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***in silico* Vascular Modeling for Personalized Nanoparticle Delivery**

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Abstract

Aims—To predict the deposition of nanoparticles in a patient-specific arterial tree as a function of the vascular architecture, flow conditions, receptor surface density, and nanoparticle properties.

Materials & methods—The patient-specific vascular geometry is reconstructed from CT Angiography images. The Isogeometric Analysis framework integrated with a special boundary condition for the firm wall adhesion of nanoparticles is implemented. A parallel plate flow chamber system is used to validate the computational model *in vitro*.

Results—Particle adhesion is dramatically affected by changes in patient-specific attributes, such as branching angle and receptor density. The adhesion pattern correlates well with the spatial and temporal distribution of the wall shear rates. For the case considered, the larger (2.0 μm) particles adhere $\approx$ 2 times more in the lower branches of the arterial tree, whereas the smaller (0.5 μm) particles deposit more in the upper branches.

Conclusion—Our computational framework in conjunction with patient specific attributes can be used to rationally select nanoparticle properties to personalize, thus optimize, therapeutic interventions.

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Keywords

nanoparticles; rational design; mathematical modeling; vascular adhesion; personalized medicine; patient-specific; wall shear rate

Introduction

It is well accepted that the outcome and safety of a therapeutic intervention is often affected by patient-specific attributes, at the gene, cell and organ levels [1, 2]. It is also increasingly recognized that results from clinical trials do not necessarily apply to individual patients, not even to the patients that were directly enrolled in the trials [3]. Every individual is shaped differently and the distribution, metabolism and elimination of drugs as well as their biochemical effects on the target cells are influenced by the patient age, genetic background and anatomical features. Computational modeling and nanomedicine are playing a major role in supporting the development of personalized therapeutic approaches [4-8].

Computational modeling can capture the hierarchical complexity of biological systems and diseases over multiple scales – temporal and spatial – and include patient-specific information to personalize the outcome of the analysis. *in silico* modeling has been proven useful in orthopedic applications [9, 10], for the treatment of cardiovascular diseases [11-14] and cancer [15, 16], and in pharmacogenomic analysis [6, 17]. Segmental bone replacements can be optimally designed after a careful analysis of patient anatomical features and computation of the mechanical loads [9]. In cardiovascular diseases, the authentic geometry of the blood vessels and their mechanical properties have been incorporated in sophisticated computational tools to predict the distribution of wall shear stresses, risk of aneurysm rupture and to optimize the deployment of vascular stents [18-20]. Multi-physic models have been developed for predicting the response of tumors to molecular-based, radiation and thermal ablation therapies [15, 16].

Computational pharmacogenomics is used to predict *in silico* the efficacy, toxicity and possible resistance of drug molecules on different cell types [6, 16].

On the other hand, a plethora of nanoparticle-based delivery systems have been developed over the last two decades for enhancing the tissue-specific accumulation of therapeutic molecules and the contrast generated by imaging agents. Indeed, the biodistribution and bioavailability of both therapeutic and imaging agents are dramatically affected by the *size*, *shape*, *surface* properties and mechanical *stiffness* (*the 4Ss*) of their carriers: the nanoparticles. This has been firstly predicted using mathematical models and then supported by experimental evidence, *in vitro* and *in vivo* [21-23]. Different fabrication strategies have been proposed to finely tune the geometrical, mechanical and surface properties of the nanoparticles [24-27]. But how such four parameters (*the 4Ss*) can be rationally exploited in conjunction with patient-specific attributes to personalize and, thus optimize, therapeutic interventions is still largely unexplored.

Along this line, a patient-specific computational model is here presented for predicting the nanoparticle lodging within an authentic vascular network. Hexahedral solid NURBS (Non-Uniform Rational B-Splines) are used to accurately mesh the tridimensional architecture of an arterial tree, derived from the Computed Tomography (CT) scan of a patient [28]. The Finite Element Method (FEM), reformulated within the Isogeometric Analysis framework [29], is employed to solve for the fluid and particle transport in the authentic vasculature (see Materials and Methods section for further details on the numerical approach). Information at the micro and nanoscale are introduced in the computational model by developing a special boundary condition at the vessel wall, accounting for cell/nanoparticle

adhesion [30]. The model directly integrates information from the macroscale (vessel geometry and permeability, blood flow condition) with data pertaining to the micro and nanoscale (particle geometry, receptor density and affinity), thus avoiding massive, computationally inefficient discretization over multiple spatial and temporal scales. A Newtonian rheological law is used for blood, which is a reasonable assumption for larger vessels [31, 32]. More complex laws, such as the Generalized Power Law [33] can be readily implemented. The proposed *in silico* model is first validated against *in vitro* parallel plate flow chamber experiments and then is applied for studying the effect of patient-specific attributes, such as the vascular geometry and receptor surface density, on the deposition of spherical particles with different sizes within an authentic arterial tree. Although we do not perform a theoretical analysis in this work because of the many complexities involved, we do carry out experimental validation of the particle adhesion model for a range of particle size and wall shear rates that defines a regime of applicability.

Materials & Methods

Reconstructing the patient-specific vascular geometry

The input CT Angiography imaging data are often of poor quality due to large motions of the heart, as it supplies blood to the circulatory system. This makes it difficult to construct analysis-suitable patient-specific coronary models. To circumvent this problem, the raw imaging data were passed through a preprocessing pipeline where the image quality is improved by enhancing the contrast, filtering noise, classifying, and segmenting regions of interest [28]. A small bifurcation portion of the coronary tree was considered here including the left coronary artery (LCA), the left anterior descending artery (LAD) and the left circumflex artery (LCX) (Figure 1). The surface model of this bifurcation structure was extracted from the processed imaging data, and the vessel path was obtained after skeletonizing the volume bounded by the local luminal surface using Voronoi and Delaunay diagrams. The generated path can also be edited according to simulation requirements, e.g., extending the included branch angles to study how geometry such as the bifurcation angle influences particle delivery processes in coronary arteries. A skeleton-based sweeping method [28] was then used to generate hexahedral control meshes by sweeping a templated quadrilateral mesh of a circle along the arterial path. A template for the bifurcation configuration was used to decompose the geometry into three mapped meshable patches using the extracted skeleton. Each patch can be meshed using one-to-one sweeping techniques. Some nodes in the control mesh lie on the surface, and some do not. We project nodes lying on the surface to the vascular surface. Finally, solid NURBS models were generated based on the constructed control meshes and they were employed in Isogeometric Analysis [34, 35] to simulate blood flow and particle delivery in the coronary arteries.

Governing equations for the fluid flow and particle transport

A continuum-based approach was adopted to simulate blood flow and particle transport within a patient-specific vascular network (Figure 1). Blood was modeled as an incompressible Newtonian fluid with a density (ρ) of 1060kg/m^3 and a dynamic viscosity (μ) of $0.003\text{ N}\cdot\text{s/m}^2$, and the governing equations were formulated accordingly. Indeed, for sufficiently larger vessels (macrocirculation), the corpuscular component of blood (red blood cells, white blood cells and platelets) can be neglected and a Newtonian model for blood provides sufficiently accurate results [31, 32]. The strong form of the continuity and momentum balance equations in the fluid domain Ω , with its boundary T divided into three non-overlapping parts, the inflow (Γ_{in}) and outflow (Γ_{out}) boundaries and the vascular wall (Γ_{s}), can be written as:

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} + \nabla p - \nabla \cdot \mu (2 \nabla^s \mathbf{u}) = \mathbf{f} \text{ in } \Omega \times (0, T) \quad (0)$$

$$\nabla \cdot \mathbf{u} = 0 \text{ in } \Omega \times (0, T) \quad (0)$$

$$\mathbf{u} = \mathbf{g} \text{ on } \Gamma_{\text{in}} \times (0, T) \quad (0)$$

$$\mathbf{u} = \mathbf{0} \text{ on } \Gamma_s \times (0, T) \quad (1)$$

$$-p \mathbf{n} + \mu (2 \nabla^s \mathbf{u}) \cdot \mathbf{n} = \mathbf{0} \text{ on } \Gamma_{\text{out}} \times (0, T) \quad (2)$$

$$\mathbf{u}(\mathbf{x}, 0) = \mathbf{u}_0(\mathbf{x}) \text{ in } \Omega \quad (3)$$

where $\mathbf{x}$ is a point in the spatial domain Ω and t is a point in the time domain $[0, T]$. In these equations, $\mathbf{u}(\mathbf{x}; t)$ represents the fluid velocity vector, $p(\mathbf{x}; t)$ the pressure, $\mathbf{f}$ the external body force, $\mathbf{n}$ the unit outward normal to the surface, denoted Γ , and $\mathbf{u}_0(\mathbf{x}; 0)$ the initial velocity vector. An inflow velocity vector $\mathbf{g}(\mathbf{x}; t)$ was specified at the inlet (Γ_{in}), a no-slip boundary condition (Eq.(1)) was prescribed at the rigid and impermeable vascular wall (Γ_s) and a stress free outflow boundary condition (Eq.(2)) was implemented at the branch outlets (Γ_{out}).

The mass transport of the particles was assumed to be governed by a scalar advection-diffusion-reaction equation. This is a reasonable assumption for sufficiently small particles navigating in large vessels [36, 37]. In the strong form, the transport problem can be stated as:

$$\frac{\partial C}{\partial t} + \mathbf{u} \cdot \nabla C - \nabla \cdot (\mathbf{K} \cdot \nabla C) + \sigma C = 0 \text{ in } \Omega \times (0, T) \quad (3)$$

$$C = C^0 \text{ on } \Gamma_{\text{in}} \times (0, T) \quad (4)$$

$$(\mathbf{K} \cdot \nabla C) \cdot \mathbf{n} = 0 \text{ on } \Gamma_{\text{out}} \times (0, T) \quad (5)$$

$$(\mathbf{K} \cdot \nabla C) \cdot \mathbf{n} + \Pi C = 0 \text{ on } \Gamma_s \times (0, T) \quad (6)$$

$$C(\mathbf{x}, 0) = 0 \text{ in } \Omega \quad (7)$$

where $C(\mathbf{x}; t)$ is the particle concentration, $\mathbf{K}$ is the diffusivity tensor, and σ is the reaction coefficient. At the inlet (particle injection site) Γ_{in} , a Dirichlet boundary condition is prescribed (Eq. (4)) where C^0 is the particle concentration given as:

$$\begin{aligned} C^0(\mathbf{x}, t) &= 1 \text{ for } 0 \leq t \leq t_i, \mathbf{x} \in \Gamma_{\text{in}} \\ C^0(\mathbf{x}, t) &= 0 \text{ for } t > t_i, \mathbf{x} \in \Gamma_{\text{in}} \end{aligned} \quad (8)$$

Here t_i denotes the duration of particle injection. At the outflow Γ_{out} , a homogenous Neumann boundary condition was specified (Eq.(5)); and a Robin-type boundary condition (Eq.(6)), a combination of the Dirichlet and Neumann conditions, was prescribed at the rigid wall interface (Γ_s), where Π is defined in the sequel as the vascular deposition parameter.

Particle diffusivity was assumed to be isotropic and constant, and was determined from the Einstein-Stokes relation

$$D = \frac{k_B T}{3\mu d_p} \quad (9)$$

as a function of the particle size, where d_p is the diameter of the particles. Here $k_B T$ represents the Boltzmann thermal energy. Then

$$\mathbf{K} = D\mathbf{I} \quad (10)$$

where $\mathbf{I}$ is the 3×3 identity matrix. The velocity field $\mathbf{u}$ in Eq.(3) was obtained from the solution of the Navier–Stokes equations (Eqs.(0)-(3)) with the assumption that the flow physics affects the mass transport, not vice versa.

Boundary condition for particle adhesion to the vessel wall

The particle surface is assumed to be decorated with ligand molecules, uniformly distributed with a surface density m_l , that can specifically interact with counter molecules (receptors) expressed on the vessel wall with a surface density m_r (Figure 1). The molecular interaction between ligands and receptors is characterized by an affinity constant K_a^0 , at zero mechanical load. From [30], a probability of particle adhesion P_a can be derived as a function of its geometry (size and shape) and surface properties (ligand density, ligand type; surface electrostatic charge). The mathematical parameter P_a is defined as the probability of having at least one close ligand–receptor bond, and can be considered as a measurement of the strength of adhesion: the larger is P_a , the larger is the avidity and strength with which the particle firmly adheres to the wall. For a spherical particle of diameter d_p , the probability of adhesion can be expressed as follows [30]:

$$P_a \simeq m_r m_l K_a^0 \pi r_0^2 \exp \left[1 - \frac{\lambda}{K_B T} \frac{6F^s \mu S}{m_r} \frac{d_p^2}{4r_0^2} \right] \quad (10)$$

where λ is a characteristic length of the ligand-receptor bond, generally of the order of 0.1 – 1 nm; $k_B T$ is the Boltzmann thermal energy ($= 4.142 \times 10^{-21}$ J); F^s is the coefficient of hydrodynamic drag force on the spherical particle; μS is the wall shear stress; and S is the wall shear rate. In Eq.(10), the parameter r_0 is the radius of adhesion

$$r_0 = \frac{d_p}{2} \sqrt{\left[1 - \left(1 - \frac{\Delta}{d_p/2} \right)^2 \right]} \quad (10)$$

with Δ the separation distance between the particle and the substrate, at equilibrium (i.e., firm particle adhesion). Note that Δ ($= 0.68$ nm) is generally much smaller than the particle diameter d_p [30]. An alternative representation of Eq.(10) is,

$$P_a \simeq \alpha_1 \alpha_2 \pi r_0^2 \exp \left[-\beta \frac{\mu S}{\alpha_2} \right] \quad (11)$$

where $\alpha_1 = m_l K_a^0 (=0.023)$ and $\alpha_2 = m_r \left[1 - \left(1 - \frac{\Delta}{d_p/2} \right)^2 \right] (\approx 1.369 \times 10^{10} \text{ \#}/\text{m}^2 \text{ for } d_p = 0.5 \text{ \mu m and } \approx 3.400 \times 10^9 \text{ \#}/\text{m}^2 \text{ for } d_p = 2 \text{ \mu m})$ are two governing parameters, and $\beta = \frac{\lambda 6 F^s}{k_B T}$ ($= 2.39 \times 10^{11} \text{ N}^{-1}$) is a constant. In Eq.(11), α_1 , α_2 , the wall shear rate S and the particle diameter d_p are the independent governing parameters. For convenience, λ has been fixed to be 0.1 nm.

The mass flux of particles (C/n) in the direction $\mathbf{n}$ normal to the wall can be related to the local increase in mass of particles adhering per unit surface $\psi(\mathbf{x};t)$ as

$$-(\mathbf{K} \cdot \nabla C) \cdot \mathbf{n}|_s = -D \frac{\partial C}{\partial n}|_s = \frac{\partial \psi}{\partial t} \quad (12)$$

which simply derives from mass balance at the surface (accumulation of mass over time). Note that Eq.(12) is not a boundary condition yet, in that $\psi(\mathbf{x};t)$ is an unknown function. To close the system, an additional relation needs to be defined between $\psi(\mathbf{x};t)$ and $C(\mathbf{x};t)$. The number of particles per unit surface $\psi(\mathbf{x};t)$ is in turn related to the volume concentration of particles at the wall through the equation

$$-D \frac{\partial C}{\partial n}|_s = \frac{\partial \psi}{\partial t} = \Pi C|_s = P_a S \frac{d_p}{2} C|_s \quad (13)$$

Note that $S d_p/2$ is the fluid velocity in the center of a particle in proximity of the wall. The term $\Pi = P_a S d_p/2$ is called the vascular deposition parameter, in that the larger is Π , the larger is the number of particle adhering stably to the vessel walls under flow.

In the Supplementary Materials, the system of governing equations (0)-(13) is specialized to the case of a channel with a rectangular cross section simulating a parallel plate flow chamber, used for the *in vitro* validation of the proposed computational approach. Note that the model presented can be also integrated with other adhesion models [38] that could predict the number of adhering particles as a function of the local biophysical conditions (wall shear rate; surface density of receptors; binding affinity) and nanoparticle features (size, shape, surface properties such as ligand density, electrostatic charge).

Finite Element Solution Approach

Eqs.(1)-(11) were solved by applying Finite Element based Isogeometric Analysis [14, 34] that uses NURBS to describe the geometry as well as the solution space. It is a technology that constructs an exact geometry, which is preserved under mesh refinement allowing for higher-order (smoother) and higher continuity discretization of complex geometries, for example the arterial system. Quadratic NURBS was used for the spatial discretization. The spatial order of error is therefore of third order. A residual-based variational multiscale method [35] was implemented to solve the system of equations, utilizing a Newton-Raphson procedure with multi-stage predictor-corrector algorithm at each time step. The generalized- α method [39, 40] was used for time advancement, which is an implicit second-order time-

accurate method that is also unconditionally stable. The readers are referred to the numerical procedures described in [29, 34, 41-43] for further details on the underlying methodology.

Results & Discussion

Predicting particle deposition in a parallel plate flow chamber apparatus

The implementation of the boundary condition for particle adhesion was first validated against *in vitro* experiments conducted in a parallel plate flow chamber apparatus. A schematic of the system and the geometry used for the computational analysis are presented in Supplementary Figure 1. The particles are injected in a 20 mm long channel with a rectangular cross section (10×0.274 mm) under controlled hydrodynamic conditions (fixed wall shear rate S). While the particles are transported downstream toward the waste, some of them can interact with and adhere firmly to the substrate. Details on the experimental conditions are provided in the Supplementary Materials.

The number of particles adhering n_{adh} per unit area A , normalized by the total number of injected particles n_{inj} , is presented in Figure 2 for different wall shear rates, namely $S = 10$, 75 and 200 s^{-1} , and particle diameters. The experimental results (crosses with standard deviation bars) are compared with the numerical predictions (gray area), which are presented for different values of the parameters α_1 and α_2 , as utilized in Eq.(11). The gray areas are obtained for a $\pm 5\%$ variation of the mean value of $\alpha_1 (= 0.023)$ (Figure 2 – left column) and $\alpha_2 (\approx 9.44 \times 10^9 \text{ for } d_p \approx 0.7 \text{ }\mu\text{m}; 1.388 \times 10^9 \text{ for } d_p \approx 5 \text{ }\mu\text{m}; \text{ and } 1.031 \times 10^9 \text{ for } d_p \approx 7 \text{ }\mu\text{m})$ (Figure 2 – right column).

Three different adhesive behaviors are depicted as a function of the wall shear rate S : i) n_{adh} grows steadily with d_p , for $S = 10 \text{ s}^{-1}$ (Figure 2A); ii) n_{adh} grows, reaches a maximum and then decreases with d_p , for $S = 75 \text{ s}^{-1}$ (Figure 2B); iii) n_{adh} decreases steadily with d_p , $S = 200 \text{ s}^{-1}$ (Figure 2C). Particle adhesion is determined by the balance between interfacial adhesive interactions (specific and non-specific) and the dislodging hydrodynamic forces. At low S , (Figure 2A) the former dominates the latter, thus the steady increase in n_{adh} up to $d_p \approx 7 \text{ }\mu\text{m}$. Conversely, at high S , the adhesive forces cannot balance the dislodging forces, and n_{adh} decreases steadily with d_p (Figure 2C). At intermediate values of S , a maximum in adhesion appears for an optimal particle diameter ($\approx 5 \text{ }\mu\text{m}$). For the conditions analyzed here, this happens for $d_p \approx 5 \text{ }\mu\text{m}$, at $S = 75 \text{ s}^{-1}$.

However, this maximum d_p , as well as its absolute value, changes with the adhesive properties of both the particle and the substrate [30]. Indeed, this maximum identifies the threshold in particle diameter below (above), which adhesive interactions prevail (do not prevail) over the dislodging hydrodynamic forces. Such a biphasic behavior was already predicted for the general case of oblate spheroidal particles as well [30], and correlates with the dependence of the vascular deposition parameter Π on d_p (Supplementary Figure 2). Note that although the particles used in the flow chamber experiments were not decorated with any ligands, their adhesive behavior would follow the biphasic relationship of Eq.(11) due to the surface adsorption of non-specific molecules, mediating the interactions with the substrate.

Figure 2 demonstrates that the implemented adhesive boundary condition can accurately predict the complex, biphasic behavior for particle deposition under flow. Only at large shear rates, $S = 200 \text{ s}^{-1}$, and for large particle diameters ($> 5 \text{ }\mu\text{m}$), the numerical predictions significantly underestimate the number of adhering particles. In this respect, however, it should be noted that for $S = 200 \text{ s}^{-1}$ and $d_p > 5 \text{ }\mu\text{m}$, the absolute number of particles adhering is extremely small ($\approx 2.5/\text{mm}^2$). Thus, both numerical and experimental inaccuracies could explain the observed discrepancy.

It is also important to note that due to the highly convective nature of the particle transport (global Péclet number Pe can be 1000 and higher for all the particle sizes considered) diffusion plays a negligible role in particle mass transport within the core of the flow. As a result there appears to be little effect of particle size on near wall accumulation of particles in terms of $C|_s$ (i.e., particle availability near the wall for adhesion), as shown in Supplementary Figure 3. This implies that adhesion/deposition pattern for particles of different size is largely governed by the vascular deposition parameter Π , under the condition considered here. Also, the surface density of the adhering particles does not vary significantly over the channel length, as demonstrated in Supplementary Figure 4.

Predicting particle transport and deposition in a patient-specific vascular network

The Isogeometric Analysis formulation was used to simulate the transport and wall adhesion of particles injected through a catheter in a patient-specific arterial tree. From the CT scan imaging data of a healthy volunteer, a hexahedral solid NURBS model for a portion of the left coronary artery (LCA) tree was generated following the steps described in [28]. The geometry of the problem is presented in Figure 3A. A time-dependent pulsatile inflow condition [44, 45] with a period of 1 s (heart rate = 60 beats per minute) was imposed at the LCA inlet, where also a cylindrical catheter was located through which particles were injected, both radially and axially at a speed of 4 cm/s, for 5 cardiac cycles (5 s). The simulations were run on a computational mesh consisting of 55,100 quadratic NURBS elements for 14 cardiac cycles (14 s total) with a time step of 0.01 s employing the general solution strategies described in the Methods. Boundary layer meshes with the finest boundary element thickness of the order of 10^{-6} cm, are used for more accurate computation of wall quantities, such as the wall shear rate. The simulations were run with a time step of 0.05 s until all the particles left the fluid domain.

The time evolution of the particle volumetric concentration within the vascular network is presented in Figures 3B-F. With time, the particle distribution front moves from the LCA inlet, where the catheter is located, toward the downstream branch and eventually into the side branches of the left anterior descending (LAD – left) and circumflex (LCX – right) artery. At 1 s, the particle front has passed the bifurcation (Figure 3C); at 5 s, the particles are uniformly distributed within the vascular tree (Figure 3D); and at 14 s, they have left the LCX and LAD (Figure 3F). This distribution was obtained for the $0.5\ \mu\text{m}$ particles. In the sequel, the particle transport and wall deposition are analyzed as a function of the particle size and patient-specific attributes, such as the vascular geometry and the receptor surface density.

First, two particles with different diameters, namely $d_p = 0.5$ and $2\ \mu\text{m}$, were injected in the LCA. Figure 4 shows a side-by-side comparison of the time evolution for the wall surface concentration of the adhering particles, normalized by the injected dose. Three times are considered: 5, 10 and 14 s. For both particles, the surface concentration increases with time and becomes higher moving down the LCA, and approaching the LCX and LAD outlets. The larger particles ($d_p = 2\ \mu\text{m}$) exhibit about twice the adhesion of the smaller particles ($d_p = 0.5\ \mu\text{m}$), with a maximum normalized surface concentration of 7×10^{-8} and $2 \times 10^{-8}\ \text{cm}^{-2}$, respectively. The smaller particles are observed to lodge more extensively in the upper branch (LCA) (Figure 4C).

As discussed in the previous section, particle adhesion is mostly governed by the vascular deposition parameter Π and the shear rate at the wall S . Therefore, the variation of S along the vascular tree and the flow conditions were carefully quantified over time, as shown in Supplementary Figure 5. In the LCA, large shear rates are computed within the first 5 cardiac cycles (i.e., continuous injection), with values of the order of $500 - 1000\ \text{s}^{-1}$, occurring in proximity of the branching point. Much lower values are computed in the LAD

and LCX with $S < 200 \text{ s}^{-1}$. After 5 s, when the flow is no longer perturbed by the catheter injection, the wall shear rate decreases along the vascular tree with characteristic values ranging between $300 - 400 \text{ s}^{-1}$ in the LCA and lower than 100 s^{-1} in the LAD and LCX. A comparison of Figure 4 and Supplementary Figure 5d reveals that the surface deposition patterns for the particles correlate well with the corresponding time averaged S distributions.

In the lower branches (LAD and LCX), before and after injection, the wall shear rate is generally equal to or lower than $\approx 100 \text{ s}^{-1}$. Within this S range, the vascular deposition parameter Π for the $2 \mu\text{m}$ particles is, on the average, larger than that for the $0.5 \mu\text{m}$ particles (Supplementary Figure 2: at $S = 50 \text{ s}^{-1}$, $\Pi \approx 3.5 \times 10^{-6} \text{ mm/s}$ for the $2 \mu\text{m}$ particles, $\Pi \approx 1.75 \times 10^{-6} \text{ mm/s}$ for the $0.5 \mu\text{m}$ particles), thus explaining the larger adhesion (≈ 2 times) of the former compared to the latter. On the other hand, for larger values of S , as those experienced in the LAD, the $0.5 \mu\text{m}$ adhere more effectively than the $2 \mu\text{m}$ particles, in agreement with what is shown in Figure 4 (see also Supplementary Figure 2: at $S = 500 \text{ s}^{-1}$, $\Pi \approx 0 \text{ mm/s}$ for the $2 \mu\text{m}$ particles, and $\Pi \approx 0.5 \times 10^{-7} \text{ mm/s}$ for the $0.5 \mu\text{m}$ particles). Incidentally, these observations are consistent with those reported in the literature where it has been shown that low and oscillating S zones are associated with enhanced deposition and uptake of lipoprotein (LDL), and correlate well with atherosclerotic regions [46-50]. Because of the pulsatile nature of blood flow in the coronaries, the associated complex flow features create recirculation zones near the bifurcation resulting in alternate areas of high and low S levels (Supplementary Figures 5c, d). It should also be noted that the injection flow rate from the catheter can significantly alter the wall shear rate distribution and thus affect the particle deposition rates and patterns.

Second, the branching angle between the LAD and LCX was increased from 76.8° to 106.8° , in the same patient-specific coronary geometry. As expected, the velocity magnitude and the wall shear rate distribution are significantly affected by such a change [51]. While the flow features appear similar in the LCA, the velocity magnitude and distribution become noticeably different as the branching point is approached, and moving downstream towards the two outlets (Supplementary Figure 5). First, a larger recirculation area is seen at the branching. Second, due to the sharper bend encountered as the blood flows from the LCA to the LAD, a higher S zone appears at the LCA-LAD junction. Finally, the flow patterns in the LAD and LCX are different, introducing an asymmetry in the vascular tree. This difference is more noticeable in the post catheter injection period. As a consequence of the change in the S distribution, particles were observed to adhere more at the walls of the LAD rather than in the LCX. For both particle sizes, this is shown in Figure 5 and additional details are provided in Supplementary Figure 6.

Third, the contribution of the over-expression of receptor molecules on particle vascular deposition is investigated. For this, the surface density m_r in the LAD is increased by a factor of 10 compared to other regions in the vascular tree. A side-by-side comparison of the time evolution for the particle distribution is presented in Figure 6. Quite expectedly, particle concentration in the LAD is observed to be larger by almost an order of magnitude compared to the previous case, with no receptor over-expression. Note that the vascular deposition parameter Π grows almost linearly with m_r . Particle adhesion is considerably enhanced because of the greater receptor availability that promotes specific interaction and increases the likelihood of ligand-receptor bond formation. It is also very interesting to observe that the increased receptor density tends to support a larger particle deposition within the recirculation zone as compared to other regions (Supplementary Figure 7). Note that the surface properties of the particles, such as density and type of ligand molecules, are accounted for in the model through the parameters m_l (surface density of ligands on the particle surface); K_a^0 (ligand-receptor affinity) and Δ (separation distance at equilibrium) in Eqs. (15-17). Therefore, the model can also be applied to explore different particle design

scenarios such as multivalent targeting, PEGylation and the inclusion of polymer spacers in between ligand molecules and the particle surface.

The results presented herein demonstrate that there are sites within the analyzed vascular network where larger particles ($2.0\ \mu\text{m}$) would tend to adhere more avidly than smaller particles ($0.5\ \mu\text{m}$). This is in qualitative agreement with the data reported in the recent work by the group of Dr. Eniola-Adefeso [52]. The vascular deposition of particles depends on the fine balance between hydrodynamic dislodging forces and interfacial adhesion forces. As a consequence, there is an optimal particle size that maximizes adhesion (see [30] and Suppl. Materials). The larger the adhesion forces (i.e., higher density of receptors/ligands and/or higher ligand-receptor affinity) and the smaller the shear rates, the larger the optimal particle size. This biphasic behavior is also evident in [52] for aVCAM-1 decorated particles, exposed to a peak wall shear rate of $200\ \text{s}^{-1}$, presenting an optimal particle size of $2\ \mu\text{m}$. Indeed, additional information on the *in vivo* local hydrodynamic conditions; level of expression of vascular receptors and overall animal particle biodistribution would be required to provide a more accurate interpretation of the experimental results described in [52].

Conclusion

The computational framework described in this work allows us to quantify over time the distribution of the shear stresses at the wall and the volumetric concentration and wall surface density of nanoparticles injected in an authentic vascular network. This information is provided as a function of physiologically relevant patient-specific attributes, such as the architecture of the vasculature; the expression of endothelial receptor molecules; and the cardiac cycle, and depends on specific properties of the nanoparticles that can be finely controlled during the fabrication process, such as the geometry and surface properties (electrostatic charge, ligand density). While this work mainly focuses on the dependence of particle size on adhesion, information such as the vessel permeability and the nanoparticle shape, surface and stiffness can be readily implemented in the current formulation.

The presented results demonstrate that the adhesion pattern of intravascularly injected particles follows the distribution of the wall shear rates and is therefore significantly affected by the vascular geometry. Larger particles ($2.0\ \mu\text{m}$ in diameter) adhere more in the lower branches of the arterial tree, where the wall shear rates S are moderate ($< 200\ \text{s}^{-1}$); whereas smaller particles ($0.5\ \mu\text{m}$ in diameter) adhere more in the upper branches, where S is higher. It is also shown that as the branching angle in the arterial tree increases, the adhesion patterns become non-symmetric: patients with larger branching angles ($\approx 106.8^\circ$) would receive more nanoparticles in the LAD than in the LCX. On the other hand, nanoparticles would distribute equally in the two arterial branches for patients with smaller branching angles ($\approx 76.8^\circ$). Additionally, upregulation in the expression of vascular receptors is responsible for a non-symmetric and non-uniform vascular adhesion of the nanoparticles. These results clearly emphasize the importance of including patient-specific information for a proper selection of vascular delivery systems.

Future Perspective

In the near future, the following scenarios can be envisioned where computational modeling and nanoparticle engineering would be intimately integrated. Currently, MRI and CT are the most easily accessible, minimally invasive systems for whole human body imaging and, in conjunction with ultrasonic measurements, can provide information on the three-dimensional architecture and velocity field in a patient-specific vasculature. Nanoparticles can be engineered as potent MRI, or CT, contrast agents (imaging nanoconstructs) [53-56],

molecularly targeted to a specific receptor family expressed over the diseased endothelial walls. This could be the integrin family on the tumor vasculature, inflammatory adhesion molecules in cardiovascular diseases and several others [57]. The number of adhering imaging nanoconstructs can be quantified by relating the contrast enhancement measured by the clinical scanner with the imaging properties of the single nanoconstruct. Knowing the number of adhering nanoparticles, the vascular geometry and mean hydrodynamic conditions, the computational model can be used to back calculate the mean receptor surface density following a reverse engineering approach. This would be extremely useful for the *in vivo* rapid screening of potential vascular targets in individual patients [57]. With all this information at hand, the optimal particle configuration, in terms of size, shape, surface and stiffness can be identified using the computational models with the objective of maximizing drug release at the target site while minimizing non-specific sequestration in healthy tissue. Indeed, these scenarios are within reach but can only be achieved with an orchestrated development of potent, safe nanoparticle-based imaging tools and accurate, efficient computational methods.

Executive Summary

Introduction

- Drug biodistribution, bioavailability, efficacy and toxicity are unavoidably patient-specific.
- Computational models are utilized to predict the deposition of nanoparticles in a patient-specific arterial tree as a function of the vascular architecture, flow conditions, receptor surface density and nanoparticle properties.

Materials & Methods

- A 3D NURBS model of the patient-specific coronary artery tree was reconstructed from CT imaging data
- A Navier-Stokes solver coupled to a scalar advection diffusion equation was employed within the Finite Element based Isogeometric Analysis framework to simulate blood flow and particle transport in the coronary artery. A special boundary condition for particle adhesion to the vessel wall was implemented.
- The particle adhesion model was validated against *in vitro* parallel plate flow chamber experiments for a range of spherical particle size and wall shear rates. There is an optimal particle size that maximizes adhesion. The larger the adhesion forces (i.e., higher density of receptors/ligands and/or higher ligand-receptor affinity) and the smaller the shear rates, the larger the optimal particle size. The model accurately predicted this complex, biphasic behavior for particle deposition under flow.

Results & Discussion

- Patient-specific attributes, such as the vascular architecture, blood flow and surface density of endothelial receptors, affect the deposition pattern of systemically injected nanoparticles.
- The deposition pattern for nanoparticles correlates with the spatio-temporal distribution of the wall shear rates.

Future perspective

- Multiscale computational modeling and novel nanoparticle-based contrast agents, enabling vascular imaging over multiple scales, could provide sufficient information for personalizing the delivery of therapeutic and imaging molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Reconstructing the patient-specific vascular geometry

The image shows, from left to right, the isocontour of a human heart, path extraction and editing of a small bifurcation portion from the left coronary artery (LCA) and reconstruction of the geometry ready for Isogeometric Analysis. Also, a nanoparticle with its ligand molecules is shown interacting with the receptor molecules decorating the surface of the endothelial cells in the vasculature.

Figure 2. Comparison between *in silico* and *in vitro* results

The number of adhering particles n_{adh} per unit surface area A normalized by the total number of injected particles n_{inj} is plotted as a function of the particle diameter d_p and for three different wall shear rates: (A) $S = 10 \text{ s}^{-1}$, (B) $S = 75 \text{ s}^{-1}$ and (C) $S = 200 \text{ s}^{-1}$. Black crosses with the standard deviation bars represent the experimental results obtained in a parallel plate flow chamber apparatus. The gray areas represent the *in silico* results obtained for values of the parameters α_1 (left) and α_2 (right) varying within $\pm 5\%$ of their average values ($\alpha_1 = 0.023$) and ($\alpha_2 \approx 9.44 \times 10^9 \text{ \#/m}^2$ for $d_p \approx 0.7 \text{ \mu m}$; $1.388 \times 10^9 \text{ \#/m}^2$ for $d_p \approx 5 \text{ \mu m}$; and $1.031 \times 10^9 \text{ \#/m}^2$ for $d_p \approx 7 \text{ \mu m}$).

Figure 3. Nanoparticle transport in a patient-specific vascular tree

(A) Schematic of the coronary artery (branches identified) with the inlet velocity profile (inset at the right) and applied boundary conditions. (B)-(F) Volumetric concentration C of $0.5 \mu\text{m}$ nanoparticles, normalized by the concentration at the catheter outlet C^0 , at various times t post injection: (B) $t = 0.2 \text{ s}$, (C) $t = 1 \text{ s}$, (D) $t = 5 \text{ s}$, (E) $t = 10 \text{ s}$, and (F) $t = 14 \text{ s}$.

Figure 4. Nanoparticle adhesion to the vessel walls: effect of nanoparticle size

The normalized surface density of adhering nanoparticles is plotted along the arterial tree at various times t post injection, namely (A) $t = 5$ s, (B) $t = 10$ s and (C) $t = 14$ s. The left and right columns present *in silico* data for the 0.5 and 2.0 μm particle, respectively, in terms of particle number per unit area normalized by the injected dose [cm^{-2}].

Figure 5. Nanoparticle adhesion to the vessel walls: effect of vascular geometry

The normalized surface density of adhering nanoparticles is plotted along the arterial tree at $t = 14$ s, post injection. The left and right columns present *in silico* data for the 0.5 and 2.0 μm particles, respectively. The top and bottom rows present *in silico* data for the smaller (76.8°) and larger (106.8°) branching angles, respectively. Data are presented in particle number per unit area normalized by the injected dose [cm^{-2}].

Figure 6. Nanoparticle adhesion to the vessel walls: effect of surface density of vascular receptors
 The normalized surface density of $0.5\ \mu\text{m}$ adhering nanoparticles is plotted along the arterial tree at various times t post injection: (A) $t = 1\ \text{s}$, (B) $t = 5\ \text{s}$ and (C) $t = 14\ \text{s}$. Data are presented for a uniform receptor density ($m_r = 10^9\ \text{\#/cm}^2$) along the vasculature (left column) and for a left anterior descending artery receptor density 10 times larger than that in the LCA and LCX (right column). Note that the color map scales are different for the two cases and give the particle number per unit area normalized by the injected dose [cm^{-2}].

Table 1

Adhesion model parameters used.

Parameters	Value
Surface density of ligand molecules	$m_l = 10^{15} \text{ \#/m}^2$
Surface density of receptor molecules	$m_r = 10^{13} \text{ \#/m}^2$
Ligand-receptor affinity constant at zero load	$K_a^0 = 2.3 \times 10^{-7} \text{ m}^2$
Characteristic length of ligand-receptor bond	$\lambda = 1 \times 10^{-10} \text{ m}$
Dynamic viscosity of water	$\mu = 0.001 \text{ N-s/m}^2$
Drag coefficient on the spherical particle	$F^s = 1.668$