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ORIGINAL ARTICLE

Phenomenology and energetics of diffusion across cell phase states

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Abstract Cell based transport properties have been mathematically addressed. Cell contained cross boundary diffusion of materials has been explained using valid formalisms and related analytical expressions have been developed. Various distinguishable physical structures and their properties raise different general structure specific diffusion mechanisms and controlled transport related parameters. Some of these parameters play phenomenological roles and some cause regulatory effects. The cell based compartments may be divided into three major physical phase states namely liquid, plasma and solid phase states. Transport of ions, nutrients, small molecules like proteins, etc. across inter phase states and intraphase states follows general transport related formalisms. Creation of some localized permanent and/or temporary structures e.g., ion channels, clustering of constituents, etc. and the transitions between such structures appear as regulators of the transport mechanisms. In this article, I have developed mainly a theoretical analysis of the commonly observed cell transport phenomena. I have attempted to develop formalisms on general cell based diffusion followed by a few numerical computations to address the analytical expression phenomenologically. I have then extended the analysis to adopting with the local structure originated energetics. Independent or correlated molecular transport naturally relies on some general parameters that define the nature of local cell environment as well as on some occasionally raised or transiently active stochastic resonance due to localized interactions. Short and long range interaction energies play crucial roles in this regard. Physical classification of cellular compartments has led us developing analytical expressions on both biologically observed diffusion mechanisms and the diffusions's occasional stochasticity causing energetics. These analytical expressions help us address the diffusion phenomena generally considering the physical properties of the biostructures across the diffusion pathways. A specific example case of single molecule transport and localized interaction energetics in a specific cell phase has been utilized to address the diffusion quite clearly. This article helps to address the mechanisms of cell based diffusion and nutrient movements and thus helps develop strategic templates to manipulate the diffusion mechanisms. Application of the

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theoretical knowledge into designing or discovering drugs or small molecule inhibitors targeting cell based structures may open up new avenues in biomedical sciences.

1. Introduction

Cell has various structural compartments. The compartments are divided into three major physical phase states namely liquid, plasma and solid states. Cell based transport of nutrients, small molecules, ions, etc. across inter-phase and intra-phase states follows general transport formalisms. Recently, we have published a paper to address this issue quite in detail (Ashrafuzzaman, 2015). We shall brief some of the aspects here. Some localized permanent and/or temporary structures and time dependent structural transitions also appear as regulators of the transport mechanisms. The minimum energy conformation (energy minimization) and stability (often refers to lifetime) of such structural complexes are found to contribute heavily into determining their transport properties and thus regulating the diffusion across them. In this article, I have developed mainly a theoretical analysis of the cell transport phenomena (Ashrafuzzaman and Tuszynski, 2012a) from cell component structural and localized interaction energetic points of view. To do so we need to present a clear analysis on the cell based various structural phase states (Ashrafuzzaman, 2015). I have then attempted to develop formalisms on general cell based diffusion followed by a special example case of ion channel (Ashrafuzzaman et al., 2006, 2012, 2014; Ashrafuzzaman and Tuszynski, 2012b,c; Huang, 1986; Andersen et al., 1999; Greisen et al., 2011). Ion channels are well known to help a cell establish communication between different distinguished cell phase states creating compartments. Ion channels are also known to help bypass certain phase states that sometimes may act as a barrier. Ion channels therefore participate directly in cell based general diffusion. Besides addressing the phenomenological aspects of general transport formalisms, I have also attempted to address the issue energetically.

As a specific example case we can try to address the cell membrane transport. Physical properties of lipid bilayers regulate integral membrane protein functions in a manner that depends on the hydrophobic coupling between the bilayer and the membrane proteins. Fig. 1 demonstrates such cases for special types of ion channels. Thus the membrane which is a plasma state may be bypassed by nutrients through some membrane residing temporary structures. The channels residing across membrane make passages for ions and various nutrients (Fig. 1). To address this issue we have theoretically developed a method to calculate the coupling energy between a lipid bilayer membrane and an integral transbilayer β-helical gramicidin A (gA) ion channel immersed in an aqueous phase using the screened Coulomb interaction often used in solving interactions between particles in a many-body condensed matter system (Ashrafuzzaman and Tuszynski, 2012b). This analysis proves that the localized structural changes as observed near the transport events play a crucial role to determine the transport phenomena. But it is also true that such structural changes appear due to mainly various physical processes like intercomponent charge based interactions, elastic coupling of the participating agents, localized aqueous dielectric condition, etc. Our theoretical calculation indicates that any change in the localized energetics of such an ion channel type structure is due to perturbations in the physical properties of the bilayer or/and gA channels should reflect through changes in the structural stability. In laboratory we can detect such structural changes in terms of lifetime of the structure, e.g., see the channel stability addressed in Ref. (Ashrafuzzaman and Tuszynski, 2012b).

2. Cell based structures and classified physical states

Biological cell has various components. Those can be classified into various physical structural classes. A detailed structural analysis may help them to be grouped among solid, liquid and plasma phase states. Fig. 2 shows model representation of a cell's various components. The general cell structure is quite known for sometime but analysis on the physical states of these structural components is yet to be made or known poorly. Here we shall make a biophysical analysis of this biological issue.

2.1. Cell's general structures

All cells are enclosed by cell envelopes which consist of cell walls covering plasma membranes. Both of the prokaryotic and eukaryotic cells have membranes. A membrane primarily separates the interior of a cell from the exterior, it regulates the selective movements of particles across it, and most importantly maintains an electric potential of the cell. The inside world is a combination of various structures as schematized in Fig. 2.

2.2. States of the general cell structures and related interactions

Biological cells are generally considered as soft matter. When we see a cell we in fact see its outside look that means we see the cell membrane. Beyond the membrane, in the cell's dissected state, there found to exist various things as shown in Fig. 2. These cellular constituents fall in different physical structure categories. Solid, liquid, and gas are the major physical states. Between solid and liquid there exists another state called plasma state. All these states appear with certain physical properties, certain kinds of inter particle interactions, certain types of shapes and sizes, etc. The mechanical and electrical properties of various states are also different. In a cell we find all of these states but gas. Some of these mentioned cellular structures permanently fall within a state while others temporarily or to be more specific many structures experience transitions between states. Sometimes some of the building blocks of any structure fall in a physical state class but the collective structure may not necessarily fall in the same class rather they are often found to be falling in a different state.

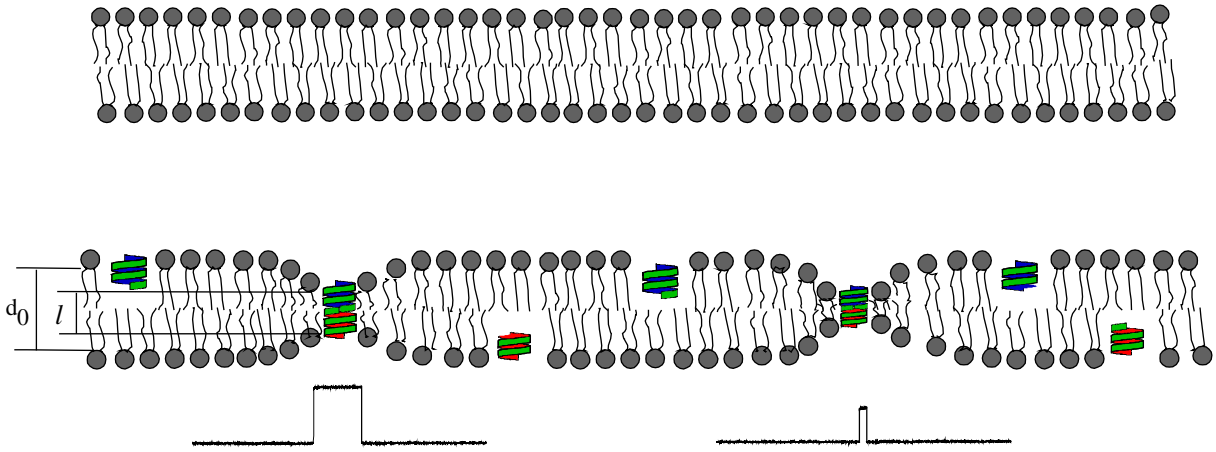

Figure 1 Cell membrane bilayer deforms at the bilayer gA channel coupling area which incurs an energetic cost. The upper panel shows a lipid bilayer without any integral membrane protein. Lower panel shows a bilayer with integral gA monomers and dimers of different lengths. When gA channels are formed inside a lipid bilayer, the bilayer conducts a current pulse with a specific average pulse width (gA channel lifetime) and height (gA channel conductance) depending on the gA channel type (the number of amino acids in the structures of gA monomers). Two types of gA monomers are schematically structured here to produce two gA channels of different lengths (l). d_0 is the unperturbed thickness of the bilayer.

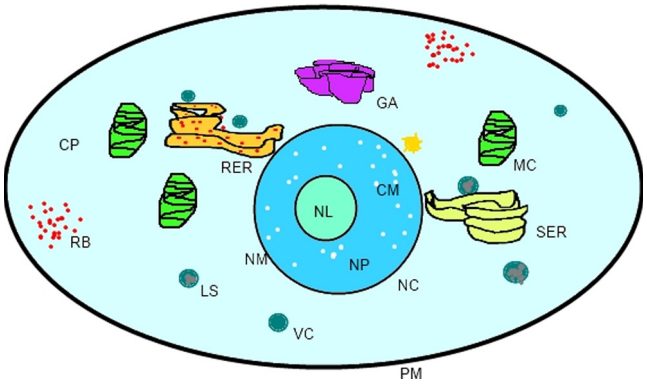

Figure 2 Schematic diagram of a cell showing different parts (taken from Ref. Ashrafuzzaman and Tuszynski, 2012a). In no way any component schematized here represents the true structure observed in biological cell. PM: Plasma membrane, CP: cytoplasm, VC: vacuole, LS: lysosome, RB: ribosome, MC: mitochondrion, GA: Golgi apparatus, RER: rough endoplasmic reticulum, SER: smooth endoplasmic reticulum, NC: nucleus, NM: nuclear membrane, NP: nucleoplasm, CM: chromatin, NL: nucleolus. The constituents shown here are found in an animal cell. In plant cell in addition to all these chloroplasts with photosynthesis ability exist. A plant cell (not an animal cell) also consists of a cell wall surrounding the plasma membrane which provides tensile strength and protection against mechanical and osmotic stress.

2.2.1. Solid state structure

Solid means something rigid in structure. Its general shape, size and structure are visibly nonchangeable at a certain thermodynamic condition. Protein structure and certain clusters like ion channels, etc. fall in solid state structure category. These structures are generally rigid, show physical stiffness and pose to follow most of the general physics mechanics laws like those of oscillator's motion following Hooke's law, for example. To obtain an in depth understanding one can read from various articles like Refs. (Castellani et al., 2002; Delaglio et al., 2000; Griffin, 1998; Shen and Bax, 2007).

2.2.2. Liquid state structure

Cytoplasm and nucleoplasm are liquids. They provide support to cell's internal structures playing the role of a medium for their suspension. They hold various non liquid substances but the liquids pose to have most of the liquid state characteristics. Although it is generally a gel type liquid its main part is cytosol consisting of huge amount of water, ions, etc. (Goodsell, 1991).

2.2.3. Plasma state structure

Cell membrane consists of lipids. Mitochondrial and nuclear membrane both behave as barrier but the barrier properties are subject to perturbation. The structure of membrane follows some average geometric properties but within there is found a lot of dynamic nature. Membrane therefore is not a true liquid, nor is it a solid. It rather takes the properties of a plasma state or we often refer it as a liquid crystal structure. The famous fluid mosaic membrane model was the first such successful cell's plasma state demonstration (Singer and Nicolson, 1972). The readers are also encouraged to read about subsequent developments that are explained in various studies listed in Refs. e.g., (Ashrafuzzaman and Tuszynski, 2012a,b,c; Ashrafuzzaman et al., 2006).

The above mentioned three different kinds of structures are usually found in cell constituents and we can simply say the above mentioned three structures together make a cell. Most of the disease states therefore occur in mainly these three states. Physical properties of those states are quite explainable or understandable using various physics laws e.g., Hooke's law for mechanical properties, Coulomb law for electrostatic interaction related properties, laws of general diffusion for the states of density imbalances, etc. (Huang, 1986; Andersen et al., 1999; Ashrafuzzaman et al., 2012, 2014; Greisen et al., 2011). Therefore, application of various physics laws to understanding

cell functioning and addressing disease states is inevitable. Similarly, the discovery of drugs to target cellular structures which are nothing but certain physical states requires the consideration of physics based mechanisms. The most important aspect of cell based communication occurs through general and controlled cell transport among various cell based compartments. We aim to address this issue here quite rigourously.

3. General analytical analysis and specific mathematical modelling of the cellular transport

Earlier we found that cell structure consists of various distinguishable physical states. Here we shall address how the transport phenomena naturally occur due to self regulated localized pro- and anti-barrier physical properties.

3.1. General representation of inter phase physical barriers and related analytic expressions

The cell based structural phase states have been reported to be of three different kinds namely liquid, plasma and solid phase states. General cell based diffusion requires cell constituents to diffuse in and across the mentioned three main phase states. Fig. 3 demonstrates the possible interphase diffusion, see the directions of arrows.

3.1.1. Analytic expressions to address transport phenomena across physical barriers

For inter phase diffusion that is while diffusing across a boundary separating two phases there are two probabilities of finding any specific cell constituent in two phase states. If we assume these probabilities are $P_{s,1}$ and $P_{s,2}$, respectively, in two phases states s,1 and s,2, respectively, then it is obvious that both of these probabilities are proportional to the mobilities of the constituents in both phase sates. That is,

$$P_{s,1} \sim \mu_{s,1}, \text{ or, } P_{s,1} = k_{s,1}\mu_{s,1}$$

$$P_{s,2} \sim \mu_{s,2}, \text{ or, } P_{s,2} = k_{s,2}\mu_{s,2}$$

In case of no extra inter phase barrier except for the differences in properties of various parameters determining the two phases we can assume at the boundary the following:

$$k_{s,1} = k_{s,2}$$

As a result,

$$\frac{\mathbf{P_{s,1}}}{\boldsymbol{\mu}_{\mathbf{s,1}}} = \frac{\mathbf{P_{s,2}}}{\boldsymbol{\mu}_{\mathbf{s,2}}}$$

This case follows from the diagrammatic representation for the mobility dependence of probability function as presented in Fig. 3. In this consideration,

$$\frac{\mathbf{P_{s,1}}}{\boldsymbol{\mu}_{\mathbf{s,1}}} = \frac{\mathbf{P_{s,2}}}{\boldsymbol{\mu}_{\mathbf{s,2}}}$$

This case follows from the diagrammatic representation for the mobility dependence of probability function as shown in Fig. 4. To understand easily, we can compare this with the condition of a frozen sea where the surface contains the solid phase (frozen water) above the liquid water phase. At the contact it is just a line where two phases are separated from each other where each phase exists with viscous properties specific for it.

In a cell there are compartments meeting each other but there exists buffer zones in between compartments. So at the junction of two phases there exists a buffer zone. These buffer zones, though by usual definition are considered as neutral zones, actually create zones of compromises in which distinctive compartments merge. If the phases are too distinctive types the buffer zone plays a considerably important role to couple the two zones on its both sides. In general, we can consider a cell membrane to create a buffer zone between cellular

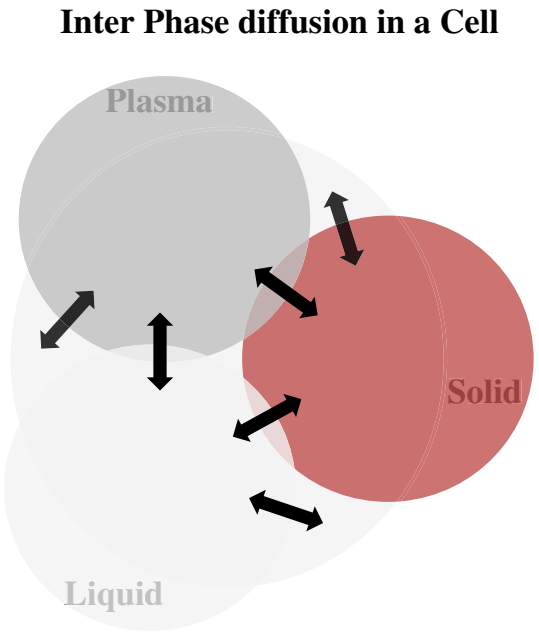

Figure 3 Diffusion happens between different phases across the inter phase boundaries in a cell. Here three equal sized spheres (size of sphere is chosen arbitrarily) represent three phases namely liquid, plasma and solid state structural phases. The background large sphere represents the cell environment which largely falls within liquid type structural phase.

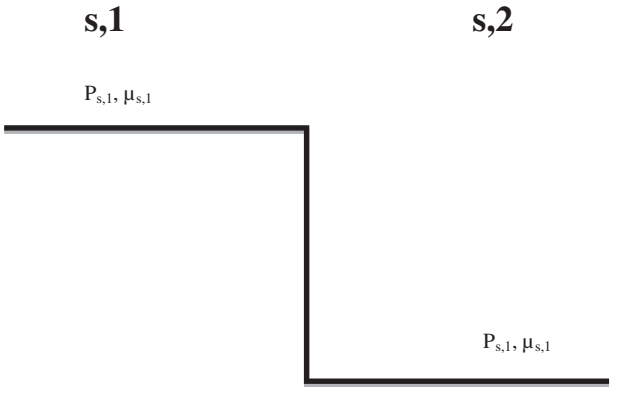

Figure 4 The two phase states s,1 and s,2 are different by only the differences of the mobilities of the constituents there. Central step down here is just to show the difference in mobilities of the constituents, not to include any (forward or reverse acting) extra interphase barrier.

exterior and cellular interior liquid states. These two liquid states may not necessarily have exactly identical biochemical and biophysical properties but both fall in liquid phase state class. Like cell membrane mitochondrial membrane also separates two identical phase states. The lipid constructed membranes, without considering the membranes' sole transport properties, make completely insulating barriers for constituents trying to cross across the membrane. But as the membrane is a pretty thick (3–5 nm) zone and it has already a different phase state (plasma phase state) constituents, while entering into cell, already face a buffer zone existing at the boundary of cellular exterior liquid phase state and membrane's plasma phase state. In this junction or buffer zone the constituents may not experience the conditions in either cellular exterior liquid phase state or membrane's plasma phase state but a condition that partially holds properties of both phase states. Therefore, the viscous friction and as a result the mobility function may have a different form or value at this buffer zone. This case follows from the diagrammatic representation for the mobility dependence of probability function as shown in Fig. 5.

In case of the presence of buffer zone, we see the previous mathematical formulas addressing the probability functions for 100% diffusion of the constituents to either phase from buffer zone take the following forms:

$$p_{s,1} = \mu_{s,1}/(\mu_{s,1} + \mu_{s,2})p_{s,1/s,2}$$

$$p_{s,2} = \mu_{s,2}/(\mu_{s,1} + \mu_{s,2})p_{s,1/s,2}$$

Here $p_{s,1/s,2}$ is the probability of the constituent to be at the boundary of two states. Therefore, the two new probability functions $p_{s,1}$ and $p_{s,2}$ are conditional probabilities of the constituents to get diffused to states s,1 and s,2, respectively from the buffer zone.

Here for simplicity we can assume mobility to be constant. This mobility is nothing but the inverse of the viscous friction of the medium. Here we have considered the probability of the constituent to be at any point within a state is equal. Analytic expression for determination of such mobility factor $\mu_{s,i}$ ($\mu_{s,1}$, $\mu_{s,2}$, etc.) depends on the structures of the corresponding state.

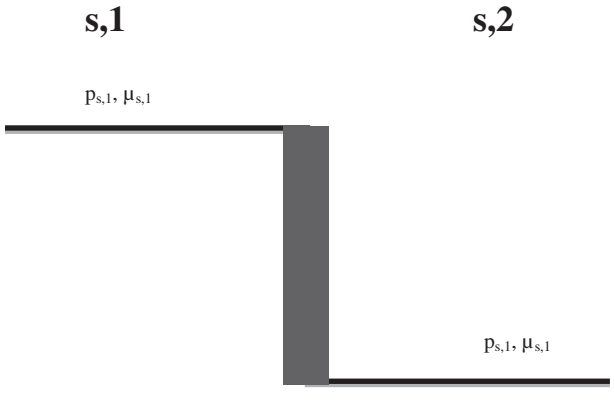

Figure 5 The two phase states s,1 and s,2 are different by only the differences of the mobilities of the constituents there. Central step down with a thicker line here (not just a demarcation line like that in previous Fig. 3) is to show the presence of a buffer zone that consists of properties of both phases of its left and right sides.

3.1.2. Permanent trap in a phase state

In special case of unidirectional flow the constituents may get trapped permanently inside a phase state. If we assume the constituents to be transferring from the liquid state (LS, s,0) to any other two states, plasma state (PS, s,1) or solid state (SS, s,2) we can assume the following:

$$p_{s,1/s,0} = \kappa_{s,1/s,0}\ P_{s,0}$$

$$p_{s,2/s,0} = \kappa_{s,2/s,0}\ P_{s,0}$$

where $P_{s,0}$ is assumed to be the probability function at liquid state. $\kappa_{s,1/s,0}$ and $\kappa_{s,2/s,0}$ are functions that are determined by the partition co-efficients active at the buffer zones of boundaries created between states s,1 and s,0, and states s,2 and s,0, respectively. We know that the physical science definition of a partition (or occasionally referred as distribution)-coefficient is the ratio of constituent concentration in a mixture of two phases. If the phases are too distinctive types the buffer zone plays a considerably important role to couple the two zones from its both sides. If we consider the concentration of a cell constituent in s,0 is greater than that at s,1 or s,2, we can assume that the constituent experiences a unidirectional, s,0 → s,1 or, s,0 → s,2 flow. In that case, the following conditions apply:

$$0 \leq \kappa_{s,1/s,0} \leq 1$$

$$0 \leq \kappa_{s,2/s,0} \leq 1$$

Then the previously mentioned state probability functions can be revised, for 100% diffusion into either state from the buffer zone, as

$$p_{s,1} = \mu_{s,1}/(\mu_{s,1} + \mu_{s,0})\kappa_{s,1/s,0}\ P_{s,0}$$

$$p_{s,2} = \mu_{s,2}/(\mu_{s,2} + \mu_{s,0})\kappa_{s,2/s,0}\ P_{s,0}$$

If the constituent instead of experiencing regular diffusion experiences interaction with various interaction causing potential sites in the state we have to develop an expression for the mobility factor which takes a complicated form. Later we shall develop such expressions.

3.2. General representation of intra phase physical barriers and related analytic expressions

In a phase state, several sub-states within the classified phase category (see Fig. 3) may exist (Ashrafuzzaman, 2015). In this case like Fig. 3 we may have several boundaries for the constituents to cross within same phase class. Fig. 6 has been shown to represent such sub-phase states and the intra phase boundaries in a major cell phase state.

3.2.1. Analytic expressions to address transport phenomena across sub-phase state physical barriers

For intra phase diffusion that is while diffusing across a boundary separating two sub-phases there are two probabilities of finding any specific cell constituent in two sub-phase states. For simplicity and of course often realistic, we assume that a major proportion of the classified phase state is occupied by a sub-phase state denoted as SPS,0 and constituents usually diffuse across the boundaries of SPS,0 (ss,0) and other sub-phase states, e.g., SPS,1 (ss,1), SPS,2 (ss,2), …, etc. In this case if we assume that the probabilities of constituents to be in SPSs

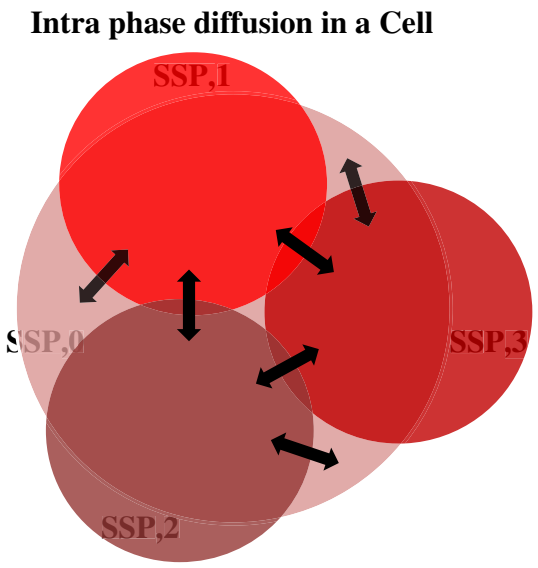

Figure 6 Diffusion happens between different sub-phases across the intra phase boundaries/inter sub-phase boundaries in a classified cell phase like liquid or plasma or solid phase. Here we have schematized various intra solid phases or sub-solid phases (SSPs) within classified solid phase of a cell. SSP,0 represents major proportion of SSP whereas SSP,1, SSP,2, SSP,3, ..., etc. (SSP,1-3 are shown here, as examples) represent various intra solid phases. The intra phase diffusion across the intra phase boundaries follows different quantitative but almost identical qualitatively mechanism as are explained for the diffusion across inter phase boundaries. Bidirectional arrows show the directions to which the diffusion may take place.

ss,1, ss,2,..., etc. are $p_{ss,1}$, $p_{ss,2}$,..., etc., respectively, then we find the following relation:

$$p_{ss,1} = \mu_{ss,1}/(\mu_{ss,1} + \mu_{ss,0})p_{ss,1/ss,0}$$
$$p_{ss,2} = \mu_{ss,2}/(\mu_{ss,2} + \mu_{ss,0})p_{ss,2/ss,0}$$
etc.

Here $p_{ss,1/ss,0}$, $p_{ss,1/ss,0}$,..., etc. are the probabilities of the constituents to be at the boundaries of ss,1/ss,0, ss,2/ss,0,..., etc. Therefore, the new probability functions $p_{ss,1}$ and $p_{ss,2}$,..., etc. are conditional probabilities of the constituents to get diffused into ss,1, ss,2,..., etc., respectively, from their buffer zones with ss,0. $\mu_{ss,0}$, $\mu_{ss,1}$, $\mu_{ss,2}$, ..., etc. are mobilities of the constituent in ss,0, ss,1, ss,2, ..., etc., respectively. Here for simplicity we can assume mobility within a specific SPS to be constant.

3.2.2. Permanent trap in a sub-phase state

In a special case where the constituents get permanently trapped inside any SPS and as we assume the constituents to get transferred from ss,0 to any of ss,1, ss,2, ..., etc. we can assume the following:

$$p_{ss,1/ss,0} = \kappa_{ss,1/ss,0}p_{ss,0}$$
$$p_{ss,2/ss,0} = \kappa_{ss,2/ss,0}p_{ss,0}$$
etc.

Here, as explained earlier, $\kappa_{ss,1/ss,0}$, $\kappa_{ss,1/ss,0}$, ..., etc. are functions that are determined by the partition co-efficients active at the buffer zones of boundaries created between ss,1 and ss,0, ss,2 and ss,0,..., etc., respectively. And,

$$0 \leq \kappa_{ss,1/ss,0} \leq 1$$

$$0 \leq \kappa_{ss,2/ss,0} \leq 1$$

Then the previously mentioned sub-state probability functions can be revised as

$$p_{ss,1} = \mu_{ss,1}/(\mu_{ss,1} + \mu_{ss,0})\kappa_{ss,1/ss,0}p_{ss,0}$$
$$p_{ss,2} = \mu_{ss,2}/(\mu_{ss,2} + \mu_{ss,0})\kappa_{ss,2/ss,0}p_{ss,0}$$
etc.

4. Numerical computation and general trends of probability functions related to the cell transport

The cell transport phenomena as addressed earlier raise some theoretical probability functions that are able to address the diffusion based on localized physical conditions of biophysical states. We shall address a few such functions here.

4.1. Phase state probability functions

We shall present here the numerical computation results and show the trends of the phase state probability functions in case of permanent trap, as mentioned earlier. According to the analytical expressions developed earlier, we get the trapping probability in a state s,i as

$$p_{s,i} = \mu_{s,i}/(\mu_{s,i} + \mu_{s,0})\kappa_{s,i/s,0}\ P_{s,0}$$

We need to plot the normalized expressions of $p_{s,i}$, $(1/\kappa_{s,i/s,0})\ p_{s,i}/P_{s,0} = 1/(1 + \mu_{s,0}/\mu_{s,i}) = 1/(1 + 1/(\mu_{s,i}/\mu_{s,0}))$ (see Fig. 7).

The plot suggests clearly that $p_{s,i} \leqslant P_{s,0}$. The value of $p_{s,i}$ depends also on the parameter $\kappa_{s,i/s,0}$ which is related to the partition coefficient.

4.2. Sub-phase state probability functions

We shall present here the numerical computation results and show the trends of the sub-phase state probability functions in case of permanent trap, as mentioned earlier. We need to plot the normalized expressions of $p_{ss,i}$ which is,

$$p_{ss,i} = \mu_{ss,i}/(\mu_{ss,i} + \mu_{ss,0})\kappa_{ss,i/ss,0}\ p_{ss,0}$$
$$= \mu_{ss,i}/(\mu_{ss,i} + \mu_{ss,0})\kappa_{ss,i/ss,0}\mu_{s,i}/(\mu_{s,i} + \mu_{s,0})\kappa_{s,i/s,0}\ P_{s,0}$$

Here $p_{ss,0}$ is the probability for the constituents to be in the most common sub state ss,0 within sate s,i and therefore $p_{ss,0} = \mu_{s,i}/(\mu_{s,i} + \mu_{s,0})\ \kappa_{s,i/s,0}\ P_{s,0}$ (see earlier).

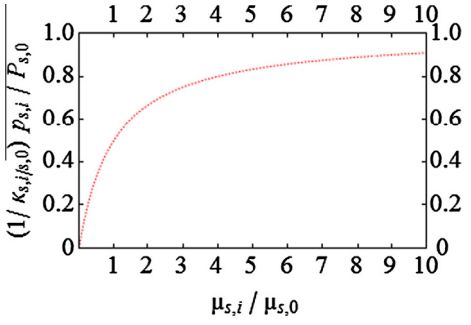

Figure 7 Plot of $(1/\kappa_{s,i/s,0})\ p_{s,i}/P_{s,0}$ as a function of $\mu_{s,i}/\mu_{s,0}$.

Therefore, we need to plot

$$(1/\kappa_{ss,i/ss,0})(1/\kappa_{s,i/s,0})p_{ss,i}/P_{s,0} = \mu_{ss,i}/(\mu_{ss,i}+\mu_{ss,0})\kappa_{ss,i/ss,0}\ \mu_{s,i}/ \times(\mu_{s,i}+\mu_{s,0}) = \{1/(1+1/ \times(\mu_{ss,i}/\mu_{ss,0})\}\{1/(1+1/(\mu_{s,i}/\mu_{s,0}))\}$$

$(1/\kappa_{ss,i/ss,0})(1/\kappa_{s,i/s,0})\ p_{ss,i}/P_{s,0}$ requires to get plotted in three dimensional (x,y,z) space where the function is plotted for two factors $\mu_{ss,i}/\mu_{ss,0}$ along x-axis and $\mu_{s,i}/\mu_{s,0}$ along y-axis. See Fig. 8.

By comparing the probability values from two different cases namely in a classified phase state and in a sub-phase state it becomes clear that the value decreases in the latter case. The deeper the constituents penetrate the lesser is the probability value to be found. 'Deeper' has been used here to mean more sub states to be crossed through by the cell constituents. The values of probabilities further need to be normalized with the values of $\kappa_{ss,i/ss,0}$ and $\kappa_{s,i/s,0}$. Phase state properties appear as strong regulators of cell based diffusion.

5. Ion channel energetics to regulate cell based nutrient diffusion

In previous sections, we have developed a few probability functions that can be generalized to demonstrate particles' observable probability in a certain phase state. Ion channel can also be physically engaged in regulating all these probability functions. The existence and non existence of the conducting ion channels across mainly cell membranes can be two distinguishable states within a class of structural phase, plasma state. The existence of ion channels also represents a probable state that relies on many factors like the density of ion channel constructing materials e.g., peptides, membrane proteins, membrane physical state, types of constituents like lipids, cholesterol, etc. that create membrane barrier, physical properties like charge density on lipid molecules, membrane surface charge density, membrane thickness, etc. Here the ion channel existence relative to non existence may be, in special case, considered as relative existence of active channels in comparison with inactive (or not constructed properly) channels. Without the existence of channels diffusion across the membrane barrier still exists but the presence of channels enhances the process and probably appear as the premier regulator of the transport properties. Therefore, certain properties in the ion channel formation implicitly or explicitly may get coupled to the conventional probability functions developed earlier for nutrient diffusion.

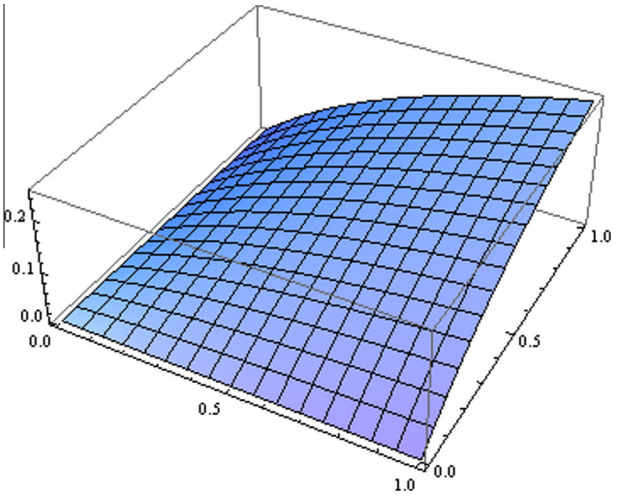

Figure 8 Plot of $(1/\kappa_{ss,i/ss,0})(1/\kappa_{s,i/s,0})\ p_{ss,i}/P_{s,0}$, along vertical axis, for $\mu_{ss,i}/\mu_{ss,0}$, along x-axis, and $\mu_{s,i}/\mu_{s,0}$, along y-axis.

Ion channel contributions into those probability functions certainly rely on the stability of channels inside cell membrane region. There comes the localized energetics or specifically speaking the locally supplied energy ($\Delta G_{I,II}$) that is primarily discovered recently to determine or regulate ion channel stability (for details see Ashrafuzzaman and Tuszynski, 2012a,b). This energy is termed as 'free energy' for a channel to transfer from active or open (conducting) state to inactive or closed (nonconducting) state and it enters into the scenario directly to determine the channel lifetime τ following the relation:

$$\tau \sim \exp\{-\Delta G_{I,II}/k_B T\}$$

Theoretical determination of $\Delta G_{I,II}$ therefore is very important to address the channel lifetime/stability. Origins of such energies are recently detected, using molecular dynamic simulation of the complex, in charge properties of the membrane active agents and the membrane constituent lipids (Ashrafuzzaman et al., 2012, 2013, 2014). Stable ion channels certainly contribute more into cell compartment diffusion and the probability of intercompartment diffused particles as addressed earlier gets regulated. A clear coupling between these two factors namely, channel stability and particle probability functions requires extended theoretical works which are in process of being developed by us. Here I wish to address how this channel stability can be detected using localized parameters that determine the energy $\Delta G_{I,II}$.

The most dramatic theoretical result is found in a recent study (Ashrafuzzaman and Tuszynski, 2012b) where we observe that $\Delta G_{I,II}$ exponentially increases with the increase of (geometric mismatch term) $d_0 - l$:

$$\Delta G_{I,II} \sim \exp\{d_0 - l\}$$

We also observe that $\Delta G_{I,II}$ gets regulated due to charge properties of the participating agents that help channels to be constructed and stabilized following:

$$\Delta G_{I,II} \sim (q_L/q_M)^s$$

where $s = 1, 2$, etc. for the first, second, etc. order lipid screening that determines the number of lipids on membrane surface under interactions with channel, respectively. Here, q_L is cell membrane constructing lipid charge, q_M stands for gA monomer charge. There are also other factors that regulate ion channel stability. The readers are highly encouraged to know the details from Refs. (Ashrafuzzaman and Tuszynski, 2012a,b).

We have developed a common theoretical platform to address the components that regulate the ion channel stability which indirectly participate in regulating cell based transport/diffusion mechanisms. Cell membrane active general agents, chemicals, drugs, etc. may also appear as regulator of such ion channels via changing the localized energetics. Earlier developed probability functions certainly require to draw information from cell based membrane residing ion channel physical properties. A rather complicated theoretical analysis may solve the issue. In this article, we just wished to draw the attention. Therefore, we would not cover the details of such theoretical manipulation of the probability functions. In future when we have completed such analysis we shall certainly present the developments in other publications.

6. Conclusions

We have developed here a general explanation on the cell based physical barriers and address the transport mechanisms across these barriers based on the physical phase state classification of the cell compartments. A clear cross examination between biological components and physical concepts have helped to inspect the issue rigorously which has been presented here in detail. A few cell based transport related functions like mobility, probability, etc. have been developed theoretically. These derived novel functions have also been inspected computationally and their trends are presented in various plots. Ion channel involvement in regulating cell based transport mechanisms has also been addressed. Energetics of channel stability is found to rely on localized components that get involved in constructing and stabilizing ion channels. The various probability functions related to the cell transport phenomena therefore are predicted to be dependent on not only geometrical aspects, phase state aspects but also the localized energetic aspect. A clear connection between all these parameters is yet to be done. Ion channel energetics is predicted to regulate the diffusion raised nutrient probability functions in various cell compartments. This theoretical article will certainly help us understand the cell based diffusion clearly and may open up some novel concepts that may be helpful for drug discovery and medical scientists.

Conflict of interest

The author declares no conflict of interests regarding the publication of this paper.

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References

Andersen, O.S., Nielsen, C., Maer, A.M., Lundbæk, J.A., Goulian, M., Koeppe II, R.E., 1999. Ion channels as tools to monitor lipid bilayer-membrane protein interactions: gramicidin channels as molecular force transducers. Methods Enzymol. 294, 208–224.

Ashrafuzzaman, M., 2015. Diffusion across cell phase states. Biomed. Sci. Today 1, e4.

Ashrafuzzaman, M., Tuszynski, J., 2012a. Membrane Biophysics, first ed. Springer, Heidelberg, Germany.

Ashrafuzzaman, M., Tuszynski, J., 2012b. Regulation of channel function due to coupling with a lipid bilayer. J. Comput. Theor. Nanosci. 9, 564–570.

Ashrafuzzaman, M., Tuszynski, J., 2012c. Ion pore formation in lipid bilayers and related energetic considerations. Curr. Med. Chem. 19, 1619–1634.

Ashrafuzzaman, M., Lampson, M.A., Greathouse, D.V., Koeppe II, R.E., Andersen, O.S., 2006. Manipulating lipid bilayer material properties using biologically active amphipathic molecules. J. Phys. Condens. Matter 18, S1235–S1255.

Ashrafuzzaman, M., Tseng, C.-Y., Duszyk, M., Tuszynski, J.A., 2012. Chemotherapy drugs form ion pores in membranes due to physical interactions with lipids. Chem. Biol. Drug Des. 80, 992–1002.

Ashrafuzzaman, M., Tseng, C.-Y., Kapty, J., Mercer, J.R., Tuszynski, J., 2013. A computationally designed DNA aptamer template with specific binding to phosphatidylserine. Nucleic Acid Ther. 23, 418–426.

Ashrafuzzaman, Md., Tseng, C.-Y., Tuszynsk, J.A., 2014. Regulation of channel function due to physical energetic coupling with a lipid bilayer. Biochem. Biophys. Res. Commun. 445, 463–468.

Castellani, F., van Rossum, B., Diehl, A., Schubert, M., Rehbein, K., Oschkinat, H., 2002. Structure of a protein determined by solid-state magic-angle-spinning NMR spectroscopy. Nature 420, 98–102.

Delaglio, F., Kontaxis, G., Bax, A., 2000. Protein structure determination using molecular fragment replacement and NMR dipolar couplings. J. Am. Chem. Soc. 122, 2142–2143.

Goodsell, D.S., 1991. Inside a living cell. Trends Biochem. Sci. 16 (6), 203–206.

Greisen, Per, Lum, Kevin, Ashrafuzzaman, Md., Greathouse, Denise V., Andersen, Olaf S., Lundbæk, Jens A., 2011. Linear rate-equilibrium relations arising from ion channel-bilayer energetic coupling. Proc. Natl. Acad. Sci. U.S.A. 108, 12717–12722.

Griffin, R.G., 1998. Dipolar recoupling in MAS spectra of biological solids. Nat. Struct. Biol. 5, 508–512.

Huang, H.W., 1986. Deformation free energy of bilayer membrane and its effect on gramicidin channel lifetime. Biophys. J. 50, 1061–1071.

Shen, Y., Bax, A., 2007. Protein backbone chemical shifts predicted from searching a database for torsion angle and sequence homology. J. Biomol. NMR 38, 289–302.

Singer, S.J., Nicolson, G.L., 1972. The fluid mosaic model of the structure of cell membranes. Science 175, 720–731.