pp. 1–16 (2021)

Frontiers in mathematical modelling of the lipid metabolism under normal conditions and its alterations in heart diseases

G. A. Bocharov*†‡, D. S. Grebennikov*†§, and R. S. Savinkov*†‡

Abstract — Pathophysiology of ischemic heart disease is a complex phenomenon determined by the interaction of multiple processes including the inflammatory, immunological, infectious, mechanical, biochemical and epigenetic ones. A predictive clinically relevant modelling of the entire trajectory of the human organism, from the initial alterations in lipid metabolism through to atherosclerotic plaque formation and finally to the pathologic state of the ischemic heart disease, is an open insufficiently explored problem. In the present review, we consider the existing mathematical frameworks which are used to describe, analyze and predict the dynamics of various processes related to cardiovascular diseases at the molecular, cellular, tissue, and holistic human organism level. The mechanistic, statistical and machine learning models are discussed in detail with special focus on the underlying assumptions and their clinical relevance. All together, they provide a solid computational platform for further expansion and tailoring for practical applications.

Keywords: Ischemic heart disease, atherosclerotic plaque, lipid metabolism, mathematical model, multiphysics, biomechanics, low-density lipoprotein.

MSC 2010: 93A30, 97M60, 35Q92, 92C17, 92C42, 92C37, 92D25

1. Lipid metabolism and heart disease

Ischemic heart disease, also known as coronary heart disease, presents a tremendous health problem worldwide [18]. It develops as a consequence of a persistent reduction in blood flow in arteries of the heart. The formation of atherosclerotic plaques inside large arteries results in a narrowing of the vessel lumen and hardening of its walls and is considered as one of the major pathological factors of the disease. Indeed, it limits the supply of the heart with an oxygen-rich blood, and in a long-term, promotes the development of the ischemic heart disease.

The pathogenesis of the atherosclerosis is a complex phenomenon resulting

*Marchuk Institute of Numerical Mathematics, Russian Academy of Sciences, Moscow 119333

†Moscow Center of Fundamental and Applied Mathematics at INM RAS

‡Institute of Computer Science and Mathematical Modelling, Sechenov First Moscow State Medical University, Moscow 119991. E-mail: g.bocharov@inm.ras.ru

§World-Class Research Center 'Digital Biodesign and Personalized Healthcare', Sechenov First Moscow State Medical University, Moscow 119991, Russia.

The reported study was supported by Moscow Center of Fundamental and Applied Mathematics (agreement with the Ministry of Education and Science of the Russian Federation No. 075-15-2019-1624).

from the interaction of multiple processes including the inflammatory, immunological, infectious, mechanical, biochemical and epigenetic ones [47] (see Fig. 1). The underlying endothelial dysfunction can be induced by factors of various physical and physiological nature with the elevated levels of serum Low-Density Lipoproteins (LDL) being among them [35]. The deposition of LDL (cholesterol) in the inner layer of arterial vessel (intima) results in plaque buildup which can grow, stagnate or regress depending on a number of biological and biomechanical mechanisms [42]. The dynamics of the atherosclerotic plaques formed by LDL determining the degree of occlusion of the vessels is not fully understood and requires the application of in silico, in vivo, and in vitro models to develop a mechanistic understanding of relationship between the lipid metabolism and the development of atherosclerosis [18, 47].

Alterations in lipid turnover (biosynthesis, transportation and degradation), i.e., the lipid metabolism, are considered to play an important role in atherosclerosis [46]. An elevated serum level of LDL cholesterol (LDL-C) is a critical factor for coronary heart diseases. The plasma levels of High-Density Lipoprotein (HDL) cholesterol show a significant negative correlation with the cardiovascular risk and atherosclerosis [22, 46]. However, the relationship between the levels of HDL cholesterol (HDL-C) and LDL-C is complex as shown in studies with CETP inhibitors [24] and additional research of the regulation loops is needed.

The networks of processes determining the lipid metabolism are extremely complex and include multiple layers of regulation [22], as depicted in Fig. 1. The link between the lipid metabolism and the molecular biology pathways in conjunction with genetic regulation are starting to be investigated on a systematic basis [23, 47]. The number of mathematical models considering the lipid metabolism regulation at a single cell level is rather limited. It goes back to the remarkable study of LDL metabolism and intracellular cholesterol regulation [4]. The multiphysics biomechanical and biochemical aspects of the atherosclerotic plaque formation at the blood vessel level were thoroughly addressed in numerous studies (see, e.g., [8, 35] and the references therein). The corresponding approaches which we refer to as mechanistic models are discussed in detail in the next sections and summarized in Fig. 1.

2. Mechanistic models

2.1. Models of lipid metabolism in a single cell

Mathematical model describing the lipoprotein metabolism in a single cell is presented in [31]. It describes the uptake of LDL and very Low-Density Lipoprotein (VLDL) by hepatocyte mediated by LDL receptors (as in [43]), the intracellular biosynthesis of cholesterol (similar to [3]) and receptors for LDL, and delipidation of VLDL to LDL. The turnover of the transcription factor, i.e., sterol regulatory element-binding protein 2 (SREBP-2), regulated by cholesterol is taken into account. The model was formulated as a system of 18 coupled nonlinear ODEs by applying the law of mass action to describe the underlying biochemical reactions. The calibrated model with about 50 estimated parameters was employed to study

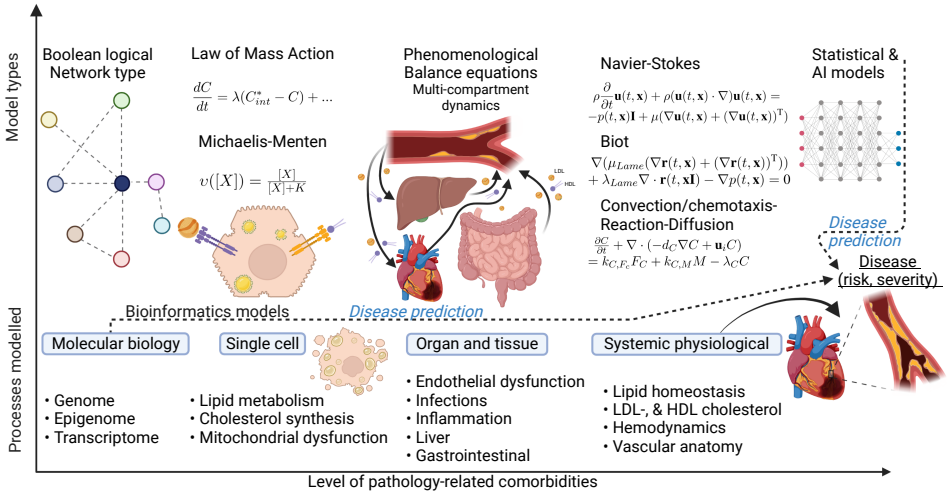

Figure 1. The processes which are described by corresponding mathematical models at various levels of pathology-related comorbidities of cardiovascular disease and the approaches for linking the processes at genomic and systemic physiological levels to the disease risk or severity. The figure was created with BioRender.com.

(1) the effects of statin therapy, which is used to lower the serum cholesterol levels, and (2) the origins of five class types of familial hypercholesterolaemia. The overall conclusion of the study was that mathematical modelling can be a useful tool for understanding lipoprotein metabolism at a single cell level. Importantly, the model of intracellular biosynthesis of cholesterol [3] is built upon the previous studies of the same group (in particular, [4, 43, 45]), and includes the SREBP-2-mediated feedback control of intracellular cholesterol on LDL-receptor (LDLR) and HMG-CoA reductase (HMGCR) transcription. This feedback control system was found to be necessary for accurate description of cholesterol metabolism [28]. Indeed, it was the only model of lipid metabolism in a cell that passed the functional tests in the meta-study [28]. The tests were used to evaluate whether the model can reproduce the effects of treatment with a statin observed in vivo by respectively perturbing the model. Namely, simulating decrease in cholesterol production by reducing the activity of HMGCR by 75% resulted in an increased uptake of LDL in the presence of LDL and in a lowering of intracellular cholesterol in the absence of LDL, as expected.

The most recent study of cholesterol metabolism at a single cell level examines the aging effect on hepatic regulatory mechanisms [26]. The computational model formulated using the Systems Biology Graphical Notation (SBGN) platform and Systems Biology Markup Language (SBML) considers the dynamics of 34 biochemical characteristics of the cholesterol regulation. It was used to analyze the mechanisms of the phenomenon of increased mortality associated with low levels of LDL-C and the observations that high blood cholesterol levels can be associated with a decreased risk of death in aged individuals. Further research is needed to gain a consistent understanding of the underlying mechanism.

2.2. Multi-compartmental models of lipid dynamics

Another approach in the study of the causes of dyslipidemia was chosen by researchers who built a multi-compartment model of lipid metabolism in the human body [6]. They were guided by the goal of constructing a model that allows tracing the entire process of lipid metabolism, since measuring the levels of lipids in the blood does not give a complete understanding of the processes taking place in the body. To track the processes of lipid metabolism, stable isotopes of the elements that make up leucine, glycerol, involved in the processes of metabolism of VLDL, lipogenesis in the liver, and HDL-mediated transport of cholesterol were used. Recent discoveries in mass spectrometry have made it possible to make accurate measurements of the amount of a traceable substance, with a small number of samples even for a low concentration of considered isotopes. Further, using the SAAM software package, multi-compartment models of the dynamics of VLDL, LDL, intermediate-density lipoproteins (IDL) and HDL were built. As the next step, the authors of the work see taking into account the metabolism of lipids in the intestine and the effect of chylomicrons on the processes of lipid metabolism.

This modelling approach should allow one to understand mechanistically the processes of lipid metabolism and identify those interactions that lead to an imbalance of lipids in various tissues and organs of the human body, including those leading to the development of atherosclerosis and other cardiovascular diseases.

2.3. Quantitative systems pharmacology modelling of lipid metabolism

A separate category of the models of lipid metabolism are those that follow the quantitative systems pharmacology (QSP) approach. These models are developed to answer certain questions related to the effects of specific therapeutic treatments and the parameterizations of drug effects are calibrated and validated extensively. For example, to study the effectiveness of two kinds of HDL-C raising drugs on increasing the rate of reverse cholesterol transport (RCT), a QSP model was developed in [24]. The ODE-based model describes the dynamics of the following 6 variables: small lipid-poor ApoA-I particles, ApoA-I particles in α-HDL pool, particle concentration in α-HDL pool, cholesterol ester (CE) in α-HDL pool, CE in LDL, and CE in VLDL. The other species from HDL proteome and lipidome that do not directly regulate RCT are represented implicitly. For example, the ratio of triglycerides to CE is assumed to be 13%. The expression for RCT rate as a function of the lipid-poor ApoA-I particles was derived. The model was calibrated using the Bayesian approach, and the maximum a posteriori estimates of parameters were computed. For model validation, the experimental data on subjects with mutations in ABCA1 and ApoA-I genes was used. The mutations were simulated by setting the respective parameters (ABCA1 activity and ApoA-I synthesis rate) to 50% and 0% of their baseline value. By sampling the model parameters from a multivariate normal distribution, the synthetically generated data was produced. These data showed that there is a strong correlation between HDL-C and RCT rate and allowed to find two candidate biomarkers for ABCA1 activity: the concentration and the percentage

of ApoA-I. By simulating HDL-C raising treatments, it was predicted that the first one, CETP inhibition, increases HDL-C but does not lead to an increased RCT rate, while the second one, ABCA1 up-regulation, increases both HDL-C and RCT rate. In [14], the model was further used to study the effects of additional treatments: enhancement of ApoA-I synthesis by RVX-208 and the infusion of reconstituted or delipidated HDL.

Recently, a multiscale QSP model was developed in [44] to study the effects of statin and anti-PCSK9 treatments on lowering plasma LDL-C. In the model, three compartments were considered: liver, small intestine and peripheral tissues. The model variables include: cholesterol concentration in three compartments, blood levels of VLDL, LDL-C, HDL, LDL receptors (LDLR) on the surface of hepatocytes and internalized LDLR, intracellular HMG-CoA concentration, PCSK9 level in blood, and three complexes which are formed as PCSK9 binds to LDLR expressed on the cell surface. The cholesterol synthesis rate was determined by using Flux Balance Analysis (FBA) to apply constraints on the comprehensive metabolic network Hepatonet [15], which includes 777 intracellular metabolites. FBA algorithm finds such steady-state fluxes for network reactions that minimize the sum of internal fluxes under a set of two-bound constraints on each flux [15, 44]. The HMG-CoA concentration was used to set the constraint to control the cholesterol synthesis rate. The Michaelis–Menten parameterization was used to incorporate the direct effect of atorvastatin drug on the cholesterol synthesis rate in the liver, while the Hill equations were used to model the indirect effect of atorvastatin on LDLR and PCSK9 synthesis rates. In contrast, to simulate the effect of anti-PCSK9, which reduces the number of PCSK9 proteins available for binding with LDLR, the two-compartment target-mediated drug disposition model [12] was used. The overall result of the study was that combination treatment is necessary to reduce LDL-C levels for patients with high levels of PCSK9 and cholesterol synthesis rates.

For a quantitative comparison of the effects of two anti-PCSK9 classes of drugs, an integrative QSP model of lipoprotein dynamics was developed in [36]. Three monoclonal antibodies (mAbs) and two small interfering RNA (siRNA) drugs were considered. The model is formulated as system of 17 ODEs describing the following variables: plasma concentrations of PCSK9, LDL-C, LDL receptors, Lp(a) (LDL-like particles containing apolipoprotein(a)), the amount of three drugs (alirocumab, evolocumab and RG-7652 mAbs) in the administration and circulation compartments, the number of complexes formed between PCSK9 and each drug, and the amount of two drugs (inclisiran and ALN-PCS siRNA) in the administration and liver compartments. The inhibitory effect of anti-PCSK9 siRNA drugs on the translation of PCSK9 is modelled using Michaelis-Menten functions. The result of the study was that, at the clinically used doses, mAbs decreased the LDL-C levels 20% lower than siRNAs. At doses leading to the same level of LDL-C reduction, there were no differences in the other lipid metabolites, even though they differ in mechanism of action. The model predicts the inhibitory level of siRNA drugs that needs to be reached by changing their biochemical properties in order to have the same effectiveness as mAbs or higher.

2.4. Models of atherosclerotic plaque formation

2.4.1. Qualitative network-type Boolean approach. The complexity of the biochemical interactions underlying the atherosclerotic plaque formation enforces the probing of various approaches to the construction of the interaction network-type dynamical models, e.g., (1) based on system identification methods, (2) the use of prior knowledge in the form of the list of regulatory interactions, (3) as well as their combination. The potential of using a prior knowledge network (PKN) for the construction of the dynamical model of the formation of atherosclerotic plaques is illustrated in [2].

The model is developed using the Boolean framework with the set space of the system represented by Boolean variables, i.e., the nodes in the network interacting via specified logical rules. The pathophysiology of atherosclerotic plaque formation is split in the following stages: (1) initial lipid accumulation, (2) monocyte infiltration, (3) platelets recruitment and (4) lipid core formation resulting in a chronic systemic inflammatory condition [2]. The model derived using PKN is composed of 729 nodes (432 proteins and 297 metabolites or biological processes) linked by 3406 interactions, of which 1841 regulations are encoded with logical operators and 1565 represent activatory or inhibitory interaction between the nodes. The model is solved by converting the Boolean network into a certain continuous dynamical system and finding its stable steady states [25]. The model was used to predict the key regulators of the signal transduction and inflammatory cytokine secretion. In particular, it was shown that a proper representation of the Akt signaling pathway is key for a consistent prediction of its contribution to the healthy and the pathological phenotypes.

Overall, the key importance of the expert curation of the complex regulatory interactions considered in experimental literature is demonstrated. In addition, the suitability of the logical modelling framework is advocated for complex and poorly understood systems.

2.4.2. Quantitative ODE-based multi-compartmental approach. The most comprehensive mathematical model of atherosclerotic plaque formation is developed in [29]. It is based on molecular biology map underlying the atherosclerosis pathophysiology. The model describes the population dynamics of 80 molecular species taking place in five human organism compartments: the liver, intestine, tunica intima, lumen, and endothelium. The model considers the dynamics of a broad spectrum of humoral and cellular factors, including lipoproteins, inflammatory components (cytokines and cells of the innate and adaptive arms of the immune system), muscle cells, and endothelial cells. The corresponding system of ODEs is set up using the law of mass action and the Michaelis–Menten kinetics formalisms. A numerous set of 179 model parameters was quantified using available literature search or estimated via model calibration. For coding of the model equations and interaction maps representation, the facilities of the SBML and SBGN proved to the critical. The computational experiments with the model enabled the identification

of hypothetical therapies based on multi-drug interventions. In particular, five drugs were predicted that can reverse the advance atheroma formation. The limitations of the model are related to a simple description of the spatial effects (compartmental approach) and the intracellular regulation of the processes.

2.4.3. Multiphysics distributed parameter systems-based approach. The description of the spatial dynamics of atherosclerosis is the subject of numerous models formulated with PDEs. For example, the model developed in [13], describes the dynamics of 18 variables: (i) lipoprotein concentrations L, H, L_{ox} (LDL, HDL, oxidized LDL (oxLDL)), (ii) densities of pro-inflammatory M1 and anti-inflammatory M2 macrophages (M_1, M_2), foam cells (F), T cells (T) and smooth muscle cells (SMCs) (S), (iii) concentration of free radicals which oxidize LDL (r), (iv) concentrations of chemoattractant protein MCP-1 P and platelet-derived growth factor (PDGF) (G), (v) density of extracellular matrix (ECM) (ρ), and concentrations of MMP and TIMP (Q, Q_r) which promote and inhibit the remodelling of ECM, (vi) concentrations of inflammatory signal IFN-γ (I_γ) and activation signal interleukin IL-12 (I_{12}), (vii) the pressure σ caused by the moving cells in the plaque and the fluid velocity in the medium of the plaque, which is assumed to be porous and therefore governed by Darcy's law $\mathbf{u} = -K\nabla\sigma$. Simulations were run in 2D planes, i.e., in the cross-section of the artery and along the artery with periodic boundary conditions. Various boundary conditions are considered for different variables and domain boundaries. For a free boundary of the intima in contact with the lumen (i.e., with blood), the Robin boundary conditions are considered for L, H, M_1, M_2, T with constant convective constants α_i for all variables except for M_1:

$$\alpha_{M_1} = \hat{\alpha}_{M_1} \frac{L_{\text{ox}}}{1+H}.$$

For other variables, except for ρ and σ, no-flux boundary condition is set. The free boundary is held together by cell-to-cell adhesion forces, which is represented by Dirichlet boundary condition for σ. The velocity of free boundary is set as $V_n = -\partial\sigma/\partial\mathbf{n}$. For the boundary of the intima in contact with the surrounding medium, no-flux boundary conditions are assumed for all variables except ρ and S. For S, the Robin boundary condition is set with convective constant

$$\alpha_S = \hat{\alpha}_S \frac{P+G}{P_0+G_0}$$

as SMCs move into the intima from the media chemotactically by sensing MCP-1 and PDGF. For ρ, the boundary conditions on both boundaries is determined by $\rho = 1 - S - F - T - M_1 - M_2$, so that the total density of all the cells and ECM is constant and is equal to 1 g/cm^3.

The PDEs of the model are in the form of reaction-diffusion equations for the molecules, and convection-reaction-diffusion for the cells. For M1 macrophages, the chemotaxis term along the gradient of MCP-1 is additionally considered. For

SMCs, the equation governing $S(\mathbf{x},t)$ consists of convection and diffusion terms, and the terms for chemotaxis along the respective gradients ∇P and ∇G, as well as haptotaxis along $\nabla\rho$:

$$\frac{\partial S}{\partial t}+\nabla\cdot(\mathbf{u}S)-D_S\Delta S=-\nabla\cdot(\chi_C S\nabla P)-\nabla\cdot(\chi_C S\nabla G)-\nabla\cdot(\chi_H S\nabla\rho).$$

The model was used to predict the dynamics of plaque formation during 60 days, and to explore four therapeutic drugs for plaque regression introduced starting from day 31. The treatments are simulated by changing the model parameters in corresponding terms. The effects of three drugs (anti-miR33, antibody and TGF-β treatments) that enhance the ABCA1 production were simulated. In each case, the parameter inhibiting the reverse cholesterol transport rate was decreased for a quantitative agreement of plaque regression with experimental data in terms of either plaque weight, M1 and ECM density, monocyte chemoattractant protein (MCP-1) concentration, or foam cell density. Next, the miR-145 drug which targets SMCs, therefore reducing plaque weight, was considered by decreasing the influx rate of SCMs. Finally, the 'risk map' on the plane of HDL and LDL concentrations was computed, which represents the percentage of plaque mass growth or shrinkage at the end of 300 days for each point of (L_0, H_0). Several strategies of personalized treatment of atherosclerosis were illustrated, which correspond to moving from high-risk to low-risk zones on the map by combining lifestyle changes such as antioxidant supplementation or quitting smoking, reducing blood pressure and anti-cholesterol medications.

The most detailed and representative multiphysics model of early atherosclerosis was developed in [35]. The biological concept underlying the model development is that atherosclerosis is a chronic inflammatory disease. The model is focused on the physiological, biochemical and biomechanical events which occur during an early phase of atherosclerosis development. The 3D domain considered in the model combines the blood vessel lumen, the intima and the endothelium layer separating them. The time- and space-dependent variables of the model are LDL, oxLDL, cytokines, factor increasing monocytopoiesis (FIM), monocytes, macrophages, foam cells. The transport of the cells and humoral factors is described by convection/chemotaxis-diffusion-reaction type of equations. The boundary conditions take into account the permeability of the endothelial wall for LDL and transmigration of monocytes from lumen to intima. The key parameterizations of the model are (1) the wall shear stress (WSS), LDL concentration and inflammatory cytokine dependence of the endothelial permeability for LDL, (2) WSS and cytokine (MCP-1) dependent (in a multiplicative way) transmigration of monocytes into intima (flux across the endothelium), and (3) differentiation of monocytes into macrophages and the oxLDL-dependent transformation of the macrophages into foam cells. The parameterizations take phenomenologically into account that low WSS increases the residence time near the arterial wall, thus favoring the transport of LDL and monocytes through endothelium to the intima. The inflammatory response is launched once the oxLDL concentration reaches a specified threshold of

1.9×10^{-7} g·cm^{-3} [35]. Importantly, a positive feedback FIM-dependent regulation of the monocytopoiesis in the bone marrow is taken into account via the extra terms in the inlet boundary condition for the vessel lumen.

The most elaborated and computationally challenging part of the model is related to the transport processes. The model considers blood flow in the vessel lumen governed by the Navier–Stokes equations for an incompressible Newtonian fluid ($\mathbf{u}(t,\mathbf{x})$ is the blood velocity):

$$\rho \frac{\partial}{\partial t}\mathbf{u}(t,\mathbf{x}) + \rho(\mathbf{u}(t,\mathbf{x})\cdot\nabla)\mathbf{u}(t,\mathbf{x}) = -\nabla\cdot\left[p(t,\mathbf{x})\mathbf{I} + \mu\left(\nabla\mathbf{u}(t,\mathbf{x}) + (\nabla\mathbf{u}(t,\mathbf{x}))^T\right)\right]$$

$$\nabla\cdot\mathbf{u}(t,\mathbf{x}) = 0.$$

The fluid flow in the intima is modelled by Biot system for a poroelastic medium with $\mathbf{r}(t,\mathbf{x})$ being the unknown displacement and $p(t,\mathbf{x})$ standing for the pressure of the medium, μ_{Lame} and λ_{Lame} being the Lamé coefficients, and k being the hydraulic conductivity:

$$\nabla\cdot\left(\mu_{\text{Lame}}(\nabla\mathbf{r}(t,\mathbf{x}) + (\nabla\mathbf{r}(t,\mathbf{x}))^T)\right) + \lambda_{\text{Lame}}\nabla\cdot\mathbf{r}(t,\mathbf{x}\mathbf{I}) - \nabla p(t,\mathbf{x}) = 0$$

$$\nabla\cdot\left(\frac{\partial}{\partial t}\mathbf{r}(t,\mathbf{x}) - k\nabla p(t,\mathbf{x})\right) = 0.$$

A central part of the modelling problem formulation for its further computational implementation of was an elaborate specification of the interface and boundary conditions for fluid flow, molecular and cellular fluxes. The numerical simulations of the reduced to 2D version of the model lead to two major conclusions: (1) the region of atherosclerotic plaque formation can not be predicted solely on the WSS but needs to be considered in relation to the spatial LDL distribution and local inflammatory conditions, and (2) endothelial permeability for monocytes is essentially influenced by MCP-1 level. In a broader context, the model provides a general platform for further development of multiscale models with a more detailed description of the regulation of pro- and anti-inflammatory immunophysiological responses of the host to link the molecular- and cellular level processes with the systemic dynamics of the host organism to a critical stage of atherosclerosis (as shown in Fig. 1).

Two biomechanical aspects of the early atherosclerosis not considered in the above model, i.e., incompressible non-Newtonian blood properties and the pulsative blood flow interacting with the elastic artery wall were thoroughly examined using a multiphysics approach in [41]. The key assumption of the model was that the low wall shear stress is the sole factor controlling the permeability of the endothelium for LDL to diffuse in the artery wall. The governing set of the model equations is categorized as a coupled fluidstructureadvectiondiffusionreaction model. In the model, the branching subclavian and common carotid arteries are considered in defining the computational region of interest. The interaction of the blood flow with the artery

wall is FSI-based considering embedded three-element Windkessels with a hyperelastic structure. The later undergoes finite deformations, anisotropic growth, LDL concentration-dependent remodelling and a change of its constitutive equation. The structure of the artery wall is reduced to consideration of two compartments, the endothelium and arterial wall. The model was calibrated using murine-specific data. The 3D numerical simulations showed that the pulsative flow regime has a crucial impact on the development of atherosclerosis and a minor effect is exhibited by the aorta compliance.

In the follow-up study, the stability of atherosclerotic plaques was analyzed to elaborate the criteria for classifying them as progression-prone and progression-resistant using the measurable parameters such as the blood cholesterol level and wall shear stresses [42]. The 3D multiphysics set of model equations consists of two groups of equations. The first one of the biomechanical transport equations considers Darcys law for the transmural flow through vessels walls, the KedemKatchalsky equations for endothelial fluxes of lipoproteins, and the model of early plaque formation [41]. The second part consists of phenomenological equations for reactions in the intima, which describe the monocyte-based metabolism of LDL to produce cholesterol, differentiation of monocytes into macrophages followed by their apoptosis, the oxidative LDL and HDL modification by macrophages and the endothelium. The unmodified HDLs function to reduce LDL oxidation. Macrophage-produced cholesterol is assumed to be stored as esterified cholesterol, thus constraining the free cholesterol level between physiologic and cytotoxic limits. The model predicts that regions in arteries with the wall shear stress dropping below 20% of the average exposure are potential regions for the development of progression-prone atherosclerotic plaques.

The accumulation of LDL in the subendothelial layer is one of the key local manifestations of pathophysiological process associated with plaque development that can finally result in atherosclerosis, i.e., a systemic disease. Most of the mechanistic mathematical models were formulated to investigate this initial stage of atherosclerosis development. To this end, a similar set of basic equations was used with major differences in the parameterization of transport processes, multilayer structure of the arterial wall, fluid structure interaction description. The core equations include those for fluid flow inside the vessel lumen (Navier–Stokes), the fluid and lipoprotein transport in lumen and through the heterogeneous porous elastic tissues of the vessel wall (Brinkman Darcy's model, Kedem–Katchalsky equations for interfacial coupling), and convection–reaction–diffusion for mass balance. Specific aspects of the impact of biomechanical parameters of the transport model components (e.g., via the sensitivity analysis [30]), the initial and inflow boundary value conditions [10] on LDL accumulations were addressed in the following studies with appropriately tuned mathematical descriptions:

- the effect of non-Newtonian behavior of fluids on LDL accumulation [11, 17];
- wall shear stress and high LDL concentration [20, 38, 39];
- effect of hypertension condition on LDL accumulation [9, 19, 33, 40];

- impact of angiogenesis from the adventitial vasa vasorum and intraplaque hemorrhage on the atherosclerotic plaque destabilization [16].

Recent study focused on formulation of multiphysics model was developed to examine the hypothesis stating that the disruption of arterial wall nourishment is the primary cause of the onset of inflammatory response of the wall tissue [37].

To examine the atheroprotective role of HDL, the mathematical model of the inflammatory processes inside intima was developed in [1]. It is formulated as a system of coupled reaction-diffusion equations for cellular and cytokine components of the inflammatory reaction and oxLDL. The impact of HDL was modelled by parameterization of the risk of plaque formation as a function of serum level of HDL. The conditions for major phenotypes of inflammation, i.e., no inflammation, stable plaque and vulnerable plaque, and the inflammation propagating as travelling wave, were obtained.

Finally, it should be noted that the multiscale/multiphysics models of arterial plaque formation available today can still benefit from adding a more detailed description of cell-level and plasma-level dynamics of lipoprotein metabolism. Moreover, the outputs of the models still need to be linked with the disease pathophysiology metrics to be used as predictive tools of the disease dynamics and outcome.

3. Statistical, bioinformatics and AI models

Another type of models is designed to identify the lipid metabolism biomarkers and associate them with pathophysiology or risk of development of cardiovascular disease (see Fig. 1). These include the regression models of various kinds and artificial neural network models, as well as bioinformatic analysis of gene networks, examples of which are provided below. Importantly, the disease risk can be linked to either genetic or plasma level lipid factors, thus providing a tool to be incorporated in the multiscale models of atherosclerotic plaque formation to predict the disease risk or severity.

3.1. Statistical analysis and regression models

The statistical models of the ischemic heart disease are based on the analysis of the associations/correlations between the serum lipid levels and specific disease progression states of the patients. They rely on the data obtained by lipidomic profiling to characterize the organ-specific alterations in the level and composition of lipid molecules. The study published in [48] identified a group of circulating lipids that were significantly altered negatively (63 lipids) and positively (62 lipids) in ischemic heart and coronary diseases. Although the coronary artery disease and blood serum lipid levels are highly correlated, the underlying regulatory molecular networks remain to be thoroughly investigated.

In [27], lipidomics was used to measure 184 lipids in plasma samples of 3865

individuals, with a follow-up approximately 20 years afterwards. At the endpoint, 536 participants developed coronary artherial disease. The Cox proportional hazards regression models were trained to predict the risk of future disease onset. To perform variable selection, i.e., to select only the most predictive risk factors and prevent overfitting, the Lasso regularization technique was applied. This method uses the l_1 norm for penalty on model coefficients term instead of traditional for ridge regression l_2 norm, which forces some coefficients to be exactly zero, thus excluding the corresponding variable candidates from the resulting model. As a result, eight new lipids in plasma were identified as predictive lipid risk factors: four different phosphatidylcholines, sphingomyelin, diacylglycerol, phosphatidylinositol, and sterol ester. Using them improved the model performance significantly compared to considering only traditional risk factors: fasting levels of triglycerides, HDL and LDL cholesterol in plasma, age, sex, body mass index, systolic blood pressure, smoking and diabetes status. Notably, the improvement was achieved for predictions as long as 20 years prior to disease onset, showing that lipidomics measurements could be useful as early markers of increased cardiovascular disease risk.

3.2. Integrative genomics analysis using bioinformatics tools

Integrative genomic analysis of genome-wide association study summary data performed in [7] led to identification of common 13 genes and pathways showing a significant overlap. It was found that the genetic contribution of the coronary artery disease is located in cell-type specific regions (aortic endothelial cells, adipose tissues cells, liver tissue cells) containing the sites of plasma lipid metabolism regulation. The key genes driving the disease include LDLR, APOB, and PCSK9. They take part in LDL uptake and degradation of LDL particles.

Similarly, integrative genomics approach was applied in [5] to identify the genetic variants associated with plasma lipid levels, i.e., total cholesterol, HDL and LDL cholesterol, and triglycerides. On top of the known key regulator genes (e.g., APOH, APOA4, and ABCA1), the researchers detected novel genes such as $F2$ gene (coagulation factor II, trombin) in adipose tissue. Knockout of this gene reduced intracellular adipocyte lipid content and increased the extracellular one. These studies use a set of bioinformatics methods and tools for analysis of gene networks. In particular, Weighted Correlation Network Analysis (WGCNA) [21] was used to build gene co-expression network modules. The identification of key genetic drivers and interacting gene hubs was performed using weighted key driver analysis (wKDA) in Mergeomics pipeline [34].

3.3. Artificial neural network models

To determine the key factors of lipid metabolism disorders in the human body, a group of researchers carried out mathematical modelling using artificial neural network of the perceptron type [32] (see Fig. 2). The authors examined 453 indicators for their influence on the risks of developing lipid metabolism disorders, including those leading to chronic heart diseases. An artificial neural network was trained to

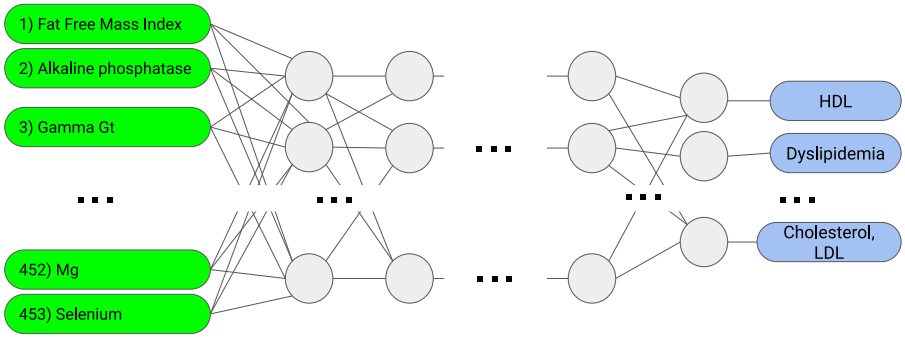

Figure 2. Schematic diagram of an artificial neural network for assessing the significance of measured variables in determining the likelihood of lipid disorder and the concentrations of lipids and lipid-containing structures in the human body.

predict the likelihood of developing lipid metabolism disorders based on combinations of the studied indicators, and then the trained network was used to assess the effect of specific indicators on the prediction results. As a result of the research, 12 key indicators were identified that affect the development of dyslipidemia. Thus, alkaline phosphatase, free fat mass index, and hemoglobin levels were effectively correlated with blood lipid markers, and the waist-to-hip ratio correlated with low-density lipids and cholesterol levels. Also, about 10 indicators were identified as key for determining the levels of high- and low-density lipids. The potential problem of the developed model can be false correlations, i.e., situations when events happen simultaneously, but do not depend on each other.

4. Conclusions: Emerging multidisciplinary approaches

The whole-organism predictive modelling integrating the entire trajectory of the human organism from the initial alterations in lipid metabolism through to atherosclerotic plaque formation and finally to the pathologic state of the ischemic heart disease remains an open, unexplored task. It is the mathematical modelling of biomechanical and (to a lesser extent) biochemical (i.e., the local LDL and HDL dynamics) aspects of the atherosclerotic plaque development which received most attention of researchers. All together, they provide a solid computational platform for expansion and tailoring for practical applications. Further mathematical modelling of the signalling and interaction networks across multiple regulation levels (see Fig. 1) with focus on assimilation of big-data gathered in experimental and clinical studies of heart diseases, and on strengthening their potential to make medically relevant predictions is urgently needed. Multidisciplinary framework represents one necessary condition for elaboration of approaches integrating the deepness of mechanistic modelling, the clarity of statistical models and the power of machine learning methods for the benefit of personalized therapies.

Acknowledgements

We thank Victor Sokolov for critically reading the manuscript and for valuable comments.

References

1. G. Abi Younes and N. El Khatib, Mathematical modeling of atherogenesis: Atheroprotective role of HDL. *J. Theor. Biology* **529** (2021), 110855.
2. A. Bekkar, A. Estreicher, A. Niknejad, C. Casals-Casas, A. Bridge, I. Xenarios, J. Dorier, and I. Crespo, Expert curation for building network-based dynamical models: a case study on atherosclerotic plaque formation. *Database* **2018** (2018), bay031.
3. B. S. Bhattacharya, P. K. Sweby, A.-M. Minihane, K. G. Jackson, and M. J. Tindall, A mathematical model of the sterol regulatory element binding protein 2 cholesterol biosynthesis pathway. *J. Theor. Biology* **349** (2014), 150–162.
4. B. S. Bhattacharya, Mathematical modelling of low density lipoprotein metabolism intracellular cholesterol regulation. *Ph.D. Thesis*. University of Reading, 2011.
5. M. Blencowe, I. S. Ahn, Z. Saleem, H. Luk, I. Cely, V.-P. Mkinen, Y. Zhao, and X. Yang, Gene networks and pathways for plasma lipid traits via multitissue multiomics systems analysis. *J. Lipid Research* **62** (2021), 100019.
6. J. Born, M.-R. Taskinen, and M. Adiels, Kinetic studies to investigate lipoprotein metabolism: Key Symposium: Kinetic studies to investigate lipoprotein metabolism. *J. Intern. Medicine* **271** (2012), 166–173.
7. L. Chen, Y. Yao, C. Jin, S. Wu, Q. Liu, J. Li, Y. Ma, Y. Xu, and Y. Zhong, Integrative genomic analysis identified common regulatory networks underlying the correlation between coronary artery disease and plasma lipid levels. *BMC Cardiovascular Disorders* **19** (2019), 310.
8. M. Cilla, E. Pea, and M. A. Martnez, Mathematical modelling of atheroma plaque formation and development in coronary arteries. *J. Royal Soc. Interface* **11** (2014), 20130866.
9. M. Dabagh, P. Jalali, and J. M. Tarbell, The transport of LDL across the deformable arterial wall: the effect of endothelial cell turnover and intimal deformation under hypertension. *Amer. J. Physiology-Heart Circ. Physiol.* **297** (2009), H983–H996.
10. G. De Nisco, P. Zhang, K. Cal, X. Liu, R. Ponzini, C. Bignardi, G. Rizzo, X. Deng, D. Gallo, and U. Morbiducci, What is needed to make low-density lipoprotein transport in human aorta computational models suitable to explore links to atherosclerosis? Impact of initial and inflow boundary conditions. *J. Biomechanics* **68** (2018), 33–42.
11. A. Deyranlou, H. Niazmand, and M.-R. Sadeghi, Low-density lipoprotein accumulation within a carotid artery with multilayer elastic porous wall: fluidstructure interaction and non-Newtonian considerations. *J. Biomechanics* **48** (2015), 2948–2959.
12. P. Dua, E. Hawkins, and Ph. van der Graaf, A tutorial on target-mediated drug disposition (TMDD) models. *CPT: Pharmacometrics & Systems Pharmacology* **4** (2015), 324–337.
13. A. Friedman and W. Hao, A mathematical model of atherosclerosis with reverse cholesterol transport and associated risk factors. *Bulletin Math. Biology* **77** (2015), 758–781.
14. K. Gadkar, J. Lu, S. Sahasranaman, J. Davis, N. A. Mazer, and S. Ramanujan, Evaluation of HDL-modulating interventions for cardiovascular risk reduction using a systems pharmacology approach. *J. Lipid Research* **57** (2016), 46–55.
15. C. Gille, C. Blling, A. Hoppe, S. Bulik, S. Hoffmann, K. Hbner, A. Karlstdt, R. Ganeshan, M. Knig, K. Rother, M. Weidlich, J. Behre, and H.-G. Holzhtter, HepatoNet1: a comprehensive

metabolic reconstruction of the human hepatocyte for the analysis of liver physiology. *Molecular Systems Biology* **6** (2010), 411.

16. M. Guo, Y. Cai, X. Yao, and Z. Li, Mathematical modeling of atherosclerotic plaque destabilization: Role of neovascularization and intraplaque hemorrhage. *J. Theor. Biology* **450** (2018), 53–65.

17. M. Iasiello, K. Vafai, A. Andreozzi, and N. Bianco, Analysis of non-Newtonian effects on Low-Density Lipoprotein accumulation in an artery. *J. Biomechanics* **49** (2016), 1437–1446.

18. L. Iop, Toward the effective bioengineering of a pathological tissue for cardiovascular disease modeling: Old strategies and new frontiers for prevention, diagnosis, and therapy. *Frontiers in Cardiovascular Medicine* **7** (2021), 373.

19. K. Jesionek and M. Kostur, Low-density lipoprotein accumulation within the right coronary artery walls for physiological and hypertension conditions. *Biosystems* **177** (2019), 39–43.

20. S. Kenjere, J. P. van der Krieke, and C. Li, Endothelium resolving simulations of wall shear-stress dependent mass transfer of LDL in diseased coronary arteries. *Computers in Biology and Medicine* **114** (2019), 103453.

21. P. Langfelder and S. Horvath, WGCNA: an R package for weighted correlation network analysis. *BMC Bioinformatics* **9** (2008), 559.

22. M. Lieberman and A. D. Marks, *Marks' Basic Medical Biochemistry: A Clinical Approach*. Lippincott Williams & Wilkins, 2009, Google-Books-ID: HHK7S7t47BEC.

23. C. Liu, W. J. Zong, A. H. Zhang, H. M. Zhang, Y. H. Luan, H. Sun, H. X. Cao, and X. J. Wang, Lipidomic characterisation discovery for coronary heart disease diagnosis based on high-throughput ultra-performance liquid chromatography and mass spectrometry. *RSC Advances* **8** (2018), 647–654.

24. J. Lu, K. Hbner, M. N. Nanjee, E. A. Brinton, and N. A. Mazer, An in-silico model of lipoprotein metabolism and kinetics for the evaluation of targets and biomarkers in the reverse cholesterol transport pathway. *PLoS Comput. Biology* **10** (2014), e1003509.

25. L. Mendoza and I. Xenarios, A method for the generation of standardized qualitative dynamical systems of regulatory networks. *Theor. Biology Medical Modelling* **3** (2006), 13.

26. A. E. Morgan and M. T. Mc Auley, Cholesterol homeostasis: An in silico investigation into how aging disrupts its key hepatic regulatory mechanisms. *Biology* **9** (2020), 314.

27. F. Ottosson, P. E. Khoonsari, M. J. Gerl, K. Simons, O. Melander, and C. Fernandez, A plasma lipid signature predicts incident coronary artery disease. *Int. J. Cardiol.* **331** (2021), 249–254.

28. Y. Paalvast, J. A. Kuivenhoven, and A. K. Groen, Evaluating computational models of cholesterol metabolism. *Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids* **1851** (2015), 1360–1376.

29. A. Parton, V. McGilligan, M. Chemaly, M. OKane, and S. Watterson, New models of atherosclerosis and multi-drug therapeutic interventions. *Bioinformatics* **35** (2019), 2449–2457.

30. R. Piemjaiswang, Y. Ding, Y. Feng, P. Piumsomboon, and B. Chalermsinsuwan, Effect of transport parameters on atherosclerotic lesion growth: A parameter sensitivity analysis. *Computer Methods and Programs in Biomedicine* **199** (2021), 105904.

31. F. Pool, P. K. Sweby, and M. J. Tindall, An integrated mathematical model of cellular cholesterol biosynthesis and lipoprotein metabolism. *Processes* **6** (2018), 134.

32. M. Rezaei, N. Fakhri, Y. Pasdar, M. Moradinazar, and F. Najafi, Modeling the risk factors for dyslipidemia and blood lipid indices: Ravansar cohort study. *Lipids in Health and Disease* **19** (2020), 176.

33. M. Roustaei, M. Reza Nikmaneshi, and B. Firoozabadi, Simulation of Low Density Lipoprotein

(LDL) permeation into multilayer coronary arterial wall: Interactive effects of wall shear stress and fluid-structure interaction in hypertension. *J. Biomechanics* **67** (2018), 114–122.

34. L. Shu, Y. Zhao, Z. Kurt, S. G. Byars, T. Tukiainen, J. Kettunen, L. D. Orozco, M. Pellegrini, A. J. Lusis, S. Ripatti, B. Zhang, M. Inouye, V.-P. Mkinen, and X. Yang, Mergeomics: multidimensional data integration to identify pathogenic perturbations to biological systems. *BMC Genomics* **17** (2016), 874.

35. T. Silva, W. Jger, M. Neuss-Radu, and A. Sequeira, Modeling of the early stage of atherosclerosis with emphasis on the regulation of the endothelial permeability. *J. Theor. Biology* **496** (2020), 110229.

36. V. Sokolov, G. Helmlinger, C. Nilsson, K. Zhudenkov, S. Skrtic, B. Hamrn, K. Peskov, E. Hurt-Camejo, and R. Jansson-Lfmark, Comparative quantitative systems pharmacology modeling of anti-PCSK9 therapeutic modalities in hypercholesterolemia. *J. Lipid Research* **60** (2019), 1610–1621.

37. M. Soleimani, A. Haverich, and P. Wriggers, Mathematical modeling and numerical simulation of atherosclerosis based on a novel surgeons view. *Archives of Computational Methods in Engineering* (2021).

38. J. V. Soulis, D. K. Fytanidis, V. C. Papaioannou, and G. D. Giannoglou, Wall shear stress on LDL accumulation in human RCAs. *Medical Engineering & Physics* **32** (2010), 867–877.

39. J. V. Soulis, M. Dimitrakopoulou, and G. D. Giannoglou, Low Density Lipoprotein transport in the normal human aortic arch. *Hippokratia* **18** (2014), 221–225.

40. N. Sun, N. B. Wood, A. D. Hughes, S. A. Thom, and X. X. Yun, Effects of transmural pressure and wall shear stress on LDL accumulation in the arterial wall: a numerical study using a multilayered model. *Amer. J. Physiology-Heart Circ. Physiol.* **292** (2007), H3148–H3157.

41. M. P. Thon, A. Hemmler, A. Glinzer, M. Mayr, M. Wildgruber, A. Zernecke-Madsen and M. W. Gee, A multiphysics approach for modeling early atherosclerosis. *Biomechanics and Modeling in Mechanobiology* **17** (2018), 617–644.

42. M. P. Thon, M. R. Myerscough, and M. W. Gee, A spatially resolved and quantitative model of early atherosclerosis. *Bulletin Math. Biology* **81** (2019), 4022–4068.

43. M. J. Tindall, J. A. D. Wattis, B. J. OMalley, L. Pickersgill, and K.G. Jackson, A continuum receptor model of hepatic lipoprotein metabolism. *J. Theor. Biology* **257** (2009), 371–384.

44. M. K. Toroghi, W. R. Cluett, and R. Mahadevan, A multi-scale model for low-density lipoprotein cholesterol (LDL-C) regulation in the human body: Application to quantitative systems pharmacology. *Computers & Chemical Engineering* **130** (2019), 106507.

45. J. A. D. Wattis, B. OMalley, H. Blackburn, L. Pickersgill, J. Panovska, H. M. Byrne, and K. G. Jackson, Mathematical model for low density lipoprotein (LDL) endocytosis by hepatocytes. *Bulletin Math. Biology* **70** (2008), 2303–2333.

46. R.-X. Xu and Y.-J. Wu, Lipid-Modifying Drugs: Pharmacology and Perspectives. In: *Coronary Artery Disease: Therapeutics and Drug Discovery* (Ed. M. Wang), Vol. 1177. Springer, Singapore, 2020, pp. 133–148.

47. S. Xu, D. Kamato, P. J. Little, S. Nakagawa, J. Pelisek, and Z. G. Jin, Targeting epigenetics and non-coding RNAs in atherosclerosis: from mechanisms to therapeutics. *Pharmacology & Therapeutics* **196** (2019), 15–43.

48. L. Yang, L. Wang, Y. Deng, L. Sun, B. Lou, Z. Yuan, Y. Wu, B. Zhou, J. Liu, and J. She, Serum lipids profiling perturbances in patients with ischemic heart disease and ischemic cardiomyopathy. *Lipids in Health and Disease* **19** (2020), 89.