

1 Diffusive Dynamics

The motion of freely dissolved ions and macromolecules is governed by diffusion, the random motion of molecules that results from fluctuating forces, e.g, density fluctuations in solutions that lead to fluctuating buoyancy forces. This picture largely holds in the presence of weak forces that merely add a slight bias to the motion, such as the case of electric fields across membrane pores.

1.1 Qualitative Aspects of Free Diffusion

A fundamental feature of diffusion is that there is no time-scale or distance-scale for this process, as opposed to a relaxation or attenuation process. We are simply left, in free diffusion, with the relation between root-mean-square distance, $|\vec{r}|^2$ and time, t , i.e.,

$$\langle |\vec{r}|^2 \rangle_{time\ or\ ensemble} = 6Dt \quad (1.1)$$

In one dimension

$$\langle x^2 \rangle_{time\ or\ ensemble} = \frac{1}{3} \langle |\vec{r}|^2 \rangle_{time\ or\ ensemble} = 2Dt \quad (1.2)$$

where the diffusion constant, D , is a measure of the mean free path between collisions, λ , to the mean time between collisions, τ , i.e., $D \propto \frac{\lambda^2}{\tau}$. In principle, D can be dependent on space and time, but we take it as a constant.

Let's do some simple dimensional analysis to see where the scale of the diffusion constant comes from. Consider the flux, $\vec{J}(\vec{r}, t)$ particles per second per unit area, that permeates a thin membrane between two concentration, $C(x - \frac{\lambda}{2}, t)$ and $C(x + \frac{\lambda}{2}, t)$.

BOARD SKETCH - GEOMETRY OF FLUX THROUGH FACE OF AREA A

We find, in one dimension, that

$$J(x, t) = \frac{\Delta N}{A\tau} = \frac{C(x - \frac{\lambda}{2}, t)\lambda^2 A}{2A\tau\lambda} - \frac{C(x + \frac{\lambda}{2}, t)\lambda^2 A}{2A\tau\lambda} \quad (1.3)$$

so that as $\lambda \rightarrow 0$ and $\tau \rightarrow 0$ we get

$$J(x, t) = - \left(\frac{\lambda^2}{2\tau} \right) \frac{dC(x, t)}{dx} \quad (1.4)$$

The term $\frac{\lambda^2}{2\tau}$ is defined as the diffusion term.

How big is D ? We consider a dimensional analysis for an order of magnitude estimate of the diffusion of protons in water. One gram of water contains

$\frac{2 \cdot 6 \cdot 10^{23} \text{ protons}}{\text{Mole}} \cdot \frac{\text{Mole}}{20 \text{ gm}} \cdot 1 \text{ gm} \approx 6 \cdot 10^{22} \text{ protons}$ and occupies 1 ml or 10^{24} \AA^3 . Thus, each water molecule occupies a volume of roughly 15 \AA^3 , so $\lambda \sim 2.5 \text{ \AA}$ where the inequality follows from the fact that the oxygen will exclude volume. We can estimate τ from $\frac{1}{2} m |\vec{v}|^2 = \frac{3}{2} k_B T$ ($\frac{1}{2} k_B T$ per degree of freedom), where $|\vec{v}|$ can be taken be the average velocity over one collision, or $|\vec{v}| \approx \frac{\lambda}{2\tau}$. Thus $\tau \approx \sqrt{\frac{m}{12k_B T}} \lambda = \sqrt{\frac{mc^2}{12k_B T}} \frac{\lambda}{c}$. This gives $D \approx \frac{\lambda^2}{2\tau} < \lambda c \sqrt{\frac{3k_B T}{mc^2}} = 60 \cdot 10^{-4} \text{ cm}^2/\text{s}$, which agrees VERY roughly with the measured value of $D_{H^+} = 0.9 \cdot 10^{-4} \text{ cm}^2/\text{s}$; the fact that our thermal averaging was flawed did not help. A more useful unit is $D_{H^+} = 9 \mu\text{m}^2/\text{ms}$.

FIGURE - Diffusion-coef.eps

The key is that for small molecules. $D \sim 1 \frac{\mu\text{m}^2}{\text{ms}}$

A secondary issue that we can take away from this analysis is to compare the relation between the relaxation time calculated from the requirement of equipartition (above) and that calculated for a particle moving in a viscous medium. We recall that for a particle of radius a in goop with viscosity η , the motion is governed by an equation of the form $m\ddot{r} + (6\pi\eta a)^{-1}\dot{r} = \text{Fluctuating Force}$ so that

$$\tau = \frac{mD}{k_B T} = \frac{m}{6\pi\eta a} \quad (1.5)$$

This is known as the Einstein-Stokes relation, and says the thicker the goop the slower the diffusion.

1.2 The Diffusion Equation

Let's move on and recall a couple of things about free diffusion in 3-dimensions. The flux, $\vec{J}(\vec{r}, t)$, in molecules per unit area and time, is related to the gradient in concentration, $C(\vec{r}, t)$, by

$$\vec{J}(\vec{r}, t) = -D \vec{\nabla} C(\vec{r}, t) \quad (1.6)$$

and the divergence of the flux is related to the rate of change of the concentration by

$$\vec{\nabla} \cdot \vec{J}(\vec{r}, t) = -\frac{\partial C(\vec{r}, t)}{\partial t} \quad (1.7)$$

so that

$$D \nabla^2 C(\vec{r}, t) - \frac{\partial C(\vec{r}, t)}{\partial t} = 0 \quad (1.8)$$

This is the diffusion equation in the absence of a source, which is useful if we want to determine how an initial concentration profile evolves. The general case involves the presence of sources, such as a constant plume of molecules that is created or absorbed in some region, so that the diffusion equation is of the form

$$D\nabla^2 C(\vec{r}, t) - \frac{\partial C(\vec{r}, t)}{\partial t} = 4\pi\rho(\vec{r}, t) \quad (1.9)$$

where $\rho(\vec{r}, t)$ has units of concentration per unit time. In order to solve this equation, we need to specify a boundary condition, i.e., the values of $C(\vec{r}, t)$ or $\frac{\partial C(\vec{r}, t)}{\partial n}$ on a surface within the volume of interest, where n is a normal to the surface at point \vec{r} . We also need to specify an initial condition, i.e., the values of $C(\vec{r}, 0)$.

The solution of the diffusion equation for a large variety of geometries is the subject of some excellent text books, such as Crank's "The mathematics of Diffusion" and Carslaw and Jaeger's "Conduction of Heat in Solids" (heat conduction and particle diffusion follow the same equations). Since we (that is I) want to avoid mathematical gymnastics, we will consider first the solution in an infinite region, so that there are no boundaries at finite distances. This precludes some biophysically relevant cases, such as the concentration in response to continuous flux into a cell.

The idea is to solve the diffusion for a source that exists only as a single point, which we take as the origin, for a single instance of time, which we take to be $t = 0$. Thus we seek to solve

$$D\nabla^2 G(\vec{r}, t) - \frac{\partial G(\vec{r}, t)}{\partial t} = \delta(\vec{r})\delta(t) \quad (1.10)$$

for which we build the source as a weighted average over the delta functions, or point sources, i.e.

$$\rho(\vec{r}, t) = \int d^3\vec{r}' \int dt' \delta(\vec{r} - \vec{r}')\delta(t - t')\rho(\vec{r}', t') \quad (1.11)$$

This is just a 4-dimensional version of the convolution integral we considered for linear filtering, and $G(\vec{r}, t)$ will play the role of the transfer function in the calculation of $C(\vec{r}, t)$. To complete the circle, as one says in "Phys-Rev-ese", it can be shown that

$$C(\vec{r}, t) = 4\pi \int d^3\vec{r}' \int dt' G(\vec{r} - \vec{r}', t - t')\rho(\vec{r}', t') - \int d^3\vec{r}' G(\vec{r} - \vec{r}', t)C(\vec{r}', 0) \quad (1.12)$$

The solution of the diffusion equation with a delta function source is best done by Fourier transforming from \vec{r} to \vec{k} and complete the square in the Gaussian integral. Again, it can be shown that

$$G(\vec{r} - \vec{r}', t - t') = \begin{cases} 0 & \text{if } t < t' \\ \frac{1}{\sqrt[3]{4\pi D(t-t')}} e^{-\frac{|\vec{r}-\vec{r}'|^2}{4D(t-t')}} & \text{if } t > t' \end{cases}$$

This function has a characteristic bell shape in $|\vec{r}-\vec{r}'|$ with a width, $\sim \sqrt{D(t-t')}$, that grows in time and a height, $\sim \sqrt[3]{D(t-t')}$ that decreases in time. The area under the curve is conserved, i.e.,

$$\int d^3\vec{r}' G(\vec{r} - \vec{r}', t - t') = 1 \quad (1.13)$$

FIGURE - Diffusion-Green.eps

Lets consider a few simple cases.

1.3 Examples

1.3.1 Diffusion in an infinite volume

The first is that we squirt N molecules into the center of a cell at time t and watch the distribution evolve, i.e., $\rho(\vec{r}, t) = N\delta(\vec{r})\delta(t)$ and $C(\vec{r}, 0) = \text{constant}$. The distribution is given by

$$C(\vec{r}, t) = \frac{N}{\sqrt[3]{4\pi Dt}} e^{-\frac{|\vec{r}|^2}{4Dt}} + \text{constant} \quad (1.14)$$

The qualitative dependence is seen in the diffusion of fluorescent molecules in the axon of a cell. In fact, the correspondence persists for at least 100's of seconds. The essential point for biophysics is that other potential factors, like convection, mixing, or active transport, do not come into play in a major way.

FIGURE - Aplysia-Ca

This case brings up an important point. We considered diffusion in 3-dimensions. But sometimes we project out one or two dimensions, as in the above data from Neher's laboratory. When this happens, we change the prefactor since each integral over a dimension brings down a factor of $\sqrt{4Dt}$. Thus, for example, the diffusion of particles along a string is governed by

$$\begin{aligned} C(z, t) &= \frac{1}{L_x L_y} \int_{-L_x/2}^{L_x/2} dx \int_{-L_y/2}^{L_y/2} dy C(\vec{r}, t) \\ &= \frac{1}{L_x L_y} \int_{-L_x/2}^{L_x/2} dx \int_{-L_y/2}^{L_y/2} dy \frac{N}{\sqrt[3]{4\pi Dt}} e^{-\frac{x^2+y^2+z^2}{4Dt}} \\ &= \lim_{L_x \rightarrow \infty} \lim_{L_y \rightarrow \infty} \left(\frac{N}{L_x L_y} \right) \frac{4Dt}{\sqrt[3]{4\pi Dt}} \int_{-\pi}^{\pi} d\phi \int_0^{\infty} r dr e^{-r^2} \\ &= \left(\frac{N}{L_x L_y} \right) \frac{2}{\sqrt{4\pi Dt}} e^{-\frac{z^2}{4Dt}} \end{aligned} \quad (1.15)$$

where $\frac{N}{L_x L_y}$ is the number of particles per unit area.

1.3.2 Diffusion near a nonabsorbing wall

The second case is when we just build up a layer of molecules at the planar surface, such as just inside the membrane of a cell (for $\delta r \ll R$ we are essentially next to a plane). If the membrane is impermeable, so that $\vec{J}(\vec{r}, t) \cdot \hat{n} = 0$ at $r = R$, the concentration profile is the same as for the previous case. Trivial as this case is, it is probably the most important, as nature seems to flood a cell with internal walls (endoplasmic reticulum) when it needs a way to dump ions, such as Ca^{2+} , rapidly throughout the cell.

1.3.3 Cross over from 3-dimensional to 1-dimensional diffusion

In general, when particles diffuse in a container that is much longer in one dimension than the other 2, such as an axon or dendrite, there is a crossover from 3-dimensional to 1-dimensional behavior. For an axon of radius a , the crossover occurs at a time $t = \frac{a^2}{4D}$, as we will see below. For example, for Ca^{2+} diffusion in a $1\mu m$ diameter axon the crossover occurs at $t \approx 10^{-4}s$. This is far shorter than the time-scale of Neher's data.

A simple way to observe the crossover is to solve the diffusion equation in a square tube of size L by L by L_z , and then let $L_z \rightarrow \infty$. This is a standard eigenvalue problem, although the limit is best done with the aid of Poisson's sum rule (thanks to Steve Potkin).

$$D \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) G(x, y, z, t) - \frac{\partial G(x, y, z, t)}{\partial t} = N \delta(x) \delta(y) \delta(z) \delta(t) \quad (1.16)$$

The solution to the homogeneous equation, subject to the constraint that the flux goes to zero at the walls, i.e., $\vec{J}(\vec{r}, t) = -D \vec{\nabla} C(\vec{r}, t) = 0$, so that

$$\frac{\partial C(x, y, z, t)}{\partial x} \Big|_{x=\pm \frac{L}{2}} = \frac{\partial C(x, y, z, t)}{\partial y} \Big|_{y=\pm \frac{L}{2}} = \frac{\partial C(x, y, z, t)}{\partial z} \Big|_{z=\pm \frac{L_z}{2}} = 0 \quad (1.17)$$

is:

$$\begin{aligned} G(x, y, z, t) = & \frac{N}{L^2 L_z} \sum_{m=-\infty}^{\infty} \sum_{n=-\infty}^{\infty} \sum_{p=-\infty}^{\infty} A_{mnp} e^{-D \left(\left(\frac{\pi m}{L} \right)^2 + \left(\frac{\pi n}{L} \right)^2 + \left(\frac{\pi p}{L_z} \right)^2 \right) t} \\ & \cdot \left(\delta_{m, \text{even}} \cos \frac{m\pi x}{L} + \delta_{m, \text{odd}} \sin \frac{m\pi x}{L} \right) \\ & \cdot \left(\delta_{n, \text{even}} \cos \frac{n\pi y}{L} + \delta_{n, \text{odd}} \sin \frac{n\pi y}{L} \right) \\ & \cdot \left(\delta_{p, \text{even}} \cos \frac{p\pi z}{L_z} + \delta_{p, \text{odd}} \sin \frac{p\pi z}{L_z} \right) \end{aligned} \quad (1.18)$$

We now apply the initial condition to determine the coefficients A_{mnp} . Only the even terms (including the zero mode) are nonzero for the concentration to be nonzero at the origin at $t = 0$, so that

$$\begin{aligned} C(x, y, z, t) = & \frac{N}{(2L)^2 2L_z} \sum_{m=-\infty}^{\infty} \sum_{n=-\infty}^{\infty} \sum_{p=-\infty}^{\infty} e^{-D \left(\left(\frac{\pi m}{L} \right)^2 + \left(\frac{\pi n}{L} \right)^2 + \left(\frac{\pi p}{L_z} \right)^2 \right) t} \\ & \cdot \cos \frac{2m\pi x}{L} \cos \frac{2n\pi y}{L} \cos \frac{2p\pi z}{L_z} \end{aligned} \quad (1.19)$$

There are two time scales in this problem. The short time is $\sim \frac{L^2}{D}$ and the long time is $\sim \frac{L_z^2}{D}$. For times shorter than both of these scales, the exponential decay term is negligible for all modes m , n , and p in the x , y and z direction, respectfully. Thus all terms in the triple summation may contribute. We can transform this expression from an itinerant to a localized basis via the Poisson summation formula, i.e.,

$$\sum_{m=1}^{\infty} \cos \frac{m\pi x}{L} e^{-D(\frac{m}{L})^2 t} = \frac{L}{\sqrt{4\pi Dt}} \sum_{m'=-\infty}^{\infty} e^{-\frac{(x+2m'L)^2}{4Dt}} - \frac{1}{2} \quad (1.20)$$

so that

$$\sum_{m=-\infty}^{\infty} \cos \frac{m\pi x}{L} e^{-D(\frac{m}{L})^2 t} = \frac{2L}{\sqrt{4\pi Dt}} \sum_{m'=-\infty}^{\infty} e^{-\frac{(x+2m'L)^2}{4Dt}} \quad (1.21)$$

This transformation is equivalent to the method of images. The problem is now one of free diffusion from a source located at $(x, y, z) = 0$ as well as an infinity of sources at $(x, y, z) = (\pm 2m'L, \pm 2n'L, \pm 2p'L_z)$ for the indices $m' > 0$, $n' > 0$, and $p' > 0$. This transformation makes it simple to visualize the evolution of the concentration near a wall. For example, to the extent that $L \ll L_z$, we see that the concentration near the wall defined by $x = -L/2$ builds up faster than for the case of diffusion without boundaries due to the presence of equally spaced sources at $x = 0$ and $x = -L$, etc.

FIGURE - Images-problem.eps

In this new basis, the $m' = 0$ mode dominates at short times. A similar situation holds for modes in the y and z directions in the transformed basis. Thus

$$\begin{aligned} C(x, y, z, t \rightarrow 0) &\approx N \left(\frac{1}{\sqrt{4\pi Dt}} \right)^3 e^{-\frac{(x)^2}{4Dt}} e^{-\frac{(y)^2}{4Dt}} e^{-\frac{(z)^2}{4Dt}} \\ &\approx \frac{N}{\sqrt[3]{4\pi Dt}} e^{-\frac{r^2}{4Dt}} \end{aligned} \quad (1.22)$$

We now consider intermediate times, i.e., $\frac{L^2}{D} \ll t \ll \frac{L_z^2}{D}$, and reexamine the normal mode expansion of the diffusion equation. The exponential decay term is appreciable for all modes m in the x direction and all modes n in the y direction, so that only the $m = 0$ and $n = 0$ contribute, while all modes p in the z direction may contribute. Thus

$$C(x, y, z, \frac{L^2}{D} \ll t \ll \frac{L_z^2}{D}) \approx \frac{N}{L^2 \cdot L_z} \sum_{p=-\infty}^{\infty} e^{-D(\frac{p}{L_z})^2 t} \cos \frac{p\pi z}{L_z} \quad (1.23)$$

We transform this expression into a localized basis in the z direction via the Poisson summation formula, for which the $p' = 0$ term dominates, so that

$$C(x, y, z, \frac{L^2}{D} \ll t \ll \frac{L_z^2}{D}) \approx \left(\frac{N}{L^2} \right) \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{z^2}{4Dt}} \quad (1.24)$$

Thus we recover diffusion in one dimension. At times $t \gg \frac{L_z^2}{D}$ the concentration goes to zero as the initial N particles are diluted into an infinite volume. In summary, we observe that a diffusing particles in a tube acts like they are in an infinite volume until they reaches a wall, and then they pile up at the closest wall and diffuse freely in the "long" direction.

1.3.4 Ionic flux through a channel

Our fourth case is an estimate of the flux of Na^+ through a channel of length $L \approx 10\text{\AA}$. We estimate

$$|J| \approx D \frac{\Delta C}{L} \approx 1.3 \cdot \frac{10^{-5} \text{cm}^2}{s} \cdot \frac{(120 \text{mM} - 5 \text{mM})}{10\text{\AA}} \approx 4 \cdot 10^6 \frac{\text{ions}}{\text{\AA}^2 \text{s}} \quad (1.25)$$

if the area of the pore is 3\AA^2 , we get a current of

$$|I| = e|J|A \approx \frac{1.6 \cdot 10^{-19} \text{C}}{\text{ion}} \cdot \frac{4 \cdot 10^6 \text{ions}}{\text{\AA}^2 \text{s}} 3\text{\AA}^2 \approx 2 \cdot 10^{-12} \text{Amperes} \quad (1.26)$$

FIGURE - Channel-currents.eps

1.3.5 Measurement of the resistance of the neck of a spine

Our final case is that of the rate of equilibration of a small volume with a big one. This occurs, for example, if the ion concentration in a spine is suddenly changed, and we want to know how fast this change relaxes. We consider the experiment of Denk, in which the concentration of a dye is jumped, and the relaxation to the equilibrium concentration of the neighboring dendritic shaft is measured. This measurement was used to infer the ratio of the cross-sectional area of the spine to the length of the spine shaft as a means to estimate the electrical resistance of the spine head.

FIGURE -Spines-1.eps

FIGURE - Spines-2.eps

The essential ideas are

- The volume of the spine is so small that diffusion causes it to mix in a time short compared to the equilibration time. For small molecules in a $10\mu\text{m}$ diameter spine, this time is less than 10 ms. Thus the concentration in the spine head, denoted C_h , may be taken as uniform
- The concentration in the dendritic shaft, denoted C_s , is essentially constant.
- The flux in the spine neck, with cross section area A and length L is constant.

The flux into (or out of) the spine head is

$$J(t) = D \frac{C_h(t) - C_s}{L} = \frac{D}{L} (C_h(t) - C_s) \quad (1.27)$$

The change in concentration is found by considering the change in number of particles in the head, $N_h(t) \equiv V_h \cdot C_h(t)$ where V_h is the volume of the head, i.e.,

$$JA = -\frac{dN_h(t)}{dt} = -V_h \frac{dC_h(t)}{dt} \quad (1.28)$$

so that

$$\frac{dC_h(t)}{dt} + \left(\frac{A}{L} \cdot \frac{D}{V_h}\right) C_h(t) = \left(\frac{A}{L} \cdot \frac{D}{V_h}\right) C_s \quad (1.29)$$

and the concentration recovers as

$$C_h(t) = C_s + \Delta C_h(0) e^{-\frac{L}{A} \cdot \frac{V_h}{D} t} \quad (1.30)$$

i.e., with a time constant

$$\tau = \frac{L V_h}{A D} \quad \text{so that} \quad \frac{A}{L} = \frac{V_h}{\tau D} \quad (1.31)$$

The volume of the spine head, V_h , may be measured via optical sectioning.

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BOARD SKETCH - 2 PHOTON SCANNING MICROSCOPY

FIGURE - Svoboda-1.eps

FIGURE - Svoboda-2.eps

Given values for D from bulk measurements, the data were used to estimate $\frac{L}{A}$. This in turn was used to calculate the conductance of the spine neck, denoted G_h , in terms of the cytoplasmic conductivity, g_c , as

$$G_h = \frac{A}{L} g_c = \frac{V_h g_c}{\tau D} \quad (1.32)$$

with $g_c = 4 \cdot \frac{10^{-3}}{\Omega \text{cm}}$ and $D = 4 \cdot \frac{10^{-7} \text{cm}^2}{\text{s}}$. We will soon see that the ratio of these quantities can be known very accurately, with $\frac{g_c}{D} = \frac{k_B T}{e^2 C_{ions}}$, so that

$$G_h = \frac{V_h}{\tau} \frac{k_B T}{e^2 C_{ions}} \quad (1.33)$$

The measured values are in the range $0.2 \mu\text{m}^3 < V_h < 0.6 \mu\text{m}^3$ and $60 \text{ms} < \tau < 100 \text{ms}$; they estimate $G_h > 10^{-8} \Omega^{-1}$. The importance of this number is that it is large compared with the presumed conductance of the spine membrane. This conductance is maximal when the postsynaptic receptors are active, yet is $G_{membrane} \sim G_{synapse} \sim 10^{-10} \Omega^{-1}$. Thus voltage attenuation within the spine may be taken to be negligible (despite a bevy of previous theoretical calculations!), so that voltage remains a global state variable while ion chemistry is spatially localized on the relatively long time-scale of $\tau \sim 100 \text{ms}$.

Diffusion Coefficients

Ion or molecule	Diffusion coefficient
H ⁺	9.3 ¹
NO	3.8 ²
Na ⁺	1.33 ¹
K ⁺	1.96 ¹
Ca ²⁺	0.6 ³
IP ₃	0.24 ⁴
Calmodulin	0.13
CaM kinase II	0.034

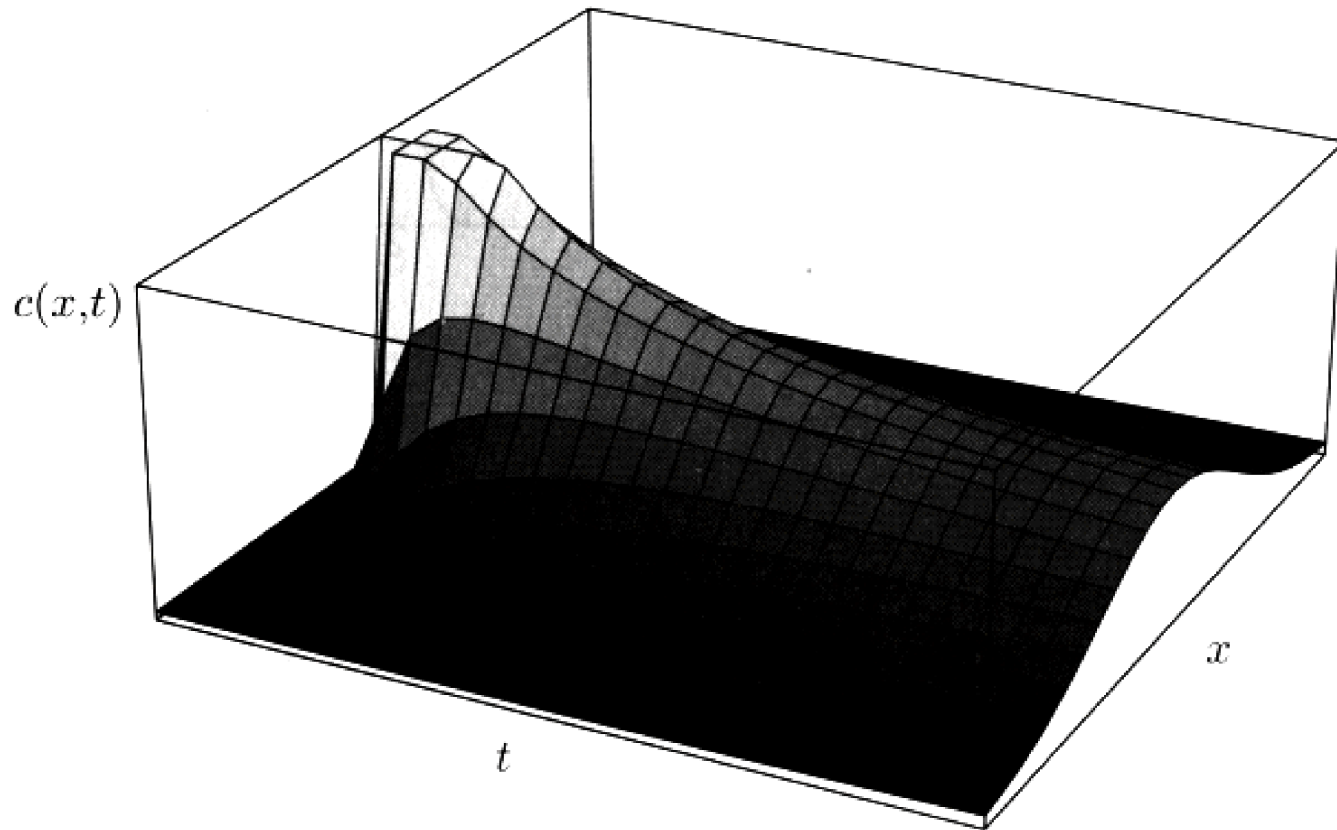
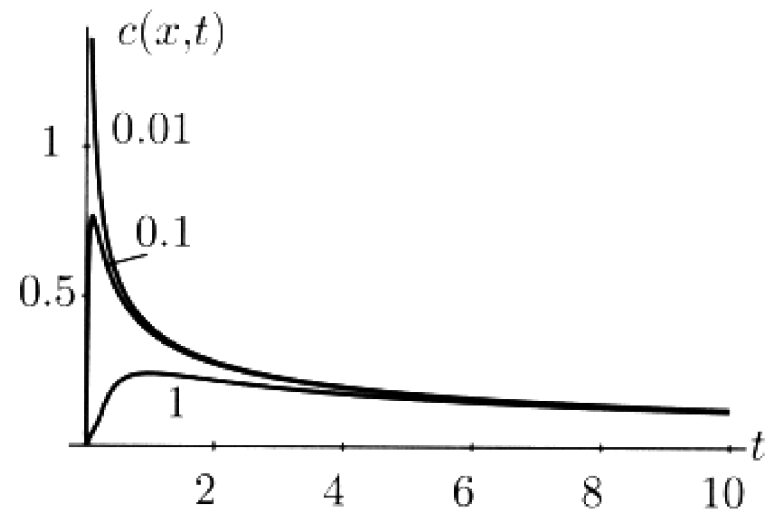
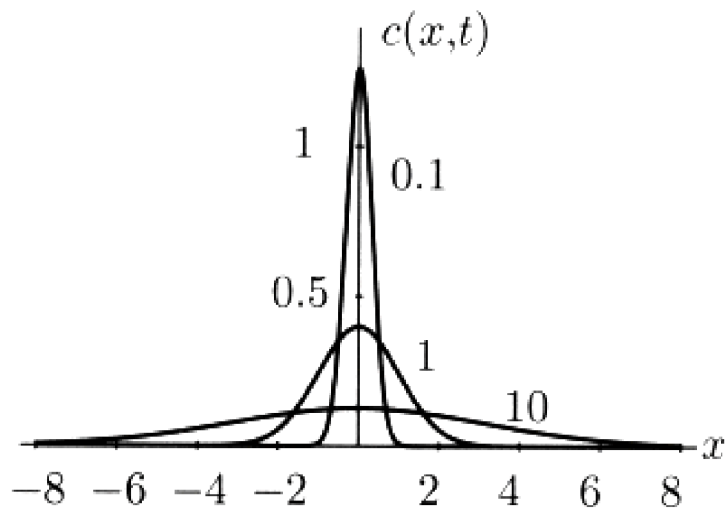
Diffusion coefficients in an aqueous environment for different ions and second messenger molecules in units of $10^{-5} \text{ cm}^2/\text{sec}$, that is $\mu\text{m}^2/\text{msec}$.

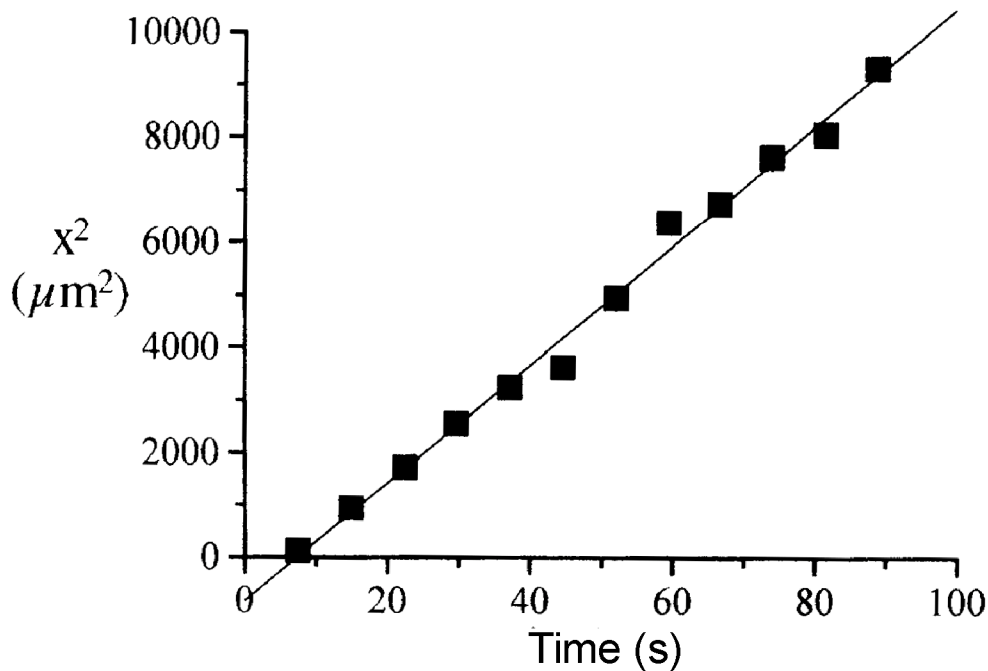
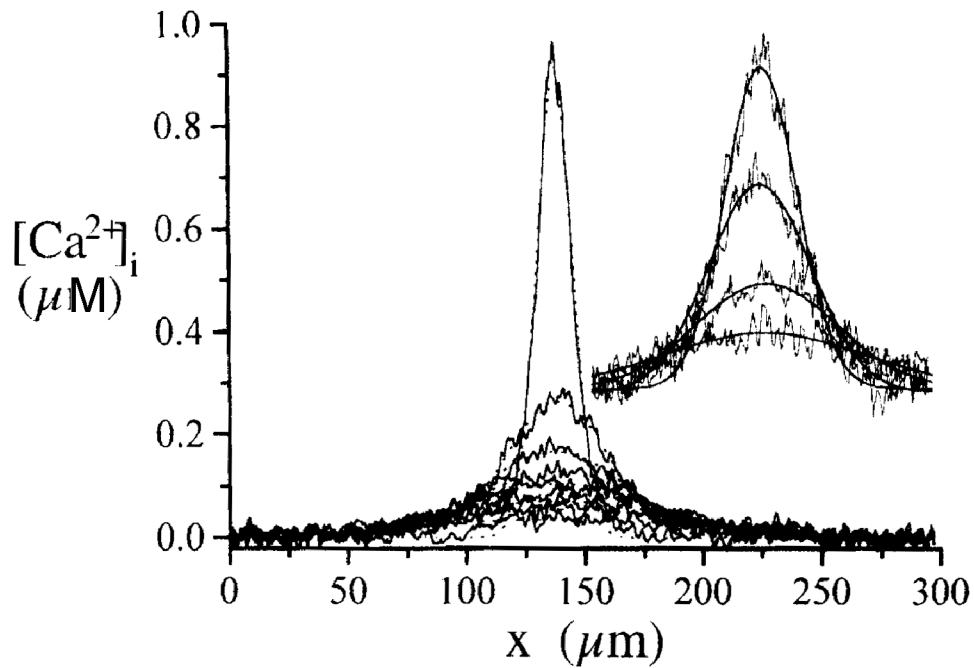
¹ Table 10.1 in Hille (1992).

² In rat cortex; Meulemans (1994); see also Wise and Houghton (1968).

³ Blaustein and Hodgkin (1969).

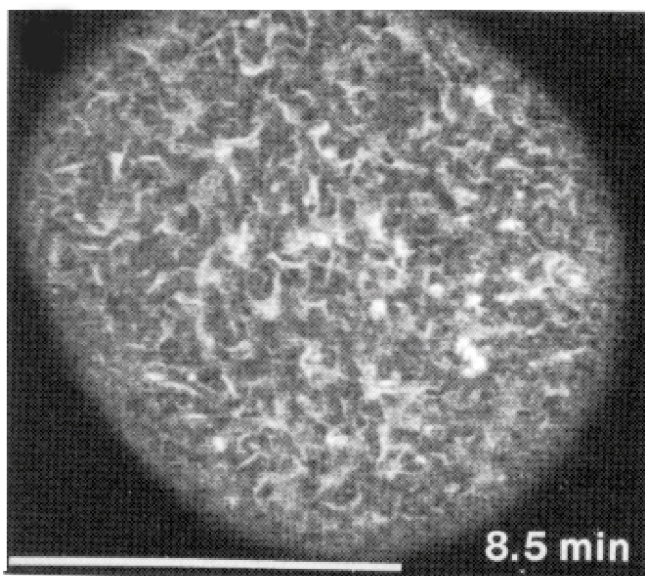
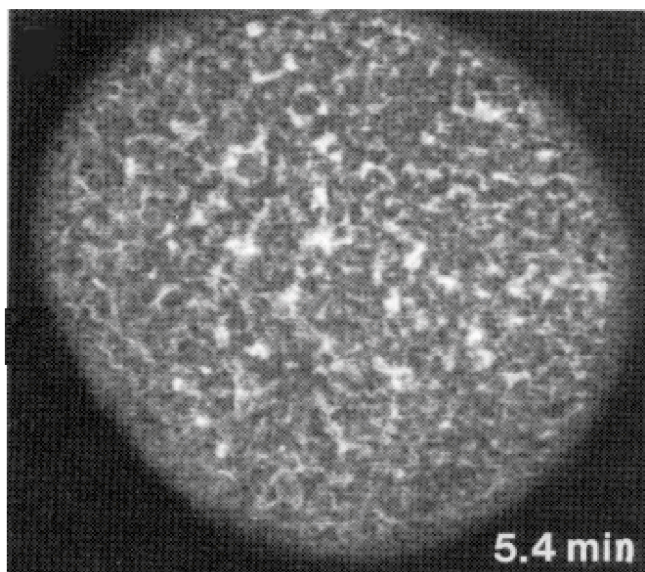
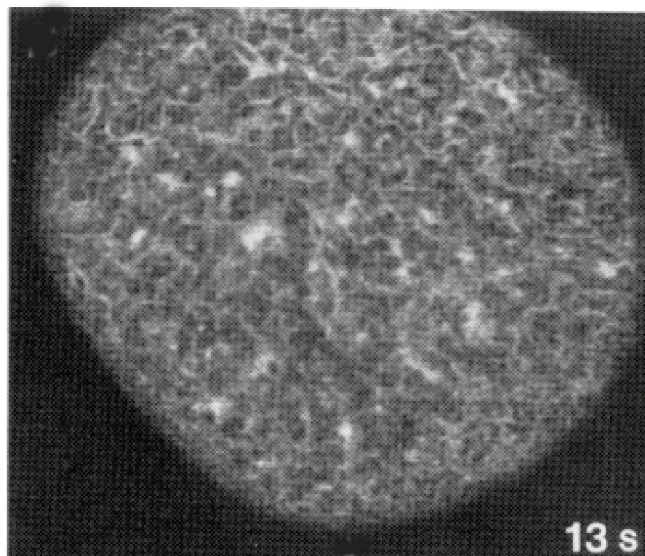
⁴ Allbritton, Meyer, and Stryer (1992).

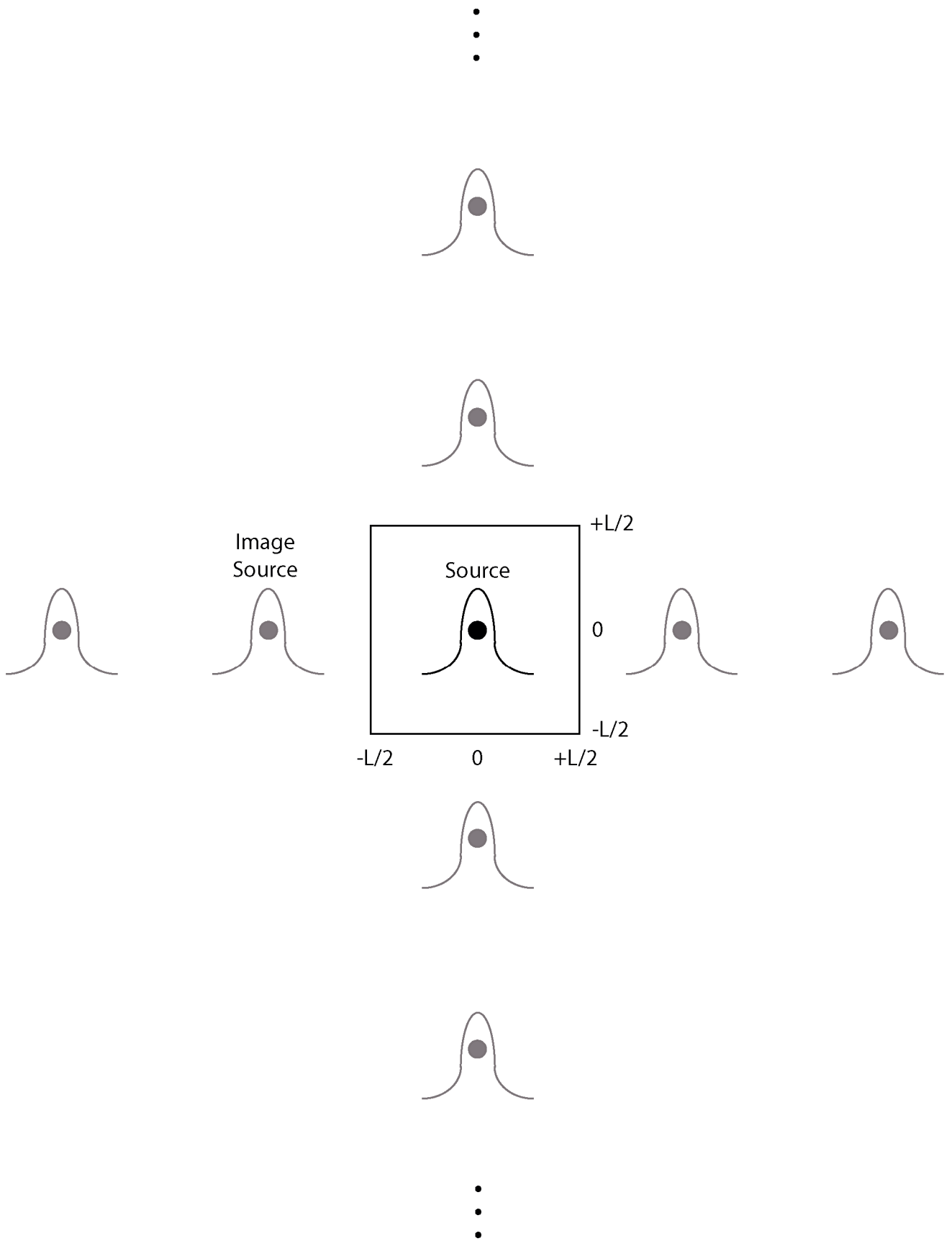




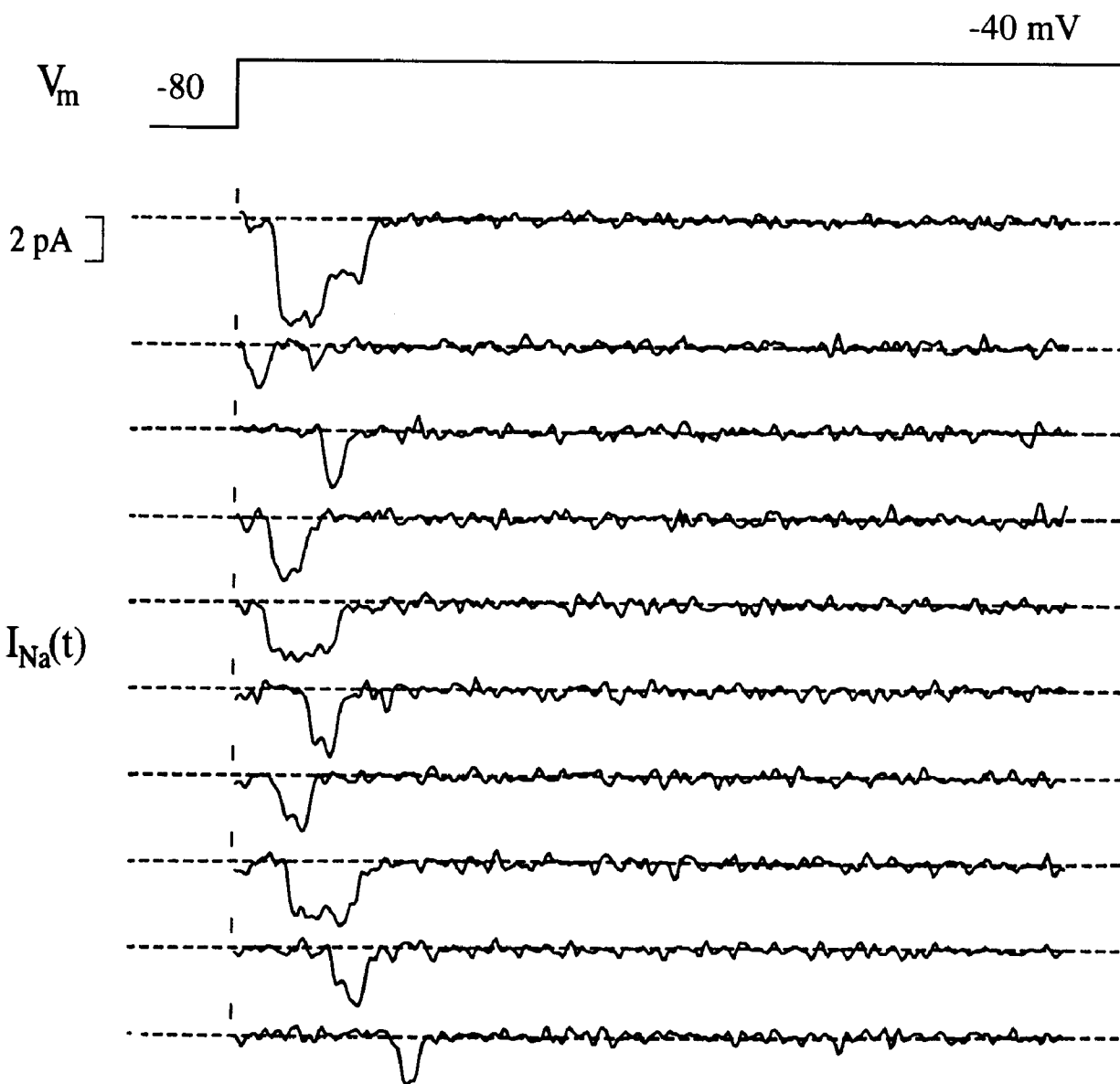
CALCIUM SPREAD ALONG AN AXON

Experimental determination of the calcium signal (recorded using the calcium-dependent fluorescent dye fura-2) following a brief intracellular injection of calcium at one point into the axon of a cultured metacerebral *Aplysia* neuron by Gabso, Neher, and Spira (1997).

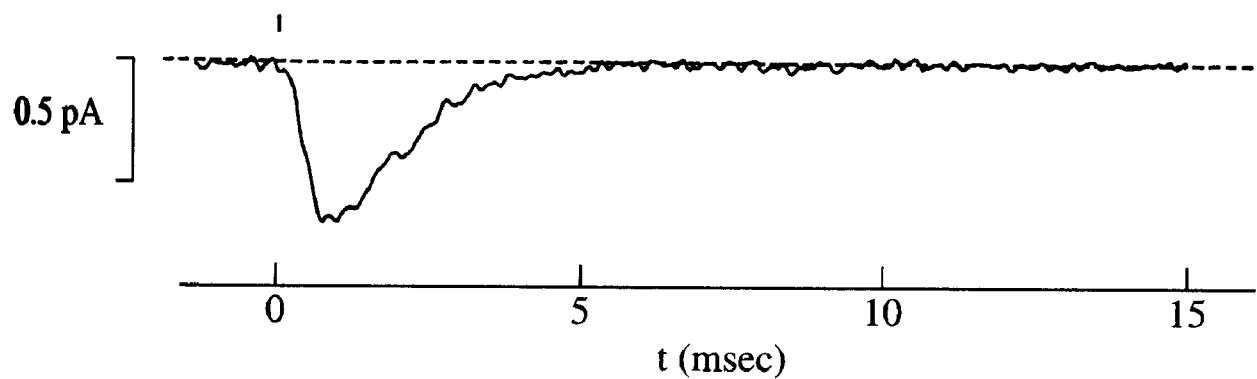


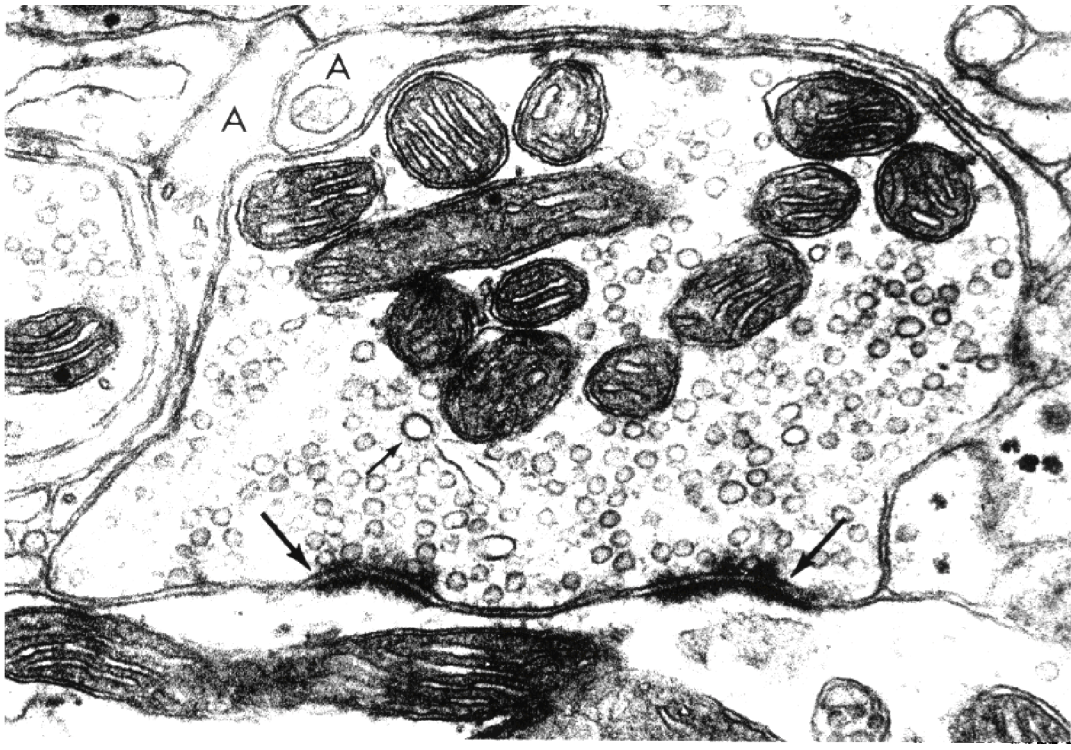


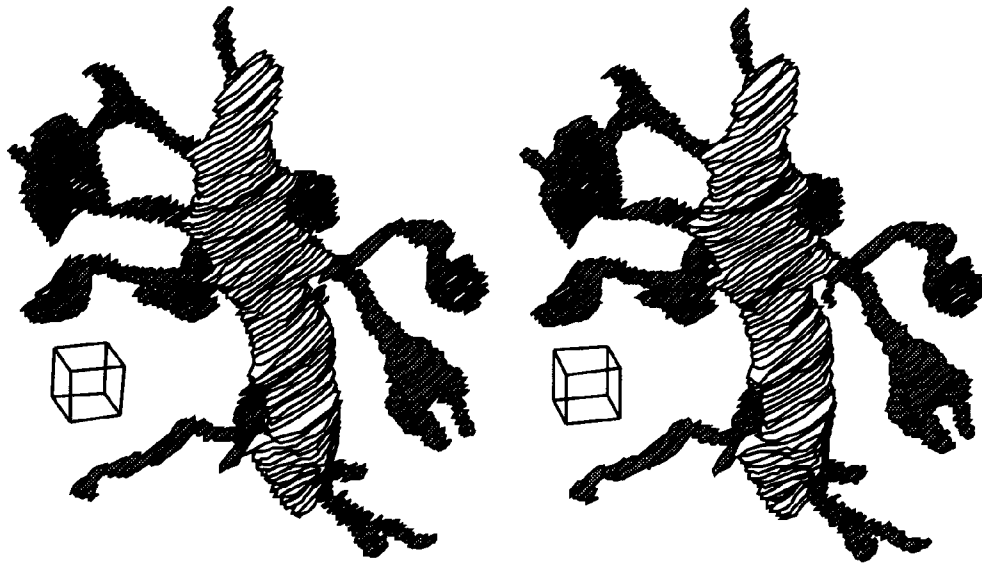
Unitary Sodium Currents



Ensemble Average







The cube has a dimension of $0.5 \mu\text{m}$



