Chem 163, Lecture 5

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0.1 Langevin equation of an overdamped particle

In the previous class we introduced the Langevin equation of motion. This equation is essentially a statement of Newton's laws, where we have added a fluctuating term to include all the random forces from interactions with the solution. The discussion was somewhat complicated, so let's start by reviewing the main results, which were actually quite simple.

We saw that for a particle moving in fluid, there is a momentum relaxation time $\tau_m = m/\gamma$ where m is the mass of the particle and γ is its drag coefficient. For aircraft carriers this time can be long, but for microscopic objects this time is very, very short (typically nanoseconds or less). To see why this time is small for small objects, note that mass scales like r^3 while drag scales like r, so τ_m scales like r^2.

If we look at timescales long compared to the momentum relaxation time, then we can ignore inertial effects. The equation of motion becomes:

$$\frac{dx}{dt} = \frac{1}{\gamma}F(t) + \frac{1}{\gamma}\xi(t), \tag{1}$$

where $F(t)$ is some externally applied force, and $\xi(t)$ is the randomly fluctuating force from the solution.

For the moment, let's assume that the external force is zero and let's integrate this equation from t to $t + \tau$, to get:

$$\Delta x(t) = \frac{1}{\gamma}\int_0^t \xi(t')dt'. \tag{2}$$

Square both sides of the equation and take an average to calculate the mean-square displacement

$$\begin{aligned}
\left\langle \Delta x^2 \right\rangle &= \frac{1}{\gamma^2}\left\langle \left(\int_0^t \xi(t')dt'\right)^2 \right\rangle & (3)\\
&= \frac{1}{\gamma^2}\int_0^t \int_0^t \left\langle \xi(t')\xi(t'') \right\rangle dt'dt''. & (4)
\end{aligned}$$

So you see how the autocorrelation function of the noise appeared when we calculated the square and averaged. This kind of thing happens all the time. To evaluate the integral, we need to know something about the autocorrelation of the noise. We assume that the force from the solution has no net direction, so

$$\langle \xi(t) \rangle = 0. \tag{5}$$

We also assume that the force varies over very short timescales, i.e. that there is no correlation between the force from one moment to the next. We can convert that statement into the mathematical abstraction that the autocorrelation of the random force is proportional to a δ-function. We'll see at the end that it doesn't matter what function we picked for the autocorrelation of the noise, provided that we pick something which goes to zero fast enough that its integral quickly converges. For the moment, let's leave the proportionality coefficient, B, unknown:

$$\langle \xi(t')\xi(t'') \rangle = \nu\delta(t' - t''), \tag{6}$$

where ν is an as-yet-unknown proportionality factor. The expression for $\langle \Delta x^2 \rangle$ then becomes

$$\begin{aligned} \left\langle \Delta x^2 \right\rangle &= \frac{1}{\gamma^2}\int_0^t \int_0^t \nu\delta(t' - t'')dt'dt'' && (7) \\ &= \frac{1}{\gamma^2}\int_0^t \nu dt' && (8) \\ &= \frac{1}{\gamma^2}\nu t. && (9) \end{aligned}$$

Something remarkable happened here. Even though we took a double integral over time, the result we got was proportional to t only, not t^2. On a plot of the integrand as a function of t' and t'', the δ function picked out the diagonal elements. We did something similar in discrete time when we considered the mean-square value of a sum of zero-mean random variables, where all the cross terms vanished upon taking the average, and only the diagonal terms (i.e. each term multiplied by itself) survived the averaging. You can see from this that any such integral where the random variable has finite correlation time will have similar linear scaling with time.

But we know from the definition of the diffusion constant $\langle \Delta x^2 \rangle = 2Dt$, so we have $2D = \nu/\gamma^2$, or $\nu = 2D\gamma^2$. But we previously showed $\nu = 2\gamma k_B T$, so $D = k_B T/\gamma$. Our final result, which turns out to be very useful is:

$$\langle \xi(t')\xi(t'') \rangle = 2\gamma k_B T \delta(t' - t'') \tag{10}$$

Here you see again that there's a relation between the magnitude of the fluctuating forces ($\langle \xi(t')\xi(t'') \rangle$), the temperature, and the drag on the particle. If you want to do a simulation of any process near equilibrium, you'll use a similar set of equations.

1 Brownian motion in a harmonic well

Let's now apply the Langevin approach to the problem of Brownian motion of a particle in a harmonic well. This is a paradigm for a great many problems, ranging from a particle held by laser tweezers to motion of subunits within a protein, to the motion of a bead tethered by a piece of DNA. Here we'll only consider motion on timescales long compared to the inertial relaxation time.

1.1 Laser Tweezers

Before we get into the particle dynamics, let me tell you a bit about optical traps. When a laser beam is tightly focused on a small particle in solution, the laser beam draws the particle into the focus where the intensity is highest. There are two physically different pictures to describe why this happens. If the particle is small, we can think of it as a small polarizable sphere that responds to the applied optical frequency electric field by producing an optical frequency oscillating dipole. The optical electric field is:

$$\mathbf{E}(\mathbf{r},t) = \mathbf{E_0}(\mathbf{r})sin(\omega t), \tag{11}$$

where ω is the optical frequency and $\mathbf{E_0}$ is governed by the shape of the laser focus. The induced dipole moment is:

$$\mathbf{p} = \alpha\mathbf{E}, \tag{12}$$

where α is a material property that describes the polarizability of the particle. It is proportional to the volume of the particle and the refractive index squared.

In an *inhomogeneous* electric field, an electric dipole experiences a net force given by

$$\mathbf{F} = \left\langle \mathbf{p}\cdot\nabla\mathbf{E}\right\rangle, \tag{13}$$

where the average is taken over multiple optical cycles. We can rewrite this equation as

$$\begin{aligned} \mathbf{F} &= \alpha\left\langle \mathbf{E}\cdot\nabla\mathbf{E}\right\rangle & (14)\\ &= \frac{1}{2}\alpha\nabla\left\langle |\mathbf{E}|^2\right\rangle. & (15) \end{aligned}$$

But the time-average electric field in a light wave is proportional to the intensity of the light via $I = c\epsilon_0 n|\mathbf{E_0}|^2/2 = c\epsilon_0 n\left\langle|\mathbf{E}|^2\right\rangle$, (recall that $\left\langle|\mathbf{E}|^2\right\rangle = |\mathbf{E_0}|^2/2$. So the force is just proportional to the gradient in the intensity:

$$\mathbf{F} = \frac{1}{2}\frac{\alpha}{c\epsilon_0 n}\nabla I. \tag{16}$$

But if the force is a gradient of something, then we can define a potential function from $U = -\int \mathbf{F}(\mathbf{r})\cdot d\mathbf{r}$, whence

$$U_{optical} = -\frac{1}{2}\frac{\alpha}{c\epsilon_0 n}I. \tag{17}$$

A laser focus is typically approximately Gaussian in cross-section, so the potential function looks like a Gaussian, which near its minimum looks like a parabola.

An alternate way to describe the same physics is to consider the momentum of the photons. Each photon carries a momentum $\mathbf{p}_1 = \hbar\mathbf{k}$, where $\mathbf{k} = (2\pi/\lambda)\hat{\mathbf{k}}$ and energy $E_1 = \hbar ck$. Thus the total momentum flux (momentum per unit area per unit time) in a light beam is $\mathbf{p} = (I/c)\hat{\mathbf{k}}$. If you look a the lensing of the beam by the spherical particle, you also get a force toward the region of highest intensity.

1.2 particle dynamics

Now we'll study a little particle in an optical trap. The Langevin equation becomes:

$$\frac{dx}{dt} = \frac{1}{\gamma}\left(-kx + \xi(t)\right), \tag{18}$$

where $\langle \xi(t) \rangle = 0$ and $\langle \xi(t')\xi(t'') \rangle = 2\gamma k_B T \delta(t' - t'')$. This equation is easy to solve. For an arbitrary time-dependent force

$$x(t) = \frac{1}{\gamma}\int_{-\infty}^{t} dt' \exp[-\frac{(t-t')}{\tau}]\xi(t'), \tag{19}$$

where

$$\tau \equiv \gamma/k \tag{20}$$

is the relaxation time of the trap. Thus

$$\begin{aligned}
\langle x(t)x(0) \rangle &= \frac{1}{\gamma^2}\int_{-\infty}^{t} dt' \int_{-\infty}^{0} dt'' \exp[-(t-t'-t'')/\tau] \langle f(t')f(t'') \rangle \\
&= \frac{1}{\gamma^2}\int_{-\infty}^{t} dt' \int_{-\infty}^{0} dt'' \exp[-(t-t'-t'')/\tau] 2\gamma k_B T \delta(t'-t'') \\
&= \frac{2k_B T}{\gamma}\int_{-\infty}^{0} dt'' \exp[-(t-2t'')/\tau] \\
&= \frac{k_B T}{k}\exp(-t/\tau).
\end{aligned} \tag{21}$$

What's the variance in the position of the particle? Well, that's just given by $\langle x(0)x(0) \rangle$ which is just $k_B T/k$. But we already knew this! Let's rearrange the equation to $k\langle x^2 \rangle = k_B T$. Or

$$\frac{1}{2}k\left\langle x^2 \right\rangle = \frac{1}{2}k_B T. \tag{22}$$

That's just equipartition!

In summary, there are two ways to describe the motion of a diffusing particle (or any stochastically fluctuating quantity, for that matter). There is the Smoluchowski approach in which one describes the time-evolution of the probability distribution, and there is the Langevin approach, in which one calculates the statistical properties of individual trajectories, and then averages over all trajectories. If handled correctly, these two approaches always give the same result. The Stokes Einstein relation is a special case of something called the fluctuation dissipation theorem which is discussed in the Appendix.

2 Fluorescence Correlation Spectroscopy

Now we will talk about two very important biophysical experimental techniques that are used to characterize solutions of biomolecules. First we'll talk about FCS, then we'll talk about dynamic light scattering (DLS).

Fluorescence correlation spectroscopy is a technique invented in the 1970's to measure physical properties of fluorescent particles, such as fluorescently labeled biomolecules. It is most commonly used to measure diffusion coefficients, but it can also be used to measure reaction kinetics, rotational dynamics, excited state lifetimes, and triplet-state lifetimes.

Here is how FCS works. You bring a laser beam to a tight focus inside a microscope. The laser beam excites molecules that pass through the focus. These molecules then emit fluorescence light at a red-shifted wavelength. A dichroic filter separates the fluorescence light from back-scattered excitation light. The fluorescence light is focused onto a pinhole, which removes light from out-of-focus sources, and then the light is re-focused onto a photodetector–either an avalanche photodiode (APD) or a photomultiplier tube (PMT). You record intensity as a function of time, as molecules of analyte pass through the detection volume.

FCS is most effective at concentrations of roughly 1 analyte molecule per detection-volume. What concentration does this correspond to? A detection volume is shaped roughly like a prolate spheroid, elongated along the z-axis, with major axis 1 micron and minor axes 0.3 microns. Thus the detection volume is about 0.1 cubic micron. This corresponds to 10^{16} molecules/Liter, or a concentration of about 10 nM. So FCS only works at low concentrations.

Incidentally, 10^{-9} M is a nanomole, 10^{-12} M is a picomole, 10^{-15} M is a femtomole. Does anybody know the prefix for a single molecule, $1/6.02 \times 10^{23}$ of a mole? It's called a guacamole. This is because it's 1/Avocado's Number.

In FCS, we calculate the normalized autocorrelation of the fluorescence intensity:

$$g^{(2)}(\tau) = \frac{\langle I(t)I(t+\tau)\rangle}{\langle I\rangle^2} - 1. \tag{23}$$

Let's look at this formula in detail. As $\tau \to \infty$ the fluorescence fluctuations are uncorrelated, so $\langle I(t)I(t+\tau)\rangle \to \langle I(t)\rangle \langle I(t+\tau)\rangle = \langle I\rangle^2$. Thus as $\tau \to \infty$, $g^{(2)}(\tau) \to 0$.

As $\tau \to 0$, the numerator becomes $\langle I^2\rangle$. We can write $-1 = -\langle I\rangle^2 / \langle I\rangle^2$, so we find

$$g^{(2)}(0) = \frac{\langle \Delta I^2\rangle}{\langle I\rangle^2}, \tag{24}$$

that is $g^{(2)}(0)$ is a measure of fractionally how big the fluctuations in intensity are.

Now let's develop a model for $g^{(2)}(0)$ and figure out how $g^{(2)}(\tau)$ decays with time. At any instant the molecules appear to be randomly distributed throughout the solution. If, on average, there are λ molecules within the confocal spot, then the exact number at any instant fluctuates according to Poisson statistics:

$$P_\lambda(n) = \frac{e^{-\lambda}\lambda^n}{n!}. \tag{25}$$

You should check that this distribution is normalized, i.e. $\sum_{n=0}^{\infty} P_\lambda(n) = 1$. The Poisson distribution has the interesting property that the mean is equal to the variance:

$$\sum_{n=0}^{\infty} nP_\lambda(n) = \lambda, \tag{26}$$

and

$$\sum_{n=0}^{\infty}(n-\lambda)^2 P_\lambda(n) = \lambda. \tag{27}$$

Let's make the reasonable assumption that the fluorescence intensity is proportional to the instantaneous number of molecules within the confocal spot: $I = an$, where a is the brightness of a single molecule. So $\langle I \rangle = a\lambda$ and $\langle \Delta I^2 \rangle = a^2\lambda$. Then we have:

$$g^{(2)}(0) = 1/\lambda. \tag{28}$$

This result tells us that we can measure the concentration of a solution by looking at the variance of the fluorescence intensity: more concentrated solutions have smaller fluctuations in the intensity relative to the mean intensity. The beauty of this approach is that you don't need to know the brightness of your laser or the brightness of the individual molecules. Those factors cancel out.

You can also calculate the average brightness per molecule by calculating $\langle \Delta I^2 \rangle / \langle I \rangle = a$. For steady-state fluorescence measurements, you have two unknowns, a and λ, but by looking at the fluctuations you can get two pieces of information, and solve for both unknowns. Similar noise analysis tricks were used to estimate the electrical conductance of a single ion channel long before electronics were sensitive enough to detect the current through a single channel.

Most of the time particles diffuse out one of the sides of the excitation volume, rather than the top, because of the prolate shape. Thus it is useful to define a characteristic timescale of $\tau_d = r_0^2/4D$, where r_0 is the radius of the excitation beam in the x-y plane, and the factor of 4 is because we're considering diffusion in the x-y plane. We can define an effective volume of the confocal spot by:

$$V_{\text{eff}} = r_0^2 z_0 \pi^{3/2}, \tag{29}$$

where z_0 is the height of the confocal spot. A more detailed analysis of diffusion in this geometry gives:

$$g^{(2)}(\tau) = \frac{1}{CV_{\text{eff}}} \cdot \frac{1}{(1+\frac{\tau}{\tau_d})} \cdot \frac{1}{\sqrt{1+\left(\frac{r_0}{z_0}\right)^2 \frac{\tau}{\tau_d}}}, \tag{30}$$

where C is the concentration of the solution. By fitting FCS curves you can extract the diffusion time. It is difficult to know the exact size and shape of the confocal illumination spot, so standard procedure is to take an FCS trace on a reference dye of known diffusion coefficient, and then to compare that curve to the curve obtained from the experimental sample.

If one looks at FCS at very short times, the above analysis breaks down. The reason is that each dye molecule fluctuates in intensity, independent of its diffusive motion in and out of the focus. Many fluorescent dye molecules blink on and off because of intersystem crossing into a dark triplet state. [EXPLAIN ISC AND TRIPLET STATES]. Environmental conditions such as the concentration of oxygen or the presence of triplet state quenchers can affect this blinking. The blinking leads to additional fluctuations in intensity that enhance $g^{(2)}(\tau)$ at short times. On shorter timescales molecules appear to flicker because of rotational diffusion. If the incident light is linearly polarized, molecules will grow and shrink in intensity as their absorption transition dipoles align and misalign with the polarization.

On very short timescales $g^{(2)}(\tau)$ actually goes to -1 because of the discreteness of photons: immediately after a molecule emits a photon, the molecule cannot emit another photon until it is re-excited and spontaneously decays. This photon "antibunching" is a signature of single quantum emitters. Most FCS experiments do not reach to short enough times to see photon antibunching, although this has been seen in the fluorescence from single quantum dots (see e.g. Lounis *et al.* "Photon antibunching in single CdSe/ZnS quantum dot fluorescence," Chemical Physics Letters 329 (2000) 399-404).

3 Dynamic Light Scattering

Dynamic light scattering is an even older technique for characterizing solutions of polymers or macromolecules. You take a macroscopic cuvette of the solution, and shine a monochromatic laser beam into it. You then position a photodetector at an angle θ relative to the incident light. Of course most of the laser light goes right through the solution and misses the photodetector, but a small portion of the incident light gets scattered at angle θ and is detected by the photodetector. The intensity of this light fluctuates with time. You measure the autocorrelation of these fluctuations, and then repeat the measurement for many values of θ.

There are two ways to approach the theory of dynamic light scattering. One may either consider discrete, independently moving scattering particles, and then calculate the interference pattern resulting from light scattering off each particle; or one may consider smoothly varying sinusoidal fluctuations in the density of particles, and calculate the diffraction of light off this variation. Of course both results give the same final answer.

We'll take the latter approach. Before we get into the light-matter interaction, let's talk about the dynamics of sinusoidal concentration fluctuations of Brownian particles. This kind of concentration fluctuation has a particularly simple time-dependent behavior. We start with the diffusion equation:

$$\frac{\partial C}{\partial t} = D\nabla^2 C. \tag{31}$$

Let's consider the 1-D version of this:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}. \tag{32}$$

Let's consider a special class of initial conditions, $C_0(x) = A(t)\sin(kx)$. This is a strange initial condition to pick, since we don't usually think about sinusoidal concentration fluctuations, but we'll see that it has interesting properties. The two spatial derivatives then just pull out a factor of $-k^2$. Then

$$\frac{dA}{dt} = -Dk^2 A. \tag{33}$$

The solution to this is simply

$$A(t) = A(0)e^{-Dk^2 t}. \tag{34}$$

So sinusoids are an eigenfunction of the diffusion equation. This surprising fact is less surprising when you think about the analogy between the diffusion equation and the Schrödinger equation. We know that for the Schrödinger equation in free space, the eigenfunctions are plane waves. So of course the same has to be true for the diffusion equation. The difference is that the factor of i in Schrödinger makes the time dependence oscillatory, while for diffusion it is a simple exponential decay.

The factor of k^2, means that high spatial frequency fluctuations decay much faster than long-wavelength fluctuations. This k^2 dependence is sort of expected when you think about the relation $\langle \Delta x^2 \rangle = 2Dt$. This equation has exactly the same form as the momentum relaxation of a particle in liquid (with the substitution $Dk^2 \to \gamma/m$), or the position relaxation of an overdamped particle in a harmonic well (with the substitution $Dk^2 \to k_{\text{spring}}/\gamma$), where in both cases γ is the drag coefficient of the particle.

When you learned about X-ray crystallography, you probably learned about the Bragg scattering condition: if you align a monochromatic light wave with a periodic structure in just the right way, the light wave will be diffracted off at a specific angle. The Bragg condition is

$$2d \sin\frac{\theta}{2} = n\lambda/n_0 \tag{35}$$

where θ is the angle between the wavevectors of the incident and the scattered waves (equivalently $\theta/2$ is the angle between the incident light and the line parallel to the surface), n is an integer, d is the spacing between the scattering planes, λ is the wavelength in free space, and n_0 is the refractive index of the medium. We'll always deal with $n = 1$. If we imagine a concentration fluctuation, the peak-to-peak distance d is related to the wavevector k by $d = 2\pi/k$. So we have

$$k = \frac{4\pi n_0}{\lambda} \sin\frac{\theta}{2}. \tag{36}$$

Next we need to relate the amplitude of the concentration fluctuations to the amplitude of the diffracted intensity. A lot of factors go into this, such as the size, shape, and refractive index of the diffusing particles. But the main point for us right now, is that the diffracted intensity, $I(t)$, is proportional to $A(\mathbf{k}, t)^2$. The square comes in because we know a concentration fluctuation and its negative, will both create the same intensity of diffracted light on the detector (equivalently, the measured intensity is proportional to the *square* of the diffracted electric field amplitude).

So if we calculate

$$g^{(2)}(\tau) = \frac{\langle I(t)I(t+\tau)\rangle}{\langle I\rangle^2} - 1 \tag{37}$$

as we did for FCS, we find that it decays as

$$g^{(2)}(\tau) \propto e^{-2Dk^2\tau}. \tag{38}$$

By fitting this decay constant at multiple values of θ one can extract the diffusion coefficient. If you have a heterogeneous mixture with multiple diffusion coefficients, you can learn something about the distribution of particle sizes.

4 Appendix: General statement of the Fluctuation Dissipation Theorem

We've been talking a lot about diffusion and correlation functions. To conclude this first part of the course we will discuss (without proof) an extremely general and powerful result called the fluctuation dissipation theorem (FDT). The proof of this is on pages 58-62 of Doi and Edwards.

In order for the statement to make sense, we need to define some quantities. Consider an arbitrary dynamical system, with some set of internal degrees of freedom $\mathbf{x}$, and two state functions of interest, $\mathbf{A}(\mathbf{x})$ and $\mathbf{B}(\mathbf{x})$ (henceforth we'll assume A and B are scalars, although the derivation is completely general). Now consider that we perturb the quantity B in some way, and measure the response of A. The way in which we will perturb B is that we'll add to the total energy of the system a time-dependent term of the form:

$$U(t) = -h(t)B. \tag{39}$$

For instance, $h(t)$ could be an external magnetic field and B the magnetic dipole moment; or h could be a force on a particle and B a position of the particle; or h could be an electric field and B an electric dipole moment; or h could be a voltage and B a charge. The only requirement is that h be not too large, so that the response of the system is linear in h.

We want to measure the response of A to the perturbation induced by h. The most general form of the response is:

$$A(t) = \langle A \rangle_0 + \int_{-\infty}^{t} d\tau G(t-\tau)h(\tau). \tag{40}$$

This response is causal (i.e. $A(t)$ only depends on h at earlier times) and linear (i.e. doubling h doubles A), but otherwise totally unconstrained. $\langle A \rangle_0$ is the equilibrium value of A in the absence of h. The FDT states that:

$$G(t) = -\frac{1}{k_B T}\frac{d}{dt}\langle A(t)B(0)\rangle, \tag{41}$$

where the average is taken over the equilibrium fluctuations in A and B.

If A and B are the same thing, then the FDT takes a particularly simple form. Define the growth function $\beta(t)$ to describe the response of A to a stepwise application of h. That is, if h is suddenly turned on, then

$$A(t) - \langle A \rangle = \beta(t)h. \tag{42}$$

This implies that

$$\beta(t) = \int_0^t dt' G(t'). \tag{43}$$

Integrating both sides of the FDT yields:

$$\begin{aligned}
\beta(t) &= \frac{1}{k_B T}(c_{AA}(0) - c_{AA}(t)) \\
&= \frac{1}{2k_B T}(\langle A(t)^2 \rangle + \langle A(0)^2 \rangle - 2\langle A(t)A(0)\rangle) \\
&= \frac{1}{2k_B T}\left\langle (A(t)-A(0))^2 \right\rangle.
\end{aligned} \tag{44}$$

In going from the first line to the second we took advantage of the fact that $c_{AA}(0) = \langle A(0)^2 \rangle = \langle A(t)^2 \rangle$.

Let's do an example. Suppose that A represents the x-coordinate of a Brownian particle. Then $\beta(t) = t/\gamma$. The FDT then states that:

$$\frac{1}{\gamma} = \frac{D}{k_B T}. \tag{45}$$

Nobody knows whether there exist nonlinear generalizations of the FDT.

The quantum version of the FDT has the same idea, but a slightly different expression.

5 Applications of the FDT

Now I'll give you another example of the FDT from my own research. I'll show you how I measured the mechanical response of a single molecule of DNA by passively watching its thermal fluctuations in solution.

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There's an analog of the Stokes Einstein formula for electric current in resistors. Consider the following circuit: [DRAW TWO RESISTORS OF RESISTANCE R, CONNECTED IN PARALLEL]. Consider that through some magical means we induce a current to flow around in a circle in this circuit. Then the voltage across each resistor obeys:

$$\frac{dq}{dt} = \frac{1}{2R} V. \tag{46}$$

This is Ohm's law, and has the same structure as the formula for the Stokes drag on a particle moving in a viscous liquid. The quantity $2R$ plays the role of the drag coefficient. We can thus calculate a "diffusion coefficient" for charge using the analog of the Stokes-Einstein relation:

$$D_{\text{charge}} = \frac{k_B T}{2R}. \tag{47}$$

This means that in time interval t, the mean-square charge flow is:

$$\begin{aligned} \left\langle \Delta q^2 \right\rangle &= 2\frac{k_B T}{2R} t \\ &= \frac{k_B T}{R} t, \end{aligned} \tag{48}$$

or equivalently, the mean-square current is ($i = \Delta q/t$):

$$\left\langle i^2 \right\rangle = \frac{k_B T}{R t}. \tag{49}$$

This implies that the voltage fluctuations in the circuit are of magnitude

$$\left\langle V^2 \right\rangle = 4R \frac{k_B T}{t}. \tag{50}$$

This unavoidable thermal noise is a feature of all electrical circuits operating at room temperature and is called Johnson-Nyquist noise.

Incidentally, the voltage noise on a capacitor can be obtained simply from the equipartition theorem. The energy required to charge up a capacitor to voltage V is:

$$U = \frac{1}{2} C V^2. \tag{51}$$

V is our quadratic internal coordinate, to which we can apply the equipartition theorem. Thus, for a capacitor:

$$\left\langle V^2 \right\rangle = \frac{k_B T}{C}. \tag{52}$$