The above examples represent some of the more common applications of the techniques of radioactive counting and isotopic dilution in medical diagnosis. Tracer methods are also widely used in biochemistry: by labeling a metabolic precursor and determining the extent of enrichment in subsequent metabolic products, one can clarify the chemical mechanisms by which the molecules are transmuted from one form into another. Examples may be found in biochemistry texts.

8.B. ELECTRICAL NOISE

In most biophysical measurements, the data appear on some sort of electrical device, ranging from pH meters to the recorders that monitor body function. Contrary to what one might expect, however, the quality of the response from such devices is sometimes determined by the intrinsic *noise* of the device, rather than the weakness of the *signal* being displayed—it is *signal-to-noise ratio* that is the critical quantity. Since the biological concentrations of most substances are rather low compared to laboratory optimum, it is clear that direct study of interesting substances will generally involve weak responses, so that one should have a feeling for the origin of the noise one will observe in the electrical device and what can be done about it. Fortunately, the nature of some kinds of electrical noise can be understood quite simply from the random walk model.

8.B.1. Shot Noise

Any circuit containing vacuum tubes or transistors contains one or more discontinuities: the cathode-anode separation in a vacuum tube or the junction in a transistor. A measurement of electric current consists of counting the electrons that cross such a junction. However, as with radioactive counting, the probability that any one electron will cross the junction is much less than one, while there are a large number of electrons that could potentially go across. We have already done the statistics for this situation: if the number of electrons crossing such a junction per unit time is (I/e), where I is the current (charge units/sec) and e is the number of charge units per electron, then the total number of electrons that will pass through the circuit in some time, τ, is just

$$\bar{m} = \frac{I\tau}{e} \qquad (8\text{-}25)$$

and the imprecision in measurement of that number is exactly analogous to the imprecision in the number of radioactive counts from a sample of many nuclei, and is given by

$$\sqrt{(m - \bar{m})^2} = \Delta m = \sqrt{\frac{I\tau}{e}} = \sqrt{\bar{m}} \qquad (8\text{-}26)$$

The signal-to-noise ratio, S/N, is thus

$$S/N = \frac{\bar{m}}{\sqrt{\bar{m}}} = \sqrt{\frac{I\tau}{e}} \tag{8-27}$$

Equation 8-27 shows that in order to increase the signal-to-noise ratio by a factor of *two*, it is necessary to increase the signal (input) by a factor of *four* (rather than by a factor of *two*, as one might expect from intuition). To understand the factor τ in Eq. 8-27, one must ask the purpose of the circuit in question. Typically, one desires that a particular circuit respond as quickly as necessary to a particular change: a recorder in a spectrophotometer must be able to register a signal by the time the monochromator has scanned the desired wavelength region; a pH meter must be able to register the pH-reading in the time it takes to deliver titrant, and so forth. The time constant, τ, represents the *shortest time during which the circuit must be able to register a response.* In electrical vernacular, it is more common to refer to the *bandwidth* of a circuit, defined as

$$\text{Bandwidth} = \frac{1}{\tau} \tag{8-28}$$

The bandwidth then represents the fastest (*largest*) *frequency* at which the circuit can respond to a change in signal. Shot noise may thus be reduced by "filtering" out the higher frequencies – that is, reducing the "bandwidth," or (equivalently) increasing the "time constant" of the circuit.

The results of the preceding paragraph, while quantified in Eq. 8-27,

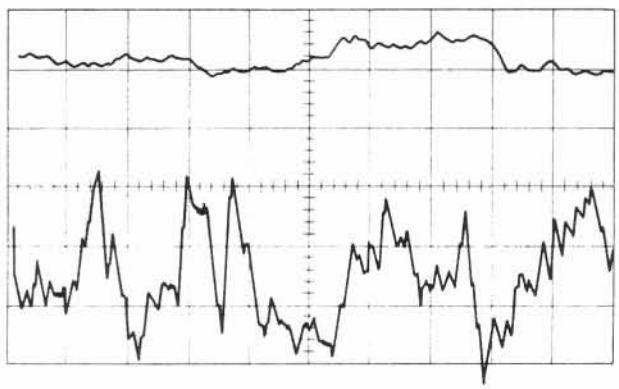

FIGURE 8-3. Oscilloscope trace of shot noise in a photocell circuit (the detector for a spectrophotometer). The upper trace corresponds to a circuit time constant of ten times that of the lower trace. In agreement with Eq. 8-27, the amplitude of the noise is reduced by a factor of about $(10)^{1/2}$ in the upper trace compared to the lower. (From N. Davidson, *Statistical Mechanics*, McGraw-Hill, N. Y., 1962, p. 300.)

$\sqrt{\frac{I\tau}{e}}$ (8-27)

increase the signal-to-noise ratio
ase the signal (input) by a factor
one might expect from intuition).
must ask the purpose of the cir-
t a particular circuit respond as
e: a recorder in a spectrophotom-
he time the monochromator has
H meter must be able to register
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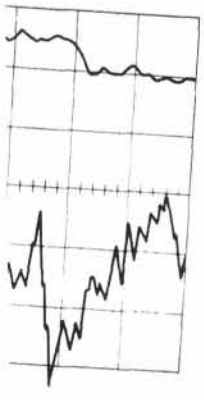
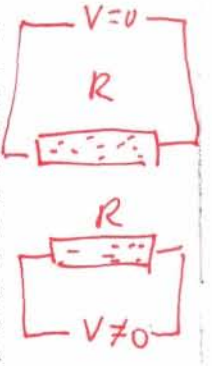


n a photocell circuit (the de-
esponds to a circuit time con-
with Eq. 8-27, the amplitude
upper trace compared to the
aw-Hill, N. Y., 1962, p. 300.)

are actually just statements of experience. It is clear that one may improve signal-to-noise by increasing signal strength, such as by widening the slit that passes incident light through a spectrophotometer. However, in doing so one lets through a wider spectrum of colors and loses "resolution," or the ability of distinguishing between absorption of light of slightly different frequency. This example is typical of experimental situations involving electronic detection—in order to obtain the most *information* (best "resolution" in this case), one is forced to give up *signal-to-noise ratio*. A similar compromise is involved in curing the "bandwidth" problem; Fig. 8-3 shows that it is simple to reduce the *noise* from a recorder pen by making it respond more slowly (then the pen no longer "sees" the rapid noise flickering), but in order for the pen to respond to the *desired signal* (say, an absorption peak as the recorder sweeps through an optical spectrum), it is necessary to slow the recorder sweep rate by a corresponding factor, making the measurement require much more time for completion. This represents the other major sort of compromise with electronic detection—if noise is to be *reduced*, the experiment takes a lot *longer* to do.

Detector-Limited Noise (Noise indep of signal)

B.2. Resistor Noise (Johnson Noise, Nyquist Noise, Thermal Noise)



The recognition that this type of electrical noise was directly related to the Brownian motion (unavoidable random motion) of electrons in resistors was reached by Nyquist shortly after discovery of the phenomenon by Johnson in 1928. Electrons in any ordinary conductor are free to roam about according to their thermal energy (see Section 5). Now, because this motion is random, there may be more electrons at one end of a resistor than at the other at a given instant, resulting in a potential difference (voltage) between the two ends of the resistor. At a later instant, there will likely be a different voltage as the electrons redistribute themselves. It is possible to treat this situation by a model in which electrons are allowed to take steps either forward or backward in the resistor, using the bags and marbles solution given at the beginning of this chapter in much the same way as it was applied to the random walk and the "random coil" (Chapter 6.A.). The imprecision in voltage may be expressed as

$$\Delta \mathbf{V} = 2\sqrt{kT \cdot \mathbf{R} \cdot B} \qquad \text{(8-29)}$$

Bandwidth

where k is the Boltzmann constant, T is absolute temperature, $\mathbf{R}$ is the resistance of the resistor, and B is the frequency bandwidth under consideration.

The most significant feature of either shot noise or resistor noise is that it is constant per unit bandwidth. This is called "white" noise, by analogy

to "white" light, which has equal intensity at all frequencies. The final type of noise to be discussed does not have this property.

8.B.3. (1/f) Noise (Flicker Noise)

Particularly in solid-state devices, a serious source of noise at low frequencies is so-called "flicker" noise, which varies inversely with frequency (see Fig. 8-4). "Drift" in direct current readings – a slow meandering of the meter or recorder – is especially troublesome. The origin of this sort of noise is obscure, but may have to do with the degree of granularity in the conductor. In any case, flicker noise may be made negligible by conducting all measurements at frequencies of 1000 Hz or higher – this is one reason that many devices that must record a d.c. ("direct current") or slowly varying response have mechanical "choppers" (as in spectrophotometers, to interrupt the light beam many times per second) or electronic rapid switching to convert a d.c. signal to an a.c. ("alternating current") signal before detection.

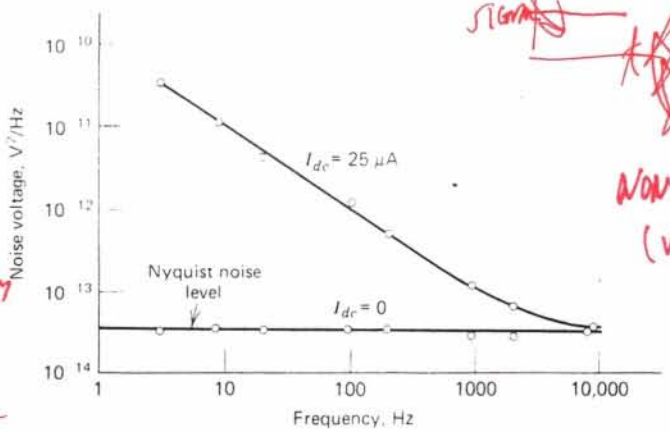


FIGURE 8-4. Experimental noise voltage of 22-MΩ composition resistor Note spectrum is $1/f$ when dc current is present and white Nyquist noise in absence of current. (From J. Brophy, *Basic Electronics for Scientists*, McGraw-Hill, N. Y., 1972.)

8.B.4. Getting Rid of Noise: Signal Averaging

The basic means for elimination of noise are filtering, modulation and phase-sensitive detection, and signal averaging. Of these, the first has been mentioned, and the second is basically the "chopping" idea of the preceding paragraph. Signal averaging is another example of the random walk at work. A simple example is provided by measurement of an absorption spectrum of a molecule.

The typical spectroscopy experiment (Section 5) is to measure the absorption of radiation by matter as a function of frequency, usually by vary-

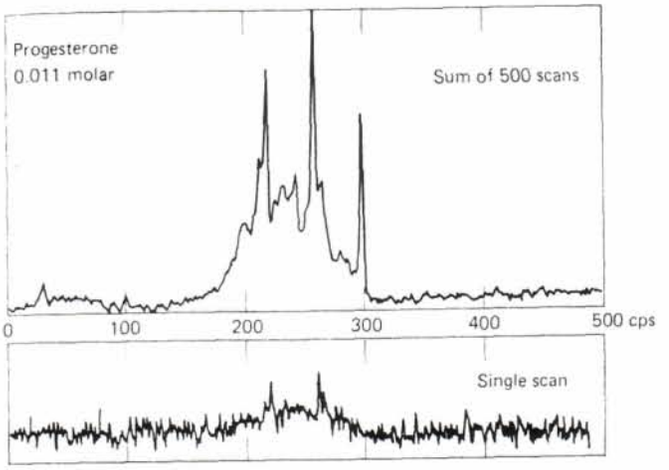


FIGURE 8-5. Proton magnetic resonance spectrum of the female sex hormone, progesterone, showing the increase in signal-to-noise that results when many individual scans are summed together to make a single composite result. (The vertical scale of the upper scan has been compressed to facilitate comparison with the lower.) [R. R. Ernst and W. A. Anderson, *Rev. Sci. Instrum. 37*, 93 (1966).]

ing the frequency of the radiation as a recorder pen moves along its chart paper. In any single such experiment, the noise in the baseline may be objectionable. However, if many scans are performed, an interesting feature appears: if a particular frequency is chosen for scrutiny, the recorder pen position in a given scan be treated as if it could move only up or down by the same amount away from the baseline. Thus (Chapter 6.A), the random walk model predicts that the average distance moved after summing many steps (many scans in this case) will increase as the square root of the number of steps (scans). This result is demonstrated graphically in Fig. 8-5, which shows the comparison between the appearance of a single scan and the sum of many scans.

EXAMPLE In a study of a dilute solution of the cell-breaking enzyme, lysozyme, by proton magnetic resonance spectroscopy, it was found that the result of adding together 30 scans of the same spectrum was to yield a single spectrum with a signal-to-noise ratio of 2:1. Assuming that the noise was "white" (i.e., random in frequency), calculate the number of scans that would have to be summed to yield a spectrum with a signal-to-noise ratio of 7:1.

Solution. The signal increases proportional to the number of scans, while the noise increases proportional to the square root of that number. Thus

$$(S/N) = (\text{constant}) \cdot \sqrt{n}$$

where n is the number of scans, so that

$$2 = (\text{constant}) \cdot \sqrt{30}$$

Now one could stop to evaluate this constant but it's quicker just to write

$$7 = (\text{constant}) \cdot \sqrt{n}$$

and take the ratio of the two equations

$$(7/2) = \sqrt{(n/30)}$$
$$n = (7/2)^2 \cdot 30 = 368 \text{ scans}$$

NOISE TYPES SUMMARY

ANALOG NOISE

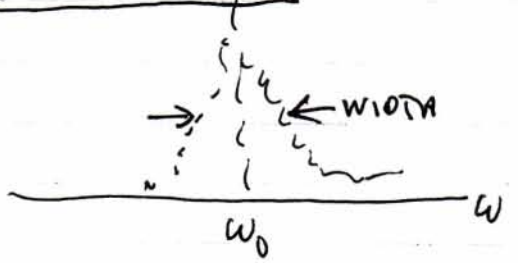
			IMPROVE?
COUNTING ("SHOT") NOISE (POISSON)	WHITE	SOURCE-LIMITED NOISE $\propto \sqrt{\text{SIGNAL}}$ $\bar{n} = \frac{I\tau}{e}$ $n = \bar{n} \pm \sqrt{\bar{n}}$ $\frac{\text{SIG}}{\text{NOISE}} = \frac{\bar{n}}{\sqrt{\bar{n}}} = \sqrt{\frac{I\tau}{e}}$	$I\uparrow, \tau\uparrow$ (LOW-PASS FILTER) $\frac{1}{\tau}$ = BANDWIDTH
RESISTOR (JOHNSON) NOISE GAUSSIAN	WHITE	DETECTOR-LIMITED NOISE INDEP OF SIGNAL $\Delta V = 2\sqrt{kT \cdot R \cdot \text{BANDWIDTH}}$	$T\downarrow$ (CRYO NMR) BANDWIDTH $\downarrow$ SIGNAL-AVERAGE (CO-ADD SCANS)
$\frac{1}{f}$ (FLICKER) NOISE	PINK $(\frac{1}{\text{FREQ}})$	SOURCE-LIMITED NOISE $\propto$ SIGNAL	CHOP AT ~1000 HZ DETECT ONLY AT THAT FREQ

DIGITAL NOISE

SAMPLING ERROR → MORE BITS/WORD ADC

SAMPLING ERROR → OVERSAMPLE

ANALOG AND DIGITAL



$\frac{\omega_0}{\sigma(\omega_0)}$ = CONSTANT

- 1/2
- 1

PK HT / NOISE $\propto \sqrt{\#\text{ PTS PER PEAK WIDTH}}$