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Multiscale Modeling of Protein Membrane Interactions for Nanoparticle Targeting in Drug Delivery

David M. Eckmann[1,2], **Ryan P. Bradley**[3], **Sreeja K. Kandy**[3], **Keshav Patil**[3], **Paul A. Janmey**[4], **Ravi Radhakrishnan**[3,5,*]

[1]Department of Anesthesiology, The Ohio State University Wexner Medical Center, The Ohio State University, Columbus OH

[2]Center for Medical and Engineering Innovation, The Ohio State University, Columbus OH

[3]Department of Chemical and Biomolecular Engineering, University of Pennsylvania, Philadelphia, PA, USA

[4]Institute for Medicine and Engineering, University of Pennsylvania, Philadelphia, PA, USA

[5]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA

Abstract

Nanoparticle (NP)-based imaging and drug delivery systems for systemic (e.g., intravenous) therapeutic and diagnostic applications are inherently a complex integration of biology and engineering. A broad range of length and time scales are essential to hydrodynamic and microscopic molecular interactions mediating NP (drug nanocarriers, imaging agents) motion in blood flow, cell binding/uptake, and tissue accumulation. A computational model of time-dependent tissue delivery, providing *in silico* prediction of organ-specific accumulation of NPs, can be leveraged in NP design and clinical applications. In this article, we provide the current state-of-the-art and future outlook for the development of predictive models for NP transport, targeting, and distribution through the integration of new computational schemes rooted in statistical mechanics and transport. The resulting multiscale model will comprehensively incorporate: (i) hydrodynamic interactions in the vascular scales relevant to NP margination; (ii)

*Address correspondence to rradhak@seas.upenn.edu.

Authorship

All listed authors meet the ICMJE criteria. We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

Intellectual Property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research Ethics

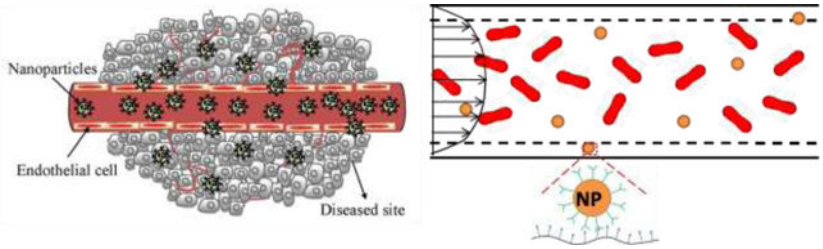
We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript

Conflict of Interest

No onflict of interest exists

physical and mechanical forces defining cellular and tissue architecture and epitope accessibility mediating NP adhesion; and (iii) subcellular and paracellular interactions including molecular-level targeting impacting NP uptake.

Graphical abstract



Caption: The objective is to develop easily computable and physiologically predictive mechanism-based multiscale pharmacodynamic models for targeted drug delivery.

Keywords

Targeted drug delivery; multiscale modeling; nanoparticle membrane interactions; nanoparticle cell adhesion; nanoparticle hydrodynamics

Introduction

Clinical medicine has entered an era of burgeoning nanotechnology through the use of drug-carrying nanoparticles (NPs) [1, 2]. Nanoparticle (NP)-based imaging and drug delivery systems for systemic (e.g., intravenous) therapeutic and diagnostic applications are inherently complex blends of biology and engineering. NPs have enormous potential to enhance imaging or drug delivery in diagnosing and treating diseases [3–5] in humans while minimizing potential toxicity [6, 7]. Some NPs (e.g., Feraheme, Doxil), are already dramatically changing clinical care by introducing new, or improving upon current, therapies and diagnostic methods, and will do more so in the future [8]. NPs have seemingly limitless possibilities for serving as tissue targeting devices, but their tremendous potential is also a significant impediment to their bench to bedside translation. Empirical determination of optimum characteristics to employ for a particular application is extremely costly [9]. Our inadequate understanding of parameters affecting NP delivery impedes NP optimization for treating human disease.

Multiscale Modeling of NP Transport and Binding

Using quantitative physiologically relevant inputs to develop and validate a computational model for *in silico* prediction of time-dependent organ-specific NP accumulation to indicate how NP characteristics impact tissue delivery will minimize the future need for empirical *in vivo* experimentation. Assessing NP delivery efficacy through computational approaches is already informing mechanisms of NP-cell interactions and the effects of many design factors such as size, chemical composition, and surface charge influencing their tissue delivery. In traditional design, the relevant estimates are typically generated using compartmental

analyses or pharmacokinetic (PK) models [10–12]; however, such models do not fully include mechanistic interactions of NPs with the vasculature. Hydrodynamic and microscopic molecular interactions mediating NP (drug nanocarriers, imaging agents) motion in blood flow, cell binding/uptake and biodistribution in different tissues involve a broad range of length and time scales warranting a multiscale modeling approach [9]. A predictive mechanism-based nanoparticle targeting model (see Fig. 1) integrates physiology, subcellular, and molecular levels and is customizable to different NP materials, chemistries, shapes, sizes, and other features. Moreover, the multiscale model should be transferable across NP architecture, chemistry, size, shape, and other factors. Recently, such models have been developed in order to provide a predictive landscape of NP hydrodynamics and margination in the vasculature, NP-cell adhesion, and ultimately NP tissue uptake. The predictive power of these methods are valuable to clinicians, academicians or researchers in the industry for applications in clinical healthcare, research, or NP development. Recent progress in modeling focused on hydrodynamics, cellular adhesion, and molecular recognition, and the multiscale integration of the three components (Fig. 1) are discussed below.

Hydrodynamic Factors

In the multiscale framework, the macroscale is focused on vascular hydrodynamics and NP margination. The transport of NPs and their approach to the endothelium in the presence of blood flow through a process called margination is mediated by the hydrodynamic (i.e., fluid-flow-mediated) interactions of the nanoparticles with the red blood cells and the vessel walls [13–21]. To develop the hydrodynamics elements of the modeling, the physiological and NP characterization parameters of interest include blood vessels diameter and length distributions, blood viscosity, cell-free layer (CFL) characteristics, flow rates or velocity distributions and physiology specific vasculature traits (such as tumor versus normal), all of which collectively dictate the NP margination from the core to the periphery of the blood vessels. Blood flow in microvascular networks have been modeled using the apparent viscosity dependence on hematocrit, vessel diameter, and reduced hematocrit in daughter vessels, and based on experimental data on tube diameter and length [22, 23]. Previous works have developed an Immersed Finite Element Method (IFEM) [24] and Lattice Boltzmann (LB) numerical method based on the Immersed Boundary Method (IBM) for the simulation of biological and particulate systems. These numerical methods have been used to model the deposition of platelets on injured vessel walls [24], 3D aggregation of red blood cells, and blood flow in a capillary [24]. In these applications, the complex deformation, motion, and binding of cells of arbitrary shapes are modeled. The transport and deposition of nanoparticles under shear and blood flow have also been investigated by coupling fluid dynamics with adhesion kinetics [24–31].

NPLive Cell Adhesion

Endothelial cells lining the luminal surface of blood vessels are the critical target and barrier for vascular therapeutic delivery. NPs (10–200 nm) coated with antibodies (Abs) or affinity peptides that bind specifically to endothelial surface receptors provide targeted delivery of therapeutic cargoes to these cells. Endothelial targeting consists of several phases, including circulation in the bloodstream, anchoring on the endothelial surface, and, in some cases,

intracellular uptake and trafficking of the internalized materials [5]. In addition to dynamic parameters of the vasculature, including the blood hydrodynamics, physiological factors such as surface density, accessibility, cell membrane mobility, and clustering of target determinants modulate NP biodistribution, particularly when targeting strategies are involved. Furthermore, controlled parameters of the design of therapeutic or diagnostic NPs such as affinity, surface density, and epitope specificity of targeting Abs, carrier size, shape, and flexibility also modulate endothelial targeting and resultant subcellular distribution [4, 5, 9].

Computational models [32–40], have been developed to delineate the roles played by targeting ligand density, target protein expression, mechanical factors of the target cell membrane as well as the glycocalyx in determining the avidity of functionalized NCs to live cells. These models can be described using a common integrative framework (Fig. 2): the input to the models can be broadly classified into three categories that represent (i) cellular phenotype, (ii) NC design parameters and (iii) non-targeted contributions (K_p) which denotes the partitioning coefficient measured in experiments. Flow chart of a computational framework to compute the association constants (K_{EC} and K_M) for NCs binding to live endothelial cells and macrophages is provided in Fig. 2. Computational techniques for computing live cell adhesion are based upon the framework of equilibrium statistical mechanics; the best models combine continuum field models for cell membranes with coarse-grained molecular-scale models for the NC, Abs, and target receptors. Fig. 2 highlights the major components of the proposed computational approach, which can be broadly classified as: (i) a set of input parameters for the coarse-grained and continuum models that define entirely the protein expression and mechanical properties of the target cell membrane, the biochemical interactions of the receptor-ligand bond, the flexural rigidity of the target receptors, and experimentally controllable quantities such as the geometry and the surface chemistry of the functionalized NC; (ii) a computational engine to accurately compute the association constant K_a, for a specified mechano-chemical microenvironment and (iii) a framework that accounts for the targeted contributions due to NC binding to other cells such as a macrophage. The expression for K_a is adopted and generalized based on studies from molecular simulations of drug binding, which have formulated techniques to compute the absolute free energy of binding [32, 41]. The main output of the model is the calculation of the free energy landscape for carrier binding to the cells, which is quantified through enhanced sampling methods [42, 43]. The primary learnings from the computational studies have been the compensation of different entropy, and the enthalpy terms are dependent on NP flexibility, membrane tension, receptor density, and receptor-ligand interaction strength [32, 33, 37–40, 44, 45].

Molecular Scale Factors in NP Membrane Interactions

There are several aspects of the multiscale problem (Fig. 1) that deserve molecular-level treatment and characterization. Engineering antibodies and studying receptor-ligand interactions using molecular modeling already has a rich literature in computational chemistry. Engineering the structural and mechanical features associated with the receptor-ligand interactions that have already been identified as critical variables through sensitivity analyses, such as flexural rigidity [34], catch-bond behavior [46], can be vastly improved

and influenced through advances in molecular simulations and multiscale methods [47–49]. Recently it was hypothesized that while targeting adhesion molecules with antibodies represent strong binding (SB) interactions, the surface protein epitopes such as Fc receptors and even albumin will represent intermediate binding (IB) and weak binding (WB) on the surface of the NP [33]. Moreover, targeting flow adapted healthy endothelial cells versus leaky endothelial cells can be different because the later presents a less stiff membrane due to lack of flow adaptation and improper glycocalyx; here, parameter variations involving cytoskeletal pinning and excess membrane area can be considered. The effect of opsonization was considered by tuning the ratios of SB:IB:WB on the NP.

Conclusion and Future Outlook

An integrative mechanism-based model for tissue biodistribution and prediction of NP tissue targeting can be obtained via a unified multiscale model combining the different modules in Fig. 1. The resultant multiscale model will power exploration of a myriad of tunable physical options for NP design for clinical tissue targeting. We envision an integrative multiscale framework to combine the different scales using formalisms discussed above. The models will need to be tightly and iteratively coupled with in vitro, cellular, as well as in vivo experimentation to validate, to predict, and to guide the design of targeted nanoparticles in translational applications of targeted nanomedicine.

One promising area of future development in design is to combine the bivalent and bispecific Abs, along with the multivalency of engaging SB, IB, and WB receptors [50]. The nature of interactions of these bivalent bispecific interactions on an immobilized NP surface, on a flexible polymeric NP or liposome, or engaging receptors on a fluid membrane. On the membrane interface, several molecular-scale considerations can impact and revolutionize the NP cell interactions: (1) membrane curvature aids and influences the NP cell adhesion [44, 51]; (2) the mechanisms through which curvature inducing proteins generate curvature and influence NP binding and subsequent internalization are hugely important [52]; (3) the clustering of receptors on the membrane interface can be mediated through formation of lipid domains often involving phosphoinositide proteins [53]; (4) lipid, and in particular, phosphoinositide nanocluster formation, has a significant influence on actin nucleation and subsequent NP internalization [54–56]; (5) the nature of the molecular assembly and curvature at the membrane interface is not only influenced by cell mechanics and the mechanics of the tissue microenvironment, but also impacts the internalization of rigid, semi-rigid, and flexible NPs differently [51].

While the previous models, including those described above, have been successful in evaluating the effects of Ab density and NP targeting to different cell types, accurate representations of specific and non-specific contributions require a more detailed description of the tissue morphology and the physiological conditions. First, in the modeling of live cell adhesion, will need to extend the analysis to include the effects of NP surface functionalization (such as PEGylation) [57], targeting of multiple receptors using bivalent and bispecific antibodies [58, 59], and NP opsonization (by surface deposition of albumin and Fc receptors on NPs to consider the architecture and chemistry of the NP). These factors will need to be considered in addition to physiological factors such as glycocalyx [35, 36,

60], cell membrane compliance and deformation [32], and vascular margination. Second, cell microenvironment effects need to be considered, such as: (*a*) the effect of the cytoskeleton and cytoskeletal heterogeneity; (*b*) the effect of cortical tension and cell-cell adhesion is considered through frame tension [61, 62]. These variables lead to significant heterogeneity in the adhesion surface by inducing/inciting morphological features. The topographical heterogeneity induced by the effects described under couples with biochemical heterogeneity because of lipids and proteins sort in the membrane phase in a curvature-dependent fashion [52, 63, 64]. These features can be included by following the methods recently described [52, 64].

New multiscale bridging algorithms warrant future development in order to realize the coupling of hydrodynamic and adhesion models and their objective validation against experimentation. One avenue could be to develop functionals incorporating relevant physicochemical and hydrodynamic interactions. An example is through the use of dynamical density functional theory, which utilizes a functional approach to treat the far-field many-body hydrodynamics [57, 65], near-field hydrodynamics [66–71], and multivalent adhesion of NPs to soft membranes can be combined into one coherent framework in order to either obtain the spatial distribution of NP [44, 45]; another example is through the use of stochastic dynamics using generalized Langevin equation methods [70, 71] to capture the temporal dynamics of NP [70–72]. A second avenue to realize the multiscale integration is to use a loosely coupled framework where a small number of parameters are passed between the different scales, and the integration is achieved through high-performance computing workflow management software such as TAVERNA [73], MUSCLE [74], or the VPH hypermodel framework [75]. As a computational scientist, one is also encouraged and optimistic about machine-learning [76, 77] enabled multiscale methods to improve accuracy, speed-up performance, and utilize the emerging high-performance computing architectures.

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Highlights

- Computational methods for modeling hydrodynamic factors in nanoparticle membrane interactions in targeted drug delivery
- Computational frameworks for predicting lice cell adhesion of nanoparticles
- Molecular-level considerations in nanoparticle cell membrane interactions
- Outlook for multiscale model integration for developing the next-generation mechanism-based pharmacokinetic models

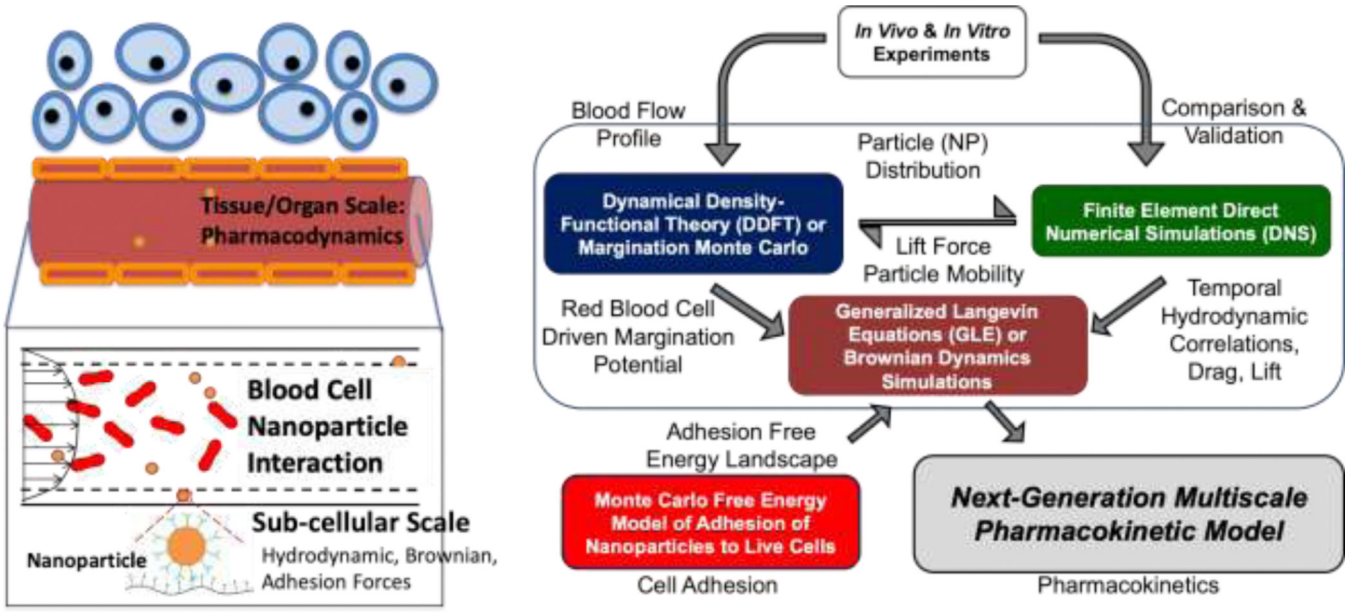

Figure 1:

(left) Schematic of the multiscale pharmacokinetic model showing the different length scales and resolutions of the transport problem in targeted drug delivery. (right) A flowchart for an algorithmic implementation of the multiscale model consisting of the “Hydrodynamics” component, the “Cellular Adhesion” component, and the “Pharmacokinetics” component. The arrows represent the flow of information between the suite of models and the flow of information for experimental validation.

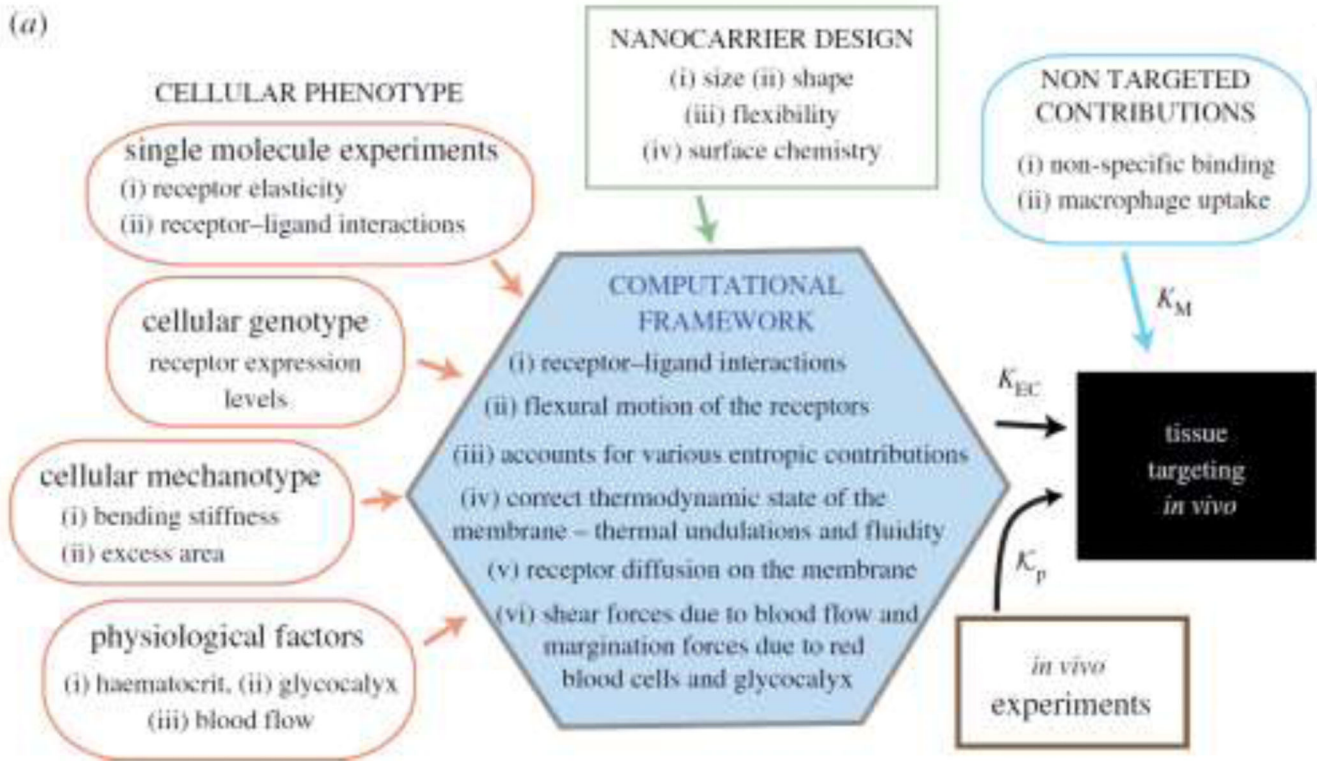

Figure 2:

(a) Depiction of the live cell adhesion NP tissue targeting highlighting the parameter mapping (inputs and outputs). A Monte Carlo framework constitutes the live cell adhesion suite.