

Problem Set 1

It might seem strange to give you a problem set before we have taught you anything. These problems are meant to remind you of things, and to get an estimate of what you have and have not seen before. Don't be worried or shy. If there is something you don't know (what is a partition function?, you might ask), ask for help from your fellow students and from Stefano, but please write down that you didn't know, so I can use this information in setting the level of the lectures.

Problem 1: In Fig 1 we plot the velocity vs time $v(t)$ for an object moving in one dimension. Sketch the corresponding plots of position $x(t)$ and acceleration $a(t)$ vs time. If you need additional assumptions, please state them clearly. Be careful about units.

Problem 2: In fact the funny looking plot in Fig 1 corresponds to

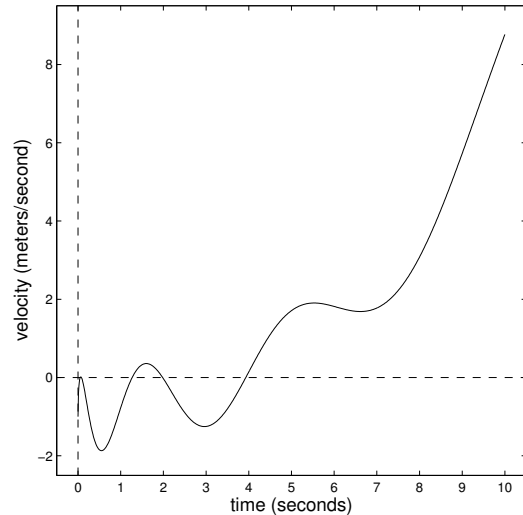


Figure 1: Velocity vs time for some hypothetical particle.

$$v(t) = \sin(2\pi\sqrt{t}) + \left(\frac{t}{5}\right)^3 - \exp(-t/4). \tag{1}$$

- a. Find analytic expressions for the position and acceleration as functions of time. You may refer to a table of integrals (or to its electronic equivalent), but you should give references in your written solutions.
- b. Use MATLAB to plot your results in [a].¹ To get you started, here's a small bit of MATLAB code that should produce something like Fig 1:

```
t = [0:0.01:10];
v = sin(2*pi*sqrt(t)) + (t/5).^3 - exp(-t/4);
figure(1)
plot(t,v); hold on
plot([-1 11],[0 0], 'k--', [0 0], [-3 10], 'k--'); hold off
axis([-0.5 10.5 -2.5 9.5])
```

¹We are going to use MATLAB extensively in this course. Please be sure that you have access to a working version on some computer, and start playing around!

Notice that there are just two lines of math, and the rest is to make the graph and have it look nice. For every command we use, you can type `help command` to get MATLAB to tell you a bit about how it works; for example, `help plot` will tell you something about those mysterious symbols 'k--'. Once you've made your plots of position and acceleration, how do they compare with your sketches in Problem 1 above?

Problem 3: Simulating a Poisson process.² Poisson processes arise (at least as approximations) in many different contexts: the random arrival of photons at the retina, the stochastic behavior of chemical reactions at the level of single molecules, even the spatial distribution of recombination events along a chromosome. Almost everything we want to know about Poisson processes can be determined analytically:

If events occur at a rate r and we count for a time τ , the mean number of events that we should see is $\bar{n} = r\tau$. The probability that we observe exactly n events is

$$P_\tau(n) = e^{-\bar{n}} \frac{\bar{n}^n}{n!}. \quad (2)$$

The variance of this distribution is equal to the mean, for all values of \bar{n} (or, equivalently, for all values of τ). The distribution of intervals between successive events is given by

$$P_{\text{int}}(t) = re^{-rt}. \quad (3)$$

All intervals are drawn independently out of this distribution.

Thus if we do simulations we know what answer we should get (!). This provides us with an opportunity to exercise our skills, even if we don't get any new answers. In particular, *doing* a simulation is never enough; you have to analyze the results, just as you analyze the results of an experiment. Now is as good a time as any to get started. If you are comfortable doing everything in a programming language like C or Fortran, that's great. On the other hand, high-level languages such as MATLAB or Mathematica have certain advantages. Here you should use MATLAB to simulate a Poisson process, and then analyze the results to be sure that you actually did what you expected to do.

- a. MATLAB has a command `rand` that generates random numbers with a uniform distribution from 0 to 1. Consider a time window of length T , and divide this window into many small bins of size dt . In each bin you can use `rand` to generate a number which you can compare with a threshold—if the random number is above threshold you put an event in the bin, and you can adjust the threshold to set the average number of events in the window. You might choose $T = 10^3$ sec and arrange that the average rate of the events is $\bar{r} \sim 10$ per second. What is the relationship between the threshold and the mean rate \bar{r} of the events? Notice that this implements (in the limit $dt \rightarrow 0$) the definition of the Poisson process as independent point events.

²Some of the problems that I use in this course (like this one) were developed together with Rob de Ruyter van Steveninck when we taught together in a summer course at the Marine Biological Laboratory in Woods Hole. Thanks to Rob for that enjoyable collaborative effort, and to several summers' worth of students for working through the problems so cheerfully.

- b. The next step is to check that the events you have made really do obey Poisson statistics. For example, make a histogram (`hist` should help) of the times between successive events (the interevent intervals); this should be an exponential function as in Eq (3), and you should work to get this into a form where it is a properly normalized probability density. Can you relate the mean rate of the events to the shape of this distribution? Then try counting events in windows of some size τ . What is the mean count? The variance? Do you have enough data to fill in the whole probability distribution $P_\tau(n)$ for counting n of events in the window? How do all of these things change as you change τ ? What if you go back and make events with a different average rate? Do your numerical results agree with the theoretical expressions?
- c. Instead of deciding within each bin about the presence or absence of an event, use `rand` to choose N random times in the big window T . Examine as before the statistics of counts in windows of size $\tau \ll T$. Do you still have an approximately Poisson process? Why? Do you see any connections to the physics or chemistry of ideal gases and ideal solutions?

Problem 4: Analytic calculations with the Poisson distribution. Starting with Eq (2), show that the mean value of n is in fact \bar{n} , and that the variance of n is equal to the mean.

Problem 5: Cooperativity and the opening of channels. The ion channels in rod photoreceptor cells seem to open in response to the binding of three cGMP molecules. Let's consider here a very simple model, which is essentially the model proposed by Monod, Wyman and Changeux for cooperativity in enzymes.³ The basic idea is shown in Fig 2. The channel molecule can exist in two states, open and closed, and in addition it can bind one, two or three molecules of cGMP. If all the binding sites are empty, the free energies of the two states are F_{open} and F_{closed} . Given that the channel is closed, the binding of a single cGMP molecule lowers the energy by an amount $F_{\text{closed}}^{\text{bind}}$, but in addition this takes one molecule out of the solution and hence the free energy of the system also goes down by μ , the chemical potential. We know that for low concentrations we have $\mu = k_B T \ln(c/c_0)$, where c_0 is some reference concentration that we need to set the units correctly. So the total free energy of the state with the channel closed and one molecule bound is

$$F_{\text{closed}}(1) = F_{\text{closed}} - F_{\text{closed}}^{\text{bind}} - \mu \quad (4)$$

$$= F_{\text{closed}} - F_{\text{closed}}^{\text{bind}} - k_B T \ln(c/c_0) \quad (5)$$

$$= F_{\text{closed}} - k_B T \ln\left(\frac{c}{K_{\text{closed}}}\right), \quad (6)$$

and similarly for the open state.

- a. Assume that the binding energy for each molecule of cGMP is the same given that the channel protein is in either the open or the closed state. Show that, with this assumption, the free energies of all the states can be written as shown in Fig 2.
- b. Show that the model in Fig 2 is equivalent to the statement that the free energy difference between open and closed states has a term proportional to the number of cGMP molecules

³J Monod, J Wyman & J-P Changeux, *J Mol Biol* **12**, 88–118 (1965).

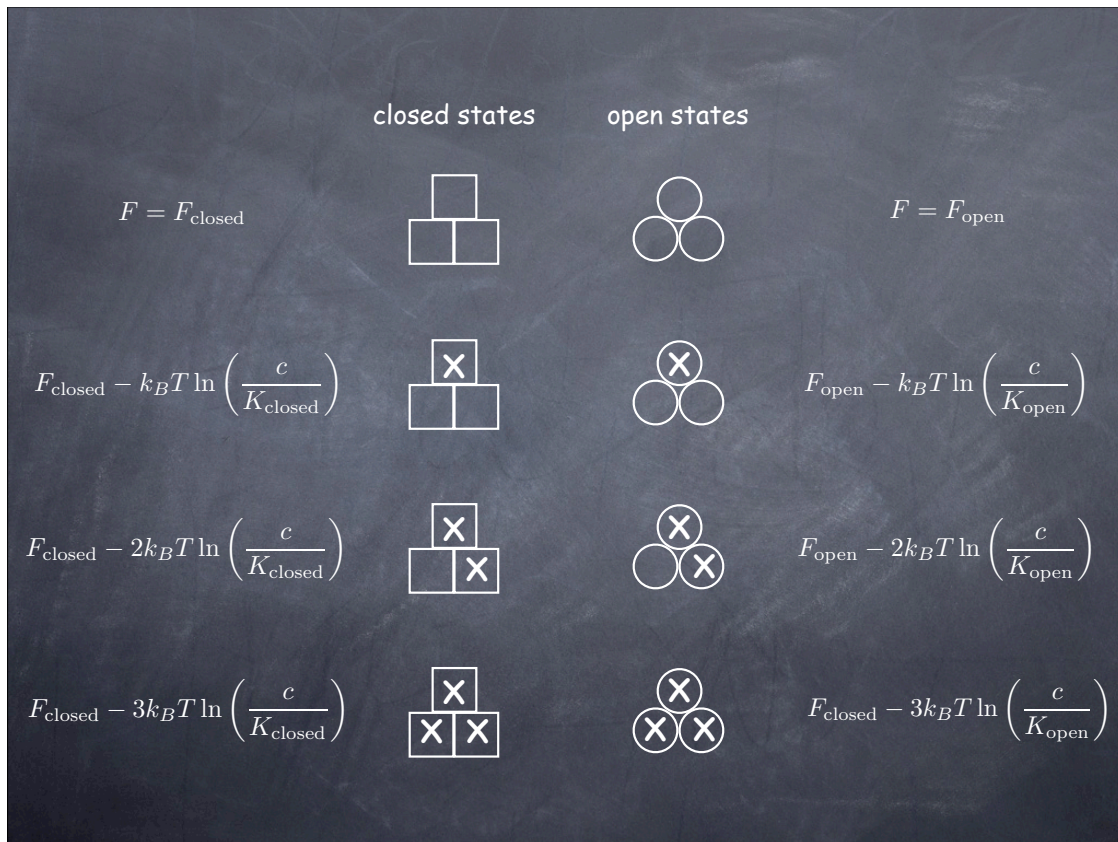


Figure 2: A model for binding of cGMP to the channels in rod cells. Cooperativity arises not from direct interactions among the cGMP molecules but rather because binding of each molecule contributes to stabilizing a different structure of the channel protein. In this case the two structures are just the open and closed states.

bound. What is this proportionality constant in terms of the other parameters? Can you explain the connection between these two points of view on the model?

- c. Evaluate the partition function for this model, summing over all possible states. Assume that the channel is symmetric, so that binding to any site has the same energy, and hence there are three degenerate states with one molecule bound, etc.. If you don't know what 'partition function' means, do you know how to use the Boltzmann distribution to write the probabilities of the various states?
- d. Use your results from [c] to evaluate the fraction f of open channels as a function of the cGMP concentration c . Can you see a limit in which $f \approx c^3/(c^3 + K^3)$ is a good approximation?