

# Random Molecular Transport around Biological Membranes

Nzerem Francis Egenti  
Department of Mathematics and Statistic  
University of Port Harcourt, Nigeria  
Email: frankjournals [AT] yahoo.com

---

**ABSTRACT----** *The spatio-temporal delivery of essential substances across biological membrane is critical to its survival and the wellbeing of the owner-organism. The process presupposes a permeable soft membrane and the transport are marked by reaction and diffusion phenomena. The spherical configuration of many biological membranes informs the present study on the reaction-diffusion phenomena around spherical membranes, with probability current. The diffusion equation describing the ensemble of reacting molecules around such membranes holds well in elucidating the delivery of drugs across biological cells.*

**Keywords----** reaction-diffusion, spherical, stochastic process, Gauss function

---

## 1. INTRODUCTION

Animated life is endowed with cells. The cells consist of outer boundaries (plasma membranes) and inner compartments (organelles). The cells are supplied with these outer boundaries and the inner compartments by the membranes. Membranes are barriers that insulate the cells against undue access. The flow of information between cells is moderated by the membranes. This is achieved either by the recognition of signal molecules received from other cells, or by transmitting electrical signals to other cells [1, 2]. Biological membranes are structured in a continuous bilayer [1, 2, 3, 4]. Both small molecules and large particles cross membranes; however, they are selectively permeable, and thus regulate the movement of substances in and out of the cells. By means of *simple* diffusion process, small hydrophobic molecules pass through phospholipid bilayers, by dissolving in the hydrophobic core. We emphasize ‘simple’ here; it is noteworthy that sugars, ions and amino-acids undergo *mediated* (facilitated) diffusion process [1, 5]. This process involves transportation by integral membrane proteins. Facilitated diffusion is known to be selective and saturable. The saturability condition inhibits the increase in diffusion, even with increasing concentration of a solute. Most biological membranes are electrically charged, and therefore the transport of ions is moderated by membrane potential.

In the mathematical details here and elsewhere [6, 7, 8], most biological membranes are spherical in configuration. We were guided by this understanding. As earlier indicated, membranes are (selectively) permeable. Their insulating propensity induces wall reaction, as molecules-in-solution tend to permeate. We target the reaction delivered in the event of an arbitrary membrane being impinged upon by molecules. The physical law governing the diffusion process is best described by Fick’s law. This law, loosely stated, relates the rate of diffusion of the molecules (in the present case) to their concentration in space. Since reaction is accompanied by diffusion, the reaction-diffusion equation is critical in determining what prevails around a spherical biological membrane. Pertinent literatures have used reaction-diffusion (RD) equations to describe various physical phenomena [9, 10, 11]. In the realm of biology, Nickolson [12] studied diffusion process in brain tissue; Lefèvre and Mangin [13] applied reaction-diffusion equation to human brain development. The diffusion of proteins on a spherical membrane engaged the attention of Amatore et al. [14]. Volpert and Petrovskii [15] reviewed reaction-diffusion in wave propagation. Away from membranes spherical configuration to cylindrical, Chaudhry et al. [16] simulated reaction-diffusion process in non-spherical cell geometry.

From statistical point of view, the space-time description of a diffusing molecule is rather stochastic than deterministic. Stochastic models are more reliable in providing understanding of the RD processes in biological structures. Thus, they are of choice when biologically observed phenomena depend on random fluctuations (see Radek et al [17]). This work therefore sought a probability density function (pdf) which is capable of furnishing the likely position of a given molecule at any time. Away from here [18], we inquired into stochastic differential equation that holds well for the position of a particle in a random walk around a circular cylinder. Fokker–Planck equation met the need. It is a second order partial differential equation which describes the time evolution of the probability density function of a stochastic process. It was employed in the present case to describe time evolution of the reaction-diffusion process around a spherical membrane.

## 2. DIFFUSION PROCESS

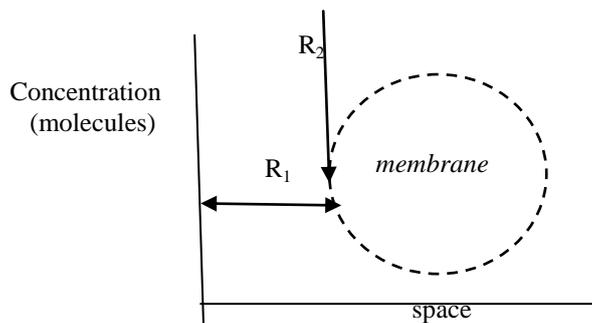
### 2.1 Reaction-diffusion equation

Here we present a general equation that holds well for reaction-diffusion systems. The systems are marked by two kinds of processes occurring on different scales: the evolution of macroscopic variables,  $x_i$  ( $i=1, \dots, n$ ) such as concentrations and the temperature  $T$ ; and the molecular dynamics, which are described by ensemble of parameters  $\gamma$ . These parameters include: the rate constant  $k_\rho$  of reaction  $\rho$ , heat or mass diffusivity coefficients  $D_i$ , or the heat  $\Delta H_\rho$  of reaction  $\rho$ . This gives rise to a set of balance equations of the form [19]; (see also [20])

$$\frac{\partial x_i}{\partial t} = V_i([x_j], \gamma) + D_i \nabla^2 x_i$$

(2.1)

where the first term in the right hand side stand for the effect of the chemical reactions, and the second term represents transport. We assume that there is no bulk motion, and there are no cross effects in transport. When the RD equations (2.1) are endowed with appropriate boundary conditions, they generate numerous spatial and spatio-temporal patterns. Such boundary conditions may include: Dirichlet, Neumann, and mixed Robin boundary conditions. The method of derivation of RD equation may be seen in [21]. Let us consider what prevails in two regions,  $R_1$  (vicinity) and  $R_2$  of the spherical membrane (refer to Fig. 1.1).



**Figure.2.1:** CONCENTRATION profile of reacting molecules in the vicinity of a porous spherical membrane.

In  $R_1$ , the transport phenomena occur outside the membrane, with the molecules diffusing through the inert boundary layer surrounding it. This region is marked by ‘external’ or ‘interphase’ transport effects. In the internal or intraphase transport region  $R_2$ , the molecules diffuse into the pores of the membrane. Each of the transport effects is important in the RD process. Consider, for simplicity, two component molecules diffusing through the stagnant boundary layer surrounding the spherical membrane. Since we are yet in the vicinity of the membrane, a trip to one spatial dimension leads to the describing Stefan-Maxwell equations which read:

$$\nabla X_i = \sum_{\substack{j=1 \\ j \neq i}}^n \frac{1}{CD_{ij}} (X_i Y_j - X_j Y_i)$$

(2.2)

where  $X_i$  is the fraction of component  $i$ ,  $C$  is the total concentration,  $Y_i$  is the flux of component  $i$ , and  $D_{ij}$  is the diffusivity of component  $i$  in  $j$ . If  $A, B$  are two components of a mixture, then relationship for diffusion of  $A$  in a two component mixture at constant total concentration may be obtained from the simplified Stefan-Maxwell equations as (see [22]):

$$\nabla C_A = \frac{1}{D_{AB}} (X_A Y_B - X_B Y_A)$$

$$= \frac{1}{D_{AB}} [X_A (Y_A + Y_B) - Y_A], \quad (\text{for } X_B = I - X_A).$$

(2.3)

By assuming that concentrations are so dilute that  $X_A (Y_A + Y_B)$  can be neglected we get the dilute molecular concentration of A as

$$Y_A = -D_{AB} \nabla C_A,$$

(2.4)

which is the well known Fick's first law. The flux of molecule A through the stagnant boundary layer surrounding membrane may be obtained by solving equation (2.4) with suitable boundary conditions. This may be found in [22]. What happens at the stagnant boundary layer may be treated as RD in the plane (1D). (We have done the treatment above for the purpose of awakening our consciousness to what obtains in the vicinity of the spherical membrane of our interest; one may find [23, 24] very suitable for more clue to diffusion in 1D (corresponding to  $R_l$  in Fig.1.1)). If we consider  $R_l$  as the drift region, wherein the molecules migrate (deterministically) toward the membrane, then the stochastic differential equation that governs the system is given by Fokker-Planck (Smoluchowski) equation which reads:

$$\frac{\partial}{\partial t} p(x, t | x_0, t_0) = -\frac{\partial}{\partial x} [D^1 p(x, t | x_0, t_0)] + D \frac{\partial^2}{\partial x^2} p(x, t | x_0, t_0),$$

(2.5)

where  $D^1$  is some distribution representing the drift process while  $D$  is the diffusion constant. The stochastic nature underscores the invitation of the probability density function  $p(x, t)$ . Observe that the associated Fick's law holds if  $D^1=0$ . We observe also that equation (2.4) contains concentration gradient while equation (2.5) contains probability gradient. This is not out of context because we are rather interested in the spatio-temporal description of the molecules than the concentration.

## 2.2 Gauss Function and spherical diffusion

The study of spherical diffusion translates to finding Green's function as an extension of Gauss function to the sphere (see Thomas [25]). In order to transit from Gauss to Green we convolve the image with the Gaussian kernel

$$G(x, t) = \frac{1}{4\pi Dt} \exp\left(\frac{-x^2}{4Dt}\right)$$

(2.6)

When expressed in plane polar co-ordinates ( $r; \theta$ ), we may write the Gauss function in r as

$$G(x, t) = \frac{r}{2Dt} \exp\left(\frac{-r^2}{4Dt}\right)$$

(2.7)

The probability  $G(x, t | x_1, 0)$  that a molecule starting at  $x_1$  at time  $t = 0$  is located between  $x + \Delta x$ , after time  $t$  is given by

$$\begin{aligned}
 G(x,t|x_1,0) &= \frac{1}{\sqrt{4\pi D_0 t}} e^{-\frac{(x-x_1)^2}{4D_0 t}}, \quad x \in [-\infty, \infty] \quad \text{unbounded} \\
 &= \frac{1}{\sqrt{4\pi D_0 t}} \left[ e^{-\frac{(x-x_1)^2}{4D_0 t}} + e^{-\frac{(x+x_1)^2}{4D_0 t}} \right], \quad x \in [0, \infty] \quad \text{reflecting boundary} \\
 &= \frac{1}{\sqrt{4\pi D_0 t}} \left[ e^{-\frac{(x-x_1)^2}{4D_0 t}} - e^{-\frac{(x+x_1)^2}{4D_0 t}} \right], \quad x \in [0, \infty] \quad \text{absorbing boundary}
 \end{aligned}$$

(2.8)

The Gaussian distribution is similar to letting the image evolve under the diffusion equation

$$\nabla u(x,t) = \frac{1}{k} \frac{\partial}{\partial t} u(x,t),$$

(2.9)

with the spherical diffusion equation given by

$$\nabla^2_S u(\varphi, \phi, t) = \frac{1}{k} \frac{\partial}{\partial t} u(\varphi, \phi, t)$$

(2.10)

where  $\nabla^2$  is the spherical Laplace operator. In spherical coordinate  $(r, \varphi, \phi)$  it is given by

$$\nabla^2 = \frac{1}{r^2} \left[ \partial_r \left( r^2 \partial_r + \frac{1}{\sin^2 \varphi} \partial^2 \phi + \frac{1}{\sin \varphi} \partial_\varphi (\sin \varphi \partial_\varphi) \right) \right]$$

(2.11)

We conceive of a situation where the diffusing molecules are distributed at initial distance  $r_0$  from the center of the membrane; we assume that the distribution preserves equal likelihood in all directions. We therefore describe the probability of finding the molecule at a distance  $r$ , and at time  $t$  by a spherically symmetric distribution  $p(r, t|r_0, t_0)$  since neither the initial condition nor the reaction-diffusion have no predilections for orientation. The diffusion equation describing the ensemble of reacting molecules reads

$$\frac{\partial p}{\partial t} p(r, t|r_0, t_0) = D \nabla^2 p(r, t|r_0, t_0)$$

(2.12)

If the molecules are uniformly distributed at a distance  $r_0$  from the center of the membrane, then initial condition is prescribed [24] such that

$$p(r, t|r_0, t_0) = \frac{1}{4\pi r_0^2} \delta(r - r_0).$$

(2.13)

where  $\delta(r)$  is the Dirac distribution. Suppose that the distribution vanishes at distances from the membrane which are much larger than  $r_0$ . We therefore impose the natural boundary condition

$$\lim_{r \rightarrow \infty} p(r, t | r_0, t_0) = 0$$

(2.14)

A radiation boundary condition (BC) may also describe the reaction at the membrane. This form of BC is known as Robin BC. In considering a spherical boundary we may write

$$\hat{n} \cdot J_r(r, t | r_0, t_0) = D \frac{\partial}{\partial t} p(r, t | r_0, t_0) = \kappa p(r, t | r_0, t_0), \quad \text{for } r = a$$

(2.15)

where  $\hat{n} \cdot (r)$  denotes a unit vector normal to some surface  $\partial\Omega_i$  at  $r$  and  $J(r)$  is the flux operator that determines the spatial boundary conditions since it allows one to measure molecule probability at the shell of the diffusion space  $\Omega$ .

Consider equation (2.11) once more. Assume that the probability distribution is spherically symmetric. It therefore depends only on  $r$ . With this, we may write the equation of the radial component as

$$\frac{1}{r} \frac{\partial}{\partial r} \left( r^2 \frac{\partial}{\partial r} f(r) \right) = \frac{1}{r} \frac{\partial^2}{\partial r^2} (rf(r)),$$

(2.16)

and we get the diffusion equation

$$\frac{\partial}{\partial t} rp(r, t | r_0, t_0) = D \frac{\partial^2}{\partial r^2} rp(r, t | r_0, t_0).$$

(2.17)

The parameter  $\kappa$  in equation (2.15) is such that if the surface is unreactive (i.e. reflective BC), then  $\kappa = 0$ ; if every collision induces reaction, then  $\kappa \rightarrow \infty$  (i.e. absorbing BC). The solution of the Robin problem (2.13, 2.14, 2.15, and 2.17) may be put in the form

$$p(r, t | r_0, t_0) = p_1(r, t | r_0, t_0) + p_2(r, t | r_0, t_0),$$

(2.18)

with initial condition

$$p_1(r, t \rightarrow t_0 | r_0, t_0) = \frac{1}{4\pi r_0^2} \delta(r - r_0)$$

(2.19)

$$p_2(r, t \rightarrow t_0 | r_0, t_0) = 0$$

(2.20)

The sum of the functions in (2.19) and (2.20) must satisfy the Robin BC. The function  $p_1(r, t \rightarrow t_0 | r_0, t_0)$  must satisfy

$$\frac{\partial}{\partial t} rp_1(r, t | r_0, t_0) = D \frac{\partial^2}{\partial r^2} rp_1(r, t | r_0, t_0)$$

(2.21)

$$rp_1(r, t \rightarrow t_0 | r_0, t_0) = \frac{1}{4\pi r_0^2} \delta(r - r_0).$$

(2.22)

The Fourier transform of equation (2.22) gives [24]

$$rp_1(r, t | r_0, t_0) = \frac{1}{4\pi r_0} \frac{1}{\sqrt{4\pi D(t-t_0)}} \exp\left[-\frac{(r-r_0)^2}{4D(t-t_0)}\right]$$

(2.23)

The solution  $p_2(r, t \rightarrow t_0 | r_0, t_0)$  must satisfy

$$\frac{\partial}{\partial t} (rp_2(r, t | r_0, t_0)) = D \frac{\partial^2}{\partial r^2} rp_2(r, t | r_0, t_0),$$

(2.24)

with initial condition

$$rp_2(r, t \rightarrow t_0 | r_0, t_0) = 0$$

(2.25)

By means of Laplace transforms we get a solution that satisfies the natural BC (2.14)

$$r\tilde{p}_2(r, s | r_0, t_0) = H(s | r_0) \exp\left[-\sqrt{\frac{s}{D}} r\right]. \tag{2.26}$$

Where the BC (2.15) determines  $H(s | r_0)$ . Taking the Laplace transform of the BC (2.15) and denoting by  $\tilde{p}(r, s | r_0, t_0)$  the Laplace transform of the solution  $p(r, t | r_0, t_0)$  (see [24] for detailed derivation) we get

$$\begin{aligned} r\tilde{p}(r, s | r_0, t_0) &= \xi \exp\left[-\sqrt{\frac{s}{D}} |r-r_0|\right] + \lambda \xi e^{-\eta} \\ &= \xi \exp\left[-\sqrt{\frac{s}{D}} |r-r_0|\right] + e^{-\eta} - \omega \xi e^{-\eta} \end{aligned}$$

(2.27)

where:

$$\xi = \frac{1}{4\pi r_0} \frac{1}{\sqrt{4\pi Ds}}, \quad \lambda = \frac{(s/D)^{1/2} - (ca+D)/(Da)}{(s/D)^{1/2} + (ca+D)/(Da)}, \quad \eta = -\sqrt{s/D}(r+r_0-2a) \quad \omega = \frac{(ca+D)/(Da)}{\sqrt{s/D} + (ca+D)/(Da)}.$$

(Note that the Fourier domain is compatible with space while the Laplace domain is compatible time.) The inverse transform gives

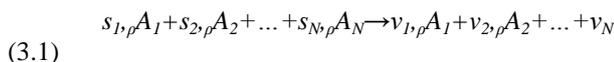
$$\begin{aligned} rp(r, t | r_0, t_0) &= \frac{1}{4\pi r_0} \frac{1}{\sqrt{4\pi D(t-t_0)}} \left( \exp\left[-\frac{(r-r_0)^2}{4D(t-t_0)}\right] + \exp\left[-\frac{(r+r_0-2a)^2}{4D(t-t_0)}\right] \right) \\ &\quad - \frac{1}{4\pi r_0} \kappa \exp\left[\kappa^2 D(t-t_0) + \kappa(r+r_0-2a)\right] \\ &\quad \times \operatorname{Erfc}\left[\kappa \sqrt{D(t-t_0)} + \frac{r+r_0-2a}{\sqrt{4D(t-t_0)}}\right], \end{aligned}$$

(2.28)

Where  $\kappa = \frac{ka+D}{Da}$

### 3. TIME EVOLUTION OF REACTING SPECIES

A homogeneous well-stirred space domain obeys a general reaction mechanism given by the equation



where  $s_{j,\rho}$  ( $\rho=1,2,\dots,R$ ) and  $v_{j,\rho}$  are the stoichiometry coefficients and  $A_j$  ( $j=1, 2, \dots, N$ ) is the molecular species. By stochastic kinetic theory, the probability of a time hallowed reaction  $\rho$  to occur in the next infinitesimal time-interval  $[t, t+dt]$  may be expressed as

$$p_\rho(\mathbf{n})dt = k_\rho \prod_{j=1}^N \binom{n_j}{s_{j,\rho}} dt \quad (3.2)$$

where:

$k_\rho$  is the probability coefficient;

$n_j$  is the number of  $A_j$  molecules present at time  $t$  in the reactive domain.

A probability density function  $p_\rho(\mathbf{n})$  is defined for each one reaction, which is dependent only on the state of the system  $\mathbf{n} = (n_1, n_2, \dots, n_N)^T$ . In a stochastic system, as being considered, the time course of all the species in the reacting systems is described by a finite difference partial differential equation known as the master equation. The reacting system is a Markov process, with probability density function. In the present case we may circumvent the intricacies of the master equation by simulating the stochastic time evolution of a reacting system [29]. By summing all  $p_\rho(\mathbf{n})$

$$P(\mathbf{n}) = \sum_{\rho} p_\rho(\mathbf{n}) = \sum_{\rho} k_\rho \prod_{j=1}^N \binom{n_j}{s_{j,\rho}} \quad (3.3)$$

(3.3)

we may obtain the jump density probability in the infinitesimal time-interval  $[t, t+dt]$ . It was shown [30] that a certain waiting-time interval  $\Delta\tau$  occurs between two consecutive reactive events as given by the relation

$$v_1(\Delta\tau|\mathbf{n}) = P(\mathbf{n}) \exp(-P(\mathbf{n})\Delta\tau) \quad (3.4)$$

(3.4)

The stochastic evolution of a reacting system is thus perceived as a sequence of waiting-time intervals accompanied by instantaneous reactive events occurring according to the probability

$$v_2(\Delta\mathbf{n}_\rho|\Delta\tau, \mathbf{n}) = \frac{p_\rho(\mathbf{n})}{P(\mathbf{n})} \quad (3.5)$$

(3.5)

where  $\Delta\mathbf{n}_\rho = (v_{1,\rho}-s_{1,\rho}, v_{2,\rho}-s_{2,\rho}, \dots, v_{N,\rho}-s_{N,\rho})^T$  represents the jump vector related to reaction  $\rho$ . Diffusion processes occur along with molecular reactions in the system after a certain waiting time. Thus, the waiting time that precedes diffusion is observed just at the absorbing boundary.

### 4. BOUNDARY CONDITIONS

We shall consider solutions, in equation (2.28), that apply to two boundary conditions: (i) reflective BC in which  $r = a$  and  $k = 0$  (ii) absorbing BC in which  $k \rightarrow \infty$ .

#### 4.1 Reflective boundary

This is a case of unreactiveness at the boundary. Thus  $k=0$  and from the above we get

$$p(r, t | r_0, t_0) = \frac{1}{4\pi r r_0} \frac{1}{\sqrt{4\pi D(t-t_0)}} \left( \exp\left(-\frac{(r-r_0)^2}{4D(t-t_0)}\right) + \exp\left[-\frac{(r+r_0-2a)^2}{4D(t-t_0)}\right] \right) - \frac{1}{4\pi a r r_0} \exp\left[\frac{D}{a^2}(t-t_0) + \frac{(r+r_0-2a)}{a}\right] \times \operatorname{erfc}\left[\frac{\sqrt{D(t-t_0)}}{Da} + \frac{r+r_0-2a}{\sqrt{4D(t-t_0)}}\right]$$

(4.1)

Observe that equation (2.29) is in harmony with the Gauss kernel (2.8) for the reflective boundary; the differential is a sequel to the convolution about the radial coordinate.

#### 4.2 Absorbing boundary

Absorption is anchored on membrane permeability (One may find [31] quite interesting). Permeability  $\chi$  is given by

$$\chi = \frac{\alpha D}{h}$$

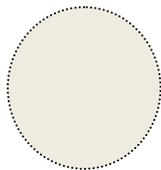
(4.2)

where  $\alpha$  is the partition constant;  $h$  is the membrane thickness. By inspection, the absorbing boundary equation (2.8) can offer some clue to the solution we need. If the membrane boundary absorbs, then we observe the asymptotic behavior of the error function and limiting the error; we find that the solution as  $k \rightarrow \infty$  (from (2.28)) is

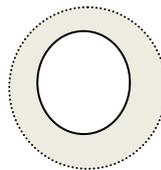
$$p(r, t | r_0, t_0) = \frac{1}{4\pi r r_0} \frac{1}{\sqrt{4\pi D(t-t_0)}} \left( \exp\left(-\frac{(r-r_0)^2}{4D(t-t_0)}\right) - \exp\left[-\frac{(r+r_0-2a)^2}{4D(t-t_0)}\right] \right).$$

(4.3)

The spatio-temporal co-ordinate of molecules undergoing reaction-diffusion processes around the membrane is given by equation (4.3). The reaction and diffusion rates are critical in the time evolution of the reaction-diffusion process. If diffusion is slow, then it dominates the process; conversely if reaction is slow, then it dominates the process. At diffusion-limited regime, the rate depends on the supply of new molecular species to the membrane surface. In this case the so-called Thiele modulus [32] is much greater than one (i.e.  $h_T \gg 1$ ). Conversely, Thiele modulus is much less than one (i.e.  $h_T \ll 1$ ) at reaction-limited regime.



$h_T \ll 1$ : substrate fills the sphere



$h_T \gg 1$ : substrate does not get to the centre

**Figure.4.1:** LIMITED regimes for reaction and diffusion

### 5. SUMMARY

Reaction-diffusion process in molecular biology was treated. The spherical configuration of the permeable membrane, as conceived, is in line with physiological state of numerous cells and tissues. There is conventionality of measuring molecular transport across a barrier or mass transport of molecules in a solution by fluxes. Molecular transport across membranes may be caused diffusion. Diffusion is the random movement of molecules in a solution, which causes only a net transport of molecules in the presence of concentration gradient. This may not be said of the movement of each solute molecule in solution, induced by an external force, which migration explains. The randomness of a diffusion process informs the invitation of probability current. It was assumed that the diffusing molecules are distributed at initial distance  $r_0$  from the center of the membrane; further to this, the distribution preserves equal likelihood in all directions. We described the probability of finding a molecule at a distance  $r$ , and at time  $t$  by a spherically symmetric distribution. In the stochastic differential equations that ensued, reflective and absorbing boundary conditions were discussed. At the membrane wall, reaction occurs at some time interval, after which diffusion takes place.

Reaction-diffusion processes find explanation in drug delivery through physiological membranes, subject to membrane permeability. Most often, passive diffusion process is induced. This enhances observability of the linear relationship between flux and concentration gradient. Thus, drug transport is examined at a range of concentration gradients. In preparation to drug delivery the choice of highest possible stirring rate, which minimizes concentration gradients in the donor and receiver compartment, is of the essence.

## 6. REFERENCES

1. Brown B.S. "Biological Membranes", Available online: [www.biochemistry.org/portals/0/education/docs/basc08\\_full.pdf](http://www.biochemistry.org/portals/0/education/docs/basc08_full.pdf) (accessed on 13-03-2015)
2. Ostro, M.E. *The Lively Membranes*, Cambridge University Press, 1983.
3. Introduction to biological membranes, Available online: <http://themedicalbiochemistrypage.org/membranes.php#composition> (accessed on 13-03-2015).
4. Milsom, D.W., "Biological membranes", *Biological Sciences Review*, 6(4), 16-20,1994.
5. Membrane permeability, Available online: <http://www.dartmouth.edu/~cbbc/courses/bio15/2004W/slides/L04.pdf> (accessed on 14-03-2015).
6. Warren B., Shinpei O, "Fusion in phospholipid spherical membranes", *The Journal of Membrane Biology*, Volume 23, Issue 1, pp 385-401,1975.
7. Bosezzi, D; Rosenberg G., Formalizing Spherical membrane structures and membranes proteins population, Available online: [http://link.springer.com/chapter/10.1007%2F11963516\\_2#page-2](http://link.springer.com/chapter/10.1007%2F11963516_2#page-2) (accessed on 10-02-2015).
8. Haslach, H. W.; Humphrey, J. D., "Dynamics of biological soft tissue and rubber: internally pressurized spherical membranes surrounded by a fluid", *International Journal of Non-Linear Mechanics*, Volume 39, Issue 3,399–420,2004.
9. Kenkre VM, Kumar N., "Nonlinearity in bacterial population dynamics: proposal for experiments for the observation of abrupt transitions in patches", *Proc Natl. Acad. Sci.*, 105:18752–7, 2008.
10. Volpert A.I.; Volpert VA. "Applications of the rotation theory of vector fields to the study of wave solutions of parabolic equations", *Trans Moscow Math Soc.*, 52:59–108, 1990.
11. Brillinger, D. R., "A Particle Migrating Randomly on a Sphere", *Journal of Theoretical Probability*, Vol. 10, No. 2, 429-443, 1997.
12. Nicholson C., "Diffusion and related transport mechanisms in brain tissue", *Rep. Prog. Phys.*, 64,815–884, 2001
13. Lefèvre J, Mangin J-F., "A Reaction-Diffusion Model of Human Brain Development", *PLoS Comput Biol.*, 6(4), 2010, e1000749. doi:10.1371/journal.pcbi.1000749,
14. Amatore, C.; Oleinick, A.; Klymenko, O.V.; Svir, I., "Theory of Long-Range Diffusion of Proteins on a Spherical Biological Membrane: Application to Protein Cluster Formation and Actin-Comet Tail Growth", *Chemphyschem*, Vol.10,1586-1592, 2009.
15. V. Volpert, S. Petrovskii, "Reaction-diffusion waves in biology", *Physics of Life Reviews*, 6,267–310, 2009.
16. Chaudhry QA, Morgenstern R, Hanke M, and Dreij K(2012), Influence of Biological Cell Geometry on Reaction and Diffusion Simulation, Available online: <http://www.diva-portal.org/smash/get/diva2:516281/FULLTEXT01.pdf> (accessed on 22-03-2015)
17. Radek, E, S; Chapman, J.; Philip K..M. , A practical guide to stochastic simulations of reaction-diffusion processes, Available online: <http://people.maths.ox.ac.uk/erban/Education/StochReacDiff.pdf>
18. Nzerem F E. Orumie C.U., "Stochastic description of the dynamics of thrombo-embolus in an arterial compartment", *International Journal of Applied Mathematical Sciences*, 3(1)(2015) 6-11, doi: 10.14419/ijams.v3i1.4062
19. Gregoire, N., Anne D. W., "Reaction-diffusion systems", *Scholarpedia*, 2(9):1475, 2007. doi:10.4249/scholarpedia.1475
20. Klemens F., *Reactions-Diffusion Equations*, Available online: <http://www.damtp.cam.ac.uk/research/apde/teaching/CamRD2010.pdf> (accessed on 22-03-2015)
21. Diffusion and Reaction, Available online: <https://www.scribd.com/doc/189241200/Chapter12-Diffusion-Reaction>, (accessed on 22-02-2015)
22. Effects of Transport Limitations on Rates of Solid-Catalyzed Reactions, Available online: <http://authors.library.caltech.edu/25070/7/FundChemReaxEngCh6.pdf> (accessed on 18-03-2015).
23. Krishna, M. G; Joseph S; Supurna, S., "Brownian motion on a sphere: distribution of solid angles" *J. Phys. A: Math. Gen.*, 33,5965–5971, 2000.
24. K. Schulten and I. Kosztin, *Lectures in Theoretical Biophysics*, Available online: [www.ks.uiuc.edu/Services/Class/NSM.pdf](http://www.ks.uiuc.edu/Services/Class/NSM.pdf) (accessed on 22-10-2014)
25. Bülow, Thomas, "Spherical Diffusion". *Technical Reports (CIS)*. Paper 718, 2001. [http://repository.upenn.edu/cis\\_reports/718](http://repository.upenn.edu/cis_reports/718)

26. Abhijit G., Joseph S., Supurna S., A “Gaussian” for diffusion on the sphere, Available online: arXiv:1303.1278 [cond.mat.stat-mech], (accessed on 22-03-2015).
27. Chapman-Kolmogorov equation for continuous paths: Fokker-Plank equation, Available online: [http://www.pd.infn.it/~orlandin/fisica\\_sis\\_comp/fokker\\_plank.pdf](http://www.pd.infn.it/~orlandin/fisica_sis_comp/fokker_plank.pdf).(accessed on 12-09-2014)
28. Pabitra, N.S., Non-Gaussian Statistics and Anomalous Diffusion in Porous Media, Available online: <http://biomedphys.sgu.ru/Files/LIB/Springer/Processes%20with%20LongRange%20Correlatio/10.NonGaussian%20Statistics%20and%20Anomalous%20diffusion%20in%20Porous%20Media.pdf> (accessed on 22-10-2014)
29. Fabio M.; Kepa R-M. Stochastic simulations of minimal self-reproducing cellular systems, Available online: DOI: 10.1098/rstb .2007.2071 (accessed on 22-03-2015)
30. Gillespie, D.T., “A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J. Comput. Phys., 22, 403–434, 1976, doi:10.1016/0021-9991(76)90041-3
31. Available online: [http://www.pharmpress.com/files/docs/MolBiopharmaceutics\\_sample.pdf](http://www.pharmpress.com/files/docs/MolBiopharmaceutics_sample.pdf) (accessed on 18-03-2015)
32. Thielle Modulus, Available online: [http://en.wikipedia.org/wiki/Thiele\\_modulus](http://en.wikipedia.org/wiki/Thiele_modulus) (accessed on 22-03-2015)