K_m + s}
\]
\[
\frac{dp}{dt} = e_0 \frac{k_2 \; s}{K_m + s}
\]
works out well in practice, but math justification flaky:

\[ \frac{dc}{dt} = 0 \Rightarrow c \text{ constant} \]

so from \( c = \frac{s e_0}{K_m+s} \Rightarrow s \) also constant

\[ \Rightarrow \text{ also } \frac{ds}{dt} = 0 \]

but then \( \frac{V_{\text{max}} s}{K_m+s} = -\frac{ds}{dt} = 0 \), which means that \( s = 0 \)

in other words, derivation can only be right if there is no substrate, i.e. no reaction is taking place at all!
better: suppose that $s$ changes much slower than $c$
so as far as $c$ is concerned, $s(t)$ looks constant
let us say $s(t) = \bar{s}$

linear eqn for $c$, converges to steady state:

\[
c = \frac{\bar{s} e_0}{K_m + \bar{s}}
\]

as $s$ changes, $c$ “catches up” very fast,
so this formula is always (approximately) valid
from “point of view” of $s$, $c$ always catching up with formula
so, as far as its slow movement is concerned, $s$ evolves according to

\[
\frac{ds}{dt} = k_{-1} \frac{s e_0}{K_m + s} - k_1 s \left( e_0 - \frac{s e_0}{K_m + s} \right) = -\frac{V_{\text{max}} s}{K_m + s}
\]

except at start, when $c(0)$ is initially far from its steady state value:
“boundary layer behavior”

“time scale analysis”: $c$’s (slow time scale) & $s$’s (fast time scale)
introduce “rescaled variables”:

\[ x = \frac{s}{s_0}, \quad y = \frac{c}{e_0}, \]

and also write \( \varepsilon := \frac{e_0}{s_0} \)

may think of \( s_0 \) as initial concentration \( s(0) \) of substrate

*assume initial concentration \( e_0 \) of enzyme \( \ll s_0 \), i.e. ratio \( \varepsilon \ll 1 \)*

would not make sense to say that “amount of enzyme is small”, because meaning of “small” depends on units

but *ratio* makes sense, if quantified all concentrations in same units

\( x, y, \varepsilon \) are “non-dimensional” variables

typical values for \( \varepsilon \): \( 10^{-7} - 10^{-2} \)
Equations in new variables

\[
\frac{ds}{dt} = k_{-1}c - k_1s(e_0 - c)
\]

\[
\frac{dc}{dt} = k_1 \left[ se_0 - (K_m + s)c \right]
\]

from \([s(t) + c(t)]' = (k_{-1} - k_1K_m)c(t) = -k_2c \leq 0,\]

if \(c(0) = 0\), then \(s(t) \leq s_0\)

and from \(e(t) + c(t) \equiv e_0\), \(c(t)\) always \(\leq e_0\)

with \(x = \frac{s}{s_0}, y = \frac{c}{e_0}, \varepsilon := \frac{e_0}{s_0}\):

\[
\frac{dx}{dt} = \varepsilon [k_{-1}y - k_1s_0x(1-y)]
\]

\[
\frac{dy}{dt} = k_1 [s_0x - (K_m + s_0x)y]
\]

and \(0 \leq x(t) \leq 1\) and \(0 \leq y(t) \leq 1\)
Nullclines

\[
\begin{align*}
\frac{dx}{dt} &= \varepsilon [k_{-1} y - k_1 s_0 x (1 - y)] \\
\frac{dy}{dt} &= k_1 [s_0 x - (K_m + s_0 x)y]
\end{align*}
\]

\(y\) nullcline is graph of:

\[y = \frac{s_0 x}{K_m + s_0 x}\]

(same as saying \(c\) nullcline is graph of \(c = \frac{se_0}{K_m + s}\))

and \(x\) nullcline is graph of:

\[y = \frac{s_0 x}{\frac{k_{-1}}{k_1} + s_0 x}\]

as \(\frac{k_{-1}}{k_1} < \frac{k_{-1} + k_2}{k_1} = K_m\), \(y\)-nullcline lies under the \(x\)-nullcline
Nullclines, ctd

\[
\begin{align*}
\frac{dx}{dt} &= \varepsilon [k_{-1} y - k_1 s_0 x (1 - y)] \\
\frac{dy}{dt} &= k_1 [s_0 x - (K_m + s_0 x)y]
\end{align*}
\]

y-nullcline lies under the x-nullcline.
and: \(\varepsilon \ll 1 \Rightarrow\) vector field \(\approx\) “vertical” if far from y-nullcline (but not close: also y component \(\approx 0\) when near y-nullcline)

so phase plane qualitatively as follows:
in fact, with
\[ s_0 = e_0 = k_- = k_{-1} = k_2 = 1: \]

generated using following MATLAB code:
```matlab
eps = 0.1; s0 = 1;
[X, Y] = meshgrid(0:0.1:1, 0:0.1:1);
z1 = eps.*(Y - s0.*X.*(1-Y)); z2 = s0.*X-((2+s0.*X).*Y);
quiver(X, Y, z1, z2, 'LineWidth', 2)
title('phase plane')
hold;
x = 0:0.1:1;
plot(x, x./(2+x), 'LineWidth', 2, 'color', 'r')
plot(x, x./(1+x), 'LineWidth', 2, 'color', 'r')```

What did we learn?

in $x, y$ coordinates, trajectories initially move almost “vertically” toward the $y$-nullcline and then stay close to nullcline

i.e. for large $t$, $c(t) \approx \frac{s(t)e_0}{K_m+s(t)}$ (MM approximation)

“$c(t) = \frac{s(t)e_0}{K_m+s(t)}$” called “quasi-steady state approximation” because it formally looks like “$dc/dt = 0$” would be like saying that $c$ component is at same value if the system were at steady state (which it really isn’t!)

more precisely mathematically, need “time scale analysis” which studies the dynamics from $c$’s point of view (slow time scale) and $s$’s (fast time scale) separately
start again from equations in $x = \frac{s}{s_0}, \ y = \frac{c}{e_0}$ coordinates:

$$\frac{dx}{dt} = \varepsilon [k_{-1} y - k_1 s_0 x (1 - y)]$$

$$\frac{dy}{dt} = k_1 [s_0 x - (K_m + s_0 x) y]$$

as $\varepsilon \approx 0$, we make approximation "$\varepsilon = 0$" and substitute $\varepsilon = 0$ so $dx/dt = 0$, which means $x(t) \equiv \bar{x}$, and second equation $\sim$

$$\frac{dc}{dt} = k_1 [e_0 \bar{s} - (K_m + \bar{s}) c]$$

($s_0 x = s \text{ and } e_0 y = c$ in terms of original vars; and $\bar{s} := s_0 \bar{x}$)

in this ODE, $c(t)$ converges as $t \to \infty$ to steady state:

$$c = \frac{e_0 \bar{s}}{K_m + \bar{s}}$$

which is also obtained by setting $dc/dt = 0$

in original equations if $s(t) \equiv \bar{s}$ assumed constant

so obtain again $\frac{dp}{dt} = k_2 \ c = \frac{V_{\text{max}} s}{K_m + s} \ (\bar{s} = \text{“present” value of } s)$
summary: if $\varepsilon \approx 0$, approximate $\varepsilon = 0 \sim dx/dt \equiv 0, x(t) \equiv \bar{x}$
but “$\varepsilon \approx 0$” not “$\varepsilon = 0$”, so $dx/dt \neq 0$ & eventually $x(t)$ changes
idea still works, but need careful time-scale separation argument

key point: $c$ approaches steady state fast relative to movement of $s$
which may be assumed constant while this convergence happens
so iterate reasoning: $s$ moves a bit, using $c$’s steady state value
then $c$ “reacts” to new value of $s$, converging to new steady state
(corresponding to new “$\bar{s}$”); repeat

but!: not true that $c$ and $s$ take turns moving:
they move simultaneously (at very different speeds)
Long-time behavior (fast time scale)

to be more precise, convenient to make a change of time scale:

\[ \tau = \frac{e_0}{s_0} k_1 t = \varepsilon k_1 t \]

think of \( \tau \) as a fast time scale: \( \tau \) small for any given \( t \)
e.g. \( \varepsilon k_1 = 1/3600 \), \( t \) measured in sec, then \( \tau = 10 \) implies \( t = 36000 \)

“\( \tau = 10 \)” is ten hours but “\( t = 10 \)” is ten seconds

substituting \( s = s_0 x \), \( c = e_0 y \), and

\[
\frac{dx}{d\tau} = \frac{1}{e_0 k_1} \frac{ds}{dt}, \quad \frac{dy}{d\tau} = \frac{s_0}{e_0^2 k_1} \frac{dc}{dt}
\]

we have:

\[
\frac{dx}{d\tau} = \frac{k_{-1}}{k_1} y - s_0 x (1 - y)
\]

\[
\varepsilon \frac{dy}{d\tau} = s_0 x - (K_m + s_0 x) y
\]
Long-time behavior (fast time scale), ctd

\[
\frac{dx}{d\tau} = \frac{k_{-1}}{k_1} y - s_0 x (1 - y)
\]

\[
\varepsilon \frac{dy}{d\tau} = s_0 x - (K_m + s_0 x)y
\]

if \(\varepsilon \ll 1\), now set \(\varepsilon = 0\) in the second equation:

\[
\varepsilon \frac{dy}{d\tau} = s_0 x - (K_m + s_0 x)y
\]

\(\sim\) algebraic equation \(s_0 x - (K_m + s_0 x)y = 0\) which we solve for \(y = y(x) = \frac{s_0 x}{K_m + s_0 x}\), or equivalently

\[
c = \frac{e_0 s}{K_m + s},
\]

and finally, substitute into the first equation:

\[
\frac{dx}{d\tau} = \frac{k_{-1}}{k_1} y - s_0 x (1 - y) = -\left(\frac{-k_{-1} + K_m k_1}{k_1(K_m + s_0 x)}\right) s_0 x = -\frac{k_2 s_0 x}{k_1(K_m + s_0 x)}
\]
in terms of original variable $s = s_0x$, using \( \frac{ds}{dt} = e_0k_1 \frac{dx}{d\tau} \), and recalling that $V_{\text{max}} = k_2e_0$, we have re-derived

\[
\frac{ds}{dt} = -\frac{V_{\text{max}}s}{K_m + s}.
\]

intuitively: after initial convergence of $c$ (or $y$) to steady state, once that $c$ has “locked into” its steady state $c = \frac{e_0s}{K_m + s}$, it quickly “catches up” with any (slow!) changes in $s$, and this catch-up is not “visible” at the time scale $\tau$, so $c$ appears to track the expression above.
short initial-time behavior (slow time scale)

special case: small initial times $t$, when $c$ (or $y$) has not yet converged to a steady state for $t \approx 0$, we may assume that $\bar{s} = s_0$, and therefore the equation for $c$ is approximated by:

$$\frac{dc}{dt} = k_1 [e_0 s_0 - (K_m + s_0)c].$$

one calls this the boundary layer equation, because it describes what happens near initial times (boundary of the time interval)
Putting it all together

suppose $s(0) = s_0$ and $c(0) = c_0$

for $t \approx 0$:
\[
\frac{dc}{dt} = k_1 \left[ e_0 s_0 - (K_m + s_0)c \right]
\]

$(c(0) = c_0)$

for $t$ large:
\[
c = \frac{e_0 s}{K_m + s}
\]
\[
\frac{ds}{dt} = -\frac{V_{\text{max}} s}{K_m + s}
\]

approximation valid if $\varepsilon \ll 1$, but works quite well even for moderate $\varepsilon$: 
Numerical example

\[ k_1 = k_{-1} = k_2 = e_0 = 1 \text{ and } s_0 = 10, \text{ so that } \varepsilon = 0.1 \text{ (} K_m = 2, \text{ } V_{max} = 1 \text{)} \]

• black: component \( c(t) \) of true solution of system

\[
\frac{ds}{dt} = c - s(1 - c), \quad \frac{dc}{dt} = s - (2 + s)c \quad s(0) = s_0, \, c(0) = 0
\]

• red: \( c = s/(2 + s) \), where \( \frac{ds}{dt} = -s/(2 + s) \) (slow system), \( s(0) = s_0 \)

• blue: soln of fast system at initial time: \( \frac{dc}{dt} = s_0 - (2 + s_0)c, \, c(0) = 0 \)

plots shown on \( t \in [0, 25] \) & \( t \in [0, 0.5] \):

blue curve approximates well for \( t \approx 0 \), red for larger \( t \)
Singular perturbation analysis

careful derivation allows better understanding of approximations

but also, ∃ methods that help quantify errors in approximation

“singular perturbation theory” applies in general to:

\[
\begin{align*}
\frac{dx}{dt} &= f(x, y) \\
\varepsilon \frac{dy}{dt} &= g(x, y)
\end{align*}
\]

with \(0 < \varepsilon \ll 1\)

components of vector \(x\) called slow variables, those of \(y\) fast

terminology: \(dy/dt = (1/\varepsilon)(\ldots)\) means that \(dy/dt\) is large, i.e., that \(y(t)\) is “fast,” and by comparison \(x(t)\) is slow

set \(\varepsilon = 0\), solve \(g(x, y) = 0\) for \(y = h(x)\) (i.e. \(g(x, h(x)) = 0\)), and then substitute back into first eqn
Singular perturbations, ctd

one studies the *reduced system*:

\[
\frac{dx}{dt} = f(x, h(x))
\]

on the “slow manifold” defined by \( g(x, y) = 0 \)

rich theory allows to mathematically justify the approximations
Modeling, Growth, Number of Parameters
Steady States and Linearized Stability Analysis
More Modeling Examples
Geometric Analysis: Vector Fields, Phase Planes
Epidemiology: SIRS Model
Chemical Kinetics
Enzymatic Reactions, QSS
Other enzyme actions, cooperativity, sigmoidal responses
Multi-Stability
Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
**Further example involving enzymes: inhibition**

*competitive inhibition*: second substrate (inhibitor) capable of binding and block binding of the primary substrate

If primary substrate cannot bind, no “product” (such as the release of signaling molecules by a receptor) can be created.

E.g., enzyme may be a cell surface receptor, and the primary substrate might be a growth factor, hormone, or histamine (protein released by immune system in response to pollen, dust, etc).
e.g. an inhibitor drug will attempt to block the binding of the substrate to receptors in cells that can react to that substrate, such as for example histamines to lung cells.

many antihistamines work in this fashion, e.g. Allegra

(in pharmacology, an agonist is a ligand which, when bound to a receptor, triggers a cellular response. an antagonist is a competitive inhibitor of an agonist. when we view the receptor as an enzyme and the agonist as a substrate)

a simple chemical model is as follows:

\[
S + E \xrightleftharpoons[k_{-1}]{k_1} C_1 \xrightarrow{k_2} P + E \quad I + E \xrightleftharpoons[k_{-3}]{k_3} C_2
\]

where \(C_1\) is the substrate/enzyme complex, \(C_2\) the inhibitor/enzyme complex, and \(I\) the inhibitor.
Competitive inhibition, ctd

i.e. ODE’s:

\[
\begin{align*}
\frac{ds}{dt} &= k_{-1}c_1 - k_1se \\
\frac{de}{dt} &= (k_{-1} + k_2)c_1 + k_3c_2 - k_1se - k_3ie \\
\frac{dc_1}{dt} &= k_1se - (k_{-1} + k_2)c_1 \\
\frac{dc_2}{dt} &= k_3ie - k_{-3}c_2 \\
\frac{di}{dt} &= k_{-3}c_2 - k_3ie \\
\frac{dp}{dt} &= k_2c_1
\end{align*}
\]

\[c_1 + c_2 + e = \text{constant (total amount of free \\& bound enzyme, } e_0)\]
so eliminate \(e\)

(conservation \(i + c_2 \equiv i_0 = \text{total amount of inhibitor allows reduction to 3; better for time-scale separation purposes to keep 4} \))
as before, may first ignore the equation for $p$
left with a set of four ODE's:
\[
\frac{ds}{dt} = k_{-1}c_1 - k_1s(e_0 - c_1 - c_2)
\]
\[
\frac{di}{dt} = k_{-3}c_2 - k_3ie
\]
\[
\frac{dc_1}{dt} = k_1s(e_0 - c_1 - c_2) - (k_{-1} + k_2)c_1
\]
\[
\frac{dc_2}{dt} = k_3i(e_0 - c_1 - c_2) - k_{-3}c_2.
\]

may now do a quasi-steady-state approximation, assuming that enzyme concentrations small relative to substrate formally, set $dc_1/dt = 0$ and $dc_2/dt = 0$:
\[
c_1 = \frac{K_i e_0 s}{K_m i + K_i s + K_m K_i}
\]
\[
c_2 = \frac{K_m e_0 i}{K_m i + K_i s + K_m K_i}
\]
\[
\left(K_m = \frac{k_{-1} + k_2}{k_1}\right)
\]
\[
\left(K_i = \frac{k_{-3}}{k_3}\right)
\]
Competitive inhibition, ctd

(rigorously should nondimensionalize, set a small $\varepsilon = 0$, etc.)

product formation rate is $dp/dt = k_2 c_1$, so, again with $V_{\text{max}} = k_2 e_0$, one has the approximate formula:

$$\frac{dp}{dt} = \frac{V_{\text{max}} s}{s + K_m (1 + i/K_i)}$$

formula reduces to previous when no inhibition ($i = 0$)

note rate of product formation is smaller than if there had been no inhibition, given the same amount of substrate $s(t)$

(at least if $i \gg 1$, $k_3 \gg 1$, $k_{-3} \ll 1$)

but for $s \gg 1$, rate saturates at $dp/dt = V_{\text{max}}$, just as if no inhibitor

(intuitively: $i$ doesn’t get chance to bind and block)

so to diminish product formed, when substrate amount large potentially huge amount of drug (inhibitor) needs to be administered – allosteric inhibition, does not have the same disadvantage:
(“steric” ∼ arrangement of atoms in space)

inhibitor does not bind in catalytic site
but at effector (regulatory or allosteric) site
shape of enzyme modified
harder for the enzyme to bind to the substrate
slightly different situation: binding of substrate can always occur, but product can only be formed (and released) if $I$ not bound we model this last situation, which is a little simpler and assume binding of $S$ or $I$ to $E$ independent of each other (else, eqs still the same, but need more kinetic constants $k$’s) a reasonable chemical model is:

\[
E + S \xrightleftharpoons[1]{k_{-1}} ES \xrightarrow[k_2]{2} P + E
\]

\[
EI + S \xrightleftharpoons[1]{k_{-1}} EIS
\]

\[
E + I \xrightarrow[k_3]{3} EI
\]

\[
ES + I \xrightleftharpoons[3]{k_{-3}} EIS
\]
Homework problem:
show (under quasi-steady state approximation):

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

for some suitable numbers \( a = a(i), \ldots \) and a suitably defined \( K_i \)

notice that the maximal possible rate, for large \( s \), is lower than in the case of competitive inhibition
intuition: no matter amount of substrate, inhibitor can still bind to the same number of enzymes, so throughput is affected
A digression on gene expression

very simple model of gene expression:
\( D, M, P = \) concentrations of
active promoter sites, mRNA transcript, and protein
(“concentration” = proportion of active sites in cell population)

network of reactions:

\[
D \xrightarrow{\alpha} D + M, \quad M \xrightarrow{\beta} 0, \quad M \xrightarrow{\theta} M + P, \quad P \xrightarrow{\delta} 0
\]

transcription and degradation of mRNA,
translation,
degradation (or dilution due to cell growth) in protein concentration

with mass-action kinetics, rates:

\[
R_1 = \alpha D, \quad R_2 = \beta M, \quad R_3 = \theta M, \quad R_4 = \delta P
\]

for some positive constants \( \alpha, \beta, \theta, \delta \), so stoichiometry matrix:

\[
\Gamma = \begin{pmatrix}
0 & 0 & 0 & 0 \\
1 & -1 & 0 & 0 \\
0 & 0 & 1 & -1
\end{pmatrix}
\]
observe: as $D$ not changed, could replace $D \xrightarrow{\alpha} D + M$ by $0 \xrightarrow{\alpha} M$
and forget about $D$
and now stoichiometry matrix:

$$\Gamma = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}$$

but, when we consider repression models, cannot simplify
Ignores huge amount of biochemistry and biophysics
e.g. dynamics of transcription
still, very useful model, and the one most often employed
Adding repression

molecule (transcription factor) $R$ can repress transcription by binding to DNA, hence affecting promoter activity; add reaction:

$$D + R \xrightleftharpoons[k_1]{k_{-1}} C$$

representing complex formation between promoter and repressor closely analogous to enzyme inhibition

Exercise: write stoichiometry matrix and ODE’s, analyze solutions
Exercise: model activation instead of repression
suppose \( n \) molecules of substrate must first get together with enzyme so reaction takes place:

\[
\begin{align*}
nS + E & \rightleftharpoons_C \frac{k_1}{k_{-1}} C \rightarrow_k P + E
\end{align*}
\]

not very realistic model
(unlikely \( n + 1 \) molecules may "meet" simultaneously)

simplification of more realistic model, bindings occur in sequence

"cooperativity degree of the reaction" is \( n \)

highly cooperative reactions extremely common in biology
e.g. in ligand binding to cell surface receptors,
or transcription factor binding to DNA, to control gene expression

only look at this simple model in course
Cooperativity: equations

\[
\begin{align*}
\frac{ds}{dt} &= nk_{-1}c - nk_1 s^n e \\
\frac{de}{dt} &= (k_{-1} + k_2)c - k_1 s^n e \\
\frac{dc}{dt} &= k_1 s^n e - (k_{-1} + k_2)c \\
\frac{dp}{dt} &= k_2 c
\end{align*}
\]

quasi-steady state approximation under assumption that enzyme concentration \( \ll \) substrate
same expression for product formation, except different exponent:

\[
\frac{dp}{dt} = \frac{V_{\text{max}} s^n}{K_m + s^n}
\]

integer \( n = \text{Hill coefficient} \).
determine $V_{\text{max}}$, $n$, and $K_m$ experimentally, from knowledge of rate of product formation $\dot{p} = dp/dt$ as function of current substrate concentration (under the quasi-steady state approximation assumption)

first, estimate $V_{\text{max}}$ from rate $\dot{p}$ corresponding to $s \to \infty$

so we can compute $\frac{\dot{p}}{V_{\text{max}} - \dot{p}}$

next observe (solve for $s^n$ and take logs):

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

so linear regression of $\ln \left( \frac{\dot{p}}{V_{\text{max}} - \dot{p}} \right)$ versus $\ln s$ gives $n$ and $K_m$
Cooperativity, ctd

cooporative mechanism often include unknown reactions, e.g. including very complicated allosteric effects, so not uncommon for fractional powers to be appear (even if the above model makes no sense in a fractional situation) when fitting parameters

often written by redefining the constant $K_m$: as

$$\frac{dp}{dt} = \frac{V_{\text{max}} s^n}{K_m^n + s^n}$$

so: $K_m =$ concentration of substrate $s$ s.t. rate of product formation $= \frac{V_{\text{max}}}{2}$
for \( n > 1 \): “sigmoidal” formation rate, vs “hyperbolic”

because: if \( f(s) = \frac{V_{\text{max}} s^n}{K_m^n + s^n} \), then \( f'(0) > 0 \) when \( n = 1 \),

but \( f'(0) = 0 \) if \( n > 1 \)

for \( n > 1 \), function increasing, graph starts with concavity-up;
but function bounded, so concavity must change to \(< 0\)

e.g. graphs with \( n = 1 \) (hyperbolic) and with \( n = 3 \) (sigmoidal):
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

fits of $V_{\text{max}}$ and $n$ ("$n_H$" for "Hill") to various data sets for allosteric reaction.
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Epidemiology: SIRS Model
Chemical Kinetics
Enzymatic Reactions, QSS
Other enzyme actions, cooperativity, sigmoidal responses

**Multi-Stability**
Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
Hypercobolic and sigmoidal responses

enzyme model, but suppose substrate not depleted
e.g. replenished and kept at a certain level by another mechanism,
or in abundance and change very slow

so we view $s$ as a constant

QSS product formation rate:

\[
\frac{dp}{dt} = \frac{V_{\text{max}} s^n}{K_m^n + s^n}
\]

with Hill coefficient $n = 1$, or $n > 1$ if the reaction is cooperative

next, make things more interesting by adding degradation $-\lambda p$
i.e. product is being produced, and used up, degraded, or diluted

\[
p(\infty) = \frac{V_{\text{max}} s^n}{K_m^n + s^n}
\]

(first redefining $V_{\text{max}} = V_{\text{max}}/\lambda$)

first consider the case $n = 1$:
“light-dimmer” behavior:
steady-state is *graded* function of “input” concentration \( s \) proportional to \( s \) over range of values, eventually saturates)

“*hyperbolic*” response
Sigmoidal responses

As $n$ gets larger, the plot of $\frac{V_{\text{max}}s^n}{K_m^n + s^n}$ closer to step function with transition at $s = K_m$

e.g. $V_{\text{max}} = 1$, $K_m = 0.5$, and $n = 3, 20$:

$s < K_m \implies$ no appreciable result ($p \approx 0$, in steady state)

but over threshold gives abrupt change ($p \approx V_{\text{max}}$, in steady state)
Sigmoidal responses, ctd

A “binary” response is thus produced from cooperative reactions

“doorbell”: must press hard enough for effect (ring)

“ultrasensitivity”
signaling pathway: should gene be transcribed”?

cascades increase: composition of functions $\Rightarrow$ multiply slopes!
Now add positive feedback

suppose substrate concentration depends monotonically on product concentration

e.g. $s$ is a TF fpr $p$ and vice versa, and QSS or $p = s$ (autocatalysis)

$$\frac{dp}{dt} = \frac{V_{\text{max}} (\alpha p)^n}{K_m^n + (\alpha p)^n} - \lambda p$$

rescale and rename parameters, so assume $\alpha = 1$ and $\lambda = 1$:  

$$\frac{dp}{dt} = \frac{V_{\text{max}} p^n}{K_m^n + p^n} - p$$

What are the possible steady states of this system with feedback?
Steady states: hyperbolic case

(first $n = 1$)

plot first term (formation rate) together with second (degradation):

for small $p$, formation rate $> \text{degradation rate}$
and for large $p$, converse
so concentration $p(t)$ converges to a unique intermediate value
Steady states: sigmoidal case

cooperative case (i.e., $n > 1$): situation far more interesting!

- for small $p$, degradation > formation rate, so concentration $p(t)$ converges to a low value
- but for large $p$, formation rate > degradation rate, so concentration $p(t)$ converges to a high value

two stable states created, “low” and “high” by this interaction of formation and degradation (there is also an intermediate, unstable state)
Equivalently:

instead of separate terms, plot RHS

\[
\frac{V_{\text{max}} p^n}{K_m^n + p^n} - p
\]

e.g.: \(V_{\text{max}} = 3\), \(K_m = 1\), and \(n = 2\)

so phase line:

\[A = 0, \quad B \approx 0.38, \quad C \approx 2.62\]

\(A, C\) stable ("sinks") and intermediate \(B\) unstable ("source")
Outline

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Epidemiology: SIRS Model
Chemical Kinetics
Enzymatic Reactions, QSS
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Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
Multicellular organisms: cells \textit{genetically} identical

differentiation results from variations of gene expression
how are these variations established and maintained?

epigenetic variations: e.g.
addition of methyl groups to DNA at CpG sites

how is patterning originally established?
\textit{positional information} (Wolpert and others):
cells acquire positional value with respect to boundaries
“coordinate system” determines fate and phenotype
(at cell division, “initial conditions” inherited from mother cells)

how is position estimated by each cell? (polarity?)
\textit{morphogens} (RNA or proteins) concentrations
initially determined in embryo, e.g. by site of sperm penetration, or
environmental factors (gravity, pH)
suppose each cell may express a protein $P$ whose level “$p$” determines a certain phenotypical characteristic morphogen $S$ (“signal”) affects expression of $P$ gene concentration $s$ of $S$ near a particular cell influences that cell concentration of $S$ highest at left end, lowest at right end and varies continuously (mother deposits at one end; diffusion)

for simplicity: one-dimensional organism

for simplicity: one-dimensional organism

<table>
<thead>
<tr>
<th>cell #1</th>
<th>cell #2</th>
<th>cell #k</th>
<th>cell #N</th>
</tr>
</thead>
<tbody>
<tr>
<td>signal $s$ highest here</td>
<td></td>
<td>signal $s$ lower</td>
<td></td>
</tr>
</tbody>
</table>

how can “sudden” changes of level of $P$ occur?

$s = 1$ $s = 0.9$ $s = 0.8$ $s = 0.7$ $s = 0.6$ $s = 0.5$ $s = 0.4$ $s = 0.3$ $s = 0.2$

$p \approx 1$ $p \approx 1$ $p \approx 1$ $p \approx 1$ $p \approx 1$ $p \approx 0$ $p \approx 0$ $p \approx 0$ $p \approx 0$

nose nose nose nose mouth mouth mouth mouth
why no “3/4 nose, 1/4 mouth”? 

“thresholding effect”? 

same genotype $\sim$ all cells described by same system of equations except for input (concentration $s$ of morphogen near given cell) (say, average value of $s$ around the cell) think of $p(\infty)$ as determining “nose-cell” vs “mouth-cell”

$$\frac{dp}{dt} = f(p, s)$$

we assume solution $p(t)$ settles to steady state $p(\infty)$ $p(\infty)$ describes the level of $P$ after a transient

will assume start all cells in same $p(0)$ need $p(\infty)$ drastically different due to small change in parameter $s$ “bifurcation” of behavior
What equations work?

$p(\infty)$ depends on the initial state $p(0)$ as well as on the value of the parameter $s$ that the particular cell measures e.g.:

$$\frac{dp}{dt} = f(p, s) = \frac{V_{\text{max}} p^n}{K_m^n + p^n} - \lambda p + ks.$$

and to be concrete:

$k = 5, \ V_{\text{max}} = 15, \ \lambda = 7, \ K_m = 1, \ \text{Hill coefficient } n = 2, \ \alpha = 1$
Plots of $f(p, s)$ versus $p$, for three values of $s$

$s < s^*$, $s = s^*$, $s > s^*$, where $s^* \approx 0.268$.

graphs and phase lines:

For $s < s^*$, two stable steady states ($A, C$) and unstable $B$
think of $A \sim$ mouth cells, $C \sim$ nose cells
exact positions of $A, B, C$ depend on one precise value of $s$
but think of “low” and a “high” stable steady state
(and an “intermediate” unstable state) in a qualitative sense
Dynamics

assume all cells start with no protein: \( p(0) = 0 \)

left-most cells \((s > s^*)\) settle into “high state” \(C\) (nose-like)
right-most cells \((s < s^*)\) \(\rightarrow\) “low state” \(A\) (mouth-like)
so we see how a sharp transition between cell types is achieved

\[
\begin{array}{cccccccc}
  s > s^* & s > s^* & s > s^* & s > s^* & s > s^* & s < s^* & s < s^* & s < s^* \\
  p \approx C & p \approx C & p \approx C & p \approx C & p \approx C & p \approx A & p \approx A & p \approx A \\
  \text{nose} & \text{nose} & \text{nose} & \text{nose} & \text{mouth} & \text{mouth} & \text{mouth} & \text{mouth}
\end{array}
\]
moreover(!): once cell’s fate determined, it will not revert: suppose after cell settled to a steady state (high or low) we “wash-out” the morphogen, i.e. set $s$ to very low value.

behavior of every cell now determined by phase line for low $s$:

cells starting with “low” protein $P$ will stay low
cells starting with “high” protein $P$ will stay high

permanent memory of morphogen effect imprinted in system even after the signal is “turned-off”
A little exercise

\[ \frac{dx}{dt} = f(x) + a \]

low \( a \)  

---

higher \( a \)

| cell #1 | cell #2 | cell #\( k \) | cell #\( N \) |

plots of \( f(x) + a \), for small, intermediate, and large \( a \) respectively:
level of expression starts at $x(0) = 0$ for every cell

(1) what pattern do we see after things settle to steady state?

(2) after system settled, suddenly change level of $a$ so that now every cell sees the same value of $a$, for which plot of $f(x) + a$:

[Graph]

what pattern will the organism settle upon?
indicate roughly “low” level of $x$ by letter “A”, etc
• cells at left see these "instructions":

```
  A
```

so starting from \( x = 0 \), they settle at a "low" gene expression level, roughly indicated by \( A \).

• cells around center see these "instructions:"

```
  B          C
```

starting from \( x = 0 \), they settle at an "intermediate" level \( B \).

• cells toward the left see these "instructions:"

```
  C
```

starting from \( x = 0 \), they will settle at a "high" level \( C \).

In summary, the pattern that we observe is:

```
AAABBBCCCC
```

(many \( A \)'s, etc., depending on how many cells there are, and graph of \( f \); 3 of each just for general idea)
next suddenly “change the rules of the game”: ask them all to follow these instructions:

- Cells that started (from the previous stage of our experiment) near A will approach A,
- near B approach B,
- near C have “their floor removed from under them” and told to move left, i.e. all the way down to B

summary:

\[ AAABBBCCC \rightarrow AAABBBBBBB \]
highly sigmoidal responses require a large Hill coefficient $n_H$

Goldbeter and Koshland (1981) made simple but strikingly interesting and influential observation:

can obtain such responses even without cooperativity starting point: reaction such as the “futile cycle”:

\[
E + P \xleftrightarrow[k_1]{k_{-1}} C \xrightarrow[k_2]{k_{-2}} E + Q, \quad F + Q \xleftrightarrow[k_3]{k_{-3}} D \xrightarrow[k_4]{k_{-4}} F + P.
\]

to simplify, take quasi-steady state approximation, so using lower case letters for concentrations:

\[
\frac{dq}{dt} = \frac{V_{\text{max}}ep}{K + p} - \frac{\tilde{V}_{\text{max}}fq}{L + q}, \quad \frac{dp}{dt} = -\frac{dq}{dt}
\]

thus $p + q$ is constant; picking appropriate units, let $q = 1 - p$ (so $p, q$ are fractions of unmodified substrate, respectively)
writing “x” instead of “p”, we have steady states are solutions of:

\[ r \frac{x}{K + x} = \frac{1 - x}{L + 1 - x} \]

where \( r := \left( \frac{V_{\text{max}}}{\tilde{V}_{\text{max}}} \right) \left( \frac{e}{f} \right) \)

proportional to ratio of concentrations of the two enzymes

so sketch the two curves to find the intersection points
“zero order” regime
(production rate approximately constant, except for \( p, q \ll 1 \))

dotted line: graph of \( \frac{1-x}{L+1-x} \); solid line: graphs of \( r \frac{x}{K+x} \)
for \( r < 1 \) (left) and \( r > 1 \) (right)

sharp dependence of steady state \( x \) on value of \( r \),
changing from \( x \approx 1 \) to \( x \approx 0 \) at \( r = 1 \)

dependence \( x = G(r) \):
in contrast, for $K$ and $L$ large ("first order" or almost linear, regime) dependence is far smoother

dotted line: graph of $\frac{1-x}{L+1-x}$; solid line: graphs of $r \frac{x}{K+x}$
dependence $x = G(r)$:

in summary, for small $K, L$, we have a very sigmoidal response, with no need for cooperativity.

solving $x = G(r)$, $G$ is the "GoldbeterKoshland function".
suppose genes code for X and Y
repressors sensitive to dimers XX, XY, YY
& inducers sensitive to resp monomer (feedback)

\[
\frac{dx}{dt} = \mu_1 x - \alpha_1 x^2 - \gamma_{12} xy
\]
\[
\frac{dy}{dt} = \mu_2 y - \alpha_2 y^2 - \gamma_{21} xy
\]

behavior depends on parameters
suppose \( \alpha_2 / \gamma_{12} < \mu_1 / \mu_2 < \gamma_{21} / \alpha_1 \)
outcome depends strongly on initial concentrations:
always \( x(\infty) = 0 \) or \( y(\infty) = 0 \)
(except starting exactly on stable manifold of saddle
(“principle of competitive exclusion”)
Phase-plane
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**Periodic Behavior**

Bifurcations
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Neurons
Periodic trajectories

Periodic behaviors (oscillations) in neurons, circadian rhythms, heartbeats, etc. Simplest: harmonic oscillator (mass spring system w/no damping):

\[
\frac{dx}{dt} = y \\
\frac{dy}{dt} = -x
\]

Trajectories are circles, or, more generally, linear systems with eigenvalues that are purely imaginary, leading to ellipsoidal trajectories:
serious limitation of linear oscillators: not robust

small perturbation in the equations:

\[
\begin{align*}
\frac{dx}{dt} &= y \\
\frac{dy}{dt} &= -x + \varepsilon y
\end{align*}
\]

(\(\varepsilon \neq 0\) small) \(\Rightarrow\) trajectories not periodic!
\(dy/dt\) doesn’t balance \(dx/dt\) just right,
so trajectory doesn’t “close”:

depending on sign of \(\varepsilon\), stable or an unstable spiral
if, for some reason, the state “jumps” to another position then system will start oscillating along a different orbit never coming back to the original trajectory:

particular oscillation depends on the initial conditions biological objects tend to reset themselves (e.g. internal clock adjusting after jetlag)
**Limit cycles**

*(stable) limit cycle*: periodic trajectory which attracts other solutions (at least those starting nearby)

Member of family of “parallel” periodic solutions (as for linear centers) is *not* a limit cycle.

Limit cycles are “robust”:

- (small) perturbations on initial state: system returns to cycle.
- Under appropriate assumptions (e.g., hyperbolicity), if dynamics changes a little, a limit cycle will still exist, close to the original one.
Example of limit cycle

\[
\begin{align*}
\frac{dx_1}{dt} &= \mu x_1 - \omega x_2 + \theta x_1(x_1^2 + x_2^2) \\
\frac{dx_2}{dt} &= \omega x_1 + \mu x_2 + \theta x_2(x_1^2 + x_2^2)
\end{align*}
\]

or, if we pick \(\theta = -1\) for definiteness:

\[
\begin{align*}
\frac{dx_1}{dt} &= \mu x_1 - \omega x_2 - x_1(x_1^2 + x_2^2) \\
\frac{dx_2}{dt} &= \omega x_1 + \mu x_2 - x_2(x_1^2 + x_2^2)
\end{align*}
\]

(\(\theta = 0\): linear, center or spirals, so no limit cycles)

two ways to rewrite help understand:

(1) complex numbers: \((x_1, x_2)\) represented by \(z = x_1 + ix_2\):

\[
\frac{dz}{dt} = (\mu + \omega i)z - |z|^2 z
\]

(to prove: use \(\frac{dz}{dt} = \frac{dx_1}{dt} + id\frac{dx_2}{dt}\))

(2) polar coordinates:
System in polar coordinates

\[ x_1 = \rho \cos \varphi, \ x_2 = \rho \sin \varphi; \text{ take } d/dt; \text{ equate terms} \]

\[ \Rightarrow \text{ obtain decoupled eqs for magnitude } \rho \text{ and argument } \varphi: \]

\[ \frac{d\rho}{dt} = \rho(\mu - \rho^2) \]

\[ \frac{d\varphi}{dt} = \omega \]

may analyze each one separately

\( \varphi \)-equation \( \frac{d\varphi}{dt} = \omega \) says solutions rotate w/speed \( \omega \)

(counter-clockwise, if \( \omega > 0 \))

\[ \frac{d\rho}{dt} = \rho(\mu - \rho^2): \]

**Case 1:** \( \mu \leq 0 \): every solution converges to zero,

so in full planar system: all trajectories spiral into the origin
Case $\mu > 0$

(passage from $\mu < 0$ to $\mu > 0$ is “supercritical Hopf bifurcation”)

origin becomes unstable for $d\rho/dt = \rho(\mu - \rho^2)$
velocity negative for $\rho > \sqrt{\mu}$ and positive for $\rho < \sqrt{\mu}$,
so sink at $\rho = \sqrt{\mu}$:

trajectories spiral into the circle of radius $\sqrt{\mu}$, a limit cycle

oscillation has magnitude $\sqrt{\mu}$ and frequency $\omega$

in general systems, hard to actually prove limit cycles exists,
but in dim=2, powerful criterion:
Poincaré-Bendixson Theorem

suppose bounded region $D$ in plane, s.t.:

- “forward-invariant” or “trapping” region: no trajectories can exit
- either no steady states in $D$, or only one and repelling

Then, there is a periodic orbit inside $D$

(also: if there is a unique periodic orbit, then must be limit cycle)
if \( \omega(x) \) compact, connected, contains only finitely many equilibria:

- \( \omega(x) \) is a steady state, or
- \( \omega(x) \) is a periodic orbit, or
- \( \omega(x) \) is a homo/hetero-clinic connection

apply usually if \( \not\exists \) equilibrium, or if repelling, \( \therefore \) periodic

in particular, no “chaos” possible in 2D; very regular behavior false in (nonlinear) 3D, unless special structure . . .
outward-pointing normal vectors at any boundary point must make an angle of at least 90 degrees with vector field i.e. dot product $\leq 0$ between normal $\vec{n}$ and vector field:

$$\left( \frac{dx}{dt}, \frac{dy}{dt} \right) \cdot \vec{n} \leq 0$$

subtle if vectors exactly perpendicular, and also if nonsmooth boundary ("nonsmooth analysis")
Previous example, via PB

\[
\frac{dx_1}{dt} = \mu x_1 - \omega x_2 - x_1(x_1^2 + x_2^2)
\]
\[
\frac{dx_2}{dt} = \omega x_1 + \mu x_2 - x_2(x_1^2 + x_2^2)
\]

with \( \mu > 0 \)
(already know circle with radius \( \sqrt{\mu} \) is limit cycle, of course)
let region \( D = \) disk with radius \( \sqrt{2\mu} \) (or larger)
boundary is circle of radius \( \sqrt{2\mu} \)
at \((x_1, x_2)\) on circle, one normal vector is \((x_1, x_2)\)
(arrows from the origin to the point is perpendicular to circle)
dot product:

\[
[\mu x_1 - \omega x_2 - x_1(x_1^2 + x_2^2)] x_1 + [\omega x_1 + \mu x_2 - x_2(x_1^2 + x_2^2)] x_2
\]

\[
= (\mu - (x_1^2 + x_2^2))(x_1^2 + x_2^2) = -2\mu^2 < 0
\]
so vector field points inside, and disk is trapping region

Only steady state is \((0, 0)\):

If \(\mu x_1 - \omega x_2 - x_1(x_1^2 + x_2^2) = 0\) and \(\omega x_1 + \mu x_2 - x_2(x_1^2 + x_2^2) = 0\) then multiply by \(x_1\) the first equation, and the second by \(x_2\), giving \((\mu + x_1^2 + x_2^2)(x_1^2 + x_2^2) = 0\), so \(x_1 = x_2 = 0\)

Linearizing at origin, prove unstable spiral

So only steady state is repelling, and P-B OK

Conclude that there is a periodic orbit inside this disk

(Can prove limit cycle: use annular regions \(1 - \varepsilon < x^2 + y^2 < 1 + \varepsilon\), so unique)
B. van der Pol and J. van der Mark, *The heartbeat considered as a relaxation oscillation, and an electrical model of the heart*, 1928

after some changes of variables:

\[
\begin{align*}
\frac{dx}{dt} &= y + x - \frac{x^3}{3} \\
\frac{dy}{dt} &= -x
\end{align*}
\]

only steady state at \((0, 0)\): repels, since Jacobian \(\det > 0\) and trace \(> 0\):

\[
\begin{vmatrix}
1 - x^2 & 1 \\
-1 & 0
\end{vmatrix}_{(0, 0)} = \begin{pmatrix} 1 & 1 \\ -1 & 0 \end{pmatrix}
\]

will show there are periodic orbits (actually limit cycle, but we will not show that)
To apply P-B, consider special region:

will show vector field point inside on the boundary
boundary made up of 6 segments; by symmetry, since region symmetric & equation odd, enough 3 segments:

\[ x = 3, \quad -3 \leq y \leq 6 \quad y = 6, \quad 0 \leq x \leq 3 \quad y = x + 6, \quad -3 \leq x \leq 0 \]

\[ x = 3, \quad -3 \leq y \leq 6: \]
pick \( \vec{v} = (1, 0) \), so \( \left( \frac{dx}{dt}, \frac{dy}{dt} \right) \cdot \vec{n} = \frac{dx}{dt} \) and, substituting
\[ x = 3 \] into \( y + x - \frac{x^3}{3} \):

\[ \frac{dx}{dt} = y - 6 \leq 0 \]

so vector field points to the left

can trajectories “escape” through a corner (red arrows)?
at \( x = 3, \ y = 6 \): \( \frac{dy}{dt} = -3 < 0 \), so point “SW”, so OK
at bottom, \( \frac{dy}{dt} = -3 < 0 \), and \( \frac{dx}{dt} = -9 \), so also OK
Boundary behavior of vector field, ctd.

\[ y = 6, \ 0 \leq x \leq 3: \]
may pick \( \vec{\nu} = (0, 1) \), so

\[
\left( \frac{dx}{dt}, \frac{dy}{dt} \right) \cdot \vec{n} = \frac{dy}{dt} = -x \leq 0
\]

and corners are also OK (for example, at \( (0, 6) \): \( dx/dt = 6 > 0 \))

\[ y = x + 6, \ -3 \leq x \leq 0: \]
pick outward normal \( \vec{\nu} = (-1, 1) \) and take dot product:

\[
\left( y + x - x^3/3 \right) \cdot \left( -1 \right) = -2x - y + x^3/3
\]

evaluated at \( y = x + 6 \), this is:

\[
\frac{x^3}{3} - 3x - 6, \ -3 \leq x \leq 0
\]

which is indeed always negative (plot, or use calculus), and one can also check corners
Bendixson’s Criterion

Consider simply-connected (no holes) region \( D \)

If divergence of vector field doesn’t change sign (but is not \( \equiv 0 \)) inside \( D \), then there cannot be a periodic orbit inside \( D \)

Sketch of proof:

Suppose \( \exists \) such periodic orbit, a simple closed curve \( C \)

Recall that the divergence of \( F(x, y) = \begin{pmatrix} f(x, y) \\ g(x, y) \end{pmatrix} \) is defined as:

\[
\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y}
\]

Gauss Divergence Theorem (“Green’s Theorem”):

\[
\int \int_D \text{div} \ F(x, y) \, dx \, dy = \int_C \vec{n} \cdot \vec{F}
\]

Since \( C \) is an orbit, \( F \) is tangent to \( C \), so \( \cdot = 0 \):

\[
\int \int_D \text{div} \ F(x, y) \, dx \, dy = 0
\]

So \( F \) must change sign.
Trivial examples

\[ \frac{dx}{dt} = x, \quad \frac{dy}{dt} = y \]
divergence \equiv 2 everywhere, so no periodic orbits (inside any region)

\[ \frac{dx}{dt} = x, \quad \frac{dy}{dt} = -y \]
divergence \equiv 0, so Bendixson criterion tells us nothing (linear saddle, so no periodic orbits)

\[ \frac{dx}{dt} = y, \quad \frac{dy}{dt} = -x \]
again divergence \equiv 0, but periodic orbits exist
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How can stability be lost?

(generic “codim 1” bifurcations for equilibria: one parameter)

- **one real eigen crosses at zero** (saddle-node, turning point, or fold)
  two equilibria formed (or disappear), saddle and node

or

- **pair of complex eigenvalues crosses imaginary axis**:
  periodic orbits arise from Poincaré-Andronov-Hopf bifurcations
\[ \frac{dx}{dt} = f(x, \mu) \]

if \( f_x(x^*, \mu^*) \) has no eigenvalues on imaginary axis (in particular, nonsingular),
then close-by have similar behaviors (by IFT)

so ask \( f_x(x^*, \mu^*) \) degenerate

(generically second derivative non-degenerate)

good ref:
w.l.o.g. $x^* = 0, u^* = 0$

generically $f_{xx}(0, 0) \neq 0$ & $f_\mu(0, 0) \neq 0$ (transversality condition)

locally topologically equivalent to normal form:

$$\frac{dx}{dt} = \mu + bx^2$$

rescale so $b = \pm 1$

assuming generic condition $b \neq 0$

add $\frac{dy}{dt} = \pm y$ if more dims; center manifold
Remark: transcritical bifurcation

(not generic)

when $f_\mu(0, 0) = 0$: may have steady states for all $\mu$ near $\mu^* = 0$
first term with $\mu$ is then $f_{x\mu}$
and normal form is $dx/dt = \mu x - x^2$ (e.g. logistic)
Pitchfork bifurcations

generically, ∃ quadratic term, unless system exhibits symmetry

e.g.: if $dx/dt = f(x, \mu)$ such that $f(-x, \mu) = -f(x, \mu)$
($Z_2$ symmetry)

this leads to the normal form $dx/dt = \mu x - x^3$

(note: similar to abs value in Hopf, but allowing negative $x$ here)

may be super- or sub-critical:

\[
\frac{du}{dt} = (\mu - u^2)u \quad \quad \quad \quad \frac{du}{dt} = (\mu + u^2)u
\]
assume 2-dim system, for simplicity:

\[ \frac{dx}{dt} = f(x, \mu) \]

for value \( \mu_0 \) of parameter, and steady state \( x_0 \), assume:

- for \( \mu < \mu_0 \), linearization at \( x_0 \) stable, and pair of complex conjugate eigens with \( \Re < 0 \)

- as \( \mu \) changes to positive, linearization goes through purely imag (at \( \mu = \mu_0 \)) to positive real part

so near \( x_0 \), motion changes from stable to unstable spiral
Example: $\theta = -1$ normal form; supercritical

as earlier:

\[
\begin{align*}
  \frac{dx_1}{dt} &= \mu x_1 - \omega x_2 + \theta x_1 (x_1^2 + x_2^2) \\
  \frac{dx_2}{dt} &= \omega x_1 + \mu x_2 + \theta x_2 (x_1^2 + x_2^2)
\end{align*}
\]

globally attractive steady states becomes limit cycle, as $\mu \sim > 0$
Example: $\theta = 1$ normal form; subcritical

magnitude $d\rho/dt = \rho(\mu + \rho^2)$, still becomes unstable as $\mu \sim > 0$
but now unstable cycle encircles the origin for $\mu < 0$
(origin not globally attractive)
sometimes, sudden large oscillation as $\mu \sim > 0$
“Soft” vs “hard” Hopf

often subcritical embedded in additional fold bifurcations:

so “sudden big oscillation” appears
from http://www.bifurcation.de/exd2/HTML/exd2.ok.html
On the dynamic behavior of continuous stirred tank reactors.

\[
\begin{align*}
\frac{dy_1}{dt} &= -y_1 + Da(1 - y_1) \exp(y_2) \\
\frac{dy_2}{dt} &= -y_2 + B \cdot Da(1 - y_1) \exp(y_2) - \beta y_2
\end{align*}
\]

\(y_1, y_2\) describe the material and energy balances
\(\beta\): heat transfer coefficient \((\beta = 3)\)
\(Da\): Damköhler number (bifurcation parameter: \(\lambda := Da\))
\(B\): rise in adiabatic temperature \((B = 16.2)\)
Bifurcation diagram:

first sub-, then super-critical bifurcation
there is a fold, not seen in picture: first branch goes backward!
the right one is supercritical Hopf as parameter *diminishes*
to appreciate phenomenon, “sweep” the parameter $\lambda$, increasing it very slowly, and simulate the system (i.e. add $d\lambda/dt = \varepsilon$)

here $\varepsilon = 0.001$, $y_1(0) = 0.1644$, $y_2(0) = 0.6658$

note the “hard” onset of oscillations (and “soft” end)
Hopf intuition: more dimensions

suppose all other \( n - 2 \) eigenvalues have \( \Re < 0 \), if \( \mu \) near \( \mu_0 \)

\( n - 2 \) negative eigendirections push dynamics towards a two-dimensional surface that looks, near \( x_0 \), like the space spanned by the two complex conjugate eigenvectors corresponding to the purely imaginary eigenvalues at \( \mu = \mu_0 \)

on this surface, the two-dimensional argument that we just gave can be applied.
Numerical packages

use continuation methods; test conditions (Jacobian)
e.g. typical output using applet from:
http://techmathuibk.ac.at/numbau/alex/dynamics/bifurcation/index.html
Modeling, Growth, Number of Parameters
Steady States and Linearized Stability Analysis
More Modeling Examples
Geometric Analysis: Vector Fields, Phase Planes
Epidemiology: SIRS Model
Chemical Kinetics
Enzymatic Reactions, QSS
Other enzyme actions, cooperativity, sigmoidal responses
Multi-Stability
Cell Differentiation and Bifurcations
Periodic Behavior
Bifurcations
Relaxation and excitable systems
Neurons
Cubic nullclines and relaxation oscillations

e.g.: like van der Pol, except that before we had $\varepsilon = 1$:

$$\frac{dx}{dt} = y + x - \frac{x^3}{3}$$
$$\frac{dy}{dt} = -\varepsilon x$$

what happens when $0 < \varepsilon \ll 1$?
y may be viewed as “constant” in comparison w/ “faster” $x$
how does $\frac{dx}{dt} = f_a(x) = a + x - \frac{x^3}{3}$ behave?
cubic nullclines, ctd.

\[ f_a(x) = a + x - \frac{x^3}{3} \text{ for } a = -1, 0, \frac{2}{3}, 1 \]

Now consider solution of ODEs if \( x(0) \ll 0 \) and \( y(0) \approx -1 \).

Since \( y(t) \approx -1 \) for a long time, \( x \) “sees” the equation \( \frac{dx}{dt} = f_{-1}(x) \), and therefore, \( x(t) \) wants to approach a negative “steady state” \( x_a \) (approximately at \(-2\)) (if \( y \) would be constant, indeed \( x(t) \to x_a \))
however, “a” not constant: slowly increasing \((y' = -\varepsilon x > 0)\)

thus “equilibrium” that \(x\) is getting attracted to is constantly moving closer and closer to \(-1\)

until, at exactly \(a = 2/3\), the “low” equilibrium disappears, and there is only the “large” one (around \(x = 2\)); thus \(x\) will quickly converge to that larger value

now \(x(t) > 0\), so \(y' = -\varepsilon x < 0\), i.e. “a” starts decreasing
repeat: periodic motion, slow increases and decreases interspersed with quick motions

*relaxation* (or “hysteresis-driven”) oscillation.
cubic nullclines, ctd.

Here are computer plots of $x(t)$ for one such solution, together with the same solution in phase-plane:
Qualitative analysis using cubic nullclines

consider system of this general form ($\varepsilon > 0$):

\[
\frac{dx}{dt} = f(x) - y \\
\frac{dy}{dt} = \varepsilon (g(x) - y)
\]

$x$ and $y$ nullclines are, respectively: $y = f(x)$ and $y = g(x)$

determine direction of arrows:
$dy/dt$ is positive if $y < g(x)$, i.e. under graph of $g$, etc
allows us to draw “SE”, etc, arrows as usual:
Now assume $\varepsilon \ll 1$

then: *dy/dt is always very small compared to dx/dt*

i.e., the arrows are (almost) horizontal

... except very close to the graph of $y=f(x)$,
where both are small (exactly vertical, when $y=f(x)$):

Note, in this picture: $f' < 0$ and $g' > 0$ at steady state
Nullclines

Jacobian of \( \begin{pmatrix} f(x) - y \\ \varepsilon(g(x) - y) \end{pmatrix} \): \( \begin{pmatrix} f'(x_0) & -1 \\ \varepsilon g'(x_0) & -\varepsilon \end{pmatrix} \)

\( f'(x_0) < 0 \implies \text{trace} < 0; \quad g'(x_0) > 0 \implies \text{det} > 0 \)

so steady state is sink (stable)

thus, we expect trajectories to look like this:
Excitability

Small disturbances have no effect, but if over threshold, large excursion before return.

Steady state stable - zooming-in:
if nullcline \( y = g(x) \) intersects nullcline \( y = f(x) \) on increasing part \( (f' > 0) \): steady state is \textit{un}stable: trace = \( f'(x_0) - \varepsilon \approx f'(x_0) > 0 \) get a relaxation oscillation, instead of an excitable system:
Relaxation oscillations

if nullcline \( y = g(x) \) intersects nullcline \( y = f(x) \) on increasing part (\( f' > 0 \)):

steady state is \textit{un}stable: trace = \( f'(x_0) - \varepsilon \approx f'(x_0) > 0 \)

get a relaxation oscillation, instead of an excitable system:
Outline

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Neurons
Neurons and networks of neurons

special type of cells (a.k.a. “nerve cells”) 
short (1mm) or very long (1m from spinal cord to foot muscles)

each neuron is a complex information processing device 
receiving signals from other neurons 
(as many as 150,000 in cerebral cortex) through synapses

mediated by neurotransmitters (electrically charged chemicals) 
in packets of $\approx 5,000$ molecules 
(abou 50 different types of neurotransmitters)

if signal $> a$ threshold, neuron “fires” 
(action potential: electrical signal travels down axon)

signals may travel at up to 100m/s 
strength of synaptic connections is one way to “memorize”
Neurons and their connections
The role of Na and K

normally, more $K^+$ inside, more $Na^+$ inside

active pumps maintain imbalance (large energy consumption):
3 $Na^+$ ions out for each 2 $K^+$ in

- The Top is the Outer membrane.
- The Bottom is the inner membrane (inside of the Cell)
at “rest”, potential difference $\approx 70\text{mV}$ (− inside)

when stimulated (touch, taste, etc., sensors, other neurons): action potential or “spike” generated at axon hillock (start)

only generated if stimulus large enough “all or (almost) nothing” response (excitable system)

*digital transmission*: signal travels along axon, regenerated — very noise-robust!

next: how is signal generated?
Voltage-gated ion channels
Channels and activation when net signal $> \text{threshold}$

1. Voltage-gated Na$^+$ channels open
   
   a. Na$^+$ in $\Rightarrow$ inside of cell more positive
   
   b. Feedback effect $\Rightarrow$ more gates open

2. When voltage difference $\approx +50\text{mV}$, K$^+$ channels open, K$^+$ out $\Rightarrow$ depolarization

3. Na$^+$ channels close

4. K$^+$ channels close, so back to resting potential

Na$^+$ channels cannot re-open for *refractory period*
Opening and closing gates

http://jimswan.com/237/channels/channel_graphics.htm
Action potentials

1. Sodium channel opens, sodium ions enter.
2. K+ channels open, K+ begins to leave cell.
3. Na+ channels become refractory, no more Na+ enters cell.
4. K+ continues to leave cell, causes membrane potential to return to resting level.
5. K+ channels close, Na+ channels reset.

Membrane Potential (mV)

Time in msec.

Threshold of excitation

Overshoot

Subthreshold Responses

Hyperpolarizing Afterpotential

Na+ Channels Resting State

K+ Channels Open

Relative Refractory Period
Action potentials

[Graph showing action potentials]
Action potentials

animation:

(Copyright 1997, Carlos Finlay and Michael R. Markham).
These diagrams are from
http://www.biologymad.com/NervousSystem/nerveimpulses.htm:
Action potentials

Voltage-gated Na⁺ channels open and Na⁺ enters the axon

A graded potential above threshold reaches the trigger zone

Na⁺ entry depolarizes the membrane, which opens additional Na⁺ channels.

Positive charge flows into adjacent sections of the axon by local current flow.
Action potentials

The trigger zone is in its refractory period. $K^+$ gates have opened and the $Na^+$ inactivation gates have closed. Loss of $K^+$ from the cytoplasm repolarizes the membrane.

In the distal parts of the axon, local current flow from the active region causes new sections of the membrane to depolarize.
Hodgkin-Huxley model of action potential generation

mathematical model given in:


1963 Nobel Prize, one of the most successful examples of mathematical modeling in biology

basic HH model is for small segment of axon

may model up to thousands of such basic compartments, or PDE with spatial variable for length of the axon

done originally for the giant axon of the squid

similar models have been validated for other neurons
variables in Hodgkin-Huxley model

\[ v = \text{potential difference across neuron membrane} \]

\[ m, n, h: \text{activity of each of three types of gates (2 Na, 1 K)} \]

think of relative fractions (“concentrations”) of open channels or equivalently probabilities of channels being open

\[ I = \text{external current} \]

\[
C \frac{dv}{dt} = -g_K(t)(v - v_K) - g_{Na}(t)(v - v_{Na}) - \bar{g}_L(v - v_L) + I
\]

\[
\tau_m(v) \frac{dm}{dt} = m_\infty(v) - m
\]

\[
\tau_n(v) \frac{dn}{dt} = n_\infty(v) - n
\]

\[
\tau_h(v) \frac{dh}{dt} = h_\infty(v) - h
\]

\[
g_K(t) = \bar{g}_K n(t)^4
\]

\[
g_{Na}(t) = \bar{g}_{Na} m(t)^3 h(t)
\]

capacitor model; \( V = IR \) same as \( I = gV \) (\( g’s \) = “conductances”)

\( v_K \), etc. Nerst resting potentials
Formulas for open probabilities and time constants $\tau$’s

for convenience, write:

$$\frac{1}{\tau_m(v)} (m_\infty(v) - m) = \alpha_m(v)(1 - m) - \beta_m(v)m$$

so that $dm/dt = \alpha_m(v)(1 - m) - \beta_m(v)m$ etc

H&H found formulas by fitting to data:

$$\alpha_m(v) = 0.1 \frac{25 - v}{e^{\frac{v}{10}} - 1}, \quad \beta_m(v) = 4e^{\frac{-v}{18}}, \quad \alpha_h(v) = 0.07e^{\frac{-v}{20}},$$

$$\beta_h(v) = \frac{1}{e^{\frac{30-v}{10}} + 1}, \quad \alpha_n(v) = 0.01 \frac{10 - v}{e^{\frac{10-v}{10}} - 1}, \quad \beta_n(v) = 0.125e^{\frac{-v}{80}}$$

$\bar{g}_K = 36, \bar{g}_{Na} = 120, \bar{g}_L = 0.3, \nu_{Na} = 115, \nu_K = -12, \nu_L = 10.6$

“voltage clamp” experiments: insert electrode into axon, allows plot of current vs voltage, to get conductances

(needed to isolate effects of the different channels)
Experimental $g_K(V)(t)$ and $g_{Na}(V)(t)$ (different $V$’s) against fits (solid curves)
Response to constant currents: frequency modulation

0.05 mA
3 spikes in interval

0.1 mA
4 spikes in interval

0.15 mA
5 spikes in interval
$n, m, h$: 1-sec stimulus at $t = 5$, current=0.1

$m$ moves faster in response to stimulus: $\tau_m \ll \tau_n$ and $\ll \tau_h$

also: $h(t) + n(t) \approx 0.8$

each of these allows a simplification:
QSS assuming \( n(t) \equiv n_0 \) and \( h \equiv h_0 \)

\[
Cd\dot{v}/dt = -\bar{g}_K n_0^4 (v - v_K) - \bar{g}_{Na} m^3 h_0 (v - v_{Na}) - \bar{g}_L (v - v_L)
\]

\[
\tau_m(v) \frac{dm}{dt} = m_\infty(v) - m
\]

phase-plane bistable: three nullcline intersections (hard to see)

initial voltage (transient \( I \));
\( \rightarrow \) stable \( v_r \)
(“resting”)
or \( v_e \)
(“excited”)
separatrix = stable manifold of saddle \( v_s \)
FitzHugh: other time scale; and use \( h(t) + n(t) \approx 0.8 \)

eliminate \( h \), and also assume \( m(t) = \text{QSS value } m_\infty(v) \)

\[
C \frac{dv}{dt} = -\bar{g}_K n^4(v - v_K) - \bar{g}_{Na} m_\infty(v)^3(0.8 - n)(v - v_{Na}) - \bar{g}_L (v - v_{Na}) - \tau_n(v) \frac{dn}{dt} = n_\infty(v) - n
\]

excitable;
or, if \( I \) large
(nullcline moves),
relaxn. osc.
same amplitude,
change speed,
if change \( I \)