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Multiscale framework for biomedical simulation from molecular dynamics to continuum mechanics

W. K. Liu[1,†], T.R. Lee[1], A. M. Kopacz[1], H. Kim[1], W. Stroberg[1], H. B. Man[1], D. Ho[1], M.K. Kim[2], J.H. Chung[3], P. Decuzzi[4]

[1] Department of Mechanical Engineering, Northwestern University, Evanston, IL, USA
[2] School of Mechanical Engineering, Sungkyunkwan University, Suwon, Kyonggi-do, Republic of Korea
[3] Department of Mechanical Engineering, University of Washington, Seattle, WA, USA
[4] The Methodist Hospital Research Institute, Department of Nanomedicine and Biomedical Engineering, Houston, TX, USA
[†] Contact Author
Department of Mechanical Engineering, Northwestern University,
2145 Sheridan Rd., Evanston, IL 60208-3111
Voice: 847-491-7094
Fax: 847-491-3915
Email: w-liu@northwestern.edu

Abstract

In biomedical engineering, computational mechanics has played an important role in understanding complex systems such as drug delivery platforms, biosensors and blood flow. In situations where a clinical test is either prohibitively difficult or required understaning, numerical experiments offer an effective way to gain important insight. For this reason computational methods have become essential tools for biomedical problems. In this paper, the multiscale framework for biomedical simulation is shown by applying various computational methods to several biomedical problems. To show the variety and breadth of the biomedical problems that can be addressed through computation, we describe several numerical methods that are capable of addressing the multiscale, multiphysics problems found in biological systems, and motivate each with sample applications. Specifically, molecular dynamics (MD), dissipate particle dynamics (DPD), elastic network model (ELM) and immersed molecular electrokinetic finite element method (IMEFEM) are introduced with state-of-the-art research topics in biotechnology.

Keywords: multiscale framework, molecular dynamics, elastic network model, immersed molecular electrokinetic finite element method

1. Introduction

Recently, biomedical research to detect and cure serious diseases has seen rapid growth through the development of high-resolution and high-sensitivity imaging technology as well as novel functional nanomaterials for disease detection, imaging, and therapy. In diagnosis, various biosensors [A M Kopacz et al, 2011] have been suggested to rapidly and accurately detect specific DNAs, viruses and diseases in a very small amount of blood or saliva. As an example,

by applying an electric field to a millimeter sized droplet of saliva, specific DNA strands or cells are picked up on the surface of a nanoscale tungsten tip immersed in the fluid. This biosensor is capable of detecting micro- and nano- sized substances such as cells, bacteria, viruses, DNA, molecules and proteins. In treatment, we highlight drug/gene delivery systems [Zhang, X.-Q. et al 2009], [Adnan, A. et al, 2011] that aim to directly cure the diseased cells with minimal dosage by using functionalized nanoconstructs that are designed to specifically target only malignant cells. In line with this, carbon nanodiamonds have attracted tremendous attention due to excellent cytotoxicity and transfection efficiency. Recently, a Nanodiamond (ND)-Polyethylenimine (PEI) complex as a gene delivery vector has been suggested by Zhang et al. [Zhang, X.-Q. et al, 2009]. In many instances, the underlying phyisico-chemical mechanisms that determine the effectiveness of novel nano-biomedical systems are unknown and exceptionally difficult to determine experimentally. However, computational methods can be used to systematically isolate specific mechanisms to gain significant understanding of the important control parameters governing the system. Through the use of large-scale computation, the important parameters can then be tuned to optimal performance, providing a roadmap for future experiments. Possibly the most important advantage of computational mechanics in biomedical research is that it gives researchers the ability to predict how such systems will perform in the human body before in vivo animal trials or clinical tests. In this paper, the potential of computational mechanics is demonstrated through several case studies related to biomedical research. Specifically, the multiscale framework for biomedical problems is displayed from molecular dynamics to the immersed molecular electrokinetic finite element method (IMEFEM). In the following sections, the multiscale framework is demonstrated through applications to 1) a drug delivery system using nanodiamonds, 2) a nanotip biosensor for DNA detection, 3) nano-pore imbibition through capillary action, and 4) biomolecular- level textiles

2. Molecular dynamic simulations of nanodiamond-PEI800-siRNA interactions for gene delivery application

Researchers have been working on gene delivery to treat diseases associated with defective genes such as cancer and cardio vascular diseases. Since naked DNA (or RNA) is most likely degraded in the blood vessel before it reaches the target cells, successful gene delivery requires the use of a vector that can deliver the DNA into target cells safely as well as efficiently. Recently, carbon nanodiamonds have attracted tremendous attention due to excellent cytotoxicity (cell survivability) and transfection (delivery) efficiency. Prof. Dean Ho's group at Northwestern University (USA) developed a Nanodiamond (ND)- Polyethylenimine (PEI) complex as a gene delivery vector [Zhang, X.-Q. et al, 2009]. It shows a 70 times improvement in transfection efficiency as compared to PEI vectors (or ND vectors) [Zhang, X.-Q. et al, 2009]. However, the principal mechanism of the ND-PEI-DNA interaction is still not clearly understood. In this manuscript, molecular dynamic (MD) simulations of ND-PEI800-siRNA (small interfering RNA) interactions are performed. The simulation results reveal that the role of PEI is very significant since it can attract more siRNA's to ND complex resulting in better delivery efficiency.

2.1 Nanodiamond (ND)

Nanodiamonds, which are made of carbon, are manufactured through detonation and several chemical processes. Individual nanodiamonds have a truncated octahedron shape and the diameters ranging from 2 – 6nm [Adnan, A. et al, 2011]. It has 8 hexagonal surfaces with [111] direction and 6 square surfaces with [100] direction (Figure 2.1a). Quantum mechanical

simulations have been carried out to obtain surface charges of the ND. Fig. 2.1b represents a high resolution TEM image of ND.

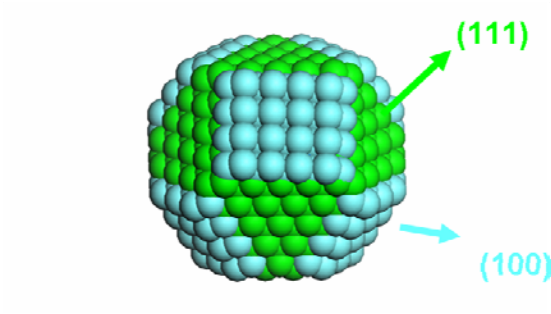


Fig. 2.1a. Nanodiamond atomic structure with directionality

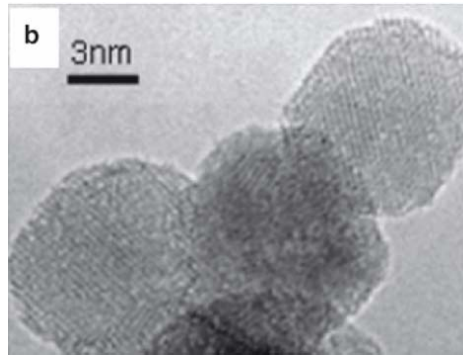


Fig. 2.1b. High resolution TEM image of ND particles [Adnan, A. et al, 2011]

2.2 Polyethylenimine (PEI) 800

There are two kinds of PEI's available for gene delivery applications: Linear PEI and branched PEI. The branched PEI's are used for our MD simulations since they are used in the experiments of Prof. Dean Ho's group. The length of the branched PEI is 3.5nm, height 1.6nm and width 1nm (Fig 2.2a). Fig 2.2b illustrates the charge distribution of PEI through CVFF (Consistent-valence forcefield).

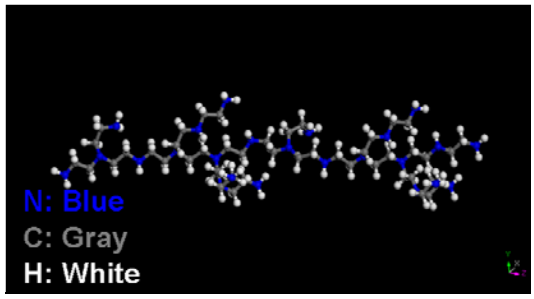


Fig. 2.2a. Atomic structure of branched PEI 800

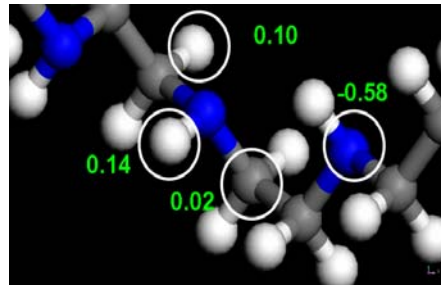


Fig. 2.2b. Charge assignment of branched PEI 800

2.3 siRNA

Small interfering RNA (siRNA), sometimes known as short interfering RNA, is a class of double-stranded RNA that plays a variety of roles in biology. The most notable role of siRNA is its involvement in the interference with the expression of a specific gene (i.e. cancer). Fig 2.3a shows the atomic structure of siRNA and Fig 2.3b illustrates the charge distribution obtained from the AMBER forcefield. The sequence of this siRNA is AACAGAAAUGUCCUGAGCAAU. The Length of siRNA in Fig 2.3a is 6.75 nm and diameter: 1.8 nm.

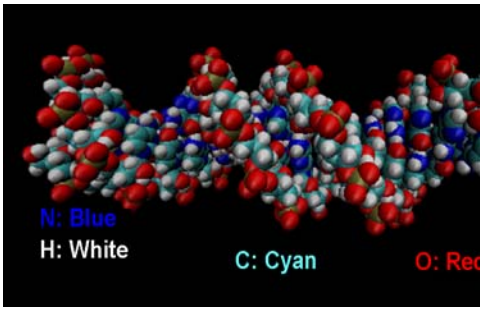


Fig. 2.3a. Atomic structure of siRNA

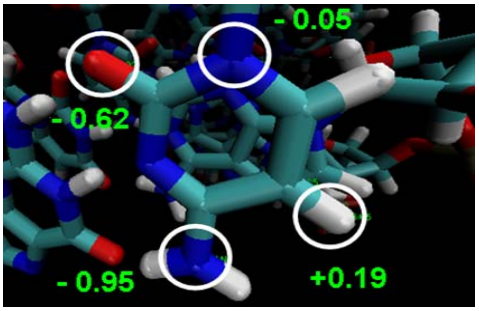


Fig. 2.3b. Charge assignment of siRNA

2.4 Molecular dynamic simulation results

Molecular dynamic simulations have been performed to investigate interactions between ND, PEI800, and siRNA in water solvent. The system dimension is 85 x 85 x 50 Å and is solvated with 11082 water molecules. The system is equilibrated with an NPT statistical ensemble (300K, 1 atm). Since real PEIs are protonated in water and become cationic polymers, all the PEI's in our simulations are also protonated. First, in order to investigate the direct interaction between a ND and siRNA, one siRNA is placed on top of (111) surface of a ND with a 2.1nm diameter (Fig 2.4a). The distance between the ND and the siRNA is about 20 Å. During the equilibration process, the siRNA drifts away from the ND surface due to the electrostatic repulsion since both siRNA and (111) surface of ND have negative electrostatic charges (Fig 2.4b).

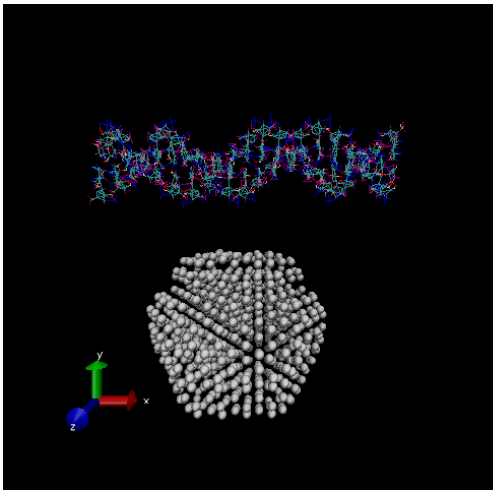


Fig. 2.4a. Initial configuration of ND and siRNA

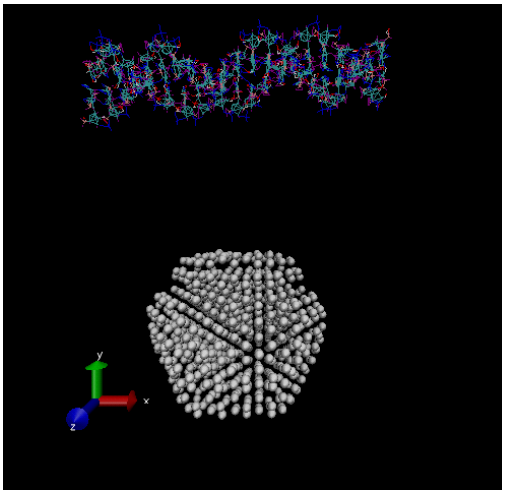


Fig. 2.4b. Final configuration of ND and siRNA after equilibration

Next, in order to investigate the role of PEI800's during the formation of the ND complex, the four PEI800's are placed between the ND and siRNA on the top of the ND surface (Fig. 2.5a). Through the equilibration, the siRNA moves toward the ND-PEI complex and attaches to the ND-PEI complex, in contrast to the previous results without PEI (Fig. 2.5b). These simulation

results reveal that PEI's can facilitate more siRNA's attachments to the ND's. It can also explain the experimental observation that the ND-PEI-siRNA complex produces better delivery efficiency compared to the ND-siRNA complex.

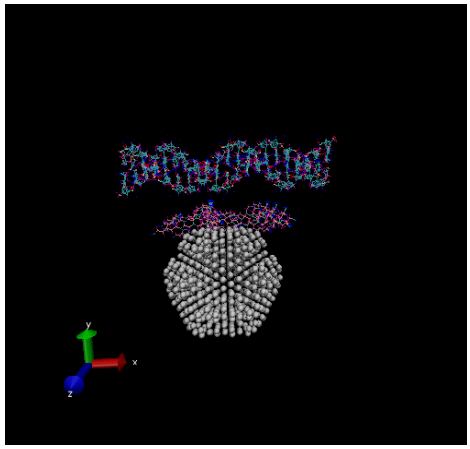


Fig. 2.5a. Initial configuration of ND, PEI800 and siRNA

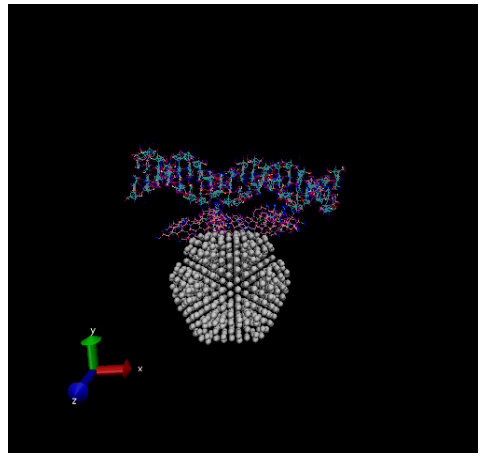


Fig. 2.5b. Final configuration of ND, PEI800, siRNA after equilibration

3. Nanotip based DNA preconcentration mechanism

Another challenge in the field of medicine is also to develop a sensor that can detect specific bacterial pathogens via a precise deoxyribonucleic acid (DNA) sequence. Bacterial pathogens cause critical illnesses and in many cases are genetically driven. Examples of hospital and community acquired infections due to bacterial pathogens include methicillin-resistant Staphylococccus aureus (MRSA), Pseudomonas aeruginosa, Clostridium difficile, Legionella, vancomycin-resistant Enterococcus, tuberculosis and related infections, Acinetobacter, urinary tract infections, and hospital-acquired pneumonia (HAP) [V. C. C. Cheng, 2005 - W. C. Yam et al, 2004]. In order to identify such biological agents in a patient's blood or other bodily fluids at the onset of infection, detection of specific pathogen genomic DNA is considered a reliable approach. Current techniques involving multiplex DNA/RNA detection arrays or immunoassays [E. Sada et al, 1992] require cumbersome sample preparation, aggressive nucleic acid amplification protocols and must be operated by trained personnel. To overcome the aforementioned obstacles, a time-dependent dielectrophoretic force driven sensor array consisting of nanostructured tips is being developed and the immersed molecular electrokinetic finite element method (IMEFEM) framework is utilized to help guide the design of the device and characterize its fundamental mechanisms at the nanometer scale [Kopacz, A. M., 2011].

3.1 Nanoscale electrokinetics, electrohydrodynamics and electrostatic interactions

Simulation based modeling is used to predict electrohydrodynamics and the dominant electrokinetic forces at the nanometer scale, which include dielectrophoresis, electrophoresis, Brownian motion and other molecular phenomena where the dimensions for a nanotip/DNA and sample volume are roughly 4-5 orders of magnitude apart. Dielectrophoresis is a phenomenon in which the dielectrophoretic force is caused by induced dipole moment on a particle which is typically predicted by the numerical analysis. Dielectrophoresis (DEP) is used

for manipulating, separating and analyzing micro- and nano- sized particles such as latex spheres, cells, bacteria, viruses, DNA, molecules and proteins. The technique is based on the motion of particles arising from the interaction of a nonuniform electric field with the dipole induced within the particles [Kopacz, A. M., 2011], [Y. Liu et al, 2008 - Y. Liu et al, 2007], [A M Kopacz et al, 2011]. A nanoscale particle, i.e. DNA molecule, suspended in a fluid experiences both a hydrodynamic force due to the average motion of the fluid around it, as governed by the Navier-Stokes equations, and a random force due to the thermal fluctuations of the fluid. In this study, Brownian dynamic are modeled as a thermal force acquired from the fluid in terms of a random force prescribed in the particle equation of motion [Kopacz, A. M., 2011], [A M Kopacz et al 2011], [A M Kopacz et al, 2011]. To incorporate the molecular DNA-DNA interactions into the IMEFEM framework, the DNA particle interaction force is applied on the surface of the deformable oligonucleotides. The required parameters are extracted from the performed molecular simulations found in literature [Kopacz, A. M., 2011].

The immersed molecular electrokinetic finite element method is utilized to examine the concentration mechanism of the nanotip and its effects on the enhanced hybridization [Kopacz, A. M., 2011]. Originally, the immersed finite element method (IFEM) [L Zhang et al, 2004], [W K Liu et al, 2006,] has been developed by integrating the concept of immersed boundary [W K Liu et al, 2006], [X Wang and W K Liu, 2004], finite element [T J R Hughes, 1987 – T.Belytschko et al, 2000] and meshfree methods [S Li and W K Liu, 2002, S Li and W K Liu, 2004]. IFEM was later extended to incorporate electrohydrodynamics, namely IEFEM [Y. Liu et al, 2008], [Y. Liu et al, 2007], and recently further enhancements incorporated molecular interactions and dynamics [Kopacz, A. M.,2011], [W K Liu et al 2006 - A M Kopacz et al, 2011]. The immersed molecular electrokinetic finite element method (IMEFEM) coupled with multiphysics features is extended and utilized to model dielectrophoresis, Brownian motion, and DNA particle-particle interactions [A M Kopacz et al, 2011].

3.2 Preliminary result for DNA preconcentration

As a preliminary result, a device composed of a 500nm in diameter nanotip immersed in a fluid medium surrounded by a coil is shown in Fig. 3.1a. The initial analysis of the system consisted of solving the governing equations of electric field where the inherent carriers are the major current carriers. A high AC frequency of 5MHz was applied across the nanotip and coil electrodes with a peak-to-peak voltage (Vpp) of 20V. It was found that the maximum electric field is present just below the apex of the nanotip and decays exponentially when moving away from the terminal end of a nanotip. As shown in Fig. 3.1b, an oligomer is place around the nanotip and considered as an elastic material in our calculation. The DEP force is the dominated force for attracting the oligomer to the nanotip. For the larger distance, the Brownian motion forces due to thermal motion are the dominating forces and the effectiveness of the DEP force exerted on an oligomer is diminished [A M Kopacz et al, 2011].

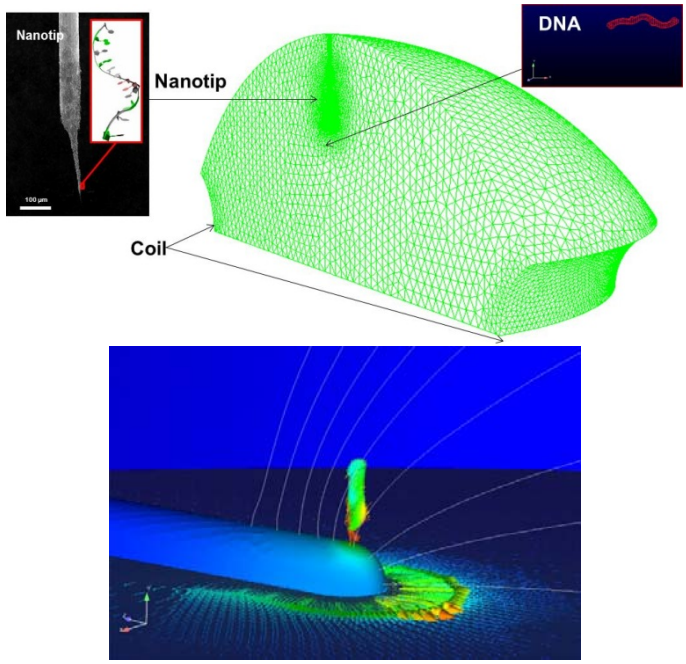


Fig. 3.1a. Nanotip and DNA simulation under fluid and AC electric field (Left) trapping mechanism of DNA onto the nanotip (Right)

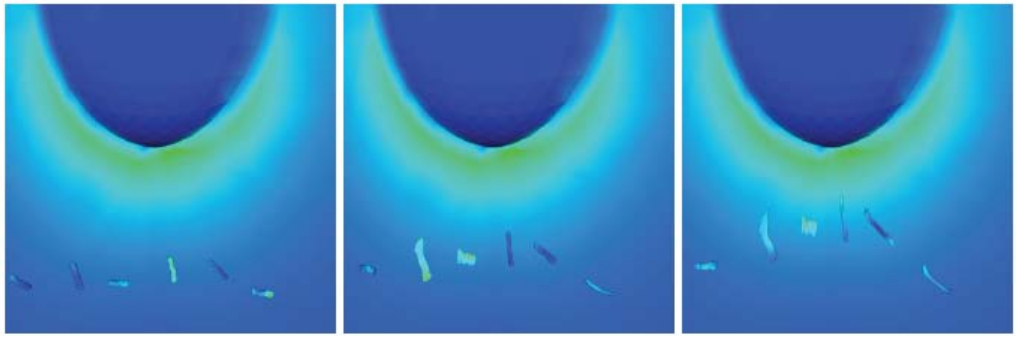


Fig. 3.1b. Trapping of DNA to the nanotip by electrokinetic force

4. Vascular transport simulation for nanoparticle-RBC interaction

Vascular transport is a main circulation system in human body. By the circulation, various nutrients and medicines are carried to individual cells. Therefore, to understand the vascular transport system is essential to predict the efficiency of various drug delivery systems in the human body. In this section, the computational framework based on the immersed finite element method (IFEM) is introduced to simulate the vascular transport system including red blood cells (RBC) and nanoparticle. In addition, as a preliminary result, the nanoparticle-red blood cell (RBC) interaction in the blood flow is discussed.

4.1 Computational framework for vascular transport simulation

The fluid-structure interaction between cells and fluid should be considered to simulate the vascular transport in human body. Specifically, in the human body, the hematocrit (volume fraction of RBCs) is about 30-50%. Therefore, the interaction between RBCs and fluid, which is most often treated as water in simulation, is the most important part of the vascular transport simulation. The shapes of RBCs are mathematically described by Evans and Fung [E.A. Evans and Y.C. Fung, 1972]. As shown in Fig. 4.1, the RBC is a discoid shape membrane with a finite thickness. The mechanical behaviors of RBCs are modeled by a hyperelastic material description. Recently, Dao et al. [M. Dao et al, 2003] observed the RBC deformation by optical tweezers and suggested the precisely selected parameters for the hyperelastic material description.

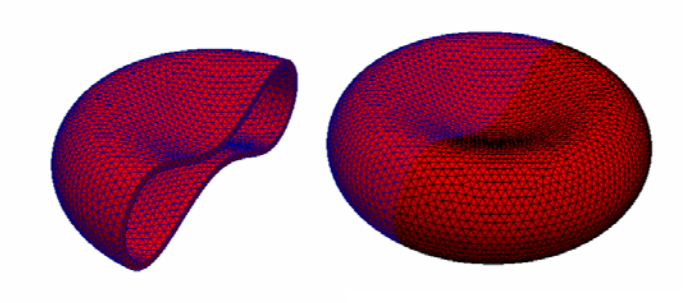
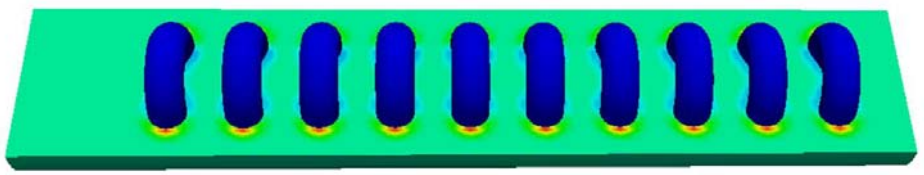
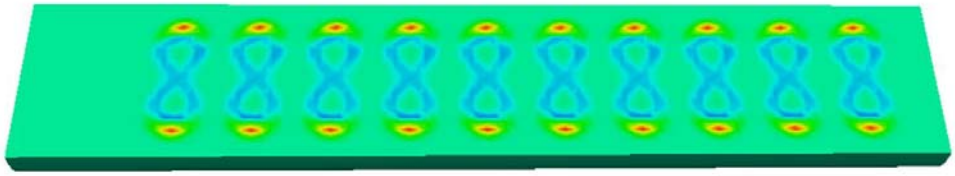


Fig. 4.1 Red Blood Cell Modeling

When the volume of a cubic fluid domain is 100 μm x 100 μm x 100 μm, approximately 3,000 ~ 5,000 RBCs should be inserted to meet the 30% ~ 50% hematocrit. The fluid-structure interaction with 3,000 RBCs requires huge computation time, even when using a brand-new parallel machine. To overcome the difficulty in computation, immersed type methods such as immersed boundary method (IBM) [Peskin CS. 1972], [Peskin CS. 2002] and Immersed Finite Element Method (IFEM) [L Zhang et al, 2004], [X Wang and W K Liu, 2004] are a good direction to pursue in order to simulate the vascular transport with detailed RBC deformations. The IFEM can handle the fluid-structure interaction without remeshings that require tremendous computation time. The detail of IFEM is referred to in many previous publications [Y. Liu et al, 2004 - Tefft BJ et al, 2011].



(a) Fluid-RBC Interaction Force for IFEM



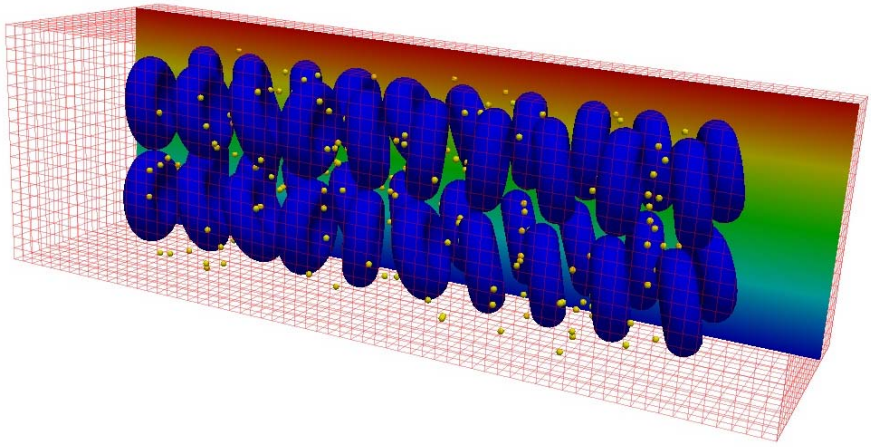
(b) FSI force acting on the immersed domain

Fig. 4.2 Fluid-Structure Interaction on the IFEM framework

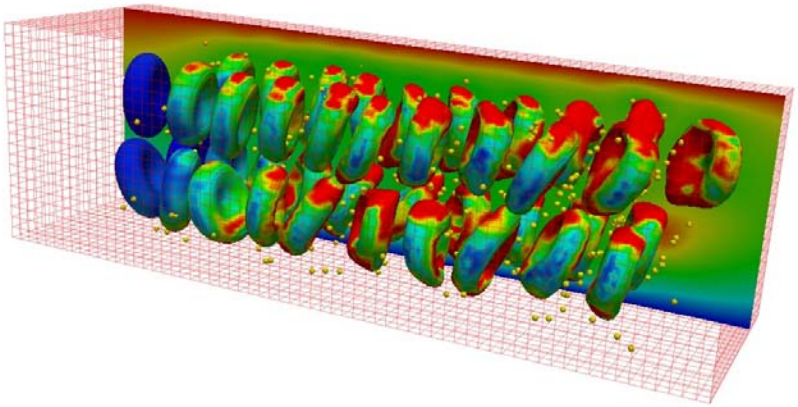
As an example, Fig. 4.2a shows the 10 RBCs in the fluid domain. On the left end, an inlet boundary condition with a constant velocity is inserted to generate the fluid force for pushing the RBCs. In IFEM, the vascular transport is conducted by applying FSI force terms that recognize the RBCs in the immersed domain. As shown in Fig. 4.2b, the RBC membranes are represented by the FSI force field that is calculated from the previous time step.

4.2 Preliminary result for nanoparticle-RBC interaction

As an application of the vascular transport simulation, nanoparticles for a drug delivery system are considered in the blood flow. The nanoparticles are used to transport drugs to the blood vessel wall. After the nanoparticles arrive on the surface of the vessel wall, the drugs attached on them penetrate into the target cells. Therefore, the drift behavior of nanoparticle in blood flow is directly connected to the drug carrier efficiency. The detail numerical simulation is helpful to quantify the drug carrier efficiency related to its size, shape and mechanical property.



(a) Randomly distributed Nanoparticles and RBCs at initial time step



(b) Nanoparticle-RBC Interaction in Flu
Fig. 4.3 Nanoparticle-RBC Interaction

In Fig. 4.3a, the computational domain was plotted to show the fluid domain with nanoparticles and RBCs. A linear shear flow was applied on the surface of the fluid domain. The nanoparticles are treated as rigid bodies and randomly positioned. Also, the deformation of RBCs is described by a hyperelastic material law. As shown in Fig. 4.3b, the RBCs were deformed and the nanoparticles drifted to the bottom of the fluid domain. From the simulation result, the average drift velocity of the nanoparticles can be calculated by tracing each particle trajectory. Furthermore, by changing the shape and the size of particles, the optimal design of drug carriers can be suggested.

5. Coarse-grained molecular dynamics simulations of nanopore loading via capillary action

In recent years, porous microparticles have found numerous uses in nano-medicine as transport vehicles. Their application has ranged from medical imaging [Ananta JS et al, 2010], to cancer therapy [Anglin E et al, 2008], and pulmonary drug delivery [Kwon MJ et al, 2007]. In many applications, drug molecules or other nanoparticles are be loaded into the pores of the microparticle then injected into the patient, allowing high concentrations of therapeutic agents to be delivered to specific locations. The ability to effectively load nanoparticles into the porous structures is essential to this process, yet typically, loading procedures in the laboratory are developed through trial-and-error processes that are time consuming and expensive. Here we present a coarse-grained molecular dynamics (CGMD) model using a dissipative particle dynamics (DPD) thermostat of capillary loading with the aim of illuminating the governing physical parameters of the imbibition process.

5.1 Dissipative particle dynamics model

Dissipative particle dynamics [Hoogerbrugge PJ and KoelmanJMVA, 1992 -44] is a particle-based model that has proven to be very useful in the simulation of mesoscale soft materials and fluids out of equilibrium, especially capillary imbibition [Chen Chen et al, 2010 - Henrich B et al, 2007]. DPD differs from other coarse-grained molecular dynamics in that the system is thermostatted through a dissipative force that acts pairwise between nearby particles so as to preserve particle momentum. A random force is then coupled to the dissipative force in accordance with the fluctuation-dissipation theorem. By conserving momentum, the system

satisfies hydrodynamics and can be used to simulate fluid flows at the nano- and microscale, whereas other methods such as Langevin thermostatting cannot since momentum is generally not conserved.

The current simulations focus on the loading of carbon nanotubes (CNTs) into a cylindrical nanopore. The bulk fluid consists of coarse-grained beads interacting via a Morse potential following Chui et al. [S.-W. Chiu et al, 2010]. The CNT's are modeled as bead spring chains with stiffness and interaction potentials based on work by Buehler et al. [M.J. Buehler, 2006]. The capillary boundary is modeled as a face-centered-cubic lattice of coarse-grained beads, each tethered to their initial position by a linear elastic spring. The interactions between different species are left as design parameters, allowing the model to explore different functionalizations of the CNT and capillary surfaces.

5.2 Preliminary results for capillary loading

The CNT loading efficiency was investigated as a function of capillary diameter, the contact angle between the fluid and the capillary wall, and the affinity between CNTs and the capillary. Figure 5.1 shows snapshots of the simulations. Initially, the CNT-fluid solution is allowed to equilibrate, then the capillary is opened and the fluid is drawn in by capillary suction.

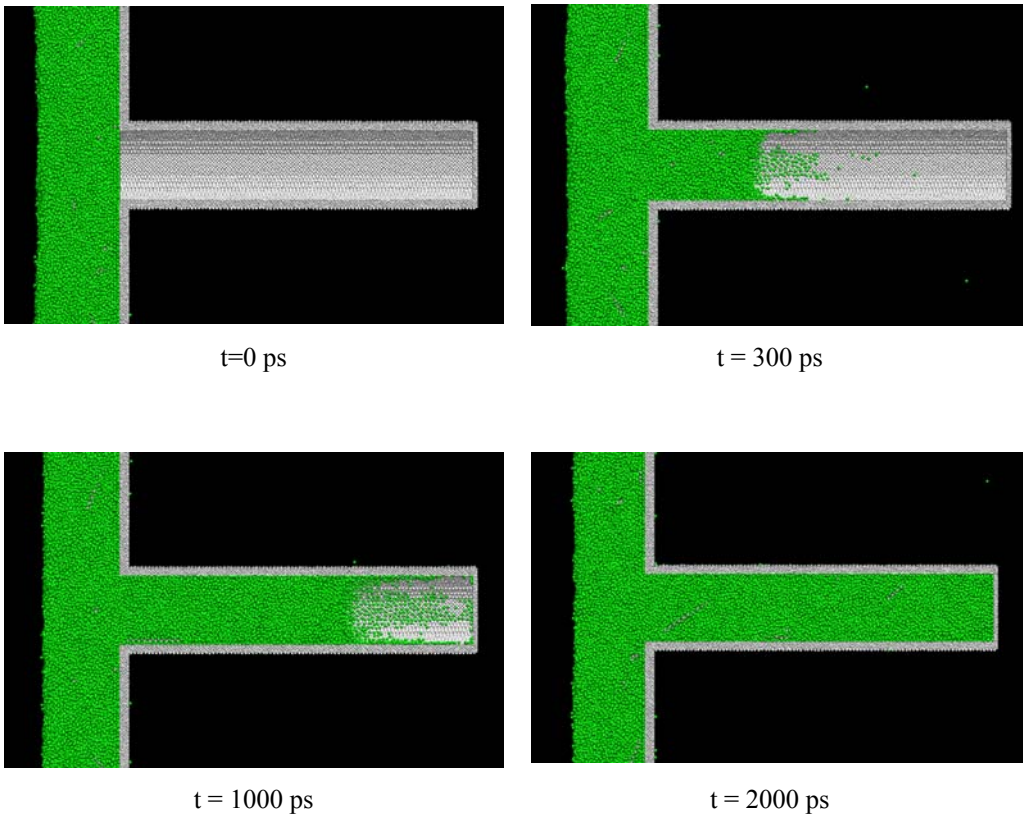
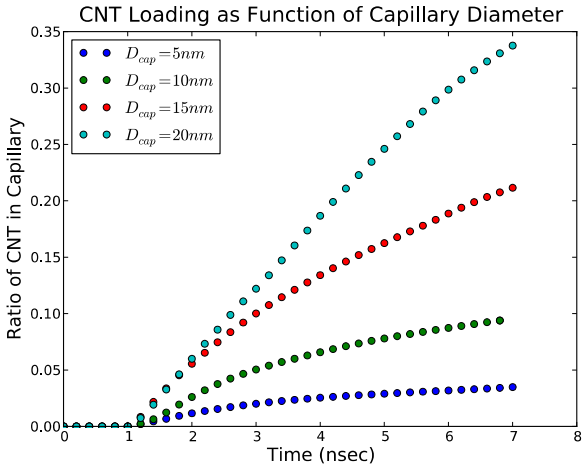
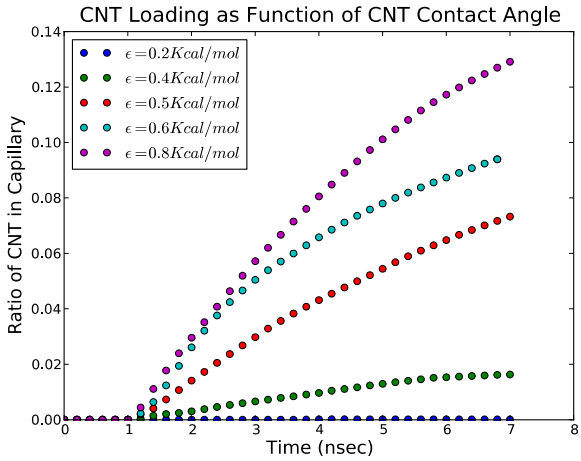


Fig. 5.1 Snapshots of imbibition process: t = 0 (top left), t = 300 (top right), t = 1000 (bottom left), t = 2000 (bottom right). All times are in picoseconds.

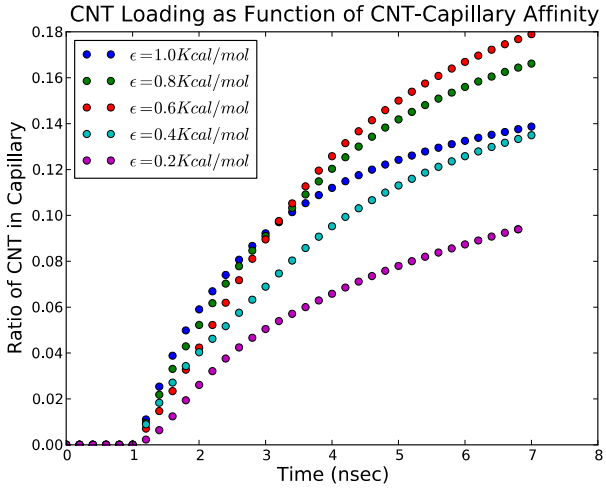
Figure 5.2 shows the percentage of CNTs initially in solution that is drawn into the capillary during the loading process for three sets of simulations. In Figure 5.2(a), it is clear that the efficiency of the loading process increases with pore diameter. This can be explained simply as the result of a greater volume of fluid entering the capillary for a larger diameter, and since the CNTs are approximately monodispersed, a larger portion is drawn into the larger pore. In Figure 5.2(b), we see that the loading efficiency increases as the contact angle increases. For highly hydrophobic surfaces (low values of ε), the fluid solution does not enter the capillary at all, and for a completely wetting fluid (high values of ε), the entire capillary is filled. Hence, when designing microparticle carriers, it would be wise to make the surface of the pores hydrophilic to increase the uptake of nanoparticles. Figure 5.2(c) shows the efficiency of loading for different CNT-capillary wall affinities. Here there appears to be an optimum value for the affinity. In the simulations, it is observed that for large interactions between the capillary and CNTs, a significant portion of the CNTs stick to the outside surface of the porous structure. In this case, the hydrodynamic forces induced by the capillary suction are not strong enough to overcome the attraction between the CNTs and the wall, thus a lower percentage of CNTs are drawn into the pore.



(a) Capillary diameter



(b) Contact angle



(c) CNT-capillary affinity

Fig. 5.2 CNT loading efficiency as a function of: (a) capillary diameter, (b) contact angle, (c) CNT-capillary affinity

This illuminates an important design criterion for the functionalization of the CNTs and the material choice for the porous microparticles. A pair where the attraction is weak enough to allow the CNTs to enter the pore, yet strong enough to prevent them from freely diffusing out aging once loaded would be ideal. These parametric studies highlight the potential contributions a CGMD model could make to the design of therapeutic and diagnostic micro systems.

6. Multiscale elastic network model for biomolecular simulation

Recent advances in experimental techniques such as Cryo EM, X-ray crystallography, and NMR yield a dramatic increase of biomolecule structure database. In the area of bioinformatics, it is one of the hottest topics to analyze such a huge database in both computationally efficient and physically precise ways in order to reveal the intrinsic relationship between structure and function in macromolecules including DNA, RNA, and proteins. In this section, we introduce a coarse-grained elastic network modeling technique suitable for biomolecular simulation in terms of modeling resolution and computation time.

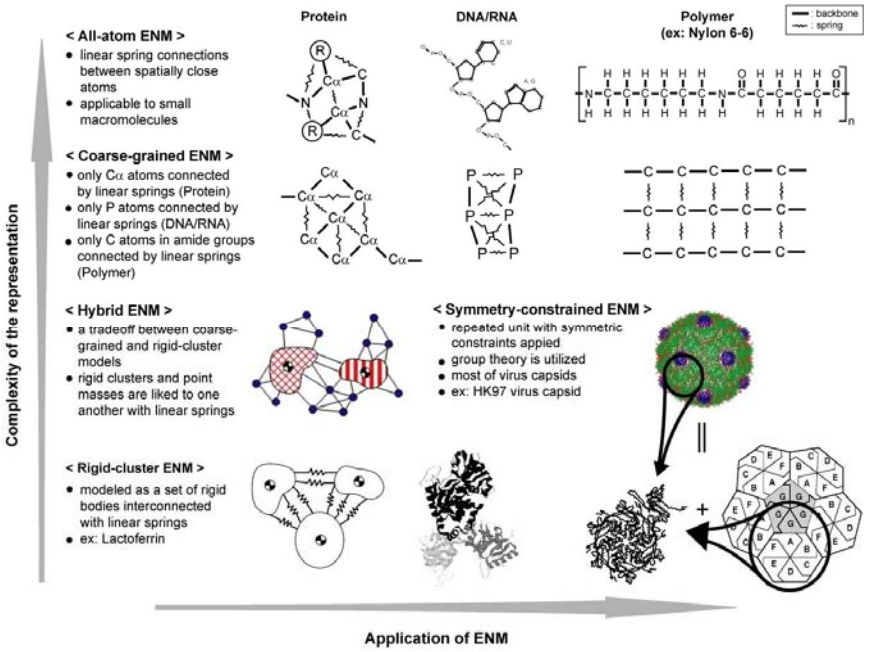


Fig. 6.1. Various coarse-grained elastic network models (Courtesy of [Kim, M.K. et al, 2006]).

6.1 Various coarse-grained elastic network models

Fig. 6.1 illustrates various coarse-grained elastic network models (ENMs) from atomic level to rigid clustering (i.e., conceptually similar to continuum) [Kim, M.K. et al, 2006]. In ENM, a biomolecule is assumed to be an elastic body of which representative points are connected by a network of linear springs. One can modulate the system resolution by selecting different levels of coarse-graining. Unlike MD, which is the most precise but often too sophisticated and too expensive tool for biomolecular simulation, ENM requires less computing power to investigate global dynamics of biomolecules without any loss of generality. The detailed mathematical derivation and computational complex study were already addresses elsewhere [Kim, M.K. et al, 2002 ~ Kim, M.K. et al, 2003b].

6.2 Applications of ENMs

To reveal the relationship between structure and function using ENMs, we perform normal mode analysis (NMA) and elastic network interpolation (ENI). The former is the traditional vibration study in mechanical engineering which indicates the intrinsic motions of the given biomolecule structure. Using these basic mode shapes, one can not only explain a specific

biological function in agreement with experimental results, but also postulate or predict unknown functions to inspire experimentalists. On the other hand, ENI is used to investigate single or multiple transient pathways from one meta-stable conformation to another, which is hardly detectable even by using state-of-art experimental techniques. The basic concept of ENI is the linear interpolation of interatomic distance during the transition [Kim, M.K. et al, 2002], [Kim, M.K. et al, 2002]. It can automatically avoid unrealistic steric clash problems that frequently occurs at other interpolation methods such as Cartesian coordinate interpolation and internal variable interpolation. Both NMA and ENI simulation are available on the KOSMOS web server at http://bioengineering. skku.ac.kr/kosmos. To deal with supramolecular protein assembly with symmetric features such as virus shell and chaperone, symmetric-constrained ENM was developed [Kim, M.K. et al, 2003]. Similar to the concept of repeated boundary condition in MD simulation, the given symmetric pattern is applied to ENM resulting in dramatic reduction of computation time. In hybrid ENM including rigid-cluster ENM, a system can be represented by a mixture of rigid clusters and point masses to compromise simulation reality with computational cost [Kim, M.K. et al, 2005]. In addition, ENM has been utilized to interpret MD simulation results by deriving its ensemble motion [Kim, M.K. et al, 2003b]. Very recently, self-assembly mechanisms of various DNA tile structures were successfully investigated by ENM and the simulation results were supported by AFM or SEM images of DNA nanostructures [Kim, S. et al, 2011]. As a summary, several examples of aforementioned applications are shown in Fig. 6.2.

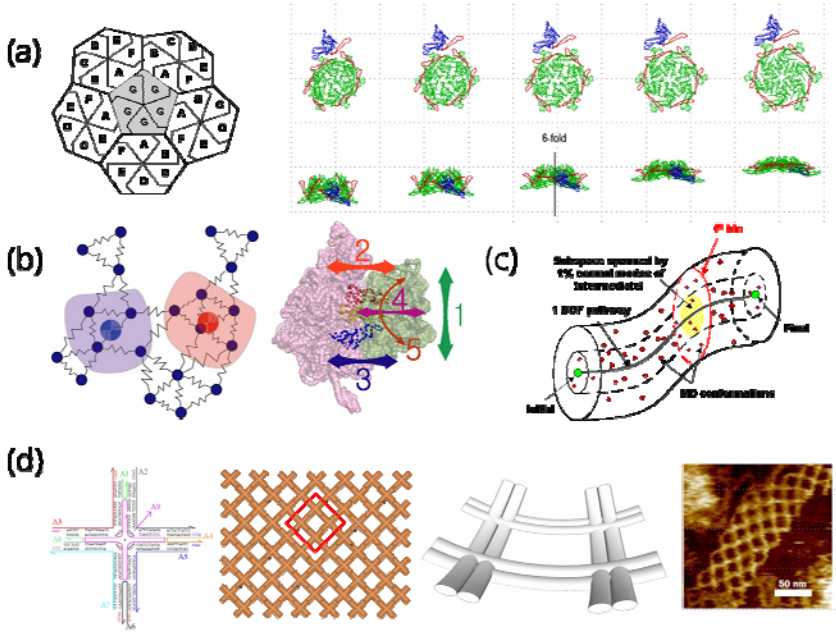


Fig. 6.2. A gallery of ENM applications. (a) Symmetry-constrained simulation of virus capsid maturation (b) Hybrid ENM based NMA for ribosome (c) An ensemble ENI pathway obtained from MD simulation data for 16S rRNA (d) DNA self-assembly mechanism revealed by NMA

7. Conclusions

In conclusion, the multiscale framework for biomedical applications was introduced through several examples ranging from MD to the continuum-scale IMEFEM. First, the drug delivery

platform combining nanodiamonds and PEI was modeled by MD. Specifically, the MD simulation showed how the ND-PEI complex was formed in solution. In the second example, the IMEFEM was used to explain the selective-capture mechanism of DNA in solution by a nanotip when applying an electric field. In vascular transport, the paths of the nanoparticles in blood flow were simulated to quantify the efficiency of the drug carriers. Also, the capillary action of a nanopore was investigated by DPD to better understand the loading of nanoparticles into porous micorstructures. Finally, an ENM was introduced to simulate various functional nanostructures by tremendously reducing the computation time. Although the possibilities for applying multiscale models to biomedical systems are far too numerous to be thoroughly covered in a single manuscript, our hope is that the examples discussed here demonstrate the vast capabilities of multi-scale computation in biomedical engineering and highlight the ability of computational modeling to illuminate underlying physical mechanism that are difficult discern experimentally.

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Извод

Основа за моделирање на више скала за биомедицинске симулације од молекуларне динамике до механике континуума

W. K. Liu[1,†], T.R. Lee[1], A. M. Kopacz[1], H. Kim[1], W. Stroberg[1], H. B. Man[1], D. Ho[1], M.K. Kim[2], J.H. Chung[3], P. Decuzzi[4]

[1] Department of Mechanical Engineering, Northwestern University, Evanston, IL, USA
[2] School of Mechanical Engineering, Sungkyunkwan University, Suwon, Kyonggi-do, Republic of Korea
[3] Department of Mechanical Engineering, University of Washington, Seattle, WA, USA
[4] The Methodist Hospital Research Institute, Department of Nanomedicine and Biomedical Engineering, Houston, TX, USA
[†] Contact Author
Department of Mechanical Engineering, Northwestern University,
2145 Sheridan Rd., Evanston, IL 60208-3111
Voice: 847-491-7094
Fax: 847-491-3915
Email: w-liu@northwestern.edu

Резиме

Рачунска механика је одувек играла важну улогу у области биомедицинског инжењеринга, и то у циљу разумевања комплексних система као што су уређаји за испоруку лекова, биосензори или крвоток. У ситуацијама где су клиничка испитивања или претерано тешка или захтевају додатно разумевање, нумерички експерименти представљају један ефикасан начин да се добије увид у поменуте проблематике. Из овог

разлога рачунске методе су постале битан алат за решавање биомедицинских проблема. У овом раду је описан основа за моделирање на више скала, са применом различитих рачунских метода на неколико биомедицинских проблема. Да бисмо показали разноврсност и ширину биомедицинких проблема који могу да се рачунски изучавају, приказали смо неколико нумеричких метода помоћу којих могу бити описани проблеми који се догађају на више скала или су сложени физички проблеми који се јављају у биолошким системима, а који су дали мотивацију за једноставне примере примене. Посебно, молекуларна динамика (МД), динамика дисипативних честица (ДПД), модел еластичних мрежа (ЕЛМ), као и метод потопољених молекуларно-електрокинетичких коначних елемената (ИМЕФЕМ), су уведени заједно са „state-of-the-art“ (последњим достигнућима) истрживачким темама у области биотехнологија.

Кључне речи: моделирање на више скала, молекуларна динамика, модел еластичне мреже, метод урођених молекуларно-електрокинетичких коначних елемената

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