Modeling and Simulation of Crossing Magnetic NanoParticles Through Blood Brain Barrier (BBB)

Maysam Z. Pedram [1], Amir Shamloo [2], Ebrahim GhafarZadeh [3] and Aria Alasty [4]

Abstract— **Crossing the Blood Brain Barrier (BBB), despite its tight junctions, is of the great importance in a plethora of medical applications. As a result, this work is dedicated to molecular dynamics (MD) simulation of crossing through the BBB particularly under the effect of magnetic force. For this purpose, two cases of a coated gold nanocparticle with insulin and uncoated gold nanoparticle have been considered ; there, the dominant governing parameters in each case are changed to identify the optimized condition for crossing nanoparticles. These parameters are of biological (ligand-receptor binding affinity), biophysical (membrane surface receptor density ratio and non-specific interaction parameter) or geometrical (size of components) origin. The most important part of this study is MD simulation of nanoparticles under the effect of magnetic field and the result shows that for crossing through BBB what force profile must be provided by the magnetic field.**

Keywords: ***Molecular Dynamics Simulation, drug delivery system, magnetic steering, Blood Brain Barrier***

I. INTRODUCTION

Even in the 21st century, many studies are focused on investigating the biological systems inside the human and animal bodies. In this area, Blood Brain Barrier (BBB) has attracted many researchers. The importance of the BBB represents itself when a research study carries out on brain diseases. In fact, treatment for some of these diseases requires analyzying BBB. Therefore, nowadays many researches have being done on modeling BBB [1].

Neural signaling by means of the central nervous system (CNS) needs a highly controlled microenvironment. Cells form resistant barriers in the gap between the blood and the CNS at three ways: 1-the blood brain barrier (BBB), 2-blood CSF barrier, 3-the arachnoid barrier. Among these barriers, BBB at the stage of brain micro vessel endothelium is the major site of the blood CNS exchange [1].

The idea of a BBB that separates the blood and brain was developed about 100 years ago. The BBB is created at the same level of the cerebral capillary endothelial cells by the formation of the tight junctions. It is known to be the largest surface area in the adult human for exchanging neutritions and its size is around 12 to 18m^2. No brain cell is farther than about 25mm from a capillary, so once the BBB is crossed, diffusion distances to neurons and glial cell bodies for solutes and drugs are short. Thus, delivery of drugs to all brain cells is done by designing the drugs optimal for crossing through the BBB [1].

Structure of the BBB has not been understood completely and an ideal model of the BBB is desireable. There are some researches on modeling BBB. In Ref. [6], a BBB model by using a microfluidic chip has been investigated. Barrier function is modulated both mechanically by exposing the cells to fluid shear stress, and biochemically, by stimulating the cells with tumor necrosis factor alpha (TNF-), respectively. electrodes have also been integrated in this chip for analyzing barrier tightness with measuring the transendothelial electrical resistance (TEER) [6]. Besides the above microfluidic modeling, there are a few other models for in vitro blood brain barrier [9, 10, 8, 5].

The most major problem in drug delivery to the brain is the limitation of drug penetration due to the presence of the BBB. In fact, BBB acts as a dam to prevent entering toxic agents, due to the brain endothelial cells that are located on the vessel walls. It shows some important features such as the presence of tight junctions between the cells, the absence of fenestrations that together restricts the crossing of compounds from the blood into the brain. The ability of tranversing the membrane affects the diffusion of drugs from the blood into the brain.

Delivering drugs to the brain by the use of magnetic nanoparticles (MNPs) to across the BBB may provide a significant advantage to current strategies. The magnetically controlled chemotherapy under MRI is a novel technique that is based on magnetically forcing a therapeutic magnetic microcarrier through a MRI system. Moreover, the surface of these nanoparticles can be bio-conjugated with specific antibodies so that the immune system would not be able to detect them. The crossing through the BBB may be due to the recognition of these nanoparticles by the receptor at the surface of the endothelial cells of the BBB. Since using MRI system is a very expensive approach, most of the studies are concentrated on numerical and computational modeling methods in order to reduce the risk and uncertainty inherent in the nanoparticle development process. This project deals with the simulation of super paramagnetic nanoparticles crossing the BBB via a hybrid approach: mechanical steering driven by a magnetic field combined with chemical surface functionalization [7]. In this paper, we are going to study the crossing of nanoparticles through the BBB by means of magnetic force. In this method, it is very important to apply a suitable magnetic density profile. In fact, this profile causes

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the exertion of a defined force to the nanoparticles. The novelty of this study concentrated to find out the suitable force profile appropriate to be exerted to nanoparticles to stimulate them to cross BBB. In section 2, several methods for permeation across the BBB is expressed. In section III, our modeling and simulation methods are described and finally in section IV the results are presented. It should be mentioned that Fe_3O_4 is one of the magnetic nanoparticle. In order this NP to be bio compatible inside the human body, it needs to be coated by a gold layer. Therefore, in this paper gold nanoparticle means a magnetic nanoparticle covered by a thin layer of gold.

II. BIOLOGICAL STRATEGIES FOR CROSSING THROUGH THE BBB

There are several potential routes for permeation across the BBB as descripbed in Ref. [1]. In this section two important applied methods are explained:

A. Ultrasound-Induced Blood Brain Barrier Opening

In this method, temporary openning of the BBB is carried out by means of focused ultrasound sonication (FUS) in the presence of microbubbles. Therefore, it makes allowing systemically administered agents into the brain. Both the targeted brain region and the size distribution in the injected microbubble volume affect the efficiency of FUS induced BBB opening [3].

B. Using External Forces and Applying to NanoParticle

Applying force to nanoparticles is one of the solution of crossing nanoparticles through the BBB. By selecting magnetic particle and applying a suitable magnetic field intensity, a magnetic force is applied to NPs and affects the trajectories of nanoparticles. The issue on this method is to find the best magnetic/force profile which must be applied to nanoparticles.

III. MODELING AND SIMULATION

A. BBB Structure (Main Membrane)

The brain microvasculature is composed of three cellular elements such as BBB endothelial cells, astrocyte end-feet, and pericytes. Tight junctions (TJs) that are present in the gap between the cerebral endothelial cells, create a diffusive barrier, which avoides entering most blood-borne substances to the brain selectively. The BBB endothelial cells differ from endothelial cells in the rest of the body by the absence of fenestrations, more extensive tight junctions (TJs), and sparse pinocytic vesicular transport. In this study, only the cell membrane is modeled, because there is no significant resistance against the nanoparticle to cross the cytoplasm. Of course, this assumption is for the case that the nanoparticle is crossing the cell membrane not the junctions between the cells. In case of crossing through tight junctions, a more complicated interaction should be modeled [2].

1) Endothelial Cell Membrane: A Phospholipid Bilayer

One of the class of lipids is Phospholipid which is a vital component of all cell membranes as they can form lipid bilayers. Most of the phospholipids contain diglyceride, a phosphate group, and a simple organic molecule as choline. Lipid bilayers are a thin polar membranes that are made of two layer lipid molecules. These membranes are flat shells that shape a continuum barrier around the cells. Phospholipids are usually named with 4 letters. The first two letters are the abbreviations of the two fatty acids in the tail. The last two letters are the abbreviations of the names of the hydrophilic heads. Phospholipids are categorized by their two last letters. In literature, DMPC (DiMyristoyl PhosphoCholine) and POPC (Palmitoyl Oleyl Phosphatidyl Choline) are mostly used to simulate BBB. Therefore, a combination of these phospholipids were chosen in the present project, too (Fig. 1).

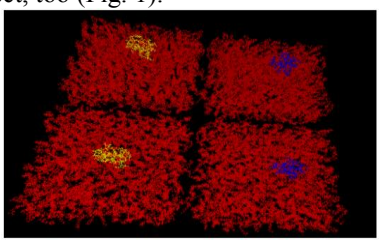


Figure 1: 200A×200A membrane with 4 receptors on it

2) Putting Insulin Receptor on the Membrane

The transport of the nanocapsule through the BBB is mediated by specialized ligands coated on the nanoparticle surface, and receptors covering the membrane including the insulin receptor (IR) or the transferrin receptor (TfR), which are highly expressed on the capillary endothelium of the brain. In the present project, insulin was used as the ligand coating the nanoparticles and insulin receptor was used to cover the membrane surface. The insulin receptor (IR) is a type of transmembrane receptor that is activated by insulin such as IGF I, IGF II and are included in the large class of tyrosine kinase receptors. Metabolically, the insulin receptor plays an important role in glucose homeostasis regulation. Interaction of the compelete domains of insulin and insulin receptor is complicated chemically and physically. Therefore, we have modeled the ectodomain of the receptor molecule as the main domain affecting this interaction. Ectodomain is the domain of the receptor protein that extends into the extracellular space. Insulin receptor ectodomain with pdb ID 3W11 was selected from Protein Data Bank: www.rcsb.org. Chains A and B were cut from the molecule. These two chains are active parts of the ectodomain; therefore, the ligand on the nanoparticle will bind to these chains. Putting the receptor on the membrane was done in VMD (Visual Molecular Dynamics Software). First, both membrane and receptor were loaded in VMD and the receptor was moved so that it locates in the middle of the surface of the membrane. Each receptor is put in a 100A×100A membrane and two 15A layers of water sandwich them as shown in Fig. 1 and 2. So, for building a 200A×200A phospholipid bilayer, the 100A×100A

membrane and receptor were merged and assembled in VMD. Fig. 2 shows a 200A×200A membrane with 4 receptors on it with 15 A layers of water.

B. NanoParticle Modeling

In this study, nano particles were modeled as rigid bodies in molecular dynamics simulation. In this way, the only interactions included in the simulations are the nonbonded interactions between nanoparticle atoms and biological molecules; in other words, there are no interactions amongst nano particle atoms. This assumption was made since the atomic bonds between the nanoparticle metalic atoms are much stronger than the chemical bonds between the nanoparticle atoms and the other organic atoms present in this study. Thiol molecule that is widely used to connect gold atoms to organic molecules was also used in this study to create the the bond between gold nanoparticles and insulin molecules. The atomic bond between gold atoms and thiol molecules was made using SPARTAN software

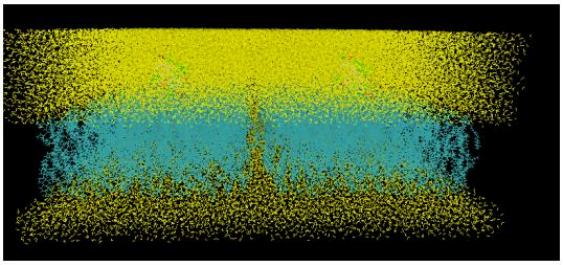


Figure 2: 200A×200A membrane with 4 receptors on it with 15 A layers of water

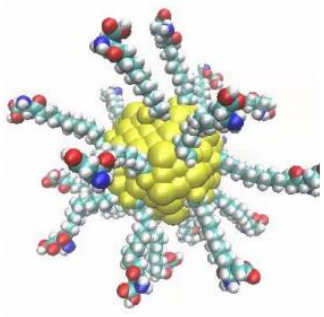
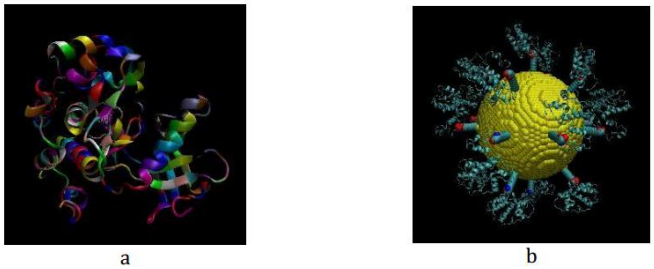


Figure 3: a gold nano particle coated symmetrically with 18 thiol residues and relaxed for 100ps

considering quantum mechanical interactions of the gold atoms and the sulfure atoms on the thiol molecule. Fig. 3 shows a 2 nm gold NP coated with 18 thiol residues after 100ps relaxation time. Fig. 4 and Fig. 5 also show a 10 nm gold nanoparticle coated with 18 insulin segments and POPC membrane with 4 nm and 10 nm gold NP above it, respectivly.

IV. RESULTS

Using MD simulations, we have predicted that coating spherical nano particles with insulin to be an effective method in facilitating the procedure of their crossing through the membrane. We have identified three governing parameters in the effectiveness of the coating: The number of segments and residues by which the nano particles are to be coated, the geometrical characteristics of nano particles and the membrane with which the nano particle is interacting. The first simulation carried out to investigate the crossing of gold nano particles through BBB was done for an uncoated 2 nm in diameter nano particle crossing a 100A×100A POPC membrane using the SMD method. The simulation was carried out in 310K (the biological temperature of the human body). After 50 ps of relaxation, the nano particle crossed the membrane in a constant 5 A/ps velocity and the force exerted on the nano particle was recorded. Since the extracted data of the force exerted on the nano particle crossing BBB was derived from SMD model, the force exerted by the dummy springs is also included. In order to derive the pure force of the membrane exerted on the nano particle, the force of dummy springs needs to be filtered. In Fig. 6 the force profile extracted in simulation has been plotted. As it shows in this figure, for crossing nano particles at the mentioned velocity similar force profile must be applied to nano particle. In fact, it almost needs 2 PN at the maximum value and after 3~4 oscillations it goes to steady state. The rise time of this profile is about 10 PS (=2000 time step). Based on our study, this figure shows that we need an alternative magentic field to make an equivalent force.



a b

Figure 4: Schematic representation of a.Human Insulin b. 10 nm gold nanoparticle coated with 18 insulin segments each containing 121 residues

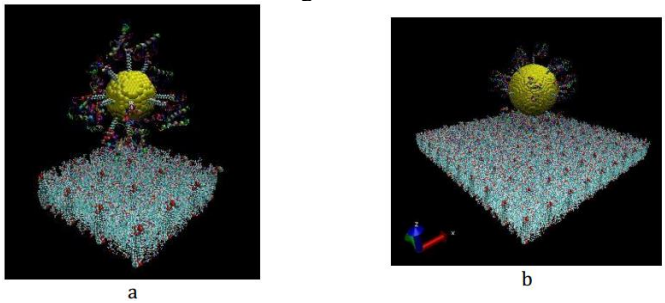


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Figure 5: Schematic representation of a.4nm coated gold nanoparticle crossing POPC membrane b. 10 nm coated gold nanoparticle crossing POPC membrane

V. CONCLUSION

In this work, we have analyzed the magnetic force profile needed to be exerted to the nanoparticles by the magnetic field in order that they cross the BBB. To achieve this purpose, we developed an atomic based model of BBB. Two kinds of BBB membrane POPC and DMPC have been considered for this model. In addition, we made gold nanoparticles with sizes of 2 nm, 4 nm and 10 nm in diameter. MD simulation has been done to extract the force

needed for nanoparticles to cross the BBB. Nanoparticles have been supposed to move in a constant velocity through the BBB and the force required for their interaction with BBB membrane has been calculated. The results of this simulation demonstrate that for an optimal crossing of nanoparticles through the BBB, they need a relatively constant straightforward force. Also, our initial results of the nanoparticles coated with insulin domain show that the force needed for NPs to cross the BBB is significantly lower than the force obtained for NPs without any coating. In continue, the bigger sizes of NPs will be investigated and the force required for their passing through BBB will be obtained. The future work of this study would be concentrated on extracting the porosity coefficient of the membrane. In fact, we are going to find out a macroscale model based on micro/nano scale computations. We also will suggest the optimal condition for the passage of the NPs which will be applicable for designing the drugs appropriate for neuronal diseases.

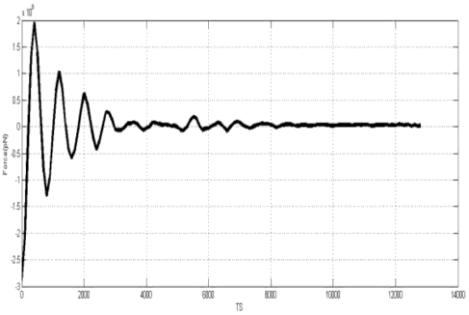

Figure 6: Interaction SMD force between 2nm nano particle and POPC membrane

REFERENCES

[1] N Joan Abbott, Adjanie AK Patabendige, Diana EM Dolman, Siti R Yusof, and David J Begley. Structure and function of the blood–brain barrier. *Neurobiology of disease*, 37(1):13–25, 2010.

[2] Praveen Ballabh, Alex Braun, and Maiken Nedergaard. The blood–brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiology of disease*, 16(1):1–13, 2004.

[3] James J Choi, Jameel A Feshitan, Babak Baseri, Shougang Wang, Yao-Sheng Tung, Mark A Borden, and Elisa E Konofagou. Microbubble-size dependence of focused ultrasound-induced blood–brain barrier opening in mice in vivo. *Biomedical Engineering, IEEE Transactions on*, 57(1):145–154, 2010.

[4] Cathrin J Czupalla, Stefan Liebner, and Kavi Devraj. In vitro models of the blood–brain barrier. In *Cerebral Angiogenesis*, pages 415–437. Springer, 2014.

[5] P Garberg, Marguerite Ball, N Borg, Roméo Cecchelli, Laurence Fenart, RD Hurst, T Lindmark, A Mabondzo, JE Nilsson, TJ Raub, et al. In vitro models for the blood–brain barrier. *Toxicology in vitro*, 19(3):299–334, 2005.

[6] LM Griep, F Wolbers, B de Wagenaar, PM ter Braak, BB Weksler, Ignacio A Romero, PO Couraud, I Vermes, AD van der Meer, and A van den Berg. Bbb on chip: microfluidic platform to mechanically and biochemically modulate blood-brain barrier function. *Biomedical microdevices*, 15(1):145–150, 2013.

[7] Mustapha Hamdi and Antoine Ferreira. Computational study of superparamagnetic nanocapsules crossing the blood-brain barrier: A robotics approach. In *Intelligent Robots and Systems (IROS), 2012 IEEE/RSJ International Conference on*, pages 2313–2318. IEEE, 2012.

[8] Pooja Naik and Luca Cucullo. In vitro blood–brain barrier models: current and perspective technologies. *Journal of pharmaceutical sciences*, 101(4):1337–1354, 2012.

[9] Kaushik K Shah, Li Yang, and Thomas J Abbruscato. In vitro models of the blood–brain barrier. In *Astrocytes*, pages 431–449. Springer, 2012.

[10] Imola Wilhelm, Csilla Fazakas, and Istvan A Krizbai. In vitro models of the blood-brain barrier. *Acta Neurobiol Exp (Wars)*, 71(1):113–28, 2011.