Exercise 7: Diffusion

Problem 1: Diffusion of neurotransmitters in the synaptic cleft

The dominant way of transporting signals between neurons (nerve cells) in the brain is by means of diffusion of particular signal molecules called *neurotransmitters* across the synaptic cleft separating the cell membranes of the two cells. A drawing of a synapse is given in Fig. 1.

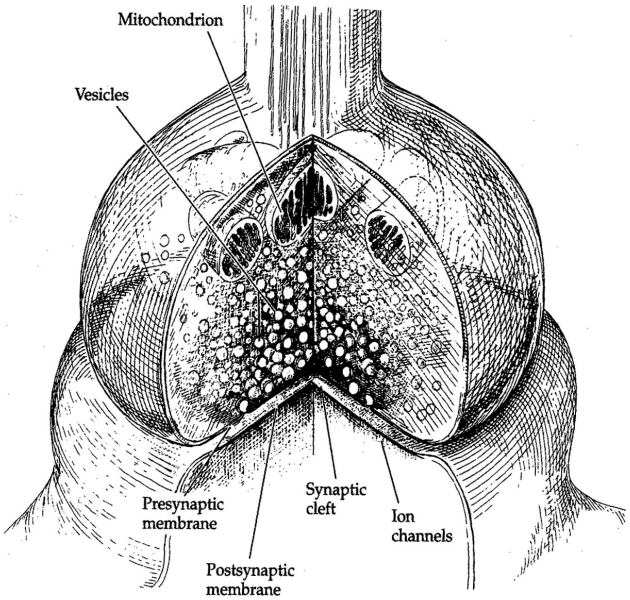

Figure 1: Drawing of a synapse. The axon terminal is the knoblike structure and the spine of the receiving neuron is the bottom one. The synaptic cleft is the small space between the presynaptic (axon) and postsynaptic (dendritic spine) membrane. (From Thompson: "The Brain", Worth Publ., 2000)

Following the arrival of an action potential in the axon terminal a process is initiated in which (i) vesicles inside the axon terminal (filled with neurotransmitter molecules) merge with the presynaptic (axon) membrane and (ii) release neurotransmitters into the synaptic cleft. These neurotransmitters diffuse across the synaptic cleft to receptors on the postsynaptic side which "receives" the signal. A schematic illustration of this process is shown in Fig. 2(left).

Since the transport process in the synaptic cleft is governed by diffusion, we

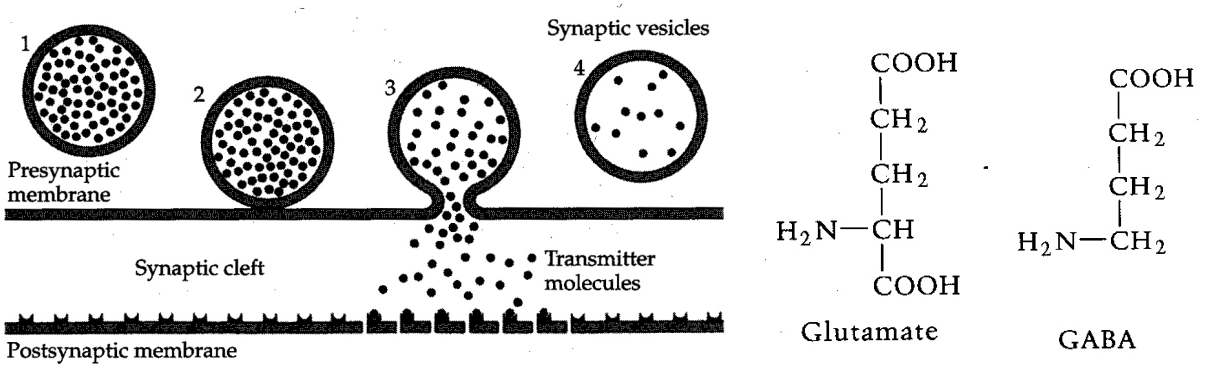

Figure 2: Left: Schematic drawing of the process of vesicle release from the axon terminal and release of transmitter molecules into the synaptic cleft. (From Thompson: "The Brain", Worth Publ., 2000). Right: Molecular structure of the two important neurotransmitters *glutamate* and *GABA*.

can describe it mathematically by

$$\frac{\partial c}{\partial t} = D\nabla^2 c, \tag{1}$$

where c is the concentration of the particular neurotransmitter, and D is the diffusion coefficient of the neurotransmitter in this particular environment (solvent in synaptic cleft).

a) If we assume (i) that the neurotransmitter moleculres are released roughly equally on the "presynaptic" side of the synaptic cleft, and (ii) that the synaptic cleft is roughly equally wide across the whole synaptic terminal, we can, given the large area of the synaptic cleft compared to its width, assume that the neurotransmitter concentration only varies in the direction across the synaptic cleft (from presynaptic to postsynaptic side). We choose this direction to be the x-direction (see Fig. 3). Show that in this case, where $c(\mathbf{r}) = c(x)$, the diffusion equation reduces to

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

b) Immediately after the release of neurotransmitter into the synaptic cleft ($t = 0$) the concentration profile in the x-direction is given by

$$c(x, t = 0) = N\,\delta(x) \quad , \tag{3}$$

where N is the number of particles released into the synaptic cleft per area of membrane.

To get an idea of the time dependence of the neurotransmitter concentration at the postsynaptic side ($x = d$), we can look at the solution of a "free" random walk (i.e., no obstacles or particle absorbers in either direction). The solution of Eq. (2) with the initial condition in Eq. (3) is given by (see, for example, Nelson, Biological Physics, 2008, p. 143):

$$c(x,t) = \frac{N}{\sqrt{4\pi Dt}} e^{-x^2/4Dt} \quad . \tag{4}$$

(1) Show that the concentration at the postsynaptic side $c(d,t)$ approaches 0 in the limit $t \to 0$ and $t \to \infty$. What is the "physical reason" for this?

(2) Sketch the concentration profile at the postsynaptic side ($x = d$) as a function of time. It is practical to use Dt/d^2 as a unit of time.

(3) In this model the concentration $c(d,t)$ will be at a maximum at a particular time t_{max}. t_{max} may serve as an estimate of the typical time is takes for the signal to cross across the synaptic cleft. Find an expression of t_{max}. Find also an expression for the maximum postsynaptic concentration $c(d, t_{max})$.

(4) The diffusion coefficient of glutamate has been estimated to be about $D = 8 \cdot 10^{-10}\, m^2/s$ (Ventriglia & DiMaio, BioSystems, 2000). Use this parameter value and $d = 50$ Å to obtain a numerical estimate for t_{max}.

c) The assumption under (b) regarding the neurotransmitter molecules undergoing a "free" random walk, is obviously a simplification, and the real process is better described by the following initial/boundary conditions:

$$c(x = 0, t > 0) = c_0, \quad c(x = d, \text{all } t) = 0, \quad c(0 < x < d, t < 0) = 0 \quad . \tag{5}$$

This corresponds to that

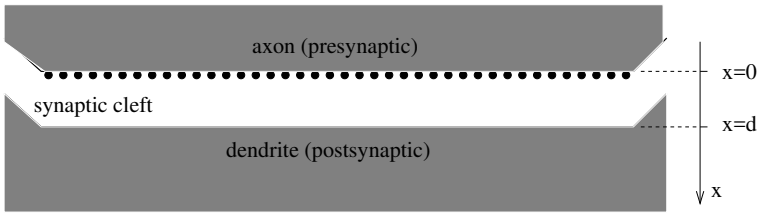

Figure 3: Schematic drawing of the synaptic cleft in our model. The black dots represent neurotransmitter molecules, and the situation shown corresponds to the situation immediately after neurotransmitter release into the synaptic cleft.

(i) for $t < 0$ the are no neurotransmitters in the synaptic cleft,

(ii) for $t > 0$ the concentration of neurotransmitters at the presynaptic boundary of the synaptic cleft (x=0) is kept fixed at $c = c_0$, and

(iii) that the postsynaptic receptors immediately absorb nearby neurotransmitters so that c=0 on the postsynaptic side of the cleft ($x = d$).

Note that assumption (ii) can be justified if the release of transmitter molecules following an arriving action potential lasts much longer than the typical time it takes to diffuse across a cleft (which the time scale of interest in this problem).

(1) We first look at the steady-state solution, $t \to \infty$. Find the concentration profile $c(x)$ and the particle flux $J = -D\frac{\partial c}{\partial x}$ in this limit (J_∞).

(2) The full solution of the diffusion equation with boundary/initial conditions in Eq. (5) can be found analytically. The particle flux J at the exit side ($x = d$) can thereafter be found, and an expression for this flux is:

$$J(t) = J_\infty\big(1 + 2\sum_{n=1}^{\infty}(-1)^n e^{-n^2\pi^2 Dt/d^2}\big), \tag{6}$$

for all $t > 0$.

(i) "Guesstimate" the qualitative shape of $J(t)$.

(ii) Plot the shape of $J(t)$ given by Eq. 6 by means of a computer program.

(iii) Describe how on the basis of experimental measurements of $J(t)$, one (at least in principle) can measure the diffusion constant D.

Problem 2: Diffusion of molecules in 3D

While the diffusion of neurotransmitters in the synaptic cleft effectively is a one-dimensional diffusion problem, molecules in extracellular spaces can diffuse in all three directions. We thus now look at diffusion of particles in 3D.

The solution for the diffusion of a point source (N particles at origin $\mathbf{r} = \mathbf{0}$ at time $t = 0$) is given by

$$c(\mathbf{r}, t) = \frac{N}{(4\pi Dt)^{3/2}} e^{-\mathbf{r}^2/4Dt} \quad . \tag{7}$$

Show that the concentration measured by an observer at at fixed distance r from the initial release point of a point source peaks at a certain time, and find that time in terms of r and D.