

## IN-SILICO SIMULATION OF CHOLESTEROL DEPOSITION AND ATHEROSCLEROTIC PLAQUE GROWTH IN HUMAN ARTERIES: A COMPREHENSIVE REVIEW

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### Abstract

Atherosclerosis is a progressive disease driven by the accumulation of cholesterol-rich low-density lipoprotein (LDL) particles within the arterial wall, followed by chronic inflammation, smooth muscle cell (SMC) migration, and extracellular matrix remodeling. These processes lead to plaque formation, luminal narrowing, and ultimately acute cardiovascular events. In recent years, in silico modeling has emerged as a powerful approach for investigating the complex, multiscale mechanisms linking systemic lipid metabolism, local hemodynamics, vascular wall biology, and plaque progression. This review provides a comprehensive overview of computational models of LDL transport, cholesterol deposition, and atherosclerotic plaque development in human arteries. We first summarize the biological basis of cholesterol metabolism and the response-to-retention paradigm underlying early atherogenesis. We then examine key biophysical determinants of LDL deposition, including wall shear stress (WSS), endothelial permeability, and transmural transport. Subsequently, we categorize existing modeling approaches into continuum mass-transport models, multilayer fluid–structure interaction (FSI) frameworks, multiscale reaction–diffusion models, hybrid CFD–agent-based models, and data-driven or machine-learning-based surrogates. We further discuss major applications of these models, including mechanistic insights into plaque initiation, patient-specific risk stratification, and the integration of systemic lipid dynamics with local arterial processes. Finally, we highlight current challenges, such as parameter uncertainty, limited validation data, and high computational cost, and outline future directions toward patient-specific “digital artery” models that combine multiscale physics with data-driven methods. With continued advances in computational techniques, data integration, and model validation, in silico approaches have the potential to become integral tools for understanding atherosclerosis and supporting personalized cardiovascular risk assessment and therapeutic decision-making.

## 1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide, accounting for a substantial proportion of deaths related to ischemic heart disease and stroke. Central to the pathogenesis of ASCVD is the progressive accumulation of cholesterol-rich lipoproteins, particularly low-density lipoprotein (LDL), within the arterial wall. Over the past several decades, extensive epidemiological, genetic, and interventional studies have firmly established the “LDL hypothesis,” which states that elevated plasma LDL cholesterol is a causal driver of atherosclerosis, and that its reduction leads to a proportional decrease in cardiovascular risk [1-4]. This relationship is often described as log-linear, with even modest reductions in LDL levels yielding measurable clinical benefits.

Despite this well-established systemic association, atherosclerosis is fundamentally a localized disease of the arterial wall. Lesions develop preferentially at specific anatomical sites, such as arterial bifurcations, curvatures, and branching regions, rather than uniformly throughout the vasculature. These regions are characterized by complex flow patterns, including low, oscillatory, and disturbed wall shear stress (WSS), which play a critical role in modulating endothelial cell function. Endothelial dysfunction in such regions leads to increased permeability, enhanced leukocyte adhesion, and a pro-inflammatory state that promotes the retention and modification of LDL particles within the subendothelial space.

The currently accepted “response-to-retention” paradigm provides a mechanistic framework for understanding early atherogenesis. According to this concept, the subendothelial retention of apolipoprotein B-containing lipoproteins—especially LDL—initiates a cascade of biochemical and cellular events. Retained LDL undergoes oxidative and enzymatic modifications, transforming into oxidized LDL (oxLDL), which is highly pro-inflammatory. This triggers recruitment of circulating monocytes, their differentiation into macrophages, and subsequent uptake of modified lipoproteins, leading to foam cell formation. Over

time, this process contributes to the development of a lipid-rich necrotic core, smooth muscle cell (SMC) proliferation, extracellular matrix deposition, and formation of a fibrous cap, all of which define the evolving atherosclerotic plaque.

While experimental and clinical studies have provided invaluable insights into these processes, they are inherently limited in their ability to simultaneously resolve the multiscale nature of atherosclerosis. The disease spans multiple spatial and temporal scales—from molecular interactions and cellular behavior to tissue-level remodeling and whole-artery hemodynamics—making it difficult to isolate causal relationships using conventional approaches alone. Moreover, direct measurement of key variables, such as local LDL concentration within the arterial wall or spatially resolved endothelial permeability, remains challenging in vivo.

In this context, in silico modeling has emerged as a powerful complementary approach for studying atherosclerosis. Advances in computational fluid dynamics (CFD), fluid–structure interaction (FSI), and multiscale modeling have enabled detailed investigation of the interplay between blood flow, arterial wall mechanics, and biochemical transport processes. These models allow researchers to simulate how systemic factors, such as plasma LDL levels and blood pressure, interact with local hemodynamic conditions to influence LDL transport, deposition, and subsequent plaque development [4-7].

Early computational models primarily focused on simplified representations of blood flow and mass transport, often using idealized geometries and steady-state assumptions. However, more recent efforts have incorporated patient-specific arterial geometries derived from medical imaging, pulsatile flow conditions, and detailed representations of the arterial wall as a multilayered porous medium. In addition, multiscale models now integrate biochemical reactions, cellular dynamics, and tissue remodeling processes, providing a more comprehensive description of plaque evolution over time. Hybrid approaches combining CFD with agent-based models (ABMs), as well as data-

driven and machine learning-based surrogates, further expand the capability to capture complex, nonlinear interactions across scales [8-12].

Another emerging frontier is the integration of whole-body cholesterol metabolism models with local arterial simulations. Such coupled frameworks aim to bridge the gap between systemic lipid regulation and site-specific plaque progression, enabling the development of “digital twin” models of individual patients. These models hold significant promise for personalized risk assessment, prediction of disease progression, and optimization of therapeutic strategies, including lipid-lowering interventions and vascular procedures.

Despite these advances, several challenges remain. These include uncertainties in model parameters, limited availability of high-resolution validation data, and the computational cost associated with fully coupled multiscale simulations [13]. Addressing these issues is essential for translating

in silico models from research tools into clinically actionable platforms.

In this review, we provide a comprehensive overview of current computational approaches for modeling cholesterol deposition and atherosclerotic plaque growth in human arteries [14]. We begin by summarizing the biological mechanisms underlying cholesterol transport and retention, followed by a discussion of key biophysical determinants such as hemodynamics and endothelial permeability [15]. We then categorize and analyze major classes of in silico models, including continuum transport models, multilayer FSI formulations, multiscale reaction-diffusion systems, hybrid CFD-agent-based frameworks, and data-driven surrogates [16-19]. Finally, we discuss current limitations, validation challenges, and future directions toward the development of patient-specific digital artery models that integrate systemic and local processes [20-25].

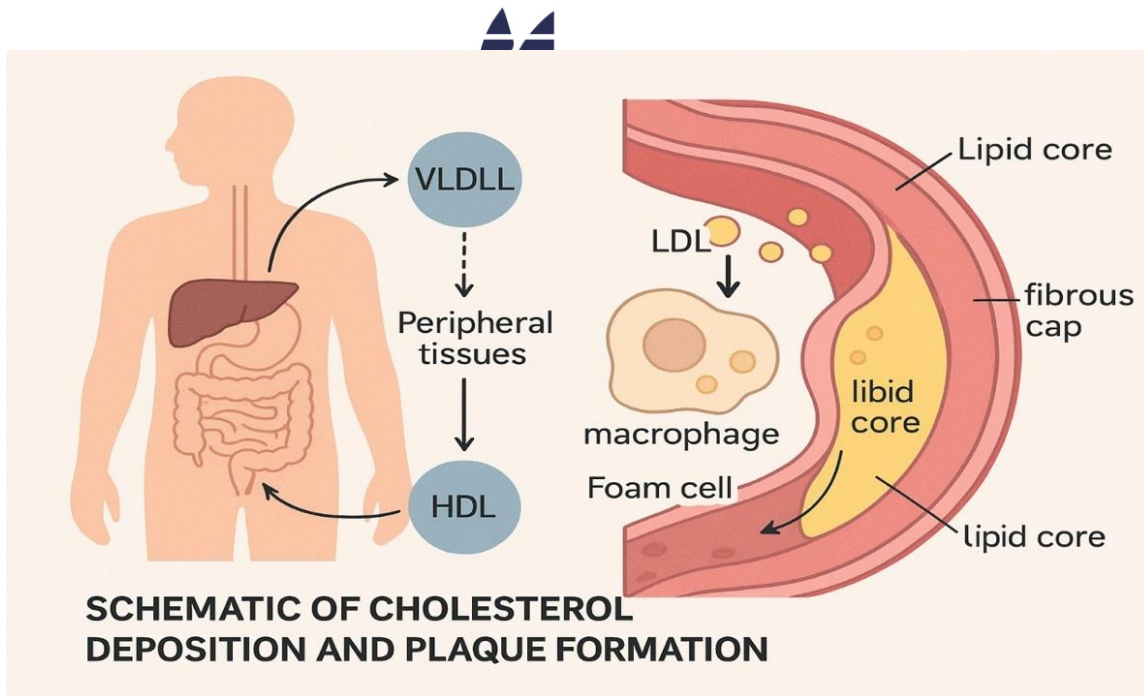


Figure 1: Schematically links systemic cholesterol metabolism with local LDL deposition and the plaque growth

## 2. Biological basis of cholesterol deposition

### 2.1 Cholesterol metabolism and lipoprotein transport

The maintenance of whole-body cholesterol homeostasis is a tightly regulated and highly coordinated process involving multiple organs,

pathways, and feedback mechanisms. It encompasses intestinal absorption of dietary cholesterol, de novo hepatic synthesis, packaging and secretion into very-low-density lipoprotein (VLDL) particles, and subsequent intravascular metabolism leading to the formation of intermediate-density lipoprotein (IDL) and ultimately low-density lipoprotein (LDL). Circulating LDL particles deliver cholesterol to peripheral tissues primarily through receptor-mediated uptake via the LDL receptor pathway, a process that is finely controlled by intracellular cholesterol levels. In parallel, excess cholesterol is removed from peripheral tissues through efflux mechanisms mediated by ATP-binding cassette (ABC) transporters, such as ABCA1 and ABCG1, and is transported back to the liver via high-density lipoprotein (HDL) in a process known as reverse cholesterol transport (RCT) [2], [3], [8], [9].

This dynamic balance between cholesterol influx, synthesis, distribution, and efflux ensures stable plasma cholesterol levels under physiological conditions. However, disturbances in any component of this network—such as increased hepatic production of apoB-containing lipoproteins, reduced LDL receptor activity, impaired HDL-mediated efflux, or genetic dysregulation of lipid metabolism—can lead to elevated circulating LDL-cholesterol concentrations. Such elevations significantly enhance the transvascular “flux” of LDL particles across the endothelium into the arterial wall, thereby increasing the likelihood of subendothelial retention and initiating the early stages of atherogenesis. Importantly, this flux is not solely determined by plasma LDL levels but also by local vascular factors, including endothelial permeability and hemodynamic conditions, which modulate the rate of LDL entry into the intimal layer.

To quantitatively capture these complex systemic processes, systems biology and ordinary differential equation (ODE)-based models have been developed to represent whole-body cholesterol metabolism in an integrative framework. These models typically incorporate compartments representing the liver, intestine,

plasma, and peripheral tissues, and describe the kinetics of lipoprotein production, transformation, and clearance through coupled nonlinear equations. Such modeling approaches have proven valuable in simulating the dynamic response of lipid profiles to pharmacological interventions, including statins, PCSK9 inhibitors, and other lipid-lowering therapies, enabling prediction of time-dependent changes in LDL and HDL concentrations under different treatment regimens [8], [10], [12].

Importantly, these whole-body models serve as a critical complement to local arterial simulations. While computational fluid dynamics (CFD) and mass-transport models focus on spatially resolved processes within specific arterial segments, they require physiologically realistic boundary conditions to accurately represent LDL availability at the blood-wall interface. Systems-level models provide these inputs by generating time-varying plasma LDL concentrations that reflect both baseline physiology and therapeutic modulation. The integration of systemic lipid metabolism models with local hemodynamic and transport simulations thus enables a multiscale representation of atherosclerosis, linking global cholesterol regulation with site-specific LDL deposition and plaque development.

## 2.2 Response-to-retention and inflammation

The response to injury concept suggested that endothelial injury triggers leukocyte recruitment and SMC proliferation [5], [6]. Later work emphasized that subendothelial retention and modification of LDL (aggregation, oxidation) are starting events that elicit a chronic inflammatory response “response-to-retention” [4], [7], [13]. Macrophages ingest modified LDL and become foam cells, creating a lipid core while SMCs and fibroblasts form a fibrous cap.

Most simulation frameworks that emphasize on “cholesterol deposition” explicitly model at least LDL transport and retention, more advanced schemes also include oxLDL, inflammatory mediators, macrophages, SMCs and necrotic core formation [24], [28], [45].



### 3. Biophysical determinants of cholesterol deposition

#### 3.1 Hemodynamics and wall shear stress

Several computational fluid dynamics (CFD) studies have consistently demonstrated that regions of low and oscillatory wall shear stress (WSS) are strongly associated with the initiation and progression of atherosclerosis, whereas regions exposed to high, steady, and unidirectional WSS tend to exhibit atheroprotective characteristics [18], [19], [32]. This spatial correlation between hemodynamic forces and lesion localization has been widely observed in both experimental and clinical studies, particularly at arterial bifurcations, curvatures, and branching points where complex flow patterns arise. In such regions, flow separation, recirculation zones, and temporal fluctuations in shear stress create a hemodynamic environment that is conducive to endothelial dysfunction and lipid accumulation.

Adverse WSS patterns exert a profound influence on endothelial cell biology through mechanotransduction pathways, whereby mechanical forces are translated into biochemical signals. Specifically, low and oscillatory WSS has been shown to upregulate the expression of pro-inflammatory and pro-atherogenic genes, including adhesion molecules (e.g., VCAM-1, ICAM-1), chemokines, and cytokines, which collectively promote leukocyte recruitment and vascular inflammation. In addition, these flow conditions increase endothelial permeability by disrupting tight junction integrity and enhancing

the formation of leaky junctions, thereby facilitating the transendothelial transport of LDL particles into the subendothelial space. Furthermore, disturbed flow promotes endothelial dysfunction, characterized by reduced nitric oxide bioavailability, increased oxidative stress, and impaired vasoregulatory capacity, all of which contribute to a pro-atherogenic vascular environment.

Another important consequence of adverse hemodynamics is the development of near-wall concentration polarization of LDL. Under conditions of low shear stress, convective transport away from the vessel wall is reduced, allowing LDL particles to accumulate in the near-wall region. This creates a localized increase in LDL concentration adjacent to the endothelium, which enhances the concentration gradient driving transmural transport into the arterial wall. As a result, even in the absence of markedly elevated systemic LDL levels, regions of disturbed flow can experience disproportionately high LDL influx.

CFD-based simulations in anatomically realistic models of the aortic arch, coronary artery bifurcations, and carotid arteries have quantitatively confirmed these phenomena. These studies show that regions characterized by disturbed flow patterns consistently exhibit elevated near-wall LDL concentrations and increased transmural flux compared to regions with stable, laminar flow [32], [33], [41], [43]. Such findings provide strong mechanistic support for the hypothesis that local hemodynamic conditions play a critical role in modulating lipid transport and deposition, thereby linking systemic risk factors with the focal nature of atherosclerotic plaque development.



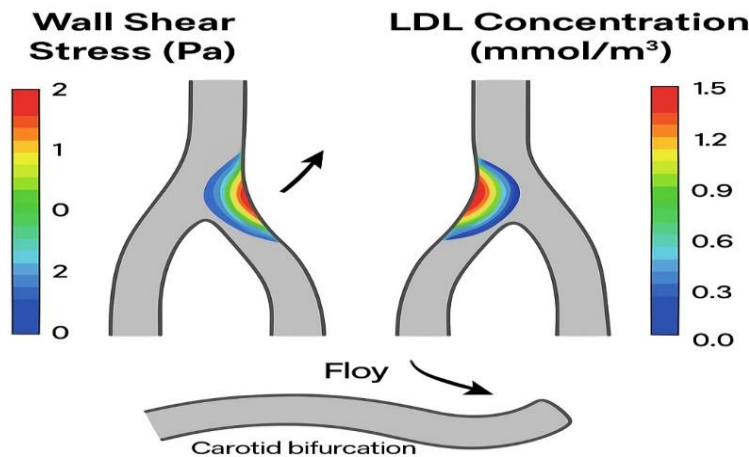


Figure 2: A typical CFD result comparing WSS and LDL concentration at a carotid bifurcation

### 3.2 Endothelial permeability and transmural LDL flux

Transendothelial transport of low-density lipoprotein (LDL) across the arterial wall is a complex process governed by multiple interacting physical and biological mechanisms. This transport is primarily influenced by endothelial permeability, which is determined by the structural and functional integrity of the endothelial layer. Under normal physiological conditions, tight junctions between endothelial cells restrict the passage of macromolecules, thereby limiting LDL entry into the arterial wall. However, the presence of leaky junctions—often associated with endothelial cell turnover such as mitosis or apoptosis—creates localized pathways that significantly enhance LDL permeability. The density and spatial distribution of these leaky junctions play a critical role in regulating the overall rate of LDL infiltration into the subendothelial space.

In addition to permeability, filtration velocity driven by transmural pressure differences across the vessel wall is a key determinant of LDL transport. This process is commonly modeled using Darcy’s law, which describes fluid flow through a porous medium. Elevated transmural pressure, as observed in hypertensive conditions, increases the convective transport of plasma and solutes, including LDL, across the endothelium and into deeper layers of the arterial wall. This pressure-driven convection acts in conjunction with diffusive transport, which is governed by

concentration gradients between the lumen and the arterial wall.

Once LDL particles enter the arterial wall, their movement is further regulated by diffusion and binding interactions within the different layers of the vessel wall, namely the intima, media, and adventitia [30], [34], [37]. The extracellular matrix, particularly proteoglycans in the intimal layer, has a high affinity for apolipoprotein B-containing lipoproteins, promoting LDL retention and accumulation. This binding not only slows the outward diffusion of LDL but also facilitates its modification (e.g., oxidation and aggregation), thereby enhancing its atherogenic potential.

To capture these multilayer transport phenomena, computational models often represent the arterial wall as a porous medium composed of distinct layers, each characterized by specific permeability coefficients, diffusivities, and reaction parameters. Such multilayer porous-media models enable a more physiologically realistic description of LDL transport and retention across the arterial wall [34], [37], [46]. These models have demonstrated that pathological conditions, such as hypertension, increased density of leaky junctions, or alterations in the composition of the intimal extracellular matrix (e.g., increased proteoglycan content), can substantially enhance LDL retention within the wall, even when plasma LDL levels remain constant. This highlights the critical interplay between systemic lipid levels and local vascular properties in determining the

susceptibility to atherosclerotic plaque development.

atherosclerosis: continuum mass-transport models, multilayer FSI, multiscale reaction-diffusion models, hybrid CFD agent based models and data-driven surrogates.

4. Classes of simulation models (overview)

Table 1: precises’ the main classes of in-silico models of cholesterol deposition and

Table 1. Main classes of in-silico models for cholesterol deposition and atherosclerosis

Model class	Key idea	Spatial / temporal scale	Strengths	Limitations	Example refs
Continuum LDL transport (blood + porous wall)	Navier-Stokes in lumen coupled with convection-diffusion-reaction in multilayer wall	3D lumen + wall; hemodynamics (cardiac cycles) to months (via quasi-steady approximations)	Mechanistically clear; directly links WSS, permeability and LDL flux	Often ignores cellular biology; parameters uncertain	[34], [41], [43], [46]
Multilayer FSI models	Coupled blood flow and deformable arterial wall with layer-specific transport	3D lumen + wall; resolves pulsatile deformation	Captures effect of wall stiffness, hypertension and remodeling on LDL uptake	High computational cost; difficult to calibrate	[31], [37], [38], [47]
Multiscale reaction-diffusion plaque models	PDE system for LDL, oxLDL, macrophages, SMCs, ECM etc.	1D-3D; days-years	Integrates lipid transport with cellular dynamics and plaque structure	Many parameters; biology simplified; often idealized geometry	[24]-[28], [35], [45]
Hybrid CFD-agent-based models	CFD/FSI for hemodynamics + ABM for cell populations	2D-3D; multi-scale in time	Captures stochastic cell behavior and micro-scale structure; directly links WSS and cell-level events	Very expensive; complex to implement; validation challenging	[22], [29], [33]
Whole-body + local artery “digital twin” models	ODE models of cholesterol metabolism and ASCVD + local CFD/transport in specific arteries	Whole body (systemic lipids) + specific arterial segments	Allows simulation of effect of systemic therapies on local plaque	Still in early stage; data-hungry; model credibility needs formal assessment	[8], [10], [12], [29], [32], [52]

Model class	Key idea	Spatial / temporal scale	Strengths	Limitations	Example refs
Data-driven / neural-network surrogates	ML models approximate outputs of mechanistic simulations	Same as training data; fast evaluation	Enables real-time prediction, UQ and optimization	Requires large, diverse training sets; may lose transparency	[23], [30], [50], [51]

**4.1 Continuum LDL transport models**

Early computational frameworks for studying cholesterol deposition were primarily based on continuum descriptions that couple blood flow dynamics with mass transport of low-density lipoprotein (LDL). In these models, blood flow within the arterial lumen is typically governed by the Navier–Stokes equations, which describe the conservation of mass and momentum for viscous, incompressible fluids. These hemodynamic equations are then coupled with convection–diffusion–reaction equations to model the transport of LDL particles both within the flowing blood and across the arterial wall [34], [41], [42]. Within this framework, the arterial wall is commonly represented as a multilayer porous medium, where LDL transport is driven by a combination of convection (associated with transmural filtration flow), diffusion (driven by concentration gradients), and biochemical interactions such as binding and degradation. Darcy’s law is often employed to describe the fluid flow through the porous wall, while layer-specific transport properties—such as permeability, diffusivity, and reaction rates—are assigned to distinct regions including the intima, media, and adventitia. This approach allows for a mechanistic representation of how systemic LDL levels and local hemodynamic forces jointly regulate LDL infiltration and retention.

Continuum LDL transport models have been widely applied across a range of geometrical and physiological settings. These include simplified, idealized geometries such as stenotic tubes and arterial bifurcations, which are useful for isolating fundamental transport mechanisms and exploring the relationship between wall shear stress (WSS) and LDL deposition [41], [42], [46]. More

advanced studies have extended these models to patient-specific arterial geometries reconstructed from medical imaging modalities such as computed tomography (CT) and magnetic resonance (MR), enabling spatially resolved predictions of LDL concentration and flux in anatomically realistic settings [43]. Additionally, sensitivity analyses have been conducted using these models to identify the most influential parameters governing LDL transport, such as endothelial permeability, filtration velocity, and diffusion coefficients, thereby highlighting key drivers of atherogenesis [27], [46].

Despite their strengths in providing mechanistic insight and computational efficiency, continuum models often rely on simplifying assumptions, such as steady or quasi-steady flow conditions and limited representation of cellular and biochemical complexity. As such, they serve as a foundational but incomplete description of the atherosclerotic process.

**4.2 Multilayer fluid structure interaction (FSI) models**

To address the limitations of rigid-wall assumptions in continuum models, fluid–structure interaction (FSI) frameworks have been developed to incorporate the mechanical behavior of the arterial wall and its interaction with pulsatile blood flow. In these models, the fluid domain (blood flow) and the solid domain (arterial wall) are fully coupled, allowing simulation of wall deformation in response to time-varying pressure and flow conditions. This is particularly important for capturing the physiological reality of compliant arteries, where cyclic stretching and relaxation occur with each cardiac cycle.



Multilayer FSI models extend this approach by representing the arterial wall as a composite structure with distinct mechanical and transport properties assigned to individual layers. These models have been used to investigate how wall elasticity, stiffness variations, and pulsatile hemodynamics influence LDL uptake and distribution under both normal and pathological conditions [37], [38]. For example, increased arterial stiffness—often associated with aging or disease—can alter local flow patterns and WSS distributions, thereby indirectly affecting LDL transport.

Key findings from multilayer FSI studies indicate that wall motion significantly modifies local hemodynamic conditions, including WSS magnitude and direction, which in turn influences endothelial permeability and transmural LDL flux. Furthermore, elevated blood pressure (hypertension) has been shown to increase filtration velocity and enhance LDL entry into the arterial wall, while progressive wall thickening during plaque development may act as a partial barrier, reducing further LDL penetration in later stages of disease [37], [38]. These dynamic interactions highlight the importance of coupling mechanical and transport processes in realistic simulations of atherosclerosis.

Beyond LDL transport, FSI models are also widely used to assess biomechanical stresses within atherosclerotic plaques, particularly within the fibrous cap. Such analyses are critical for evaluating plaque stability and the risk of rupture, which is a major trigger of acute cardiovascular events such as myocardial infarction and stroke [31]. However, the increased physiological realism of FSI models comes at the cost of significantly higher computational complexity and challenges in parameter calibration.

### 4.3 Multiscale plaque-growth models

Atherosclerosis is inherently a multiscale disease, involving tightly coupled processes that span molecular, cellular, tissue, and organ levels over widely varying time scales. To capture this complexity, multiscale plaque-growth models have been developed that integrate hemodynamics,

biochemical transport, and cellular dynamics into a unified mathematical framework. These models are typically formulated as systems of coupled partial differential equations (PDEs) that describe the spatiotemporal evolution of multiple interacting species, including LDL, oxidized LDL (oxLDL), inflammatory mediators, macrophages, foam cells, smooth muscle cells (SMCs), and extracellular matrix components such as collagen [24], [28], [35].

A key strength of multiscale models is their ability to resolve processes occurring over different temporal scales. Fast processes, such as pulsatile blood flow and associated hemodynamic forces, are captured over timescales of seconds corresponding to cardiac cycles. Intermediate processes, including LDL transport, oxidation, and cytokine signaling, evolve over days to weeks. In contrast, long-term processes such as plaque growth, arterial remodeling, and changes in tissue composition occur over months to years. By integrating these dynamics, multiscale models provide a comprehensive description of plaque initiation, progression, and structural evolution.

These models have been successfully applied to investigate the formation of lipid-rich necrotic cores, the development of fibrous caps, and the spatial distribution of inflammatory cells within plaques. Furthermore, extensions of multiscale frameworks have been used to study related vascular pathologies, such as atherosclerotic aneurysm formation and arterial remodeling under conditions of chronically low or oscillatory WSS [25], [28].

Despite their comprehensive nature, multiscale models face significant challenges, including the need for a large number of parameters—many of which are difficult to measure experimentally—as well as high computational cost. Nevertheless, they represent a critical step toward realistic, predictive simulations of atherosclerosis and form the foundation for future patient-specific “digital twin” models that integrate systemic and local disease mechanisms.

4.4 Hybrid CFD-agent-based models

Hybrid models combine macroscopic CFD/transport with agent-based models (ABMs) of separate cells. ABMs capture stochastic cell

behavior, chemotaxis and clonal expansion [22], [29], [33]. A fully coupled hybrid CFD-ABM framework for coronary plaque progression was lately reported and is briefed in Table 2 [22]

Table 2. Selected computational studies of LDL/cholesterol deposition and plaque modelling

Study	Geometry setting	Physics / model	Main outputs	Key finding
Olgac et al. (2008) [41]	Axisymmetric stenotic model	CFD + wall mass transport	WSS and LDL patterns	Demonstrated correlation between low WSS regions and elevated LDL transport
Mpairaktaris et al. (2017) [43]	Patient-specific thoracic aorta	CFD + LDL transport in porous wall	Wall LDL concentration maps	Identified focal LDL hotspots in realistic geometries
Chen et al. (2021) [38]	Patient-specific left coronary bifurcation	Multilayer FSI + three-pore endothelial model	LDL uptake distribution	Showed that hypertension and elasticity strongly modulate LDL uptake
Liu et al. (2023) [26]	Idealized artery	Multiscale PDE model for LDL, oxLDL, cells	Plaque thickness, cell distributions	Reproduced early plaque growth and spatial patterns
Abi Younes et al. (2022) [25]	1D arterial segment	Reaction-diffusion model of inflammation	Macrophage/SMC profiles, lesion size	Explored role of inflammatory parameters on early lesion development
Johari et al. (2023) [36]	Carotid bifurcation with stent	CFD + LDL transport	LDL accumulation near stent struts	Showed dependence of LDL hotspots on stent design and positioning
Corti et al. (2020, 2021) [29], [33]	2D plaque cross-section	Hybrid CFD-ABM multiscale model	Plaque growth, composition, WSS	Demonstrated coupling between WSS, cell kinetics and plaque evolution
Caballero et al. (2025) [22]	Coronary artery	Fully coupled CFD-transport-ABM	Time-resolved plaque morphology	Provided comprehensive hybrid in-silico framework for plaque progression
Davies et al. (2023) [8]	Whole-body (no explicit geometry)	ODE model of cholesterol metabolism + plaque	LDL trajectories, plaque volume	Illustrated how LDL-lowering therapies impact long-term plaque growth

4.5 Data-driven and surrogate models

Machine-learning (ML) and neural-network-based surrogate models are increasingly being employed to accelerate computational workflows in atherosclerosis research, particularly for tasks such as parameter sweeps, optimization, and uncertainty quantification. Traditional high-fidelity models—such as CFD, fluid–structure interaction (FSI), and multiscale reaction–diffusion frameworks—are computationally expensive, often requiring substantial time and resources for a single simulation. This limitation becomes especially pronounced when exploring large parameter spaces or performing sensitivity analyses. To address this challenge, data-driven approaches have emerged as efficient alternatives or complements to physics-based models, enabling

rapid approximation of complex system behavior while retaining acceptable levels of accuracy.

One prominent approach involves the use of multiphysics-informed neural networks, which are trained to approximate the solutions of governing partial differential equations (PDEs) describing plaque growth and associated transport processes. These models incorporate physical laws—such as conservation equations—either directly into the loss function or through hybrid training strategies, thereby improving generalization and reducing the amount of training data required. Such approaches have demonstrated the ability to replicate spatiotemporal patterns of LDL transport, oxidation, and plaque evolution with significantly reduced computational cost compared to conventional solvers [23].

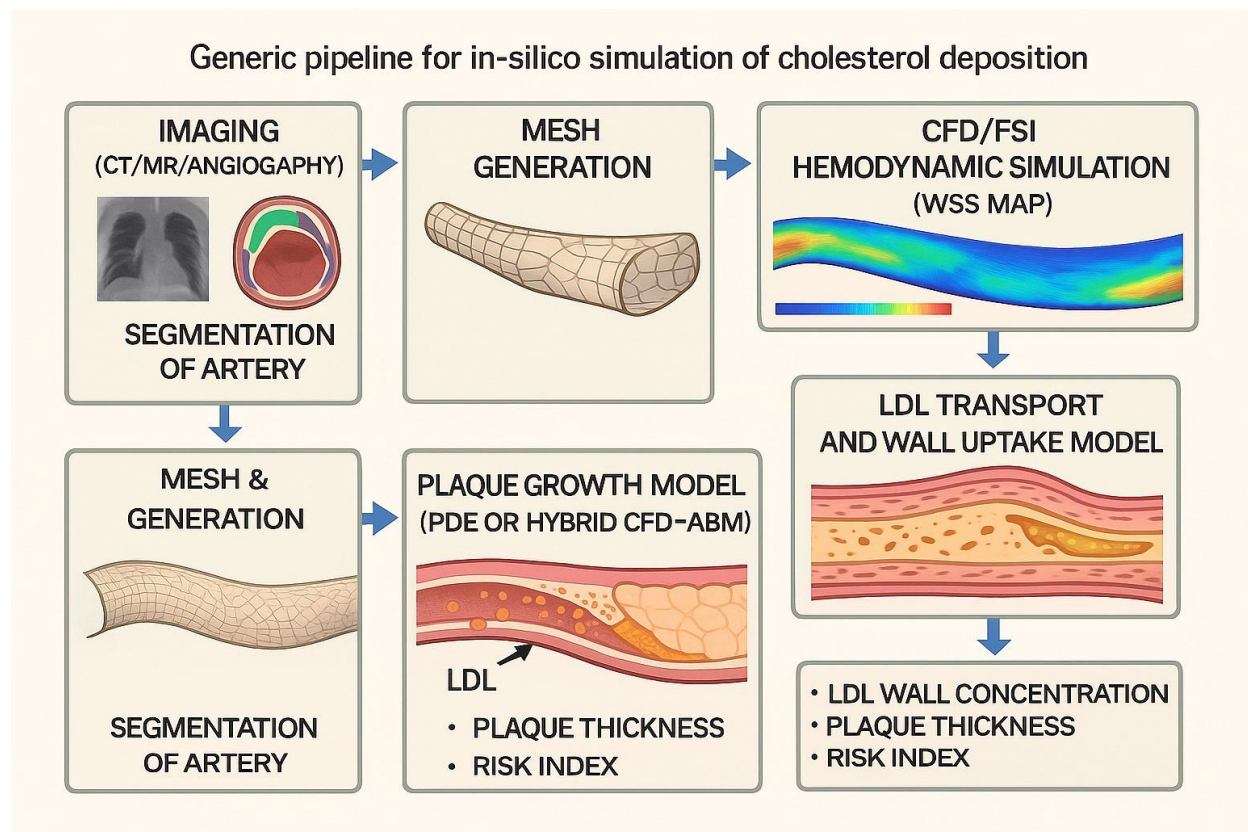


Figure 2: A generic simulation pipeline combining imaging, CFD/FSI, wall transport and plaque-growth modelling

5. Applications and case studies

5.1 Mechanistic insight

In silico modeling has significantly advanced the mechanistic understanding of atherosclerosis by enabling controlled investigation of complex

interactions between hemodynamics, transport phenomena, and vascular biology. One of the most consistent findings across computational studies is the critical role of wall shear stress (WSS) in regulating lipid transport and endothelial behavior. Specifically, regions exposed to low and oscillatory WSS have been shown to promote the formation of near-wall LDL concentration “hotspots,” which enhance the concentration gradient across the endothelium and lead to increased transmural LDL flux [18], [19], [32], [43]. These localized elevations in LDL exposure create favorable conditions for subendothelial retention and subsequent plaque initiation.

In addition to hemodynamic factors, systemic conditions such as hypertension play a crucial role in modulating LDL transport. Elevated blood pressure increases transmural filtration velocity, thereby enhancing the convective transport of LDL particles into the arterial wall. Computational models incorporating pressure-driven flow through porous media have demonstrated that even moderate increases in filtration velocity can substantially elevate LDL penetration and accumulation within the intima [30], [37]. This highlights the synergistic interaction between systemic risk factors and local vascular conditions in accelerating atherogenesis.

## 5.2 Patient specific risk stratification

One of the most promising applications of computational modeling in atherosclerosis is the development of patient-specific simulations for risk assessment and clinical decision-making. Advances in medical imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and intravascular imaging techniques, have enabled the reconstruction of anatomically accurate arterial geometries for individual patients. When combined with CFD-based transport models, these geometries allow for detailed mapping of hemodynamic parameters such as WSS, as well as spatially resolved predictions of LDL concentration and transmural flux.

Such patient-specific simulations are increasingly being used to identify “vulnerable” arterial

segments that are predisposed to plaque development and progression. These high-risk regions are typically characterized by a combination of adverse features, including low or oscillatory WSS, elevated LDL deposition, and unfavorable plaque morphology, such as thin fibrous caps or large lipid cores [20], [21], [32], [43]. By integrating these factors, computational models provide a more comprehensive assessment of risk than traditional metrics based solely on luminal stenosis.

## 5.3 Linking systemic lipids to local plaque growth

A key challenge in atherosclerosis research is bridging the gap between systemic lipid metabolism and localized plaque development. Whole-body cholesterol metabolism models [10], [12], [54], as well as integrated cholesterol-metabolism-plus-plaque models [8], [46], [40], provide a valuable framework for addressing this challenge. These models describe the dynamics of lipoprotein production, transformation, and clearance across different physiological compartments, enabling prediction of time-dependent changes in plasma LDL and HDL levels under various conditions, including pharmacological interventions.

By coupling these systemic models with local arterial simulations, it becomes possible to incorporate time-varying LDL concentrations as inlet boundary conditions at the blood-wall interface. This multiscale integration allows for the simulation of how long-term changes in systemic lipid levels—such as those induced by statins, PCSK9 inhibitors, or lifestyle modifications—translate into changes in local LDL deposition, plaque growth, and ultimately cardiovascular risk.

## 6. Limitations and Future Directions

Despite substantial progress, several limitations continue to constrain the accuracy, applicability, and clinical translation of *in silico* models of atherosclerosis. One of the primary challenges is parameter uncertainty, as many model inputs—such as endothelial permeability, reaction rates, and cellular kinetics—are difficult to measure

directly in vivo and may vary significantly across individuals and disease states. This heterogeneity introduces uncertainty into model predictions and complicates efforts to generalize findings.

Another important limitation is the simplification of biological processes. While many models incorporate key elements of lipid transport and inflammation, they often omit or oversimplify complex mechanisms such as detailed immune signaling networks, efferocytosis (clearance of apoptotic cells), calcification, and intraplaque hemorrhage. These processes play critical roles in plaque progression and destabilization, and their exclusion may limit the ability of models to accurately predict advanced disease behavior.

Validation remains a significant bottleneck, particularly for early-stage LDL deposition. Direct experimental or clinical measurements of LDL concentration within the arterial wall are scarce, making it difficult to rigorously validate model predictions. Most validation efforts rely on indirect comparisons with imaging data or histological observations, which may not fully capture the underlying transport dynamics.

In addition, the computational cost of high-fidelity simulations—especially those involving fully coupled three-dimensional (3D), FSI, multiscale, and agent-based models—remains substantial. This limits their routine use in clinical settings, where rapid turnaround times are often required.

Looking forward, several promising directions may help overcome these challenges. These include tighter integration of whole-body cholesterol metabolism models with local arterial simulations to enable truly multiscale representations of disease [10], [12], [32], [46]. The development of patient-specific multiscale “digital twin” models, informed by advanced imaging, omics data, and longitudinal clinical information, holds significant potential for personalized medicine [21], [29], [30].

Furthermore, the incorporation of uncertainty quantification and sensitivity analysis techniques will be essential for assessing model robustness and identifying key drivers of variability [27], [35]. Finally, advances in computational methods, including physics-informed neural networks and

reduced-order modeling, offer opportunities to dramatically reduce computational cost and enable near real-time simulations, thereby facilitating clinical translation [23], [30].

## 7. Conclusion

The simulation of cholesterol deposition and atherosclerotic plaque growth has evolved considerably over the past decades, progressing from simplified diffusion-based models to sophisticated three-dimensional, multiscale, and hybrid computational frameworks. Modern in silico models integrate hemodynamics, arterial wall mechanics, mass transport, and cellular dynamics to provide a comprehensive representation of the complex processes underlying atherosclerosis.

These models have significantly enhanced mechanistic understanding of how systemic factors, such as elevated LDL levels, interact with local vascular conditions to drive site-specific plaque development. In addition, they offer a powerful virtual platform for testing hypotheses, evaluating interventions, and exploring disease progression under controlled conditions that are difficult to achieve experimentally.

With continued advances in data acquisition, model calibration, and computational efficiency, in silico approaches are poised to play an increasingly important role in cardiovascular research and clinical practice. In particular, the integration of multiscale models into patient-specific “digital twin” frameworks holds great promise for improving risk prediction, guiding therapeutic decision-making, and advancing personalized medicine.

## Bibliography

- Y. Duan and Y. Du, “Regulation of cholesterol homeostasis in health and diseases,” *Signal Transduct. Target. Ther.*, vol. 7, 2022.
- J. Guo and K. Xu, “Cholesterol metabolism: physiological regulation and clinical implications,” *MedComm*, 2024.

- J. Borén et al., “Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights,” *Eur. Heart J.*, vol. 41, no. 24, pp. 2313–2330, 2020.
- C. Davies, A. E. Morgan and M. T. McAuley, “Computationally modelling cholesterol metabolism and atherosclerosis,” *Biology*, vol. 12, no. 8, p. 1133, 2023. MDPI+1
- K. R. Feingold, “Introduction to lipids and lipoproteins,” in *Endotext* [Online]. NCBI Bookshelf, 2024.
- F. Zhang, B. Macshane, R. Searcy and Z. Huang, “Mathematical models for cholesterol metabolism and transport,” *Processes*, vol. 10, no. 1, p. 155, 2022. MDPI
- P. E. Carstensen et al., “A whole-body mathematical model of cholesterol metabolism,” *IFAC-Pap. Online*, 2024. ScienceDirect
- C. Davies, A. E. Morgan and M. T. McAuley, “Modeling cholesterol metabolism and atherosclerosis,” Ph.D. thesis, Univ. of Ulster, 2019. Pure+1
- S. Mundi et al., “Endothelial permeability, LDL deposition, and cardiovascular risk,” *Curr. Atheroscler. Rep.*, vol. 19, no. 6, 2017.
- S. Patial et al., “Atherosclerosis: progression, risk factors, diagnosis, treatment, and the role of probiotics,” *Clin. Nutr. Open Sci.*, 2024.
- S. M. Grundy et al., “Guidelines for the management of high blood cholesterol,” in *Endotext* [Online]. NCBI Bookshelf, 2022.
- P. Parini and M. Eriksson, “HDL, reverse cholesterol transport, and atherosclerosis,” *Atherosclerosis*, 2024.
- M. Playford and J. Rye, “Reverse cholesterol transport: current assay methods and clinical implications,” *Front. Cardiovasc. Med.*, 2025.
- M. Zhou, X. Li and Y. Wang, “Wall shear stress and its role in atherosclerosis,” *Front. Cardiovasc. Med.*, vol. 10, 2023.
- M. Cho et al., “Wall shear stress analysis in atherosclerosis using non-Newtonian CFD,” *Int. J. Mol. Sci.*, vol. 25, no. 18, 2024.
- A. Parton, J. McCoy and N. Curzen, “Computational modelling of atherosclerosis,” *Brief. Bioinform.*, vol. 17, no. 4, pp. 562–575, 2016. OUP Academic
- C. Simonetto et al., “A mechanistic model for atherosclerosis and its application to coronary artery disease in the Danish population,” *PLoS One*, vol. 12, e0175386, 2017.
- R. Caballero et al., “Fully coupled hybrid in-silico modeling of atherosclerosis,” *Front. Bioeng. Biotechnol.*, vol. 13, 2025. Frontiers+1
- M. Soleimani, A. Haverich and P. Wriggers, “Mathematical modeling and numerical simulation of atherosclerosis based on a novel surgeon’s view,” *Arch. Comput. Methods Eng.*, vol. 28, pp. 5043–5067, 2021. SpringerLink
- A. Younes et al., “Mathematical modeling of inflammatory processes of atherosclerosis,” *Math. Model. Nat. Phenom.*, vol. 17, 2022. MMNP Journal
- Y. Liu et al., “Mathematical modeling and simulation of atherosclerotic plaque formation,” *Biomed. Signal Process. Control*, vol. 81, 2023. ScienceDirect
- R. Piemjaiswang et al., “Effect of transport parameters on atherosclerotic lesion growth: a parameter sensitivity analysis,” *Comput. Biol. Med.*, vol. 131, 2021.
- G. Ke, X. Zhang and X. Liu, “Mathematical model of atherosclerotic aneurysm,” *Math. Biosci. Eng.*, vol. 18, no. 6, pp. 7745–7773, 2021. Pure
- A. Corti et al., “A fully coupled CFD-agent-based model of atherosclerotic plaque development: multiscale modeling framework,” *Comput. Methods Programs Biomed.*, vol. 189, 2020. ScienceDirect+1

- L. Spahić et al., “Development of a surrogate model for predicting atherosclerotic plaque progression using agent-based simulation data,” *J. Biomech.*, 2025 (in press).
- O. Kafi et al., “Numerical simulations of a 3D fluid–structure interaction model of atherosclerotic arteries,” *Math. Biosci. Eng.*, vol. 14, pp. 73–94, 2017. AIMS Press
- T. N. A. M. Vuong et al., “Integrating computational and biological hemodynamic approaches to improve modeling of atherosclerotic arteries,” *Adv. Sci.*, vol. 11, no. 26, e2307627, 2024. PubMed+1
- A. Corti et al., “A systems biology approach using agent-based models for atherosclerosis,” *Front. Bioeng. Biotechnol.*, vol. 9, 2021. RePublic
- S. Pozzi, A. Manzoni and A. Quarteroni, “Mathematical modeling, analysis and numerical approximation of early atherosclerotic plaque formation,” *Math. Fluid Mech.*, vol. 23, 2021. ADS+1
- N. H. Johari, C. Menichini, M. S. Hamady and Y. Xu, “Computational modeling of low-density lipoprotein accumulation at the carotid artery bifurcation after stenting,” *Int. J. Numer. Methods Biomed. Eng.*, vol. 39, no. 12, e3772, 2023. PubMed+1
- X. Chen et al., “Fluid–structure interactions-based study of low-density lipoproteins uptake in the left coronary artery,” *Sci. Rep.*, vol. 11, 5862, 2021. Nature+1
- D. G. Mpairaktaris et al., “Numerical simulation of LDL mass transport in a multilayered arterial wall,” *Biomed. Eng.*, vol. 17, pp. S543–S552, 2018. SAGE Journals
- D. G. Mpairaktaris et al., “Low-density lipoprotein transport through patient-specific thoracic aortas,” *Comput. Biol. Med.*, vol. 89, pp. 329–341, 2017.
- S. Chen et al., “Multiscale modeling of vascular remodeling induced by wall shear stress,” *Front. Physiol.*, vol. 13, 2022. Frontiers
- V. Evren et al., “Computational fluid dynamics and numeric analysis of stenotic arteries and endothelial shear stress,” *Appl. Sci.*, vol. 14, no. 7, 2851, 2024. MDPI
- S. A. Rahman et al., “Numerical simulation of mass transport phenomena on stenosed arteries,” *CFD Lett.*, vol. 16, no. 12, 2024.
- N. Alagbe et al., “Computational simulation of the effects of blood flow velocity on atherosclerosis,” *F1000Research*, vol. 13, 426, 2024. ScienceDirect
- N. Filipovic, *Computational Modeling of Atherosclerosis*, in *Computational Modeling in Bioengineering and Bioinformatics*. Academic Press, 2019. PubMed
- F. Zhang et al., “Mathematical models for cholesterol metabolism and transport: a review,” *Processes*, vol. 10, 2022. PSE Community
- Y. Wang et al., “Credibility assessment of a mechanistic model of atherosclerosis to predict cardiovascular outcomes under lipid-lowering therapy,” *NPJ Digit. Med.*, vol. 8, no. 1, p. 171, 2025. Nature+1
- Z. Zhang, B. Macshane, R. Searcy and Z. Huang, “Mathematical models for cholesterol metabolism and transport: implications for drug targeting,” *Processes*, vol. 10, 2022. MDPI+1
- J. Warren et al., “A new agent-based model with tetrahedral mesh integration for coronary plaque progression,” *J. Theor. Biol.*, 2025 (in press).
- N. Tishchenko, “Bidirectional in-situ analysis and visualization of fluid–structure interactions in atherosclerotic arteries,” M.S. thesis, Northern Illinois Univ., 2024.
- R. T. Zaman et al., “A dual-modality hybrid imaging system for characterization of atherosclerotic plaques,” *Sci. Rep.*, vol. 8, 2018. Nature

Z. A. Saib and J. Nithiarasu, "A review of fluid-structure interaction: blood flow in arteries," *Biomed. Eng. Adv.*, vol. 6, 100106, 2025. ScienceDirect

F. Zhang et al., "Mathematical models for cholesterol metabolism and transport: an overview," *Processes*, vol. 10, 2022.

