

Ryan Hoffman provided the material for Sec. 1.2; Joseph Platzner provided the one for Sec. 2.2 and 3.3; Rafael Díaz did the mathematical analysis required in the different sections.

1 Correlation Functions and Power Spectrum

1.1 Mathematical properties of noise.

In this project we studied the relation between the *Power Spectrum* of a function, $x(t)$, and its *Correlation Function*, $C(t)$. We produced random numbers with a normal distribution to simulate white noise at different times, $n(t)$. We filter the noise using a Lorentzian filter and analyze the results in the view of the *Wiener Khinchin Theorem* (WKT). In Fig. 1 we show the results obtained.

As expected, the filter reduced the higher frequencies yielding a smoother function (compare Figs. 1d and 1d). Also, the histogram of Fig. 1a shows that even though the higher frequencies have been attenuated, the distribution is still a Gaussian one. This can be explained considering that all the frequencies are distributed in the same way, independently of their value, thus, even when the higher ones are suppressed, the remaining ones will still be normally distributed, but with a narrower variance.

The most important part is to note the relation between figures 1b and 1c, *i.e.* between the $C(t)$ and $\langle |\hat{x}_\omega|^2 \rangle$. According to the WKT,

$$\langle |\hat{x}_\omega|^2 \rangle = \mathcal{F}\{C(t)\} \quad (1)$$

where, $\mathcal{F}\{f(t)\}$ is the Fourier Transform of $f(t)$. So, in the view of this theorem we can also establish, by the Fourier Inversion Theorem that,

$$C(t) = \mathcal{F}^{-1}\{\langle |\hat{x}_\omega|^2 \rangle\}. \quad (2)$$

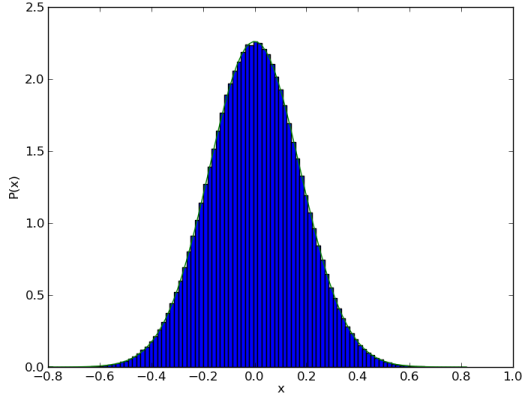
Thus, recalling that the (inverse) Fourier Transform of a Lorentzian is a decaying exponential of the form $C(t) = C_0 e^{-\alpha|t|}$, we can verify that the simulation reproduces the expected results since $\langle |\hat{x}_\omega|^2 \rangle$ is a Lorentzian as shown by the fit of Fig. 1c and $C(t)$ is the mentioned decaying exponential as confirmed by the fit of Fig. 1b.

To study further this relation, we ran the program once more changing the filter to a *cut-off* one (*i.e.* all the frequencies above a specified value are totally suppressed). The results are shown in Fig. 2.

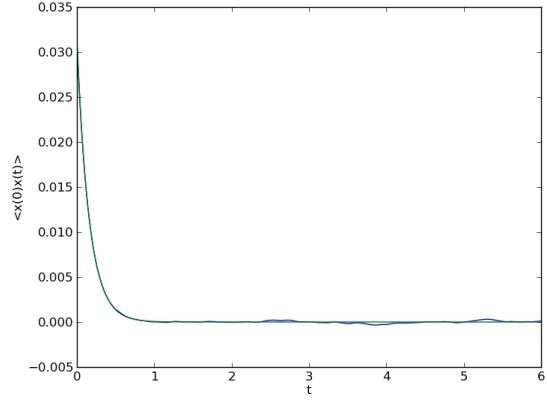
As can be seen, the histogram is still a normal distribution, but now the filtered noise is a much smoother function. Besides, the fits do not reproduce any more the numerical results, as expected, since they were made for the Lorentzian filter. Clearly, $\langle |\hat{x}_\omega|^2 \rangle$ reproduces, fairly well, the rectangular pulse expected from the *cut-off* filter (Fig. 2c). More important, the Fourier Transform of a pulse like this one is proportional to the $\text{sinc}(t) = \frac{\sin(t)}{t}$ function and this is exactly what Fig. 2b shows.

1.2 Noise in Biological Systems.

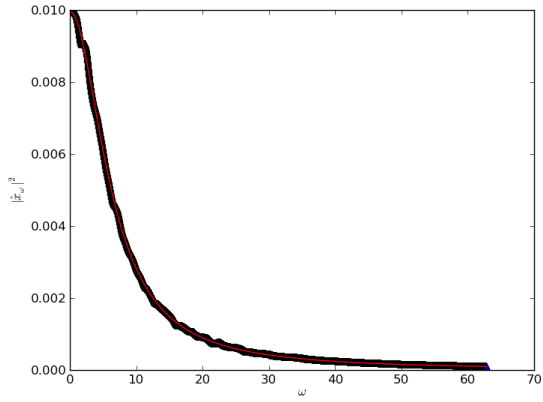
1. When recording neuronal activity in vivo, there is a high degree of irregularity. Both the spike train of single neurons and the firing relations between several neurons are far from regular. One would think that the spike train, or sequence of action potentials, would be seen to be periodic over some rate of time; in addition, it would not be crazy to think that the firing between several neurons could be reduced to a pattern. However, both the spike train of a single neuron along with the firing pattern between several neurons seems to be random. What is the factor causing this irregularity



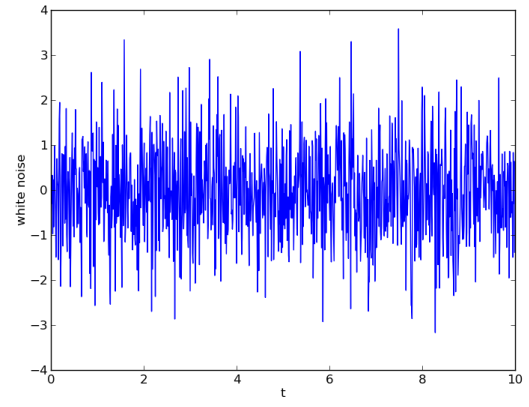
(a) Histogram of the filtered noise.



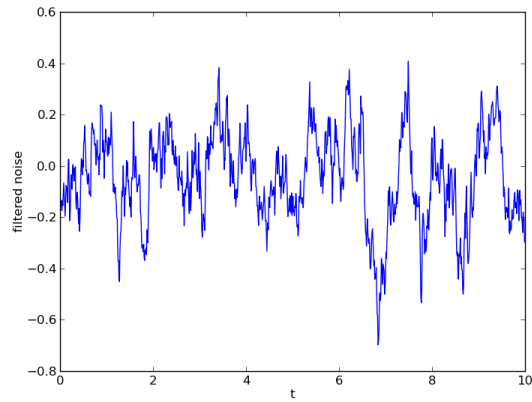
(b) $C(t)$ (blue line) with an exponential fit superimposed (green line)



(c) $\langle |\hat{x}_\omega|^2 \rangle$ (black) with a Lorentzian fit superimposed (red line).

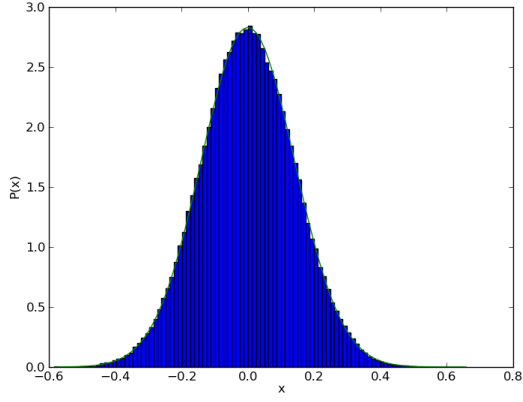


(d) $n(t)$.

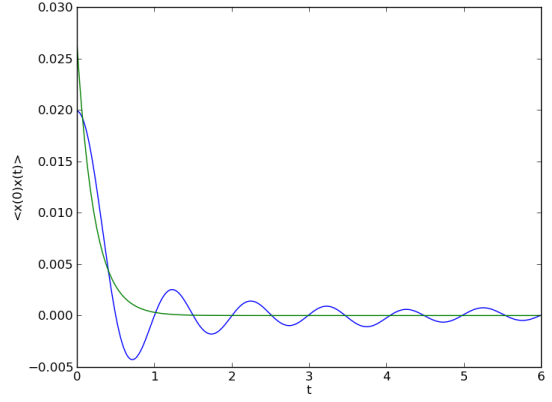


(e) Noise with the Lorentzian filter.

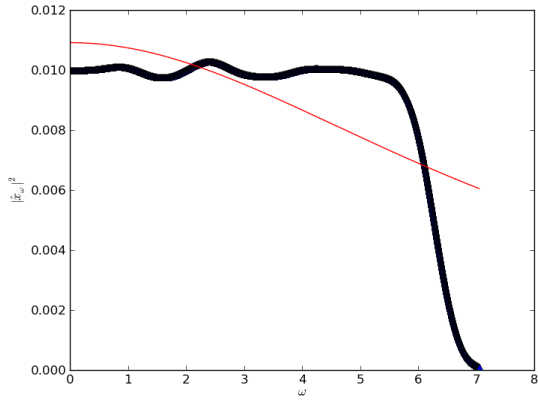
Figure 1: Results using a Lorentzian filter.



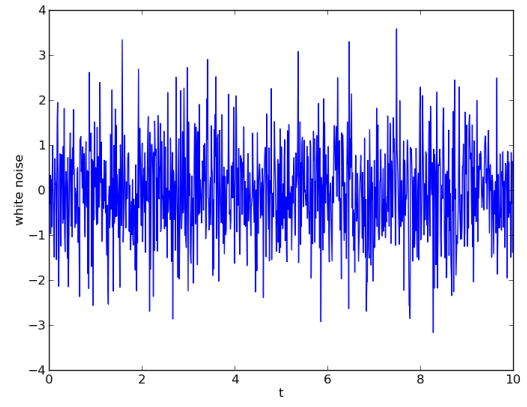
(a) Histogram of the filtered noise.



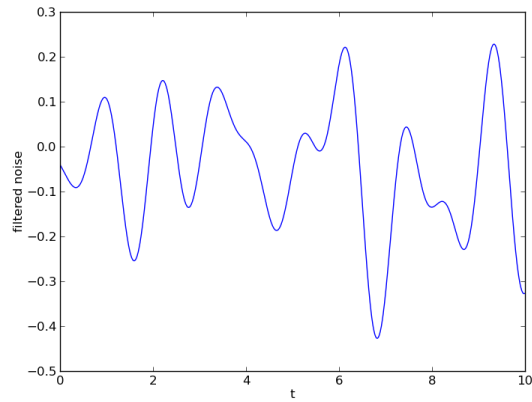
(b) $C(t)$ (blue line) with an exponential fit superimposed (green line)



(c) $\langle |\hat{x}_\omega|^2 \rangle$ (black) with a Lorentzian fit superimposed (red line).



(d) $n(t)$.



(e) Noise with the cut-off filter.

Figure 2: Results using a *cut-off* filter.

in the pattern of neuronal action potentials? Brownian noise is a factor that exists at every microscopic level and can cause some significant affects. Noise is produced by the Brownian motion, random walking, of molecules in a system. In a neuron, neural noise refers to random fluctuations of charged ion within a neuronal network. For the most part, this refers to random motion of charged ions such as Na^+ , K^+ , Ca^{2+} , and Cl^- across the neuronal plasma membrane. Usually this random fluctuation in the charge across the membrane is well below the voltage-threshold needed to propagate an action potential. However, sometime noise by itself is able to, by random chance, reach the voltage-threshold and elicit an action potential.

A typical interneuron has the resting potential of about -70 mV and the voltage-threshold of about -55 mV , meaning that in order for a typical neuron to fire, the voltage potential across the membrane must be depolarized by 15 mV . Although this may not sound like much, it requires the movement of a lot of ions across the membrane. Almost all of the time this is done by facilitated diffusion triggered by the depolarization caused by neurotransmitters or physical graded potentials, yet every once in a while Brownian noise can trigger such a cascade.

The conserved action potential is depolarized on the magnitude of about 1ms and is repolarized on the magnitude of another 1ms . When taking into account the inhibitory undershoot of the repolarization mechanism, an action potential takes about 4ms to pass. When the action potential is at the peak of being depolarized, the internal transmembrane voltage potential is around $+40\text{mV}$. This means that in about 1ms the membrane depolarizes from -55mV to $+40\text{mV}$ (a difference of 95mV) and in the next millisecond the membrane repolarizes from $+40\text{mV}$ to less than -70mV (a difference of over 110mV). The extraordinary speed of these transmembrane voltage changes is accomplished by the use of two transmembrane voltage-gated protein channels. Conversely, the transmembrane voltage change as a function of time due to noise is several orders of magnitude lower than that of facilitated diffusion. The cause of this is the voltage-gated ion channels. A certain transmembrane voltage (the threshold voltage) must be reached in order to open the voltage-gated channels, whereas, noise is independent of voltage and thus is independent of the voltage-gated channels. Noise is dependent only on the random walking of the ions across non-voltage-gated protein transporters. This causes noise to be a slower and less effective way to move ions across the membrane.

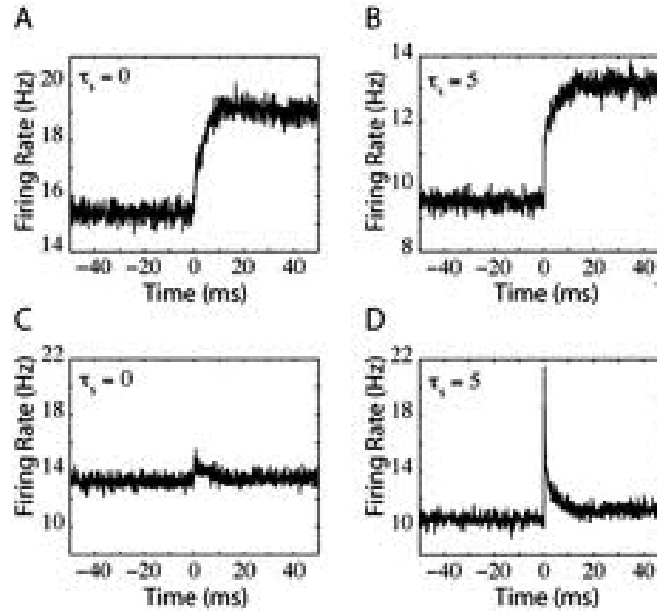
Not all neurons behave the same when it comes to their action potential. Certain neurons, such as neurons in the neuromuscular junction have a lower resting potential of -90mV , yet the threshold voltage to propagate an action potential is the same. This means that to innervate a muscle the neuron must depolarized the cells more. This reduces the affect of neuronal noise on muscle contraction.

In addition to cells in the neuromuscular junction, most types of sensory cells operate in an atypical way. Sensory cells use what is called a graded potential, which is used to elicit an action potential in interneurons. A graded potential is unlike an action potential in the fact that it is not all-or-none. A graded potential is a transmembrane voltage potential that can take on any voltage and propagates through the cell via simple diffusion. These potentials are much slower and weaker. Noise has a larger affect on cells that use graded potentials to transmit information.

There are two types of neuronal noise: ionic and synaptic. Noise in both cases arise from the human body maintaining a temperature of 37°C , which increases the kinetic energy and thus motion of the particles in the system. A system of particles that have more movement will have more noise.

Ionic noise is the result of ions being leaked across the membrane in effort to equalize the ionic gradient produced by ATPase channels in the membrane. Leaky ion channels permit the movement of ions across the membrane and thus cause these small fluctuations in membrane potential called noise. The second type of neuronal noise is that of synaptic noise. Synaptic noise is the result of random exocytosis of vesicles containing neurotransmitters in the terminal buds. This will release a small amount of neural transmitters into the synapsis and will create a small graded potential in the postsynaptic neuron. Since neurotransmitters cause ion channels on the postsynaptic cell to open, synaptic noise is considered the largest-amplitude noise source in the cerebral cortex.

Neuronal noise has a very high temporal resolution, meaning that the noise fluctuations happen within a fraction of a millisecond. Since the noise a transmembrane potential experiences is an example of Gaussian noise, meaning the random walkers are equally likely to move in any direction each time they take a step, such a high temporal resolution means that noise has a very minor affect on the overall transmembrane potential.



Gaussian noise is a good approximation of the noise that occurs across the neuronal membrane. However, this biological noise will not occur at all frequencies like white noise will. Since this is a biological system, most of the high frequency noise is filtered out naturally. This confines neuronal noise to a narrower range of frequencies that still present a Gaussian distribution. This Gaussian function is given by,

$$f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}} \quad (3)$$

Often times, a single neuron will have many inhibitory and excitatory synapses. The summation of the influx and efflux of ions produced by these synapses is what defines if the postsynaptic cell will fire an action potential. Excitatory junctions innervate together to increase the depolarization of the dendrites to the threshold voltage in order to cause a postsynaptic action potential, while inhibitory junctions will innervate the polarization or repolarization of the dendrite in order to inhibit the influx of a net positive charge, causing the postsynaptic cell to be less likely to fire an action potential. For neurons that have a complex network of innervating cells, each cell will typically

only cause a small degree of depolarization. Thus the postsynaptic cell requires innervation from several presynaptic neurons. This means that a postsynaptic cell may have been depolarized, but is still under the threshold voltage needed to cause an action potential. Ultimately, this means that postsynaptic cells with this kind of networked innervation are often depolarized to a transmembrane potential very close to the threshold potential. In cases like this, noise can easily depolarize the cell to reach the threshold potential causing an action potential to fire. This noise is able to propagate action potentials very well when the cell has already been depolarized close the threshold potential. The closer the cell is depolarized to the threshold, the more noise will be likely to create an action potential. This gives the cell an addition way to compute information. This noise creates a firing gradient of unwarranted action potentials as the cell depolarizes closer to the threshold voltage. When the postsynaptic cell is near resting potential, the noise of the system has little affect on if the cell will fire an action potential. As the cell becomes more depolarized, the noise has a greater likelihood is eliciting an action potential. This gives the cell the ability to fire action potentials before the threshold potential is reached, with the likelihood of noise eliciting an action potential increasing exponentially as the cell becomes depolarized closer to the threshold potential. This additional computational ability gives cells a larger range of firing rates and patterns. The firing pattern and rate of a cell is the encoded digital information that other cells are able to translate into behavior.

2. Gene expression is absolutely susceptible to noise. Noise and diffusion play a critical role in assembling regulatory protein complexes along with the binding of protein regulators to the DNA. Protein subunits do not have an intrinsic attraction to one another; they rely on the random event of bumping into one another due to Brownian noise. Once the proteins collide in the right way, they are able to bind at specific binding sites. A good example of how this process works was done on E. Coli. Transcription factors are factors that bind to the DNA at different sequences and help “recruit” the RNA Pol II in order to begin transcription. However, there is no intrinsic attraction of any of these molecules to one another until their binding sites are touching. Transcription factors are moving around at the microscopic level due to Brownian noise and will eventually bump into a sequence on the DNA that they recognize. It will then bind. Through the same process several other transcription factors will bind to the first, creating a regulatory complex of proteins attached to the DNA. Although the protein units are bound to one another and to the DNA, the attachment is not permanent. Noise is also able to remove these transcription factors from their binding sites. This is usually less likely to happen due to the protein complex being more stable when bound, but if a molecule hits the complex hard enough or is able to interrupt the binding sites, the complex will dissociate. Once noise has bumped all of the protein subunits together, this regulatory subunit will “recruit” RNA Pol II. The word recruit is very misleading in this sense. The complex is not at all recruiting the polymerase; in reality, noise is what recruits the protein. By the same way noise brought all of the protein subunits together, this random movement of molecules will cause a free RNA Pol to bump into the binding site on the protein complex. Once bound, RNA Pol II is far more stable when bound to the complex, which prevents a majority of the noise from removing it from the mediator complex, however, noise can still dissociate these molecules.

The physical ability for noisy movements to access binding sites on proteins and DNA can cause large fluctuations in gene expression. Structures like chromatin, certain secondary and tertiary structures, and methylation of DNA can protect binding sites from access of binding domains via Brownian motion. By making the binding site unexposed, the cell has prevented molecules access to accidentally bump into the binding site via noise.

Although the cell relies on it to assemble protein complexes, noise can cause the cell some trouble when transcribing DNA and translating RNA. Noise can cause the dissociation of regulatory complexes and other transcriptional and translational machinery, which will cause some major complications in maintaining homeostasis. However, the cell has come up with some ways to reduce the affect of noise on the fidelity of these processes. Both RNA Pol II and the Ribosome are extremely stable molecules when bound to all of the appropriate factors. This stability causes an attractive force between the subunits and causes noise to become less influential on the fidelity of the process, allowing transcription and translation to run to completion.

Noise is a necessary part of biological workings, yet it can also cause processes to work less efficiently and can even create some pretty bad mistakes. The good news, however, is that evolution has designed the machinery of the cell to capitalize on the passive noisy movement of molecules throughout the cell, while minimizing its affect on increasing entropy on organized processes. A good example of this is RNA Pol II. Noise is necessary for the polymerase to be recruited to the transcriptional start site, yet noise must be minimized in order to maximize the fidelity of transcription. This is done by serine phosphorylation of the CTD subunit of the polymerase. When the C-Terminus Domain (CTD) is phosphorylated, RNA Pol II binds extremely strongly to DNA, which increases its fidelity and allows it to run to completion. However, the cell once again relies on noise again once transcription is finished in order to remove RNA pol II. Phosphorylases will dephosphorylate the serines on the CTD, weakening the binding strength. Then noise will take over and cause a dissociation of the mediator complex. Through the maximization and minimization of the affect of noise on molecules in the cell along with altering the access of molecules binding sites, the cell is able to regulate the fluctuations in the expression level of genes.

2 Brownian Motion in and Optical Trap

2.1 Mathematical Analysis

In this section we study the solution of the *Langevin Equation*,

$$\dot{x} = -\kappa x + n(t), \quad (4)$$

where κ plays the role of a spring constant and $n(t)$ is a function that describes a random force acting on the particle (as white noise). First of all, to solve this equation numerically we need to discretize it. For this, let $x_n = x(t_n)$ be the position of the particle at the time t_n . We can approximate $\dot{x}$, to first order, as

$$\dot{x} \approx \frac{x_{n+1} - x_n}{\Delta t}$$

where $\Delta t = t_{n+1} - t_n$. Plugging this into Eq. (4) and solving for x_{n+1} we obtain,

$$x_{n+1} = x_n + \Delta t(-\kappa x_n + n_n). \quad (5)$$

This is what is implemented in the code used in the line

```
x += dt*(-k*x + amplitude*standard_normal())
```

where `amplitude*standard_normal()` represent a random perturbation normally distributed multiplied by an amplitude whose value we will determine below.

Now, let's find the value of $\langle x^2 \rangle$ using the Equipartition Theorem. This theorem states that the average energy associated with each degree of freedom is equal to $\frac{1}{2}k_B T$ where k_B is the Boltzmann Constant. So, assuming the particle is driven by a spring like force, we have,

$$U(x) = \frac{1}{2}\kappa x^2$$

Therefore,

$$\langle x^2 \rangle = \frac{2}{\kappa} \langle U \rangle = \frac{2}{\kappa} \left(\frac{1}{2} k_B T \right) = \frac{k_B T}{\kappa}. \quad (6)$$

On the other hand, a basic result of Statistical Mechanics is that, for a system at temperature T , its probability of being in a state with energy $U(x) = U_x$ is given by

$$P(x) = \frac{e^{-U_x \beta}}{Z} \quad (7)$$

where $\beta = 1/k_B T$ and $Z = \int \exp(-U(x)\beta) dx$ is a normalization constant. So, in this case we have

$$P(x) = \frac{1}{Z} e^{-\frac{1}{2}\kappa x^2 \beta}. \quad (8)$$

This is a Gaussian distribution with a variance of $\sigma^2 = 1/\beta\kappa = \frac{k_B T}{\kappa}$. So, for `Temperature = 0.25` the program gives `sigma = 0.500814803861`, while for `Temperature = 1.0` we get `sigma = 1.00162960772`. These values are the expected ones since, in the code, $k_B T = \text{Temperature}$ and $\kappa = 1$.

Let us now derive the correlation function $C(t)$. First note that if $n(t) = 0$ we would have the ODE

$$\dot{x} = -\kappa x, \quad (9)$$

whose solution is

$$x(t) = x_0 e^{-\kappa t}. \quad (10)$$

Considering the noise we would get $x(t) = x_0 e^{-\kappa t} + f(t)$ where $f(t)$ is a term that varies randomly. So, if we have many trajectories, all of them starting at $x(0) = x_0$ and make an average over them, the random term would cancel out, thus, obtaining,

$$\langle x(t) \rangle = x_0 e^{-\kappa t}. \quad (11)$$

With this in mind, we can calculate the correlation function $C(t) = \langle x(0)x(t) \rangle$ noting that the system will evolve, statistically, if we fix it so $x(0) = x_0$ always, or, we let it evolve until it reaches that position by itself. So, averaging *over all initial conditions* we get

$$C(t) = \langle x(0)x(t) \rangle = \langle x^2 \rangle e^{-\kappa|t|}, \quad (12)$$

where the absolute value in the exponential is used because $C(t) = C(-t)$.

We now present the results obtained with the code provided in the course web page using $k_B T = 1$

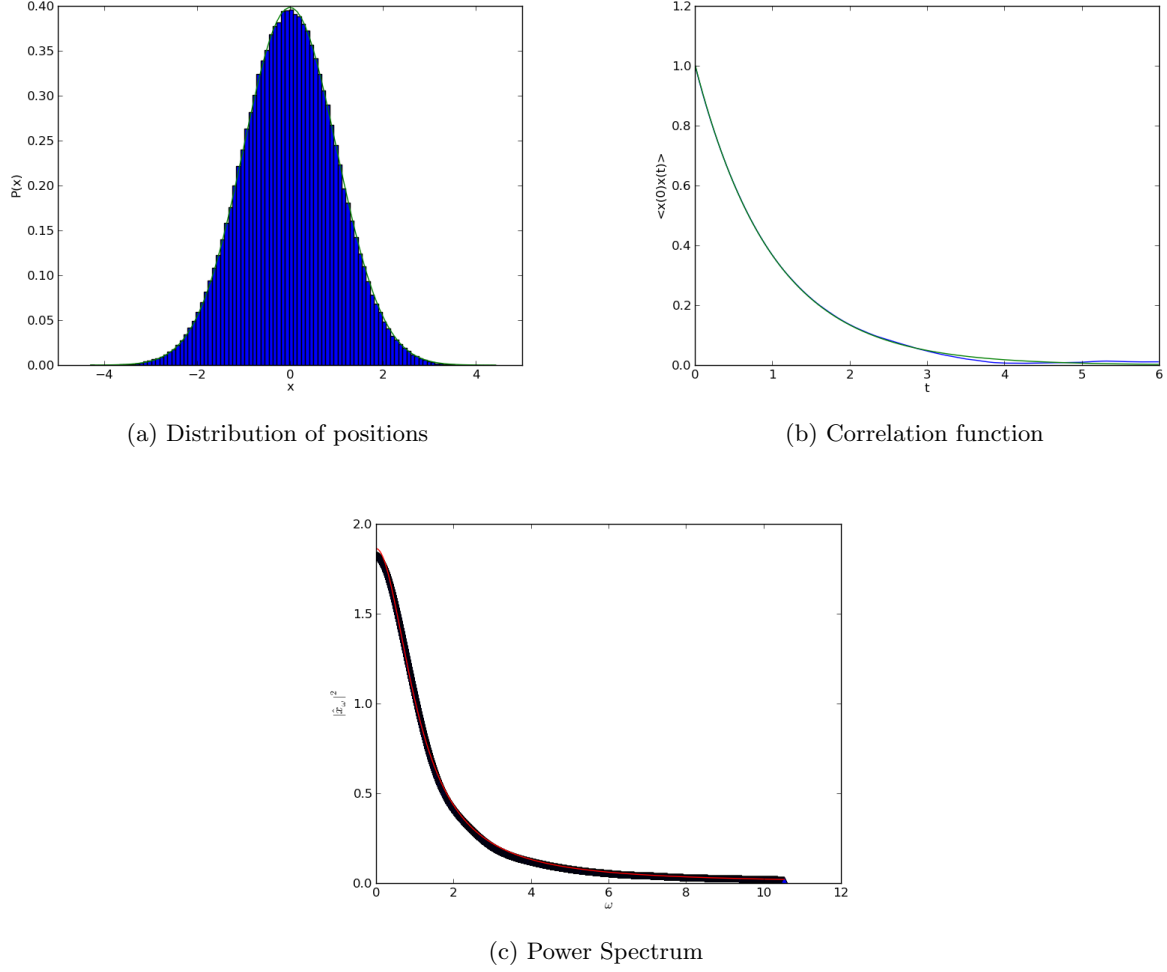


Figure 3: Results of the Brownian Motion simulation.

As Fig. 3a shows, the distribution obtained is the Gaussian predicted by Eq. (8). Also, the correlation function has the decaying exponential behavior expected from Eq. (12) with a corresponding Lorentzian for $\langle |\hat{x}_\omega|^2 \rangle$. The fitting parameters of the exponential obtained with the code are

$$\text{—p1 = [1.00573377 0.99309207]—}$$

where the first entry corresponds to $\sqrt{\langle x^2 \rangle} = \sqrt{\frac{k_B T}{\kappa}}$ and the second one to κ . Since we fixed $k_B T = 1$ and $\kappa = 1$, we can see the fit agrees with these values.

As an alternative verification of the WKT we can derive the value of the amplitude expected for the noise term. For this, let us solve the Langevin Equation using the Fourier Transforms method and denote $\mathcal{F}\{x(t)\} = \hat{x}_\omega$ and $\mathcal{F}\{n(t)\} = \hat{n}_\omega$. Besides, let's recall that if $\mathcal{F}\{f(t)\} = \hat{f}_\omega$, then $\mathcal{F}\{f'(t)\} = -2\pi i \omega \hat{f}_\omega$, hence, Eq. (4) turns to

$$\begin{aligned} -2\pi i \omega \hat{x}_\omega &= -\kappa \hat{x}_\omega + \hat{n}_\omega \\ \Rightarrow \hat{x}_\omega &= \frac{\hat{n}_\omega}{\kappa - 2\pi i \omega} \end{aligned}$$

therefore,

$$|\hat{x}_\omega|^2 = \frac{|\hat{n}_\omega|^2}{4\pi^2\omega^2 + \kappa^2}. \quad (13)$$

Next, to get $\langle |\hat{x}_\omega|^2 \rangle$ we only need to integrate the last equation on all the frequency range

$$\langle |\hat{x}_\omega|^2 \rangle = \int_{-\infty}^{\infty} \frac{|\hat{n}_\omega|^2}{4\pi^2\omega^2 + \kappa^2} = \frac{\langle |\hat{n}_\omega|^2 \rangle}{2\kappa}. \quad (14)$$

On the other hand, we know that $\langle |\hat{n}_\omega|^2 \rangle = cT_{measure}$. For the present case, $T_{measure} = \Delta t$, so from Eq. (14) we get

$$c\Delta t = 2\kappa \langle |\hat{x}_\omega|^2 \rangle. \quad (15)$$

As a last step, let's use the *Plancherel's Theorem* which establishes that the norm of a function is preserved when it is fourier transformed, *i.e.* if $\mathcal{F}\{f(t)\} = \hat{f}_\omega$, then $|f(t)|^2 = |\hat{f}_\omega|^2$; thus

$$\langle |\hat{x}_\omega|^2 \rangle = \langle x^2 \rangle = \frac{k_B T}{\kappa}$$

plugging this into (15) we get

$$c\Delta t = 2k_B T$$

and since $c = \text{amplitude}^2$, we finally conclude that

$$\text{amplitude} = \sqrt{\frac{2k_B T}{\Delta t}}. \quad (16)$$

This is exactly what the code uses: `amplitude = sqrt(2.0*Temperature/dt)`.

2.2 Applications to Experiments

1. In real experiments, the fluctuations in position are often large compared to the positions that are useful to measure. Give a method for how the noise in the answer can be reduced to a level where interesting behavior can be observed. Give an example of one experiment that employs such a technique.

To account for the random noise recorded in optical trapping, it is possible to use a combined method of a CCD camera, a piezo stage stabilized micropipette holder, and a quadrant photodiode (QPD) to measure the deflections of the laser used. In this experiment, a bead is attached to a micropipette which is attached to a piezo stage. To this bead, is attached a strand of DNA. The other end of the DNA is attached to another bead which is trapped in a laser beam. Under the laser beam is a QPD which records the deflection of light produced by the motion of the DNA strand tethered to the bead. The sub-nanometer resolution of DNA movement recorded by the piezo stage and the QPD allow for noise reduction by measuring movement when no force is applied to the DNA. By subtracting the noise displacement recorded by the piezo stage from the displacement recorded by the QPD it is possible to reduce noise from DNA movement observations. The CCD camera comes into play by being used to measure the distance between the two beads. The CCD camera is insensitive to noise due to its 5 nm resolution, so it is a good tool for determining bead-bead distance.

$$n_{stage}(t) \approx s_{stage}^{piezo}(t) - s_{stage}^{QPD}(t) = 0 - s_{stage}^{QPD}(t) \quad (17)$$

Where n is the noise on the stage and s is the displacement measured by either the light trapped bead or the piezo-bound bead.

In addition, use of a second trap to probe the input noise of the system may also be used to assist in noise reduction.

2. Give an example of an experiment probing conformations of a single molecule, where you can think of the particle as being in a potential that no longer has a single minimum and the noise plays an important role in understanding the molecule's internal states.

An example would be measuring the force generated and distance traveled in the single step of a myosin motor along a microtubule, tethered to dsDNA in an optical trap. As the myosin motor moves, it will step outside of the potential minimum of the optical trap, thus a force will be acted on it. This stretches the DNA tethered to the motor, which can be measured to determine the force generated and distance moved. Allowing many steps of the myosin motor, it is possible to gradually remove the noise to resolve the dynamics of each single step made by the motor, and to infer the conformation of the motor at each step. The myosin motor has multiple potential minimums depending on the stage of the power stroke it is in. Noise could possibly obscure which step of the power stroke the myosin motor is, so reduction of said noise is key to understanding the dynamics of these molecular motors.

3 Diffusion in a Double Well Potential

3.1 Equilibrium

In this section we study a system as the one of Sec. 2.1 but with a force more general than $f(x) - \kappa x$. Actually, we use a potential that will yield a “double well”:

$$V(x) = \kappa(x - x^2)^2, \quad (18)$$

whence

$$f(x) = -2\kappa x(1 - x)(1 - 2x). \quad (19)$$

in the code this is expressed as

```
def f(x):
    return -2*k*(x*(1-x))*(1-2*x)
```

and

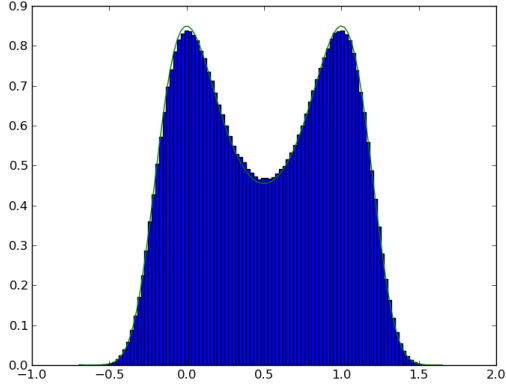
```
x += dt*(f(x) + T_*standard_normal())
```

with $T_ = \sqrt{2.0*T/dt}$.

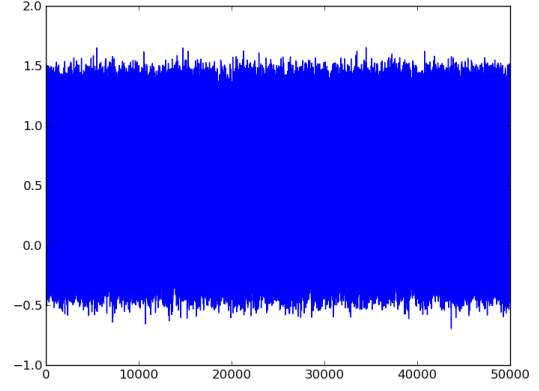
With this code we compared the distribution of position with the one predicted by the *Maxwell Distribution*,

$$P(x) = \frac{1}{Z} e^{-V(x)\beta} \quad (20)$$

with $V(x)$ given by Eq. (18). We now show the results obtained with the code provided for different values of $T = k_B T$ and assuming the particle begins at $x(0) = 0$ (center of the well on the left).

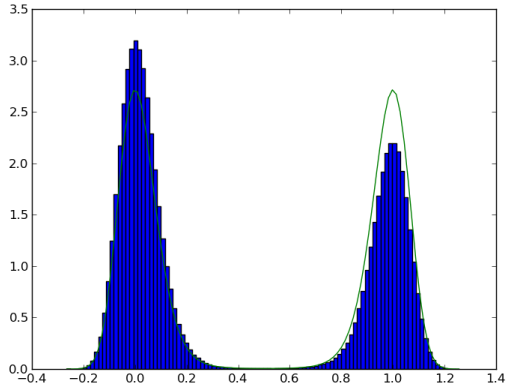


(a) $P(x)$ with the theoretical distribution superimposed

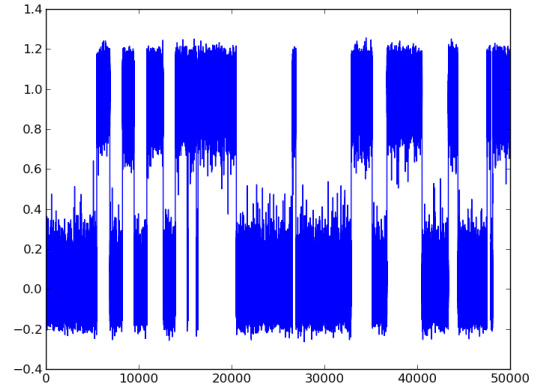


(b) Particle position as a function of time

Figure 4: Results for $k_B T = 0.1$

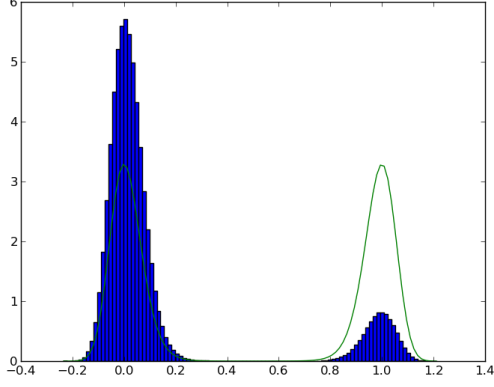


(a) $P(x)$ with the theoretical distribution superimposed

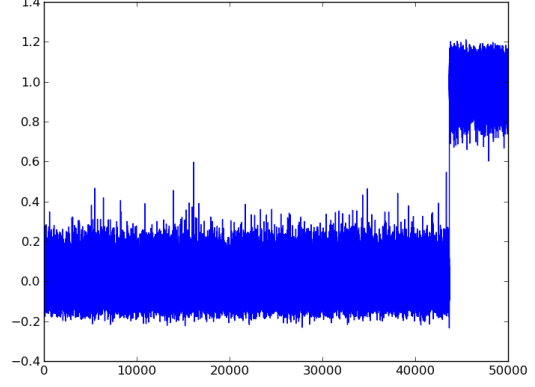


(b) Particle position as a function of time

Figure 5: Results for $k_B T = 0.01$



(a) $P(x)$ with the theoretical distribution superimposed



(b) Particle position as a function of time

Figure 6: Results for $k_B T = 0.007$

We can see that only Fig. 4 follows the expected distribution according to Eq. (20) and as we decrease the value of the temperature, the deviations become bigger. This is due to the lack of time for the system to achieve the predicted conditions. This is clearly depicted in Fig. 6b where only during the last part of the time interval the particle does move to the well on the right. For the intermediate value of T Fig. 5b shows that there is “tunneling”, but the corresponding distribution makes clear that most of the time the particle is in the well on the left.

3.2 Escape Time over a Barrier

Finally, we studied the time it takes the particle to escape from the first well as a function of temperature. In Fig. 7 we show the results obtained with two different fits proposed.

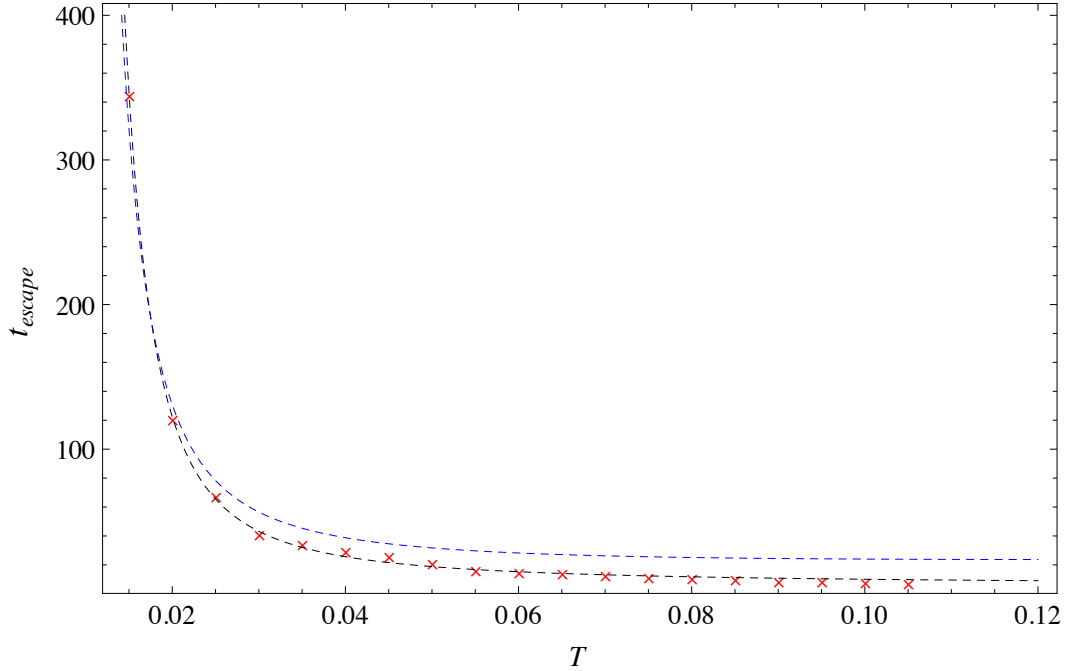


Figure 7: Numerical results of the escape time as a function of temperature

The first fit (blue line) is a function of the form

$$t_{\text{escape}}(T) = \tau \sqrt{T} e^{\alpha/T}, \quad (21)$$

where τ and α are only parameters. This functional form was taken from the discussion of Cavendish Lab. However, they state that for it to be valid it is required that $U_{\text{max}} \gg k_B T$ where U_{max} is the maximum of the potential in region between the wells. In this case, this corresponds to $U_{\text{max}} = 0.0625$ which is not much bigger than the values used for the temperature.

On the other hand, the second fit (black line) is of the form

$$t_{\text{escape}}(T) = \tau e^{U_{\text{max}}/k_B T}. \quad (22)$$

As we can see from Fig. 7, this fits much better the numerical results. This was proposed only on the assumption that the Boltzmann Distribution is valid:

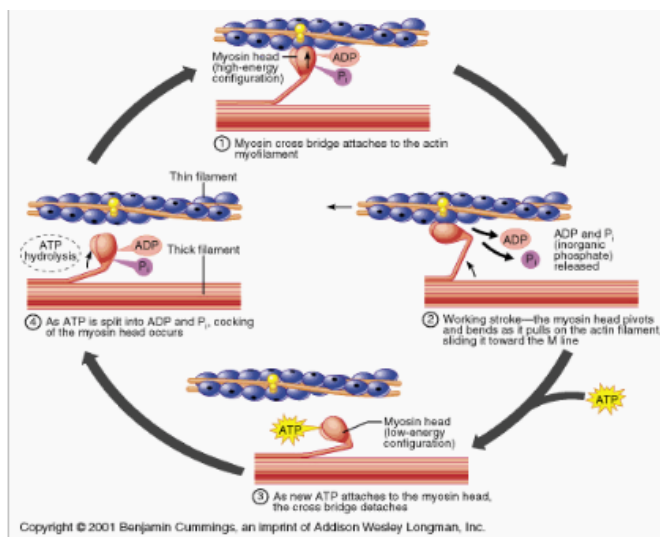
$$t_{12} = \frac{P(x_1)}{P(x_2)} = e^{-\Delta U_{12}\beta} \quad (23)$$

where the t_{12} is the time it takes the particle to get from x_1 to x_2 and ΔU_{12} is the energy difference between these two positions. In this case $x_1 = 0$ and $x_2 = 1$, therefore $\Delta U_{12} = U_{\text{max}}$.

3.3 Applications

1. Give at least one example of a chemical reaction where the barrier height is so large that equilibrium is not reached on reasonable time scales.

One example of a reaction that does not proceed to equilibrium on reasonable time scales is the power stroke motion of the myosin II, the active motion within sarcomeres of skeletal muscles that are responsible for filament movement and overall movement of the muscle. In frogs, the kinetics of the power stroke has been studied thoroughly. The figure below illustrates how binding of ATP, at the bottom of the figure, is necessary for the rest of the cycle to complete. The binding of ATP brings the myosin II head group from its more stable “down” position, to the less stable “up” position. The activation energy of this transition in conformation in frogs is roughly 33.30 ± 4.49 kJ/mol at 20°C (1). This barrier is too large to overcome at STP on a reasonable time scale.



2. What biochemical process can speed up equilibration? Explain briefly how this works by altering the the picture of a particle diffusing over a barrier of fixed height.

Figure 8 shows how the presence of a catalyst can alter the activation energy of a given reaction. In biochemistry, enzymes act as catalysts and lower the activation barrier by hydrolysis of the high energy bond between the beta and gamma phosphoryl groups in ATP. Given that the activation barrier is now less, it is easier for substrates to overcome the barrier. The hydrolysis of the high energy bond in ATP is the active mechanism behind the reduction in activation energy for biochemical reactions.

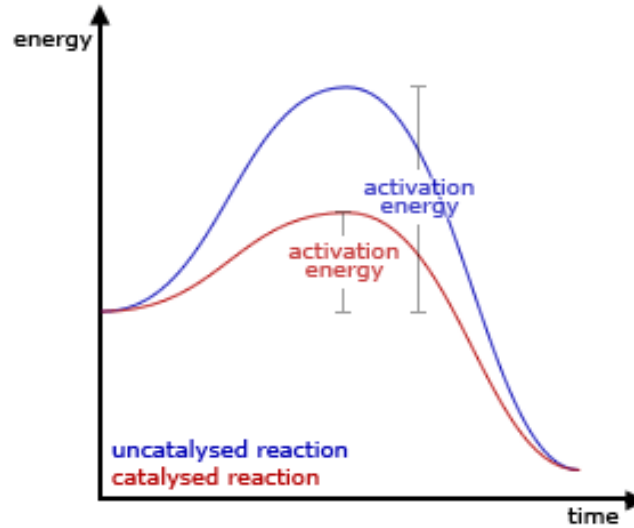


Figure 8: Catalyst altering the activation energy.

3. Can you see how diffusion over a barrier is related to the motion of molecular motors such as myosin?

The above two figures applies to the motion of the myosin heavy chains. Binding of ATP to the myosin heavy chain (head group) causes a dissociation from the actin filament of the sarcomere. The hydrolysis of ATP $\text{ADP} + \text{Pi}$ causes a change in the conformation of myosin heavy chain that allows it to rebind to the actin filament. The hydrolysis of the phosphate group lowers the activation energy which allows the myosin heavy chain to change conformations. Subsequent release of the Pi and ADP cause the myosin head chain to power stroke, that is, change conformation again. The release of both parts allows for the power stroke by changing the conformation of the myosin head again with the unbinding of ADP and Pi . Overall, ATP is used here directly by the myosin head groups to provide movement by surmounting the activation barrier. In that way, the movement of myosin is a direct visual cue that the energy barrier has been overcome.