

2.4 Linearization and stability

The harmonic oscillator is an interesting problem, but we don't teach you about it because we expect you to encounter lots of masses and springs in your scientific career. Rather, it is an example of how one can analyze a system to reveal its stability and oscillations. To place this in a more general context, realize that our standard problem

$$m \frac{d^2x}{dt^2} + \gamma \frac{dx}{dt} + \kappa x = 0 \quad (2.190)$$

is a linear differential equation with constant coefficients. “Linear” because the variable x appears only raised to the first power (that is, there are no terms like x^2 or x^3), and “constant coefficients” because there is no explicit dependence on time. We have learned that equations like this can be solved by looking for solutions of the form $x(t) = Ae^{\lambda t}$, and that such solutions can be found provided that λ takes on some very specific values. If the allowed values of λ have imaginary parts, then this signals an oscillation. If the real part of λ is negative, then any initial displacement will decay with time, while if the real part of λ were positive this would mean that initial displacements grow—in fact blow up—with time (although we haven't seen an example of this yet). In this lecture we'd like to show you how these same ideas can be used in very different contexts.

Consider the all too familiar interaction between a loudspeaker and a microphone, as sketched in Fig 2.6. A modern electrostatic loudspeaker is essentially a stiff plate, and when we apply a voltage $V(t)$ this generates a force on the plate. So the equation describing the displacement $x(t)$ of the plate is pretty simple:

$$\kappa x(t) = aV(t), \quad (2.191)$$

where the constant a is a property of the particular loudspeaker we are looking at.⁴ When the loudspeaker moves, it generates a sound pressure $p(t)$ where we are standing. But because sound propagates through the air at finite speed, the sound pressure that the microphone detects at time t must be related to the motion of loudspeaker at some time $t - \tau$ in the past, where τ is the time for propagation of the sound waves. Again this is a simplification, since in the real world there are many paths from loudspeaker

⁴Clearly this can't be exactly true: If we change the voltage quickly enough, the plate can't possibly follow instantaneously. But it's a good approximation over some range of conditions that we care about in practice, and in fact loudspeakers are designed in part to make this a approximation work as well as possible.

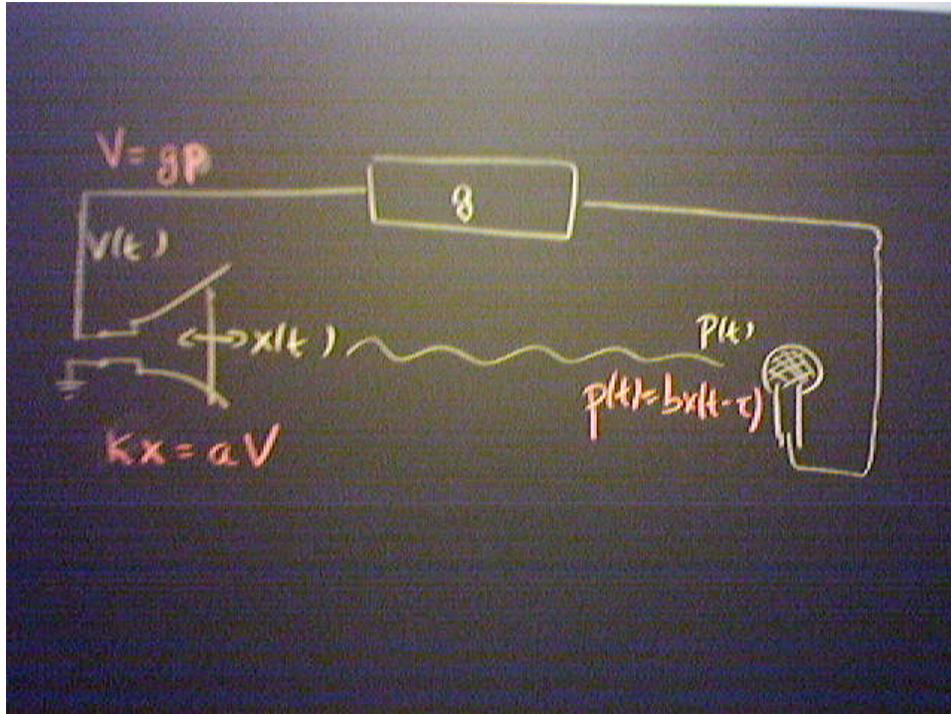


Figure 2.6: A loudspeaker generates sound, and a microphone picks up these signals. Inevitably, there is some feedback. In the text we analyze this to explain the howling instabilities that we all have experienced.

to microphone (echoing off the walls of the room, for example), each of which has its own time delay; here we're going to approximate that there is just one path with one delay. Thus we have

$$p(t) = bx(t - \tau), \quad (2.192)$$

where b is a constant that measures the efficiency of the loudspeaker.

The whole point of the the microphone, of course, is that sound pressure gets converted into an electrical voltage that we can use to drive the loudspeaker. There is some factor g that expresses the “gain” in this transformation; if we have an amplifier in the system then turning the knob on the amplifier adjusts this gain:

$$V(t) = gp(t). \quad (2.193)$$

Putting all of these thing together we have

$$\kappa x(t) = aV(t)$$

$$= agp(t) \quad (2.194)$$

$$= agbx(t - \tau) \quad (2.195)$$

$$x(t) = \frac{agb}{\kappa}x(t - \tau). \quad (2.196)$$

It's useful to call the combination of parameters $agb/\kappa = G$, so the dynamics of our system is determined simply by

$$x(t) = Gx(t - \tau). \quad (2.197)$$

It is interesting that Eq (2.197) looks nothing like the differential equations we have been solving. In fact, there are no derivatives, just a delay. Still, the equation is linear, so we might try our usual trick of looking for solutions in the form $x(t) = Ae^{\lambda t}$. Substituting, we find:

$$\begin{aligned} x(t) &= Gx(t - \tau) \\ Ae^{\lambda t} &= GAe^{\lambda(t-\tau)} \end{aligned} \quad (2.198)$$

$$= GAe^{-\lambda\tau}e^{\lambda t}. \quad (2.199)$$

As usual, we can divide through by A and by $e^{\lambda t}$, to obtain

$$1 = Ge^{-\lambda\tau}, \quad (2.200)$$

or equivalently

$$e^{\lambda\tau} = G. \quad (2.201)$$

This looks easy to solve: take the (natural) log of both sides, then divide through by τ :

$$\begin{aligned} e^{\lambda\tau} &= G \\ \lambda\tau &= \ln G \end{aligned} \quad (2.202)$$

$$\lambda = \frac{\ln G}{\tau}. \quad (2.203)$$

We see that if $G < 1$, then λ will be negative, but if $G > 1$ then λ will be positive. Since our solutions are of the form $x(t) \sim e^{\lambda t}$, positive λ means that the displacement of the loudspeaker will blow up with time. This certainly starts to seem like an explanation of what happens in real life: if we have too large a gain in our amplifier (g and hence G is too big), then the “feedback” from microphone to amplifier can lead to an instability in which the system starts to make its own sounds. The sound pressure can rise from the point where we barely hear it to the point where it is painful, which corresponds to p or x growing by a factor of 10^6 .

Actually we don't quite have a theory of the blow up in our audio system. So far, $x(t)$ is growing exponentially, but it's not oscillating. We know that the real instabilities of audio systems occur with the sound pressure oscillating at some frequency, since we hear (admittedly badly tuned) 'notes' or whistles. Are these somehow hiding in our equations?

We are trying to solve the equation $\exp(\lambda\tau) = G$. We have found one solution, but is this the unique solution? Recall that

$$\exp(2\pi i) = 1, \quad (2.204)$$

and also that

$$[\exp(2\pi i)]^2 = \exp(4\pi i) = 1, \quad (2.205)$$

and so on, so that

$$\exp(2n\pi i) = 1, \quad (2.206)$$

for any integer $n = \pm 1, \pm 2, \pm 3, \dots$. This means that once we open our minds to complex numbers, taking logarithms is no longer so easy. For example, we can write that

$$e^{\ln 3} = 3. \quad (2.207)$$

But it's also true that

$$e^{\ln 3} e^{2\pi i} = e^{\ln 3 + 2\pi i} = 3. \quad (2.208)$$

So when take the natural log of 3 we might mean what we always meant by the number $\ln 3$, but we might also mean $\ln 3 + 2\pi i$, and it's worse because we could mean $\ln 3 \pm 2\pi i$, $\ln 3 \pm 4\pi i$, and so on. All this craziness means that our simple equation $\exp(\lambda\tau) = G$ actually has many solutions:

$$\lambda\tau = \ln G \pm 2n\pi i \quad (2.209)$$

$$\lambda = \frac{\ln G}{\tau} \pm i \frac{2n\pi}{\tau}, \quad (2.210)$$

where $n = 0, 1, 2, \dots$. Now we see that λ can have imaginary parts, at frequencies which are integer multiples of $\omega = 2\pi/\tau$.

So, what we have seen is that our trick of looking for solutions in the form $x \sim e^{\lambda t}$ allows to understand what happens in the microphone-loudspeaker system. There are oscillations with a frequency such that the period matches the delay, which makes sense because this is the condition that the signal from the microphone reinforces the motion of the loudspeaker. In fact there isn't a single frequency, but a whole set of "harmonics" at integer multiples

of a “fundamental” frequency, just like when we play a note on a musical instrument. If the gain of the amplifier in the system is small, then these oscillations die away, but if the gain becomes too large then there is an instability and the amplitude of the oscillations will grow exponentially. Presumably this is stopped by the fact that amplifier can’t put out infinite power.

Problem 40: The time τ which appears in our analysis of the loudspeaker and microphone is the time for sound to propagate from one element to the other. Given that the speed of sound is 330 m/s in air, what are typical values of τ in a classroom? The difference between a barely audible sound and one that is painful is a factor of $\sim 10^6$ in p ; if we set the amplifier so that the gain $G = 2$, how long should it take for the signal to grow by this amount? Does this make sense in terms of your experience?

Problem 41: One can think of the mechanics of muscles as having two components—a passive part that is mostly stiffness and drag, and an active part in which the muscle generates extra force when you pull on it. If we call this active force $F_{\text{active}}(t)$, then the length of the muscle should obey the differential equation

$$\gamma \frac{dL(t)}{dt} + \kappa L(t) = F_{\text{active}}(t), \quad (2.211)$$

where as usual γ describes the drag and κ the stiffness. Consider a simple model for the dynamics of $F_{\text{active}}(t)$: The active force acts like a stiffness, but it takes a little while to develop in response to the changes in muscle length. An equation that can describe this is

$$\tau \frac{dF_{\text{active}}(t)}{dt} + F_{\text{active}}(t) = -\kappa' L(t), \quad (2.212)$$

where τ is (roughly) the time it takes for the active force to develop and κ' is the “active stiffness.” Look for a solution of the form $L(t) = L_0 \exp(\lambda t)$ and $F_{\text{active}}(t) = F_0 \exp(\lambda t)$.

(a.) Show that a solution of this form does work provided that L_0 , F_0 and λ obey some conditions. Write these conditions as two equations for these three variables.

(b.) Show that the two equations you found in [a] are equivalent to a single quadratic equation for λ , as in the case of the harmonic oscillator. Hint: First use one of the equations to solve for F_0 , then substitute into the second equation. You should find that L_0 drops out, leaving just one equation for λ .

(c.) In general, what is the condition on λ that corresponds to underdamped oscillations?

(d.) For this particular problem, what is the condition that all the parameters have to obey in order to generate underdamped oscillations? If the “active stiffness” κ' is big enough, will this generate oscillations?

(e.) Does anything special happen when the time scale for the active force τ matches the time scale for relaxation of the passive dynamics, $\tau_0 = \gamma/\kappa$?

Problem 42: There is a process that synthesizes molecule A at a constant rate s (as in “zeroth order” kinetics). Once synthesized, these molecules decay into B with a first order rate constant k_{AB} , and B decays into C with another first order rate constant k_{BC} :



The B molecules also have the unusual feature that they act as a catalyst, causing A to convert directly into C through a second order reaction with rate constant k_2 :



- (a.) What are the units of all the parameters in the problem, s , k_{AB} , k_{BC} and k_2 ?
- (b.) Write out the differential equations that describe the concentrations of A and B . Start by assuming $k_2 = 0$, so that only the reactions in (1) are occurring. How are the equations changed by including the catalytic reaction in (2)?
- (c.) Find the steady state concentrations, $[A] = \bar{A}$ and $[B] = \bar{B}$, that will stay unchanged over time. Again, start with the easier case in which $k_2 = 0$ and then see how things change when the catalytic reaction is significant.
- (d.) Assume that concentrations of A and B are close to their steady state values, and find the linear differential equations that describe the final approach to the steady state. Hint: think about the approach to terminal velocity in mechanics. Note: You can keep these equations in terms of \bar{A} and \bar{B} ; there is no need to substitute from [c].
- (e.) Show that if $k_2 = 0$, then the concentrations of A and B will relax to their steady state values as exponential decays.
- (f.) Can the equations in [d] describe oscillations when we include the effects of k_2 ?

To emphasize the generality of these ideas, let’s look at something completely different. Every cell in your body has the same DNA. Sequences along the DNA code for proteins, but what makes different cells (e.g., in your liver and your brain) different from one another is that they *express* different proteins. You recall from your high school biology classes that to make protein, the cell first transcribes the relevant segment of DNA into messenger RNA, and then this is translated into protein. One way that the cell regulates this process is to have other proteins, called transcription factors, bind to the DNA and inhibit or assist the process of transcription. Sweeping lots of things under the rug, one can make a sketch as in Fig 2.7, showing how the rate of protein synthesis for a particular gene depends on the concentration of the transcription factor.

If we take the sketch in Fig 2.7 seriously, we can write the rate of protein synthesis as $r(F)$, where F is the concentration of the transcription factor. Once the proteins are made, they also are degraded by a variety of processes, and let’s assume that we can lump all these together into some first order

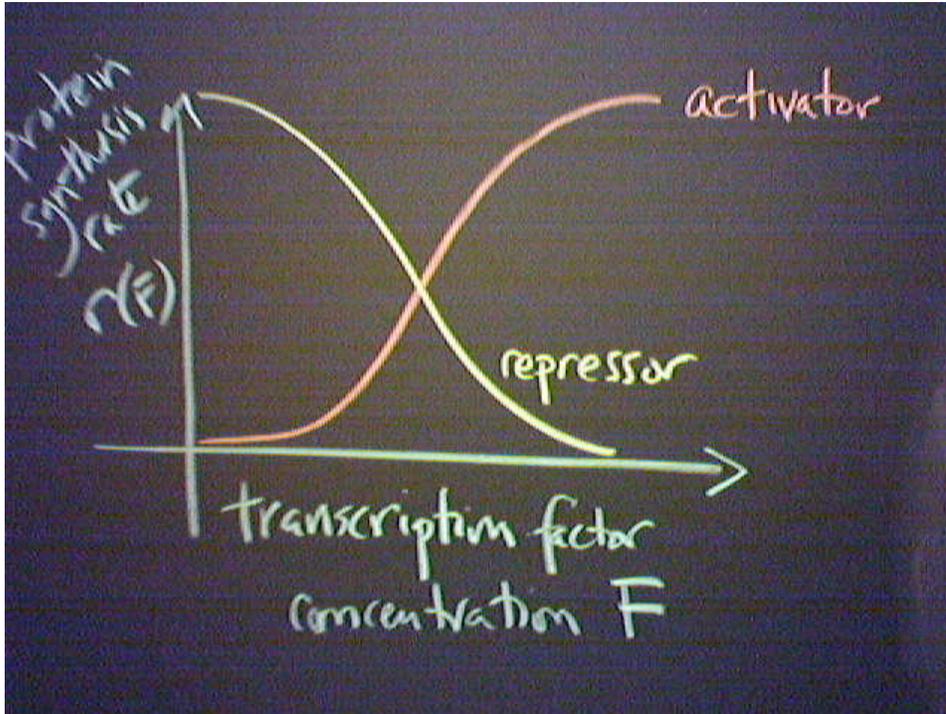


Figure 2.7: Regulation of gene expression. In the simplest picture, proteins are synthesized at a rate $r(F)$ that depends on the concentration F of some transcription factor. The transcription factor can be an activator or a repressor.

rate constant k for degradation. Then the dynamics of protein concentration are given by

$$\frac{dP}{dt} = r(F) - kP. \quad (2.215)$$

Of course, the transcription factor is itself a protein, and so some similar dynamics are being played out at another point along the genome. The real problem of understanding the dynamics of transcriptional regulation is to think about these coupled dynamics of different genes. But, to get a feeling for what can happen, let's make a drastic simplification and imagine that the protein we are looking at actually regulates itself. Then "the transcription factor" really is the protein we have been discussing, and hence $F = P$; the dynamics then are described by

$$\frac{dP}{dt} = r(P) - kP. \quad (2.216)$$

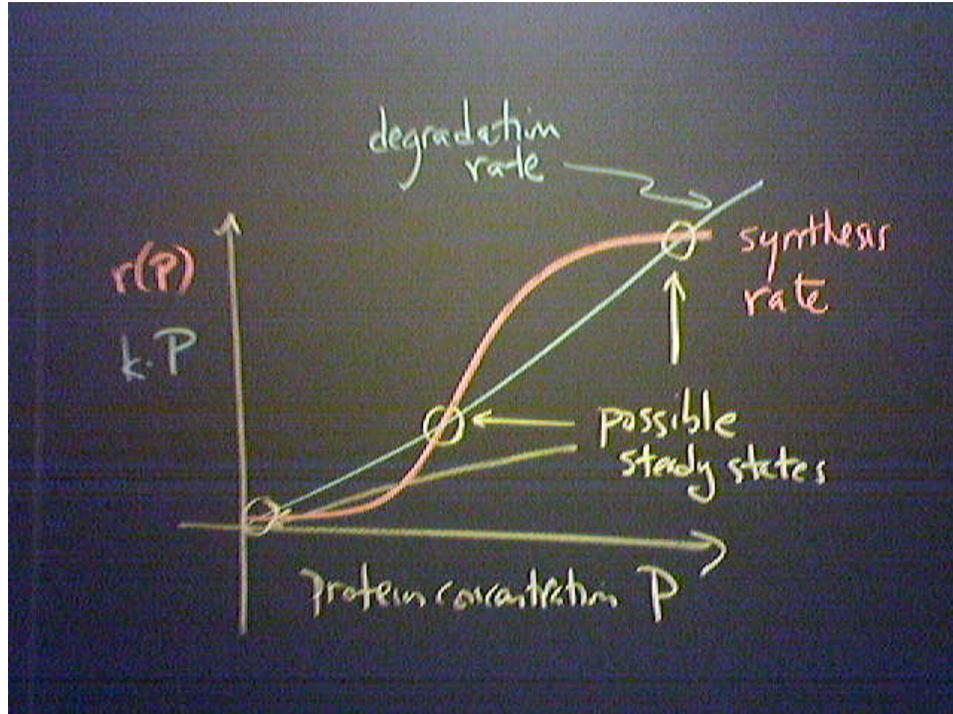


Figure 2.8: Steady states of a gene that activates its own expression. With dynamics as in Eq (2.216), steady states are possible when the rate of protein synthesis $r(P)$ balances the rate of degradation kP . With the parameters chosen here, there are three possible steady states.

Just to be clear, there is no case in nature that is quite this simple. On the other hand, there are examples that aren't too much more complicated (e.g., two proteins which regulate each other), and with modern methods of molecular biology one can engineer bacteria to implement something like the simple model we are discussing here. So, it's oversimplified, but maybe not ridiculously oversimplified (!).

How, then, do we attack a model like that in Eq (2.216)? We can start by asking if there is any way for the system to come to a steady state. This will happen when $dP/dt = 0$, which is equivalent to $r(P) = kP$. Let's consider the case of an activator. Then graphically our problem is shown in Fig 2.8. We can plot $r(P)$ vs P , and we can also plot kP vs P (the last plot just being a straight line). Whenever these two plots cross, we have a possible steady state. At least in some range of parameters, it's clear that there are three possible steady states.

Now we know that not all steady states are created equal. If we balance a ball on top of a hill, there is no force and so it will stay there forever—as long as nobody kicks it. On the other hand, if the ball is sitting at the bottom of a valley, even kicking it a little bit doesn't change anything, since after a while it will roll back to the bottom of the valley and come to rest. We say that the bottom of the valley is a stable steady state, the top of the hill is an unstable steady state. Sometimes we call these steady states “fixed points” of the dynamics. So it's natural to ask, of the three fixed points in our problem (Fig 2.8), which ones are stable and which ones are unstable?

To examine the stability of steady states let's do the mathematical version of giving the ball a small kick. Suppose that we have identified a steady state P_0 . Imagine that $P = P_0 + \delta P(t)$, where the difference δP is going to be small. We can derive an equation which describes the dynamics of δP by substituting into Eq (2.216):

$$\begin{aligned} \frac{dP}{dt} &= r(P) - kP \\ \frac{d(P_0 + \delta P)}{dt} &= r(P_0 + \delta P) - k(P_0 + \delta P) & (2.217) \\ \frac{d(P_0)}{dt} + \frac{d(\delta P)}{dt} &\approx r(P_0) + \left. \frac{dr(P)}{dP} \right|_{P=P_0} \cdot \delta P - kP_0 - k\delta P, & (2.218) \end{aligned}$$

where in the last step we have used a Taylor series expansion to approximate $r(P)$ in the neighborhood of P_0 ; since δP is small we just stop with the first term.

Now we can simplify things in Eq (2.218) considerably. To begin, P_0 is a number, so taking its derivative with respect to time gives us zero, so that we have

$$\frac{d(\delta P)}{dt} \approx r(P_0) + \left. \frac{dr(P)}{dP} \right|_{P=P_0} \cdot \delta P - kP_0 - k\delta P. \quad (2.219)$$

Next we notice that we can group the terms together on the right hand side:

$$\frac{d(\delta P)}{dt} \approx [r(P_0) - kP_0] + \left[\left. \frac{dr(P)}{dP} \right|_{P=P_0} - k \right] \delta P. \quad (2.220)$$

But P_0 was defined to be a steady state, which means that $r(P_0) = kP_0$, and hence the first term in $[\dots]$ vanishes. All we have left is

$$\frac{d(\delta P)}{dt} = \left[\left. \frac{dr(P)}{dP} \right|_{P=P_0} - k \right] \delta P, \quad (2.221)$$

and if we remember that δP has to be small, then it's OK to write $=$ instead of \approx .

But we have seen Eq (2.221) before, in other forms. This equation is just

$$\frac{d(\delta P)}{dt} = \alpha \delta P, \quad (2.222)$$

where the constant

$$\alpha = \left[\left. \frac{dr(P)}{dP} \right|_{P=P_0} - k \right]. \quad (2.223)$$

We know the solution of Eq (2.222), it's just $\delta P(t) = \delta P(0) \exp(\alpha t)$. So if $\alpha < 0$ the fixed point P_0 is stable, since a small kick away from the steady state will decay away. If on the other hand we have $\alpha > 0$, the fixed point P_0 is unstable, since a small kick away from the steady state will grow, much as with the ball on top of the hill. The conclusion from all of this is that the steady state protein concentration P_0 will be stable if $dr(P)/dP$ is less than k when we evaluate it at $P = P_0$. Looking at Fig 2.8, we can see that the two fixed points at large and small P satisfy this condition; the intermediate fixed point does not. This means that really we have a “bistable” system, in which there are exactly two stable states separated by an unstable point. This is like having two valleys separated by a hill—you can sit stably in either valley, and you'll always fall into one or the other, depending on which side of the mountain top you find yourself.

Problem 43: Let's fill in the details of the calculation above using a more concrete model. Specifically, let's formalize the sketches of the function $r(F)$ in Fig 2.7, by writing equations for $r(F)$ that look like our sketches:

$$r_{\text{act}}(F) = r_{\text{max}} \frac{F^n}{F^n + F_{1/2}^n}, \quad (2.224)$$

$$r_{\text{rep}}(F) = r_{\text{max}} \frac{F_{1/2}^n}{F^n + F_{1/2}^n}. \quad (2.225)$$

(a.) Plot⁵ the functions $r_{\text{act}}(F)$ and $r_{\text{rep}}(F)$. Explain the significance of the parameters r_{max} and $F_{1/2}$.

⁵Since we already have the sketches, “plot” here means to use a computer to get exact values and plot the results. Think about how to choose the parameters. Maybe you can choose your units in some way to make some of the parameters disappear?

(b.) Consider the case of “auto-regulation,” in which the protein is its own transcription factor, so that $P = F$. As discussed above, the case of activator can have three steady states where $dP/dt = 0$. Show that for the repressor there is only one steady state. You should be able to make a qualitative, graphical argument, and then use the equations to make things precise.

(c.) Let the steady state that you found in [c] correspond to $P = P_0$. Assume that $P(t) = P_0 + \delta P(t)$ and derive an approximate, linear equation for $\delta P(t)$ assuming that it is small. How small does it need to be in order for your approximation to be accurate?

(d.) Solve the linear equation from [c]. How does the behavior of the solution depend on the parameters r_{\max} , n , $F_{1/2}$, and k ?

Problem 44: Let’s continue the analysis of a self-activating gene. We have written the dynamics of the protein concentration P as

$$\frac{dP}{dt} = r(P) - kP, \quad (2.226)$$

where k is the first order rate constant for degradation of the protein, and $r(P)$ is the rate of protein synthesis, which depends on P because the protein acts as its own activator. To be explicit, we consider the functional form

$$r(P) = r_{\max} \frac{P^n}{P^n + F_{1/2}^n}. \quad (2.227)$$

(a.) Consider normalized variables $p = P/F_{1/2}$ and $\tau = kt$. Show that

$$\frac{dp}{d\tau} = a \frac{p^n}{p^n + 1} - p, \quad (2.228)$$

and give a formula that relates a to the original parameters in the problem.

(b.) Consider the specific case $n = 3$. Notice that the condition for a steady state can be written as the problem of finding the roots of a polynomial:

$$0 = a \frac{p^3}{p^3 + 1} - p \quad (2.229)$$

$$p = a \frac{p^3}{p^3 + 1} \quad (2.230)$$

$$p^{n+1} + p = ap^n \quad (2.231)$$

$$p^{n+1} - ap^n + p = 0. \quad (2.232)$$

Find all the steady state values of p , and plot these as a function of the parameter a . You might find the MATLAB function `roots` to be useful here. Be careful about whether the solutions you find are real! Can you verify that there are three steady states, as explained in the notes? What is the condition on a for this to be true? What happens when this condition is violated?

(c.) Write a program that solves Eq (??).

(d.) Choose a value for the parameter a which generates (from [b]) three steady states. To run your program you will need to choose a value for the discrete time step. Justify your choice, and explain how you will test whether this is a reasonable choice.

(e.) Now run the program, starting at $\tau = 0$ and running out to $\tau = 10$. Try different initial values of $p(\tau = 0)$. In particular, try initial values that are close to the steady state values. Can you verify that two of the steady states are stable, so that if you start near

them the solution will evolve toward the steady state? What happens if, in contrast, you start near the unstable state?

Problem 45: As we have noted, the model we have been analyzing is over-simplified. For example, binding of a transcription factor to DNA can't directly change the rate of protein synthesis. Instead, it changes the rate at which mRNA is made, and this in turn changes the rate of protein synthesis. Let's call the mRNA concentration M . Then instead of Eq (2.215) we can write

$$\frac{dM}{dt} = r(F) - k_{\text{RNA}}M, \quad (2.233)$$

where k_{RNA} is the rate at which mRNA decays. Then if the rate of protein synthesis is proportional to the mRNA concentration we also have

$$\frac{dP}{dt} = sM - k_{\text{P}}P, \quad (2.234)$$

where s is the rate at which one mRNA molecule gets translated into protein and k_{P} is the rate at which the protein decays. Again let's consider a repressor that regulates itself. Then our equations become

$$\frac{dM}{dt} = r_{\text{max}} \frac{F_{1/2}^n}{P^n + F_{1/2}^n} - k_{\text{RNA}}M, \quad (2.235)$$

$$\frac{dP}{dt} = sM - k_{\text{P}}P, \quad (2.236)$$

(a.) Find the conditions for the system to be at a steady state. Reduce your results to a single equation that determines the steady state protein concentration P_0 . Does this equation have a single solution or multiple solutions?

(b.) Express the protein concentration as a ratio with $F_{1/2}$, that is $\tilde{P} = P/F_{1/2}$. Can you simplify the steady state condition and show that there is only one combination of parameters that determines the value of the steady state \tilde{P}_0 ? Plot the dependence of \tilde{P}_0 on this combined parameter.

(c.) Assume that the system is close to the steady state, so that $P = P_0 + \delta P(t)$ and $M = M_0 + \delta M(t)$, with δP and δM small. Find the approximate, linear equations that describe the dynamics of δP and δM .

(d.) Look for solutions of these linear equations in the form $\delta P(t) = Ae^{\lambda t}$ and $\delta M(t) = Be^{\lambda t}$. Show that there is a solution of this form if λ is the solution of a quadratic equation.

(e.) Does the quadratic equation for λ allow for complex solutions? As a hint, try the (admittedly unrealistic) case where the protein and mRNA have the same decay rates, $k_{\text{P}} = k_{\text{RNA}}$. In contrast, what happens if the mRNA lifetime is very short, that is if k_{RNA} is very large? Explain in words why this system can oscillate, and why these tend to go away if the mRNA is short lived.

Biologically, our simple example of a gene activating itself corresponds to a switch. Given these dynamics, the cell can live happily in two different

possible states, one in which the expression of the protein is very low and one in which it is almost as high as it can be. If no extra signals come in from the outside, once a cell picks one of these “valleys,” it could (in principle) stay there forever. We can think of this as being a much oversimplified model for differentiation: Two cells, each with exactly the same DNA, can nonetheless adopt two different fates and look to the outside world like two different cells (think again about liver and brain). Alternatively, if our model was describing a single celled organism then the two stable states could represent two very different lifestyles, perhaps appropriate to different environments.

2.5 Stability in real biochemical circuits

This section remains to be written. Current students should check on blackboard to see if some more informal notes are posted.

Problem 46: When we discussed simple models for a genetic switch, we considered a protein that could activate its own transcription in a “cooperative” way, so that the rate of protein synthesis was a very steep function of the protein concentration. This actually wouldn’t be true if activation depended on the binding of just one molecule to the relevant site along the DNA. Then the synthesis rate would look more like

$$r_{\text{syn}}(c) = r_{\text{max}} \frac{c}{c + K}, \quad (2.237)$$

where c is the protein concentration, K is a constant, and r_{max} is the maximum rate. The dynamics of c would then be given by

$$\frac{dc}{dt} = r_{\text{syn}}(c) - \frac{c}{\tau}, \quad (2.238)$$

where τ is the lifetime of the protein.

(a.) Sketch the behavior of $r_{\text{syn}}(c)$. Use this sketch to determine the conditions for a steady state, $dc/dt = 0$. Is there more than one steady state? Does your answer depend on the lifetime τ ?

(b.) Are the steady states that you found in [a] stable? This requires a real calculation, not just a sketch.

(c.) Can this system function as a switch? Explain why or why not.

