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Multi-scale Modeling of the Cardiovascular System: Disease Development, Progression, and Clinical Intervention

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Abstract

Cardiovascular diseases (CVDs) are the leading cause of death in the western world. With the current development of clinical diagnostics to more accurately measure the extent and specifics of CVDs, a laudable goal is a better understanding of the structure-function relation in the cardiovascular system. Much of this fundamental understanding comes from the development and study of models that integrate biology, medicine, imaging, and biomechanics. Information from these models provides guidance for developing diagnostics, and implementation of these diagnostics to the clinical setting, in turn, provides data for refining the models. In this review, we introduce multi-scale and multi-physical models for understanding disease development, progression, and designing clinical interventions. We begin with multi-scale models of cardiac electrophysiology and mechanics for diagnosis, clinical decision support, personalized and precision medicine in cardiology with examples in arrhythmia and heart failure. We then introduce computational models of vasculature mechanics and associated mechanical forces for understanding vascular disease progression, designing clinical interventions, and elucidating mechanisms that underlie diverse vascular conditions. We conclude with a discussion of barriers

that must be overcome to provide enhanced insights, predictions, and decisions in pre-clinical and clinical applications.

Keywords

Cardiac mechanics; Electrophysiological modeling; Cardiovascular fluid mechanics; Vascular mechanics; Extracellular matrix; Mechanical forces; Pathway network analysis; Constitutive model; Multi-scale modeling

I. Cardiac electrophysiological and mechanical models

Abnormal electrical and mechanical function in the heart is notoriously difficult to manage with drugs, devices or surgical intervention. Disordered cardiac rhythms may emerge from abnormalities in genes, proteins, cell signaling networks, cellular coupling, tissue heterogeneity and other components that can promote, modify and/or exacerbate cardiac disease. Subcellular processes interact nonlinearly in cardiac cells, leading to complex cellular dynamics that promote, across the scales of structural hierarchy, ***emergent electrical behavior*** at the level of the whole heart. Briefly, cardiac excitation occurs due to depolarization of cardiac myocytes, primarily due to the activation of fast voltage-dependent Na^+ channels that underlie the action potential upstroke. Activation is followed by a long phase of depolarization, corresponding to the action potential plateau, which allows time for Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum, binding of Ca^{2+} to contractile proteins on the sarcomeres, and coordinated contraction. Repolarization follows due to the time and voltage dependent activation of repolarizing potassium currents. Relaxation of contraction is coupled to the electrical repolarization phase, which allows filling of the ventricles prior to the next excitation. Each of these electrical processes can be detected on the body surface electrocardiogram (ECG) as a signal average of the temporal and spatial gradients of membrane potential generated during each phase[37, 44, 80, 169]. Electrical excitation gradients in the atria (atrial depolarization) manifest on the ECG as P waves, while gradients of ventricular depolarization are seen as the QRS complex. Gradients in ventricular repolarization are reflected in the T wave. Abnormalities that are observed on the body surface are directly linked to perturbations at the subcellular, cellular or tissue levels. In this section we discuss bottom up models of cardiac electrical and mechanical function from molecular to organ scales (Figure 1).

Many technologies have been developed recently to allow for better characterization of cardiac electromechanics including medium- and high-throughput measurements of electrophysiology, optical imaging innovation that allows tracking of electrical propagation, high-throughput calcium imaging in isolated cells and hearts to assay contractile triggers, new stem-cell derived cell and tissue model systems for investigating cardiac function, and rapidly improving imaging technologies for *in-vivo* and clinical evaluation. All of these developing technologies are innovative and critical for precise and efficient data collection, but they focus only on constituent elements of the system.

A major challenge is to develop methodologies and new approaches to integrate data in physiological networks to reveal emergent mechanisms of disease and to facilitate prediction

and development of therapeutic interventions[2, 11, 76, 91, 103, 110, 136, 145]. *No reasonable, efficient and cost-effective experimental or clinical strategy that can achieve these goals is currently available*. The dearth of alternative approaches has motivated the community to develop multiscale cardiac electrophysiological and mechanical models that comprise systems for: 1) preclinical of physiological and pathophysiological cardiac mechanisms throughout a large, clinically relevant parameter range; 2) determination of the effects of system perturbations; and 3) prediction of therapeutic approaches including pharmacology, device and interventional therapy for specific clinical manifestations of rhythm and contractile disorders.

I.1 Bottom up approaches to cardiac multiscale modeling of electrophysiology

a. Protein scale – ion channel modeling—The general approach to develop the computationally based models of cardiac ion channels is as follows: First, the drug free channel data is collected from the literature: (1) Kinetic parameters are extracted from electrophysiological experiments for use as initial values as rate constants in the parameter optimization procedure. (2) Parameters are optimized via various optimization methods to multiple experimental data sets. (3) Sensitivity analysis is performed to identify key components and quantities underlying model dynamics, examine the limits on parameter estimation from experimental measurements, improve numerical stability, and test hypotheses.

b. Cell Scale – cardiac cellular models—Ion channel models can be incorporated into computationally based cardiac cells models to predict effects of perturbations on cellular level electrical activity and to simulate common arrhythmia triggers[111]. At this scale, multiple additional perturbations can be included, such as mutations, drugs, homeostatic or disease effects[110]. Other complex effects can also be included, such as the effect of cell signaling cascades, which directly and indirectly modify downstream processes[14, 48, 131, 171]. Prediction of arrhythmia mechanisms in simulated cardiac cells is typically carried out as follows: (1) A perturbation of interest will be incorporated into computational cardiac cell with various desired effects included. (2) Simulations will be run and arrhythmia vulnerability parameters tracked including cell excitability (max. upstroke velocity of the action potential (AP) (V/s)), action potential duration (APD), early after depolarizations (EADs), cell refractoriness and APD restitution[60]. (3) Sensitivity analysis will be performed and, when possible, (4) select predictions will be validated experimentally.

c. Tissue Scale – cardiac tissue models—Although cellular level studies can plausibly suggest reduced or increased arrhythmia vulnerability, reentrant arrhythmias are fundamentally an emergent property of the cardiac system that can only be observed and studied in tissue. Tissue level studies can be extended to investigate anatomical abnormalities, reduced coupling, anisotropy and even pathological settings such as the infarct border zone and end-stage heart failure[45, 54, 111, 146]. Models are generally developed as follows: (1) Models of normal or diseased myocardium are developed based on experimental data sets. (2) Simulations are carried out and arrhythmia vulnerability parameters tracked including APD restitution, conduction velocity (CV), and CV restitution.

Because conduction block promotes reentrant arrhythmias and wavebreak causing fibrillation[144], conduction block can also be tracked. The "vulnerable window" can be calculated to determine the likelihood of unidirectional block and retrograde conduction, which is expected to promote reentrant arrhythmia in higher dimensions[132–134, 164]. (3). Sensitivity analysis is performed and, when possible, as above (4) select predictions will be validated experimentally.

d. Organ Scale – Patient specific modeling—In modeling of heart rhythm and contractile disorders, focus has recently turned to clinically-driven problems and patient-specific modeling approaches, where the geometry and structure of the heart (including structural remodeling such as infarction or fibrosis) and in some cases, the torso geometry, are reconstructed from clinical imaging modalities[92, 102, 148, 149]. These geometrical models are combined with tissue-specific cellular models to develop dynamic patient-specific models. Clinical electrophysiological and mechanical information has also begun to be incorporated in simulation studies. This new level of modeling has rendered heart models capable of being utilized in personalized diagnosis, treatment planning, and prevention of sudden cardiac death, and their translation to the clinic is also slowly becoming a reality. Simulation studies have ventured into exploring cardiac electrophysiology in patients with implanted devices, and progress has been made in determining the most appropriate implantable defibrillator configuration in congenital heart disease and pediatric patients, where no standard of therapy exists[86]. Biophysically detailed models of the atria and ventricles assembled with data from clinical imaging modalities that incorporate electrophysiological and structural remodeling in cardiac disease could become a first line of screening for new atrial and ventricular antiarrhythmia therapies and approaches, new diagnostic developments, and new methods for arrhythmia prevention[5, 7, 87, 96, 107]. Future directions are likely to also include the prediction of sympathetic and parasympathetic activation and interaction and imbalance between the two branches of the autonomic nervous system.

I.2 Bottom-up approaches to cardiac multi-scale modeling of mechanics

a. Protein scale – myofilament and sarcomere modeling—The starting point for most multi-scale cardiac mechanical modeling at the macromolecular level has been models of the crossbridge and actomyosin interactions[150]. As these models have improved in biochemical detail they have provided a natural link between biomechanics and adenosine triphosphate (ATP) hydrolysis and energy metabolism[51, 63]. The main source of data for these models are kinetic experiments in isolated molecular motors (such as myosin motility assays) and isolated myofilaments. But in the cardiac myocyte, even more important than crossbridge cycling dynamics is the kinetics of filament activation by calcium *via* the troponintropomyosin complex on the actin filament. Until recently most multi-scale models have relied primarily on skinned fiber data on steady-state force-calcium relations that are also modulated by sarcomere length. However, newer models are now including the crosstalk between crossbridge attachment and calcium binding between neighboring regulatory units on the actin filament that gives rise to the cooperativity of contractile activation. Helping to inform these models are molecular dynamics models of troponin-C, troponin-I and actin[143]. Finally at the sarcomere level, the arrangement of the thick and thin

filaments determines myofilament overlap which underlies the length-dependence of cardiac contraction and gives rise to the Frank-Starling response in the whole heart[24]. These models are useful for investigating relationships between length, velocity and force generation by cardiac myofilaments as well as for studying the regulation of contraction by energy metabolism or post-translational modifications to regulatory proteins such as myosin light chain and troponin I.

b. Cell Scale – calcium regulation and multi-axial myocyte stress development —Myofilament and sarcomere models typically yield a one-dimensional tension or contractile force. There incorporation into whole cell models involves at least two additional processes. The lateral displacement between thick and thin filaments and the hexagonal arrangement of the sarcomeric lattice, result in crossbridge tensions being distributed both axially and transversely with respect to the myofibril axis of the myocyte[122, 141]. The role of changes in myofilament lattice spacing in regulating cardiac muscle contraction has been a question for many years that still remains unresolved. The other important whole component is excitation-contraction coupling. This is the point where the ionic models described above link with mechanical models. Inward calcium current due to membrane depolarization results in calcium-induced calcium release from the sarcoplasmic reticulum (SR) *via* ryanodine receptor release channels. Ionic models of cardiac myocytes routinely include this process, though it is worth noting and well recognized that the control of cardiac contraction by calcium-induced calcium release is a highly localized process distributed over several thousand release sites in each cell. The result is a graded release of SR calcium in response to a graded increase calcium current that ordinary lumped-parameter systems models do not properly represent[137]. Fortunately, detailed data from two-photon imaging of calcium kinetics[135] and super-resolution[130] and electron tomographic imaging[129] of subcellular microanatomy have allowed these mechanisms to be modeled in subcellular detail[33, 118], and for appropriate modifications to lumped parameter ordinary differential equation (ODE) models to be derived[47].

At this scale, multiple additional details can be included, such as the effects of mutations, drugs, homeostatic or disease effects. Regulatory mechanisms can also be included, such as the effect of cell signaling cascades, which directly and indirectly modify downstream processes[57, 70]. Since 2003, when the first myocyte model of excitation-contraction coupling to include the regulatory actions of a receptor-mediated signaling pathway (the β-adrenergic receptor pathway) was published,[119] increasingly detailed models of regulatory mechanisms have been reported.[52, 115] Prediction of mechanical alterations is then carried out as follows: (1) A perturbation of interest will be incorporated into computational cardiac cell with various desired effects included. (2) Simulations will be run and contractile parameters such as twitch force dynamics, shortening velocities and peak forces computed. (3) Sensitivity analysis will be performed and, (4) Specific predictions are then tested experimentally.

c. Tissue Scale – myocardial constitutive models—Although cellular level studies can plausibly suggest altered contractile function, regional and global ventricular pumping mechanics are integrative properties of the heart and cardiovascular system that are strongly influenced by the extracellular matrix and three-dimensional mechanics of the heart walls.

Tissue level properties must therefore be included such as the microarchitecture of myofibers, laminar sheets of myocytes, fibrous extracellular matrix, and the vasculature as well as the influence of pathologies such as, myocardial ischemia, infarcts and fibrosis.

Cardiac muscle fiber architecture has been primarily modeled as a spatially varying material coordinate transformation that defines axes of material symmetry based on histological measurements[120] or diffusion tensor magnetic resonance imaging (MRI) in *ex-vivo* tissues[95]. The mean muscle fiber orientations and laminar sheet planes at each wall location define a local structural coordinate frame that is used to define the material anisotropy of the tissue. Models have helped to establish that fiber architecture serves an important function in generating torsion during systole and diastole that helps to maintain transmural uniformity of sarcomere stress and strain[6, 71]. However, fewer models have investigated the contributions of laminar sheet orientations to wall mechanics and the experimental observation that they contribute to wall thickening[46, 78]. Even less explored is the role of the substantial dispersion of myofiber and sheet orientations in the ventricular walls and their regional variations that more detailed measurements are now quantifying.

Constitutive models were traditionally phenomenological but the success of microstructural models of the myocardial matrix[29] and valves[84] is encouraging the use of similar approaches to the myofiber architecture, and is creating a foundation for more biologically detailed agent based models of the cellular mechanisms that regulate tissue architecture[38]. Models of coronary vascular anatomy and blood flow[114] have been extended to include the mechanical effects perfusion on muscle mechanics using poroelasticity approaches[128].

Another area of accelerating activity is continuum models of tissue growth and remodeling. While the basic kinematic theory of growth is well established[152], new computational methods[69, 112] and constrained mixture approaches to modeling the effects of tissue restructuring[77] are extending the time-scales of biomechanical models to that of the natural history of cardiovascular diseases.

Constitutive parameters identified from individual subjects are notoriously variable and parameter estimation is complicated by strong material nonlinearities. However, reformulation of constitutive models so that response terms are orthogonal or nearly so[151] also has the consequence of making material parameter estimation better conditioned. Of critical importance in myocardial mechanical modeling is validation. *In-vivo* measurement of three-dimensional strains under well controlled loading conditions are perhaps the most stringent test of a three-dimensional cardiac model. MRI tagging and analysis using efficient three-dimensional strain analysis techniques such as harmonic phase (HARP) and displacement encoding with stimulated echoes (DENSE), and strain-rate imaging are some of the ways that are allowing *in-vivo* myocardial strain distributions to be measured non-invasively in humans as well as animals.

d. Organ Scale – whole heart and system electromechanics—Whole heart models of cardiac mechanics and electromechanics are now quite well established[31, 67, 147]and the emergence of cardiac atlas databases[16] will make the development of human models of disease easier. But there remain challenges to developing

human models, especially patient-specific models. These include deformably mapping measurements of ventricular fiber anatomy to patient-specific geometries[40], identifying the parameters of models that couple circulatory dynamics to myocardial mechanics[53], finding the unloaded reference geometry in models based on *in-vivo* measurements of cardiac anatomy[68], including the effects of the papillary muscles, valves and conducting system, identifying patient-specific material parameters, accounting for residual stresses, and determining disease specific parameters of underlying cellular models. Progress on all of these problems is opening up a new era in which patient-specific models of cardiac electrophysiology, mechanics, electromechanics, perfusion, metabolism and growth will aid in the diagnosis and management of heart disease, acquired and genetic, adult and pediatric.

II. Cardiovascular fluid mechanics

Cardiovascular fluid dynamics is an important topic for clinical translation, in large part because cardiovascular disease, as summarized in Table 2, is one of the leading causes of death in developed nations, and also because fluid dynamics has matured as a field involving computational methods[81]. With regard to multi-scale modeling, cardiovascular fluid dynamics and vascular disease progression (e.g., atheromatous disease, aneurysm growth) typically involve phenomena occurring over wide ranges of time scales (e.g., cardiac cycle, diffusion time, viscous, tissue relaxation) and length scales (e.g., vessel dimensions, endothelial and circulating blood cell size, clotting factor molecular dimensions). Multi-scale modeling of fluid mechanical aspects of cardiovascular physiology and of vascular disease development and progression, related medical diagnostic as well as clinical interventions are also yielding new and advancing translational impact into patient care. Development of multi-scale models which incorporate cardiovascular fluid dynamics as well as anatomical and physiological features of cardiovascular diseases are leading to the design of a multitude of clinical interventions involving advances in the structure of surgical vascular anastomoses, driving endovascular stent design, promoting new understanding of valvular and arterial stenotic disease, and guiding vascular repair of congenital and acquired cardiac abnormalities. Multi-scale modeling also has important implications for implementation of cardiac output support mechanical devices such as ventricular assist devices, intra-aortic balloon pumps and blood flow impellers.

II.1 Characterizing blood flow by disease, anatomy and imaging across scales

A major, broad goal for modelers in this field is to develop clinically useful approaches for maintaining or improving blood flow, which is the primary underpinning of end organ perfusion and oxygen delivery to tissue. A number of cardiovascular diseases are characterized by localized anomalous anatomical structure that endangers the patient by alterations in blood flow. These include vessel luminal obstruction by advancing atheromatous disease or thrombus growth, vessel wall abnormalities such as aneurysmal expansion or rupture, and failing heart pump function resulting from valvular defects, congenital cardiac malformations or impairment of cardiac contractility. Therefore knowledge of the normal and abnormal anatomical structures of the vascular system and blood flow patterns are required. These are commonly acquired via a number of available clinical imaging methods including magnetic resonance imaging[89], computed

tomography[27], ultrasound or Doppler flow assessment[101] and fluoroscopy. Both structural and flow detail derived from imaging can then be used to understand fluid-structure interactions[138], to develop models of blood flow[140] and to simulate computationally or numerically alternative methods and approaches to clinical patient management. Advancements in medical imaging and image segmentation now make it possible for patient specific image-based fluid dynamic calculations to be performed, enabling integration of multi-scale modeling into personalized medicine.

While obtaining accurate representations of blood flow *via* multi-scale modeling and simulation is challenging, it is fulfilling the promise of delivering sufficiently high quality information that it can be used as a virtual tool for guiding clinical decision making in surgical planning, device design and other forms of cardiovascular therapy. This is a result of the level of sophistication of multiscale methods and approaches, which have grown out of decades of computational fluid dynamics work and the associated difficulties therein. These have included addressing such complexities as i) the challenges in instituting appropriate boundary conditions in order to get correct representations of local flows; ii) recognition and accommodation of local hemodynamic properties which depend on a global circulation system yet have any number of control feedback mechanisms that are reactive to local disturbances; iii) treatment of the vascular tissues not just as blood flow conduits but rather as adaptive biological systems having distinctly variable mechanical properties that are part of the dynamic of fluid-solid interactions influencing blood flow conditions. We represent in Figure 2 a simplified form of the multitude of coupled phenomena influencing cardiovascular fluid dynamics which multi-scale models incorporate to provide clinically useful guidance for administration of systemic drugs or performance of surgical maneuvers (green hexagons) which serve mainly as control mechanisms (or, in clinical terms, treatments or therapies) to set back on track a local vascular system that is otherwise afflicted by the disease process.

II.2 Framework for multi-scale modeling elements in cardiovascular fluid mechanics

Our objective in this review is to present how multi-scale modeling has been used to complement the equations of motion describing blood flow, e.g., the Navier Stokes equations, that are the core elements of the model either for understanding specific diseases or for providing model-based clinical decision making tools for treatment planning such as surgical approach or initiation of drug therapy. No single model incorporates all the genetic, molecular, cellular, tissue-based and systems network issues represented in Figure 2. Therefore the art in developing effective multi-scale efforts has depended on the ability to incorporate only the minimum set of model element couplings necessary to reach a particular output goal as relates to a particular disease associated problem or a patient specific set of questions. The clinical context for formulating the problem is often limited by what can and cannot be measured and at what scales in both healthy and diseased states. The clinical and translational multi-scale models we have included in this review, while limited in number, are the outcome of pragmatic approaches often inspired by the needs of physicians in caring for their sick patients. We refer to these models in the context of the specific inter-linkages between elements shown in Figure 2.

LINK 1: *System/Network Flow and Transport → Local Hemodynamics Flow and Transport*.

Many investigators have addressed the problem of missing boundary conditions in the Navier Stokes equations One popular method is to construct a so called lump model that is a one dimensional network to describe the overall circulation system using a set of ODEs or dynamical system. This global system brought its core methods from electrical engineering. We refer to the original work of A. Quarteroni et al.[41, 104] for rigorous examination of mathematical algorithms for coupling the global scale of the system with the three dimensional Navier Stokes equations for an incompressible fluid. This system network flow approximation has been used extensively to provide missing boundary conditions to local flow simulation[154]. Less work has been focused on either taking advantage of similar approaches for controlling or utilizing the vascular system flow at the global scale[1, 75, 153], yet such work would enhance applications of multi-scale modeling to cardiovascular research.

Advancements in establishing proper boundary conditions based on anatomical relationships should follow with continued progress of medical imaging technologies including ultrasonography, MRI and computerized tomography (CT) scanning and other applications. A number of new techniques such as phase contrast MRI enable derivation of accurate time dependent boundary conditions[97] and may even suppress the need for multi-scale descriptions at the global system scale. However this argument does not apply when future surgical interventions on existing anatomy are to be analyzed. In those situations it is essential that new boundary conditions be predicted from multi-scale approaches.

LINK 12: *Tissue Deformation → Local Hemodynamics Flow and Transport*.

Fluid-structure interactions coupling hemodynamic phenomena with soft tissue mechanical properties are an exceedingly important aspect of multi-scale modeling[99, 139]. This has been a key focus of computational research in cardiac valvular mechanics[108, 163] as well as aortic and cerebral aneurysmal diseases and their clinical management[124, 125]. Real time ultrasound evaluation has long been used to provide detailed cardiac wall and valve motions. Recently live imaging techniques performed in vitro[12] and in vivo[158] have been utilized for extraction of mechanical properties of non17 cardiac vascular tissues. These techniques provide a basis for developing advanced models involving fluid-solid coupling. Inherently, both cardiac and vascular tissues are subject to time at multiple scales as a dominant aspect in normal physiology and disease progression. While cardiac valvular or arterial aneurysmal tissue changes often progress slowly at the scale of months to years, the time scale of the hemodynamic system operates at about one Hertz. Therefore an obvious question for clinical purposes is whether or not multi-scale temporal analysis is required to provide important analysis that will guide the scheduled timing of interventions (e.g., aneurysm stenting, valve replacement) as the pathophysiology progresses[139]. For instance, a very practical question that modeling in this field can address is whether or not control of systolic or diastolic blood pressure alters the risk of aneurysm rupture and thereby delays or eliminates the need for surgery.

Fluid-structure interactions also exert a major influence on blood flow distribution from the macro to the micro scale since tissue compliance is one of the major mechanisms by which blood flow is to peripheral tissues. While explanted human and animal tissues are still frequently studied for understanding the mechanics of normal and diseased states, and advances in imaging and image processing[12, 158] are making the extraction of mechanical properties of vascular tissue in vivo possible, it remains particularly challenging to obtain information regarding patient specific tissues and to measure the effect of supporting tissue for model construction. While these may limit modeling capabilities for personalized medicine, they still provide important insights regarding long term tissue growth and remodeling that are characteristic of the evolution of a disease or a component of postsurgical recovery. For example, anatomical changes such as vessel restenosis, including in-stent restenosis following vaso-occlusive disease treatment do indeed have a major impact on blood flow and are topics of multi-scale modeling that facilitates *in silico* hypothesis testing for treatment strategies[15].

LINK 10: *Tissue Remodeling → Local Hemodynamics Flow and Transport*

LINK 11: *Tissue Remodeling → Tissue Deformation*

Up to this point all the multi-scale model parts we have described can be approximated by partial differential equations (PDEs) that are derived from mechanical laws. This approach can logically be extended by imbedding a model that accounts for time-dependent changes in tissue into the constitutive equation of the relevant biological tissue or anatomical structure. This approach will incorporate the temporal evolution of a tissue's mechanical plasticity in response to environmental exposure conditions, or can reflect advancing disease, injury or healing processes affecting tissue properties[3]. Mechanical stress within the tissue wall resulting from application of a transmural pressure gradient or shear stress at the endothelial cell layer due to blood flow strongly impacts vascular disease progression and tissue responses following surgery[42, 43] and is therefore an important consideration in multi-scale approaches that yield clinically relevant predictions. Even greater sophistication will be achieved for modeling to aid cardiovascular healthcare by advancing algorithms that include molecular events in mechanotransduction, internal cell trafficking and signaling mechanisms and other phenomena contributing to overall tissue responses to mechanical and pharmacological stimuli. These are potent topics for future *in silico* treatment.

LINK 5: *Local Hemodynamics Flow and Transport → Molecules*

LINK 7: *Molecules → Tissue Response*

LINK 9: *Tissue Response → Tissue Remodeling*

The reaction diffusion convection PDE framework can be applied nicely to describe the engine that drives tissue transformation described above. At a molecular and tissue level this includes phenomena such as atheromatous plaque formation[65] and the mechanical behavior of stress fibers maintaining vessel wall structure[15, 155]. Critical to the coupling mechanism in multi-scale modeling is the manner by which the interface conditions account for molecular transfer from blood flow to the tissue wall, or for changes in molecular conformation and density affecting elasticity[105]. It should also be appreciated that mass transfer and mechanics are also coupled with interventional devices such as drug eluting

stents designed to take specific advantage of that mechanism to contribute to control of the disease[90]. Modeling interactions between drug eluting devices and the local surrounding media may require a reaction diffusion convection system driven by the interface condition with the device, and that can be quite geometrically complex and involve multiple time scales.

LINK 4: *Local Hemodynamics Flow and Transport → Genes*

LINK 6: *Genes → Cells*

LINK 8: *Cells → Tissue Remodeling*

Why should modelers pursue multi-scale approaches if the more simple PDE models are sufficient to understand the progression of cardiovascular diseases or the impact of a surgical maneuver (e.g., bypass vein graft, stent deployment, valve replacement) on resultant blood flow distribution and cardiovascular health? Do we need to model cells and genes? We are learning that mechanical (e.g., wall shear stress, strain energy inside the wall) and chemical (e.g., pharmaceutical) environmental conditions are determinants of cell mitosis, apoptosis, matrix production or degeneration, stress fibers conformation and other factors affecting vascular tissues[15, 43, 155], and hence gene- and cell-level phenomena influence fluid-structure interactions. A number of cellular automata and/or agent based model have been developed specifically to capture the impact on tissue plasticity especially in the field of cancer[32]. We refer in particular to the work of Walpole et al.[157] for application of multi-scale approaches to vascular diseases. Informatively, PDE-based approximations have inherent limitations when it comes to understanding small cell systems or situation where discrete events may percolate into dramat ic change of the overall system.; thus multi-scale integration may yield better insights.

LINK 2: *Systemic Drugs → Local Hemodynamics Flow and Transport*

LINK 3: *Systemic Drugs → Genes*

These are nascent areas of research in cardiovascular research, yet their relationship to the relevant blood flow dynamics will be foundational for developing and administering drugs and other therapies in order to control or treat vascular disease. A body of knowledge is already emerging regarding how drugs can be used to modulate gene expression, which in turn will affect cell behavior. This is another frontier for modeling advancements in cardiac health[10].

Finally, there are two additional unnumbered links represented on Figure 2 for the relationships of devices and surgery to cardiovascular fluid dynamics interactions. We have left these unnumbered to indicate both the lack of sufficient multi-scale models having yet been developed to address these interactions and also to indicate that even basic anatomical and physiological effects of these interventions in terms of wall deformation or local hemodynamics, flow and transport are rich for future investigation.

III. Vascular biology, imaging, and biomechanics

Multi-scale modeling of patient-specific vascular disease progression, clinical interventions, and mechanisms that underlie diverse vascular conditions will advance our understanding of

the casual relation between vascular biomechanical changes and CVD. This understanding can be used to develop clinically impactful diagnostics and therapeutics for vascular dysfunction. Noninvasive diagnostic should allow monitoring of disease progression, especially the initiation and progression of arterial remodeling in CVDs. As a prerequisite, several questions remain to be addressed such as the translatability of models derived from *in vitro* studies to the clinic, the most appropriate choice of simulation parameters, material assumptions, three-dimensional (3-D) images of vascular anatomy and structure, and utility of validations using clinical data. With the intent to identify challenges of patient specific multi-scale modeling, we describe future advances needed in vascular biology, medical imaging, and biomechanics to attain well-informed and validated patient-specific models.

III.1 Current status on vascular multi-scale modeling (Figure 3)

A blood vessel is made of three distinct layers with various fibrous structure in each layer. The thinnest layer is the innermost layer, the tunica intima, which is made up of a single layer of endothelial cells and its main purpose is to provide hemocompatibility with the blood. In arteries, the thickest layer is the tunica media, i.e., the middle layer of the vessel wall. The tunica media layer contains smooth muscle cells that are embedded in an extracellular matrix (ECM) of elastic lamella, collagen fibers, as well as aqueous ground substance matrix containing proteoglycans. Arteries tend to have a thicker tunica media layer in order to accommodate the pulsatile blood flow. The outermost layer in vessels is the tunica adventitia or tunica externa, which provides structural stability of the vessels. It is consists primarily of a dense network of type I collagen fibers.

a. Physics-based models—Blood vessels are anisotropic materials with orthotropic behavior and display nonlinear stressstrain response and viscoelasticity[82, 98, 174–178]. Over the last forty years, several models have been proposed for constitutive laws of passive blood vessels. Most of these models are phenomenological which mainly represent mathematical curve fits of the experimental data. The major shortcoming of phenomenological models is that the material constants have no direct physical meaning and hence do not facilitate an understanding of the connection between tissue architecture and the mechanical behavior (response to load, remodeling, growth, disease, etc.). Recently, there has been a trend towards incorporation of structural information into the constitutive relations[20, 23]. Microstructure-based constitutive models provide more accurate predictions of the overall mechanical responses of tissues than phenomenological approaches. Based on standard approximations in nonlinear mechanics, the microstructural models can be classified into three categories: 1) uniform-field models with solid-like matrix[59], 2) uniform-field models with fluid-like matrix[58, 73, 74], and 3) second-order estimate models[17, 18]. The first two categories assume affine deformation field where the deformation of microstructure is the same as that of the tissue, regardless of material heterogeneities; i.e., they represent the upper bounds of the exact effective strain energy and stress of soft tissues. In addition, the first type is not purely structurally motivated and hence cannot accurately predict the microscopic mechanical behaviors of soft tissues. The third category considers realistic geometrical features, material properties of microstructure and interactions among them and allows for flexible deformation in each constituent[19, 21, 22, 179]. The uniform-field model

with fluid-like matrix and the second-order estimate model are microstructure-based, and can be applied to different tissues based on microstructural features.

Structure-based models are essential for analysis of tissue mechanical response and understanding the individual role of each of tissue constituents in health and disease. Since several vascular pathologies are related to the degradation of tissue fibers, the prediction of the onset of these diseases can be done only by using a model which adequately incorporates the influence of each fiber type. Furthermore, the determination of microstructural stress requires a constitutive model based on the ultrastructure and the corresponding material properties. Complex microstructure and strong nonlinear mechanical behaviors of soft tissue, however, present significant challenges in constitutive modeling. Despite the complexity, the current trend in biomechanics is to move from phenomenological to micromechanical models in order to predict the overall nonlinear and microstructural responses of inhomogeneous soft tissues[20, 21, 58]. New developments in imaging and biochemistry will continue to provide more details of the constitutive properties of soft tissues, and continue to advance the development of structure-based models. The determination of the relative importance of the contribution of the various microstructural components can be assessed by a sensitivity analysis. The various microstructural and mechanical parameters can be varied over a large range (model inputs) and their effect (model outputs) on the parameters of interest (e.g., fiber or cell stress or strain, etc.) can be assessed. This approach can guide the focus of experiments on those parameters of greatest sensitivity.

As biological living organisms can autonomously respond to environmental stimuli, significant efforts have been made on continuum constitutive modeling of growth and remodeling. Here, we refer to several excellent recent reviews[8, 30, 88]. These models adequately account for the exchange of mass and change in structure of ECM constituents, and have been successfully applied to important problems in biology and medicine.

b. Agent-based models—An agent-based model (ABM) is a technique for simulating the actions and interactions of autonomous agents in order to assess their effects on the system as a whole. Agent based models are becoming more widespread because they are ideally suited for the analysis of complex, emergent phenomena. Accurately identifying agents and their characteristics (behaviors and interactions) is the key to a successful and useful agent model, but is also its most challenging task.

The vascular system is multi-scale in nature in both space and time. Modeling of this system could span from nanometer (molecule) to meter (whole organism), and range from milliseconds (molecular interactions) to years (diseases). Because of this difficulty and computational limitations, the work on multi-scale modeling using agent-based models is very sparse. For reviews on the integrations of computational models across scales, see for example[4, 93, 156]. Two of the most comprehensive multi-scale models for vascular biology use: (a) a lump analysis coupled with ODEs in order to create a model for the cardiovascular system[41]. The differences in time and space dimensions within the circulatory system are exemplified with blood flow and plaque formation (time dimension) and morphology of vascular districts (space dimension); and (b) an ABM coupled with PDEs in order to model

vascular adaptation[43]. This model accounts for multiple scales in both time and space, with a continuous mechanic description of flow and tissue deformation scaled in seconds and tissue adaption measured in hours. The spatial resolution of this model operates at a scale where the density of tissue is in millimeter scale. These modules are kept separate for computation and coupled weekly. In addition to the computational and theoretical challenges, the availability of appropriate biological data to both feed and validate the models is critical in order to successfully predict complex biological systems.

III.2 Existing Databases on Vascular biology for modeling

When generating any model in the cardiovascular system, several important relationships and databases are critical. For example, in vein graft remodeling[64, 106], many factors must be considered. The relationship between shear forces and endothelium cells is important[28, 34, 79]. In addition to shear stress, factors affecting the function of the endothelium need to be addressed, notably the impact of Nitric Oxide (NO) levels and blood pressure on vascular endothelial function, which can be found in Refs[55,36], respectively. Vascular endothelial growth factors and the corresponding receptor system should also be considered and addressed with regards to their impact on the agents for modeling vascular grafting[117, 121, 127]. The inclusion of receptor systems in multiscale modeling is critical to exhibit a wide range of regulatory properties. These include the ability to propagate information across different time scales and to function as switches and oscillators. The mechanisms underlying these complex behaviors involve many interacting components and cannot be understood by experiments alone. Mathematical models have been used to assist in the elucidation of regulatory mechanisms behind phenomena of importance in vascular physiology[50, 94, 170]. The integrative modeling of the vasculature is often adapted from the modeling of the heart[61, 62, 66].

The inclusion of genetic material can lead to a more accurate ABM model for vascular biology. The mechanisms behind how genes affect biological systems are currently being studied in vascular biology. For example, clinical studies have shown that a “single nucleotide in the $p27^{kip1}$ gene” affects the likelihood of success versus failure following vein bypass grafting[35]. The mechanical response of the graft to the high arterial pressure – or of medial-layer smooth muscle to loading in the case of arterial remodeling – should also be considered, so it is imperative that one understands the mechanical properties of the tissue at the continuum scale and also at the microscopic scale. Continuum-level studies of course abound, but microstructural data[100, 123], cellular mechanics data[85, 113, 166], and protein mechanical data are all emerging from both theoretical[13] and experimental studies[126]. Unfortunately, these data are often dispersed widely throughout the literature rather than concentrated into an easily accessible form, and the studies that generate the data are not always designed to assist the multi-scale modeler. Because of the nature of the biological processes in the human body, there are many other factors that are as important as the ones mentioned above in influencing the overall behavior of the system. The challenge in this field is not in the collection of single variable data sets but in our ability to design and analyze experiments that produce large multivariable data sets. This will allow us to explain how cell level functions arise, and to predict cellular behaviors leading to disease states and in response to therapeutic treatments.

III.3 Imaging Methods

Imaging modalities include MRI, CT, positron emission tomography (PET) and ultrasound at the organ level, micro-CT, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) at the tissue level, confocal, multi-photon microscopy, coherent anti-stokes Raman scattering (CARS) and electron tomography at the cellular level, and x-ray crystallography at the molecular level (Table 3). Structural imaging is necessary for quantifying organ, tissue, cellular and molecular structures which serve as a basis for the construction of mathematical and integrative models. Functional imaging is necessary for validation of the mathematical predictions of the biophysical models. Hence, imaging is essential to modeling.

Histology staining qualitatively distinguishes different cells and ECM components as well as their distribution. Advances in optical methods and image processing techniques have made it possible to study and quantify the architecture of structural components of soft tissues at different scales. Small angle light scattering, polarized microscope, nonlinear optical microscopy, and confocal laser scanning microscopy has been used and validated in quantifications of the collagen architecture in many biological tissues[109, 116, 123, 142, 165]. Using multiphoton microscopy, (second harmonic generation) SHG and two-photon excitation fluorescence (2PEF) signals have been simultaneously captured from arterial elastin and collagen in many studies[25, 26, 39, 56, 159, 172, 173].

Currently, the major challenge lies in the extraction of quantitative data from 3-D images of vascular systems[83, 167, 168]. The qualitative information necessary to make a clinical diagnosis is not sufficient to construct mathematical models. There is a great need for the development of computational algorithms that allow extraction of precise morphometric data efficiently and automatically. The main emphasis should be on in-vivo, 3-D imaging with sufficient spatial and temporal resolution that allows faithful mapping of imaging data into quantitative models. The predictions of these models should then be amenable to experimental validation with functional imaging or other experimental techniques. Patient specific modeling based on medical imaging has the potential to enhance our understanding of vascular biomechanics in health and in various disease processes such as hypertension, diabetes, atherosclerosis and heart failure.

IV. Future directions and challenges

In conclusion, we recognize that in spite of the many advances that have been made in multiscale modeling of cardiovascular systems and in its application to clinical problems and to biomedical problems in general, there remain many challenges. Perhaps the greatest challenge is *connecting the disparate scales*. We may be able to make an excellent model on the microscopic scale or of a small piece of tissue, but problem of interest may involve a large vessel and/or the heart, and the connection between the microscopic and macroscopic is rarely simple. Related to this is the challenge of *integrating multiple physical and biological processes*. Bridging across physics may prove to be as difficult as bridging across scales, and both are clearly essential. An additional concern is that the additional scales and physics necessarily complicate the model, leading to *increased computational demand*. Hardware and algorithm advances afford the potential for sufficient efficiency to overcome

this barrier, and we in the multi-scale modeling community would be well advised to follow and adopt such advances.

The personalization of the multi-scale model for patient-specific use is the great goal of much of our work, but it also entails additional challenge beyond those listed above. If one wishes to make patient-specific models effective, one must run simulations in real time or near real time, aggravating the problem of computational demand. One also must be prepared to use patient-specific data as input and to supplement those data with generic data to fill in gaps in the specific profile. Here statistical methods become important as well as an understanding of what data must be patient-specific and what data can be taken from generic databases; also it is imperative to understand the sensitivity of the specific answer to be obtained (e.g., should a surgery be performed) to the model outputs and therefore to the model inputs. As multi-scale models continue to improve, opportunities to apply them and to inform them with data from across biomedical science are expected to increase and to broaden.

As this review has shown, there are a wide variety of modeling approaches needed to bridge multiple scales and account for the different physics and biology that many problems in cardiovascular disease modeling demand. The Multi-Scale Modeling (MSM) Consortium wiki of the Interagency Modeling and Analysis Group (IMAG) maintained by the National Institute for Biomedical Imaging and Bioengineering maintains an up-to-date listing of modeling tools, platforms and databases at https://www.imagwiki.nibib.nih.gov/modeling-tools-databases. These resources include software tools for continuum modeling of solid mechanics, fluid mechanics and transport problems, particle-based methods for micro-scale simulations, and agent-based models for meso-scale multi-cellular modeling. There is no single paradigm for bridging scales though there are some recurring themes. Table 4, for example, illustrates parallels between some common approaches to multi-scale modeling in biomechanics, electrophysiology and biotransport.

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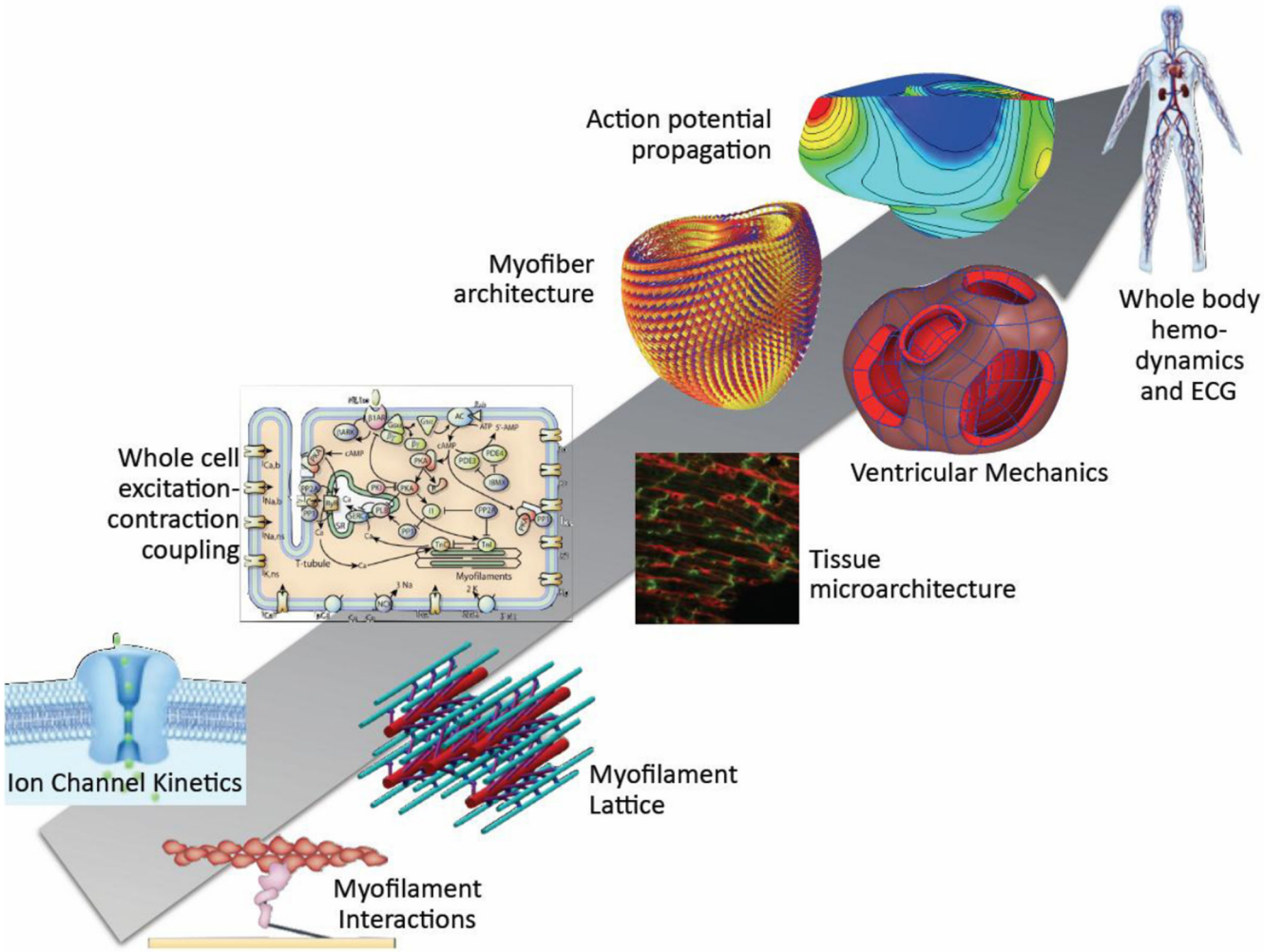

Figure 1.
Bottom-up multi-scale modeling of ventricular electromechanics.

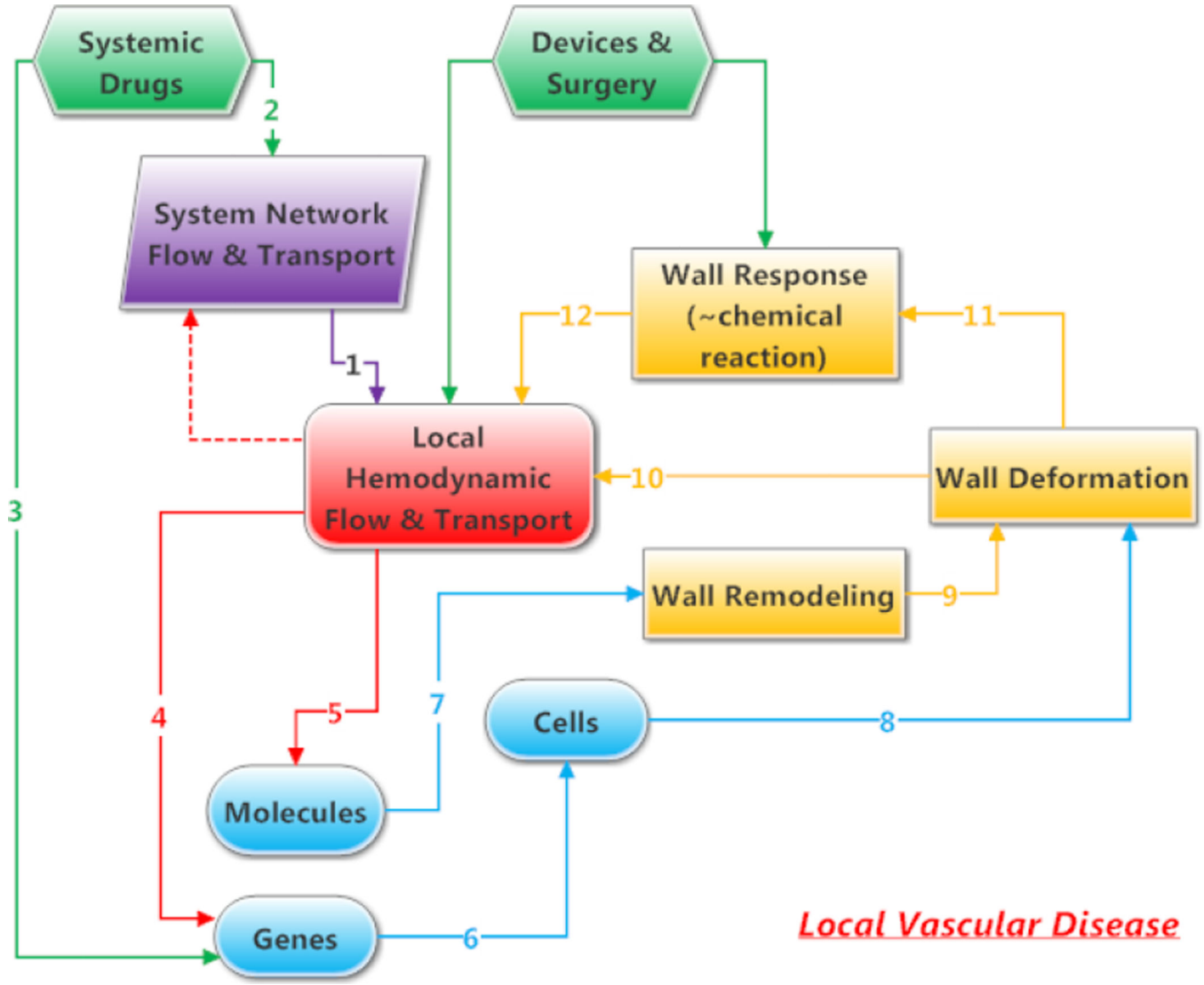

Figure 2.
Conceptual diagram of the modular organization of multi-scale modeling.

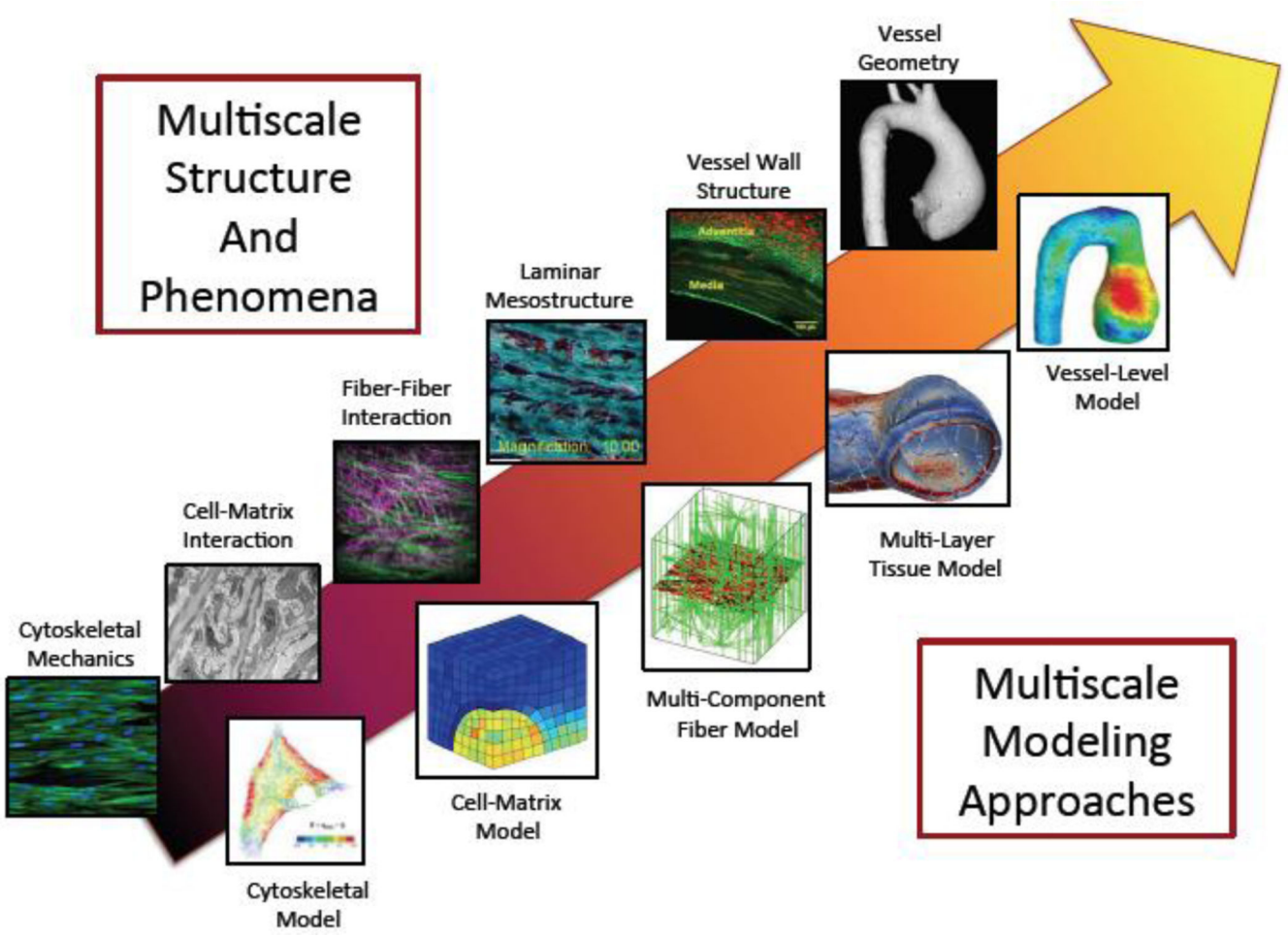

Figure 3.

Different scales of interest and models thereof in arterial mechanics. On the upper side of the arrow, phenomena from cytoskeletal mechanics (sub-micron scale) up to vessel geometry (centimeter scale) must be considered. Models that bridge those scales are shown on the lower side of the arrow. Cytoskeletal mechanics figure courtesy P. Alford; cytoskeletal model figure courtesy W. Ronan; tissue model figure courtesy G. Holzapfel. For further reference, see[9, 19, 21, 49, 72, 160–162].

Table 1

List of Acronyms and definition.

Acronym	Definition
2PEF	Two-photon excitation fluorescence
3-D	Three-dimensional
ABM	Agent-based model
APD	Action potential duration
ATP	Adenosine triphosphate
CARS	Coherent anti-stokes Raman scattering
CT	Computerized tomography
CV	Conduction velocity
CVD	Cardiovascular disease
DENSE	Displacement encoding with stimulated echoes
EADs	Early afterdepolarizations
ECG	Electrocardiogram
ECM	Extracellular matrix
HARP	Harmonic phase
IVUS	Intravascular ultrasound
MRI	Magnetic resonance imaging
NO	Nitric Oxide
OCT	Optical coherence tomography
ODE	Ordinary differential equation
PDE	Partial differential equation
PET	Positron emission tomography
SHG	Second harmonic generation
SR	Sarcoplasmic reticulum

Table 2

Common types of cardiovascular diseases, anatomic location, and brief description.

Cardiovascular Disease		Anatomic Location	Brief Description	Common Association
Congenital	I	Valvular Defects	Abnormal cardiac valve anatomy, typically stenotic	IV
	II	Cardiac Septal Defects	Direct, non-valvular communication between atria (atrial septal defect) or ventricles (ventricular septal defect)	
	III	Major Cardiovascular Abnormality	Includes Tetrology of Fallot, Transposition of Great Vessels and Hypoplastic Left Heart Syndrome	IV
	IV	Heart Failure	Loss of cardiac pump function	
Acquired	V	Valvular Disease	Abnormal function of a cardiac valve, including stenotic or regurgitant lesions	VI, IX
	VI	Coronary Artery Disease	Plaque accumulation in the arteries supplying blood to the heart	V, VII, VIII, IX
	VII	Peripheral Vascular Disease	Includes vaso-occlusive disease (plaque accumulation in the arteries supplying blood to the extremities) and aneurysmal disease (dilation and thinning of the vessel wall, occuring primarily in the aorta)	VI, VIII
	VIII	Carotid Artery Disease	Plaque accumulation in the arteries supplying blood to the brain	VI, VII
	IX	Heart Failure	Loss of cardiac pump function	

Table 3

Imaging methods of microstructure.

Method	Spatial Level
Micro-CT	Vessel
IVUS	Vessel
OCT	Intima
Microscopy (Confocal, 2PEF, SHG, CARS)	Cell and fibers
Electron Microscopy (Transmission and scanning)	Subcellular
Electron Tomography	Subcellular and macro-molecular
X-ray Crystallography	Molecular

Table 4

Common classes of multi-scale model of cardiovascular system biophysics and physiology.

Class of Model	Biomechanics	Electrophysiology	Biotransport
Continuum PDEs	Equations of motion	Monodomain equation	Reaction-diffusion equation
Constitutive Model	Strain energy formulation	Anisotropic conductivities	Diffusive properties
Systems Model	Myofilament activation and interactions	Ionic currents and action potential	Reaction network model
Statistical mechanics & thermodynamics	Filament mechanics	Ionic motions	Diffusing reactants
Brownian Dynamics model	XB binding	Channel state transitions	Molecular diffusion
Molecular model	Conformation	Permeation	Binding