Lecture Notes in Mathematical Biology

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These notes were prepared for Math 336, Dynamical Models in Biology (formerly "Differential Equations in Biology"), a junior-level course designed for Rutgers Biomathematics undergraduate majors and attended as well by math, computer science, genetics, biomedical engineering, and other students. Math 336 does not cover discrete and probabilistic methods (genetics, DNA sequencing, protein alignment, etc.), which are the subject of a companion course.

The pre-requisites for Math 336 are four semesters of calculus, up to and including sophomore ordinary differential equations, plus an introductory linear algebra course. Students should be familiar with basic qualitative ideas (phase line, phase plane) as well as simple methods such as separation of variables for scalar ODE's.

However, it may be possible to use these notes without the ODE and linear algebra prerequisites, provided that the student does some additional reading.

The companion website

http://www.math.rutgers.edu/~sontag/336.html

is an integral part of these notes, and should be consulted for many additional homework problems (and answers), computer exercises, and other information.

An introduction to basic concepts in molecular biology can be found in that website as well.

The organization and much of the material were heavily inspired by Leah Keshet's beautiful book *Mathematical Models in Biology*, McGraw-Hill, 1988, as well as other sources, but there is a little more of an emphasis on "systems biology" ideas and less of an emphasis on traditional population dynamics and ecology. Topics like Lotka-Volterra predator-prey models are assumed to have been covered as examples in a previous ODE course.

The material in principle fits in a 1-semester course (but in pratice, due to time devoted to exam reviews, working out of homework problems, quizzes, etc., the last few topics may not all fit), and the goal was to provide students with an overview of the field. With more time, one would include much other material, such as Turing pattern-formation and detailed tissue modeling.

The writing is not textbook-like, but is "telegraphic" and streamlined. It is suited for easy reading and review, and is punctuated so as to make it easy for instructors to use directly during class, with no need to produce a separate outline.

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Please address comments, suggestions, and corrections to the author, whose email address can be found in the above website.

These notes will be continuously revised and updated. This is version 2, final for 2006.

Contents

1 Modeling, Growth, Number of Parameters

1.1 Exponential Growth: Modeling

Let us start by reviewing a subject treated in the basic differential equations course, namely how one derives differential equations for simple exponential growth,

Suppose that $N(t)$ counts the population of a microorganism in culture, at time t, and write the increment in a time interval $[t, t+h]$ as "$g(N(t), h)$", so that we have:

$$N(t+h) \;=\; N(t) \;+\; g(N(t), h)\,.$$

(The increment depends on the previous $N(t)$, as well as on the length of the time interval.)

We expand g using a Taylor series to second order:

$$g(N, h) \;=\; a + bN + ch + eN^2 + fh^2 + KNh \;+ \text{cubic and higher order terms}$$

($a, b, \ldots$ are some constants). Observe that

$$g(0, h) \equiv 0 \;\text{ and } g(N, 0) \equiv 0\,,$$

since there is no increment if there is no population or if no time has elapsed. The first condition tells us that

$$a + ch + fh^2 + \ldots \;\equiv\; 0\,,$$

for all h, so $a = c = f = 0$, and the second condition (check!) says that also $b = N = 0$.
Thus, we conclude that:

$$g(N, h) \;=\; KNh \;+ \text{ cubic and higher order terms.}$$

So, *for h and N small:*

$$N(t+h) \;=\; N(t) + KN(t)h\,, \tag{1}$$

which says that

the increase in population during a (small) time interval
is proportional to the interval length and initial population size.

This means, for example, that if we double the initial population or if we double the interval, the resulting population is doubled.

Obviously, (1) should not be expected to be true for large h, because of "compounding" effects. It may or may not be true for large N, as we will discuss later.

We next explore the consequences of assuming Equation (1) holds for all small $h{>}0$ and all N.

As usual in applied mathematics, the "*proof is in the pudding*":
one makes such an assumption, explores mathematical consequences that follow from it,
and generates predictions to be *validated experimentally*.
If the predictions pan out, we might want to keep the model.
If they do not, it is back to the drawing board and a new model has to be developed!

1.2 Exponential Growth: Math

From our approximation

$$KN(t)h \;=\; N(t+h) - N(t)$$

we have that

$$KN(t) \;=\; \frac{1}{h}(N(t+h) - N(t))$$

Taking the limit as $h \to 0$, and remembering the definition of derivative, we conclude that the right-hand side converges to $\dfrac{dN}{dt}(t)$. We conclude that N satisfies the following differential equation:

$$\boxed{\frac{dN}{dt} = KN}. \tag{2}$$

We may solve this equation by the method of *separation of variables*, as follows:

$$\frac{dN}{N} \;=\; K\,dt \;\Rightarrow\; \int \frac{dN}{N} \;=\; \int K\,dt \;\Rightarrow\; \ln N \;=\; Kt + c\,.$$

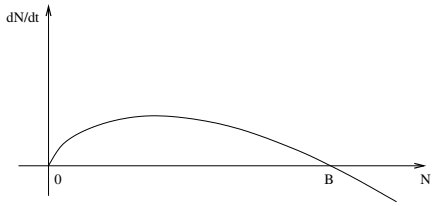
Evaluating at $t = 0$, we have $\ln N_0 = c$, so that $\ln(N(t)/N_0) = Kt$. Taking exponentials, we have:

$$\boxed{N(t) \;=\; N_0 e^{Kt}} \qquad \text{(exponential growth: Malthus, 1798)}$$

Bacterial populations tend to growth exponentially, so long as enough nutrients are available.

1.3 Limits to Growth: Modeling

Suppose now there is some number B (the *carrying capacity of the environment*) so that populations $N > B$ are not sustainable, i.e.. $dN/dt < 0$ whenever $N = N(t) > B$:



It is reasonable to pick the simplest function that satisfies the stated requirement;
in this case, a parabola:

$$\boxed{\frac{dN}{dt} \;=\; rN\left(1 - \frac{N}{B}\right)} \qquad \text{(for some constant } r > 0) \tag{3}$$

But there is a *different way to obtain the same equation*, as follows.
Suppose that the growth rate "K" in Equation (2) depends on *availability of a nutrient*:

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

where $C = C(t)$ denotes the amount of the nutrient, which is depleted in proportion to the population change: [1]

$$\frac{dC}{dt} \;=\; -\alpha \frac{dN}{dt} = -\alpha K N$$

[1] if $N(t)$ counts the number of individuals, this is somewhat unrealistic, as it the ignores depletion of nutrient due to the growth or individuals once they are born; it is sometimes better to think of $N(t)$ as the *total biomass* at time t

("20 new individuals formed $\Rightarrow \alpha \times 20$ less nutrient"). It follows that

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

and therefore $C(t) + \alpha N(t)$ must be constant, which we call "C_0"[2]
(we use this notation because $C(0) + \alpha N(0) \approx C(0)$, if the population starts as $N(0) \approx 0$).

So $K = \kappa C = \kappa(C_0 - \alpha N)$, and Equation (2) becomes the same equation as (3), just with different names of constants:

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

1.4 Logistic Equation: Math

We solve $\dfrac{dN}{dt} \;=\; rN\left(1 - \dfrac{N}{B}\right) \;=\; r\dfrac{N(B-N)}{B}$ using again the method of separation of variables:

$$\int \frac{B\,dN}{N(B-N)} = \int r\,dt\,.$$

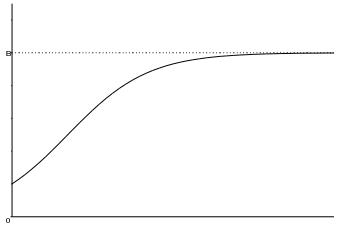
We compute the integral using a partial fractions expansion:

$$\int \left(\frac{1}{N} + \frac{1}{B-N}\right) dN \;=\; \int r\,dt \;\Rightarrow\; \ln\left(\frac{N}{B-N}\right) \;=\; rt + c \;\Rightarrow\; \frac{N}{B-N} \;=\; \widetilde{c}e^{rt} \;\Rightarrow\; N(t) \;=\; \frac{\widetilde{c}B}{\widetilde{c} + e^{-rt}}$$

$$\Rightarrow\; \widetilde{c} = N_0/(B - N_0) \quad \Rightarrow \quad \boxed{N(t) \;=\; \frac{N_0 B}{N_0 + (B - N_0)e^{-rt}}}$$

We can see that there is a B asymptote as $t \to \infty$. Let's graph with Maple:

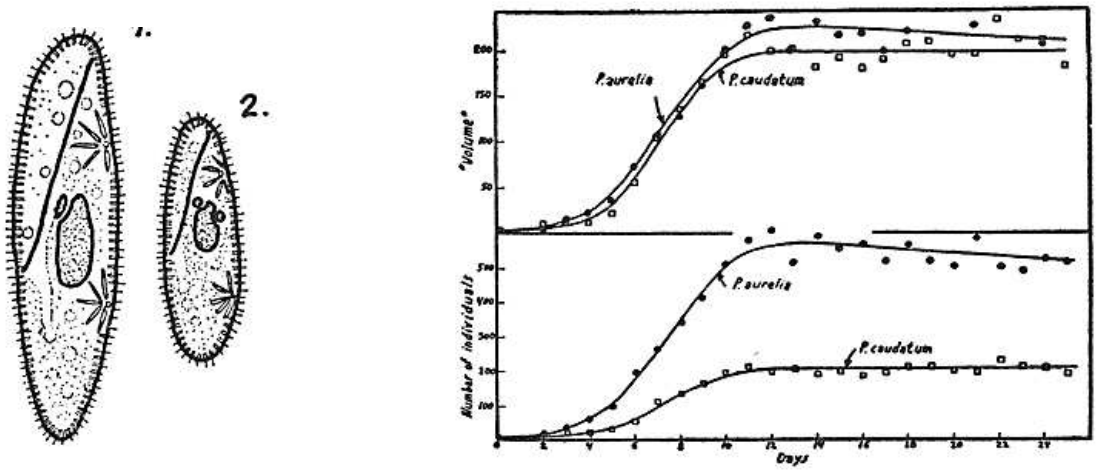
```
with(plots):
f(t):=t->(0.2)/(0.2+0.8*exp(-t)):
p1:=plot(f(t),0..8,0..1.3,tickmarks=[0,2],thickness=3,color=black):
g:=t->1:
p2:=plot(g(t),0..8,tickmarks=[0,2],thickness=2,linestyle=2,color=black):
display(p1,p2);
```



Gause's 1934 Experiments

G.F. Gause carried out experiments in 1934, involving Paramecium caudatum and Paramecium aurelia, which show clearly logistic growth:

[2] this is an example of a "conservation law", as we'll discuss later



(# individuals and volume of P. caudatum and P. aurelia, cultivated separately, medium changed daily, 25 days.)

1.5 Changing Variables, Rescaling Time

We had this equation for growth under nutrient limitations:

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

which we solved explicitly and graphed for some special values of the parameters C_0, κ, α.
But how do we know that "qualitatively" the solution "looks the same" for other parameter values?

Can the *qualitative* behavior of solutions depend upon the actual numbers C_0, κ, α?

First of all, we notice that we could collect terms as

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

(where $\widetilde{C}_0 = \kappa C_0$ and $\widetilde{\alpha} = \kappa\alpha$), so that we might as well suppose that $\kappa = 1$ (but change α, C_0).

But we can do even better and use changes of variables in N and t in order to eliminate the two remaining parameters!

We will always proceed as follows:

- Write each variable (in this example, N and t) as a product of a new variable and a still-to-be-determined constant.
- Substitute into the equations, simplify, and collect terms.
- Finally, pick values for the constants so that the equations (in this example, there is only one differential equation, but in other examples there may be several) have as few remaining parameters as possible.

The procedure can be done in many ways (depending on how you collect terms, etc.), so different people may get different solutions.

Let's follow the above procedure with our example. We start by writing: $N = N^*\hat{N}$ and $t = t^*\hat{t}$, *where stars indicate new variables and the hats are constants to be chosen*.

$$\frac{d\left(N^*\hat{N}\right)}{d\left(t^*\hat{t}\right)} \;=\; \kappa\left(C_0 - \alpha N^*\hat{N}\right)N^*\hat{N} \quad \rightsquigarrow \quad \frac{dN^*}{dt^*} \;=\; \kappa\hat{t}\alpha\hat{N}\left(\frac{C_0}{\alpha\hat{N}} - N^*\right)N^*$$

$\Big($We used $\frac{dN}{dt}=\frac{d(N^*\hat{N})}{d(t^*\hat{t})}=\frac{\hat{N}}{\hat{t}}\frac{dN^*}{dt^*}$, which is justified by the chain rule: $N^*(t^*)=\frac{1}{\hat{N}}N(t^*\hat{t}) \Rightarrow \frac{dN^*}{dt^*}(t^*)=\frac{1}{\hat{N}}\hat{t}\,\frac{dN}{dt}(t^*\hat{t})\Big)$

Look at this last equation: we'd like to make $\frac{C_0}{\alpha\hat{N}} = 1$ and $\kappa\hat{t}\alpha\hat{N} = 1$.

But this can be done! Just pick: $\boxed{\hat{N} := \frac{C_0}{\alpha}}$ and $\hat{t} = \frac{1}{\kappa\alpha\hat{N}}$, that is: $\boxed{\hat{t} := \frac{1}{\kappa C_0}}$

$$\rightsquigarrow \quad \frac{dN^*}{dt} = (1 - N^*)\,N^* \quad \text{or, drop stars, and write just} \quad \frac{dN}{dt} = (1 - N)\,N$$

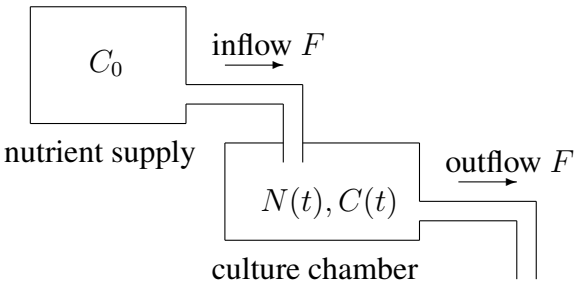
but we should remember that the new "N" and "t" are rescaled versions of the old ones

In other words, $N(t) = \hat{N}N^*(\hat{t}t^*) = \frac{C_0}{\alpha}N^*\left(\frac{1}{\kappa C_0}t^*\right)$.

We may solve the above equation and plot, and then the plot in original variables can be seen as a "stretching" of the plot in the new variables.

(We may think of N^*, t^* as quantity & time in some new units of measurement. This procedure is related to "nondimensionalization" of equations, which we'll mention later.)

1.6 A More Interesting Example: the Chemostat



$V =$ constant volume of solution in culture chamber
$F =$ (constant and equal) flows in vol/sec, e.g. m^3/s
$N(t) =$ bacterial concentration in mass/vol, e.g. g/m^3
$C_0, C(t) =$ nutrient concentrations in mass/vol
(C_0 assumed constant)
chamber is well-mixed
("continuously stirred tank reactor (CSTR)" in chem engr)

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:

  $$N(t + \Delta t) - N(t) \;\text{ due to growth} \quad = \; K(C(t))\,N(t)\,\Delta t$$

  (function $K(C)$ discussed below)

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

  $$C(t + \Delta t) - C(t) \;\text{ due to consumption} \quad = \; -\alpha\,[N(t + \Delta t) - N(t)]$$

1.7 Chemostat: Mathematical Model

total biomass: $N(t)\,V$ and total nutrient in culture chamber: $C(t)\,V$

biomass change in interval Δt 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 Δt, the volume out is: $F \cdot \Delta t$ ($\frac{m^3}{s} s =) m^3$
so, since the concentration is $N(t)$ g/m^3, the mass out is: $N(t) \cdot F \cdot \Delta t$ g
and so the contribution to $d(NV)/dt$ is "$-N(t)F$"

for $d(CV)/dt$ equation:
we have three terms: $-\alpha K(C)NV$ (depletion), $-C(t)F$ (outflow), and $+C_0F$ (inflow), $\rightsquigarrow$

$$\begin{aligned}\frac{d(NV)}{dt} &= K(C)NV - NF\\ \frac{d(CV)}{dt} &= -\alpha K(C)NV - CF + C_0F\,.\end{aligned}$$

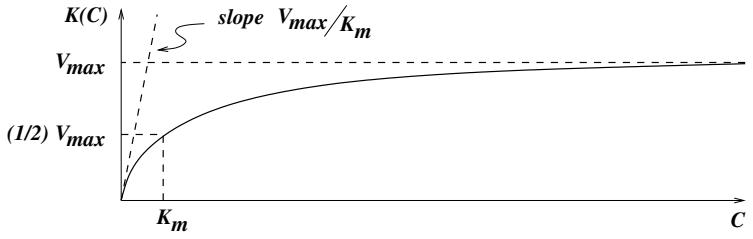
Finally, divide by the constant V to get this system of equations on N, C:

$$\begin{aligned}\frac{dN}{dt} &= K(C)N - NF/V\\ \frac{dC}{dt} &= -\alpha K(C)N - CF/V + C_0F/V\end{aligned}$$

1.8 Michaelis-Menten Kinetics

A reasonable choice for "$K(C)$" is as follows (later, we come back to this topic in much more detail):

$$K(C) \;=\; \frac{k_{\max}\,C}{k_n + C} \qquad \text{or, in another very usual notation: } \frac{V_{\max}\,C}{K_{\mathrm{m}} + C}\;.$$



This gives linear growth for small nutrient concentrations:

$$K(C) \approx K(0) + K'(0)C \;=\; \frac{V_{\max}\,C}{K_{\mathrm{m}}}$$

but saturates at $V_{\max}$ as $C \to \infty$.

(More nutrient $\Rightarrow$ more growth, but only up to certain limits — think of a buffet dinner!)

Note that when $C = K_{\rm m}$, the growth rate is 1/2 ("m" for middle) of maximal, i.e. $V_{\max}/2$,

We thus have these equations for the chemostat with MM Kinetics:

$$\begin{aligned}\frac{dN}{dt} &= \frac{k_{\max} C}{k_n + C} N - (F/V)N \\ \frac{dC}{dt} &= -\alpha \frac{k_{\max} C}{k_n + C} N - (F/V)C + (F/V)C_0\end{aligned}$$

Our next goal is to study the behavior of this system of two ODE's for all possible values of the six parameters $k_{\max}, k_n, F, V, C_0, \alpha$.

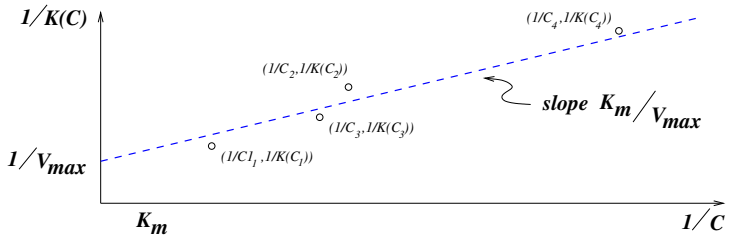
1.9 Side Remark: "Lineweaver-Burk plot" to Estimate Parameters

Suppose we measured experimentally $K(C_i)$ for various values C_i.
How does one estimate $K_{\rm m}$ and $V_{\max}$?

Solution: observe that

$$\frac{1}{K(C)} = \frac{K_{\rm m} + C}{V_{\max} C} = \frac{1}{V_{\max}} + \frac{K_{\rm m}}{V_{\max}} \cdot \frac{1}{C}$$

therefore, $1/K(C)$ is a *linear* function of $1/C$!
Thus, just plot $1/K(C)$ against $1/C$ and fit a line (linear regression).



1.10 Chemostat: Reducing Number of Parameters

Following the procedure outlined earlier, we write: $C = C^*\hat{C},\ N = N^*\hat{N},\ t = t^*\hat{t}$, and substitute:

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

$\frac{dN}{dt} = \frac{d(N^*\hat{N})}{d(t^*\hat{t})} = \frac{\hat{N}}{\hat{t}}\frac{dN^*}{dt^*}$ & $\frac{dC}{dt} = \frac{d(C^*\hat{C})}{d(t^*\hat{t})} = \frac{\hat{C}}{\hat{t}}\frac{dC^*}{dt^*} \rightsquigarrow$

$$\begin{aligned}\frac{dN^*}{dt^*} &= \frac{\hat{t}\, k_{\max} C^*\hat{C}}{k_n + C^*\hat{C}} N^* - \frac{\hat{t}F}{V} N^* \\ \frac{dC^*}{dt^*} &= -\alpha \frac{\hat{t}\, k_{\max} C^*}{k_n + C^*\hat{C}} N^*\hat{N} - \frac{\hat{t}F}{V} C^* + \frac{\hat{t}F}{\hat{C}V} C_0\end{aligned}$$

or equivalently:

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

It would be nice, for example, to make $k_n/\hat{C}=1$, $\dfrac{\hat{t}F}{V}=1$, and $\dfrac{\alpha\hat{t}\,k_{\max}\hat{N}}{\hat{C}}=1$. This can indeed be done, provided that we define: $\hat{C}:=k_n$, $\quad \hat{t}:=\dfrac{V}{F}$, $\quad$ and $\hat{N}:=\dfrac{\hat{C}}{\alpha\hat{t}\,k_{\max}}=\dfrac{k_n}{\alpha\hat{t}\,k_{\max}}=\dfrac{k_nF}{\alpha V\,k_{\max}}$

$$\rightsquigarrow \quad \begin{aligned}\frac{dN^*}{dt^*} &= \left(\frac{Vk_{\max}}{F}\right)\frac{C^*}{1+C^*}\,N^* - N^* \\ \frac{dC^*}{dt^*} &= -\frac{C^*}{1+C^*}\,N^* - C^* + \frac{C_0}{k_n}\end{aligned}$$

or, dropping stars and introducing two new constants $\alpha_1 = \left(\frac{Vk_{\max}}{F}\right)$ and $\alpha_2=\dfrac{C_0}{k_n}$ we end up with:

$$\begin{aligned}\frac{dN}{dt} &= \alpha_1\frac{C}{1+C}\,N - N \\ \frac{dC}{dt} &= -\frac{C}{1+C}\,N - C + \alpha_2\end{aligned}$$

We will study how the behavior of the chemostat depends on these two parameters, always remembering to "translate back" into the original parameters and units.

The old and new variables are related as follows:

$$N(t)=\hat{N}N^*(\hat{t}t^*)=\frac{k_nF}{\alpha V\,k_{\max}}N^*\left(\frac{V}{F}\,t\right), \qquad C(t)=\hat{C}C^*(\hat{t}t^*)=k_nC^*\left(\frac{V}{F}\,t\right)$$

Additional homework problem: show that with $\hat{t}=\frac{1}{k_{max}}$, $\hat{C}=\frac{\hat{t}FC_0}{V}$, and same $\hat{N}$, we also can reduce to two parameters.

Remark on units

Since $k_{\max}$ is a rate (obtained at saturation), it has units time^{-1}; thus, α_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 $k_{\max}$), so also α_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?) We do not have time to cover the topic of units and non-dimensionalization in this course, however.

2 Steady States and Linearized Stability Analysis

2.1 Steady States

The key to the "geometric" analysis of systems of ODE's is to write them in vector form:

$$\frac{dX}{dt} \;=\; F(X) \qquad \text{(where } F \text{ is a vector function and } X \text{ is a vector)}\,.$$

The vector $X = X(t)$ has some number n of components, each of which is a function of time.
One writes the 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 one uses notations that are related to the problem being studied,
like N and C for the number (or biomass) of a population and C for the concentration of a nutrient.
For example, the chemostat

$$\begin{aligned}\frac{dN}{dt} &= \alpha_1 \frac{C}{1+C}\, N - N \\ \frac{dC}{dt} &= -\frac{C}{1+C}\, N - C + \alpha_2\end{aligned}$$

may be written as $\dfrac{dx}{dt} = F(X) = \begin{pmatrix} f(N,C) \\ g(N,C) \end{pmatrix}$, provided that we define:

$$\begin{aligned} f(N,C) &= \alpha_1 \frac{C}{1+C}\, N - N \\ g(N,C) &= -\frac{C}{1+C}\, N - C + \alpha_2\,. \end{aligned}$$

By definition, a *steady state* or *equilibrium*[3] is any root of the algebraic equation

$$F(\bar{X}) \;=\; 0$$

that results when we set the right-hand side to zero.

For example, for the chemostat, a steady state is the same thing as a solution $X = (N, C)$ of the two simultaneous equations

$$\begin{aligned} \alpha_1 \frac{C}{1+C}\, N - N &= 0 \\ -\frac{C}{1+C}\, N - C + \alpha_2 &= 0\,. \end{aligned}$$

Let us find the equilibria for this example.

A trick which sometimes works for chemical and population problems, is as follows.
We factor the first equation:

$$\left(\alpha_1 \frac{C}{1+C} - 1\right) N \;=\; 0\,.$$

[3] the word "equilibrium" is used in mathematics as a synonym for steady state, but the term has a more restrictive meaning for physicists and chemists

So, for an equilibrium $\bar{X} = (\bar{N}, \bar{C})$,

$$\text{either} \quad \bar{N} \,=\, 0 \quad \text{or} \quad \alpha_1 \frac{\bar{C}}{1+\bar{C}} \,=\, 1\,.$$

We consider each of these two possibilities separately.

In the first case, $\bar{N} = 0$. Since also it must hold that

$$-\frac{\bar{C}}{1+\bar{C}}\,\bar{N} - \bar{C} + \alpha_2 \,=\, -\bar{C} + \alpha_2 \,=\, 0\,,$$

we conclude that $\bar{X} = (0, \alpha_2)$ (no bacteria alive, and nutrient concentration α_2).

In the second case, $\bar{C} = \frac{1}{\alpha_1 - 1}$, and therefore the second equation gives $\bar{N} = \alpha_1 \left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right)$ (check!).

So we found two equilibria:

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

However, observe that 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.*[4]

The first steady state is always well-defined in this sense, but not the second.

This equilibrium $\bar{X}_2$ is well-defined and makes physical sense only if

$$\alpha_1 > 1 \;\text{ and }\; \alpha_2 > \frac{1}{\alpha_1 - 1} \tag{4}$$

or equivalently:

$$\alpha_1 > 1 \;\text{ and }\; \alpha_2(\alpha_1 - 1) > 1\,. \tag{5}$$

Reducing the number of parameters to just two (α_1 and α_2) allowed us to obtain this very elegant and compact condition. *But this is not a satisfactory way to explain our conclusions, because α_1, α_2 were only introduced for mathematical convenience, but were not part of the original problem.*

Since, $\hat{t} := \frac{V}{F}$, $\alpha_1 = \hat{t}\, k_{\max} = \frac{V}{F} k_{\max}$ and $\alpha_2 = \frac{\hat{t}F}{\hat{C}V} C_0 = \frac{C_0}{\hat{C}} = \frac{C_0}{k_n}$, the conditions are:

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

The first condition means roughly that the maximal possible bacterial reproductive rate is larger than the tank emptying rate, which makes intuitive sense. *As an exercise, you should similarly interpret "in words" the various things that the second condition is saying.*

Meaning of Equilibria: If a point $\bar{X}$ is an equilibrium, then the 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.

In other words, an equilibrium is a point where the solution stays forever.

As you studied in your ODE class, an equilibrium may be stable or unstable (think of a pencil perfectly balanced on the upright position). We next review stability.

[4] Analogy: we are told that the length L of some object is a root of the equation $L^2 - 4 = 0$. We can then conclude that the length must be $L = 2$, since the other root, $L = -2$, cannot correspond to a length.

2.2 Linearization

We wish to analyze the behavior of solutions of the ODE system $dX/dt = F(X)$ *near a given steady state* $\bar{X}$. For this purpose, it is convenient to introduce the displacement (translation) relative to $\bar{X}$:

$$\hat{X} = X - \bar{X}$$

and to write an equation for the variables $\hat{X}$. We have:

$$\frac{d\hat{X}}{dt} \;=\; \frac{dX}{dt} - \frac{d\bar{X}}{dt} \;=\; \frac{dX}{dt} - 0 \;=\; \frac{dX}{dt} \;=\; F(\hat{X}+\bar{X}) \;=\; \underbrace{F(\bar{X})}_{=0} + F'(\bar{X})\hat{X} + \underbrace{o(\hat{X})}_{\approx 0} \;\approx\; A\hat{X}$$

where $A = F'(\bar{X})$ is the *Jacobian* of F evaluated at $\bar{X}$.
We dropped higher-order-than-linear terms in $\hat{X}$ because we are only interested in $\hat{X} \approx 0$ (small displacements $X \approx \bar{X}$ from $\bar{X}$ are the same as small $\hat{X}$'s).

Recall that the Jacobian, or "derivative of a vector function," is defined as the $n \times n$ matrix whose (i,j)th entry is $\partial f_i/\partial x_j$, if f_i is the ith coordinate of F and x_j is the jth coordinate of x.

One often drops the "hats" and writes the above *linearization* simply as $dX/dt = AX$,
but it is extremely important to remember that what this equation represents:
it is an equation for the displacement from a particular equilibrium $\bar{X}$.
More precisely, it is an equation for *small* displacements from $\bar{X}$.
(And, for any other equilibrium $\bar{X}$, a different matrix A will, generally speaking, result).

For example, let us take the chemostat, after a reduction of the number of parameters:

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

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

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

In particular, at the point $\bar{X}_2$, where $\bar{C} = \frac{1}{\alpha_1 - 1}$, $\bar{N} = \frac{\alpha_1(\alpha_1\alpha_2 - \alpha_2 - 1)}{\alpha_1 - 1}$ we have:

$$\begin{bmatrix} 0 & \beta\,(\alpha_1 - 1) \\ -\dfrac{1}{\alpha_1} & -\dfrac{\beta(\alpha_1 - 1) + \alpha_1}{\alpha_1} \end{bmatrix}$$

where we used the shorthand: $\beta = \alpha_2(\alpha_1 - 1) - 1$. (Prove this as an exercise!)

Remark. An important result, the Hartman-Grobman Theorem, justifies the study of linearizations. It states that solutions of the nonlinear system $\frac{dX}{dt} = F(X)$ in the vicinity of the steady state $\bar{X}$ look "qualitatively" just like solutions of the linearized equation $dX/dt = AX$ do in the vicinity of the point $X = 0$.[5]

For linear systems, stability may be analyzed by looking at the eigenvalues of A, as we see next.

[5]The theorem assumes that none of the eigenvalues of A have zero real part ("hyperbolic fixed point"). "Looking like" is defined in a mathematically precise way using the notion of "homeomorphism" which means that the trajectories look the same after a continuous invertible transformation, that is, a sort of "nonlinear distortion" of the phase space.

2.3 Review of (Local) Stability

For the purposes of this course, we'll say that a linear system $dX/dt = AX$, where A is $n \times n$ matrix, is *stable* if all solutions $X(t)$ have the property that $X(t) \to 0$ as $t \to \infty$. The main theorem is:

stability is equivalent to: the real parts of all the eigenvalues of A are negative

For nonlinear systems $dX/dt = F(X)$, one applies this condition as follows:[6]

- For each steady state $\bar{X}$, compute A, the Jacobian of F evaluated at $\bar{X}$, and test its eigenvalues.
- If *all* the eigenvalues of A have negative real part, conclude *local stability*:
  every solution of $dX/dt = F(X)$ that starts near $X = \bar{X}$ converges to $\bar{X}$ as $t \to \infty$.
- If A has even one eigenvalue with positive real part, then the corresponding nonlinear system $dX/dt = F(X)$ is *unstable* around $\bar{X}$, meaning that at least some solutions that start near $\bar{X}$ will move away from $\bar{X}$.

The linearization $dX/dt = AX$ at a steady state $\bar{X}$ *says nothing at all about global stability, that is to say, about behaviors of $dX/dt = F(X)$ that start at initial conditions that are far away from $\bar{X}$.*
For example, compare the two equations: $dx/dt = -x - x^3$ and $dx/dt = -x + x^2$.
In both cases, the linearization at $x = 0$ is just $dx/dt = -x$, which is stable.
In the first case, it turns out that all the solutions of the nonlinear system also converge to zero.
(Just look at the phase line.)
However, in the second case, even though the linearization is the same, it is not true that all solutions converge to zero. For example, starting at a state $x(0) > 1$, solutions diverge to $+\infty$ as $t \to \infty$.
(Again, this is clear from looking at the phase line.)

It is often confusing to students that from the fact that all solutions of $dX/dt = AX$ converge to *zero*, one concludes for the nonlinear system that all solutions converge to $\bar{X}$.
The confusion is due simply to notations: we are really studying $d\hat{X}/dt = A\hat{X}$, where $\hat{X} = X - \bar{X}$, but we usually drop the hats when looking at the linear equation $dX/dt = AX$.

Regarding the eigenvalue test for linear systems, let us recall, informally, the basic ideas.

The general solution of $dX/dt = AX$, assuming[7] distinct eigenvalues λ_i for A, can be written as:

$$X(t) \;=\; \sum_{i=1}^{n} c_i\, e^{\lambda_i t} v_i$$

where for each i, $Av_i = \lambda_i v_i$ (an eigenvalue/eigenvector pair) and the c_i are constants (that can be fit to initial conditions).

It is not surprising that eigen-pairs appear: if $X(t) = e^{\lambda t} v$ is solution, then $\lambda e^{\lambda t} v = dX/dt = Ae^{\lambda t} v$, which implies (divide by $e^{\lambda t}$) that $Av = \lambda v$.

[6] Things get very technical and difficult if A has eigenvalues with exactly zero real part. The field of mathematics called Center Manifold Theory studies that problem.

[7] If there are repeated eigenvalues, one must fine-tune a bit: it is necessary to replace some terms $c_i\, e^{\lambda_i t} v_i$ by $c_i\, t\, e^{\lambda_i t} v_i$ (or higher powers of t) and to consider "generalized eigenvectors."

We also recall that everything works in the same way even if some eigenvalues are complex, though it is more informative to express things in alternative real form (using Euler's formula).

To summarize:

- Real eigenvalues λ correspond[8] to terms in solutions that involve real exponentials $e^{\lambda t}$, which can only approach zero as $t \to +\infty$ if $\lambda < 0$.
- Non-real complex eigenvalues $\lambda = a + ib$ are associated to oscillations. They correspond[9] to terms in solutions that involve complex exponentials $e^{\lambda t}$. Since one has the general formula $e^{\lambda t} = e^{at+ibt} = e^{at}(\cos bt + i \sin bt)$, solutions, when re-written in real-only form, contain terms of the form $e^{at}\cos bt$ and $e^{at}\sin bt$, and therefore converge to zero (with decaying oscillations of "period" $2\pi/b$) provided that $a < 0$, that is to say, that the real part of λ is negative. Another way to see this if to notice that asking that $e^{\lambda t} \to 0$ is the same as requiring that the magnitude $\left|e^{\lambda t}\right| \to 0$. Since $\left|e^{\lambda t}\right| = e^{at}\sqrt{(\cos bt)^2 + (\sin bt)^2} = e^{at}$, we see once again that $a < 0$ is the condition needed in order to insure that $e^{\lambda t} \to 0$

Special Case: 2 by 2 Matrices

In the case $n = 2$, it is easy to check directly if $dX/dt = AX$ is stable, without having to actually compute the eigenvalues. Suppose that

$$A = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}$$

and remember that

$$\text{trace } A = a_{11} + a_{22}\,, \quad \det A = a_{11}a_{22} - a_{12}a_{21}\,.$$

Then:

$$\boxed{\textit{stability is equivalent to: trace } A < 0 \textit{ and } \det A > 0.}$$

(Proof: the characteristic polynomial is $\lambda^2 + b\lambda + c$ where $c = \det A$ and $b = -\text{trace } A$. Both roots have negative real part if

$$\text{(complex case)} \quad b^2 - 4c < 0 \;\text{ and }\; b > 0$$

or

$$\text{(real case)} \;\; b^2 - 4c \geq 0 \;\text{ and }\; -b \pm \sqrt{b^2 - 4c} < 0$$

and the last condition is equivalent to $\sqrt{b^2 - 4c} < b$, i.e. $b > 0$ and $b^2 > b^2 - 4c$, i.e. $b > 0$ and $c > 0$.)

Moreover, solutions are oscillatory (complex eigenvalues) if $(\text{trace } A)^2 < 4 \det A$, and exponential (real eigenvalues) otherwise. We come back to this later (trace/determinant plane).

(If you are interested: for higher dimensions (n>2), one can also check stability without computing eigenvalues, although the conditions are more complicated; google *Routh-Hurwitz Theorem*.)

[8] To be precise, if there are repeated eigenvalues, one may need to also consider terms of the slightly more complicated form "$t^k e^{\lambda t}$" but the reasoning is exactly the same in that case.

[9] For complex repeated eigenvalues, one may need to consider terms $t^k e^{\lambda t}$.

2.4 Chemostat: Local Stability

Let us assume that the positive equilibrium $\bar{X}_2$ exists, that is:

$$\alpha_1 > 1 \text{ and } \beta = \alpha_2(\alpha_1 - 1) > 1\,.$$

In that case, the Jacobian is:

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

where we used the shorthand: $\beta = \alpha_2(\alpha_1 - 1) - 1$.

The trace of this matrix A is negative, and the determinant is positive, because:

$$\alpha_1 - 1 > 0 \quad \text{and} \quad \beta > 0 \quad \Rightarrow \quad \frac{\beta(\alpha_1 - 1)}{\alpha_1} \;>\; 0\,.$$

So we conclude (local) stability of the positive equilibrium.

So, at least, if the initial the concentration $X(0)$ is close to $\bar{X}_2$, then $X(t) \to \bar{X}_2$ as $t \to \infty$.
(We later see that global convergence holds as well.)

What about the other equilibrium, $\bar{X}_1 = (0, \alpha_2)$? We compute the Jacobian:

$$A \;=\; F'(\bar{X}_1) \;=\; \left(\begin{array}{cc} \alpha_1 \dfrac{C}{1+C} - 1 & \dfrac{\alpha_1 N}{(1+C)^2} \\ -\dfrac{C}{1+C} & -\dfrac{N}{(1+C)^2} - 1 \end{array} \right) \Bigg|_{N=0, C=\alpha_2} \;=\; \left(\begin{array}{cc} \alpha_1 \dfrac{\alpha_2}{1+\alpha_2} - 1 & 0 \\ -\dfrac{\alpha_2}{1+\alpha_2} & -1 \end{array} \right)$$

and thus see that its determinant is:

$$1 - \alpha_1 \frac{\alpha_2}{1+\alpha_2} \;=\; \frac{1 + \alpha_2 - \alpha_1\alpha_2}{1+\alpha_2} \;=\; \frac{1 + \alpha_2(1-\alpha_1)}{1+\alpha_2} \;=\; \frac{1-\alpha}{1+\alpha_2} \;<\; 0$$

and therefore the steady state $\bar{X}_1$ is *unstable*.

It turns out that the point $\bar{X}_1$ is a saddle: small perturbations, where $N(0) > 0$, will tend away from $\bar{X}_1$. (Intuitively, if even a small amount of bacteria is initially present, growth will occur. As it turns out, the growth is so that the other equilibrium $\bar{X}_1$ is approached.)

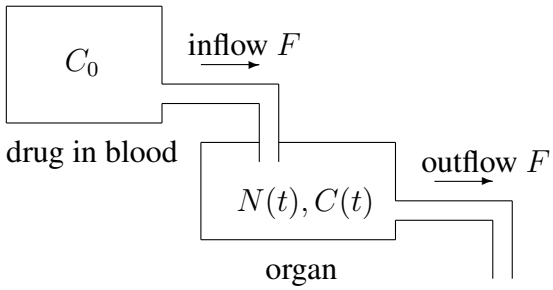
Additional homework problem: Analyze stability of $\bar{X}_1$ when the parameters are chosen such that the equilibrium $\bar{X}_2$ does not exist.

3 More Modeling Examples

3.1 Effect of Drug on Cells in an Organ

A modification of the chemostat model can be used as a simple model of how
a drug in the blood (e.g. a chemotherapy agent) affects a cells in a certain organ
(or more specifically, a subset of cells, such as cancer cells).

Now, "C_0" represents the concentration of the drug in the blood flowing in,
and V is the volume of blood in the organ, or, more precisely,
the volume of blood in the region where the cells being treated (e.g., a tumor).



$V =$ volume of blood
$F = F_{\text{in}} = F_{\text{out}}$ are the blood flows
$N(t) =$ number of cells (assumed equal in mass) exposed to drug
$C_0, C(t) =$ drug concentrations

In drug infusion models, if a pump delivers the drug at a certain concentration,
the actual C_0 would account for the dilution rate when injected into the blood.

We assume that things are "well-mixed" although more realistic models use the fact
that drugs may only affect e.g. the outside layers of a tumor.

The flow F represents blood brought into the organ through an artery, and the blood coming out.

The key differences with the chemostat are:

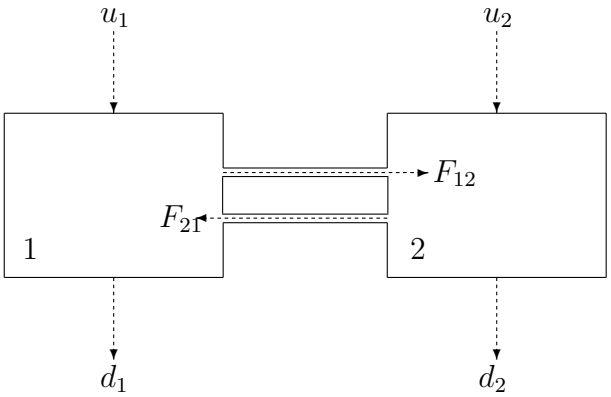
- the cells in question reproduce at a rate that is, in principle, independent of the drug,
- but the drug has a negative effect on the growth, a "kill rate" that we model by some function $K(C)$, and
- the outflow contains only (unused) drug, and not any cells.

If we assume that cells reproduce exponentially and the drug is consumed at a rate proportional to the kill rate $K(C)N$, we are led to:

$$\begin{aligned} \frac{dN}{dt} &= -K(C)N + kN \\ \frac{dC}{dt} &= -\alpha K(C)N - \frac{CF}{V} + \frac{C_0 F}{V}\,. \end{aligned}$$

A homework problem asks you to analyze these equations, as well as a variation of the model,
in which the reproduction rate follows a different law (Gompertz law)

3.2 Compartmental Models



Compartmental models are very common in pharmacology and many other biochemical applications.

They are used to account for different behaviors in different tissues.

In the simplest case, there are two compartments, such as an organ and the blood in circulation.

We model the two-compartment case now (the general case is similar).

We use two variables x_1, x_2, for the concentrations (mass/vol) of a substance
(such as a drug, a hormone, a metabolite, a protein, or some other chemical) in each compartment, and m_1, m_2 for the respective masses.

The flow (vol/sec) from compartment i to compartment j is denoted by F_{ij}.

When the substance happens to be in compartment i, a fraction $d_i\,\Delta t$ of its mass, degrades, or is consumed, in any small interval of time Δt,

Sometimes, there may may also be an external source of the substance, being externally injected; in that case, we let u_i denote the inflow (mass/sec) into compartment i.

On a small interval Δt, the increase (or decrease, if the number is negative) in the mass in the ith compartment is:

$$m_i(t+\Delta t) - m_i(t) \;=\; -F_{12}x_1\Delta t + F_{21}x_2\Delta t - d_1m_1\Delta t + u_1\Delta t\,.$$

(For example, the mass flowing in from compartment 1 to compartment 2 is computed as:

$$\text{flow} \times \text{concentration in } 1 \times \text{time} \;=\; \frac{\text{vol}}{\text{time}} \times \frac{\text{mass}}{\text{vol}} \times \text{time}\;\;.)$$

Similarly, we have an equation of m_2. We divide by Δt and take limits as $\tau \to 0$, leading to the following system of two linear differential equations:

$$\begin{aligned}
\frac{dm_1}{dt} &= -F_{12}m_1/V_1 + F_{21}m_2/V_1 - d_1m_1 + u_1\\
\frac{dm_2}{dt} &= \;\;F_{12}m_1/V_1 - F_{21}m_2/V_2 - d_2m_1 + u_2
\end{aligned}$$

(we used that $x_i = m_i/V_i$). So, for the concentrations $x_i = m_i/V_i$, we have:

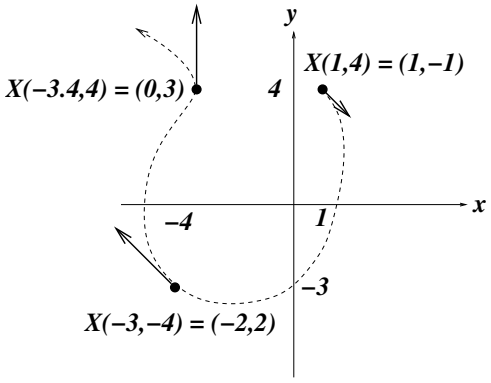
$$\begin{aligned}
\frac{dx_1}{dt} &= -\frac{F_{12}}{V_1}x_1 + \frac{F_{21}}{V_1}x_2 - d_1x_1 + \frac{u_1}{V_1}\\
\frac{dx_2}{dt} &= \;\;\frac{F_{12}}{V_2}x_1 - \frac{F_{21}}{V_2}x_2 - d_2m_1 + \frac{u_2}{V_2}
\end{aligned}$$

A homework problem asks you to analyze an example of such a system.

4 Geometric Analysis: Vector Fields, Phase Planes

4.1 Review: Vector Fields

One interprets $\frac{dX}{dt}=F(X)$ as a "flow" in $\mathbb{R}^n$: at each position X, $F(X)$ is a vector that indicates in which direction to move (and its magnitude says at what speed).



("go with the flow" or "follow directions").

We draw pictures in two dimensions, but this geometric interpretation is valid in any dimension.

"Zooming in" at steady states[10] $\bar{X}$ amounts to looking at the linearization $F(X) \approx AX$,
where $A =$ Jacobian $F'(\bar{X})$ evaluated at this equilibrium.

You should work-out some phase planes using JOde or some other package.

4.2 Review: Linear Phase Planes

Cases of distinct real and nonzero[11] eigenvalues $\lambda_1 \neq \lambda_2$:

1. both λ_1, λ_2 are negative: *sink* (stable node)

   all trajectories approach the origin, tangent to the direction of eigenvectors corresponding to the eigenvalue which is closer to zero.

2. both λ_1, λ_2 are positive: *source* (unstable node)

   all trajectories go away from the origin, tangent to the direction of eigenvectors corresponding to the eigenvalue which is closer to zero.

3. λ_1, λ_2 have opposite signs: *saddle*

Cases of complex eigenvalues λ_1, λ_2, i.e. $= a \pm ib$ ($b \neq 0$):

1. $a = 0$: *center*

[10] Zooming into points that are not equilibria is not interesting; a theorem called the "flow box theorem" says (for a vector field defined by differentiable funcions) that the flow picture near a point $\bar{X}$ that is not an equilibrium is quite "boring" as it consists essentially of a bundle of parallel lines.

[11] The cases when one or both eigenvalues are zero, or are both nonzero but equal, can be also analyzed, but they are a little more complicated.

solutions[12] look like ellipses (or circles);

to decide if they more clockwise or counterclockwise, just pick one point in the plane and see which direction Ax points to;

the plots of $x(t)$ and $y(t)$ vs. time look roughly like a graph of sine or cosine.

2. $\underline{a < 0}$: *spiral sink* (stable spiral)

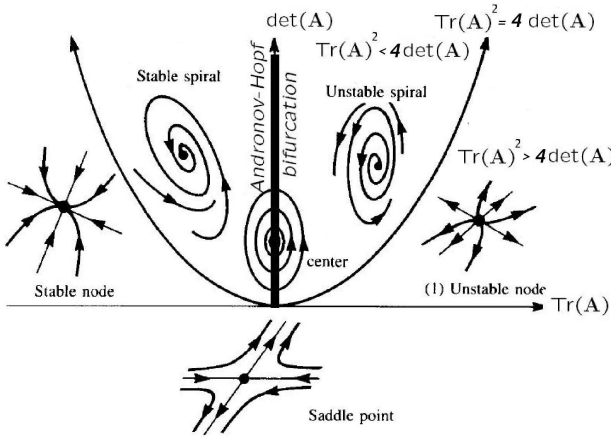
   trajectories go toward the origin while spiraling around it, and direction can be figured out as above;

   the plots of $x(t)$ and $y(t)$ vs. time look roughly like the graph of a sine or cosine that is dying out (damped oscillation).

3. $\underline{a > 0}$: *spiral source* (unstable spiral)

   trajectories go away from the origin while spiraling around it, and direction can be figured out as above;

   the plots of $x(t)$ and $y(t)$ vs. time look roughly like the graph of a sine or cosine that that is exploding (increasing oscillation).



Trace/Determinant Plane

We next compute the type of the local equilibria for the chemostat example,
assuming that $\alpha_1 > 1$ and $\alpha_2(\alpha_1 - 1) - 1 > 0$ (so $\bar{X}_2$ is positive).

Recall that the we had computed the Jacobian at the positive equilibrium $\bar{X}_2 = \left(\alpha_1\left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right), \frac{1}{\alpha_1 - 1}\right)$:

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

where we used the shorthand: $\beta = \alpha_2(\alpha_1 - 1) - 1$.

We already say that the trace is negative. Note that:

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

and therefore $\text{tr}^2 - 4\det = 1 + 2\Delta + \Delta^2 - 4\Delta = (1 - \Delta)^2 > 0$, so the point $\bar{X}_2$ is a *stable node*.[13]

Show as an exercise that $\bar{X}_1$ is a saddle.

[12] Centers are highly "non-robust" in a way that we will discuss later, so they rarely appear in realistic biological models.

[13] If $\Delta \neq 1$; otherwise there are repeated real eigenvalues; we still have stability, but we'll ignore that very special case.

4.3 Nullclines

Linearization helps understand the "local" picture of flows.[14]

It is much harder to get *global* information, telling us how these local pictures fit together ("connecting the dots" so to speak).

One useful technique when drawing global pictures is that of *nullclines*.

The x_i-nullcline (if the variables are called $x_1, x_2, \ldots$) is the set where $\frac{dx_i}{dt} = 0$.
This set may be the union of several curves and lines, or just one such curve.

The intersections between the nullclines are the steady states. This is because each nullcline is the set where $dx_1/dt = 0, dx_2/dt = 0, \ldots$, so intersecting gives points at which *all* $dx_i/dt = 0$, that is to say $F(X) = 0$ which is the definition of steady states.

As an example, let us take the chemostat, for which the vector field is $F(X) = \begin{pmatrix} f(N,C) \\ g(N,C) \end{pmatrix}$, where:

$$\begin{aligned} f(N,C) &= \alpha_1 \frac{C}{1+C} N - N \\ g(N,C) &= -\frac{C}{1+C} N - C + \alpha_2 \,. \end{aligned}$$

The N-nullcline is the set where $dN/dt = 0$, that is, where $\alpha_1 \frac{C}{1+C} N - N = 0$.
Since we can factor this as $N(\alpha_1 \frac{C}{1+C} - 1) = 0$, we see that:

$$\text{the } N\text{-nullcline is the union of a horizontal and a vertical line:} \quad C = \frac{1}{\alpha_1 - 1} \quad \text{and} \quad N = 0 \,.$$

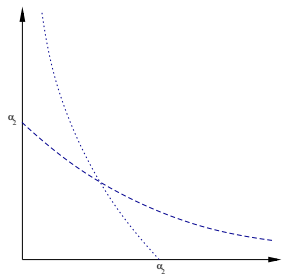
On this set, the arrows are vertical, because $dN/dt = 0$ (no movement in N direction).

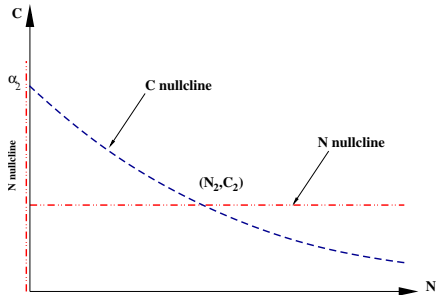
The C-nullcline is obtained by setting $-\frac{C}{1+C} N - C + \alpha_2 = 0$.
We can describe a curve in any way we want; in this case, it is a little simpler to solve $N = N(C)$ than $C = C(N)$:

$$\text{the } C\text{-nullcline is the curve:} \quad N = (\alpha_2 - C)\frac{1+C}{C} = -1 - C + \frac{\alpha_2}{C} + \alpha_2 \,.$$

On this set, the arrows are parallel to the N*-axis, because* $dC/dt = 0$ (no movement in C direction).

To plot, note that $N(\alpha_2) = 0$ and $N(C)$ is a decreasing function of C and goes to $+\infty$ as $C \searrow 0$, and then obtain $C = C(N)$ by flipping along the main diagonal (dotted and dashed curves in the graph, respectively). We show this construction and the nullclines look as follows:





[14] Actually, linearization is sometimes not sufficient even for local analysis. Think of $dx/dt = x^3$ and $dx/dt = -x^3$, which have the same linearization ($dx/dt = 0$) but very different local pictures at zero. The area of mathematics called "Center manifold theory" deals with such very special situations, where eigenvalues may be zero or more generally have zero real part.

Assuming that $\alpha_1 > 1$ and $\alpha_2 > 1/(\alpha_1 - 1)$, so that a 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).

To decide whether the arrows point up or down on the N-nullcline, we need to look at dC/dt.

On the line $N = 0$ we have:

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

so the arrow points up if $C < \alpha_2$ and down otherwise. On the line $C = \frac{1}{\alpha_1 - 1}$:

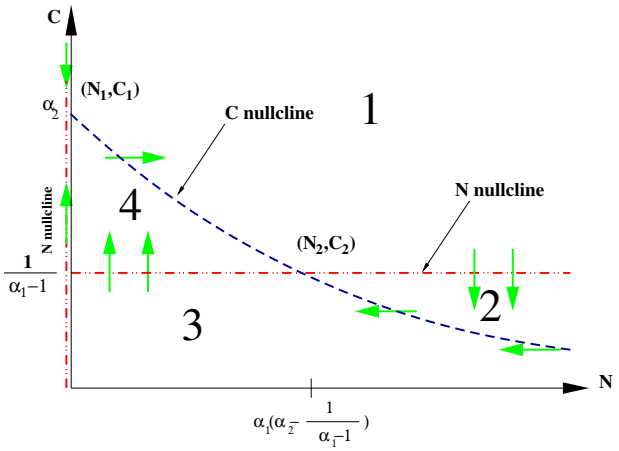
$$\frac{dC}{dt} = -\frac{C}{1+C}N - C + \alpha_2 = \frac{-N\alpha_1 + N - \alpha_1 - \alpha_2\alpha_1^2 + \alpha_1\alpha_2}{\alpha_1(\alpha_1 - 1)} \begin{cases} > 0 & \text{if } N < \alpha_1\left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right) \\ < 0 & \text{if } N > \alpha_1\left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right) \end{cases}$$

so the arrow points up if $N < \alpha_1\left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right)$ and down otherwise.

To decide whether the arrows point right or left (sign of dN/dt) on the C-nullcline, we look at:

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

(since $N \geq 0$, the sign of the expression is the same as the sign of $\alpha_1 \frac{C}{1+C} - 1$).
We have, therefore, this picture:



What about the direction of the vector field elsewhere, not just on nullclines?

The key observation is that the *only way* that arrows can "reverse direction" is by crossing a nullcline.

For example, if dx_1/dt is positive at some point A, and it is negative at some other point B, then A and B must be on opposite sides of the x_1 nullcline. The reason is that, were we to trace a path between A and B (any path, not necessarily a solution of the system), the derivative dx_1/dt at the points in the path varies continuously[15] and therefore (intermediate value theorem) there must be a point in this path where $dx_1/dt = 0$.

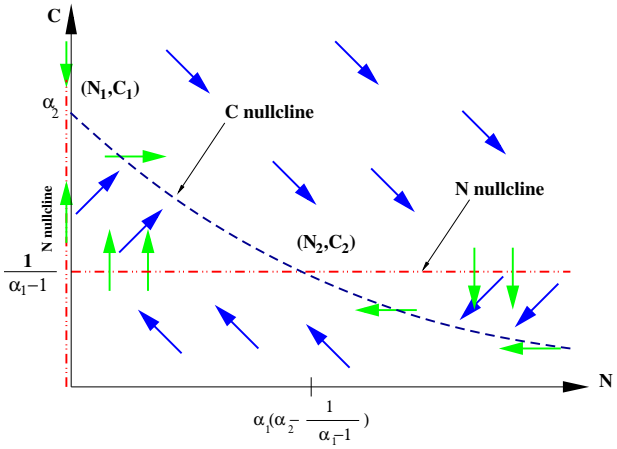
[15] assuming that the vector field is continuously differentiable

In summary: if we look at regions demarcated by the nullclines[16] then the orientations of arrows remain the same in each such region.

For example, for the chemostat, we have 4 regions, as shown in the figure.

In region 1, $dN/dt > 0$ and $dC/dt < 0$, since these are the values in the boundaries of the region. Therefore the flow is "Southeast" ($\searrow$) in that region. Similarly for the other three regions.

We indicate this information in the phase plane:



Note that the arrows are just "icons" intended to indicate if the flow is
generally "SE" ($dN/dt > 0$ and $dC/dt < 0$), "NE," etc, but the actual numerical slopes will vary (for example, near the nullclines, the arrows must become either horizontal or vertical).

4.4 Global Behavior

We already know that trajectories that start *near* the positive steady state $\bar{X}_2$ converge to it (local stability)

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

(Still assuming, obviously, that the parameters have been chosen in such a way that the positive steady state exists.)

Let us now sketch a proof that, in fact, *every* trajectory converges to $\bar{X}_2$
(with the exception only of those trajectories that start with $N(0) = 0$).

The practical consequences of this "global attraction" result are that,
no matter what the initial conditions, the chemostat will settle into the steady state $\bar{X}_2$.

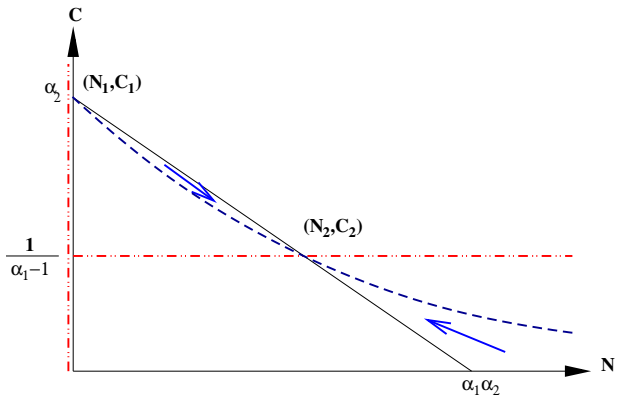
It is helpful to consider the following line:

$$(L) \qquad N + \alpha_1 C - \alpha_1 \alpha_2 = 0$$

which passes through the points $\bar{X}_1 = (0, \alpha_2)$ and $\bar{X}_2 = \left(\alpha_1 \left(\alpha_2 - \frac{1}{\alpha_1 - 1}\right), \frac{1}{\alpha_1 - 1}\right)$.
Note that $(\alpha_1\alpha_2, 0)$ is also in this line.
The picture is as follows[17] where the arrows are obtained from the flow direction, as shown earlier.

[16] the "connected components" of the complement of the nullclines

[17] you may try as an exercise to show that the C-nullcline is concave up, so it must intersect L at just two points, as shown



We claim that this line is *invariant*, that is, solutions that start in L must remain in L. Even more interesting, all trajectories (except those that start with $N(0) = 0$) converge to L.

For any trajectory, consider the following function:

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

and observe that

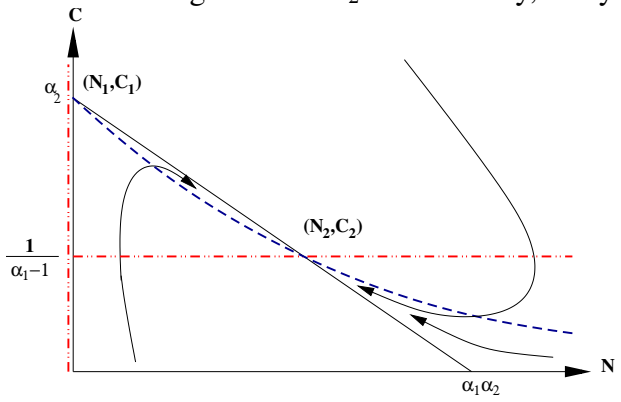
$$z' = N' + \alpha_1 C' = \alpha_1 \frac{C}{1+C} N - N - \alpha_1 \left(\frac{C}{1+C} N - C + \alpha_2 \right) = -z$$

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.

Since L is invariant and there are no steady states in L except $\bar{X}_1$ and $\bar{X}_2$, the open segment from $\bar{X}_1$ to $\bar{X}_2$ is a trajectory that "connects" the unstable state $\bar{X}_1$ to the stable state $\bar{X}_2$. Such a trajectory is called a *heteroclinic connection*.[18]

Now, we know that all trajectories approach L, and cannot cross L (no trajectories can ever cross, by uniqueness of solutions, as seen in your ODE class).

Suppose that a trajectory starts, and hence remains, on top of L (the argument is similar if remains under L), and with $N(0) > 0$.
Since the trajectory gets closer and closer to L, and must stay in the first quadrant (why?), it will either converge to $\bar{X}_2$ "from the NW" or it will eventually enter the region with the "NW arrow" – at which point it must have turned and start moving towards $\bar{X}_2$. In summary, every trajectory converges.



[18] Exercise: check eigenvectors at $\bar{X}_1$ and $\bar{X}_2$ to see that L matches the linearized eigen-directions.

5 Epidemiology: SIRS Model

The modeling of infectious diseases and their spread is an important part of mathematical biology, part of the field of mathematical epidemiology.

Modeling is an important tool for gauging the impact of different vaccination programs on the control or eradication of diseases.

We will only study here a simple ODE model, which does not take into account age structure nor geographical distribution. More sophisticated models can be based on compartmental systems, with compartments corresponding to different age groups, partial differential equations, where independent variables specify location, and so on, but the simple ODE model already brings up many of the fundamental ideas.

The classical work on epidemics dates back to Kermack and McKendrick, in 1927. We will study their SIR and SIRS models without "vital dynamics" (births and deaths; see a homework problem with a model with vital dynamics).

To explain the model, let us think of a flu epidemic, but the ideas are very general.

In the population, there will be a group of people who are *Susceptible* to being passed on the virus by the *Infected* individuals.

At some point, the infected individuals get so sick that they have to stay home, and become part of the *Removed* group. Once that they recover, they still cannot infect others, nor can they be infected since they developed immunity.

The numbers of individuals in the three classes with be denoted by S, I, and R respectively, and hence the name "SIR" model.

Depending on the time-scale of interest for analysis, one may also allow for the fact that individuals in the Removed group may eventually return to the Susceptible population, which would happen if immunity is only temporary. This is the "$SIRS$" model (the last S to indicate flow from R to S), which we will study next.

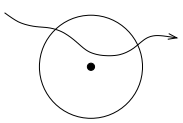
We assume that these numbers are all functions of time t, and that the numbers can be modeled as real numbers. (Non-integers make no sense for populations, but it is a mathematical convenience. Or, if one studies probabilistic instead of deterministic models, these numbers represent expected values of random variables, which can easily be non-integers.)

The basic modeling assumption is that the number of new infectives $I(t+\Delta t)-I(t)$ in a small interval of time $[t, t+\Delta t]$ is proportional to the product $S(t)I(t)\,\Delta t$.

Let us try to justify intuitively why it makes sense. (As usual, experimentation and fitting to data should determine if this is a good assumption. In fact, alternative models have been proposed as well.)

Suppose that transmission of the disease can happen only if a susceptible and infective are very close to each other, for instance by direct contact, sneezing, etc.

We suppose that there is some region around a given susceptible individual, so that he can only get infected if an infective enters that region:



We assume that, for each infective individual, there is a probability $p = \beta\Delta t$ that this infective will happen to pass through this region in the time interval $[t, t + \Delta t]$, where β is some positive constant that depends on the size of the region, how fast the infectives are moving, etc. (Think of the infective traveling at a fixed speed: in twice the length of time, there is twice the chance that it will pass by this region.) We take $\Delta t \ll 0$, so also $p \ll 0$.

The probability that this particular infective will *not* enter the region is $1 - p$, and, assuming independence, the probability than *no infective* enters is $(1 - p)^I$.

So the probability that *some* infective comes close to our susceptible is, using a binomial expansion: $1 - (1 - p)^I \approx 1 - (1 - pI + \binom{I}{2}p^2 + \ldots) \approx pI$ since $p \ll 1$.

Thus, we can say that a particular susceptible has a probability pI of being infected. Since there are S of them, we may assume, if S is large, that the total number infected will be $S \times pI$.

We conclude that the number of new infections is:

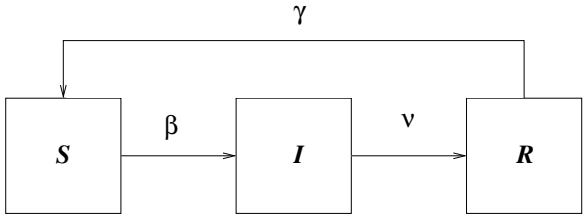
$$I(t + \Delta t) - I(t) = pSI = \beta SI\,\Delta t$$

and dividing by Δt and taking limits, we have a term βSI in $\frac{dI}{dt}$, and similarly a term $-\beta SI$ in $\frac{dS}{dt}$.

This is called a *mass action kinetics* assumption, and is also used when writing elementary chemical reactions. In chemical reaction theory, one derives this mass action formula using "collision theory" among particles (for instance, molecules), taking into account temperature (which affects how fast particles are moving), shapes, etc.

We also have to model infectives being removed: it is reasonable to assume that a certain fraction of them is removed per unit of time, giving terms νI, for some constant ν.

Similarly, there are terms γR for the "flow" of removeds back into the susceptible population.



The figure is a little misleading: this is *not* a compartmental system, in which the flow from S to I is just proportional to S. For example, when $I = 0$, no one gets infected; hence the product term in the equations:

$$\begin{aligned}
\frac{dS}{dt} &= -\beta SI + \gamma R \\
\frac{dI}{dt} &= \beta SI - \nu I \\
\frac{dR}{dt} &= \nu I - \gamma R
\end{aligned}$$

(There are many variations possible; here are some. In a model with vital dynamics –see homework assignments,– one also adds birth and death rates to this model. Another one: a vaccine is given to a certain percentage of the susceptibles, at a given rate, causing the vaccinated individuals to become "removed". Yet another one: there is a type of mosquito that makes people infected.)

5.1 Analysis of Equations

Let $N = S(t) + I(t) + R(t)$. Since $dN/dt = 0$, N is constant, the total size of the population.

Therefore, even though we are interested in a system of three equations, this *conservation law* allows us to eliminate one equation, for example, using $R = N - S - I$.

We are led to the study of the following two dimensional system:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + \gamma(N - S - I) \\ \frac{dI}{dt} &= \beta SI - \nu I \end{aligned}$$

I-nullcline: union of lines $I = 0$ and $S = \nu/\beta$.

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

The steady states are

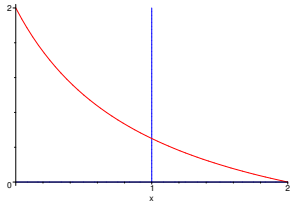
$$\bar{X}_1 = (N, 0) \quad \text{and} \quad \bar{X}_2 = \left(\frac{\nu}{\beta}, \frac{\gamma(N - \frac{\nu}{\beta})}{\nu + \gamma} \right) ,$$

where $\bar{X}_2$ only makes physical sense if the following condition is satisfied:

$$\boxed{\text{“}\sigma\text{”} \text{ or } \text{“}R_0\text{”} = N\beta/\nu > 1}$$

For example, if $N = 2$, $\beta = 1$, $\nu = 1$, and $\gamma = 1$, the I-nullcline is the union of I=0 and S=1, the S-nullcline is given by $I = \frac{(2-S)}{S+1}$, and the equilibria are at $(2, 0)$ and $(1, 1/2)$

Some estimated values of σ: AIDS: 2 to 5, smallpox: 3 to 5, measles: 16 to 18, malaria: > 100.



The Jacobian is, at any point:

$$\begin{bmatrix} -I\beta - \gamma & -S\beta - \gamma \\ I\beta & S\beta - \nu \end{bmatrix}$$

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

$$-\gamma + N\beta - \nu \text{ and } \quad -\gamma(N\beta - \nu)$$

and thus, provided $\sigma = N\beta/\nu > 1$, we have det< 0 and hence a saddle.

At $\bar{X}_2$ we have: trace$= -I\beta - \gamma < 0$ and det$= I\beta(\nu + \gamma) > 0$, and hence this steady state is stable.

Therefore, at least for close enough initial conditions (since the analysis is local, we cannot say more), and assuming $\sigma > 1$, the number of infected individuals will approach

$$I_{\text{steady state}} = \frac{\gamma(N - \frac{\nu}{\beta})}{\nu + \gamma} .$$

Homework problem: Suppose that $\beta = \nu = \gamma = 1$. For what values of N does one have stable spirals and for what values does one get stable nodes, for $\bar{X}_2$?

5.2 Interpreting σ

Let us give an intuitive interpretation of σ.

We make the following "thought experiment":
suppose that we isolate a group of P infected individuals, and allow them to recover.

Since there are no susceptibles in our imagined experiment, $S(t) \equiv 0$, so $\frac{dI}{dt} = -\nu I$, so $I(t) = Pe^{-\nu t}$.

Suppose that the ith individual is infected for a total of d_i days, and look at the following table:

cal. days→ / Individuals	0	1	2		...	d_1	∞	
Ind. 1	X	X	X	X	X	X		= d_1 days
Ind. 2	X	X	X	X				= d_2 days
Ind. 3	X	X	X	X	X			= d_3 days
...								
Ind. P	X	X	X	X				= d_P days
	=I_0	=I_1	=I_2	...				

It is clear that $d_1 + d_2 + \ldots = I_0 + I_1 + I_2 + \ldots$
(supposing that we count on integer days, or hours, or some other discrete time unit).

Therefore, the average number of days that individuals are infected is:

$$\frac{1}{P}\sum d_i \;=\; \frac{1}{P}\sum I_i \;\approx\; \frac{1}{P}\int_0^\infty I(t)\,dt \;=\; \frac{1}{P}\int_0^\infty e^{-\nu t}\,dt \;=\frac{1}{\nu}\,.$$

On the other hand, back to the original model, what is the meaning of the term "βSI" in dI/dt?

It means that $I(\Delta t) - I(0) \approx \beta S(0) I(0) \Delta t$.

Therefore, if we start with $I(0)$ infectives, and we look at an interval of time of length $\Delta t = 1/\nu$, which we agreed represents the average time of an infection, we end up with the following number of new infectives:

$$\beta(N - I(0))I(0)/\nu \;\approx\; \beta N I(0)/\nu$$

if $I(0) \ll N$, which means that each individual, on the average, infected $(\beta N I(0)/\nu)/I(0) = \sigma$ new individuals.

We conclude, from this admittedly hand-waving argument[19], that σ represents the *expected number infected by a single individual* (in epidemiology, the *intrinsic reproductive rate* of the disease).

[19] among other things, we'd need to know that ν is large, so that Δt is small

5.3 Nullcline Analysis

For the previous example, $N = 2$, $\beta = 1$, $\nu = 1$, and $\gamma = 1$:

$$\begin{aligned} \frac{dS}{dt} &= -SI + 2 - S - I \\ \frac{dI}{dt} &= SI - I \end{aligned}$$

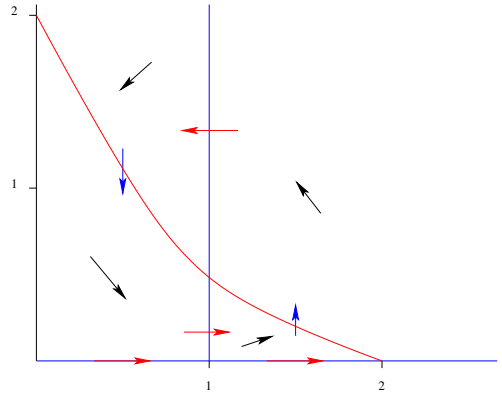
with equilibria at $(2, 0)$ and $(1, 1/2)$, the I-nullcline is the union of I=0 and S=1.

When $I = 0$, $dS/dt = 2 - S$,
and on $S = 1$, $dS/dt = 1 - 2I$,
so we can find if arrows are right or left pointing.

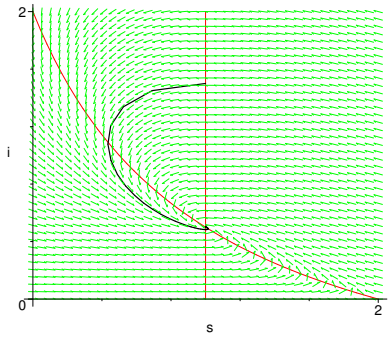
On the S-nullcline $I = \frac{(2-S)}{S+1}$ we have

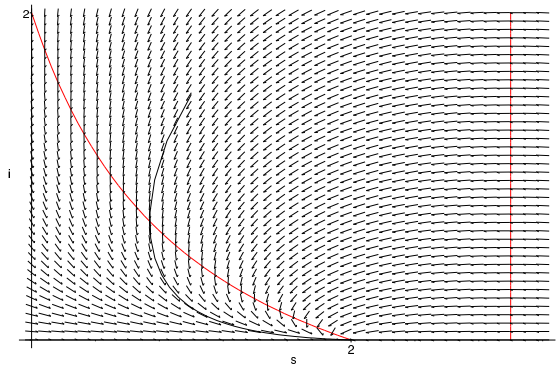
$$\frac{dI}{dt} = \frac{(S-1)(2-S)}{S+1}$$

and therefore arrows point down if $S < 1$, and up if $S \in (1, 2)$. This in turn allows us to know the general orientation (NE, etc) of the vector field.



Here are computer-generated phase-planes[20] for this example as well as for a modification in which we took $\nu = 3$ (so $\sigma < 1$).





In the first case, the system settles to the positive steady state, no matter where started, as long as $I(0) > 0$.

In the second case, there is only one equilibrium, since the vertical component of the I-nullcline is at $S = 3/1 = 3$, which does not intersect the other nullcline. The disease will disappear in this case.

5.4 Immunizations

The effect of immunizations is to reduce the "threshold" N needed for a disease to take hold.

In other words, for N small, the condition $\sigma = N\beta/\nu > 1$ will fail, and no positive steady state will exist.

Vaccinations have the effect to permanently remove a certain proportion p of individuals from the population, so that, in effect, N is replaced by pN. Vaccinating just $p > 1 - \frac{1}{\sigma}$ individuals gives $(1 - p)\sigma < 1$, and hence suffices to eradicate a disease!

[20] Physically, only initial conditions with $I + S \leq 2$ make sense; why?

5.5 A Variation: STD's

Suppose that we wish to study a virus that can only be passed on by heterosexual sex. Then we should consider two separate populations, male and female. We use $\bar{S}$ to indicate the susceptible males and S for the females, and similarly for I and R.

The equations analogous to the SIRS model are:

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{S}I + \bar{\gamma}\bar{R} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{S}I - \bar{\nu}\bar{I} \\
\frac{d\bar{R}}{dt} &= \bar{\nu}\bar{I} - \bar{\gamma}\bar{R} \\
\frac{dS}{dt} &= -\beta S\bar{I} + \gamma R \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I \\
\frac{dR}{dt} &= \nu I - \gamma R\,.
\end{aligned}$$

This model is a little difficult to study, but in many STD's (especially asymptomatic), there is no "removed" class, but instead the infecteds get back into the susceptible population. This gives:

$$\begin{aligned}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{S}I + \bar{\nu}\bar{I} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{S}I - \bar{\nu}\bar{I} \\
\frac{dS}{dt} &= -\beta S\bar{I} + \nu I \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I\,.
\end{aligned}$$

Writing $\bar{N} = \bar{S}(t) + \bar{I}(t)$ and $N = S(t) + I(t)$ for the total numbers of males and females, and using these two conservation laws, we can just study the following set of two ODE's:

$$\begin{aligned}
\frac{d\bar{I}}{dt} &= \bar{\beta}(\bar{N} - \bar{I})I - \bar{\nu}\bar{I} \\
\frac{dI}{dt} &= \beta(N - I)\bar{I} - \nu I\,.
\end{aligned}$$

Homework: Prove that there are two equilibria, $I = \bar{I} = 0$ and, provided that

$$\sigma\bar{\sigma} = \left(\frac{N\beta}{\nu}\right)\left(\frac{\bar{N}\bar{\beta}}{\bar{\nu}}\right) > 1$$

also $I = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\nu/\beta + \bar{N}}$, $\bar{I} = \frac{N\bar{N} - (\nu\bar{\nu})/(\beta\bar{\beta})}{\bar{\nu}/\bar{\beta} + N}$.

Furthermore, prove that the first equilibrium is unstable, and the second one stable.

What vaccination strategies could be used to eradicate the disease?

6 Chemical Kinetics

Elementary reactions (in a gas or liquid) are due to collisions of particles (molecules, atoms).

Particles move at a velocity that depends on temperature (higher temperature ⇒ faster).

The *law of mass action* is:

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

This law may be justified intuitively in various ways, for instance, using an argument like the one that we presented for disease transmission.

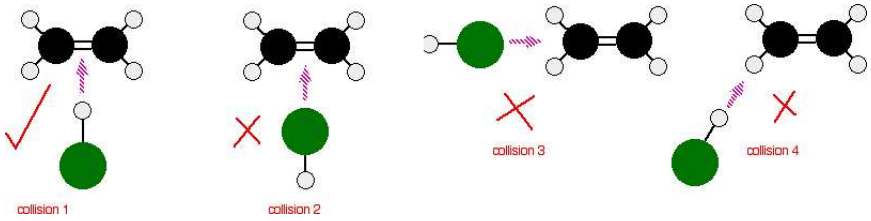
In chemistry, *collision theory* studies this question and justifies mass-action kinetics.

To be precise, it isn't enough for collisions to happen - the collisions have to happen in the "right way" and with enough energy for bonds to break.

For example[21] consider the following simple reaction involving a collision between two molecules: ethene (CH2=CH2) and hydrogen chloride (HCl), which results om chloroethane.

As a result of the collision between the two molecules, the double bond between the two carbons is converted into a single bond, a hydrogen atom gets attached to one of the carbons, and a chlorine atom to the other.

But 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.



The proportionality factor (the *rate constant*) in the law of mass action accounts for temperature, probabilities of the right collision happening if the molecules are near each other, etc.

We will derive ordinary differential equations based on mass action kinetics. However, it is important to remember several points:
• If the medium is not "well mixed" then mass-action kinetics might not be valid.
• If the number of molecules is small, a probabilistic model should be used. Mass-action ODE models are only valid as averages when dealing with large numbers of particles in a small volume.
• If a catalyst is required for a reaction to take place, then doubling the concentration of a reactants does not mean that the reaction will proceed twice as fast.[22] We later study some catalytic reactions.

[21] discussion borrowed from http://www.chemguide.co.uk/physical/basicrates/introduction.html

[22] As an example, consider the following analog of a chemical reaction, happening in a cafeteria: $A + B \to C$, where A is the number of students, B is the food on the counters, and C represents students with a full tray walking away from the counter. If each student would be allowed to, at random times, pick food from the counters, then twice the number of students, twice the number walking away per unit of time. But if there is a person who must hand out food (our "catalyst"), then there is a maximal rate at which students will leave the counter, a rate determined by how fast the cafeteria worker can serve each student. In this case, doubling the number of students does not mean that twice the number will walking away with their food per unit of time.

6.1 Equations

We will use capital letters $A, B, \ldots$ for *names* of chemical substances (molecules, ions, etc), and lower-case $a, b, \ldots$ for their corresponding *concentrations*.

There is a systematic way to write down equations for chemical reactions, using a graph description of the reactions and formulas for the different kinetic terms. We discuss this systematic approach later, but for now we consider some very simple reactions, for which we can write equations directly. We simply use the mass-action principle for each separate reaction, and add up all the effects.

The simplest "reaction" is one where there is only one reactant, that can degrade[23] or decay (as in radioactive decay), or be transformed into another species, or split into several constituents.

In either case, the rate of the reaction is proportional to the concentration:
if we have twice the amount of substance X in a certain volume, then, per (small) unit of time, a certain % of the substance in this volume will disappear, which means that the concentration will diminish by that fraction.
A corresponding number of the new substances is then produced, per unit of time.

So, decay $X \xrightarrow{k} \cdot$ gives the ODE:

$$dx/dt = -kx\,,$$

a transformation $X \xrightarrow{k} Y$ gives:

$$\begin{aligned} dx/dt &= -kx \\ dy/dt &= kx\,, \end{aligned}$$

and a dissociation reaction $Z \xrightarrow{k} X + Y$ gives:

$$\begin{aligned} dx/dt &= kz \\ dy/dt &= kz \\ dz/dt &= -kz\,. \end{aligned}$$

A bimolecular reaction $X + Y \xrightarrow{k_+} Z$ gives:

$$\begin{aligned} dx/dt &= -k_+xy \\ dy/dt &= -k_+xy \\ dz/dt &= k_+xy \end{aligned}$$

and if the reverse reaction $Z \xrightarrow{k_-} X + Y$ also takes place:

$$\begin{aligned} \dot{x} &= -k_+xy + k_-z \\ \dot{y} &= -k_+xy + k_-z \\ \dot{z} &= k_+xy - k_-z\,. \end{aligned}$$

[23] Of course, "degrade" is a relative concept, because the separate parts of the decaying substance should be taken account of. However, if these parts are not active in any further reactions, one ignores them and simply thinks of the reactant as disappearing!

Note the subscripts being used to distinguish between the "forward" and "backward" rate constants.

Incidentally, another way to symbolize the two reactions $X + Y \xrightarrow{k_+} Z$ and $Z \xrightarrow{k_-} X + Y$ is as follows:

$$X + Y \underset{k_-}{\overset{k_+}{\rightleftarrows}} Z\,.$$

Here is one last example: $X + Y \xrightarrow{k} Z$ and $Z \xrightarrow{k'} X$ give:

$$\begin{aligned} dx/dt &= -kxy + k'z \\ dy/dt &= -kxy \\ dz/dt &= kxy - k'z\,. \end{aligned}$$

(More examples are given in the homework problems.)

Conservation laws are often very useful in simplifying the study of chemical reactions.

For example, take the reversible bimolecular reaction that we just saw:

$$\begin{aligned} \dot{x} &= -k_+xy + k_-z \\ \dot{y} &= -k_+xy + k_-z \\ \dot{z} &= k_+xy - k_-z\,. \end{aligned}$$

Since, clearly, $d(x+z)/dt \equiv 0$ and $d(y+z)/dt \equiv 0$, then, for every solution, there are constants x_0 and y_0 such that $x + z \equiv x_0$ and $y + z \equiv y_0$. Therefore, once that these constants are known, we only need to study the following scalar first-order ODE:

$$\dot{z} \;=\; k_+(x_0 - z)(y_0 - z) - k_-z\,.$$

in order to understand the time-dependence of solutions. Once that $z(t)$ is solved for, we can find $x(t)$ by the formula $x(t) = x_0 - z(t)$ and $y(t)$ by the formula $y(t) = y_0 - z(t)$.

We'll see an example of the use of conservation laws when modeling enzymatic reactions.

6.2 Chemical Networks

We next discuss a formalism that allows one to easily write up differential equations associated with chemical reactions given by diagrams like

$$2H + O \leftrightarrow H_2O\,. \tag{6}$$

In generally, we consider a collection of chemical reactions that involves a set of n_s "species":

$$S_j,\ j \in \{1, 2, \ldots n_s\}\,.$$

These "species" may be ions, atoms, or molecules (even large molecules, such as proteins). We'll just say "molecules", for simplicity. For example, (6) represents a set of two reactions that involve the following $n_s = 3$ species (hydrogen, oxygen, water):

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

one going forward and one going backward. In general, a *chemical reaction network* ("CRN", for short) is a set of chemical reactions $\mathcal{R}_i$, $i \in \{1, 2, \ldots, n_r\}$:

$$\mathcal{R}_i: \quad \sum_{j=1}^{n_s} \alpha_{ij} S_j \to \sum_{j=1}^{n_s} \beta_{ij} S_j \tag{7}$$

where the α_{ij} and β_{ij} are some nonnegative integers, called the *stoichiometry coefficients*.

The species with nonzero coefficients on the left-hand side are usually referred to as the *reactants*, and the ones on the right-hand side are called the *products*, of the respective reaction. (Zero coefficients are not shown in diagrams.) The interpretation is that, in reaction 1, α_{11} molecules of species S_1 combine with α_{12} molecules of species S_2, etc., to produce β_{11} molecules of species S_1, β_{12} molecules of species S_2, etc., and similarly for each of the other $n_r - 1$ reactions.

The forward arrow means that the transformation of reactants into products only happens in the direction of the arrow. For example, the reversible reaction (6) is represented by the following CRN, with $n_r = 2$ reactions:

$$\begin{aligned} \mathcal{R}_1: &\quad 2H + O \to H_2O \\ \mathcal{R}_2: &\quad H_2O \to \quad 2H + O\,. \end{aligned}$$

So, in this example,

$$\alpha_{11} = 2, \quad \alpha_{12} = 1, \quad \alpha_{13} = 0, \quad \beta_{11} = 0, \quad \beta_{12} = 0, \quad \beta_{13} = 1,$$

and

$$\alpha_{21} = 0, \quad \alpha_{22} = 0, \quad \alpha_{23} = 1, \quad \beta_{21} = 2, \quad \beta_{22} = 1, \quad \beta_{23} = 0\,.$$

It is convenient to arrange the stoichiometry coefficients into an $n_s \times n_r$ matrix, called the *stoichiometry matrix* $\Gamma = \Gamma_{ij}$, defined as follows:

$$\Gamma_{ji} \ = \ \beta_{ij} - \alpha_{ij}\,, \quad i = 1, \ldots, n_r\,, \quad j = 1, \ldots, n_s \tag{8}$$

(notice the reversal of indices).

The matrix Γ has as many columns as there are reactions. Each column shows, for all species (ordered according to their index i), the net "produced−consumed". For example, for the reaction (6), Γ is the following matrix:

$$\begin{pmatrix} -2 & 2 \\ -1 & 1 \\ 1 & -1 \end{pmatrix} .$$

Notice that we allow degradation reactions like $A \to 0$ (all β's are zero for this reaction).

Homework: Find the matrix Γ for each of the reactions shown in Section 6.1 of the notes as well as in the homework problems in the course website.

We now describe how the state of the network evolves over time, for a given CRN. We need to find a rule for the evolution of the vector:

$$\begin{pmatrix} [S_1(t)] \\ [S_2(t)] \\ \vdots \\ [S_{n_s}(t)] \end{pmatrix}$$

where the notation $[S_i(t)]$ means the concentration of the species S_i at time t. For simplicity, we drop the brackets and write S_i also for the concentration of S_i (sometimes, to avoid confusion, we use instead lower-case letters like s_i to denote concentrations). As usual with differential equations, we also drop the argument "t" if it is clear from the context. Observe that only nonnegative concentrations make physical sense (a zero concentration means that a species is not present at all).

The graphical information given by reaction diagrams is summarized by the matrix Γ. Another ingredient that we require is a formula for the actual rate at which the individual reactions take place.

We denote by $R_i(S)$ be algebraic form of the jth reaction. The most common assumption is that of *mass-action kinetics*, where:

$$R_i(S) = k_i \prod_{j=1}^{n_s} S_j^{\alpha_{ij}} \text{ for all } i = 1, \ldots, n_r \, .$$

This says simply that the reaction rate is proportional to the products of concentrations of the reactants, with higher exponents when more than one molecule is needed. The coefficients k_i are "reaction constants" which usually label the arrows in diagrams. Let us write the vector of reactions as $R(S)$:

$$R(S) := \begin{pmatrix} R_1(S) \\ R_2(S) \\ \vdots \\ R_{n_r}(S) \end{pmatrix} .$$

With these conventions, the system of differential equations associated to the CRN is given as follows:

$$\frac{dS}{dt} \;=\; \Gamma \, R(S) \, . \tag{9}$$

Example

As an illustrative example, let us consider the following set of chemical reactions:

$$E + P \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} E + Q, \qquad F + Q \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} D \xrightarrow{k_4} F + P, \tag{10}$$

which may be thought of as a model of the activation of a protein substrate P by an enzyme E; C is an intermediate complex, which dissociates either back into the original components or into a product (activated protein) Q and the enzyme. The second reaction transforms Q back into P, and is catalyzed by another enzyme (a phosphatase denoted by F). A system of reactions of this type is sometimes called a "futile cycle", and reactions of this type are ubiquitous in cell biology. The mass-action kinetics model is then obtained as follows. Denoting concentrations with the same letters (P, etc) as the species themselves, we have the following vector of species, stoichiometry matrix Γ and vector of reaction rates $R(S)$:

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

From here, we can write the equations (9). For example,

$$\frac{dP}{dt} \;=\; (-1)(k_1 EP) + (1)(k_{-1}C) + (1)(k_4 D) \;=\; k_4 D - k_1 EP + k_{-1} C\,.$$

Conservation Laws

Let us consider the set of row vectors c such that $c\Gamma = 0$. Any such vector is a *conservation law*, because

$$\frac{d(cS)}{dt} \;=\; c\frac{dS}{dt} \;=\; c\,\Gamma R(S) = 0$$

for all t, in other words,

$$c\,S(t) \;=\; \text{constant}$$

along all solutions (a "first integral" of the motion). The set of such vectors forms a linear subspace (of the vector space consisting of all row vectors of size n_s).

For instance, in the previous example, we have that, along all solutions, one has that

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

because $(1, 1, 0, 0, 1, 1)\Gamma = 0$. Similarly, we have two more linearly independent conservation laws, namely $(0, 0, 1, 0, 1, 0)$ and $(0, 0, 0, 1, 0, 1)$, so also

$$E(t) + C(t) \quad \text{and} \quad F(t) + D(t)$$

are constant along trajectories. Since Γ has rank 3 (easy to check) and has 6 rows, its left-nullspace has dimension three. Thus, a basis of the set of conservation laws is given by the three that we have found.

Homework. Find, for each of the problems in the notes and web-posted homework assignment, a basis of conservation laws.

Optional homework. This one is a bit more complicated, but also very interesting. The example covered before can be summarized as in Figure 1(a). Many cell signaling processes involve double instead of single transformations such as addition of phosphate groups. A model for a double double-phosphorylation as in Figure 1(b) corresponds to reactions as follows (we use double arrows for

Figure 1: *(a) One-step and (b) two-step transformations*

simplicity, to indicate reversible reactions):

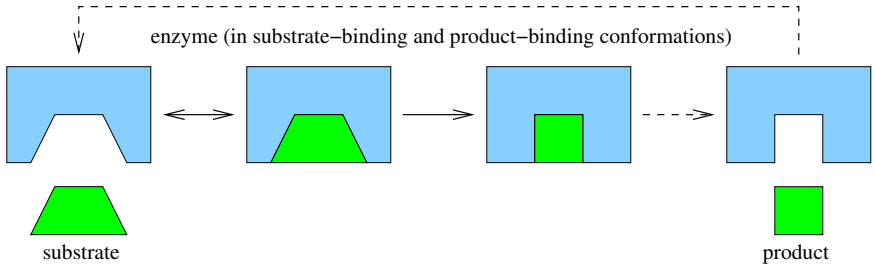
$$\begin{array}{ccccccccc} E+S_0 & \leftrightarrow & ES_0 & \rightarrow & E+S_1 & \leftrightarrow & ES_1 & \rightarrow & E+S_2 \\ F+S_2 & \leftrightarrow & FS_2 & \rightarrow & F+S_1 & \leftrightarrow & FS_1 & \rightarrow & F+S_0 \end{array} \tag{11}$$

where "ES_0" represents the complex consisting of E bound to S_0 and so forth. You should attach constants to all arrows and write up the system of ODE's. Show also that there is a basis of conservation laws consisting of three vectors.

6.3 Introduction to Enzymatic Reactions

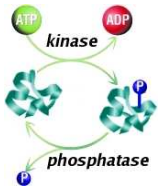
Catalysts facilitate reactions, converting *substrates* into *products*, while remaining basically unchanged.

Catalysts may act as "pliers" that place an appropriate stress to help break a bond,
they may bring substrates together, or they may help place a chemical group on a substrate.



In molecular biology, certain types of proteins, called *enzymes*, act as catalysts.

Enzymatic reactions are one of the main ways in which information flows in cells.



One important type of enzymatic reaction is *phosphorylation*, when an enzyme X (called a *kinase* when playing this role) transfers a phosphate group (PO_4) from a "donor" molecule such as ATP to another protein Y, which becomes "activated" in the sense that its energy is increased.

(Adenosine triphosphate (ATP) is a nucleotide that is the major energy currency of the cell.)

Once activated, protein Y may then influence other cellular components, including other proteins, acting itself as a kinase.

Normally, proteins do not stay activated forever; another type of enzyme, called a *phosphatase*, eventually takes away the phosphate group.

In this manner, signaling is "turned off" after a while, so that the system is ready to detect new signals.

Chemical and electrical signals from the outside of the cell are sensed by *receptors*.

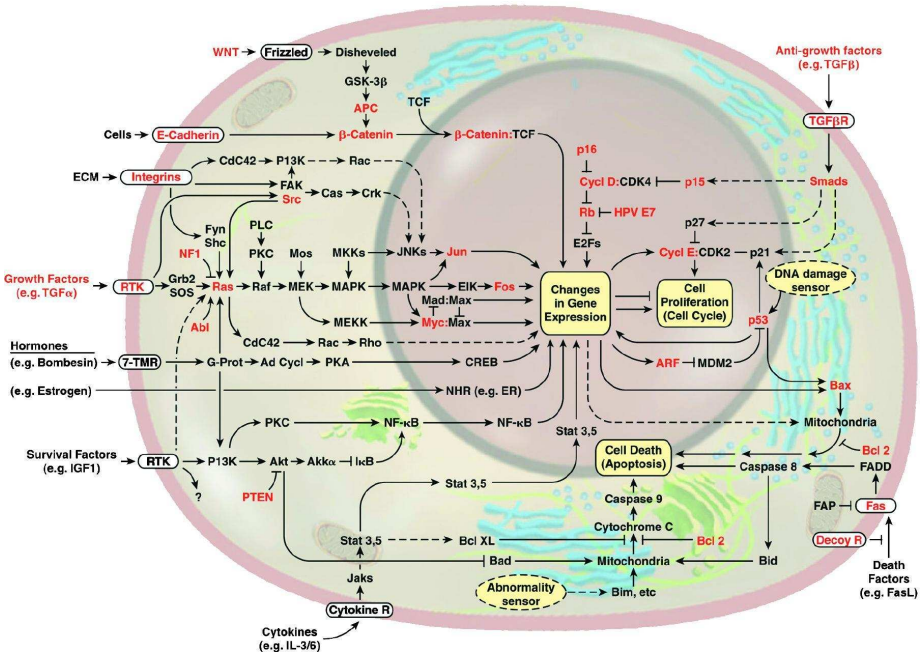
Receptors are proteins that act as the cell's sensors of outside conditions, relaying information to the inside of the cell.

In some ways, receptors may be viewed as enzymes: the "substrate" is an extracellular ligand (a molecule, usually small, outside the cell, for instance a hormone or a growth factor), and the "product' might be, for example, a small molecule (a *second messenger*) that is released in response to the binding of ligand to the receptor.

This release, in turn, may trigger signaling through a series of chemical reactions inside the cell.

Cascades and feedbacks involving enzymatic (and other) reactions, as well as the action of proteins on DNA (directing transcription of genes) are "life".

Below we show one signaling pathway, extracted from a recent paper by Hananan and Weinberg on cancer research. It describes the top-level schematics of the wiring diagram of the circuitry (in mammalian cells) responsible for growth, differentiation, and apoptosis (commands which instruct the cell to die). Highlighted in red are some of the genes known to be functionally altered in cancer cells. Almost all the main species shown are proteins, acting many of them as enzymes in catalyzing "downstream" reactions.



Some More on Receptors

As shown in the above diagram, most receptors are designed to recognize a specific type of ligand.

Receptors are usually made up of several parts.

• An extracellular domain ("domains" are parts of a protein) is exposed to the exterior of the cell, and this is where ligands bind.

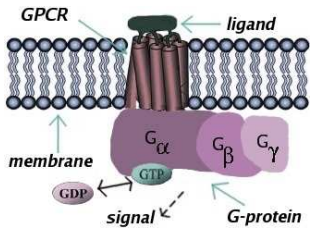
• A transmembrane domain serves to "anchor" the receptor to the cell membrane.

• A cytoplasmic domain helps initiate reactions inside the cell in response to exterior signals, by interacting with other proteins.

As an example, a special class of receptors which constitute a common target of pharmaceutical drugs are G-protein-coupled receptors (GPCR's).

The name of these receptors arises from the fact that, when their conformation changes in response to a ligand binding event, they activate G-proteins, so called because they employ guanine triphosphate (GTP) and guanine diphosphate (GDP) in their operation.

GPCR's are made up of several subunits (G_α, G_β, G_γ) and are involved in the detection of metabolites, odorants, hormones, neurotransmitters, and even light (rhodopsin, a visual pigment).



6.4 Differential Equations

The basic elementary reaction is:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} P + E$$

and therefore the equations that relate the concentrations of substrate, (free) enzyme, complex (enzyme with substrate together), and product are:

$$\begin{aligned}
\frac{ds}{dt} &= k_{-1}c - k_1 se \\
\frac{de}{dt} &= (k_{-1} + k_2)c - k_1 se \\
\frac{dc}{dt} &= k_1 se - (k_{-1} + k_2)c \\
\frac{dp}{dt} &= k_2 c
\end{aligned}$$

which is a 4-dimensional system.
Since the last equation, for product formation, does not feed back into the first three,
we can simply ignore it at first, and later, after solving for $c(t)$, just integrate so as to get $p(t)$.

Moreover, since $\frac{de}{dt} + \frac{dc}{dt} \equiv 0$, we also know that $e + c$ is constant. We will write "e_0" for this sum:

$$e(t) + c(t) \;=\; e_0\,.$$

(Often $c(0) = 0$ (no substrate), so that $e_0 = e(0)$, the initial concentration of free enzyme.)

So, we can eliminate e from the equations:

$$\begin{aligned}
\frac{ds}{dt} &= k_{-1}c - k_1 s(e_0 - c) \\
\frac{dc}{dt} &= k_1 s(e_0 - c) - (k_{-1} + k_2)c\,.
\end{aligned}$$

We are down to two dimensions, and could proceed using the methods that we have been discussing.

However, Leonor Michaelis and Maud Leonora Menten formulated in 1913 an approach that allows one to reduce the problem even further, by doing an approximation. Next, we review this approach, as reformulated by Briggs and Haldane in 1925[24], and interpret it in the more modern language of singular perturbation theory.

Although a two-dimensional system is not hard to study, the reduction to one dimension is very useful:
• When "connecting" many enzymatic reactions, one can make a similar reduction for each one of the reactions, which provides a great overall reduction in complexity.
• It is often not possible, or it is very hard, to measure the kinetic constants (k_1, etc), but it may be easier to measure the parameters in the reduced model.

[24]Michaelis and Menten originally made an the "equilibrium approximation" $k_{-1}c(t) - k_1 s(t)e(t) = 0$ in which one assumes that the first reaction is in equilibrium. This approximation is very hard to justify. The Briggs and Haldane approach makes a different approximation. The final form of the production rate (see later) turns out to be algebraically the same as in the original Michaelis and Menten work, but the parameters have different physical interpretations in terms of the elementary reactions.

6.5 Quasi-Steady State Approximations and Michaelis-Menten Reactions

Let us write

$$\begin{aligned}\frac{ds}{dt} &= k_{-1}c - k_1 s(e_0 - c)\\ \frac{dc}{dt} &= k_1 s(e_0 - c) - (k_{-1} + k_2)c \;=\; k_1\Big[s\,e_0 - (K_{\rm m} + s)c\Big]\,, \qquad \text{where} \quad K_{\rm m} = \frac{k_{-1} + k_2}{k_1}\,.\end{aligned}$$

The MM approximation amounts to setting $dc/dt = 0$. The biochemical justification is that, after a transient period during which the free enzymes "fill up," the amount complexed stays more or less constant.

This allows us, by solving the algebraic equation:

$$s\,e_0 - (K_{\rm m} + s)c \;=\; 0$$

to express c in terms of s:

$$c \;=\; \frac{s\,e_0}{K_{\rm m} + s}\,. \tag{12}$$

We then have, for the production rate:

$$\frac{dp}{dt} \;=\; k_2\,c \;=\; \frac{V_{\rm max}\,s}{K_{\rm m} + s}\,. \tag{13}$$

Also, substituting into the s equation we have:

$$\frac{ds}{dt} \;=\; k_{-1}\frac{s\,e_0}{K_{\rm m} + s} \;-\; k_1 s\left(e_0 - \frac{s\,e_0}{K_{\rm m} + s}\right) \;=\; -\frac{V_{\rm max}\,s}{K_{\rm m} + s} \tag{14}$$

where we denote $V_{\rm max} = k_2 e_0$. If we prefer to explicitly show the role of the enzyme as an "input", we can write these two equations as follows:

$$\begin{aligned}\frac{ds}{dt} &= -e_0\frac{k_2\,s}{K_{\rm m} + s}\\ \frac{dp}{dt} &= e_0\frac{k_2\,s}{K_{\rm m} + s}\end{aligned}$$

showing the rate at which substrate gets transformed into product with the help of the enzyme.

This is all very nice, and works out well in practice, but the mathematical justification is flaky: setting $dc/dt = 0$ means that c is constant. But then, the equation $c = \frac{s\,e_0}{K_{\rm m}+s}$ implies that s must be constant, too. Therefore, also $ds/dt = 0$.

But then $\frac{V_{\rm max}\,s}{K_{\rm m}+s} = -ds/dt = 0$, which means that $s = 0$. In other words, our derivation can only be right if there is no substrate, so no reaction is taking place at all!

One way to justify these derivations is as follows. Under appropriate conditions, s changes much more slowly than c.
So, as far as c is concerned, we may assume that $s(t)$ is constant, let us say $s(t) = \bar{s}$.
Then, the equation for c becomes a linear equation, which converges to its steady state, which is given by formula (12) (with $s = \bar{s}$) obtained by setting $dc/dt = 0$.
Now, as s changes, c "catches up" very fast, so that this formula is always (approximately) valid.

From the "point of view" of s, the variable c is always catching up with its expression given by formula (12), so, as far as its slow movement is concerned, s evolves according to formula (14).
(An exception is at the start of the whole process, when $c(0)$ is initially far from its steady state value. This is the "boundary layer behavior".)
To make this more precise, we need to do a "time scale analysis" which studies the dynamics from c's point of view (slow time scale) and s's (fast time scale) separately.
We now do all this analysis carefully.

6.6 Fast and Slow Behavior

We introduce these rescaled variables:

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

and write also $\varepsilon = e_0/s_0$, where we think of s_0 as the initial concentration $s(0)$ of substrate.
Note that x, y, ε are "non-dimensional" variables.

Using the new variables, the equations become:

$$\begin{aligned} \frac{dx}{dt} &= \varepsilon\,[k_{-1}\,y \;-\; k_1 s_0\,x\,(1-y)] \\ \frac{dy}{dt} &= k_1[s_0\,x \;-\; (K_{\rm m} + s_0\,x)y]\,. \end{aligned}$$

Next, suppose that the initial amount of enzyme e is small compared to that of substrate.

This means that the ratio ε is small[25].

Since $\varepsilon \approx 0$, we make the approximation "$\varepsilon = 0$" and substitute $\varepsilon = 0$ into these equations. So $dx/dt = 0$, which means that $x(t)$ equals a constant $\bar{x}$, and hence the second equation becomes:

$$\frac{dc}{dt} \;=\; k_1[e_0\,\bar{s} \;-\; (K_{\rm m} + \bar{s})c]$$

(substituting $s_0 x = s$ and $e_0 y = c$ to express in terms of the original variables, and letting $\bar{s} = s_0\bar{x}$).
In this differential equation, $c(t)$ converges as $t \to \infty$ to the steady state

$$c \;=\; \frac{e_0\,\bar{s}}{K_{\rm m} + \bar{s}}$$

which is also obtained by setting $dc/dt = 0$ in the original equations if $s(t) \equiv \bar{s}$ is assumed constant.

In this way, we again obtain formula (13) for dp/dt ($\bar{s}$ is the "present" value of s).

This procedure is called a "quasi-steady state approximation" (QSS), reflecting the fact that one replaces c by its "steady state" value $\frac{e_0\,s}{K_{\rm m}+s}$ obtained by pretending that s would be constant. This is not a true steady state of the original equations, of course.

The assumptions that went into our approximation were that $\varepsilon \ll 1$ and, implicitly, that the time interval that we considered wasn't "too long" (because, otherwise, dx/dt does change, even if $\varepsilon \ll 1$).

[25] It would not make sense to just say that the amount of enzyme is "small," since the meaning of "small" depends on units. On the other hand, the *ratio* makes sense, assuming of course that we quantified concentrations of enzyme and substrate in the same units. Typical values for ε may be in the range 10^{-2} to 10^{-7}.

One may argue that saying that the time interval is "short" is not consistent with the assumption that $c(t)$ has converged to steady state.

However, the constants appearing in the c equation are not "small" compared to ε: the speed of convergence is determined by $k_1(K_m + \bar{s})$, which does not get small as $\varepsilon \to 0$.

So, *for small enough* ε, the argument makes sense (on any fixed time interval). In other words, the approximation is justitied provided that the initial amount of enzyme is much smaller than the amount of susbtrate.

(By comparison, notice that we did not have a way to know when our first derivation (merely setting $dc/dt = 0$) was reasonable.)

One special case is that of small times t, in which case we may assume that $\bar{s} = s_0$, and therefore the equation for c is approximated by:

$$\frac{dc}{dt} \;=\; k_1[e_0\, s_0 \;-\; (K_m + s_0)c]\,. \tag{15}$$

One calls this the *boundary layer* equation, because it describes what happens near initial times (boundary of the time interval).

Homework problem: Suppose that, instead of $e_0 \ll s_0$, we know only the weaker condition

$$e_0 \ll (s_0 + K_m)\,.$$

Show that the same formula for product formation is obtained. Specifically, now pick:

$$x = \frac{s}{s_0 + K_m}\,,\;\; y = \frac{c}{e_0}\,,\;\; \varepsilon = \frac{e_0}{s_0 + K_m}$$

and show that the equations become:

$$\begin{aligned}\frac{dx}{dt} &= \varepsilon\Big[k_{-1}\, y \;-\; k_1(s_0 + K_m)\, x\,(1 - y)\Big]\\ \frac{dy}{dt} &= k_1\Big[\,(s_0 + K_m)\, x \;-\; (K_m + (s_0 + K_m)\, x)\, y\,\Big]\,.\end{aligned}$$

Now set $\varepsilon = 0$. In conclusion, one doesn't need $e_0 \ll s_0$ for the QSS approximation to hold. It is enough that K_m be very large, that is to say, for the rate of formation of complex k_1 to be very small compared to $k_{-1} + k_2$ (sum of dissociation rates).

Long-time behavior (fast time scale)

Next, we ask what happens for those t "large enough" so that $dx/dt \approx 0$ is not valid.

This is a question involving *time-scale separation*.

The intuitive idea is that c approaches its steady state value fast relative to the movement of s, which is, therefore, supposed to be constant while this convergence happens.

Now we "iterate" the reasoning: s moves a bit, using c's steady state value.

But then, c "reacts" to this new value of s, converging to a new steady state value (corresponding to the new $\bar{s}$), and the process is iterated in this fashion.

The problem with saying things in this manner is that, of course, it is not true that c and s take turns moving, but both move simultaneously (although at very different speeds).

In order to be more precise, it is convenient to make a change of time scale, using:

$$\tau = \frac{e_0}{s_0}\, k_1 t\,.$$

We may think of τ as a *fast time scale*, because $\tau = \varepsilon k_1 t$, and therefore τ is small for any given t.

For example, if $\varepsilon k_1 = 1/3600$ and t is measured in seconds, then $\tau = 10$ implies that $t = 36000$; thus, "$\tau = 10$" means that ten *hours* have elapsed, while "$t = 10$" means that only ten seconds elapsed.

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:

$$\begin{aligned} \frac{dx}{d\tau} &= \frac{k_{-1}}{k_1}\, y \;-\; s_0\, x\,(1-y) \\ \varepsilon\frac{dy}{d\tau} &= s_0\, x \;-\; (K_{\text{m}} + s_0\, x) y\,. \end{aligned}$$

Still assuming that $\varepsilon \ll 1$, we make an approximation by setting $\varepsilon = 0$ in the second equation:

$$\varepsilon\frac{dy}{d\tau} \;=\; s_0\, x \;-\; (K_{\text{m}} + s_0\, x) y$$

leading to the algebraic equation $s_0 x - (K_{\text{m}} + s_0\, x) y \;=\; 0$ which we solve for $y = y(x) = \frac{s_0 x}{K_{\text{m}} + s_0\, x}$, or equivalently

$$c = \frac{e_0 s}{K_{\text{m}} + s}\,, \tag{16}$$

and finally we substitute into the first equation:

$$\frac{dx}{d\tau} \;=\; \frac{k_{-1}}{k_1}\, y \;-\; s_0\, x\,(1-y) \;=\; -\frac{(-k_{-1} + K_{\text{m}} k_1)\, s_0\, x}{k_1 (K_{\text{m}} + s_0\, x)} \;=\; -\frac{k_2\, s_0\, x}{k_1 (K_{\text{m}} + s_0\, x)}$$

(recall that $K_{\text{m}} = \frac{k_{-1} + k_2}{k_1}$).

In terms of the original variable $s{=}s_0 x$, using $\dfrac{ds}{dt} = e_0 k_1 \dfrac{dx}{d\tau}$, and recalling that $V_{\text{max}} = k_2 e_0$, we have re-derived (14):

$$\frac{ds}{dt} \;=\; -\frac{V_{\text{max}}\, s}{K_{\text{m}} + s}\,.$$

The important point to realize is that, after an initial convergence of c (or y) to its steady state, once that c has "locked into" its steady state (16), it quickly "catches up" with any (slow!) changes in s, and this catch-up is not "visible" at the time scale τ, so c appears to track the expression (16).

6.7 Putting it all Together

Let's suppose that $s(0) = s_0$ and $c(0) = c_0$.

(1) As we remarked earlier, for $t \approx 0$ we have equation (15) (with initial condition $c(0) = c_0$).

(2) For t large , we have the approximations given by (16) for c, and (14) for s.

The approximation is best if ε is very small, but it works quite well even for moderate ε.
Here is a numerical example.

Let us take $k_1 = k_{-1} = k_2 = e_0 = 1$ and $s_0 = 10$, so that $\varepsilon = 0.1$. Note that $K_{\text{m}} = 2$ and $V_{\text{max}} = 1$.

We show below, together, the following plots:

• in black, the component $c(t)$ of the true solution of the system

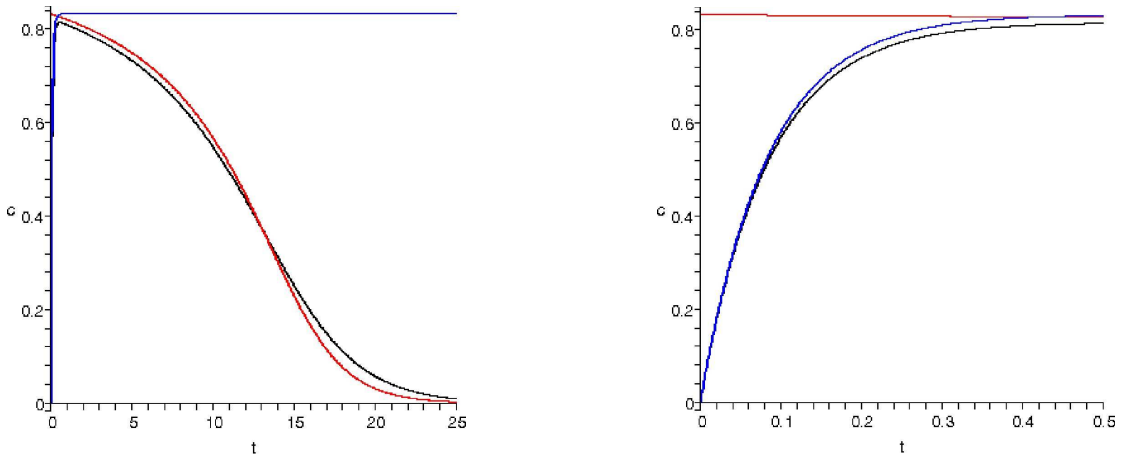
$$\frac{ds}{dt} = c - s(1-c)\,, \quad \frac{dc}{dt} = s - (2+s)c$$

with initial conditions $s(0) = s_0$, $c(0) = 0$,

• in red, $c = s/(2+s)$, where $s(t)$ solves $\frac{ds}{dt} = -s/(2+s)$ (slow system) with $s(0) = s_0$,

• in blue, the solution of the fast system at the initial time, $\frac{dc}{dt} = s_0 - (2+s_0)c$, with $c(0) = 0$.

Since it is difficult to see the curves for small t, we show plots both for $t \in [0, 25]$ and for $t \in [0, 0.5]$:



As expected, the blue curve approximates well for small t and the red one for larger t.

FYI, here is the Maple code that was used (for Tmax = 0.5 and 25):

```
restart:with(plots):with(DEtools):
s0:=10:Tmax:=0.5:N:=500:
sys:=diff(s(t),t)=c(t)-s(t)*(1-c(t)),diff(c(t),t)=s(t)-(2+s(t))*c(t):
sol:=dsolve(sys,s(0)=s0,c(0)=0,type=numeric):
plot1:=odeplot(sol,[[t,c(t)]],0..Tmax,numpoints=N,color=black,thickness=3):
sysslow:= diff(s(t),t) = - s(t)/(2+s(t)):
solslow:=dsolve(sysslow,s(0)=s0,type=numeric):
solns:= t → op(2,op(2,solslow(t))):
plot2:=plot(solns/(2+solns),0..Tmax,numpoints=N,color=red,thickness=3):
sysfast:=diff(c(t),t)=s0-(2+s0)*c(t):
solfast:=dsolve(sysfast,c(0)=0,type=numeric):
plot3:=odeplot(solfast,[[t,c(t)]],0..Tmax,numpoints=N,color=blue,thickness=3):
display(plot1,plot2,plot3);
```

6.8 Singular Perturbation Analysis

The advantage of deriving things in this careful fashion is that we have a better understanding of what went into the approximations. Even more importantly, there are methods in mathematics that help to quantify the errors made in the approximation. The area of mathematics that deals with this type of argument is *singular perturbation theory*.

The theory applies, in general, to equations like this:

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \\ \varepsilon\frac{dy}{dt} &= g(x,y) \end{aligned}$$

with $0 < \varepsilon \ll 1$. The components of the vector x are called *slow* variables, and those of y *fast* variables.

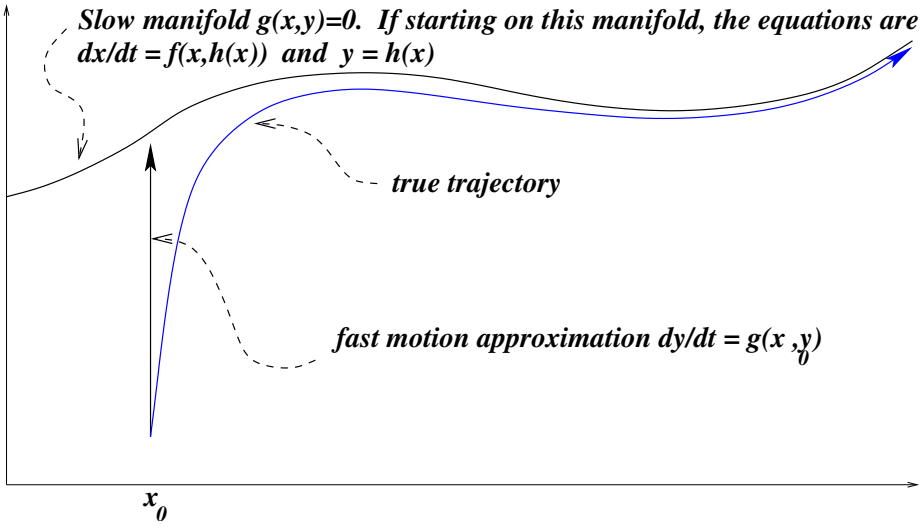
The terminology is easy to understand: $dy/dt = (1/\varepsilon)(\ldots)$ means that dy/dt is large, i.e., that $y(t)$ is "fast," and by comparison $x(t)$ is slow.[26]

The singular perturbation approach starts by setting $\varepsilon = 0$,
then solving (if possible) $g(x,y) = 0$ for $y = h(x)$ (that is, $g(x,h(x)) = 0$),
and then substituting back into the first equation.

Thus, one studies the *reduced system*:

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

on the "slow manifold" defined by $g(x,y) = 0$.



There is a rich theory that allows one to mathematically justify the approximations.

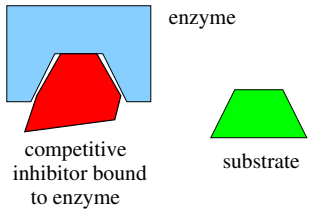
A particularly useful point of view us that of "geometric singular perturbation theory." We will not cover any of that in this course, though.

[26] The theory covers also multiple, not just two, time scales, as well partial differential equations where the domain is subject to small deformations, and many other situations as well.

6.9 Inhibition

Let us discuss next inhibition, as a further example involving enzymes.

In *competitive inhibition*, a second substrate, called an inhibitor, is capable of binding to an enzyme, thus block binding of the primary substrate.



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

For example, the enzyme may be a cell surface receptor, and the primary substrate might be a growth factor, hormone, or histamine (a protein released by the immune system in response to pollen, dust, etc).

Competitive inhibition is one mechanism by which drugs act. For example, 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.[27]

A simple chemical model is as follows:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C_1 \xrightarrow{k_2} P + E \qquad\qquad I + E \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} C_2$$

where C_1 is the substrate/enzyme complex, C_2 the inhibitor/enzyme complex, and I the inhibitor.

In terms of ODE's, we have:

$$\begin{aligned}
\frac{ds}{dt} &= k_{-1}c_1 - k_1 se \\
\frac{de}{dt} &= (k_{-1} + k_2)c_1 + k_{-3}c_2 - k_1 se - k_3 ie \\
\frac{dc_1}{dt} &= k_1 se - (k_{-1} + k_2)c_1 \\
\frac{dc_2}{dt} &= k_3 ie - k_{-3}c_2 \\
\frac{di}{dt} &= k_{-3}c_2 - k_3 ie \\
\frac{dp}{dt} &= k_2 c_1 \,.
\end{aligned}$$

It is easy to see that $c_1 + c_2 + e$ is constant (it represents the total amount of free or bound enzyme, which we'll denote as e_0), and similarly $i + c_2 = i_0$ is constant (total amount of inhibitor, free or bound to enzyme). This allows us to eliminate e and i from the equations. Furthermore, as before, we

[27] 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.

may first ignore the equation for p. We are left with a set of three ODE's:

$$\begin{aligned}\frac{ds}{dt} &= k_{-1}c_1 - k_1 s(e_0 - c_1 - c_2)\\ \frac{dc_1}{dt} &= k_1 s(e_0 - c_1 - c_2) - (k_{-1} + k_2)c_1\\ \frac{dc_2}{dt} &= k_3(i_0 - c_2)(e_0 - c_1 - c_2) - k_{-3}c_2\end{aligned}$$

One may now do a quasi-steady-state approximation, assuming that the enzyme concentrations are small relative to substrate.

We omit the steps; essentially, we need to nondimensionalize as earlier, set an appropriate small ε to zero, etc.

Formally, we can just set $dc_1/dt = 0$ and $dc_2/dt = 0$. Doing so gives:

$$\begin{aligned}c_1 &= \frac{K_{\mathbf{i}} e_0 s}{K_{\mathrm{m}} i + K_{\mathbf{i}} s + K_{\mathrm{m}} K_{\mathbf{i}}} \qquad \left(K_{\mathrm{m}} = \frac{k_{-1} + k_2}{k_1}\right)\\ c_2 &= \frac{K_{\mathrm{m}} e_0 i}{K_{\mathrm{m}} i + K_{\mathbf{i}} s + K_{\mathrm{m}} K_{\mathbf{i}}} \qquad \left(K_{\mathbf{i}} = \frac{k_{-3}}{k_3}\right)\end{aligned}$$

(not eliminating i).

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

$$\frac{dp}{dt} = \frac{V_{\max}\, s}{s + K_{\mathrm{m}}(1 + i/K_{\mathbf{i}})}$$

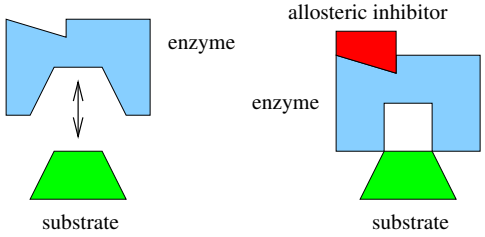
The formula reduces to the previous one when there is no inhibition ($i = 0$).

We see that the 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 very large, the rate saturates at $\dot{p} = V_{\max}$, just as if there was no inhibitor (intuitively, there is so much s that i doesn't get chance to bind and block).

6.10 Allosteric Inhibition

In *allosteric inhibition*[28], an inhibitor does not bind in the same place where the catalytic activity occurs, but instead binds at a different *effector* site (other names are *regulatory* or *allosteric* site), with the result that the shape of the enzyme is modified. In the new shape, it is harder for the enzyme to bind to the substrate.



A slightly different situation is if binding of substrate can always occur, but product can only be formed (and released) if I is not bound. We model this last situation, which is a little simpler.
Also, for simplicity, we will assume that binding of S or I to E are independent of each other.
(If we don't assume this, the equations are still the same, but we need to introduce some more kinetic constants k's.)

A reasonable chemical model is, then:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} P + E$$

$$EI + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} EIS$$

$$E + I \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} EI$$

$$ES + I \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} EIS$$

where "EI" denotes the complex of enzyme and inhibitor, etc.

It is possible to prove (see e.g. Keener-Sneyd's *Math Physiology*, exercise 1.5) that there results under quasi-steady state approximation a rate

$$\frac{dp}{dt} = \frac{V_{\max}}{1 + i/K_{\mathrm{i}}} \cdot \frac{s^2 + as + b}{s^2 + cx + d}$$

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.

One intuition is that, no matter what is the amount of substrate, the inhibitor can still bind, so maximal throughput is affected.

[28] Merriam-Webster: allosteric: "all+steric"; and steric means "relating to or involving the arrangement of atoms in space" and originates with the word "solid" in Greek

6.11 Cooperativity

Let's take a situation where n molecules of substrate must first get together with the enzyme in order for the reaction to take place:

$$nS + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} P + E$$

This is not a very realistic model, since it is unlikely that $n+1$ molecules may "meet" simultaneously.

It is, nonetheless, a simplification of a more realistic model in which the bindings may occur in sequence.

One says that the cooperativity degree of the reaction is n, because n molecules of S must be present for the reaction to take place.

Highly cooperative reactions are extremely common in biology, for instance, in ligand binding to cell surface receptors, or in binding of transcription factors to DNA to control gene expression.

We only look at this simple model in this course. We have these equations:

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

Doing a quasi-steady state approximation, under the assumption that enzyme concentration is small compared to substrate, we may repeat the previous steps (*do it as a homework problem!*), which lead to the same expression as earlier for product formation, except for a different exponent:

$$\frac{dp}{dt} = \frac{V_{\max}\, s^n}{K_{\mathrm{m}} + s^n}$$

The integer n is called the *Hill coefficient*.

One may determine $V_{\max}$, n, and K_{m} experimentally, from knowledge of the rate of product formation $\dot{p} = dp/dt$ as a function of current substrate concentration (under the quasi-steady state approximation assumption).

First, $V_{\max}$ may be estimated from the rate $\dot{p}$ corresponding to $s \to \infty$. This allows the computation of the quantity $\frac{\dot{p}}{V_{\max} - \dot{p}}$. Then, one observes that the following equality holds (solve for s^n and take logs):

$$n \ln s = \ln K_{\mathrm{m}} + \ln \left(\frac{\dot{p}}{V_{\max} - \dot{p}} \right) .$$

Thus, by a linear regression of $\ln \left(\frac{\dot{p}}{V_{\max} - \dot{p}} \right)$ versus $\ln s$, and looking at slope and intersects, n and K_{m} can be estimated.

Since the cooperative mechanism may include many unknown and complicated reactions, including very complicated allosteric effects, it is not uncommon for fractional powers to be appear (even if the above model makes no sense in a fractional situation) when fitting parameters.

One often writes the product formation rate, redefining the constant $K_{\rm m}$, as $\frac{dp}{dt} = \frac{V_{\max} s^n}{K_{\rm m}^n + s^n}$.

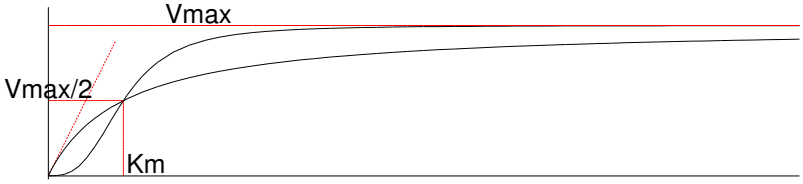
This has the advantage that, just as earlier, $K_{\rm m}$ has an interpretation as the value of substrate s for which the rate of formation of product is half of $V_{\max}$.

For our subsequent studies, the main fact that we observe is that, for $n > 1$, one obtains a "sigmoidal" shape for the formation rate, instead of a "hyperbolic" shape.

This is because, if $f(s) = \frac{V_{\max} s^n}{K_{\rm m}^n + s^n}$, then $f'(0) > 0$ when $n = 1$, but $f'(0) = 0$ if $n > 1$.

In other words, for $n > 1$, and as the function is clearly increasing, the graph must start with concavity-up. But, since the function is bounded, the concavity must change to negative at some point.

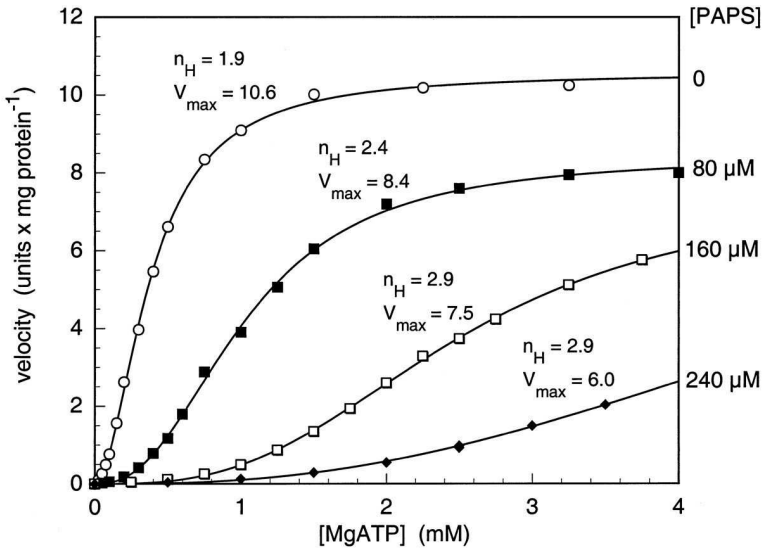
Here are graphs of two formation rates, one with $n = 1$ (hyperbolic) and one with $n = 3$ (sigmoidal):



Cooperativity plays a central role in allowing for multi-stable systems, memory, and development, as we'll see soon.

Here is a more or less random example from the literature[29] which shows fits of $V_{\max}$ and n ("n_H" for "Hill") to various data sets corresponding to an allosteric reaction.

(Since you asked: the paper has to do with an intracellular reaction having to do with the incorporation of inorganic sulfate into organic molecules by sulfate assimilating organisms; the allosteric effector is PAPS, 3'-phosphoadenosine-5'-phosphosulfate.)



The fit to the Hill model is quite striking.

[29] 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

7 Multi-Stability

7.1 Hyperbolic and Sigmoidal Responses

Let us now look at the enzyme model again, but this time assuming that the substrate is not being depleted.

This is not as strange a notion as it may seem.

For example, in receptor models, the "substrate" is ligand, and the "product" is a different chemical (such as a second messenger released inside the cell when binding occurs), so the substrate is not really "consumed."

Or, substrate may be replenished and kept at a certain level by another mechanism.

Or, the change in substrate may be so slow that we may assume that its concentration remains constant.

In this case, instead of writing

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} P + E\,,$$

it makes more sense to write

$$E \underset{k_{-1}}{\overset{k_1 s}{\rightleftarrows}} C \xrightarrow{k_2} P + E\,.$$

The equations are as before:

$$\begin{aligned}
\frac{de}{dt} &= (k_{-1} + k_2)c - k_1 se \\
\frac{dc}{dt} &= k_1 se - (k_{-1} + k_2)c \\
\frac{dp}{dt} &= k_2 c
\end{aligned}$$

except for the fact that we view s as a constant.

Repeating exactly all the previous steps, a quasi-steady state approximation leads us to the product formation rate:

$$\frac{dp}{dt} = \frac{V_{\max}\, s^n}{K_{\mathrm{m}}^n + s^n}$$

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

Next, let us make things more interesting by adding a degradation term $-\lambda p$.

In other words, we suppose that product is being produced, but it is also being used up or degraded, at some linear rate λp, where λ is some positive constant.

We obtain the following equation:

$$\frac{dp}{dt} = \frac{V_{\max}\, s^n}{K_{\mathrm{m}}^n + s^n} - \lambda p$$

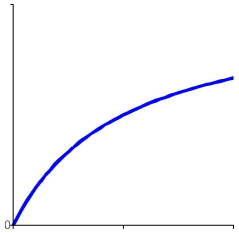
for $p(t)$.

As far as p is concerned, this looks like an equation $\frac{dp}{dt} = \mu - \lambda p$, so as $t \to \infty$ we have that $p(t) \to \frac{\mu}{\lambda}$.

Let us take $\lambda = 1$ just to make notations easier.[30] Then the steady state obtained for p is:

$$p(\infty) \;=\; \frac{V_{\max}\, s^n}{K_{\mathrm{m}}^n + s^n}$$

Let us first consider the case $n = 1$.



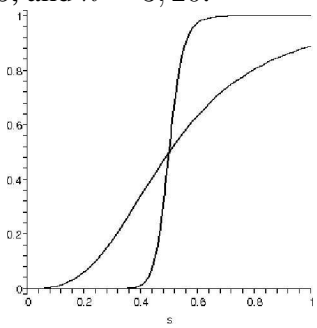
By analogy, if s would be the displacement of a slider or dial, a light-dimmer behaves in this way:

the steady-state as a function of the "input" concentration s (which we are assuming is some constant) is *graded*, in the sense that it is proportional to the parameter s (over a large range of values s; eventually, it saturates).

The case $n = 1$ gives what is called a *hyperbolic* response, in contrast to *sigmoidal* response that arises from cooperativity ($n > 1$).

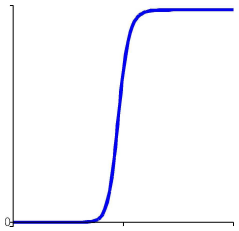
As n gets larger, the plot of $\frac{V_{\max} s^n}{K_{\mathrm{m}}^n + s^n}$ becomes essentially a step function with a transition at $s = K_{\mathrm{m}}$.

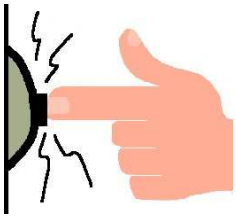
Here are plots with $V_{\max} = 1$, $K_{\mathrm{m}} = 0.5$, and $n = 3, 20$:



The sharp increase, and saturation, means that a value of s which is under some threshold (roughly, $s < K_{\mathrm{m}}$) will not result in an appreciable result ($p \approx 0$, in steady state) while a value that is over this threshold will give an abrupt change in result ($p \approx V_{max}$, in steady state).

A "binary" response is thus produced from cooperative reactions.





The behavior of closer to that of a doorbell: if we don't press hard enough, nothing happens; if we press with the right amount of force (or more), the bell rings.

[30] If λ is arbitrary, just replace $V_{\max}$ by $V_{\max}/\lambda$ everywhere.

Ultrasensitivity

Sigmoidal responses are characteristic of many signaling cascades, which display what biologists call an *ultrasensitive* response to inputs. If the purpose of a signaling pathway is to decide whether a gene should be transcribed or not, depending on some external signal sensed by a cell, for instance the concentration of a ligand as compared to some default value, such a binary response is required.

Cascades of enzymatic reactions can be made to display ultrasensitive response, as long as at each step there is a Hill coefficient $n > 1$, since the derivative of a composition of functions $f_1 \circ f_2 \circ \ldots \circ f_k$ is, by the chain rule, a product of derivatives of the functions making up the composition.

Thus, the slopes get multiplied, and a steeper nonlinearity is produced. In this manner, a high effective cooperativity index may in reality represent the result of composing several reactions, perhaps taking place at a faster time scale, each of which has only a mildly nonlinear behavior.

7.2 Adding Positive Feedback

Next, we build up a more complicated situation by adding *feedback* to the system.

Let us suppose that the substrate concentration is not constant, but instead it depends monotonically on the product concentration.[31]

For example, the "substrate" s might represent a transcription factor which binds to DNA and instructs the production of mRNA for a protein p, and the protein p, in turn, instructs the transcription of s.

Or, possibly, $p = s$, meaning that p serves to enhance its own transcription. (autocatalytic process).

The effect of p on s may be very complex, involving several intermediaries.
However, since all we want to do here is to illustrate the main ideas, we'll simply say that $s(t) = \alpha p(t)$, for some constant α.

Therefore, the equation for p becomes now:

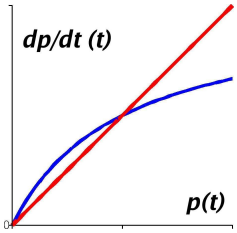
$$\frac{dp}{dt} = \frac{V_{\max}\,(\alpha p)^n}{K_{\mathrm{m}}^n + (\alpha p)^n} - \lambda p$$

or, if we take for simplicity[32] $\alpha = 1$ and $\lambda = 1$:

$$\frac{dp}{dt} = \frac{V_{\max}\,p^n}{K_{\mathrm{m}}^n + p^n} - p\,.$$

What are the possible steady states of this system with feedback?

Let us analyze the solutions of the differential equation, first with $n = 1$.
We plot the first term (formation rate) together with the second one (degradation):



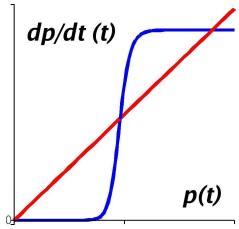
[31] If we wanted to give a careful mathematical argument, we'd need to do a time-scale separation argument in detail. We will proceed very informally.

[32] Actually, we can always rescale p and t and rename parameters so that we have this simpler situation, anyway.

Observe that, for small p, the formation rate is larger than the degradation rate,
while, for large p, the degradation rate exceeds the formation rate.
Thus, the concentration $p(t)$ *converges to a unique intermediate value.*

Bistability arises from sigmoidal formation rates

In the cooperative case (i.e., $n > 1$), however, the situation is far more interesting!



• for small p the degradation rate is larger than the formation rate, so the concentration $p(t)$ *converges to a low value*,

• but for large p the formation rate is larger than the degradation rate, and so the concentration $p(t)$ *converges to a high value* instead.

In summary, two stable states are created, one "low" and one "high", by this interaction of formation and degradation, if one of the two terms is sigmoidal.
(There is also an intermediate, unstable state.)

Instead of graphing the formation rate and degradation rate separately, one may (and we will, from now on) graph the right hand side

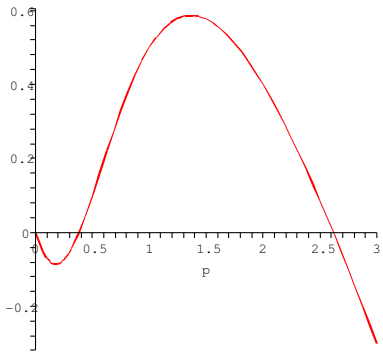
$$\frac{V_{\max}\, p^n}{K_{\mathrm{m}}^n + p^n} - p$$

as a function of p. From this, the phase line can be read-out, as done in your ODE course.

For example, here is the graph of

$$\frac{V_{\max}\, p^n}{K_{\mathrm{m}}^n + p^n} - p$$

with $V_{\max} = 3$, $K_{\mathrm{m}} = 1$, and $n = 2$.



The phase line is as follows:

where $A = 0$, $B = 3/2 - 1/2 * 5^(1/2) \approx 0.38$, and $C = 3/2 + 1/2 * 5^(1/2) \approx 2.62$.

We see that A and C are stable (i.e., sinks) and the intermediate point B is a unstable (i.e., a source)

7.3 Cell Differentiation and Bifurcations

In unicellular organisms, cell division results in cells that are identical to each other and to the original ("mother") cell. In multicellular organisms, in contrast, cells differentiate.

Since all cells in the same organism are genetically identical, the differences among cells must result from variations of gene expression.

A central question in developmental biology is: how are these variations established and maintained?

A possible mechanism by which spatial patterns of cell differentiation could be specified during embryonic development and regeneration is based on *positional information*.[33] Cells acquire a positional value with respect to boundaries, and then use this "coordinate system" information during gene expression, to determine their fate and phenotype.
(Daughter cells inherit as "initial conditions" the gene expression pattern of the mother cells, so that a developmental history is maintained.)

In other words, the basic premise is that position in the embryo determines cell fate.
But how could this position be estimated by each individual cell?

One explanation is that there are chemicals, called *morphogens*, which are nonuniformly distributed.
Typically, morphogens are RNA or proteins.
They instruct cells to express certain genes, depending on position-dependent concentrations (and slopes of concentrations, i.e. gradients).
When different cells express different genes, the cells develop into distinct parts of the organism.

An important concept is that of *polarity*: opposite ends of a whole organism or of a given tissue (or sometimes, of a single cell) are different, and this difference is due to morphogen concentration differences.

Polarity is initially determined in the embryo.
It may be established initially by the site of sperm penetration, as well as environmental factors such as gravity or pH.

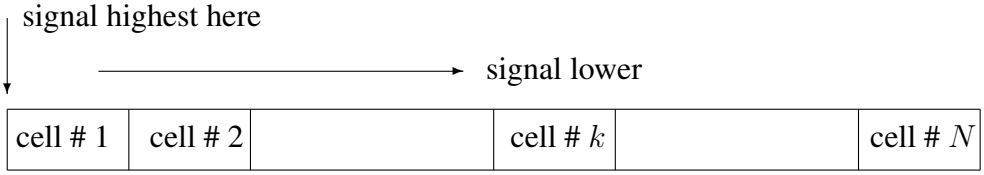
The existence of morphogens and their role in development were for a long time just an elegant mathematical theory, but recent work in developmental biology has succeeded in demonstrating that embryos do in fact use morphogen gradients. This has been shown for many different species, although most of the work is done in fruit flies. A nice expository article (focusing on frogs) is: Jeremy Green, "Morphogen gradients, positional information, and Xenopus: Interplay of theory and experiment," *Developmental Dynamics*, 2002, 225: 392-408. There is a link for this paper in the course webpage:
http://www.math.rutgers.edu/~ sontag/336/morphogen_gradients_exposition_green_dev_dynamics02.pdf

Using mathematical models of morphogens and positional information, it is in principle possible to predict how mutations affect phenotype. Indeed, the equations might predict, say, that antennae in fruit flies will grow in the wrong part of the body, as a consequence of a mutation. One can then perform the actual mutation and validate the prediction by letting the mutant fly develop.

[33] The idea of positional information is an old one in biology, but it was Louis Wolpert in 1971 who formalized it, see: Lewis, J., J.M. Slack, and L. Wolpert, "Thresholds in development," J. Theor. Biol. 1977, 65: 579-590.
A good, non-mathematical, review article is "One hundred years of positional information" by Louis Wolpert, appeared in *Trends in Genetics*, 1996, 12:359-64.
This last paper is posted to the course website:
http://www.math.rutgers.edu/~ sontag/336/wolpert_hundred_years_positional_info_TIGS96.pdf

How can small differences in morphogen lead to abrupt changes in cell fate?

For simplicity, let us think of a "wormy" one-dimensional organism, but the same ideas apply to a full 3-d model.



We suppose that each cell may express a protein P whose level (concentration, if you wish) "p" determines a certain phenotypical (i.e., observable) characteristic.

As a purely hypothetical and artificial example, it may be the case that P can attain two very distinct levels of expression: "very low" (or zero) or "very high," and that a cell will look like a "nose" cell if p is high, and like a "mouth" cell if p is low.[34]

Moreover, we suppose that a certain morphogen S (we use S for "signal") affects the expression mechanism for the gene for P, so that the concentration s of S in the vicinity of a particular cell influences what will happen to that particular cell.

The concentration of the signaling molecule S is supposed to be highest at the left end, and lowest at the right end, of the organism, and it varies continuously. (This may be due to the mother depositing S at one end of the egg, and S diffusing to the other end, for example.)

The main issue to understand is: since nearby cells detect only slightly different concentrations of S, how can "sudden" changes of level of P occur?

$s = 1$	$s = 0.9$	$s = 0.8$	$s = 0.7$	$s = 0.6$	$s = 0.5$	$s = 0.4$	$s = 0.3$	$s = 0.2$
$p \approx 1$ nose cell	$p \approx 1$ nose cell	$p \approx 1$ nose cell	$p \approx 1$ nose cell	$p \approx 1$ nose cell	$p \approx 0$ mouth cell	$p \approx 0$ mouth cell	$p \approx 0$ mouth cell	$p \approx 0$ mouth cell

In other words, why don't we find, in-between cells that are part of the "nose" (high p) and cells that are part of the "mouth" (low p), cells that are, say, "3/4 nose, 1/4 mouth"?

We want to understand how this "thresholding effect" could arise.

The fact that the DNA in all cells of an organism is, in principle, identical, is translated mathematically into the statement that all cells are described by the same system of equations, but we include an input parameter in these equations to represent the concentration s of the morphogen near any given cell.[35]

In other words, we'll think of the evolution on time of chemicals (such as the concentration of the protein P) as given by a differential equation:

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

(of course, realistic models contain many proteins or other substances, interacting with each other through mechanisms such as control of gene expression and signaling; we use an unrealistic single equation just to illustrate the basic principle).

[34] Of course, a real nose has different types of cells in it, but for this silly example, we'll just suppose that they all look the same, but they look very different from mouth-like cells, which we also assume all look the same.

[35] We assume, for simplicity, that s constant for each cell, or maybe the cell samples the average value of s around the cell.

We assume that from each given initial condition $p(0)$, the solution $p(t)$ will settle to some steady state $p(\infty)$; the value $p(\infty)$ describes what the level of P will be after a transient period.
We think of $p(\infty)$ as determining whether we have a "nose-cell" or a "mouth-cell."

Of course, $p(\infty)$ depends on the initial state $p(0)$ as well as on the value of the parameter s that the particular cell measures.
We will assume that, at the start of the process, all cells are in the same initial state $p(0)$.
So, we need that $p(\infty)$ be drastically different only due to a change in the parameter s.[36]

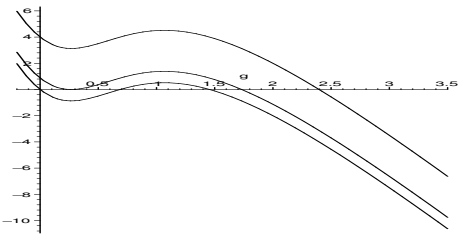
To design a realistic "f," we start with the positive feedback system that we had earlier used to illustrate bi-stability, and we add a term "$+ks$" as the simplest possible mechanism by which the concentration of signaling molecule may influence the system.[37]:

$$\frac{dp}{dt} \;=\; f(p,s) \;=\; \frac{V_{\max}\, p^n}{K_{\mathrm{m}}^n + p^n} \;-\; \lambda p \;+\; ks\,.$$

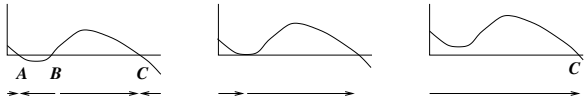
Let us take, to be concrete, k=5, $V_{\max}$=15, λ=7, K_{m}=1, Hill coefficient n=2, and α=1.

There follow the plots of $f(p,s)$ versus p, for three values of s:

$$s < s^*\,, \quad s = s^*\,, \quad s > s^*\,, \quad \text{where } \; s^* \approx .268\,.$$



The respective phase lines are now shown below the graphs:



We see that for $s < s^*$, there are two sinks (stable steady states), marked A and C respectively, as well as a source (unstable steady state), marked B.

We think of A as the steady state protein concentration $p(\infty)$ representing mouth-like cells, and C as that for nose-like cells.

Of course, the exact position of A depends on the precise value of s. Increasing s by a small amount means that the plot moves up a little, which means that A moves slightly to the right. Similarly, B moves to the left and C to the right.

However, we may still think of a "low" and a "high" stable steady state (and an "intermediate" unstable state) in a qualitative sense.

Note that B, being an unstable state, will never be found in practice: the smallest perturbation makes the solution flow away from it.

[36] This is the phenomenon of "bifurcations," which you should have encountered in the previous differential equations course.

[37] This term could represent the role of s as a transcription factor for p. The model that we are considering is the one proposed in the original paper by Lewis et al.

For $s > s^*$, there is only one steady state, which is stable. We denote this state as C, because it corresponds to a high concentration level of P.

Once again, the precise value of C depends on the precise value of s, but it is still true that C represents a "high" concentration.

Incidentally, a value of s *exactly* equal to s^* will never be sensed by a cell: there is zero probability to have this precise value.

Now, assume that all cells in the organism start with no protein, that is, $p(0) = 0$.

The left-most cells, having $s > s^*$, will settle into the "high state" C, i.e., they will become nose-like.

The right-most cells, having $s < s^*$, will settle into the "low state" A, i.e., they will become mouth-like.

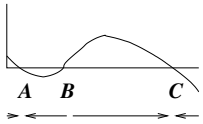
So we see how a sharp transition between cell types is achieved, merely due to a change from $s > s^*$ to $s < s^*$ as we consider cells from the left to the right end of the organism.

$s > s^*$	$s > s^*$	$s > s^*$	$s > s^*$	$s > s^*$	$s < s^*$	$s < s^*$	$s < s^*$	$s < s^*$
$p \approx C$ nose cell	$p \approx C$ nose cell	$p \approx C$ nose cell	$p \approx C$ nose cell	$p \approx C$ nose cell	$p \approx A$ mouth cell	$p \approx A$ mouth cell	$p \approx A$ mouth cell	$p \approx A$ mouth cell

Moreover, this model has a most amazing feature, which corresponds to the fact that, once a cell's fate is determined, it will not revert[38] to the original state.

Indeed, suppose that, after a cell has settled to its steady state (high or low), we now suddenly "wash-out" the morphogen, i.e., we set s to a very low value.

The behavior of *every* cell will now be determined by the phase line for low s:



This means that any cell starting with "low" protein P will stay low, and any cell starting with "high" protein P will stay high.

A permanent memory of the morphogen effect is thus imprinted in the system, even after the signal is "turned-off"!

Optional homework: Show that a Hill coefficient $n = 1$ would not have worked:

$$\frac{dp}{dt} \;=\; f(p,s) \;=\; \frac{V_{\max}\, p}{K_{\mathrm{m}} + p} \;-\; \lambda p \;+\; ks$$

has the property that there is only one steady state, which depends continuously on the signal s.

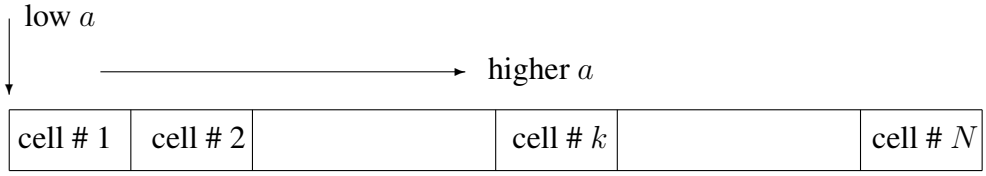
[38] As with stem cells differentiating into different tissue types.

A little exercise to test understanding of these ideas.

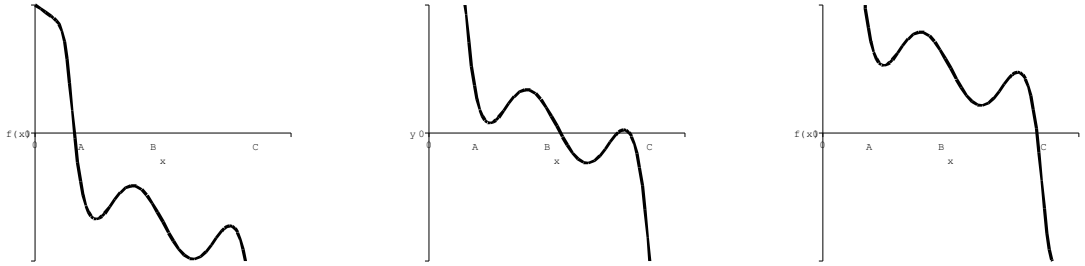
A multicellular 1-d organism as before is considered. Each cell expresses a certain gene X according to the same differential equation

$$\frac{dx}{dt} \;=\; f(x) + a\,.$$

The cells at the left end receive a low signal a, while those at the right end see a high signal a (and the signal changes continuously in between).



The following plots show the graph of $f(x) + a$, for small, intermediate, and large a respectively.

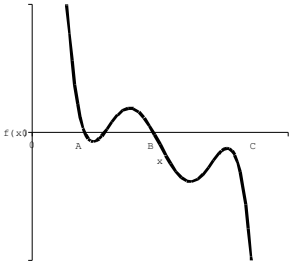


We indicate a roughly "low" level of x by the letter "A," an "intermediate" level by "B," and a "high" level by "C."

Question: Suppose that the level of expression starts at $x(0) = 0$ for every cell.

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

(2) Next suppose that, *after* the system has so settled, we now suddenly change the level of the signal a so that now *every* cell sees the *same* value of a. This value of a that every cell is exposed to, corresponds to this plot of $f(x) + a$:



What pattern will the organism settle upon?

Answer:

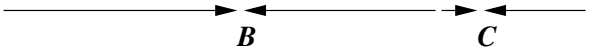
Let us use this picture:

left cell	left cell	left cell	center cell	center cell	center cell	right cell	right cell	right cell

• Those cells located toward the left will see these "instructions of what speed to move at:"

Therefore, starting from $x = 0$, they settle at a "low" gene expression level, roughly indicated by A.

• Cells around the center will see these "instructions:"



Thus, starting from $x = 0$, they settle at an "intermediate" level B.

• Finally, those cells toward the left will see these "instructions:"

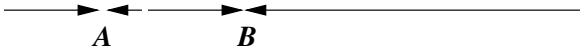
Therefore, starting from $x = 0$, they will settle at a "high" level C.

In summary, the pattern that we observe is:

$$AAABBBCCC\,.$$

(There may be many A's, etc., depending on how many cells there are, and what exactly is the graph of f. We displayed 3 of each just to give the general idea!)

Next, we suddenly "change the rules of the game" and ask them *all* to follow these instructions:



Now, cells that started (from the previous stage of our experiment) near A will approach A, cells that were near B approach B, and cells that were near C have "their floor removed from under them" so to speak, and they are being now told to move left, i.e. all the way down to B.

In summary, we have that starting at $x = 0$ at time zero, the pattern observed after the first part of the experiment is:

$$AAABBBCCC\,,$$

and after the second part of the experiment we obtain this final configuration:

$$AAABBBBBB\,.$$

(Exactly how many A's and B's depends on the precise form of the function f, etc. We are just representing the general pattern.)

The next page has a homework problem.

The answer is posted to the course website.

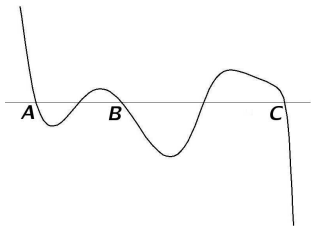
Homework Problem:

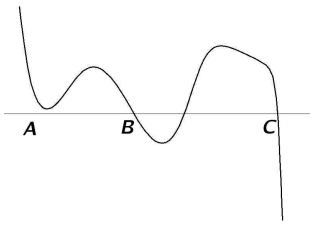
We consider a 1-d organism, with cells are arranged on a line.
Each cell expresses a certain gene X according to the same differential equation

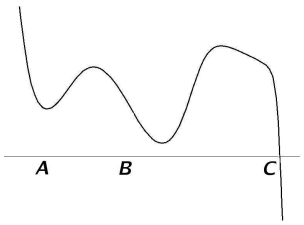
$$\frac{dx}{dt} = f(x) + a$$

but the cells toward the left end receive a low signal $a \approx 0$, while those toward the right end see a high signal a (and the signal changes continuously in between).
The level of expression starts at $x(0) = 0$ for every cell.

This is what $f + a$ looks like, for low, intermediate, and high values of a respectively:







We let the system settle to steady state.

After the system has so settled, we next suddenly change the level of the signal a, so that from now on *every* cell sees the *same* value of a. The value of a that every cell is exposed to, in the second part of the experiment, corresponds to an intermediate value that gives a graph like the second (right) one above.

Like in the example worked out above, we ask what the patterns will be after the first and second experiments.

Here are a few possibilities of what will be seen after the first and the second parts of the experiment. Circle the correct one (no need to explain).

1. 000000000000 → AAAABBBBCCCC → AAAAAABBBBBB
2. 000000000000 → AAAAAABBBBBB → BBBBBBBBBBBB
3. 000000000000 → AAAAAAAAAAAA → BBBBBBBBBBBB
4. 000000000000 → BBBBAAAACCCC → AAAAAACCCCCC
5. 000000000000 → AAAABBBBCCCC → BBBBCCCCCCCC
6. 000000000000 → AAAAAABBBBBB → AAAAAABBBBBB
7. 000000000000 → AAAABBBBCCCC → CCCCCCAAAAAA
8. 000000000000 → AAAABBBBCCCC → AAAAAABBBBBB
9. 000000000000 → AAAABBBBCCCC → BBBBBBBBCCCC
10. 000000000000 → AAAABBBBCCCC → CCCCCCCCCCCC
11. 000000000000 → CCCCCCCCCCCC → BBBBBBBBBBBB

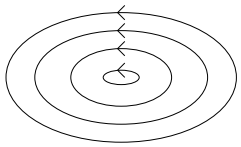
8 Periodic Behavior

Periodic behaviors (i.e, oscillations) are very important in biology, appearing in diverse areas such as neural signaling, circadian rythms, and heart beats.

You have seen examples of periodic behavior in the differential equations course, most probably the harmonic oscillator (mass spring system with no damping)

$$\begin{aligned} \frac{dx}{dt} &= y \\ \frac{dy}{dt} &= -x \end{aligned}$$

whose trajectories are circles, or, more generally, linear systems with eigenvalues that are purely imaginary, leading to ellipsoidal trajectories:



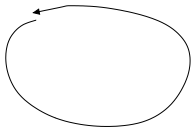
A serious limitation of such linear oscillators is that they are not *robust*:

Suppose that there is a small perturbation in the equations:

$$\begin{aligned} \frac{dx}{dt} &= y \\ \frac{dy}{dt} &= -x + \varepsilon y \end{aligned}$$

where $\varepsilon \neq 0$ is small. The trajectories are not periodic anymore!

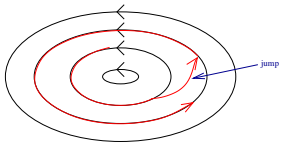
Now dy/dt doesn't balance dx/dt just right, so the trajectory doesn't "close" on itself:



Depending on the sign of ε, we get a stable or an unstable spiral.

When dealing with electrical or mechanical systems, it is often possible to construct things with precise components and low error tolerance. In biology, in contrast, things are too "messy" and oscillators, if they are to be reliable, must be more "robust" than simple harmonic oscillators.

Another disadvantage of simple linear oscillations is that if, for some reason, the state "jumps" to another position[39] then the system will simply start oscillating along a different orbit and never come back to the original trajectory:

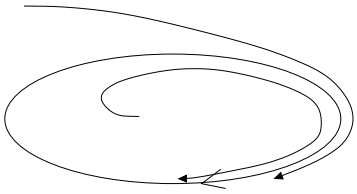


To put it in different terms, the particular oscillation depends on the initial conditions. Biological objects, in contrast, tend to reset themselves (e.g., your internal clock adjusting after jetlag).

[39] the "jump" is not described by the differential equation; think of the effect of some external disturbance that gives a "kick" to the system

8.1 Periodic Orbits and Limit Cycles

A *(stable) limit cycle* is a periodic trajectory which attracts other solutions (at least those starting nearby) to it.[40]



Thus, a member of a family of "parallel" periodic solutions (as for linear centers) is *not* called a limit cycle, because other close-by trajectories remain at a fixed distance away, and do not converge to it.

Limit cyles are "robust" in ways that linear periodic solutions are not:

• If a (small) perturbation moves the state to a different initial state away from the cycle, the system will return to the cycle by itself.

• If the dynamics changes a little, a limit cycle will still exist, close to the original one.

The first property is obvious from the definition of limit cycle. The second property is not very difficult to prove either, using a "Lyapunov function" argument. (I'll explain the idea in class.)

8.2 An Example of Limit Cycle

In order to understand the definition, and to have an example that we can use for various purposes later, we will consider the following system[41]:

$$\begin{aligned}\dot{x}_1 &= \mu x_1 - \omega x_2 + \theta x_1(x_1^2 + x_2^2)\\ \dot{x}_2 &= \omega x_1 + \mu x_2 + \theta x_2(x_1^2 + x_2^2)\,.\end{aligned}$$

where we pick $\theta = -1$ for definiteness, so that the system is:

$$\begin{aligned}\dot{x}_1 &= \mu x_1 - \omega x_2 - x_1(x_1^2 + x_2^2)\\ \dot{x}_2 &= \omega x_1 + \mu x_2 - x_2(x_1^2 + x_2^2)\,.\end{aligned}$$

(Note that if picked $\theta = 0$, we would have a linear harmonic oscillator, which has no limit cycles.)

There are two other ways to write this system which help us understand it better.

The first is to use polar coordinates.

We let $x_1 = \rho\cos\varphi$ and $x_2 = \rho\sin\varphi$, and differentiate with respect to time. Equating terms, we obtain separate equations for the magnitude ρ and the argument φ, as follows:

$$\begin{aligned}\dot{\rho} &= \rho(\mu - \rho^2)\\ \dot{\varphi} &= \omega\,.\end{aligned}$$

(The equation in polar coordinates is only valid for $x \neq 0$, that is, if $\rho \neq 0$ and φ is well-defined.)

[40] Stable limit cycles are to all periodic trajectories as stable steady states are to all steady states.

[41] of course, this is a purely mathematical example

Another useful way to rewrite the system is in terms of complex numbers: we represent the pair (x_1, x_2) by the complex number $z = x_1 + ix_2$. Then the equation becomes, for $z = z(t)$:

$$\dot{z} \;=\; (\mu + \omega i)z - |z|^2 z\,.$$

Prove that this equation is true, as a homework problem (use that $dz/dt = dx_1/dt + idx_2/dt$).

We now analyze the system using polar coordinates.

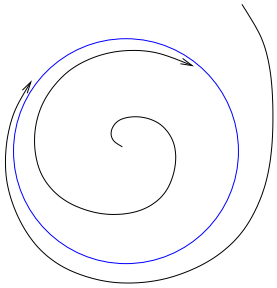
Since the differential equations for ρ and φ are decoupled, we may analyze each of them separately.

The φ-equation $\dot{\varphi} = \omega$ tells us that the solutions must be rotating at speed ω (counter-clockwise, if $\omega > 0$).

Let us look next at the scalar differential equation $\dot{\rho} = \rho(\mu - \rho^2)$ for the magnitude r.

When $\mu \leq 0$, the origin is the only steady state, and every solution converges to zero. *This means that the full planar system is so that all trajectories spiral into the origin.*

When $\mu \geq 0$, the origin of the scalar differential equation $\dot{\rho} = \rho(\mu - \rho^2)$ becomes unstable[42], as we can see from the phase line. In fact, the the velocity is negative for $\rho > \sqrt{\mu}$ and positive for $\rho < \sqrt{\mu}$, so that there is a sink at $\rho = \sqrt{\mu}$. *This means that the full planar system is so that all trajectories spiral into the circle of radius $\sqrt{\mu}$, which is, therefore, a limit cycle.*



(Expressed in terms of complex-numbers, $z(t) = \sqrt{\mu}e^{i\omega t}$ is the limit cycle.)

Note that the oscillation has magnitude $\sqrt{\mu}$ and frequency ω.

Unfortunately, it is quite difficult to actually prove that a limit cycle exists, in general.

But for systems of **two** equations, there is a very powerful criterion.

8.3 Poincaré-Bendixson Theorem

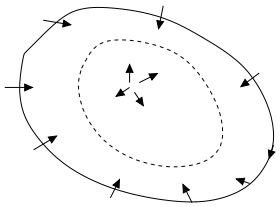
Suppose *a bounded region D in the plane is so that* **no trajectories can exit** D,

(in other words, we have a "forward-invariant" or "trapping" region, which is the same as saying that, on the boundary of the region, the vector fields point inside or tangentially)

and either that there are **no steady states** *inside, or there is a single steady state that is repelling.*

Then, *there is a periodic orbit inside D.*

[42] the passage from $\mu < 0$ to $\mu > 0$ is a typical example of what is called a "supercritical Hopf bifurcation"



This theorem is proved in advanced differential equations books; the basic idea is easy to understand: if we start near the boundary, we must go towards the inside, and cannot cross back (because trajectories cannot cross). Since it cannot approach a source, the trajectory must approach a periodic orbit. (I'll explain the idea in class.)

We gave a simple version, sufficient for our purposes; one can state the theorem a little more generally, saying that all trajectories will converge to either steady states, limit cycles, or "connections" among steady states.

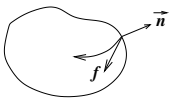
It is also possible to prove that if there is a unique periodic orbit, then it must be a limit cycle.

In general, finding an appropriate region D is usually quite hard; often one uses plots of solutions and/or nullclines in order to guess a region.[43]

Invariance of a region D can be checked by using the following test: the outward-pointing normal vectors, at any point of the boundary of D, must make an angle of at least 90 degrees with the vector field at that point. Algebraically, this means that the dot product must be ≤ 0 between a normal $\vec{n}$ and the vector field:

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

at any boundary point.[44]



Let us work out the example:

$$\begin{aligned} \dot{x}_1 &= \mu x_1 - \omega x_2 - x_1(x_1^2 + x_2^2) \\ \dot{x}_2 &= \omega x_1 + \mu x_2 - x_2(x_1^2 + x_2^2) \end{aligned}$$

with $\mu > 0$, using P-B. (Of course, we already know that the circle with radius $\sqrt{\mu}$ is a limit cycle, since we showed this by using polar coordinates.)

We must find a suitable invariant region, one that contains the periodic orbit that we want to show exists. Cheating (because if we already know it is there, we don't need to find it!), we take as our region D the disk with radius $\sqrt{2\mu}$. (Any large enough disk would have done the trick.)

To show that D is a trapping region, we must look at its boundary, which is the circle of radius $\sqrt{2\mu}$, and show that the normal vectors, at any point of the boundary, form an angle of at least 90 degrees with the vector field at that point. This is exactly the same as showing that the dot product between the normal and the vector field is negative (or zero, if tangent).

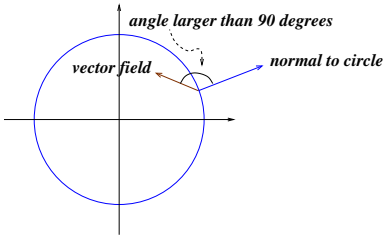
[43] In problems, I might give you a differential equation and a region, and ask you to prove that it is a trapping region.

[44] If the dot product is strictly negative, this is fairly obvious, since the vector field must then "point to the inside" of D. When the vectors are exactly perpendicular, the situation is a little more subtle, especially if there are corners in the boundary of D (what is a "normal" at a corner?), but the equivalence is still true. The mathematical field of "nonsmooth analysis" studies such problems of invariance, especially for regions with possible corners.

At any point on the circle $x_1^2 + x_2^2 = 2\mu$, a normal vector is (x_1, x_2) (since the arrow from the origin to the point is perpendicular to circle), and the dot product is:

$$[\mu x_1 - \omega x_2 - x_1(x_1^2+x_2^2)]\, x_1 + [\omega x_1 + \mu x_2 - x_2(x_1^2+x_2^2)]\, x_2 \;=\; (\mu - (x_1^2+x_2^2))(x_1^2+x_2^2) \;=\; -2\mu^2 \;<\; 0\,.$$

Thus, the vector field points inside and the disk of radius $2\sqrt{\mu}$ is a trapping region.



The only steady state is $(0, 0)$, which we can see by noticing that 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 multiplying by x_1 the first equation, and the second by x_2, we obtain that $(\mu + x_1^2 + x_2^2)(x_1^2 + x_2^2) = 0$, so $x_1 = x_2 = 0$.

Linearizing at the origin, we have an unstable spiral. (Homework: check!) Thus, the only steady state is repelling, which is the other property that we needed. So, we can apply the P-B Theorem.

We conclude that there is a periodic orbit inside this disk.[45]

8.4 The Van der Pol Oscillator

A typical way in which periodic orbits arise in models in biology and many other fields can be illustrated with the well-known *Van der Pol oscillator*.[46] After some changes of variables, which we do not discuss here, the van der Pol oscillator becomes this system:

$$\begin{aligned} \frac{dx}{dt} &= y + x - \frac{x^3}{3} \\ \frac{dy}{dt} &= -x \end{aligned}$$

The only steady state is at $(0, 0)$, which repels, since the Jacobian has positive determinant and trace:

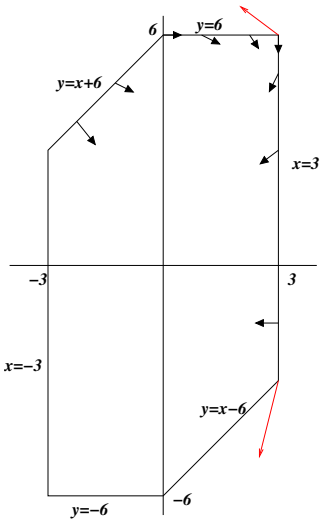
$$\left.\begin{pmatrix} 1 - x^2 & 1 \\ -1 & 0 \end{pmatrix}\right|_{(0,0)} = \begin{pmatrix} 1 & 1 \\ -1 & 0 \end{pmatrix}.$$

We will show that there are periodic orbits (one can also show there is a limit cycle, but we will not do so), by applying Poincaré-Bendixson.

To apply P-B, we consider the following special region:

[45] In fact, using annular regions $\sqrt{\mu} - \varepsilon < x_1^2 + x_2^2 < \sqrt{\mu} + \varepsilon$, one can prove by a similar argument that the periodic orbit is unique, and, therefore, is a limit cycle.

[46] Balthazar van der Pol was a Dutch electrical engineer, whose oscillator models of vacuum tubes are a routine example in the theory of limit cycles; his work was motivated by models of the human heart and an interest in arrhythmias. The original paper was: B. van der Pol and J. van der Mark, *The heartbeat considered as a relaxation oscillation, and an electrical model of the heart*, Phil. Mag. Suppl. #6 (1928), pp. 763–775.



We will prove that, on the boundary, the vector field point inside, as shown by the arrows.
The boundary is made up of 6 segments, but, by symmetry,
(since the region is symmetric and the equation is odd), it is enough to consider 3 segments:

$$x = 3,\ -3 \le y \le 6 \qquad y = 6,\ 0 \le x \le 3 \qquad y = x + 6,\ -3 \le x \le 0\,.$$

$x = 3, -3 \le y \le 6$:
we may pick $\vec{\nu} = (1, 0)$, so $\left(\frac{dx}{dt}, \frac{dy}{dt}\right) \cdot \vec{n} = \frac{dx}{dt}$ and, substituting $x = 3$ into $y + x - \frac{x^3}{3}$, we obtain:

$$\frac{dx}{dt} = y - 6 \le 0\,.$$

Therefore, we know that the vector field points to the left, on this boundary segment.

We still need to make sure that things do not "escape" through a corner, though. In other words, we need to check that, on the corners, there cannot be any arrows as the red ones.
At the top corner, $x = 3, y = 6$, we have $dy/dt = -3 < 0$, so that the corner arrow must point down, and hence "SW", so we are OK. At the bottom corner, also $dy/dt = -3 < 0$, and $dx/dt = -9$, so the vector field at that point also points inside.

$y = 6, 0 \le x \le 3$:
we may pick $\vec{\nu} = (0, 1)$, so

$$\left(\frac{dx}{dt}, \frac{dy}{dt}\right) \cdot \vec{n} = \frac{dy}{dt} = -x \le 0\,,$$

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

$y = x + 6, -3 \le x \le 0$:

We pick the outward normal $\vec{\nu} = (-1, 1)$ and take dot product:

$$\begin{pmatrix} y + x - x^3/3 \\ -x \end{pmatrix} \cdot \begin{pmatrix} -1 \\ 1 \end{pmatrix} = -2x - y + x^3/3\,.$$

Evaluated at $y = x + 6$, this is:

$$\frac{x^3}{3} - 3x - 6,\ -3 \le x \le 0$$

which is indeed always negative (plot, or use calculus), and one can also check corners.

8.5 Bendixson's Criterion

There is a useful criterion to help conclude *there cannot be any* periodic orbit in a given a simply-connected (no holes) region D:

If *the divergence of the vector field is everywhere positive*[47] *or is everywhere negative inside* D*,* **then** *there cannot be a periodic orbit inside* D*.*

Sketch of proof (by contradiction):

Suppose that there is some such periodic orbit, which describes 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:

$$\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y}\,.$$

The Gauss Divergence Theorem (or "Green's Theorem") says that:

$$\int\int_D \operatorname{div} F(x,y)\,dxdy \;=\; \int_C \vec{n}\cdot F$$

(the right-hand expression is the line integral of the dot product of a unit outward normal with F).[48]

Now, saying that C is an orbit means that F is tangent to C, so the dot product is zero, and therefore

$$\int\int_D \operatorname{div} F(x,y)\,dxdy \;=\; 0\,.$$

But, if $\operatorname{div} F(x,y)$ is everywhere positive, then the integral is positive, and we get a contradiction. Similarly if it is everywhere negative.

Example: $dx/dt = x$, $dy/dt = y$. Here the divergence is $= 2$ everywhere, so there cannot exist any periodic orbits (inside any region).

It is very important to realize what the theorem *does not* say:

Suppose that we take the example $dx/dt = x$, $dy/dt = -y$. Since the divergence is identically zero, the Bendixson criterion tells us nothing. In fact, this is a linear saddle, so we know (for other reasons) that there are no periodic obits.

On the other hand, for the example $dx/dt = y$, $dy/dt = -x$, which also has divergence identically zero, periodic orbits exist!

Homework: For the van der Pol oscillator:

(1) Show that there are no periodic orbits contained entirely inside the half-plane $\{(x,y), x > 1\}$.

(2) Show that there are no periodic orbits contained entirely inside the half-plane $\{(x,y), x < 1\}$.

(Use Bendixon's criterion to rule out such orbits.)

[47] To be precise, everywhere nonnegative but not everywhere zero

[48] The one-dimensional analog of this is the Fundamental Theorem of Calculus: the integral of F' (which is the divergence, when there is only one variable) over an interval $[a,b]$ is equal to the integral over the boundary $\{a,b\}$ of $[a,b]$, that is, $F(b) - F(a)$.

8.6 Hopf Bifurcations

Mathematically, periodic orbits often arise from the *Hopf Bifurcation* phenomenon.

The Hopf (or "Poincaré-Andronov-Hopf") bifurcation occurs when a pair of complex eigenvalues "crosses the imaginary axis" as a parameter is moved (and, in dimensions, bigger than two, the remaining eigenvalues have negative real part), provided that some additional technical conditions hold. (These conditions tend to be satisfied in examples.)

It is very easy to understand the basic idea.

We consider a system:

$$\frac{dx}{dt} \;=\; f_\mu(x)$$

in which a parameter "μ" appears.

We assume that the system has dimension two.

Suppose that there are a value μ_0 of this parameter, and a steady state x_0, with the following properties:

• For $\mu < \mu_0$, the linearization at the steady state x_0 is stable, and there is a pair of complex conjugate eigenvalues with negative real part.

• As μ changes from negative to positive, the linearization goes through having a pair of purely imaginary eigenvalues (at $\mu = \mu_0$) to having a pair of complex conjugate eigenvalues with positive real part.

Thus, near x_0, the motion changes from a stable spiral to an unstable spiral as μ crosses μ_0.

If the steady state happens to be a sink even when $\mu = \mu_0$, it must mean that there are nonlinear terms "pushing back" towards x_0 (see the example below).

These terms will still be there for $\mu > \mu_0$, $\mu \approx \mu_0$.

Thus, the spiraling-out trajectories cannot go very far, and a limit cycle is approached.

(Another way to think of this is that, in typical biological problems, trajectories cannot escape to infinity, because of conservation of mass, etc.)

In arbitrary dimensions, the situation is similar. One assumes that all other $n-2$ eigenvalues have negative real part, for all μ near μ_0.

The $n-2$ everywhere-negative eigenvalues have the effect of pushing the 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.

Let us give more details.

Consider the example that we met earlier:

$$\begin{aligned}\dot{x}_1 &= \mu x_1 - \omega x_2 + \theta x_1(x_1^2 + x_2^2)\\ \dot{x}_2 &= \omega x_1 + \mu x_2 + \theta x_2(x_1^2 + x_2^2)\end{aligned}$$

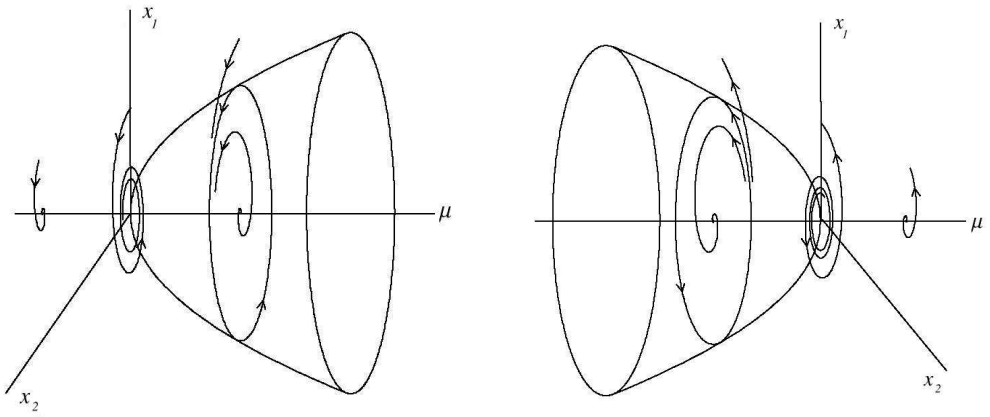
With $\theta = -1$, this is the "supercritical Hopf bifurcation" case in which we go, as already shown, from a globally asymptotically stable equilibrium to a limit cycle as μ crosses from negative to positive (μ_0 is zero).

In contrast, suppose now that $\theta = 1$. The magnitude satisfies the equation $\dot{\rho} = \rho(\mu + \rho^2)$.

Hence, one goes again from stable to unstable as μ goes through zero, but now an *unstable* cycle encircles the origin for $\mu < 0$ (so, the origin is not globally attractive).

For $\mu \geq 0$, there is now no cycle that prevents solutions that start near zero from escaping very far. (Once again, in typical biochemical problems, solutions cannot go to infinity. So, for example, a limit cycle of large magnitude might perhaps appear for $\mu > 0$.)

These pictures shows what happens for each fixed value of μ for the supercritical (limit cycle occurs after going from stable to unstable) and subcritical (limit cycle occurs before μ_0) cases, respectively:



Now suppose given a general system (I will not ask questions in tests about this material; it is merely FYI)[49]:

$$\dot{x} = f(x, \mu)$$

in dimension 2, where μ is a scalar parameter and f is assumed smooth. Suppose that for all μ near zero there is a steady-state $\xi(\mu)$, with eigenvalues $\lambda(\mu) = r(\mu) \pm i\omega(\mu)$, with $r(0) = 0$ and $\omega(0) = \omega_0 > 0$, and that $r'(0) \neq 0$ ("eigenvalues cross the imaginary axis with nonzero velocity") and that the quantity α defined below is nonzero. Then, up to a local topological equivalence and time-reparametrization, one can reduce the system to the form given in the previous example, and there is a Hopf bifurcation, supercritical or subcritical depending on $\theta =$ the sign of α.[50] There is no need to perform the transformation, if all we want is to decide if there is a Hopf bifurcation. The general "recipe" is as follows.

Let A be the Jacobian of f evaluated at $\xi_0 = \xi(0)$, $\mu = 0$. and find two complex vectors p, q such that

$$Aq = i\omega_0 q\,, \quad A^T p = -i\omega_0 p\,, \quad p \cdot q = 1\,.$$

Compute the dot product $H(z, \bar{z}) = p \cdot F(\xi_0 + zq + \bar{z}\bar{q}, \mu(0))$ and consider the formal Taylor series:

$$H(z, \bar{z}) = i\omega_0 z + \sum_{j+k \geq 2} \frac{1}{j!k!} g_{jk} z^j \bar{z}^k\,.$$

Then $\alpha = \dfrac{1}{2\omega_0^2}\,\mathrm{Re}\,(ig_{20}g_{11} + \omega_0 g_{21})$.

[49] See e.g. Yu.A. Kuznetsov. Elements of Applied Bifurcation Theory. 2nd ed., Springer-Verlag, New York, 1998

[50] One may interpret the condition on α in terms of a Lyapunov function that guarantees stability at $\mu = 0$, for the supercritical case; see e.g.: Mees , A.I. Dynamics of Feedback Systems, John Wiley & Sons, New York, 1981.

One may use the following Maple commands, which are copied from "NLDV computer session XI: Using Maple to analyse Andronov-Hopf bifurcation in planar ODEs," by Yu.A. Kuznetsov, Mathematical Institute, Utrecht University, November 16, 1999. They are illustrated by the following chemical model (Brusselator):

$$\dot{x}_1 = A - (B+1)x_1 + x_1^2 x_2, \;\; \dot{x}_2 = Bx_1 - x_1^2 x_2$$

where one fixes $A > 0$ and takes B as a bifurcation parameter. The conclusion is that at $B = 1 + A^2$ the system exhibits a supercritical Hopf bifurcation.

```
restart:
with(linalg):
readlib(mtaylor):
readlib(coeftayl):
F[1]:=A-(B+1)*X[1]+X[1]^2*X[2];
F[2]:=B*X[1]-X[1]^2*X[2];
J:=jacobian([F[1],F[2]],[X[1],X[2]]);
K:=transpose(J);
sol:=solve({F[1]=0,F[2]=0},{X[1],X[2]});
assign(sol);
T:=trace(J);
diff(T,B);
sol:=solve({T=0},{B});
assign(sol);
assume(A>0);
omega:=sqrt(det(J));
ev:=eigenvects(J,'radical');
q:=ev[1][3][1];
et:=eigenvects(K,'radical');
P:=et[2][3][1];
s1:=simplify(evalc(conjugate(P[1])*q[1]+conjugate(P[2])*q[2]));
c:=simplify(evalc(1/conjugate(s1)));
p[1]:=simplify(evalc(c*P[1]));
p[2]:=simplify(evalc(c*P[2]));
simplify(evalc(conjugate(p[1])*q[1]+conjugate(p[2])*q[2]));
F[1]:=A-(B+1)*x[1]+x[1]^2*x[2];
F[2]:=B*x[1]-x[1]^2*x[2];
# use z1 for the conjugate of z:
x[1]:=evalc(X[1]+z*q[1]+z1*conjugate(q[1]));
x[2]:=evalc(X[2]+z*q[2]+z1*conjugate(q[2]));
H:=simplify(evalc(conjugate(p[1])*F[1]+conjugate(p[2])*F[2]));
# get Taylor expansion:
g[2,0]:=simplify(2*evalc(coeftayl(H,[z,z1]=[0,0],[2,0])));
g[1,1]:=simplify(evalc(coeftayl(H,[z,z1]=[0,0],[1,1])));
g[2,1]:=simplify(2*evalc(coeftayl(H,[z,z1]=[0,0],[2,1])));
alpha:=factor(1/(2*omega^2)*Re(I*g[2,0]*g[1,1]+omega*g[2,1]));
evalc(alpha);
# above needed to see that this is a negative number (so supercritical)
```

8.7 Cubic Nullclines and Relaxation Oscillations

Let us consider this system, which is exactly as in our version of the van der Pol oscillator, except that, before, we had $\varepsilon = 1$:

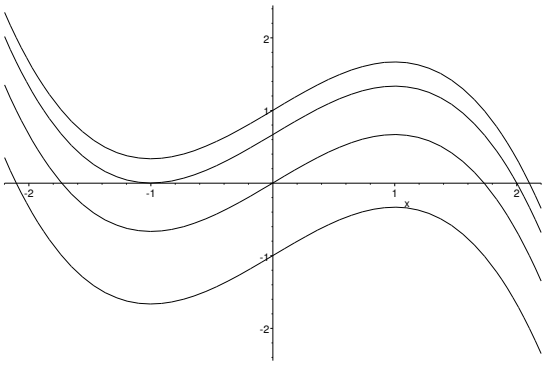
$$\begin{aligned} \frac{dx}{dt} &= y + x - \frac{x^3}{3} \\ \frac{dy}{dt} &= -\varepsilon x \end{aligned}$$

We are interested specifically in what happens when ε is positive but small ("$0 < \varepsilon \ll 1$").

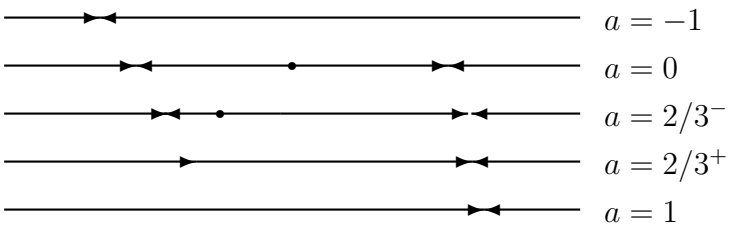
Notice that then y changes slowly.

So, we may think of y as a "constant" in so far as its effect on x (the "faster" variable) is concerned.

How does $\frac{dx}{dt} = f_a(x) = a + x - \frac{x^3}{3}$ behave?



$f_a(x) = a + x - \frac{x^3}{3}$ for $a = -1, 0, \frac{2}{3}, 1$



Now let us consider what the solution of the system of differential equations looks like, if starting at a point with $x(0) \ll 0$ and $y(0) \approx -1$.

Since $y(t) \approx -1$ for a long time, x "sees" the equation $dx/dt = f_{-1}(x)$, 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" is not constant, but it is slowly increasing ($y' = -\varepsilon x > 0$).

Thus, the "equilibrium" that x is getting attracted to is constantly moving closer and closer to -1,

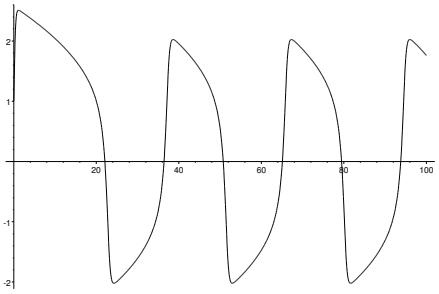
until, at exactly $a = 2/3$, the "low" equilibrium dissappears, and there is only the "large" one (around $x = 2$); thus x will quickly converge to that larger value.

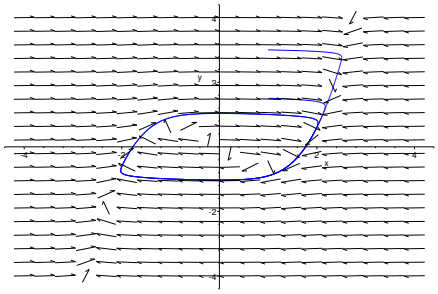
Now, however, $x(t)$ is positive, so $y' = -\varepsilon x < 0$, that is, "a" starts *decreasing*.

Repeating this process, one obtains a periodic motion in which slow increases and decreases are interspersed with quick motions.

This is what is often called a *relaxation* (or "hysteresis-driven") oscillation.

Here are computer plot of $x(t)$ for one such solution, together the same solution in phase-plane:





8.8 A Qualitative Analysis using Cubic Nullclines

Let us now analyze a somewhat more general situation.

We will assume given a system of this general form:

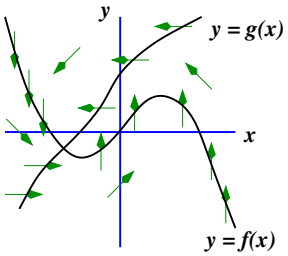
$$\begin{aligned} \frac{dx}{dt} &= f(x) - y \\ \frac{dy}{dt} &= \varepsilon\,(g(x) - y) \end{aligned}$$

where $\varepsilon > 0$. (Soon, we will assume that $\varepsilon \ll 1$, but not yet.)

The x and y nullclines are, respectively: $y = f(x)$ and $y = g(x)$.

It is easy, for these very special equations, to determine the direction of arrows: dy/dt is positive if $y < g(x)$, i.e. under the graph of g, and so forth.

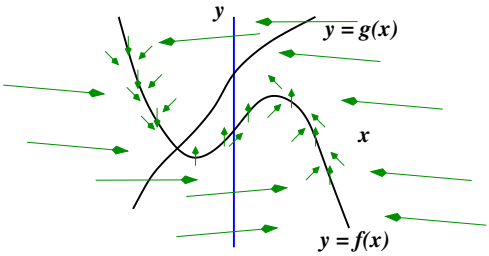
This allows us to draw "SE", etc, arrows as usual:



Now let us use the information that ε is small: this means that

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 $y{=}f(x)$):



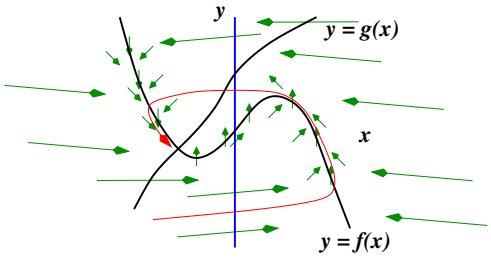
Now, suppose that the nullclines look exactly as in these pictures, so that $f' < 0$ and $g' > 0$ at the steady state.

The Jacobian of $\begin{pmatrix} f(x) - y \\ \varepsilon(g(x) - y) \end{pmatrix}$ is

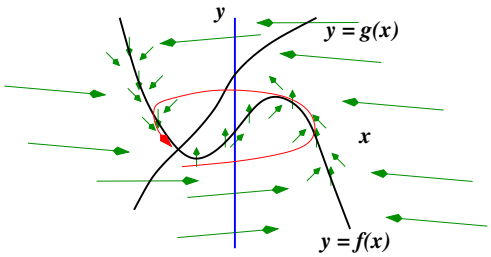
$$\begin{pmatrix} f'(x_0) & -1 \\ \varepsilon g'(x_0) & -\varepsilon \end{pmatrix}$$

and therefore (remember that $f'(x_0) < 0$) the trace is negative, and the determinant is positive (because $g'(x_0) > 0$), and the steady state is a sink (stable).

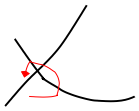
Thus, we expect trajectories to look like this:



Observe that a "large enough" perturbation from the steady state leads to a large excursion (the trajectory is carried very quicky to the other side) before the trajectory can return.



In contrast, a small perturbation does not result in such excursions, since the steady state is stable. Zooming-in:

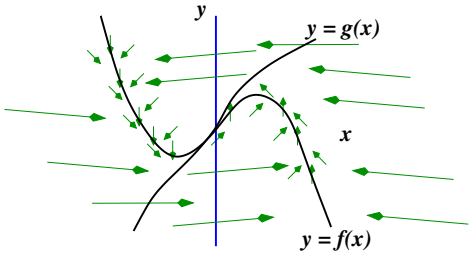


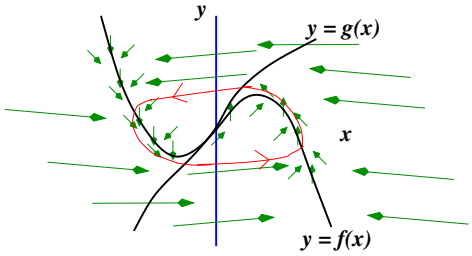
This type of behavior is called *excitability*: low enough disturbances have no effect, but when over a threshold, a large reaction occurs.

In contrast, suppose that the nullcline $y = g(x)$ intersects the nullcline $y = f(x)$ on the increasing part of the latter ($f' > 0$).

Then, the steady state is *un*stable, for small ε, since the trace is $f'(x_0) - \varepsilon \approx f'(x_0) > 0$.

We then get a relaxation oscillation, instead of an excitable system:





8.9 Neurons

Neurons are nerve cells; there are about 100 billion (10^{11}) in the human brain.

Neurons may be short (1mm) or very long (1m from the spinal cord to foot muscles).

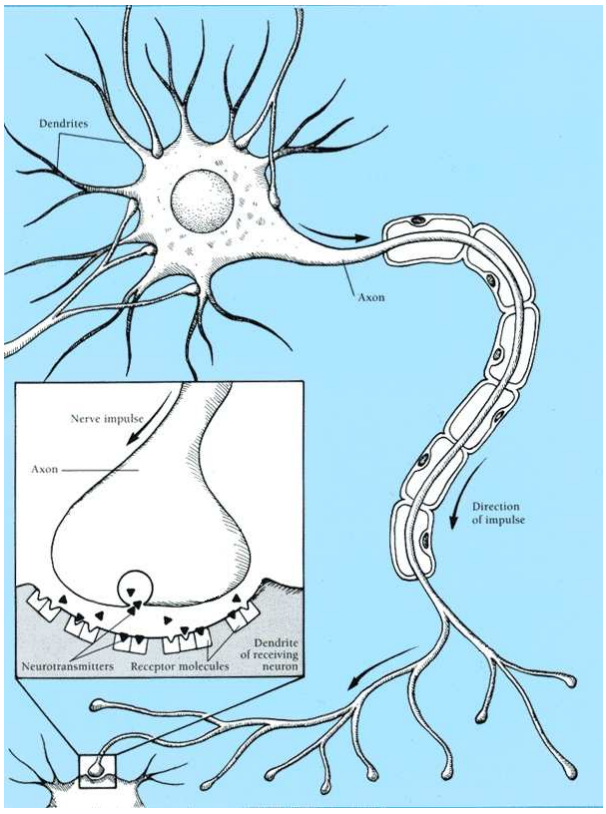
Each neuron is a complex information processing device, whose inputs are neurotransmitters (electrically charged chemicals) which accumulate at the *dendrites*.

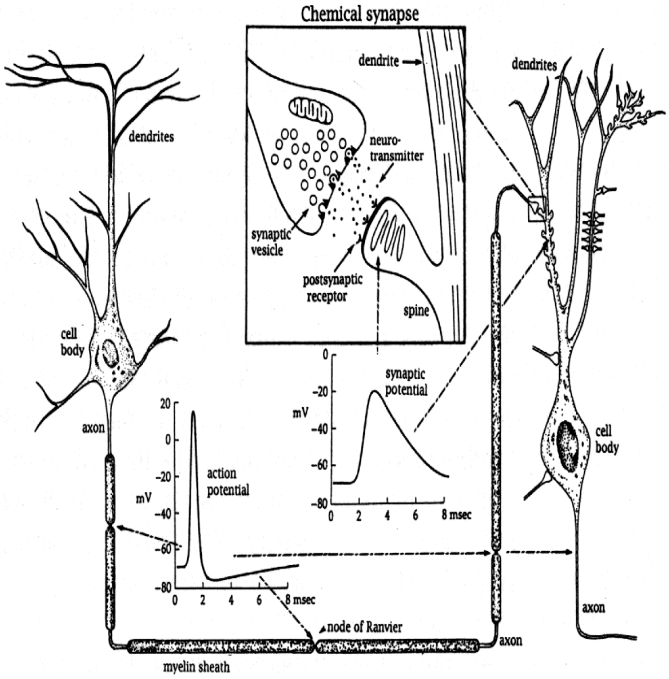
Neurons receive signals from other neurons (from as many as 150,000, in the the cerebral cortex, the center of cognition) connected to it at *synapses*.

When the net voltage received by a neuron is higher than a certain threshold (about 1/10 of a volt), the neuron "fires" an *action potential*, which is an electrical signal that travels down the *axon*, sort of an "output wire" of the neuron. Signals can travel at up to 100m/s; the higher speeds are achieved when the axon is covered in a fatty insulation (myelin).

At the ends of axons, neurotransmitters are released into the dendrites of other neurons.

Information processing and computation arise from these networks of neurons.
The strength of synaptic connections is one way to "program" networks; memory (in part) consists of finely tuning these strengths.





The mechanism for action potential generation is well understood. A mathematical model given in: Hodgkin, A.L. and Huxley, A.F., "A Quantitative Description of Membrane Current and its Application to Conduction and Excitation in Nerve", Journal of Physiology 117 (1952): 500-544 won the authors a Nobel Prize (in 1963), and is still one of the most successful examples of mathematical modeling in biology. Let us sketch it next.

8.10 Action Potential Generation

The basic premise is that currents are due to Na and K ion pathways. Normally, there is more K^+ inside than outside the cell, and the opposite holds for Na^+. Diffusion through channels works against this imbalance, which is maintained by active pumps (which account for about 2/3 of the cell's energy consumption!). These pumps act against a steep gradient, exchanging 3 Na^+ ions out for each 2 K^+ that are allowed in. An overall potential difference of about 70mV is maintained (negative inside the cell) when the cell is "at rest".

A neuron can be stimulated by external signals (touch, taste, etc., sensors), or by an appropriate weighted sum of inhibitory and excitatory inputs from other neurons through dendrites (or, in the Hodgkin-Huxley and usual lab experiments, artificially with electrodes).

A large enough potential change triggers a nerve impulse (action potential or "spike"), starting from the axon hillock (start of axon) as follows:

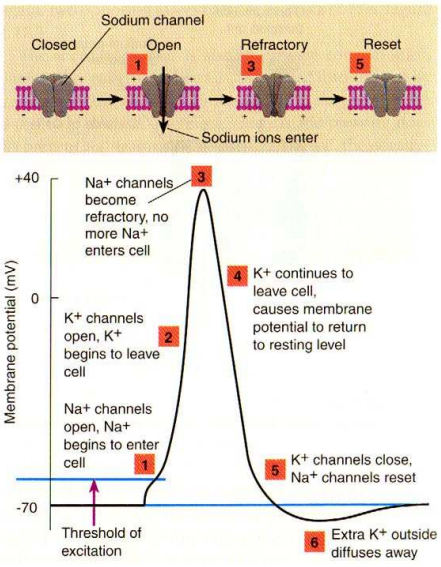
(1) voltage-gated Na^+ channels open (think of a "gate" opening); these let sodium ions in, so the inside of the cell becomes more positive, and, through a feedback effect, even more gates open;

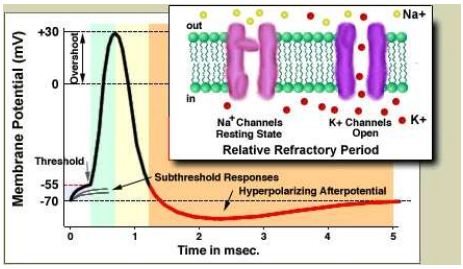
(2) when the voltage difference is $\approx +50$mV, voltage-gated K^+ channels open and quickly let potassium out;

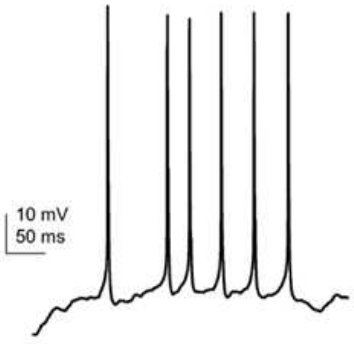
(3) the Na^+ channels close;

(4) the K^+ channels close, so we are back to resting potential.

The Na^+ channels cannot open again for some minimum time, giving the cell a *refractory period*.





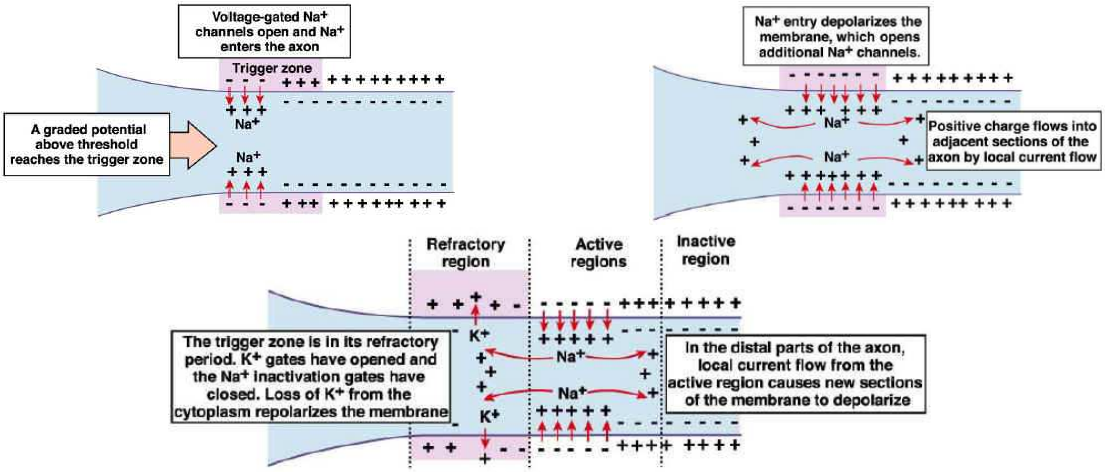


This activity, locally in the axon, affects neighboring areas, which then go through the same process, a chain-reaction along the axon. Because of the refractory period, the signal "cannot go back", and a direction of travel for the signal is well-defined. See an animation in the course website:

http://www.math.rutgers.edu/~ sontag/336/finlay-markham-chain-action-potentials.gif

(Copyright 1997, Carlos Finlay and Michael R. Markham).

These diagrams are from http://www.biologymad.com/NervousSystem/nerveimpulses.htm:



It is important to realize that the action potential is only generated if the stimulus is large enough. It is an "all or (almost) nothing" response. An advantage is that the signal travels along the axon without decay - it is regenerated along the way. The "binary" (digital) character of the signal makes it very robust to noise.

There is another aspect that is remarkable, too: a continuous stimulus of high intensity will result in a higher frequency of spiking. Amplitude modulation (as in AM radio) gets transformed into frequency modulation (as in FM radio, which is far more robust to noise).

8.11 Model

The basic HH model is for a small segment of the axon. Their model was done originally for the giant axon of the squid (large enough to stick electrodes into, with the technology available at the time), but similar models have been validated for other neurons.

(Typical simulations put together perhaps thousands of such basic compartments, or alternatively set up a partial differential equation, with a spatial variable to represent the length of the axon.)

The model has four variables: the potential difference $v(t)$ between the inside and outside of the neuron, and the activity of each of the three types of gates (two types of gates for sodium and one for potassium). These activities may be thought of as relative fractions ("concentrations") of open channels, or probabilities of channels being open. There is also a term I for the external current being applied.

$$\begin{aligned} C\dot{v} &= -g_K(t)(v-v_K) - g_{Na}(t)(v-v_{Na}) - \bar{g}_L(v-v_L) + I \\ \tau_m(v)\dot{m} &= m_\infty(v) - m \\ \tau_n(v)\dot{n} &= n_\infty(v) - n \\ \tau_h(v)\dot{h} &= h_\infty(v) - h \\ g_K(t) &= \bar{g}_K\, n(t)^4 \\ g_{Na}(t) &= \bar{g}_{Na}\, m(t)^3\, h(t) \end{aligned}$$

The equation for v comes from a capacitor model of membranes as charge storage elements. The three first terms in the right correspond to the currents flowing through the Na and K gates (plus an additional "L" that accounts for all other gates and channels, not voltage-dependent).

The currents are proportional to the difference between the actual voltage and the "Nernst potentials" for each of the species (the potential that would result in balance between electrical and chemical imbalances), multiplied by "conductances" g that represent how open the channels are.

The conductances, in turn, are proportional to certain powers of the open probabilities of the different gates. (The powers were fit to data, but can be justified in terms of cooperativity effects.)

The open probabilities, in turn, as well as the time-constants (τ's) depend on the current net voltage difference $v(t)$. H&H found the following formulas by fitting to data. Let us write:

$$\frac{1}{\tau_m(v)}\,(m_\infty(v)-m) = \alpha_m(v)(1-m) - \beta_m(v)m$$

(so that $dm/dt = \alpha_m(v)(1-m) - \beta_m(v)m$), and similarly for n, h. In terms of the α's and β's, H&H's formulas are as follows:

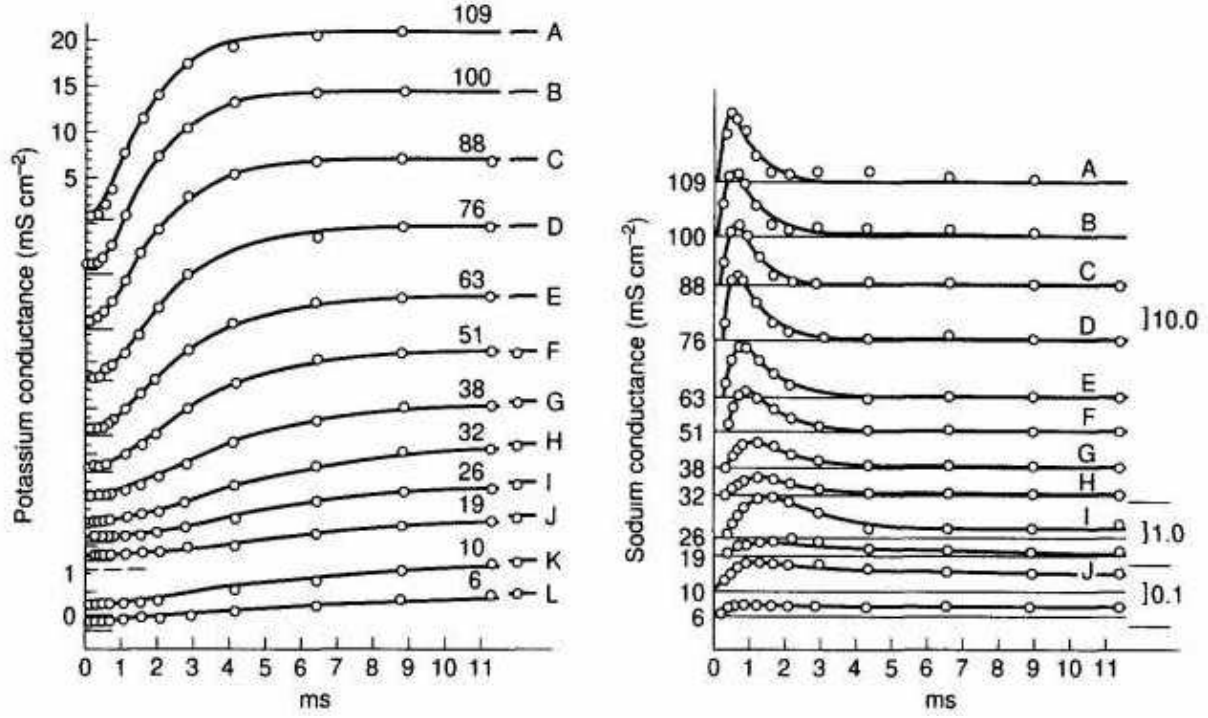
$$\alpha_m(v) = 0.1\frac{25-v}{\exp\left(\frac{25-v}{10}\right)-1},\ \beta_m(v) = 4\exp\left(\frac{-v}{18}\right),\ \alpha_h(v) = 0.07\exp\left(\frac{-v}{20}\right),$$

$$\beta_h(v) = \frac{1}{\exp\left(\frac{30-v}{10}\right)+1},\ \alpha_n(v) = 0.01\frac{10-v}{\exp\left(\frac{10-v}{10}\right)-1},\ \beta_n(v) = 0.125\exp\left(\frac{-v}{80}\right)$$

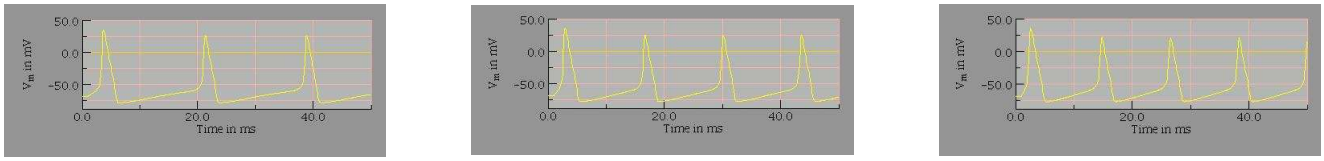
where the constants are $\bar{g}_K = 36$, $\bar{g}_{Na} = 120$, $\bar{g}_L = 0.3$ $v_{Na} = 115$ $v_K = -12$, and $v_L = 10.6$.

The way in which H&H did this fit is, to a large extent, the best part of the story. Basically, they performed a "voltage clamp" experiment, by inserting an electrode into the axon, thus permitting a plot of current against voltage, and deducing conductances for each channel. (They needed to isolate the effects of the different channels; the experiments are quite involved, and we don't have time to go over them in this course.)

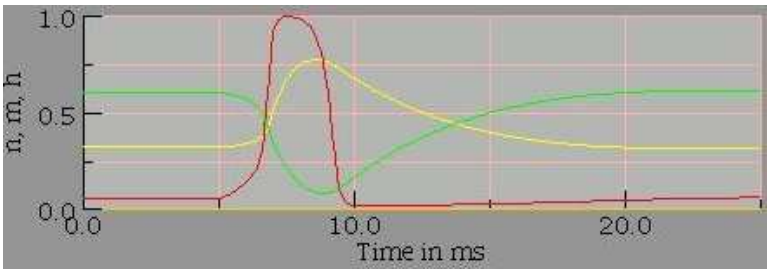
For an idea of how good the fits are, look at these plots of experimental $g_K(V)(t)$ and $g_{Na}(V)(t)$, for different clamped V's (circles) compared to the model predictions (solid curves).



Simulations of the system show frequency encoding of amplitude.
We show here the responses to constant currents of 0.05 (3 spikes in the shown time-interval), 0.1 (4), 0.15 (5) mA:



Here are the plots of n, m, h in response to a stimulus at $t = 5$ of duration 1sec, with current=0.1:



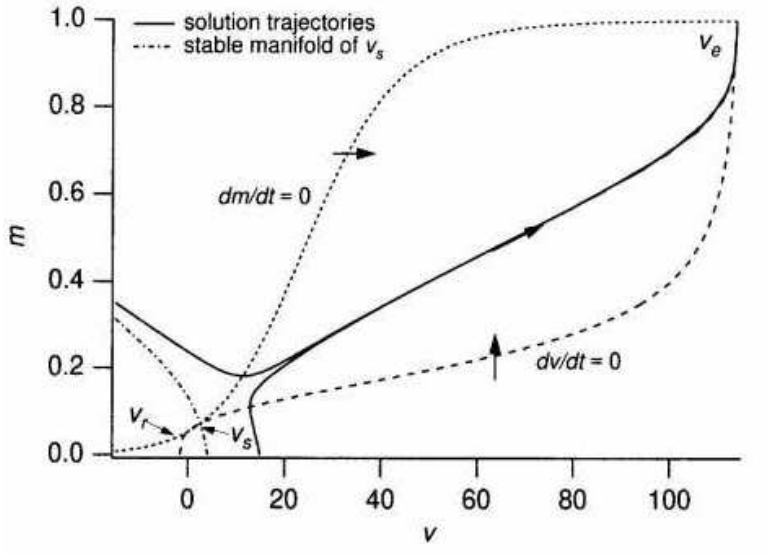
(color code: yellow=n, red=m, green=h)

Observe how m moves faster in response to stimulus.

It is an important feature of the model that $\tau_m \ll \tau_n$ and $\ll \tau_h$. This allows a time-scale separation analysis (due to FitzHugh): for short enough intervals, one may assume that $n(t) \equiv n_0$ and $h \equiv h_0$, so we obtain just two equations:

$$\begin{aligned} C\dot{v} &= -\bar{g}_K n_0^4 (v - v_K) - \bar{g}_{Na} m^3 h_0 (v - v_{Na}) - \bar{g}_L (v - v_L) \\ \tau_m(v)\dot{m} &= m_\infty(v) - m\,. \end{aligned}$$

The phase-plane shows bistability (dashed curve is nullcline $\dot{v} = 0$, dash-dot is $\dot{m} = 0$; two solutions are shown with a solid curve)[51]:



There are two stable steady states: v_r ("resting") and v_e ("excited"), as well as a saddle v_s. Depending on where the initial voltage (set by a transient current I) is relative to a separatrix, trajectories converge as $t \to \infty$ to either the "excited" state or stay near the resting one.

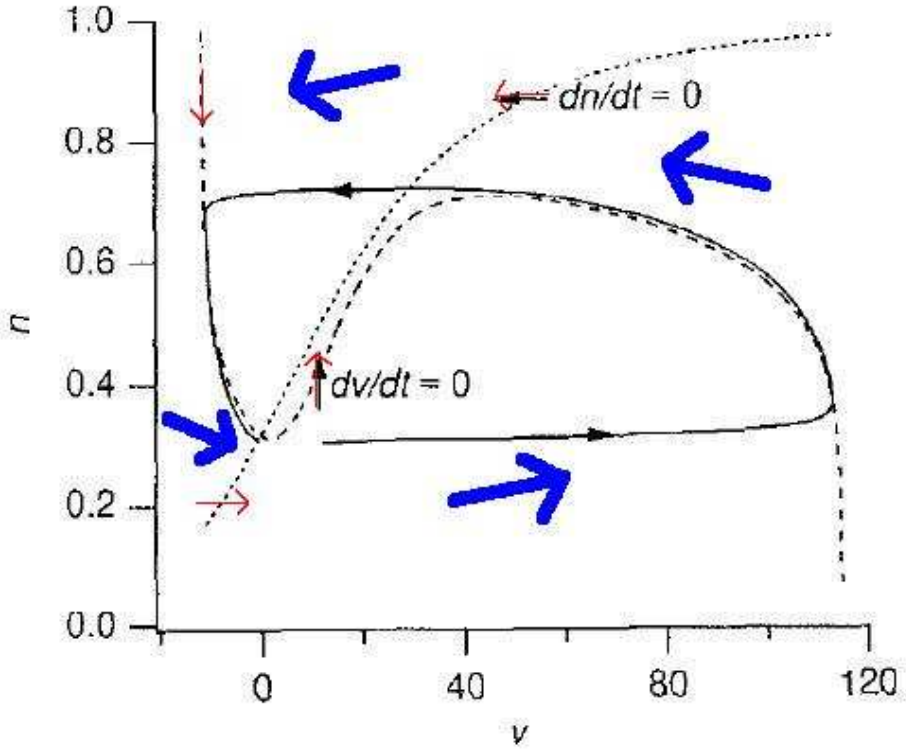
[51] next two plots borrowed from Keener & Sneyd textbook

(Of course, h, n are not really constant, so the analysis must be complemented with consideration of small changes in h, n. We do not provide details here.)

An alternative view, on a longer time scale, is also possible. FitzHugh observed (and you will, too, in an assigned project; see also the graph shown earlier) that : $h(t) + n(t) \approx 0.8$, constant during an action potential. (Notice the approximate symmetry of h, n in plots.) This allows one to eliminate h from the equations. Also, assuming that $\tau_m \ll 1$ (because we are looking at a longer time scale), we may replace $m(t)$ by its quasi-steady state value $m_\infty(v)$. We end up with a new two-dimensional system:

$$\begin{aligned} C\dot{v} &= -\bar{g}_K n^4(v - v_K) - \bar{g}_{Na} m_\infty(v)^3(0.8 - n)(v - v_{Na}) - \bar{g}_L(v - v_L) \\ \tau_n(v)\dot{n} &= n_\infty(v) - n \end{aligned}$$

which has these nullclines (dots for $\dot{n}$=0, dashes for $\dot{v}$=0) and phase plane behavior:



We have fast behaviors on the horizontal direction (n=constant), leading to v approaching nullclines fast, with a slow drift on n that then produces, as we saw earlier when studying a somewhat simpler model of excitable behavior, a "spike" of activity.

Note that if the nullclines are perturbed so that they now intersect in the middle part of the "cubic-looking" curve (for v, this would be achieved by considering the external current I as a constant), then a relaxation oscillator will result. Moreover, if the perturbation is larger, so that the intersection is away from the "elbows", the velocity of the trajectories should be higher (because trajectories do not slow-down near the steady state). This explains "frequency modulation" as well.

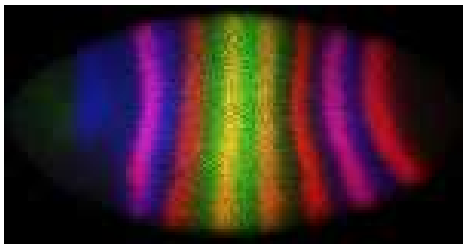
Much of the qualitative theory of relaxation oscillations and excitable systems originated in the analysis of this example and its mathematical simplifications.

9 PDE Models

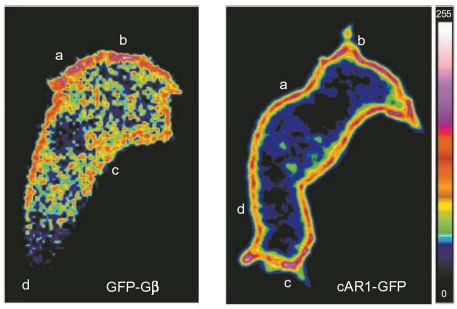
Until now, we only considered functions of time (concentrations, populations, etc).
From now on, we consider functions that also depend on *space*.

A typical biological example of space-dependence would be the concentration of a morphogen as a function of space as well as time.

For example, this is a color-coded where a *Drosophila* embryo has been stained for the protein products of genes *giant* (blue), *eve* (red), and *Kruppel* (other colors indicate areas where two or all genes are expressed):



One may also study space-dependence of a particular protein in a single cell. For example, this picture[52] shows the gradients of G-proteins in response to chemoattractant binding to receptors in the surface of *Dictyostelium discoideum* amoebas:



9.1 Densities

We write space variables as $x{=}(x_1, x_2, x_3)$ (or just (x, y) in dimension 2, or (x, y, z) in dimension 3).

We will work with *densities* "$c(x, t)$", which are understood intuitively in the following sense.

Suppose that we denote by $C(R, t)$ the amount of a type of particle (or number of individuals, mass of proteins of a certain type, etc.) in a region R of space, at time t.

Then, the density around point x, at time t, $c(x, t)$, is:

$$c(x,t) = \frac{C(\Delta R, t)}{\text{vol}(\Delta R)}$$

for "small" cubes ΔR around x, i.e. a "local average".

[52] from Jin, Tian, Zhang, Ning, Long, Yu, Parent, Carole A., Devreotes, Peter N., "Localization of the G Protein Complex in Living Cells During Chemotaxis," *Science* 287(2000): 1034-1036.

This means that $C(R,T) = \int\int\int_R c(x,t)\,dx$ for all regions R.
(A single or a double integral, if x is one- or two-dimensional, of course.)[53]

For now, we consider only scalar quantities $c(x,t)$; later we consider also vectors.

9.2 Reaction Term: Creation or Degradation Rate

We will assume that, at each point in space, there might take place a "reaction" that results in particles (individuals, proteins, bacteria, whatever) being created (or destroyed, depending on the sign).

This production (or decay) occurs at a certain rate "$\sigma(x,t)$" which, in general, depends on the location x and time t. (If there is no reaction, then $\sigma(x,t) = 0$.)

For scalar c, s will typically be a formation or degradation rate.
More generally, if one considers vectors $c(x,t)$, with the coordinates of c representing for example the densities of different chemicals, then $\sigma(x,t)$ would represent the reactions among chemicals that happen to be in the same place at the same time.

The rate σ is a rate per unit volume per unit of time. That is, if $\Sigma(R,[a,b])$ is number of particles created (eliminated, if < 0) in a region R during time interval $[a,b]$, then the *average rate of growth* is:

$$\sigma(x,t) = \frac{\Sigma(\Delta R, [t, t+\Delta t])}{\mathrm{vol}(\Delta R) \times \Delta t}\,,$$

for "small" cubes ΔR around x and "small" time increments Δt. This means that

$$\Sigma(R,[a,b]) = \int_a^b \int\int\int_R \sigma(x,t)\,dx\,dt$$

for all regions R and time intervals $[a,b]$.

9.3 Conservation or Balance Principle

This is quite obvious:

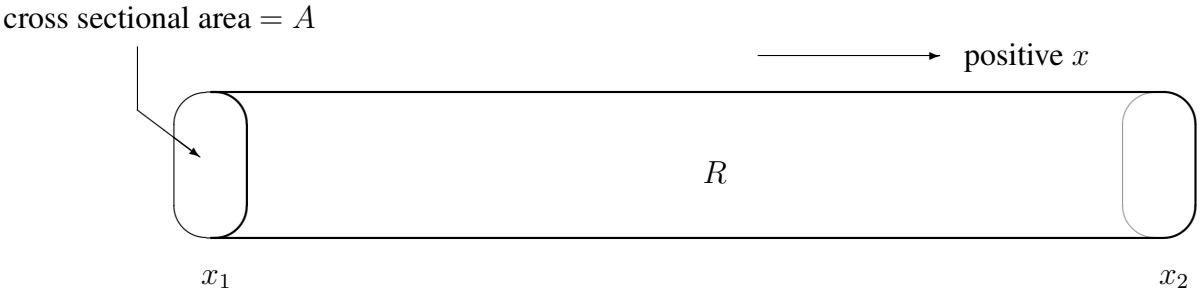
increase (possibly negative) of quantity in a region = net creation + net influx.

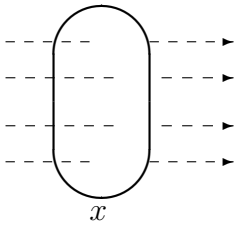
Let us formalize this observation into an equation, studying first the one-dimensional case.

Suppose that R is a one-dimensional region along the x coordinate, defined by $x_1 \leq x \leq x_2$, and $c(x,t)$ and $\sigma(x,t)$ denote densities and reaction rates as a function of the scalar coordinate x.

Actually, it will be more convenient (and, in fact, is more realistic) to think of R as a three-dimensional volume, with a uniform cross-section in the y,z axes. Accordingly, we also think of the density $c(x,y,z,t) = c(x,t)$ and reaction rate $\sigma(x,y,z,t) = \sigma(x,t)$ as functions of a three-dimensional position (x,y,z), both uniform on each cross-section. We assume that nothing can "escape" through the y,z directions.

[53] In a more theoretical treatment of the subject, one would start with C, defined as a "measure" on subsets of $\mathbb{R}^3$, and the density c would be defined as a "derivative" of this measure C.





We need another important concept, the *flux*. It is defined as follows.
The flux at (x,t), written "$J(x,t)$", is the number of particles that cross a *unit area* perpendicular to x, in the positive direction, *per unit of time*.

Therefore, the net flow through a cross-sectional area during a time interval $[a,b]$ is:

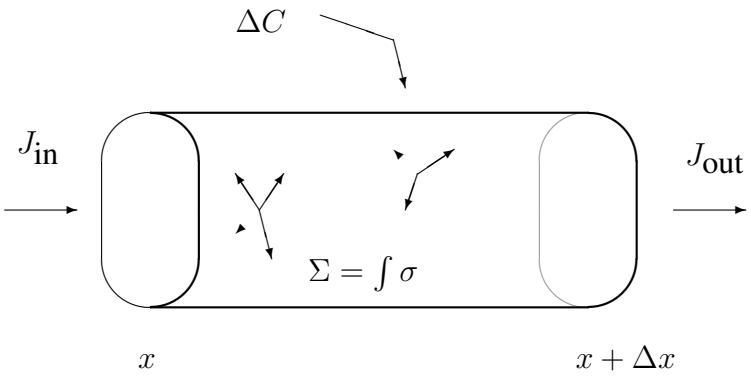
$$\int_a^b J(x,t)A\,dt\,.$$

We also need the following formulas, which follow from $\int_y \int_z = A$:

$$C(R,t) = \iiint_R c(\vec{x},t)\,d\vec{x} = \int_{x_1}^{x_2} c(x,t)A\,dx\,,$$

$$\Sigma(R,[a,b]) = \int_a^b \iiint_R \sigma(\vec{x},t)\,d\vec{x}dt = \int_a^b \int_{x_1}^{x_2} \sigma(x,t)A\,dxdt\,.$$

We consider a segment $x \leq \xi \leq x+\Delta x$ and a time interval $[t, t+\Delta t]$.



We have these equalities:

- net flow through cross-area at x: $J_{\text{in}} = \int_t^{t+\Delta t} J(x,\tau)A\,d\tau$
- net flow through cross-area at $x+\Delta x$: $J_{\text{out}} = \int_t^{t+\Delta t} J(x+\Delta x,\tau)A\,d\tau$
- net creation (elimination): $\Sigma = \int_t^{t+\Delta t}\int_x^{x+\Delta x} \sigma(\xi,\tau)A\,d\xi d\tau$

- starting amount in segment: $C_t \;=\; \int_x^{x+\Delta x} c(\xi,t)A\,d\xi$
- ending amount in segment: $C_{t+\Delta t} \;=\; \int_x^{x+\Delta x} c(\xi,t+\Delta t)A\,d\xi.$

Finally, the change in total amount must balance-out:

$$C_{t+\Delta t} - C_t \;=\; \Delta C \;=\; J_{\text{in}} - J_{\text{out}} + \Sigma\,.$$

We have, putting it all together:

$$\int_x^{x+\Delta x} (c(\xi,t+\Delta t) - c(\xi,t))\,A\,d\xi \;=\; \int_t^{t+\Delta t} (J(x,\tau) - J(x+\Delta x,\tau))\,A\,d\tau + \int_t^{t+\Delta t}\int_x^{x+\Delta x} \sigma(\xi,\tau)A\,d\xi d\tau\,.$$

So, dividing by "$A\Delta t$", letting $\Delta t \to 0$, and applying the Fundamental Theorem of Calculus:

$$\int_x^{x+\Delta x} \frac{\partial c}{\partial t}(\xi,t)\,d\xi \;=\; J(x,t) - J(x+\Delta x,t) + \int_x^{x+\Delta x} \sigma(\xi,t)d\xi\,.$$

Finally, dividing by Δx, taking $\Delta x \to 0$, and once again using the FTC, we conclude:

$$\boxed{\frac{\partial c}{\partial t} \;=\; -\,\frac{\partial J}{\partial x} + \sigma}$$

This is the basic equation that we will use from now on.

We only treated the one-dimensional (i.e., uniform cross-section) case. However, the general case, when R is an arbitrary region in 3-space (or in 2-space) is totally analogous. One must define the flux $J(x,t)$ as a *vector* which indicates the maximal-flow direction at (x,t); its magnitude indicates the number of particles crossing, per unit time, a unit area perpendicular to J.

One derives, using Gauss' theorem, the following equation:

$$\boxed{\frac{\partial c}{\partial t} \;=\; -\,\operatorname{div} J + \sigma}$$

where the *divergence* of $J = (J_1, J_2, J_3)$ at $x = (x_1, x_2, x_3)$ is

$$\operatorname{div} J \;=\; \text{"}\nabla \cdot J\text{"} \;=\; \frac{\partial J_1}{\partial x_1} + \frac{\partial J_2}{\partial x_2} + \frac{\partial J_3}{\partial x_3}\,.$$

In the scalar case, $\operatorname{div} J$ is just $\frac{\partial J}{\partial x}$, of course.

Until now, everything was quite abstract. Now we specialize to very different types of fluxes.

9.4 Transport Equation

We start with the simplest type of equation, the *transport* (also known as the "convection" or the "advection" equation[54]).

[54] In meteorology, convection and advection refer respectively to vertical and horizontal motion; the Latin origin is "advectio" = act of bringing.

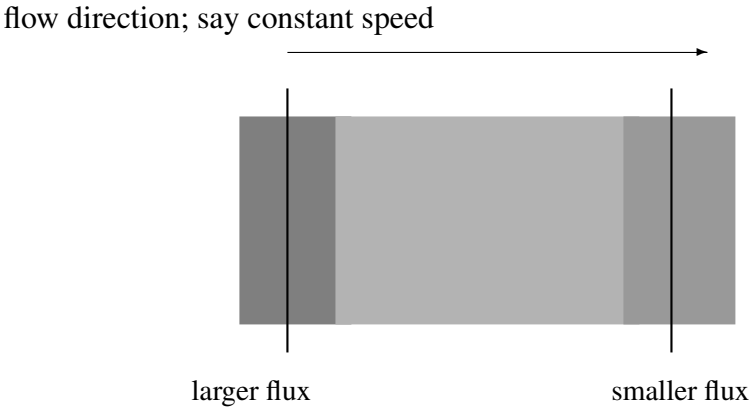
We consider here *flux is due to transport*: a transporting tape as in an airport luggage pick-up, wind carrying particles, water carrying a dissolved substance, etc.

The main observation is that, in this case:

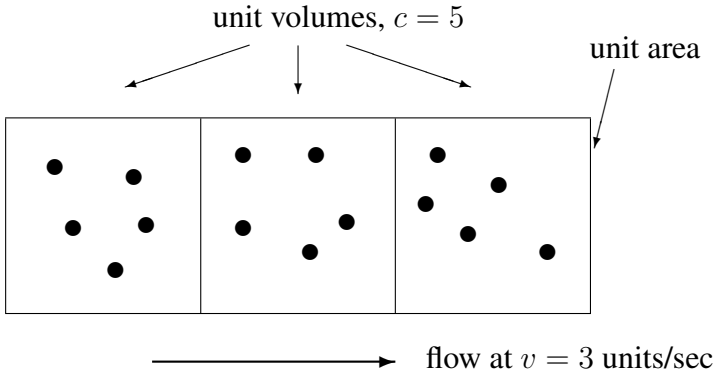
$$\text{flux} = \text{concentration} \times \text{velocity}$$

(depending on local conditions: x and t).

The following pictures may help in understanding why this is true.



Let us zoom-in, approximating by a locally-constant density:



Imagine a counter that "clicks" when each particle passes by the right endpoint. The total flux in one second is 15 units. In other words, it equals cv. This will probably convince you of the following formula:

$$\boxed{J(x,t) \;=\; c(x,t)\, v(x,t)}$$

Since $\frac{\partial c}{\partial t} = -\text{div}\, J + \sigma$, we obtain the *transport equation*:

$$\boxed{\frac{\partial c}{\partial t} \;=\; -\,\frac{\partial (cv)}{\partial x} \;+\; \sigma} \quad \text{or, equivalently:} \quad \boxed{\frac{\partial c}{\partial t} \;+\; \frac{\partial (cv)}{\partial x} \;=\; \sigma}$$

or more generally, in any dimension:

$$\boxed{\frac{\partial c}{\partial t} \;=\; -\,\text{div}\,(cv) \;+\; \sigma} \quad \text{or, equivalently:} \quad \boxed{\frac{\partial c}{\partial t} \;+\; \text{div}\,(cv) \;=\; \sigma}$$

This equation describes collective behavior, that of individual particles just "going with the flow".

Later, we will consider additional (and more interesting!) particle behavior, such as random movement, or movement in the direction of food. Typically, many such effects will be superimposed into the formula for J.

A special case is that of constant velocity $v(x,t) \equiv v$. For constant velocities, the above simplifies to:

$$\boxed{\frac{\partial c}{\partial t} \;=\; -\,v\frac{\partial c}{\partial x} \;+\; \sigma} \quad \text{or, equivalently:} \quad \boxed{\frac{\partial c}{\partial t} \;+\; v\frac{\partial c}{\partial x} \;=\; \sigma}$$

in dimension one, or more generally, in any dimension:

$$\boxed{\frac{\partial c}{\partial t} == \; -v\,\mathrm{div}\,c \;+\; \sigma} \quad \text{or, equivalently:} \quad \boxed{\frac{\partial c}{\partial t} \;+\; \mathrm{div}\,c \;=\; \sigma}$$

Remark. If $\sigma = 0$, the equation becomes that of pure flow:

$$\frac{\partial c}{\partial t} + \mathrm{div}\,(cf) \;=\; 0$$

where are now writing "f" instead of "v" for the velocity, for reasons to be explained next. As before, let $c(x,t)$ denote the density of particles at location x and time t. The formula can be interpreted as follows. Particles move individually according to a differential equation $\frac{dx}{dt} = f(x,t)$. That is, when a particle is in location x at time t, its velocity should be $f(x,t)$. The equation then shows how the differential equation $\frac{dx}{dt} = f(x,t)$ for individual particles translates into a partial differential equation for densities. Seen in this way, the transport equation is sometimes called the *Liouville equation*. A special case is that in which $\mathrm{div}\,(f) = 0$, which is what happens in Hamiltonian mechanics. In that case, just as with constant velocity, we get the simplified equation $\frac{\partial c}{\partial t} + \sum_i \frac{\partial c}{\partial x_i} f_i$, where f_i is the ith coordinate of f. A probabilistic interpretation is also possible. Suppose that we think of single particles, whose initial conditions are distributed according to the density $c(x,0)$, and ask what is the probability density at time t. This density will be given by the solution of $\frac{\partial c}{\partial t} + \mathrm{div}\,(cf) = 0$, because we may think of an ensemble of particles, all evolving simultaneously. (It is implicit in this argument that particles are small enough that they never collide.)

9.5 Solution for Constant Velocity and Exponential Growth or Decay

Let us take the even more special case in which the reaction is linear: $\sigma = \lambda c$. This corresponds to a decay or growth that is proportional to the population (at a given time and place). The equation is:

$$\frac{\partial c}{\partial t} + v\frac{\partial c}{\partial x} \;=\; \lambda c$$

($\lambda > 0$ growth, $\lambda < 0$ decay).

Theorem: *Every solution (in dimension 1) of the above equation is of the form:*

$$c(x,t) \;=\; e^{\lambda t} f(x - vt)$$

for some (unspecified) differentiable single-variable function f.
Conversely, $e^{\lambda t} f(x - vt)$ is a solution, for any λ and f.

Notice that, in particular, when $t = 0$, we have that $c(x, 0) = f(x)$. Therefore, the function f plays the role of an "initial condition" in time (but which depends, generally, on space).

The last part of the theorem is very easy to prove, as we only need to verify the PDE:

$$\left[\lambda e^{\lambda t} f(x - vt) - ve^{\lambda t} f'(x - vt)\right] + ve^{\lambda t} f'(x - vt) \;=\; \lambda\, e^{\lambda t} f(x - vt)\,.$$

Proving that the *only* solutions are these is a little more work:

we must prove that every solution of $\frac{\partial c}{\partial t} + v\frac{\partial c}{\partial x} = \lambda c$, where v and λ are given real constants), *must* have the form $c(x, t) = e^{\lambda t} f(x - vt)$, for some appropriate "$f$".

We start with the very special case $v = 0$. In this case, *for each fixed x, we have an ODE*: $\frac{\partial c}{\partial t} = \lambda c$.

Clearly, for each x, this ODE has the unique solution $c(x, t) = e^{\lambda t} c(x, 0)$, so we can take $f(x)$ as the function $c(x, 0)$.

The key step is to reduce the general case to this case, by "traveling" along the solution.
Formally, given a solution $c(x, t)$, we introduce a new variable $z = x - vt$, so that $x = z + vt$, and we define the auxiliary function $\alpha(z, t) := c(z + vt, t)$.

We note that $\frac{\partial \alpha}{\partial z}(z, t) = \frac{\partial c}{\partial x}(z + vt, t)$, but, more interestingly:

$$\frac{\partial \alpha}{\partial t}(z, t) \;=\; v\,\frac{\partial c}{\partial x}(z + vt, t) \;+\; \frac{\partial c}{\partial t}(z + vt, t)\,.$$

We now use the PDE $v\frac{\partial c}{\partial x} = \lambda c - \frac{\partial c}{\partial t}$ to get:

$$\frac{\partial \alpha}{\partial t}(z, t) \;=\; \left[\lambda c - \frac{\partial c}{\partial t}\right] + \frac{\partial c}{\partial t} \;=\; \lambda\, c(z + vt, t) \;=\; \lambda \alpha(z, t)\,.$$

We have thus reduced to the case $v = 0$ for α! So, $\alpha(z, t) = e^{\lambda t}\alpha(z, 0)$. Therefore, substituting back:

$$c(x, t) = \alpha(x - vt, t) = e^{\lambda t}\alpha(x - vt, 0)\,.$$

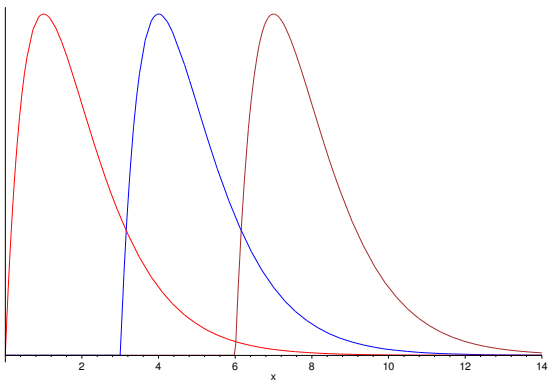
We conclude that

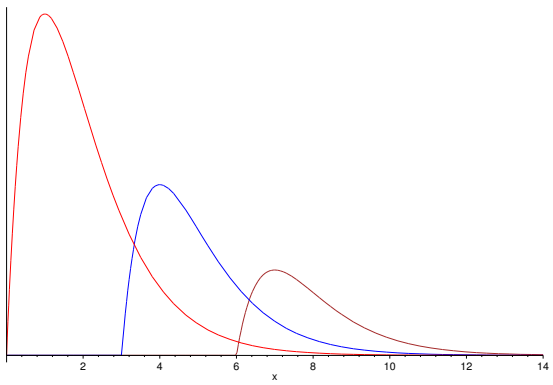
$$c(x, t) \;=\; e^{\lambda t} f(x - vt)$$

as claimed (writing $f(z) := \alpha(z, 0)$).

Thus, all solutions are *traveling waves*, with decay or growth depending on the sign of λ.

These are typical figures, assuming that $v = 3$ and that $\lambda = 0$ and $\lambda < 0$ respectively (snapshots taken at $t = 0, 1, 2$):





To determine uniquely $c(x,t) = e^{\lambda t} f(x - vt)$, need to know what the "initial condition f" is.

This could be done in various ways, for instance by specifying an initial distribution $c(x,0)$, or by giving the values $c(x_0,t)$ at some point x_0.

Example: a nuclear plant is leaking radioactivity, and we measure a certain type of radioactive particle by a detector placed at $x = 0$. Let us assume that the signal detected is described by the following function:

$$h(t) = \begin{cases} 0 & t < 0 \\ \frac{1}{1+t} & t \geq 0 \end{cases} ,$$

the wind blows eastward with constant velocity $v = 2$ m/s and particles decay with rate 3 s^{-1} ($\lambda = -3$). What is the solution $c(x,t)$?

We know that the solution is $c(x,t) = e^{-3t} f(x - 2t)$, but what is "$f$"?

We need to find f. Let us write the dummy-variable argument of f as "z" so as not to get confused with x and t. So we look for a formula for $f(z)$. *After we found* $f(z)$, we'll substitute $z = x - 2t$.

Since at position $x = 0$ we have that $c(0,t) = h(t)$, we know that $h(t) = c(0,t) = e^{-3t} f(-2t)$, which is to say, $f(-2t) = e^{3t} h(t)$.

We wanted $f(z)$, so we substitute $z = -2t$, and then obtain (since $t = -z/2$):

$$f(z) = e^{3(-z/2)} h(-z/2) \, .$$

To be more explicit, let us substitute the definition of h. Note that $t \geq 0$ is the same as $z \leq 0$. Therefore, we have:

$$f(z) = \begin{cases} \dfrac{e^{-3z/2}}{1 - z/2} & z \leq 0 \\ 0 & z > 0 \end{cases}$$

Finally, we conclude that the solution is:

$$c(x,t) \;=\; \begin{cases} \dfrac{e^{-3x/2}}{1 + t - x/2} & t \geq x/2 \\ 0 & t < x/2 \end{cases}$$

where we used the following facts: $z = x - 2t \leq 0$ is equivalent to $t \geq x/2$, $e^{-3t} e^{-(3/2)(x-2t)} = e^{-3x/2}$, and $1 - (x - 2t)/2 = 1 + t - x/2$.

We can now answer more questions. For instance: what is the concentration at position $x = 10$ and time $t = 6$? The answer is

$$c(10,6) = \frac{e^{-15}}{2} \, .$$

Homework Problems

1. Suppose $c(x,t)$ is the density of bacterial population being carried east by a wind blowing at 4 mph. The bacteria reproduce exponentially, with a doubling time of 5 hours.

(a) Find the density $c(x,t)$ in each of these cases:

(1) $c(x,0) \equiv 1$ (2) $c(x,0) = 2 + \cos x$ (3) $c(x,0) = \frac{1}{1+x^2}$ (4) $c(x,1) = 2 + \cos x$
(5) $c(0,t) \equiv 1$ (6) $c(0,t) = \sin t$ (7) $c(1,t) = \frac{1}{1+e^t}$.

(b) Sketch the density $c(x,10)$ at time $t = 10$.

2. Prove the following analog of the theorem in dimension 3 (the constant velocity v is now a vector): $c(x,y,z,t) = f(x - v_1 t, y - v_2 t, z - v_3 t)e^{-\lambda t}$.
(Hint: use $\alpha(x,y,z,t) = c(x + v_1 t, y + v_2 t, z + v_3 t)$.)

9.6 Attraction, Chemotaxis

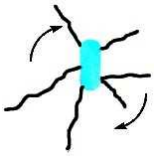
Chemotaxis is the term used to describe movement in response to chemoattractants or repellants, such as nutrients and poisons, respectively.

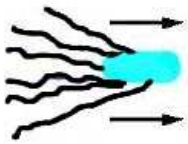
Perhaps the best-studied example of chemotaxis involves *E. coli* bacteria. In this course we will not study the behavior of individual bacteria, but will concentrate instead on the evolution equation for population density. However, it is worth digressing on the topic of individual bacteria, since it is so fascinating.

A Digression

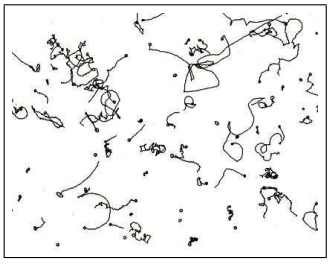
E. coli bacteria are single-celled organisms, about 2 μm long, which possess up to six flagella for movement.

Chemotaxis in *E. coli* has been studied extensively. These bacteria can move in basically two modes: a "tumble" mode in which flagella turn clockwise and reorientation occurs, or a "run" mode in which flagella turn counterclockwise, forming a bundle which helps propel them forward.



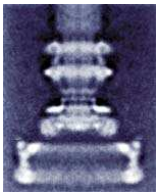


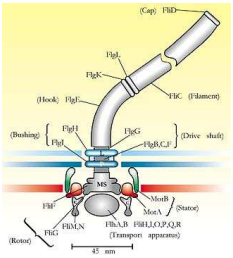
Basically, when the cell senses a change in nutrient in a certain direction, it "runs" in that direction. When the sensed change is very low, a "tumble" mode is entered, with random reorientations, until a new direction is decided upon. One may view the bacterium as performing a stochastic gradient search in a nutrient-potential landscape. These are pictures of "runs" and "tumbles" performed by *E. coli*:



The runs are biased, drifting about 30 deg/s due to viscous drag and asymmetry. There is very little inertia (very low Reynolds number). The mean run interval is about 1 second and the mean tumble interval is about 1/10 sec.

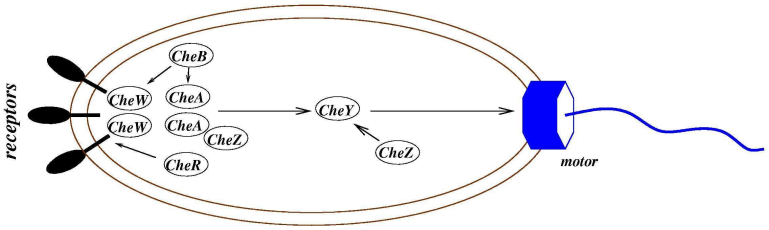
The motors actuating the flagella are made up of several proteins. In the terms used by Harvard's Howard Berg[55], they constitute "a nanotechnologist's dream," consisting as they do of "engines, propellers, . . . , particle counters, rate meters, [and] gear boxes." These are an actual electron micrograph and a schematic diagram of the flagellar motor:





The signaling pathways involved in *E. coli* chemotaxis are fairly well understood. Aspartate or other nutrients bind to receptors, reducing the rate at which a protein called CheA ("Che" for "chemotaxis") phosphorylates another protein called CheY transforming it into CheY-P. A third protein, called CheZ, continuously reverses this phosphorylation; thus, when ligand is present, there is less CheY-P and more CheY. Normally, CheY-P binds to the base of the motor, helping clockwise movement and hence tumbling, so the lower concentration of CheY-P has the effect of less tumbling and more running (presumably, in the direction of the nutrient).

A separate feedback loop, which includes two other proteins, CheR and CheB, causes adaptation to constant nutrient concentrations, resulting in a resumption of tumbling and consequent re-orientation. In effect, the bacterium is able to take derivatives, as it were, and decide which way to go.



There are many papers (ask instructor for references if interested) describing biochemical models of how these proteins interact and mathematically analyzing the dynamics of the system.

Modeling how Densities Change due to Chemotaxis

Let us suppose given a function $V = V(x)$ which denotes the *concentration of a food source or chemical (or friends, or foes), at location*[56] x.

We think of V as a "potential" function, very much as with an electromagnetic or force field in physics.

The basic principle that we wish to model is: *the population is attracted toward places where V is larger*.

We often assume that either $V(x) \geq 0$ for all x or $V(x) \leq 0$ for all x.

We use the positive case to model attraction towards nutrient.

[55] H. Berg, Motile behavior of bacteria, Physics Today, January 2000

[56] One could also consider time-varying functions $V(x,t)$. Time-varying V could help model a situation in which the "food" (e.g. a prey population) keeps moving.

If V has negative values, then movement towards larger values of V means movement away from places where V is large in absolute value, that is to say, repulsion from such values, which might represent the locations of high concentrations of poisons or predator populations.

To be more precise: we will assume that individuals (in the population of which $c(x,t)$ measures the density) move at any given time *in the direction in which $V(x)$ increases the fastest when taking a small step*, and with a velocity that is proportional[57] to the perceived rate of change in magnitude of V.

We recall from multivariate calculus that $V(x+\Delta x)-V(x)$ maximized in the direction of its gradient.

The proof is as follows. We need to find a direction, i.e., unit vector "u", so that $V(x+hu)-V(x)$ is maximized, for any small stepsize h.

We take a linearization (Taylor expansion) for $h>0$ small:

$$V(x+hu)-V(x) \;=\; [\nabla V(x)\cdot u]\,h \;+\; o(h)\,.$$

This implies the following formula for the average change in V when taking a small step:

$$\frac{1}{h}\Delta V \;=\; \nabla V(x)\cdot u + O(h) \;\approx\; \nabla V(x)\cdot u$$

and therefore the maximum value is obtained precisely when the vector u is picked in the same direction as ∇V. Thus, the direction of movement is given by the gradient of V.

The magnitude of the vector $\frac{1}{h}\Delta V$ is the approximately $\nabla V(x)$. Thus, our assumptions give us that chemotaxis results in a velocity "$\alpha\,\nabla V(x)$" proportional to $\nabla V(x)$.

Since, in general, flux = density$\times$velocity, we conclude:

$$J(x,t) \;=\; \alpha\, c(x,t)\,\nabla V(x)$$

for some α, so that the obtained equation (ignoring reaction or transport effects) is:

$$\boxed{\frac{\partial c}{\partial t} \;=\; -\,\mathrm{div}\;(\alpha\, c\,\nabla V)} \quad \text{or, equivalently:} \quad \boxed{\frac{\partial c}{\partial t} \;+\; \mathrm{div}\;(\alpha\, c\,\nabla V) \;=\; 0}$$

and in particular, in the special case of dimension one:

$$\boxed{\frac{\partial c}{\partial t} \;=\; -\,\frac{\partial\,(\alpha\, c\, V')}{\partial x}} \quad \text{or, equivalently:} \quad \boxed{\frac{\partial c}{\partial t} \;+\; \frac{\partial\,(\alpha\, c\, V')}{\partial x} \;=\; 0}$$

and therefore, using the product rule for x-derivatives:

$$\frac{\partial c}{\partial t} \;=\; -\alpha\frac{\partial c}{\partial x}V' - \alpha c V''\,.$$

Homework problem: Give an example of an equation that would model this situation: the speed of movement is an increasing function of the norm of the gradient, but is bounded by some maximal possible speed.

Of course, one can superimpose not only reactions but also different effects, such as transport, to this basic equation; the fluxes due to each effect add up to a total flux.

[57] This is not always reasonable! Some other choices are: there is a maximum speed at which one can move, or movement is only possible at a fixed speed. See the homework problem.

Example

Air flows (on a plane) Northward at 3 m/s, carrying bacteria. There is a food source as well, placed at $x = 1, y = 0$, which attracts according to the following potential:

$$V(x,y) = \frac{1}{(x-1)^2 + y^2 + 1}$$

(take $\alpha = 1$ and appropriate units).[58] The partial derivatives of V are:

$$\frac{\partial V}{\partial x} = -\frac{2\,x - 2}{((x-1)^2 + y^2 + 1)^2} \quad \text{and} \quad \frac{\partial V}{\partial y} = -2\,\frac{y}{((x-1)^2 + y^2 + 1)^2}\,.$$

The differential equation is, then:

$$\frac{\partial c}{\partial t} \;=\; -\mathrm{div}\,(c\nabla V) - \mathrm{div}\,(\begin{pmatrix} 0 \\ 3 \end{pmatrix} c) \;=\; -2\frac{\partial (c\frac{\partial V}{\partial x})}{\partial x} - 2\frac{\partial (c\frac{\partial V}{\partial y})}{\partial y} - 3\frac{\partial c}{\partial y}$$

or, expanding:

$$\frac{\partial c}{\partial t} \;=\; 2\,\frac{\partial c}{\partial x}\,\frac{(2\,x-2)}{N^2} - 4\,c\,\frac{(2\,x-2)^2}{N^3} + 8\,\frac{c}{N^2} + 4\,\frac{\partial c}{\partial y}\frac{y}{N^2} - 16\,c\,\frac{y^2}{N^3} \;- 3\,\frac{\partial c}{\partial y}$$

where we wrote $N = (x-1)^2 + y^2 + 1$.

Here is a homework problem:

Problem che1

We are given this chemotaxis equation (one space dimension) for the concentration of a microorganism (assuming no additional reactions, transport, etc):

$$\frac{\partial c}{\partial t} \;=\; \frac{\partial c}{\partial x}\,\frac{(2\,x-6)}{\left(2 + (x-3)^2\right)^2} \;-\; 2c\,\left(\frac{(2\,x-6)^2}{\left(2 + (x-3)^2\right)^3} - \frac{1}{\left(2 + (x-3)^2\right)^2}\right)\,.$$

(1) What is the potential function? (Give a formula for it.)

(2) Where (at $x =$?) is the largest amount of food?

(Answers on website.)

Some Intuition

Let us develop some intuition regarding the chemotaxis equation, at least in dimension one.

Suppose that we study what happens at a critical point of V. That is, we take a point for which $V'(x_0) = 0$. Suppose, further, that the concavity of V at that point is down: $V''(x_0) < 0$. Then, $\frac{\partial c}{\partial t}(x_0, t) > 0$, because:

$$\frac{\partial c}{\partial t}(x_0,t) \;=\; -\alpha\frac{\partial c}{\partial x}(x_0,t)\,V'(x_0) \;-\; \alpha c V''(x_0) \;=\; 0 - \alpha c V''(x_0) \;>\; 0\,.$$

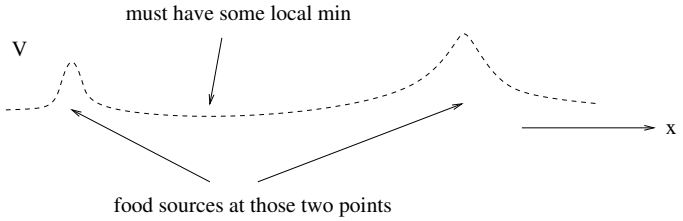
[58] We assume that the food is not being carried by the wind, but stays fixed. (How would you model a situation where the food is also being carried by the wind?) Also, this model assumes that the amount of food is large enough that we need not worry about its decrease due to consumption by the bacteria. (How would you model food consumption?)

In other words, the concentration at such a point increases in time. Why is this so, intuitively?

Answer: the conditions $V'(x_0) = 0$, $V''(x_0) > 0$ characterize a local maximum of V. Therefore, nearby particles (bacteria, whatever it is that we are studying) will move toward this point x_0, and the concentration there will increase in time.

Conversely, if $V''(x_0) > 0$, then the formula shows that $\frac{\partial c}{\partial t}(x_0, t) < 0$, that is to say, the density decreases. To understand this intuitively, we can think as follows.

The point x_0 is a local minimum of V. Particles that start *exactly* at this point would not move, but any nearby particles will move "uphill" towards food. Thus, as nearby particles move away, the density at x_0, which is an average over small segments around x_0, indeed goes down.

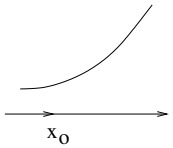


Next, let us analyze what happens when $V'(x_0) > 0$ and $V''(x_0) > 0$, under the additional assumption that $\frac{\partial c}{\partial x}(x_0, t) \approx 0$, that is, we assume that the density $c(x, t)$ is approximately constant around x_0. Then

$$\frac{\partial c}{\partial t}(x_0, t) \;=\; -\alpha \frac{\partial c}{\partial x}(x_0, t)\, V'(x_0) \;-\; \alpha c V''(x_0) \;\approx\; -\alpha c V''(x_0) \;<\; 0\,.$$

How can we interpret this inequality?

This picture of what the graph of V around x_0 looks like should help:



The derivative (gradient) of V is less to the left of x_0 than to the right of x_0, because $V'' > 0$ means that V' is increasing. So, the flux is less to the left of x_0 than to its right. This means that particles to the left of x_0 are arriving to the region around x_0 much slower than particles are leaving this region in the rightward direction. So the density at x_0 diminishes.

Homework: analyze, in an analogous manner:

(a) $V'(x_0) > 0, V''(x_0) < 0$
(b) $V'(x_0) < 0, V''(x_0) > 0$.

10 Diffusion

Diffusion is one of the fundamental processes by which "particles" (atoms, molecules, even bigger objects) move.

Fick's Law, proposed in 1855, and based upon experimental observations, postulated that diffusion is due to movement from higher to lower concentration regions. Mathematically:

$$J(x,t) \ \propto \ -\nabla c(x,t)$$

(we use "$\propto$" for "proportional").

This formula applies to movement of particles in a solution, where the proportionality constant will depend on the sizes of the molecules involved (solvent and solute) as well as temperature. It also applies in many other situations, such as for instance diffusion across membranes, in which case the constant depends on permeability and thickness as well.

The main physical explanation of diffusion is probabilistic, based on the thermal motion of individual particles due to the environment (e.g., molecules of solvent) constantly "kicking" the particles. "Brownian motion", named after the botanist Robert Brown, refers to such random thermal motion.

> One often finds the claim that Brown in his 1828 paper observed that pollen grains suspended in water move in a rapid but very irregular fashion.
>
> However, in *Nature*'s 10 March 2005 issue (see also errata in the 24 March issue), David Wilkinson states: "... several authors repeat the mistaken idea that the botanist Robert Brown observed the motion that now carries his name while watching the irregular motion of pollen grains in water. The microscopic particles involved in the characteristic jiggling dance Brown described were much smaller particles. I have regularly studied pollen grains in water suspension under a microscope without ever observing Brownian motion.
>
> From the title of Brown's 1828 paper "A Brief Account of Microscopical Observations ... on the Particles contained in the Pollen of Plants...", it is clear that he knew he was looking at smaller particles (which he estimated at about 1/500 of an inch in diameter) than the pollen grains.
>
> Having observed 'vivid motion' in these particles, he next wondered if they were alive, as they had come from a living plant. So he looked at particles from pollen collected from old herbarium sheets (and so presumably dead) but also found the motion. He then looked at powdered fossil plant material and finally inanimate material, which all showed similar motion.
>
> Brown's observations convinced him that life was not necessary for the movement of these microscopic particles."

The relation to Fick's Law was explained mathematically in Einstein's Ph.D. thesis (1905).[59]

When diffusion acts, and if there are no additional constraints, the eventual result is a homogeneous concentration over space. However, usually there are additional boundary conditions, creation and absorption rates, etc., which are superimposed on pure diffusion. This results in a "trade-off" between the "smoothing out" effects of diffusion and other influences, and the results can be very interesting.

We should also remark that diffusion is often used to model macroscopic situations analogous to movement of particles from high to low density regions. For example, a human population may shift towards areas with less density of population, because there is more free land to cultivate.

[59] A course project asks you to run a java applet simulation of Einstein's description of Brownian motion.

We have that $J(x,t) = -D\,\nabla c(x,t)$, for some constant D called the *diffusion coefficient*. Since, in general, $\frac{\partial c}{\partial t} = -\mathrm{div}\, J$, we conclude that:

$$\boxed{\frac{\partial c}{\partial t} \;=\; D\nabla^2 c}$$

where ∇^2 is the "Laplacian" (often "Δ") operator:

$$\frac{\partial c}{\partial t} \;=\; D\left(\frac{\partial^2 c}{\partial x_1^2} + \frac{\partial^2 c}{\partial x_2^2} + \frac{\partial^2 c}{\partial x_3^2}\right) .$$

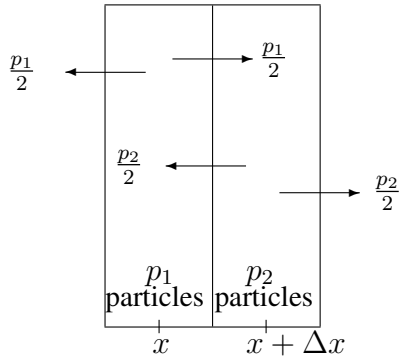
The notation ∇^2 originates as follows: the divergence can be thought of as "dot product by ∇". So "$\nabla \cdot (\nabla c)$" is written as $\nabla^2 c$. This is the same as the "heat equation" in physics (which studies diffusion of heat).

Note that the equation is just:

$$\frac{\partial c}{\partial t} \;=\; D\,\frac{\partial^2 c}{\partial x^2}$$

in dimension one.

Let us consider the following very sketchy probabilistic intuition to justify why it is reasonable that the flux should be proportional to the gradient of the concentration, if particles move at random. Consider the following picture:



We assume that, in some small interval of time Δt, particles jump right or left with equal probabilities, so half of the p_1 particles in the first box move right, and the other half move left. Similarly for the p_2 particles in the second box. (We assume that the jumps are big enough that particles exit the box in which they started.)

The net number of particles (counting rightward as positive) through the segment shown in the middle is proportional to $\frac{p_1}{2} - \frac{p_2}{2}$, which is proportional roughly to $c(x,t) - c(x+\Delta x, t)$. This last difference, in turn, is proportional to $-\frac{\partial c}{\partial x}$.

This argument is not really correct, because we have said nothing about the velocity of the particles and how they relate to the scales of space and time. But it does intuitively help on seeing why the flux is proportional to the negative of the gradient of c.

A game can help understand. Suppose that students in a classroom all initially sit in the front rows, but then start to randomly (and repeatedly) change chairs, flipping coins to decide if to move backward (or forward if they had already moved back). Since no one is sitting in the back, initially there is a net flux towards the back. Even after a while, there will be still less students flipping coins in the back than in the front, so there are more possibilities of students moving backward than forward. Eventually, once that the students are well-distributed, about the same number will move forward as move backward: this is the equalizing effect of diffusion.

10.1 Time of Diffusion (in dimension 1)

It is often said that "diffusion results in movement proportional to $\sqrt{t}$". The following theorem gives one way to make that statement precise. A different interpretation is in the next section, and later, we will discuss a probabilistic interpretation and relations to random walks as well.

Theorem. Suppose that c satisfies diffusion equation

$$\frac{\partial c}{\partial t} \;=\; D\frac{\partial^2 c}{\partial x^2}\,.$$

Assume also that the following hold:

$$C = \int_{-\infty}^{+\infty} c(x,t)\,dx$$

is independent of t (constant population), and c is "small at infinity":

$$\text{for all } t \geq 0, \qquad \lim_{x\to\pm\infty} x^2\frac{\partial c}{\partial x}(x,t) = 0 \quad \text{and} \quad \lim_{x\to\pm\infty} xc(x,t) = 0\,.$$

Define, for each t, the following integral which measures how the density "spreads out":

$$\sigma^2(t) = \frac{1}{C}\int_{-\infty}^{+\infty} x^2 c(x,t)\,dx$$

(the second moment, which we assume is finite). Then:

$$\sigma^2(t) \;=\; 2D\,t \;+\; \sigma^2(0)$$

for all t. In particular, if the initial (at time $t = 0$) population is concentrated near $x = 0$ (a "δ function"), then $\sigma^2(t) \approx 2D\,t$.

Proof:

We use the diffusion PDE, and integrate by parts twice:

$$\begin{aligned}
\frac{C}{D}\frac{d\sigma^2}{dt} &= \frac{1}{D}\frac{\partial}{\partial t}\int_{-\infty}^{+\infty} x^2 c\,dx \;=\; \frac{1}{D}\int_{-\infty}^{+\infty} x^2\frac{\partial c}{\partial t}\,dx \;=\; \int_{-\infty}^{+\infty} x^2\frac{\partial^2 c}{\partial x^2}\,dx \\
&= \left[x^2\frac{\partial c}{\partial x}\right]_{-\infty}^{+\infty} - \int_{-\infty}^{+\infty} 2x\frac{\partial c}{\partial x}\,dx \\
&= -\left[2xc\right]_{-\infty}^{+\infty} + \int_{-\infty}^{+\infty} 2c\,dx \;=\; 2\int_{-\infty}^{+\infty} c(x,t)\,dx \;=\; 2\,C
\end{aligned}$$

Canceling C, we obtain:

$$\frac{d\sigma^2}{dt}(t) \;=\; 2D$$

and hence, integrating over t, we have, as wanted:

$$\sigma^2(t) \;=\; 2Dt + \sigma^2(0)\,.$$

If, in particular, particles start concentrated in a small interval around $x = 0$, we have that $c(x,0) = 0$ for all $|x| > \varepsilon$. then (with $c = c(x,0)$):

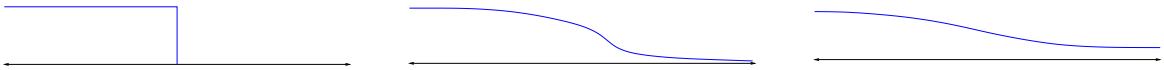
$$\int_{-\infty}^{+\infty} x^2 c\,dx = \int_{-\varepsilon}^{+\varepsilon} x^2 c\,dx \leq \varepsilon^2\int_{-\varepsilon}^{+\varepsilon} c\,dx = \varepsilon^2 C$$

so $\sigma^2(0) = \varepsilon \approx 0$.

10.2 Another Interpretation of Diffusion Times (in dimension one)

There are many ways to state precisely what is meant by saying that diffusion takes time r^2 to move distance r. As diffusion is basically a model of a population of individuals which move randomly, one cannot talk about any particular particle, bacterium, etc. One must make a statement about the whole population. One explanation is in terms of the second moment of the density c, as done earlier. Another one is probabilistic, and one could also argue in terms of the Gaussian fundamental solution. We sketch another one next.

Suppose that we consider the diffusion equation $\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$ for $x \in \mathbb{R}$, and an initial condition at $t = 0$ which is a step function, a uniform population density of one in the interval $(-\infty, 0]$ and zero for $x > 0$. It is quite intuitively clear that diffusion will result in population densities that look like the two subsequent figures, eventually converging to a constant value of 0.5.



Consider, for any given coordinate point $p > 0$, a time $T = T(p)$ for which it is true that (let us say) $c(p, T) = 0.1$. It is intuitively clear (we will not prove it) that the function $T(p)$ is increasing on p: for those points p that are farther to the right, it will take longer for the graph to rise enough. So, $T(p)$ is uniquely defined for any given p. We sketch now a proof of the fact that $T(p)$ is proportional to p^2.

Suppose that $c(x, t)$ is a solution of the diffusion equation, and, for any given positive constant r, introduce the new function f defined by:

$$f(x, t) = c(rx, r^2 t)\,.$$

Observe (chain rule) that $\frac{\partial f}{\partial t} = r^2\frac{\partial c}{\partial t}$ and $\frac{\partial^2 f}{\partial x^2} = r^2\frac{\partial^2 c}{\partial x^2}$. Therefore,

$$\frac{\partial f}{\partial t} - D\frac{\partial^2 f}{\partial x^2} \;=\; r^2\left(D\frac{\partial c}{\partial t} - D\frac{\partial^2 c}{\partial x^2}\right) \;=\; 0\,.$$

In other words, the function f also satisfies the same equation. Moreover, c and f have the same initial condition: $f(x, 0) = c(rx, 0) = 1$ for $x \leq 0$ and $f(x, 0) = c(rx, 0) = 0$ for $x > 0$. Therefore f and c must be the same function.[60] In summary, for every positive number r, the following scaling law is true:

$$c(x, t) \;=\; c(rx, r^2 t) \quad \forall\, x, t\,.$$

For any $p > 0$, if we plug-in $r = p$, $x = 1$, and $t = T(p)/p^2$ in the above formula, we obtain that:

$$c(1, T(p)/p^2) = c(p.1, p^2.(T(p)/p^2)) = c(p, T(p)) = 0.1\,,$$

and therefore $T(1) = T(p)/p^2$, that is, $T(p) = \alpha p^2$ for some constant.

Some Homework Problems

(1) In dimension 2, compute the Laplacian in polar coordinates. That is, write

$$f(r, \varphi, t) = c(r\cos\varphi, r\sin\varphi, t)\,,$$

[60] Of course, uniqueness of solutions requires a proof. The fact that f and c satisfy the same "boundary conditions at infinity" is used in such a proof, which we omit here.

so that f is really the same as the function c, but thought of as a function of magnitude, argument, and time. Prove that:

$$(\nabla^2 c)(r\cos\varphi, r\sin\varphi, t) \;=\; \frac{\partial^2 f}{\partial r^2} + \frac{1}{r}\frac{\partial f}{\partial r} + \frac{1}{r^2}\frac{\partial^2 f}{\partial \varphi^2}$$

(all terms on the RHS evaluated at r, φ, t). Writing f just as c (but remembering that c is now viewed as a function of (r, φ, t)), this means that the diffusion equation in polar coordinates is:

$$\frac{\partial c}{\partial t} \;=\; \frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{1}{r^2}\frac{\partial^2 c}{\partial \varphi^2}\,.$$

Conclude that, for radially symmetric c, the diffusion equation in polar coordinates is:

$$\frac{\partial c}{\partial t} \;=\; \frac{D}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right)$$

It is also possible to prove that for spherically symmetric c in three dimensions, the Laplacian is $\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right)$.

2. (harder and optional) Show that, under analogous conditions to those in the theorem shown for dimension 1, in dimension d (e.g.: $d = 2, 3$) one has the formula:

$$\sigma^2(t) \;=\; 2dDt + \sigma^2(0)$$

(for $d = 1$, this is the same as previously). The proof will be completely analogous, except that the first step in integration by parts ($uv' = (uv)' - u'v$, which is just the Leibniz rule for derivatives) must be generalized to vectors (use that $\nabla\cdot$ acts like a derivative) and the second step (the Fundamental Theorem of Calculus) should be replaced by an application of Gauss' divergence theorem.

3. Prove that (for $n = 1$), the following function is a particular solution of the diffusion equation:

$$c_0(x,t) \;=\; \frac{C}{\sqrt{4\pi Dt}}\, e^{-\frac{x^2}{4Dt}}$$

(where C is any constant). Also, verify that, indeed for this example, $\sigma^2(t) = 2Dt$.

In dimension $n = 3$ (or even any other dimension), there is a similar formula. If you have access to Maple or Mathematica, check that the following function is a solution, for $t > 0$:

$$c_0(x,t) \;=\; \frac{C}{(4\pi Dt)^{3/2}}\, e^{-\frac{r^2}{4Dt}}$$

where $r^2 = x_1^2 + x_2^2 + x_3^2$.

(At $t = 0$, this particular solution is not well-defined; it tends to a "δ" function; think of it as the "spread from a point source".)

4. For any arbitrary continuous function f, show that the function[61]

$$c(x,t) \;=\; \int_{-\infty}^{+\infty} \frac{C}{\sqrt{4\pi Dt}} e^{-\frac{(x-\xi)^2}{4Dt}} f(\xi)\, d\xi$$

solves the diffusion equation for $t > 0$, and has the initial condition $c(x, 0) = f(x)$.

[61] This is the *convolution* $c_0 * f$ of f with the "Green's function" c_0 for the PDE

10.3 Separation of Variables

Let us try to find a solution of the diffusion equation, in dimension 1:

$$\frac{\partial c}{\partial t} \;=\; D\,\frac{\partial^2 c}{\partial x^2}$$

of the special form $c(x,t) = X(x)T(t)$.

Substituting into the PDE, we conclude that X, T must satisfy:

$$T'(t)X(x) \;=\; D\,T(t)X''(x)$$

(using primes for derivatives with respect to t and x), and this must hold for all t and x, or equivalently:

$$D\,\frac{X''(x)}{X(x)} \;=\; \frac{T'(t)}{T(t)} \quad \forall\, x,t\,.$$

Now define:

$$\lambda := \frac{T'(0)}{T(0)}$$

so:

$$D\frac{X''(x)}{X(x)} \;=\; \frac{T'(0)}{T(0)} \;=\; \lambda$$

for all x (since the above equality holds, in particular, at $t = 0$). Thus, we conclude, applying the equality yet again:

$$\boxed{D\,\frac{X''(x)}{X(x)} \;=\; \frac{T'(t)}{T(t)} \;=\; \lambda \quad \forall\, x,t}$$

for this fixed (and so far unknown) real number λ.

In other words, each of X and T satisfy an *ordinary* (and linear) differential equation, but the two equations share the same λ:

$$\begin{aligned} X''(x) &= \lambda X(x) \\ T'(t) &= \lambda T(t)\,. \end{aligned}$$

(We take D=1 for simplicity.) The second of these says that $T' = \lambda T$, i.e.

$$T(t) = e^{\lambda t}T(0)$$

and the first equation has the general solution (if $\lambda \neq 0$) $X(x) = ae^{\mu_1 x} + be^{\mu_2 x}$, where the μ_i's are the two square roots of λ, and a, b are arbitrary constants. As you saw in your diff equs course, when $\lambda < 0$, it is more user-friendly to write complex exponentials as trigonometric functions, which also has the advantage that a, b can then be taken as real numbers (especially useful since a and b are usually fit to initial conditions). In summary, for $\lambda > 0$ one has:

$$X(x) = ae^{\mu x} + be^{-\mu x}$$

(with $\mu = \sqrt{\lambda}$), while for $\lambda < 0$ one has:

$$X(x) = a\cos kx + b\sin kx$$

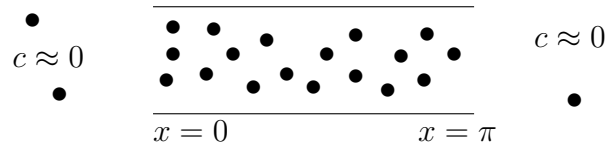
(with $k = \sqrt{-\lambda}$).

10.4 Examples of Separation of Variables

Suppose that a set of particles undergo diffusion (e.g., bacteria doing a purely random motion) inside a thin tube.

The tube is open at both ends, so part of the population is constantly being lost (the density of the organisms outside the tube is small enough that we may take it to be zero).

We model the tube in dimension 1, along the x axis, with endpoints at $x = 0$ and $x = \pi$:



We model the problem by a diffusion (for simplicity, we again take D=1) with boundary conditions:

$$\frac{\partial c}{\partial t} \;=\; \frac{\partial^2 c}{\partial x^2}\,, \qquad c(0,t) = c(\pi,t) = 0\,.$$

Note that c identically zero is always a solution. Let's look for a bounded and nonzero solution.

Solution: we look for a $c(x,t)$ of the form $X(x)T(t)$. As we saw, if there is such a solution, then then there is a number λ so that $X''(x) = \lambda X(x)$ and $T'(t) = \lambda T(t)$ for all x, t, so, in particular, $T(t) = e^{\lambda t}T(0)$. Since we were asked to obtain a *bounded* solution, the only possibility is $\lambda \leq 0$ (otherwise, $T(t) \to \infty$ as $t \to \infty$).

It cannot be that $\lambda = 0$. Indeed, if that were to be the case, then $X''(x) = 0$ implies that X is a line: $X(x) = ax + b$. But then, the boundary conditions $X(0)T(t) = 0$ and $X(\pi)T(t) = 0$ for all t imply that $ax + b = 0$ at $x = 0$ and $x = \pi$, giving $a = b = 0$, so $X \equiv 0$, but we are looking for a nonzero solution.

We write $\lambda = -k^2$, for some $k > 0$ and consider the general form of the X solution:

$$X(x) = a \sin kx + b \cos kx\,.$$

The boundary condition at $x = 0$ can be used to obtain more information:

$$X(0)T(t) = 0 \;\text{ for all } t \;\;\Rightarrow\; X(0) = 0 \;\Rightarrow\; b = 0\,.$$

Therefore, $X(x) = a \sin kx$, and $a \neq 0$ (otherwise, $c \equiv 0$). Now using the second boundary condition:

$$X(\pi)T(t) = 0 \;\text{ for all } t \;\;\Rightarrow\; X(\pi) = 0 \;\Rightarrow\; \sin k\pi = 0$$

Therefore, k *must be an integer* (nonzero, since otherwise $c \equiv 0$).

We conclude that any separated-form solution must have the form

$$c(x,t) \;=\; a\, e^{-k^2 t} \sin kx$$

for some nonzero integer k. One can easily check that, indeed, any such function is a solution. (Do it as a homework problem!).

Moreover, since the diffusion equation is linear, any linear combination of solutions of this form is also a solution.

For example,

$$5e^{-9t} \sin 3x - 33e^{-16t} \sin 4x$$

is a solution of our problem.

Fitting Initial Conditions

Next let's add the requirement that the *initial condition* must be:

$$c(x,0) = 3\sin 5x - 2\sin 8x\,.$$

Now, we know that any linear combination of the form

$$\sum_{k \text{ integer}} a_k e^{-k^2 t}\sin kx$$

solves the equation. Since the initial condition has the two frequencies $5, 8$, we should obviously try for a solution of the form:

$$c(x,t) \;=\; a_5 e^{-25t}\sin 5x + a_8 e^{-64t}\sin 8x\,.$$

We find the coefficients by plugging-in $t = 0$:

$$c(x,0) \;=\; a_5 \sin 5x + a_8 \sin 8x \;=\; 3\sin 5x - 2\sin 8x\,.$$

So we take $a_5 = 3$ and $a_8 = -2$; and thus obtain finally:

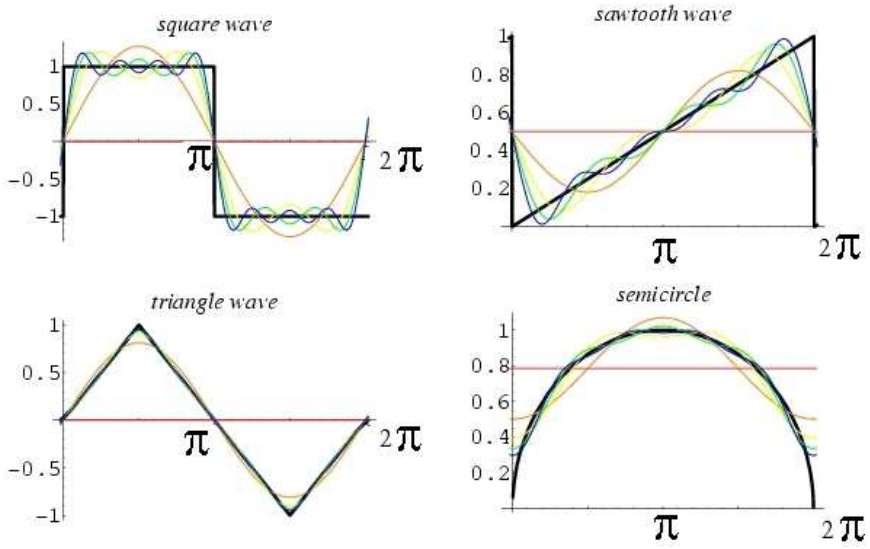
$$c(x,t) = 3e^{-25t}\sin 5x - 2e^{-64t}\sin 8x\,.$$

One can prove, although we will not do so in this course, that this is the unique solution with the given boundary and initial conditions.

This works in exactly the same way whenever the initial condition is a finite sum $\sum_k a_k \sin kx$. Ignoring questions of convergence, the same idea even works for an infinite sum $\sum_{k=0}^{\infty} a_k \sin kx$. But what if initial condition is not a sum of sines? A beautiful area of mathematics, *Fourier analysis*, tells us that it is possible to write *any* function defined on an interval as an infinite sum of this form. This is analogous to the idea of writing any function of x (not just polynomials) as a sum of powers x^i. You saw such expansions (Taylor series) in a calculus course.

The theory of expansions into sines and cosines is more involved (convergence of the series must be interpreted in a very careful way), and we will not say anything more about that topic in this course.

Here are some pictures of approximations, though, for an interval of the form $[0, 2\pi]$. In each picture, we see a function together with various approximants consisting of sums of an increasing number of sinusoidal functions (red is constant; orange is $a_0 + a_1 \sin x$, etc).



Another Example

Suppose now that, in addition to diffusion, there is a reaction. A population of bacteria grows exponentially inside the same thin tube that we considered earlier, still also moving at random.

Question: was is the smallest possible growth rate which guarantees that the population can grow?

The question, mathematically, is: for what growth rates α are there unbounded solutions of this problem?:

$$\frac{\partial c}{\partial t} \;=\; \frac{\partial^2 c}{\partial x^2} \;+\; \alpha c\,, \quad c(0,t) = c(\pi,t) = 0\,.$$

We only address here the easier question: for what α's is there some unbounded solution of the separated form $c(x,t) = X(x)T(t)$?

We follow the same idea as earlier:

$$X(x)T'(t) \;=\; X''(x)T(t) + \alpha X(x)T(t)$$

for all x, t, so there must exist some real number λ so that:

$$\frac{T'(t)}{T(t)} \;=\; \frac{X''(x)}{X(x)} + \alpha \;=\; \lambda\,.$$

This gives us the coupled equations:

$$\begin{aligned} T'(t) &= \lambda T(t) \\ X''(x) &= (\lambda - \alpha)X(x) \end{aligned}$$

with boundary conditions $X(0) = X(\pi) = 0$.

It must be the case that $\lambda \geq 0$, since otherwise $T(t) = e^{\lambda t}T(0) \to 0$ as $t \to 0$, or $T(t)$ is constant, and the solution would not be unbounded.

We claim that, also, it must be true that and $\lambda < \alpha$, since otherwise one cannot satisfy the boundary conditions. We prove this inequality by contradiction.

Suppose that $\lambda - \alpha \geq 0$. Then there is a real number μ such that $\mu^2 = \lambda - \alpha$ and X satisfies the equation $X'' = \mu^2 X$.

If $\mu = 0$, then the equation says that $X = a + bx$ for some a, b. But $X(0) = X(\pi) = 0$ would then imply $a = b = 0$, so $X \equiv 0$ and the solution is identically zero (and so not unbounded).

So let us assume that $\mu \neq 0$. Thus:

$$X \;=\; ae^{\mu x} + be^{-\mu x}$$

and, using the two boundary conditions, we have $a + b = ae^{\mu\pi} + be^{-\mu\pi} = 0$, or in matrix form:

$$\begin{pmatrix} 1 & 1 \\ e^{\mu\pi} & e^{-\mu\pi} \end{pmatrix} \begin{pmatrix} a \\ b \end{pmatrix} \;=\; 0\,.$$

Since

$$\det \begin{pmatrix} 1 & 1 \\ e^{\mu\pi} & e^{-\mu\pi} \end{pmatrix} = e^{-\mu\pi} - e^{\mu\pi} = e^{-\mu\pi}(1 - e^{2\mu\pi}) \neq 0\,,$$

we obtain that $a = b = 0$, again contradicting $X \not\equiv 0$. In summary, $\lambda - \alpha \geq 0$ leads to a contradiction, so $\lambda < \alpha$.

Let k be a real number such that $k^2 := \alpha - \lambda$. Then,

$$X'' + k^2 X = 0 \;\Rightarrow\; X(x) = a \sin kx + b \cos kx$$

and $X(0) = X(\pi) = 0$ implies that $b = 0$ and that k must be a nonzero integer.

So $\lambda = \alpha - k^2$ must be positive, for some nonzero integer k. This means that we need precisely that:

$$\alpha > 1$$

in order for the population to be able to grow. For any give rate α, every separable solution is of form

$$a\, e^{(\alpha - k^2)t}\, \sin kx$$

with a nonzero integer k such that $k < \sqrt{\alpha}$, and some constant $a \neq 0$, and, conversely, every such function (or a linear combination thereof) is a solution (check!). If c represents a density of a population, a separable solution only makes sense if $k = 1$, since otherwise there will be negative values; however, sums of several such terms may well be positive.

Homework: Under what conditions is there an unbounded (separated form) solution of:

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} + \alpha c, \quad c(0,t) = c(1,t) = 0\ ?$$

Provide the general form of such solutions. What about boundary condition $\frac{\partial c}{\partial x}(1,t) = 0$?

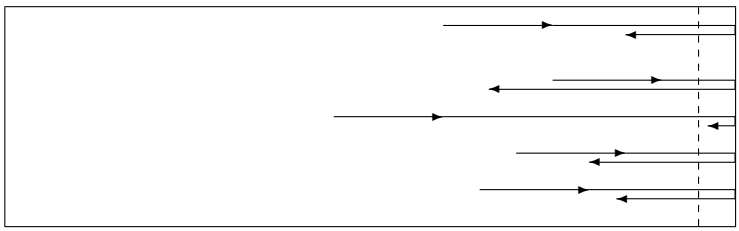
(Answers: $\alpha > \pi^2$, $a\, e^{(\alpha - k^2\pi^2)t} \sin k\pi x$. In the second case, we need that $\alpha > \pi^2/4$ and get the solution $ae^{\alpha - ((k+1/2)\pi)^2 t} \sin(k + 1/2)\pi x$.)

10.5 No-flux Boundary Conditions

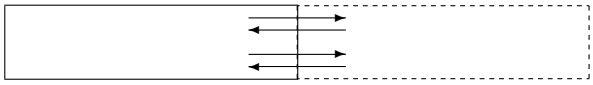
Suppose that the tube in the previous examples is closed at the end $x = L$ (a similar argument applies if it is closed at $x = 0$). We assume that, in that case, particles "bounce" at a "wall" placed at $x = L$.

One models this situation by a "no flux" or *Neumann* boundary condition $J(L,t) \equiv 0$, which, for the pure diffusion equation, is the same as $\frac{\partial c}{\partial x}(L,t) \equiv 0$.

One way to think of this is as follows. Imagine a narrow strip (of width ε) about the wall. For very small ε, most particles bounce back far into region, so the flux at $x = L - \varepsilon$ is ≈ 0.



Another way to think of this is using the reflecting boundary method. We replace the wall by a "virtual wall" and look at equation in a larger region obtained by adding a mirror image of the original region. Every time that there is a bounce, we think of the particle as continuing to the mirror image section. Since everything is symmetric (we can start with a symmetric initial condition), clearly the net flow across this wall balances out, so even if individual particles would exit, *on the average* the same number leave as enter, and so the population density is exactly the same as if no particles would exit. As we just said, the flux at the wall must be zero, again explaining the boundary condition.



10.6 Probabilistic Interpretation

We make now some very informal and intuitive remarks.

In a population of indistinguishable particles (bacteria, etc.) undergoing random motion, we may track what happens to *each individual particle* (assumed small enough so that they don't collide with each other).

Since the particles are indistinguishable, one could imagine performing a huge number of one-particle experiments, and estimating the distribution of positions $x(t)$ by averaging over runs, instead of just performing one big experiment with many particles at once and measuring population density.

The probability of a single particle ending up, at time t, in a given region R, is proportional to how many particles there are in R, i.e. to Prob(particle in R) $\propto C(R,t) = \int_R c(x,t)\,dx$.

If we normalize to $C = 1$, we have that Prob(particle in R) = $\int_R c(x,t)\,dx$ (a triple integral, in 3 space).

Therefore, we may view $c(x,t)$ is the *probability density* of the random variable giving the position of an individual particle at time t (a *random walk*). In this interpretation, $\sigma^2(t)$ is then the *variance* of the random variable, and its standard deviation $\sigma(t)$ is proportional to $\sqrt{t}$ (a rough estimate on approximate distance traveled).

Specifically, for particles undergoing random motion with distribution c_0 (a "standard random walk"), the position has a Gaussian (normal) distribution.

For Gaussians, the mean distance from zero (up a to constant factor) coincides with the standard deviation:

$$E(|X|) \;=\; \frac{2}{\sigma\sqrt{2\pi}} \int_0^\infty x e^{-x^2/(2\sigma^2)}\,dx \;=\; \frac{\sigma}{\sqrt{\pi}}$$

(substitute $u = x/\sigma$), and similarly in any dimension for $E(\sqrt{x_1^2 + \ldots + x_d^2})$.

So we have that the *average displacement of a diffusing particle is proportional to* $\sqrt{t}$.

To put it in another way: *traveling average distance L requires time L^2.*

Since "life is motion" (basically by definition), this has fundamental implications for living organisms.

Diffusion is simple and energetically relatively "cheap": there is no need for building machinery for locomotion, etc., and no loss due to conversion to mechanical energy when running cellular motors and muscles.

At small scales, diffusion is very efficient (L^2 is tiny for small L), and hence it is a fast method for nutrients and signals to be carried along for *short* distances.

However, this is not the case for long distances (since L^2 is huge if L is large). Let's do some quick calculations.

Suppose that a particle travels by diffusion covering 10^{-6}m (= 1μm) in 10^{-3} seconds (a typical order of magnitude in a cell), Then, how much time is required to travel 1 meter?

Answer: since $x^2 = 2Dt$, we solve $(10^{-6})^2 = 2D10^{-3}$ to obtain $D = 10^{-9}/2$. So, $1 = 10^{-9}t$ means that $t = 10^9$ seconds, i.e. about 27 years!

Obviously, this is not a feasible way to move things along a large organism, or even a big cell (e.g., long neuron). That's one reason why there are circulatory systems, cell motors, microtubules, etc.

More on Random Walks

Let is develop a little more intuition on random walks. A discrete analog is as follows: suppose that a particle can move left or right with a unit displacement and equal probability, each step independent of the rest. What is the position after t steps? Let is check 4 steps, making a histogram:

ending	possible sequences	count	
-4	$-1-1-1-1$	1	x
-2	$-1-1-1+1, -1-1+1-1, \ldots$	4	xxxx
0	$-1-1+1+1, -1+1+1-1, \ldots$	6	xxxxxx
2	$1+1+1-1, 1+1-1+1, \ldots$	4	xxxx
4	$1+1+1+1$	1	x

The Central Limit Theorem tells us that the distribution (as $t \to \infty$ tends to be normal, with variance:

$$\sigma^2(t) = E(X_1 + \ldots + X_t)^2 = \sum \sum EX_iX_j = \sum EX_i^2 = \sigma^2 t$$

(since the steps are independent, $EX_iX_j = 0$ for $i \neq j$). We see then that $\sigma^2(t)$ is proportional to $\sqrt{t}$.

The theory of Brownian motion makes a similar analysis for continuous walks.

10.7 Another Diffusion Example: Population Growth

We consider now the equation

$$\frac{\partial c}{\partial t} \;=\; D\nabla^2 c + \alpha c$$

on the entire space (no boundary conditions).

This equation models a population which is diffusing and also reproducing at some rate α. It is an example of a *reaction-diffusion* equation, meaning that there is a reaction ($dc/dt = \alpha c$) taking place in addition to diffusion.

We use an integrating factor trick in order to reduce this equation to a pure diffusion equation. The trick is entirely analogous to what is done for solving the transport equation with a similar added reaction.

We introduce the new dependent variable $p(x,t) := e^{-\alpha t}c(x,t)$. Then (homework problem!), p satisfies the pure diffusion equation

$$\frac{\partial p}{\partial t} \;=\; D\nabla^2 p\,.$$

Therefore, the "point-source" solution for p is the fundamental solution seen earlier. For example, in dimension 1,

$$p_0(x,t) = \frac{C}{\sqrt{4\pi D t}} \exp\left(-\frac{x^2}{4Dt}\right),$$

and therefore

$$c(x,t) \;=\; \frac{C}{\sqrt{4\pi D t}} \exp\left(\alpha t - \frac{x^2}{4Dt}\right).$$

Homework: Verify that this is indeed a solution (plug-into equation). Then show that the equipopulation contours $c =$ constant have $x \approx \beta t$ for large t, where β is some positive constant. That is to say, prove that, if $c(x,t) = c_0$ (for any fixed c_0 that you pick) then

$$\lim_{t\to\infty} \frac{x}{t} = \beta$$

for some β (which depends on the c_0 that you chose). (Hint: solve $\frac{C}{\sqrt{4\pi Dt}}\, e^{\alpha t - \frac{x^2}{4Dt}} = c_0$ for x and show that $x = \sqrt{a_1 t^2 + a_2 t + a_3 t \ln t}$ for some constants a_i.

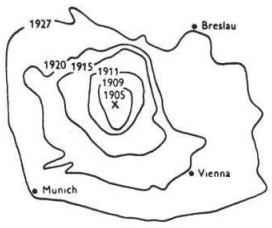
This is noteworthy because, in contrast to the population dispersing a distance proportional to $\sqrt{t}$ (as with pure diffusion), the distance is, instead, proportional to t (which is much larger than $\sqrt{t}$). One intuitive explanation is that reproduction increases the gradient (the "populated" area has an even larger population) and hence the flux.

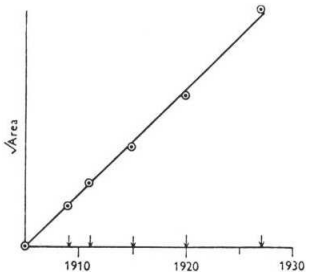
Similar results hold for the multivariate version, not just in dimension one.

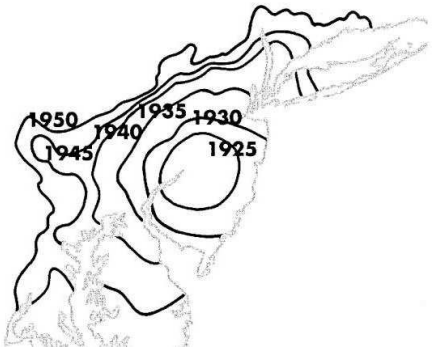
Skellam[62] studied the spread of muskrats (*Ondatra zibethica*, a large aquatic rodent that originated in North America) in central Europe. Although common in Europe nowadays, it appears that their spread in Europe originated when a Bohemian farmer accidentally allowed several muskrats to escape, about 50 kilometers southwest of Prague. Diffusion with exponential growth followed.

The next two figures show the equipopulation contours and a plot of the square root of areas of spread versus time. (The square root of the area would be proportional to the distance from the source, if the equipopulation contours would have been perfect circles. Obviously, terrain conditions and locations of cities make these contours not be perfect circles.) Notice the match to the prediction of a linear dependence on time.

The third figure is an example[63] for the spread of Japanese beetles *Popillia japonica* in the Eastern United States, with invasion fronts shown.







Remark. Continuing on the topic of the Remark in page 89, suppose that each particle in a population evolves according to a differential equation $dx/dt = f(x,t) + w$, where "w" represents a "noise" effect which, in the absence of the f term, would make the particles undergo purely random motion and the population density satisfy the diffusion equation with diffusion coefficient D. When both effects are superimposed, we obtain, for the density an equation like $\partial c/\partial t = -\mathrm{div}\,(cf) + D\nabla^2 c$. This is usually called a *Fokker-Planck* equation. (To be more precise, the Fokker-Planck equation describes a more general situation, in which the "noise" term affects the dynamics in a way that depends on the current value of x. We'll work out details in a future version of these notes.)

[62] J.G. Skellam, Random dispersal in theoretical populations, Biometrika 38: 196-218, 1951.

[63] from M.A. Lewis and S. Pacala, Modeling and analysis of stochastic invasion processes, J. Mathematical Biology 41, 387-429, 2000

10.8 Systems of PDE's

Of course, one often must study *systems* of partial differential equations, not just single PDE's.

We just discuss one example, that of diffusion with growth and nutrient depletion, since the idea should be easy to understand. This example nicely connects with the material that we started the course with.

We assume that a population of bacteria, with density $n(x,t)$, move at random (diffusion), and in addition also reproduce with a rate $K(c(x,t))$ that depends on the local concentration $c(x,t)$ of nutrient.

The nutrient is depleted at a rate proportional to its use, and it itself diffuses. Finally, we assume that there is a linear death rate kn for the bacteria.

A model is:

$$\begin{aligned} \frac{\partial n}{\partial t} &= D_n \nabla^2 n + (K(c) - k)n \\ \frac{\partial c}{\partial t} &= D_c \nabla^2 c - \alpha K(c) n \end{aligned}$$

where D_n and D_c are diffusion constants. The function $K(c)$ could be, for example, a Michaelis-Menten rate $K(c) = \frac{k\max c}{k_n + c}$

You should ask yourself, as a homework problem, what the equations would be like if c were to denote, instead, a toxic agent, as well as formulate other variations of the idea.

Another example, related to this one, is that of chemotaxis with diffusion. We look at this example later, in the context of analyzing steady state solutions.

11 Steady-State Behavior of PDE's

In the study of ordinary differential equations (and systems) $\frac{dX}{dt} = F(X)$, a central role is played by steady states, that is, those states X for which $F(X) = 0$.

The vector field is only "interesting" near such states. One studies their stability, often using linearizations, in order to understand the behavior of the system under small perturbations from the steady state, and also as a way to gain insight into the global behavior of the system.

For a partial differential equation of the form $\frac{\partial c}{\partial t} = F(c, c_x, c_{xx}, \ldots)$, where c_x, etc., denote partial derivatives with respect to space variables, or more generally for systems of such equations, one may also look for steady states, and steady states also play an important role.

It is important to notice that, for PDE's, in general finding steady states involves not just solving an algebraic equation like $F(X) = 0$ in the ODE case, but a partial differential equation. This is because setting $F(c, c_x, c_{xx}, \ldots)$ to zero is a PDE on the space variables. The solution will generally be a function of x, not a constant. Still, the steady state equation is in general easier to solve; for one thing, there are less partial derivatives (no $\frac{\partial c}{\partial t}$).

For example, take the diffusion equation, which we write now as:

$$\frac{\partial c}{\partial t} \;=\; \mathcal{L}(c)$$

and where "$\mathcal{L}$" is the operator $\mathcal{L}(c) = \nabla^2 c$. A steady state is a function $c(x)$ that satisfies $\mathcal{L}(c) = 0$, that is,

$$\nabla^2 c = 0$$

(subject to whatever boundary conditions were imposed). This is the *Laplace equation*.

We note (but we have no time to cover in the course) that one may study stability for PDE's via "spectrum" (i.e., eigenvalue) techniques for a linearized system, just as done for ODE's.

To check if a steady state c_0 of $\frac{\partial c}{\partial t} = F(c)$ is stable, one linearizes at $c = c_0$, leading to $\frac{\partial c}{\partial t} = Ac$, and then studies the stability of the zero solution of $\frac{\partial c}{\partial t} = Ac$. To do that, in turn, one must find the eigenvalues and eigenvectors (now eigen-functions) of A (now an operator on functions, not a matrix), that is, solve

$$Ac \;=\; \lambda c$$

(and appropriate boundary conditions) for nonzero functions $c(x)$ and real numbers λ. There are many theorems in PDE theory that provide analogues to "stability of a linear PDE is equivalent to all eigenvalues having negative real part". To see why you may expect such theorems to be true, suppose that we have found a solution of $Ac = \lambda c$, for some $c \not\equiv 0$. Then, the function

$$\hat{c}(x,t) \;=\; e^{\lambda t} c(x)$$

also solves the equation: $\frac{\partial \hat{c}}{\partial t} = A\hat{c}$. So, if for example, $\lambda > 0$, then $|\hat{c}(t,x)| \to \infty$ for those points x where $c(x) \neq 0$, as $t \to \infty$, and the zero solution is unstable. On the other hand, if $\lambda < 0$, then $\hat{c}(t,x) \to 0$.

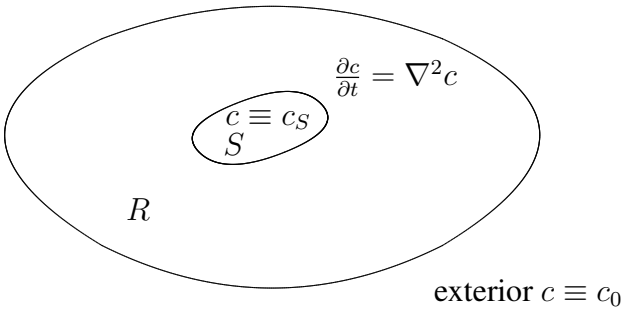
For the Laplace equation, it is possible to prove that there are a countably infinite number of eigenvalues. If we write $\mathcal{L} = -\nabla^2 c$ (the negative is more usual in mathematics, for reasons that we will not explain here), then the eigenvalues of $\mathcal{L}$ form a sequence $0 < \lambda_0 < \lambda_1 < \ldots$, with $\lambda_n \to \infty$ as $n \to \infty$, when Dirichlet conditions (zero at boundary) are imposed, and $0 = \lambda_0 < \lambda_1 < \ldots$

when Neumann conditions (no-flux) are used. The eigenvectors that one obtains for domains that are intervals are the trigonometric functions that we found when solving by separation of variables (the eigenvalue/eigenvector equation, for one space variable, is precisely $X''(x) + \lambda X = 0$).

In what follows, we just study steady states, and do not mention stability. (However, the steady states that we find turn out, most of them, to be stable.)

11.1 Steady State for Laplace Equation on Some Simple Domains

Many problems in biology (and other fields) involve the following situation. We have two regions, R and S, so that R "wraps around" S. A substance, such as a nutrient, is at a constant concentration, equal to c_0, on the exterior of R. It is also constant, equal to some other value c_S (typically, $c_S = 0$) in the region S. In between, the substance diffuses. See this figure:



Examples abound in biology. For example, R might be a cell membrane, the exterior the extra-cellular environment, and S the the cytoplasm.
In a different example, R might represent the cytoplasm and S the nucleus.
Yet another variation (which we mention later) is that in which the region R represents the immediate environment of a single-cell organism, and the region S is the organism itself.

In such examples, the external concentration is taken to be constant because one assumes that nutrients are so abundant that they are not affected by consumption. The concentration in S is also assumed constant, either because S is very large (this is reasonable if S would the cytoplasm and R the cell membrane) or because once nutrients enter S they get absorbed immediately (and so the concentration in S is $c_S = 0$).

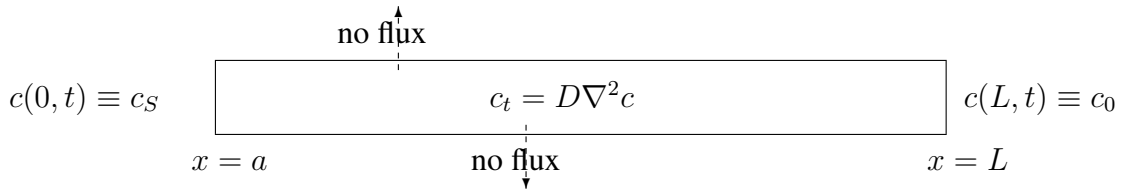
Other examples typically modeled in this way include chemical transmitters at synapses, macrophages fighting infection at air sacs in lungs, and many others.

In this Section, we only study steady states, that is, we look for solutions of $\nabla^2 c = 0$ on R, with boundary conditions c_S and c_0.

Dimension 1

We start with the one-dimensional case, where S is the interval $[0, a]$, for some $a \geq 0$, and R is the interval $[a, L]$, for some $L > a$.

We view the space variable x appearing in the concentration $c(x, t)$ as one dimensional. However, one could also interpret this problem as follows: S and R are cylinders, there is no flux in the directions orthogonal to the x-axis, and we are only interested in solutions which are constant on cross-sections.



The steady-state problem is that of finding a function c of one variable satisfying the following ODE and boundary conditions:

$$D\frac{d^2c}{dx^2} \;=\; 0\,, \quad c(a) = c_S\,,\; c(L) = c_0\,.$$

Since $c'' = 0$, $c(x)$ is linear, and fitting the boundary conditions gives the following unique solution:

$$c(x) \;=\; c_S \;+\; (c_0 - c_S)\,\frac{x-a}{L-a}\,.$$

Notice that, therefore, the gradient of c is $\frac{dc}{dx} = \frac{c_0 - c_S}{L-a}$.

Since, in general, the flux due to diffusion is $-D\nabla c$, we conclude that the flux is, in steady-state, the following constant:

$$J \;=\; -\frac{D}{L-a}(c_0 - c_S)\,.$$

Suppose that $c_0 > c_S$. Then $J < 0$. In other words, an amount $\frac{D}{L-a}(c_0 - c_S)$ of nutrient transverses (from right to the left) the region $R = [a, L]$ per unit of time and per unit of cross-sectional area.

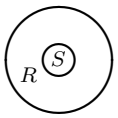
This formula gives an "Ohm's law for diffusion across a membrane" when we think of R as a cell membrane. To see this, we write the above equality in the following way:

$$c_S - c_0 \;=\; J\,\frac{L-a}{D}$$

which makes it entirely analogous to Ohm's law in electricity, $V = IR$. We interpret the potential difference V as the difference between inside and outside concentrations, the flux as current I, and the resistance of the circuit as the length divided by the diffusion coefficient. (Faster diffusion or shorter length results in less "resistance".)

Radially Symmetric Solutions in Dimensions 2 and 3

In dimension 2, we assume now that S is a disk of radius a and R is a washer with outside radius L. For simplicity, we take the concentration in S to be $c_S = 0$.



Since the boundary conditions are radially symmetric, we look for a radially symmetric solution, that is, a function c that depends only on the radius r.

Recalling the formula for the Laplacian as a function of polar coordinates (previous homework), the diffusion PDE is:

$$\frac{\partial c}{\partial t} \;=\; \frac{D}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c}{\partial r}\right)\,, \quad c(a,t) = 0\,,\; c(L,t) = c_0\,.$$

Since we are looking only for a steady-state solution, we set the right-hand side to zero and look for $c = c(r)$ such that

$$(rc')' = 0 \quad c(a) = 0\,,\ c(L) = c_0\,,$$

where prime indicates derivative with respect to r.

Homework: show that the solution is

$$c(r) \ = \ c_0 \frac{\ln(r/a)}{\ln(L/a)}\,.$$

Similarly, in dimension 3, taking S as a ball of radius a and R as the spherical shell with inside radius a and outside radius L, we have:

$$\frac{\partial c}{\partial t} \ = \ \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right)\,, \quad c(t,a) = 0\,,\ c(L,t) = c_0$$

Homework: show that the solution is

$$c(r) \ = \ \frac{Lc_0}{L-a}\left(1 - \frac{a}{r}\right)\,.$$

Notice the different forms of the solutions in dimensions 1, 2, and 3.

In the dimension 3 case, the derivative of c in the radial direction is, therefore:

$$c'(r) \ = \ \frac{Lc_0 a}{(L-a)r^2}\,.$$

We now specialize to the example in which the region R represents the environment surrounding a single-cell organism, the region S is the organism itself, and c models nutrient concentration.

We assume that the concentration of nutrient is constant far away from the organism, let us say farther than distance L, and $L \gg a$.

Then $c'(r) = \frac{c_0 a}{(1-a/L)r^2} \approx \frac{c_0 a}{r^2}$.

In general, the steady-state flux due to diffusion, in the radial direction, is $-Dc'(r)$. In particular, on the boundary of S, where $r = a$, we have:

$$J = -\frac{Dc_0}{a}\,.$$

Thus $-J$ is the amount of nutrient that passes, in steady state, through each unit of area of the boundary, per unit of time. (The negative sign because the flow is toward the inside, i.e. toward smaller r, since $J < 0$.)

Since the boundary of S is a sphere of radius a, it has surface area $4\pi a^2$. Therefore, nutrients enter S at a rate of

$$\frac{Dc_0}{a} \times 4\pi a^2 \ = \ 4\pi D c_0 a$$

per unit of time.

On the other hand, the metabolic need is roughly proportional to the volume of the organism. Thus, the amount of nutrients needed per unit of time is:

$$\frac{4}{3}\pi a^3 M\,,$$

where M is the metabolic rate per unit of volume per unit of time.

For the organism to survive, enough nutrients must pass through its boundary. If diffusion is the only mechanism for nutrients to come in, then survivability imposes the following constraint:

$$4\pi D c_0 a \;\geq\; \frac{4}{3}\pi a^3 M\,,$$

that is,

$$a \;\leq\; a_{\text{critical}} \;=\; \sqrt{\frac{3Dc_0}{M}}\,.$$

Phytoplankton[64] are free-floating aquatic organisms, and use bicarbonate ions (which enter by diffusion) as a source of carbon for photosynthesis, consuming one mole of bicarbonate per second per cubic meter of cell. The concentration of bicarbonate in seawater is about 1.5 moles per cubic meter, and $D \approx 1.5 \times 10^{-9} m^2 s^{-1}$. This gives

$$a_{\text{critical}} \;=\; \sqrt{3 \times 1.5 \times 10^{-9} \times 1.5\, m^2} \;\approx\; 82 \times 10^{-6}\, m = 82\,\mu m\,(\text{microns})\,.$$

This is, indeed, about the size of a typical "diatom" in the sea.

Larger organisms must use active transport mechanisms to ingest nutrients!

11.2 Steady States for a Diffusion/Chemotaxis Model

A very often used model that combines diffusion and chemotaxis is due to Keller and Segel. The model simply adds the diffusion and chemotaxis fluxes. In dimension 1, we have, then:

$$\frac{\partial c}{\partial t} \;=\; -\text{div}\, J \;=\; -\,\frac{\partial}{\partial x}\left(\alpha\, c\, V' - D\frac{\partial c}{\partial x}\right)\,.$$

We assume that the bacteria live on the one-dimensional interval $[0, L]$ and that no bacteria can enter or leave through the endpoints. That is, we have no flux on the boundary:[65]

$$J(0,t) = J(L,t) = 0 \quad \forall\, t\,.$$

Let us find the steady states.

Setting $\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = 0$, and viewing now c as a function of x alone, and using primes for $\frac{d}{dx}$, gives:

$$J = \alpha\, c\, V' - Dc' \;=\; J_0 \quad (\text{some constant})\,.$$

[64] We borrow this example from M. Denny and S. Gaines, *Chance in Biology*, Princeton University Press, 2000. The authors point out there that the metabolic need is more accurately proportional, for multicellular organisms, to (mass)$^{3/4}$, but it is not so clear what the correct scaling law is for unicellular ones.

[65] Notice that this is not the same as asking that $\frac{\partial c}{\partial x}(0,t) = \frac{\partial c}{\partial x}(L,t) = 0$. The density might be constant near a boundary, but this does not mean that the population will not get redistributed, since there is also movement due to chemotaxis. Only for a pure diffusion, when $J = -D\frac{\partial c}{\partial x}$, is no-flux the same as $\frac{\partial c}{\partial x} = 0$.

Since $J_0 = 0$, because it vanishes at the endpoints, we have that $(\ln c)' = c'/c = -(\alpha V/D)'$, and therefore

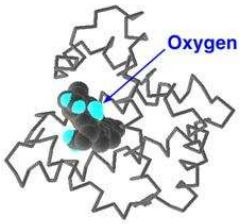
$$c \;=\; k\,\exp(\alpha V/D)$$

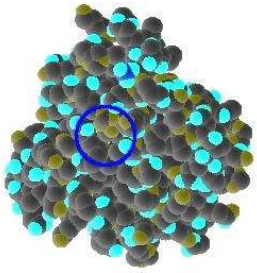
for some constant. Thus, the steady state concentration is proportional to the exponential of the nutrient concentration, which is definitely not something that would be obvious.

11.3 Facilitated Diffusion

Let us now work out an example[66] involving a *system* of PDE's, diffusion, chemical reactions, and quasi-steady state approximations.

Myoglobin[67] is a protein that helps in the transport of oxygen in muscle fibers. The binding of oxygen to myoglobin results in oxymyoglobin, and this binding results in enhanced diffusion.





The facilitation of diffusion is somewhat counterintuitive, because the Mb molecule is much larger than oxygen (about 500 times larger), and so diffuses slower. A mathematical model helps in understanding what happens, and in quantifying the effect.

In the model, we take a muscle fibre to be one-dimensional, and no flux of Mb and MbO_2 in or out. (Only unbound oxygen can pass the boundaries.)

$$s(0,t) \equiv s_0 \qquad \underset{x=0}{\boxed{s = O_2,\; e = Mb,\; c = MbO_2}} \qquad \underset{x=L}{s(L,0) \equiv s_L \ll s_0}$$

The chemical reaction is just that of binding and unbinding:

$$O_2 + Mb \underset{k_-}{\overset{k_+}{\rightleftarrows}} MbO_2$$

[66] Borrowing from J.P. Keener and J. Sneyd, Mathematical Physiology, Springer-Verlag New York, 1998.

[67] From Protein Data Bank, PDB, http://www.rcsb.org/pdb/molecules/mb3.html:
"myoglobin is where the science of protein structure really began... John Kendrew and his coworkers determined the atomic structure of myoglobin, laying the foundation for an era of biological understanding"
"The iron atom at the center of the heme group holds the oxygen molecule tightly. Compare the two pictures. The first shows only a set of thin tubes to represent the protein chain, and the oxygen is easily seen. But when all of the atoms in the protein are shown in the second picture, the oxygen disappears, buried inside the protein."
"So how does the oxygen get in and out, if it is totally surrounded by protein? In reality, myoglobin (and all other proteins) are constantly in motion, performing small flexing and breathing motions. Temporary openings constantly appear and disappear, allowing oxygen in and out. The structure in the PDB is merely one snapshot of the protein, caught when it is in a tightly-closed form"

with equations:

$$\begin{aligned}\frac{\partial s}{\partial t} &= D_s \frac{\partial^2 s}{\partial x^2} + k_- c - k_+ se \\ \frac{\partial e}{\partial t} &= D_e \frac{\partial^2 e}{\partial x^2} + k_- c - k_+ se \\ \frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} - k_- c + k_+ se\,,\end{aligned}$$

where we assume that $D_e = D_c$ (since Mb and MbO_2 have comparable sizes). The boundary conditions are $\frac{\partial e}{\partial x} = \frac{\partial c}{\partial x} \equiv 0$ at $x = 0, L$, and $s(0) = s_0$, $s(L) = s_L$.

We next do a steady-state analysis of this problem, setting:

$$\begin{aligned}D_s s_{xx} + k_- c - k_+ se &= 0 \\ D_e e_{xx} + k_- c - k_+ se &= 0 \\ D_c c_{xx} - k_- c + k_+ se &= 0\end{aligned}$$

Since $D_e = D_c$, we have that $(e + c)_{xx} \equiv 0$.
So, $e + c$ is a linear function of x, whose derivative is zero at the boundaries (no flux).
Therefore, $e + c$ is constant, let us say equal to e_0.

On the other hand, adding the first and third equations gives us that

$$(D_s s_x + D_c c_x)_x \;=\; D_s s_{xx} + D_c c_{xx} \;=\; 0\,.$$

This means that $D_s s_x + D_c c_x$ is also constant:

$$D_s s_x + D_c c_x \;=\; -J\,.$$

Observe that J is the *the total flux of oxygen* (bound or not), since it is the sum of the fluxes $-D_s s_x$ of $s = O_2$ and $-D_c c_x$ of $c = MbO_2$.

Let $f(x) = D_s s(x) + D_c c(x)$. Since $f' = -J$, it follows that $f(0) - f(L) = JL$, which means:

$$J \;=\; \frac{D_s}{L}\,(s_0 - s_L) + \frac{D_c}{L}\,(c_0 - c_L)$$

(where one knows the oxygen concentrations s_0 and s_L, but not necessarily c_0 and c_L).

We will next do a quasi-steady state approximation, under the hypothesis that D_s is very small compared to the other numbers appearing in:

$$D_s s_{xx} + k_- c - k_+ s(e_0 - c) \;=\; 0$$

and this allows us to write[68]

$$c \;=\; e_0\,\frac{s}{K + s}$$

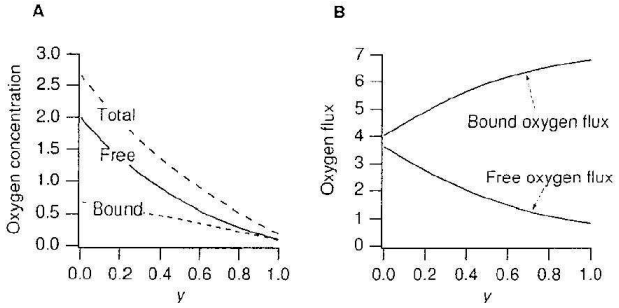
[68]Changing variables $\sigma = (k_+/k_-)s$, $u = c/e_0$, and $y = x/L$, one obtains $\varepsilon \sigma_{yy} = \sigma(1 - u) - u$, $\varepsilon = D_s/(e_0 k_+ L^2)$. A typical value of ε is estimated to be $\varepsilon \approx 10^{-7}$. This says that $\sigma(1 - u) - u \approx 0$, and from here one can solve for u as a function of σ, or equivalently, c as a function of s.

where $K = k_-/k_+$. This allows us, in particular, to substitute c_0 in terms of s_0, and c_L in terms of s_L, in the above formula for the flux, obtaining:

$$J \;=\; \frac{D_s}{L}\,(s_0 - s_L) + \frac{D_c}{L} e_0 \left(\frac{s_0}{K + s_0} - \frac{s_L}{K + s_L} \right) .$$

This formula exhibits the flux as sum of the "Ohm's law" term plus plus a term that depends on diffusion constant D_c of myoglobin.
(Note that this second term, which quantifies the advantage of using myoglobin, is positive, since $s/(K+s)$ is increasing.)

With a little more work, which we omit here[69], one can solve for $c(x)$ and $s(x)$, using the quasi-steady state approximation. These are the graphs that one obtains, for the concentrations and fluxes respectively, of bound and free oxygen (note that the total flux J is constant, as already shown):



An intuition for why myoglobin helps is as follows. By binding to myoglobin, there is less free oxygen near the left endpoint. As the boundary conditions say that the concentration is s_0 outside, there is more flow into the cell (diffusion tends to equalize). Similarly, at the other end, the opposite happens, and more flows out.

11.4 Density-Dependent Dispersal

Here is yet another example[70] of modeling with a system of PDE's and steady-state calculations.

Suppose that the flux is proportional to $-c\nabla c$, not to $-\nabla c$ as with diffusion: a transport-like equation, where the velocity is determined by the gradient. In the scalar case, this would mean that the flux is proportional to $-cc_x$, which is the derivative of $-c^2$. Such a situation would occur if, for instance, overcrowding encourages more movement.

To make the problem even more interesting, assume that there are two interacting populations, with densities u and v respectively, and each moves with a velocity that is proportional to the gradient of the *total* population $u + v$.

We obtain these equations:

$$\begin{aligned} \frac{\partial u}{\partial t} &= -\nabla\left(-\alpha u \nabla(u+v)\right) \\ \frac{\partial v}{\partial t} &= -\nabla\left(-\beta v \nabla(u+v)\right) \end{aligned}$$

[69] see the Keener-Sneyd book for details
[70] from Keshet's book

and, in particular, in dimension 1:

$$\begin{aligned}\frac{\partial u}{\partial t} &= \alpha\frac{\partial}{\partial x}\left(u\frac{\partial(u+v)}{\partial x}\right)\\ \frac{\partial v}{\partial t} &= \beta\frac{\partial}{\partial x}\left(v\frac{\partial(u+v)}{\partial x}\right).\end{aligned}$$

Let us look for steady states: $u = u(x)$ and $v = v(x)$ solving (with $u' = \frac{\partial u}{\partial x}$, $v' = \frac{\partial v}{\partial x}$):

$$(u(u+v)')' \;=\; (v(u+v)')' \;=\; 0\,.$$

There must exist constants c_1, c_2 so that:

$$u(u+v)' = c_1\,,\; v(u+v)' = c_2\,.$$

We study three separate cases:
(1) $c_1 = c_2 = 0$
(2) $c_2 \neq 0$ and $c_1 = 0$,
(3) $c_1 c_2 \neq 0$
(the case $c_1 \neq 0$ and $c_2 = 0$ is similar to (2)).

Case (1):
here $[(u+v)^2]' = 2(u+v)(u+v)' = u(u+v)' + v(u+v)' = 0$, so $u+v$ is constant. That's the best that we can say.

Case (2):

$$c_2 \neq 0 \;\Rightarrow v(x) \neq 0, (u+v)'(x) \neq 0\;\forall\, x\,.$$

Also,

$$c_1 = 0 \;\Rightarrow u \equiv 0 \;\Rightarrow vv' \equiv c_2 \;\Rightarrow (v^2)' \equiv 2c_2$$

implies $v^2 = 2c_2 x + K$ for some constant K, so (taking the positive square root, because $v \geq 0$, being a population):

$$v \;=\; \sqrt{2c_2 x + K}\,, \quad u \equiv 0\,.$$

Case (3):
Necessarily $u(x) \neq 0$ and $v(x) \neq 0$ for all x, so can divide and obtain:

$$(u+v)' = \frac{c_1}{u} = \frac{c_2}{v}\,.$$

Hence $u = (c_1/c_2)v$ can be substituted into $u' + v' = \frac{c_2}{v}$ to obtain $(1 + c_1/c_2)v' = c_2/v$, i.e. $vv' = c_2/(1 + c_1/c_2)$, or $(v^2)' = 2c_2/(1 + c_1/c_2)$, from which:

$$v^2(x) = \frac{2c_2 x}{1 + c_1/c_2} + K$$

for some K, and so:

$$v(x) = \left(\frac{2c_2 x}{1 + c_2/c_1} + K\right)^{1/2}.$$

Since $u = (c_1/c_2)v$,

$$u(x) = \left(\frac{2c_1 x}{1 + c_1/c_2} + K c_1^2/c_2^2\right)^{1/2}.$$

12 Traveling Wave Solutions of Reaction-Diffusion Systems

It is rather interesting that reaction-diffusion systems can exhibit traveling-wave behavior. Examples arise from systems exhibiting bistability, such as the developmental biology examples considered earlier, or, in a more complicated system form, for species competition.

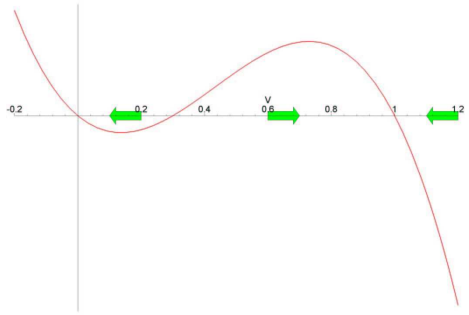
The reason that this is surprising is that diffusion times tend to scale like the square root of distance, not linearly. (But we have seen a similar phenomenon when discussing diffusion with exponential growth.)

We illustrate with a simple example, the following equation:

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + f(V)$$

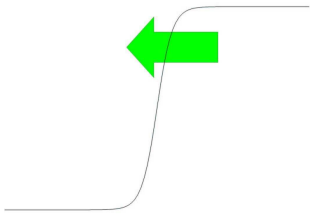
where f is a function that has zeroes at $0, \alpha, 1$, $\alpha < 1/2$, and satisfies:

$$f'(0) < 0, \;\; f'(1) < 0, \;\; f'(\alpha) > 0$$



so that the differential equation $dV/dt = f(V)$ by itself, without diffusion, would be a bistable system.[71]

We would like to know if there's any solution that looks like a "traveling front" moving to the left (we could also ask about right-moving solutions, or course).



In other words, we look for $V(x,t)$ such that, for some "waveform" U that "travels" at some speed c, V can be written as a translation of U by ct:

$$V(x,t) = U(x+ct)\,.$$

In accordance with the above picture, we also want that these four conditions hold:

$$V(-\infty,t) = 0\,,\;\; V(+\infty,t) = 1\,,\;\; V_x(-\infty,t) = 0\,,\;\; V_x(+\infty,t) = 0\,.$$

[71] Another classical example is that in which f represents logistic growth. That is the Fisher equation, which is used in genetics to model the spread in a population of a given allele.

The key step is to realize that the PDE for V induces an ordinary differential equation for the waveform U, and that these boundary conditions constrain what U and the speed c can be.

To get an equation for U, we plug-in $V(x,t) = U(x+ct)$ into $V_t = V_{xx} + f(V)$, obtaining:

$$cU' \;=\; U'' + f(U)\,.$$

Furthermore, $V(-\infty,t) = 0$, $V(+\infty,t) = 1$, $V_x(-\infty,t) = 0$, $V_x(+\infty,t) = 0$ translate into:

$$U(-\infty) = 0\,,\; U(+\infty) = 1\,,\; U'(-\infty) = 0\,,\; U'(+\infty) = 0\,.$$

The theory can be developed quite generally, but here we'll only study in detail this very special case:

$$f(V) = -A^2 V(V-\alpha)(V-1)$$

which is easy to treat with explicit formulas.

Since U will satisfy $U' = 0$ when $U = 0, 1$, we *guess* the functional relation:

$$U'(\xi) \;=\; BU(\xi)\,(1-U(\xi))$$

(note that we are looking for a U satisfying $0 \leq U \leq 1$, so $1-U \geq 0$). We write "ξ" for the argument of U so as to not confuse it with x.

We substitute $U' = BU(1-U)$ and (taking derivatives of this expression)

$$U'' = B^2 U(1-U)(1-2U)$$

into the differential equation $cU' = U'' + A^2 U(U-\alpha)(U-1)$, and cancel $U(U-1)$, obtaining (do the calculation as a homework problem):

$$B^2(2U-1) + cB - A^2(U-\alpha) \;=\; 0\,.$$

Since U is not constant (because $U(-\infty) = 0$ and $U(+\infty) = 1$), this means that we can compare coefficients of U in this expression, and conclude: that $2B^2 - A^2 = 0$ and $-B^2 + cB + \alpha A^2 = 0$. Therefore:

$$B = A/\sqrt{2}\,, \quad c = \frac{(1-2\alpha)A}{\sqrt{2}}\,.$$

Substituting back into the differential equation for U, we have:

$$U' \;=\; BU(1-U) \;=\; \frac{A}{\sqrt{2}} U(1-U)\,,$$

an ODE that now does not involve the unknown B. We solve this ODE by separation of variables and partial fractions, using for example $U(0) = 1/2$ as an initial condition, getting:

$$U(\xi) \;=\; \frac{1}{2}\left[1 + \tanh\left(\frac{A}{2\sqrt{2}}\xi\right)\right]$$

(obtain this solution, as a homework problem). Finally, since $V(x,t) = U(x+ct)$, we conclude that:

$$V(x,t) \;=\; \frac{1}{2}\left[1 + \tanh\left(\frac{A}{2\sqrt{2}}\,(x-ct)\right)\right]$$

where $c = \frac{(1-2\alpha)A}{\sqrt{2}}$.

Observe that the speed c was uniquely determined; it will be larger if $\alpha \approx 0$, or if the reaction is stronger (larger A). This is not surprising! (Why?)

General Case

To study the general case (f not the explicit cubic that we used), we look at the following set of two ODE's for U and its derivative (using "$'$" for $d/d\xi$):

$$\begin{aligned} U' &= W \\ W' &= -f(U) + cW \,. \end{aligned}$$

The steady states satisfy $W = 0$ and $f(U) = 0$, so they are $(0,0)$ and $(1,0)$. The Jacobian is

$$J = \begin{pmatrix} 0 & 1 \\ -f' & c \end{pmatrix}$$

and has determinant $f' < 0$ at the steady states, so they are both saddles. The conditions on U translate into the requirements that:

$$(U, W) \to (0,0) \text{ as } \xi \to -\infty \text{ and } (U, W) \to (1,0) \text{ as } \xi \to \infty$$

for the function $U(\xi)$ and its derivative, seen as a solution of this system of two ODE's. (Note that "ξ" is now "time".) In dynamical systems language, we need to show the existence of an "heteroclinic connection" between these two saddles. One first proves that, for $c \approx 0$ and $c \gg 1$, there result trajectories that "undershoot" or "overshoot" the desired connection, so, by a continuity argument (similar to the intermediate value theorem), there must be some value c for which the connection exactly happens. Details are given in many mathematical biology books.