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Regular Article

Diffusion Across Cell Phase States

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Abstract
Cell has various distinguishable physical structural compartments. The compartments may be divided into three major physical phase states namely liquid, plasma and solid phase states. Cell based transport of ions, nutrients, small molecules like proteins, etc. across inter phase states and intraphase states follow general transport formalisms. Creation of some localized permanent and/or temporary structures and the transitions between 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 computation to address the analytical expression phenomenologically. Here we have merged biological observations with the physical classification of cellular compartments. Then developed analytical expressions that help us address the diffusion phenomena generally considering the physical properties of the biostructures across the diffusion pathways. This article helps to address the mechanisms of cell based diffusion and nutrients movements and thus help develop strategic templates to manipulate the diffusion mechanisms. Therefore, it may be considered an important article for biophysical modelling of the biological functions of cell.

Key words. Cell, physical structural phase, diffusion, modelling, computation.

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1. GENERAL CELL STRUCTURES AND VARIOUS 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. Figure 1 shows model representation of a cell's various components. The general cell structure is quite known for sometimes but analysis on the physical states of these structural components is yet to be made or knows poorly. Here we shall make a biophysical analysis of this biological issue.

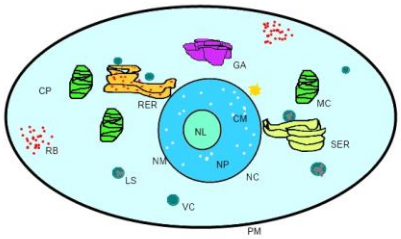

Figure 1. Schematic diagram of a cell showing different parts (taken from ref. [1]). In no way any component schematized here represents the true structure observed in biological cell. PM: Plasma membrane, CP: cytoplasm, VC: vacuole, LS: lysosome, RB: ribosome, MC: mitochondrion, GA: Golgi apparatus, 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.

1.1 Cell's general structures

All cells are enclosed by cell envelopes which consist of cell walls covering plasma membranes. Both of the prokaryotic or 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 Figure 1.

1.2 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 disected state, there found to exist various things as shown in Figure 1. These cellular constituents fall in different physical structure categories. Solid, liquid, gas these 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.

1.2.1 Solid State Structure

Solid means something rigid in structure. It's 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. [2-5].

1.2.2 Liquid State Structure

Cytoplasm and nucleoplasm are liquids. They provides 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 it's main part is cytosol consisting of huge amount of water, ions, etc. [6].

1.2.3 Plasma State Structure

Cell membrane consists of lipids. Mitochondreal and nuclear membrane both behave as barrier but the barrier properties are subject to perturbation. The structure of membrane follows some average

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geometric properties but within there is found a lot of dynamic nature. Membrane therefore is not a true liquid, nor it is 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 [7]. The readers are also encouraged to read about subsequent developments that are explained in various studies listed in refs. e.g. [1, 8-10].

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. [11-15] . Therefore, application of various physics laws to understanding cell finctioning and addressing disease states is inevitable. Similarly, the discovery of drugs to target cellular structures which are nothing but certain physical states require 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 compatments. We aim to address this isssue here quite rigoirously.

2. CELL BASED PHYSICAL BARRIERS AGAINST GENERAL CELLULAR TRANSPORT. AN ANALYTICAL ANALYSIS.

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

2.1 General representation of inter phase physical barriers and related analytic expressions

The cell based structural phase states have been reported to be 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. Figure 2 demonstrates the possible interphase diffusion, see the directions of arrows.

Inter Phase diffusion in a Cell

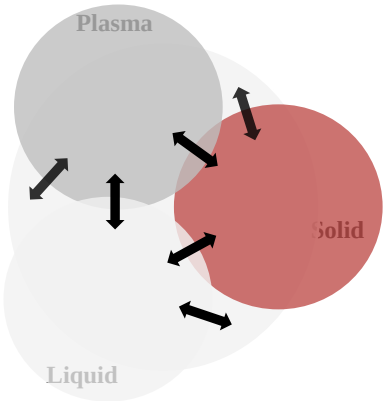

Figure 2. Diffusion happens between different phases across the inter phase boundaries in a cell. Here three equal sized spheres (size of sphere is chosen arbitrarily) represent three phases namely liquid, plasma and solid state structural phases. The background large sphere represents the cell environment which largely falls within liquid type structural phase.

2.1.1 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 corresponding 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,

$$\frac{P_{s,1}}{\mu_{s,1}} = \frac{P_{s,2}}{\mu_{s,2}}$$

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

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$$\frac{P_{s,1}}{\mu_{s,1}} = \frac{P_{s,2}}{\mu_{s,2}}$$

This case follows from the diagrammatic representation for the mobility dependence of probability function as shown in Figure 3. To understand easily, we can compare this with the condition of a frozen sea where the surface contains solid phase (frozen water) above the liquid water phase. At the contact it's just a line where two phases are separated from each other where each phase exists with viscous properties specific for it.

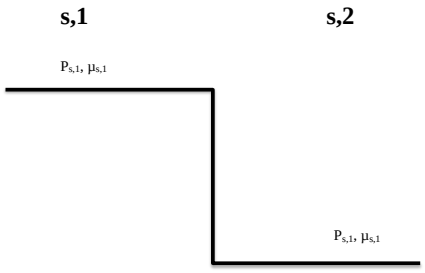

Figure 3. The two phase states s,1 and s,2 are different by only the differences of the mobilities of the constituents there. Central step down here is just to show the difference in mobilities of the constituents, not to include any (forward or reverse acting) extra interphase barrier.

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 a neutral zones, they actually create zones of compromises in which distinctive compartments merge. If the phases are too distinctive types the buffer zone plays considerably important role to couple the two zones on it's both sides. In general, we can consider a cell membrane to create a buffer zone between cellular 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 Figure 3.

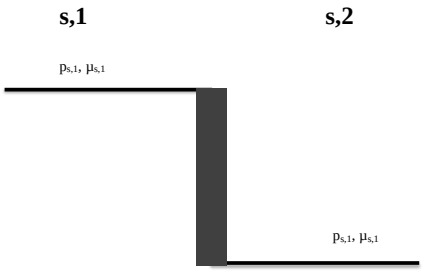

Figure 4. The two phase states s,1 and s,2 are different by only the differences of the mobilities of the constituents there. Central step down with a thicker line here (not just a demarcation line like that in previous Figure 3) is to show the presence of a buffer zone that consists of properties of both phases of it's left and right sides.

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 phases 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.

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2.1.2 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 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 sates 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 considerably important role to couple the two zones from it's 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 → s2 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 states 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.

2.2 General representation of intra phase physical barriers and related analytic expressions

In a phase state, several sub-states within the classified phase category (see Figure 2) may exist. In this case like the Figure 2 we may have several boundaries for the constituents to cross within same phase class. We can schematically diagram this case as shown in Figure 5. Several sub-phases within a classified phase state category may arise due to mainly the presence of different category state defining materials in different regions within a phase category (Figure 2). For example, in a solid state phase various solid state materials may exist and thus various sub-phases within solid state phase category may emerge. Similarly, due to various other causes like chemical, thermodynamic, etc. several localized sub-phase states are generally expected to emerge although altogether those sub-states are defined by the gross biophysical properties of a specific phase state in a cell. Figure 5. has been shown to represent such sub-phase states and the intra phase boundaries in a major cell phase state.

Intra phase diffusion in a Cell

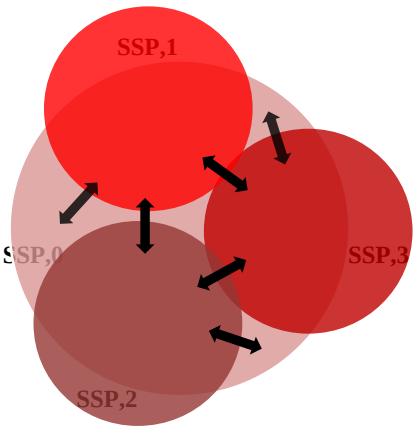

Figure 5. Diffusion happens between different sub-phases across the intra phase boundaries/inter sub-phase boundaries in a classified cell phase like liquid or plasma or solid phase. Here we have schematized various intra solid phases or sub-solid phases (SSPs) within classified solid phase of a cell. 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 follow 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.

2.2.1 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 major

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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 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.

2.2.2 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,

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

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.

3. NUMERICAL COMPUTATION AND GENERAL TRENDS OF PROBABILITY FUNCTIONS RELATED TO THE CELL TRANPORT

The cell transport phenomena as addressed earlier raises 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.

3.1 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 is

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

Therefore, we need to plot the normalized expressions of $p_{s,i}$ that is $(1/\ \kappa_{s,i/s,0})\ p_{s,i}\ /\ P_{s,0} = 1\ /\ (1+\ \mu_{s,0}\ /\ \mu_{s,i}) = 1/(1+\ 1\ /\ (\mu_{s,i}\ /\ \mu_{s,0}))$. This is shown in Figure 6.

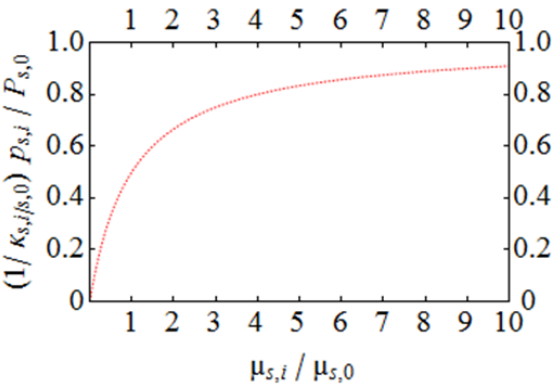

Figure 6. Plot of $1/\ \kappa_{s,i/s,0})\ p_{s,i}\ /\ P_{s,0}$ as a function of $\mu_{s,i}\ /\ \mu_{s,0}$.

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

3.2 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 susbstate 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). Therefore, we need to plot

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

$(1 / \kappa_{ss,i/ss,0})(1 / \kappa_{s,i/s,0})\ p_{ss,i} / P_{s,0}$ requires to get plotted in three dimensional (x,y,z) space where the function is 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 Figure 7.

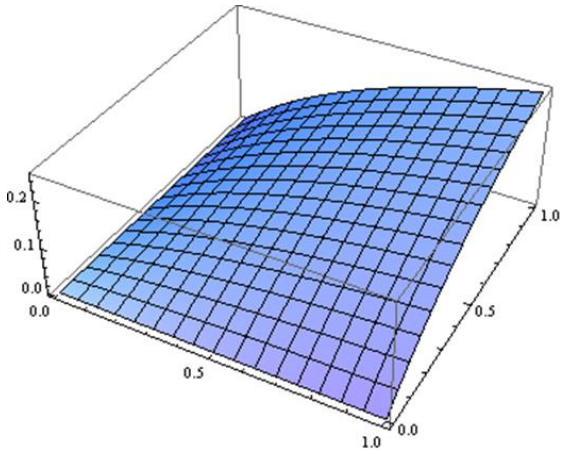

Figure 7. Plot of $(1 / \kappa_{ss,i/ss,0})(1 / \kappa_{s,i/s,0})\ p_{ss,i} / P_{s,0}$, along vertical axis, for $\mu_{ss,i} / \mu_{ss,0}$, along x-axis, and $\mu_{s,i} / \mu_{s,0}$, along y-axis.

If we compare the probability values from two different cases namely in a classified phase state and in a sub-phase state it is 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 $\kappa_{s,i/s,0}$.

4. CONCLUSIONS

The aim of this article was to provide a general explanation of 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 details. 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. This article will thus help biochemists, biophysicists and drug discovery scientists to raise their thoughts and create strategies based on clear biophysical understanding of the problem while addressing cell transport phenomena. Further example studies using cell active membrane proteins, drugs or novel molecules are underway which will soon reveal more applicable strategies as far as cell based transport phenomena matter.

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

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Author's Biosketch

Prof. Ashrafuzzaman

Dr. Ashrafuzzaman works in the domain of biophysics. Stability of the structures of biomolecules, their independent random existence, coexistence with other molecules <complex biological structures> in biological environment, especially in cellular environment (cell membrane, cellular interior and exterior regions where various proteins exist) are often energy- based biophysical problems. Going beyond simple biochemical approaches we apply various biophysical techniques to not just observe things or measure the effects but also try to understand the hidden causes of responses, underlying mechanisms and aftermath effects using response theory based science. We apply all three common methodologies of investigations: theory, experiments and computation to penetrate dip into the problems. Our techniques are dedicated mainly to first finding the equilibrium structures, calculating the energies corresponding to specific structures, then raising the understanding of phenomenological structural transitions between various energy landscapes that represent various functional aspects. For more contact at mashrafuzzaman@ksu.edu.sa.

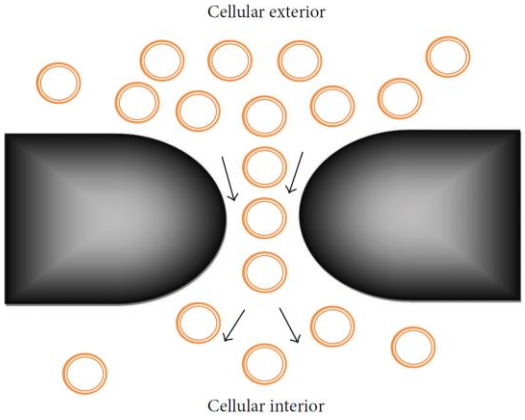

Figure demonstrates the cell membrane diffusion of nanoparticles that is explored biophysically and biochemically in Dr. Ashrafuzzaman's laboratory.