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Computational Cardiology

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Abstract

Computational cardiology is the scientific field devoted to the development of methodologies that enhance our mechanistic understanding, diagnosis and treatment of cardiovascular disease. In this regard, the field embraces the extraordinary pace of discovery in imaging, computational modeling and cardiovascular informatics at the intersection of atherogenesis and vascular biology. This article highlights existing methods, practices, and computational models and proposes new strategies to support a multidisciplinary effort in this space. We focus on the means by which to leverage and coalesce these multiple disciplines to advance translational science and computational cardiology. Analyzing the scientific trends and understanding the current needs we present our perspective for the future of cardiovascular treatment.

Keywords

Cardiovascular imaging; Computational modeling; Cardiovascular informatics; Machine learning

I. INTRODUCTION

The growth and destabilization of high-risk atherosclerotic lesions is the root cause of the leading diseases that affect society today – myocardial infarction (heart attack) and cerebrovascular accidents (stroke). Until recently the genesis and evolution of these lesions could only be followed histologically and post-mortem. Today modern imaging increasingly provides in-life visualization of pathologies of the vessel wall and the circulatory system and is the primary means of early identification of patients at high risk of cardiovascular events. In addition, innovations in technology and data analysis, coupled with advanced

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computerized methods can change clinical practice and help establish a rapid, accurate, and reliable diagnosis of cardiovascular syndromes.

Computational cardiology is devoted to advancing mechanistic insight, inspired diagnosis and innovative therapies for cardiovascular disease by melding imaging sciences, computational modeling, informatics, and cardiovascular biology. Advances and sectors within *computational cardiology* have segregated along three major domain lines: imaging, health informatics and computational modeling. However, as the field is by its very nature interdisciplinary, incorporating elements of diverse disciplines, we are slowly seeing a blurring of line and coalescence of a single unified community.

The three domains are then coming together as a coherent whole. Imaging plays a prominent role in research and clinical practice, on the bench and at the bedside, and similar to most scientific fields, advances in the one area propels the other. The implementation of imaging differs in various domain spaces and, though the domains are converging, there remains domain-specific development. Advances in medical imaging facilitate acquisition of the structure of vessels and the whole heart with high resolution, enabling generation of realistic three-dimensional (3D) computational models. Moreover, they increase the amount of clinical data, boosting the field of cardiovascular informatics. The use of 3D computational models of cardiac anatomy and function combined with clinical data, advance patient-specific modelling and enhance our understanding of cardiovascular disease in particular. Research and development of novel computational methods, is increasing concurrent with translational investigation.

This article relates the exciting advances and future potential of these exciting areas and bridges the gaps between them (Fig. 1) to advance our understanding and provide novel treatments for critical cardiovascular diseases. Space precludes complete incorporation of all processes and so we primarily focus on atherosclerotic vascular disease (ASVD).

II. CARDIOVASCULAR IMAGING SYSTEMS

A. Imaging at bench

Imaging of the biological processes associated with plaque progression and destabilization is a primary step in understanding ASVD. Molecular imaging with Positron Emission Tomography (PET) [1] allows the detection and quantification of metabolic processes within the aortic wall. PET involves nuclear functional imaging, which detects pairs of gamma rays produced by a positron-emitting tracer. The tracer is inserted into the targeted tissue using a biologically active molecule. More specifically, the metabolite ^{18}F-fluorodeoxyglucose tracer (^{18}F-FDG PET) is a glucose analogue, which accumulates in macrophages residing with high density in fatty ASVD lesions [2]. ^{18}F-FDG PET is used to quantify carotid plaque inflammation [3] and there is a convincing evidence that it can depict the early stage of foam cell formation in vulnerable plaques [4].

Inflammation can also be measured using molecular imaging in the near-infrared region (700–1,000 nm) based on exogenous chromophores [5]. Fluorescence imaging provides an extremely useful platform for *in vivo* molecular imaging. Specific molecules, i.e.

fluorophores absorb and emit the light in a non-ionizing process. Near Infrared Fluorescence (NIRF) imaging can also highlight high-risk lesions in human carotids [6]. Recently, it was shown that non-destructive two-photon excited fluorescence imaging can identify early presence of calcification in aortic valves [7]. NIRS imaging [8] is another imaging modality capable to determine the chemical compositions of substances near-infrared light, which can distinguish lipid-rich and high risk-vulnerable atherosclerotic plaques [9]. The spectral analysis of the reflected near-infra-red light allows evaluation of the chemical composition of the plaque and identification of the lipid component.

Optical imaging is advantageous in that it provides fine resolution visualization (down to nm and intercellular scales) of biochemical and physiological processes without destructive processing [10].

B. Imaging at bedside

Cardiovascular imaging at bedside involves real-time methods to guide physicians in ASVD diagnosis and intervention. Cardiac catheterization, a.k.a. coronary angiography [11], is an invasive imaging technique which involves the use of X-ray combined with a contrast fluid, injected from the tip of the catheter, and is widely used to visualize the coronary arterial tree. Although coronary angiography can estimate the degree of arterial stenosis it gives no information regarding the morphology and structure of the blood vessel wall, or synthetic or metabolic state of the plaque. Therefore, other imaging modalities were developed which are capable of sufficiently imaging the coronary arterial wall.

Intravascular ultrasound (IVUS) is a catheter-based imaging modality that can be applied in parallel with coronary angiography. A small ultrasonic probe is mounted at the distal end of a catheter attached through the catheter proximal end to reconstruction computer [11], [12]. The reflected signals of the transducer are received and processed to produce cross sectional images of the arterial wall. Although IVUS is a reliable method for detecting plaque composition, it cannot depict accurately stented segments and large calcified plaques [13], due to the limited penetration of sound in hard tissue. Additionally, as a result of its low axial resolution (150μm) IVUS cannot detect fibrous cap thickness or any micro-calcifications which are highly associated with increased plaque vulnerability [14]. To overcome these limitations, optical coherence tomography (OCT) was adapted for intracoronary imaging [15]. Using light instead of mechanical waves OCT measures the time delay and magnitude of the backscattered light and generates cross sectional images of the wall in a similar way to IVUS. OCT is, however, capable of detecting atherosclerosis in detail as its axial resolution (15 μm) allows visualization of plaque micro-structures including the presence of neovascularization and micro-calcifications [15], [16], which correlate with plaque vulnerability. Visualization of the entire arterial wall is limited in OCT due to its poor signal penetration (2 mm). Lipid-rich tissue detection is also not reliable as light cannot penetrate soft tissue.

In contrast to intravascular imaging, which are mainly used for the visualization of coronary arteries, other imaging modalities were developed to depict larger arteries and parts of the cardiovascular system. These imaging modalities are noninvasive and have the potential for structural and functional discrimination – now widely used to study the anatomy of the heart

and of major vessels and to analyze plaque synthesis. Magnetic resonance imaging (MRI) uses strong magnetic fields at various resonance frequencies circular to the targeted vessel. The radio signal can represent position and tissue synthesis information. Different signal intensities are reflected from different tissue types using various image sequences [17]; T1-weighted (T1W), T2-weighted (T2W), Time of Flight (TOF), and proton density weighted (PDW). MRI, although expensive and logistically cumbersome, is considered an effective imaging method to define the anatomy of the cardiovascular system and evaluate atherosclerosis in the carotid and coronary circulations. In addition, four-dimensional flow or phase-contrast MRI (4D-MRI) enables comprehensive, yet coarse, hemodynamic flow assessments by measuring the velocity in all directions of the gradient magnetic field. 4D-MRI is used mostly to analyze, ventricle function, aortic valve disease, and aortic coarctation [18].

Similar to MRI, computed tomography (CT) is non-invasive emitting X-rays circular to the targeted tissue, producing cross-sectional (tomographic) images [11]. CT has the ability to identify the degree of stenosis and to image bones and different tissue types of tissue [19].

C. Combined imaging

Contemporary imaging techniques have fundamental limitations e.g. inaccurate evaluation of well-known plaque types, and failure in detecting high-risk lesions and providing simultaneously biochemical and anatomical state. Ongoing research in novel imaging methods and intravascular atheter development seeks to avoid these issues and to provide reliable identification of high-risk lsions and local metabolic state. However, no single imaging method can alone provide all that is rquired. Thus, multimodal approaches are continuously being developed to provide comprehensive vsualization of plaque biology and composition within arterial anatomy.

Combined NIRS-IVUS imaging [20] is an intravascular imaging technology approved for clinical use in the USA which aims to provide a detailed assessment of plaque composition. The combination of IVUS and NIRS in a single catheter provides an IVUS image within a lipid-rich area. This unique image includes information about a potentially-vulnerable plaque in patients with stable coronary artery disease [21] and is used to associate plaque characteristics with future clinical events [9]. Limitations attributed to low resolution remain - imaging high risk plaque characteristics as thin fibrous cap atheroma and estimating the neo-intimal stent strut coverage is still not feasible using NIRS-IVUS. Thus, similar to IVUSNIRS, a NIRS-OCT catheter was developed [22] which integrates OCT and NIRS imaging utilizing a wavelength-swept light source for both imaging modalities. NIRS-OCT is expected to enable the correlation between lipid rich plaques and microstructural features to serve the research in plaque progression. NIRF imaging is a molecular imaging used as an intravascular clinically-translatable method revealing biological details of coronary arteries [23]. NIRF-OCT is an imaging method similar to NIRS-OCT which combines OCT and NIRF signals to give an OCT image with a color coded ring around it [24]. OCT-NIRF has advantage of detecting and quantifying plaque inflammation [25].

IVUS and OCT, though seemingly interchangeable, are two imaging modalities which can be combined [26] to improve structural arterial representation. OCT has higher resolution

but limited tissue penetration and cannot depict sufficiently soft plaque [15], while IVUS can image the outer vessel border (media-adventitia) limited to sufficiently detect calcium [27]. The use of IVUS-OCT catheter in human patients with a real-time image acquisition is still under development [28]. Attempts also were made to integrate fluorescence imaging into the IVUS-OCT catheter and were tested *ex vivo* [29].

Cardiac PET imaging is also a non-invasive imaging modality which is often combined with CT or MRI. In PET-CT or PET-MRI the images are acquired simultaneously and then co-registered and combined into a single output. In this image there is information regarding the spatial distribution of biochemical and metabolic activity, and anatomy of the cardiovascular system. PET-CT has proven to be promising for evaluating atherosclerosis and inflammation in coronary arteries [30]. There is as well increasing enthusiasm for PET MRI imaging due to reduced radiation and ability to correct the heart motion with logistic and cost-related concerns [31].

III. COMPUTATIONAL MODELING

A. Computer-aided methods

Several methods have been developed in the last three decades to process imaging data, allowing fast and reliable detection of the structure and synthesis of the arterial wall. The majority of computational imaging methods are designed for coronary clinical applications at the bedside and involve processing images derived from IVUS, OCT, MRI, CT and angiographic systems. Widely used IVUS-based imaging allows automatic detection of lumen and media-adventitia borders [32]–[34], as well as definition of the synthetic state of atherosclerotic plaque [35]–[38]. Similarly, OCT-based computational methods can accurately detect the lumen [39]–[41], estimate the media-adventitia border [42] and depict major plaque formations [43]–[47]. The ability of OCT to image endovascular implants in high detail led to computerized methods for automatic detection and accurate measurement of those devices [48], [49]. The lack of information regarding the curvature of the artery in both IVUS and OCT, though, entailed combining their outputs with angiographic images [50]–[52]. The result is accurate and realistic 3D reconstructed coronary arteries which can be reproduced only using 3D non-invasive imaging methods, i.e. CT and MRI. The amount of data acquired by such non-invasive imaging methods led to the development of computational methods which automatically are able to create, in 3D, the arterial tree and major plaque formations such as calcified and lipid plaque.

Dedicated software (CAAS QCA 3D®) and methods [53] have been developed for the rapid reconstruction of the 3D coronary tree from angiographic images. Though they can provide additional information regarding pressure characteristics, they lack any plaque information. CT and MRI applications were also developed for reconstructing the heart and the valves and to perform accurate measurements [54], [55]. These software are used for research and radiological perspective, many of which are open source and freely available, e.g. Osirix Lite® and 3D Slicer®. Commercially available software allow the processing of images acquired by different image-capturing non-invasive modalities and more advanced image applications than segmentation, e.g. VITREA2® and AW VolumeShare 5®.

Computational imaging remains a leading element of the diagnosis, treatment, and study of ASVD outcomes. developed methods are used during intervention [56] or in the research arena [57]. However, mining and advanced analysis of large data in cardiovascular imaging might offer the potential not only to perform *in silico* research but also to provide novel diagnostics and prognostics based on cutting-edge computational methods. An attempt to schematically present the connection between different imaging models and their propagation from imaging and big data to complex cardiovascular models is shown in Fig. 2.

B. Computational models

Computer-aided methods can automatically detect the anatomy and plaque synthesis of the vessels wall and are widely used in the research and clinical arena. However, their role is limited in examining mechanistic understanding of the natural history of atherosclerosis, where biological and biomechanical forces dominate [58]. The biological cascade of events associated with transport of macromolecules such as Low Density Lipoprotein (LDL) and hemodynamic metrics such as Wall Shear Stress (WSS) play an important role in the pathogenesis and progression of atherosclerosis.

Physical models that seek to present these events can lead to better understanding of atherosclerosis. However, their relevance is limited by the accuracy in defining architecture and boundary conditions, and it becomes prohibitive to scan through all possible permutations and combinations. To this end, computational simulations were proposed to cost-efficiently model the mechanics and the biology of important components of the cardiovascular system. For instance, a mathematical model can be developed to simulate the electrophysiological behavior of the myocardium once heart anatomy and structure of the heart is defined in 3D [59]. Moreover, electromechanical heart models can attribute the overall organ function to structures from molecular level [60]. Pathological changes, which cause structural and functional cardiac remodeling, may affect the cardiac electromechanical performance and methods aiming to simulate both types of remodeling were developed [61]. There have been a number of methods focused on long-term patho-biological processes of the cardiovascular system, e.g. atherosclerosis [62]. Major mechanisms of atherosclerotic plaque growth have been presented using numerical growth models [63], [64]. Though here too precision is of paramount importance, and there remains a balance between ease of considering multiple conformations in a computer model and amount of data, processing, subsequent analysis, and model fitting for the production of patient-specific realistic 3D models [65].

Cardiovascular modeling has matured and is advancing towards personalized medicine [66]. Models are now *de rigueur* in a variety of disciplines including electrophysiology (EP), structural heart disease as well as vascular disease and involve solid mechanics, biochemistry, and computational fluid dynamics (CFD) verified by benchtop/preclinical experiments [67]. These mechanistic models of heart physiology extend to a variety of cardiovascular phenomena including electrical impulse propagation throughout the myocardial tissue [68], as well as hemodynamics in the ventricles [69], aorta, coronaries, cerebral and peripheral arteries [70] in addition to cardiac valves [71]. Models study wide range of pathologies such as aneurysms, stenoses [72], and malperfusion as well as valvular,

congenital [73], and ventricular diseases. Several clinical scenarios have been extensively studied including coronary artery bypass grafting (CABG), stent angioplasty, left ventricular assist devices, extracorporal membrane oxygenation (ECMO) life supports, cardiac resynchronization therapy, ablation therapy, and vascular surgeries [67].

The study of cardiac flow is divided into cardiac and vascular hemodynamics [74]. The former includes blood flow in heart chambers, while the latter discusses blood transport to/from these chambers via cardiac vessels. As simplified models can be readily applied in large vessels the more sophisticated computational modeling focuses on the circulation of smaller arteries by incorporating mathematical lumped-parameter models [75] to simulate the heart cycle. As boundary conditions play a significant role in computational hemodynamics their proper setting is important for the validity of the computational models. Therefore, lumped-parameter models can serve computational studies of larger vessels hemodynamics to tune the boundary conditions of the peripheral arteries [76].

In a more applied approach, computational modeling has been recognized by manufacturers and regulatory officials as an economical, yet reliable tool to advance the device design with optimized efficacy. As a case in point, drug-eluting stent development and evaluation has benefited tremendously from computational models in optimizing strut geometry, pharmacokinetics and pharmacodynamics of released drug, and procedural routines of implantation [77], [78]. Hemodynamic metrics of disrupted flow such as WSS, as well, has been extensively studied using computer models and correlated to atherogenesis and clinical events such as restenosis. [79]–[81] These local metrics of flow alteration are difficult to measure via *in vivo* imaging or benchtop experiments, yet accurately resulted from CFD [82]. Virtual intervention/surgery planning is a promising future step for computational models, wherein device type, sizing, and procedural guidelines might potentially be optimized in complex clinical cases [83], [84].

Computational models of heart still face several challenges that unless addressed would hinder introduction of personalized computational medicine into clinics[85]. Cardiovascular pathogenesis is accompanied by several other co-morbidities, such as diabetes and pulmonary edema, and initiated and accompanied by several risk factors including smoking, obesity, and other negative life habits. However, computational study of heart disease thus far has focused only on mechanisms and consequences of atherosclerosis and arrhythmia. More realistic prognoses and diagnoses would only be obtained if these confounding factors are also included.

Moreover, despite daily advances in medical imaging the resolution of *in vivo* data and their comprehensive calibration and validation are still the bottleneck of patient-specific models [86]. This will limit the application of personalized models to animal models wherein abundant *in vivo* and *ex vivo* data are available to tweak the computational models. In addition, more advanced numerical approaches, instantaneous access to patient-specific parameters, ease of immediate model adjustment, and high-speed computational hardware are required to achieve real-time simulations of clinical cases to facilitate the use of computational models in daily medical practices. Scientists, thus, are required to achieve an

optimal combination of imaging and computation to address critical issues of cardiovascular diseases in clinics [86].

Computational models possess the potential to open new vistas on diagnoses, prognoses, treatment, surgical planning, and disease prevention. The critical step towards introduction of computational medicine to daily medical practices is the automation of model creation to offer a scalable user-friendly platform to medical experts [87]. Thus, sufficient practical evidences are required to convince regulatory officials to allow clinical trials for this concept [85]. Needless to say continued advances in imaging modalities and image processing tools, as the most critical pre-requisite of computations, will push the borders of cardiac modeling above and beyond the preclinical/bench-top settings [88].

Research conducted in cardiovascular imaging is boosting studies towards understanding atherosclerosis. Advances in imaging atherosclerosis, computerized methods in cardiology, and methods developed that associate plaque development and shear stresses to atherosclerosis are significantly increasing over the last decade (Fig. 3). It is quite remarkable that the pace of research in imaging, computerized methods, shear stress, and plaque development are highly correlated and matched over the last 3 decades (Fig. 3 and TABLE II).

IV. CARDIOVASCULAR INFORMATICS & MACHINE LEARNING

Health informatics, the processing, storage, and retrieval of health data has changed the detection, diagnosis and treatment of diseases [89]. Like many explosive fields though success has bred challenges, especially in cardiovascular informatics [89]. The plethora of computer-aided and computational methods developed over the last two decade have increased significantly the amount of data produced and stored within hospital databases and research institutes [90] and yet not access to these images or signals.

Data sharing makes valuable information accessible to those who did not participate in the original trial, increasing the impact and reach of each study. Indeed, many journal publishers require data reuse and provide tools for data archival. Cardiovascular sciences strives to match the advanced insight extent in genomics and neuroscience [91] [92]. Yet, much work needs to be done for though publicly available cardiovascular imaging databases exist data demand exceeds supply.

Data sharing is expected to enhance cardiovascular research in the years to come. Until recently, the process of maintaining, sharing and accessing enormous amount of data was not feasible and therefore connecting datasets from different hospitals and research centers was not a high priority. Lately, the use of convolutional neural networks (CNNs) or deep learning in cardiovascular image analysis highlighted the need for large scale imaging datasets. CNNs are a class of machine learning where discriminative features are not pre-specified by experts but rather automatically learned from the trained images. Once a CNN model is trained on a sufficiently large dataset, it is able to generalize to new images. Yet, the mass of data required has hindered use of deep learning and we still rely on more basic

means of machine learning (Fig. 4, TABLE II) – a pattern we expect to see reversed as data becomes increasingly available.

V. THE FUTURE OF CARDIOVASCULAR TREATMENT

Computational cardiology remains yet, an unrealized challenge as the connection between imaging, informatics and modeling is inconsistent. The future of cardiovascular treatment lies in connecting the different elements and in leveraging future advances in hardware and software. Although imaging, computerized methods and computational modeling are related (Fig. 3 and 4, and TABLE II) there is still a gap between the recent technological developments in computer science; correlation is low between cardiovascular informatics and deep learning/machine learning in cardiology.

The challenges are clear. Only integration of simultaneous advances in medicine, imaging, data storage and computer science will allow computational models to enable clinical application and directed therapeutics (Fig. 5). Medical education most evolve to integrate computational and imaging sciences to create a new class of scientists well versed in all relevant domains to explain what these new tools are telling us and how to achieve critical treatment decisions [93].

VI. CONCLUSIONS

Computational cardiology is the scientific field devoted to the development of methodologies focusing on understanding the mechanisms of cardiovascular disease and in driving diagnosis and treatment. Technological progress in medical imaging, computational modeling and cardiovascular informatics proved to be crucial for understanding and treating cardiac diseases. They provide new premises in the field of computational cardiology and reveal new disease mechanisms. Following the technological and scientific trends of the last decades we can further understand how this progress took effect. *Studying history always shows us the way on how to move in future*; studying the scientific achievements in different scientific fields we advance each other. Moreover, we are able to make suggestions on how we can bring the fields of imaging, informatics, and computational modeling closer to advance translational science and computational cardiology. Riding on the heels of modern technological and scientific achievements we can present new approaches to treat cardiovascular disease. The journey has begun.

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Biography

Lambros Athanasiou was born in Ioannina, Greece, in 1985. He received his diploma degree from the Department of Information and Communication Systems Engineering, University of the Aegean, Greece, in 2009 and his PhD degree from the University of Ioannina, Greece, in 2015. Dr. Athanasiou is currently working as a Postdoctoral Research

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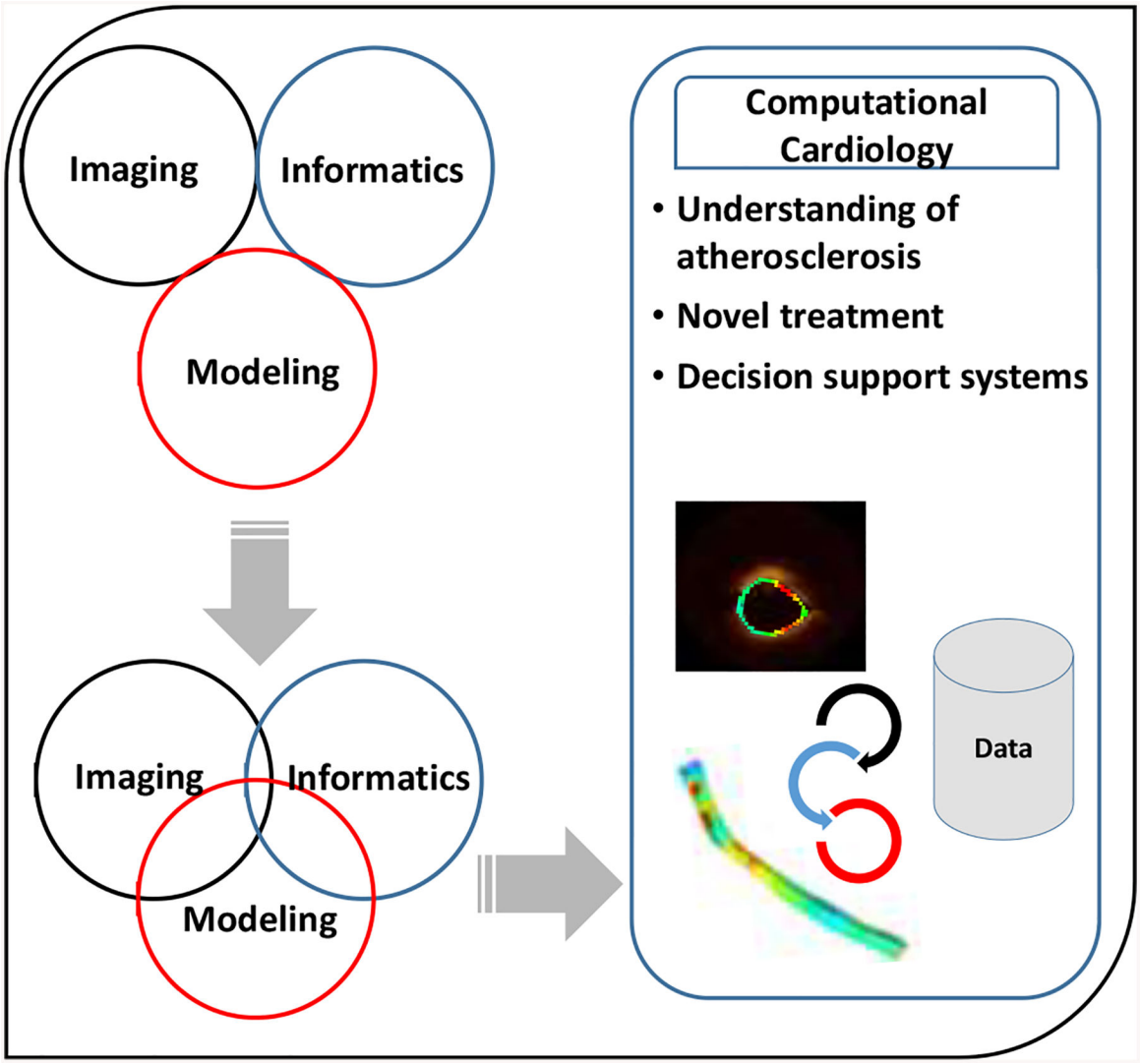

Fig. 1:
Schematic presentation of the propagation from basic science to computational cardiology. Following the flow arrows three major fields overlap, supplement each other and form computational cardiology.

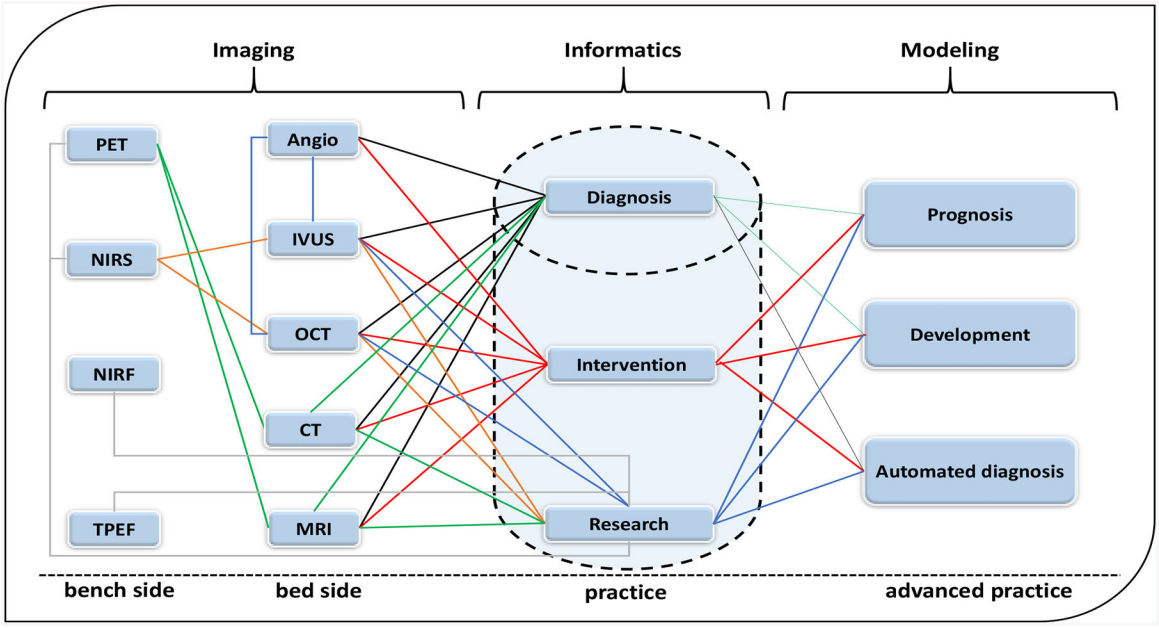

Fig. 2:

Interconnected group of imaging methods, clinical data and advanced treatment showing the existing dependence between them.

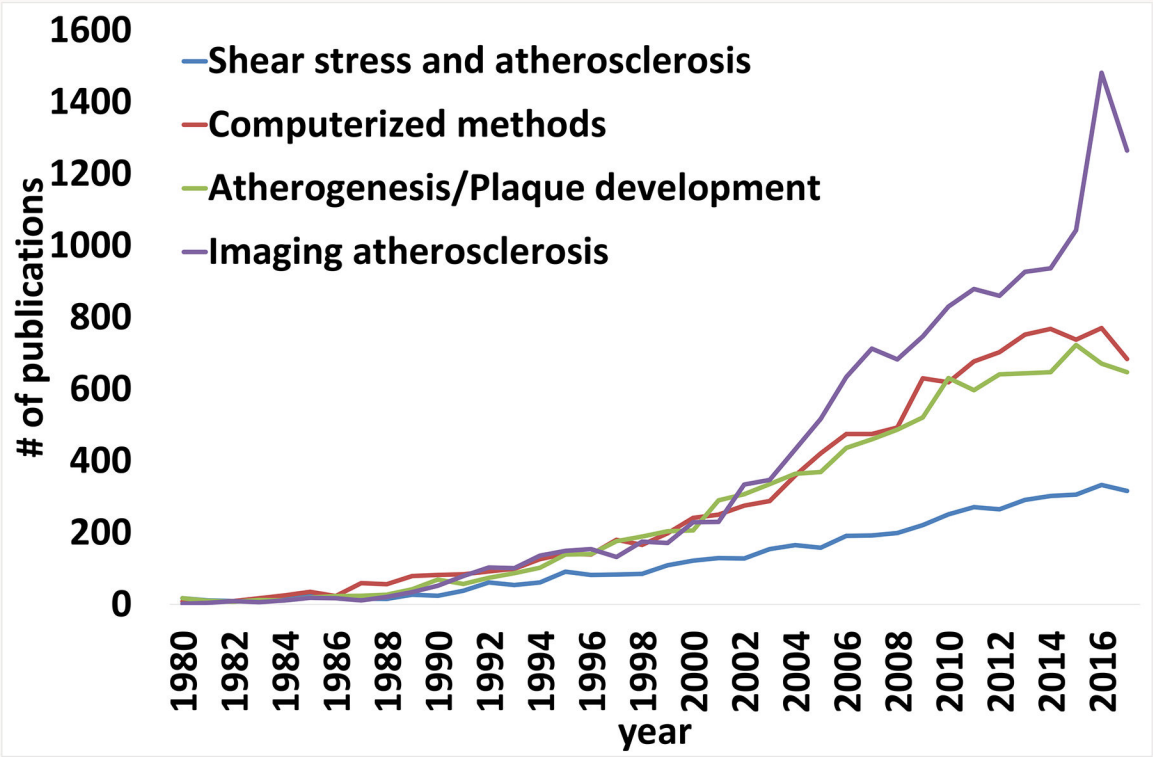

Fig. 3:

Distribution of published studies, within the last 37 years employing atherosclerosis and shear stress, computerized methods or algorithms, plaque development and imaging. Source: scopus.com.

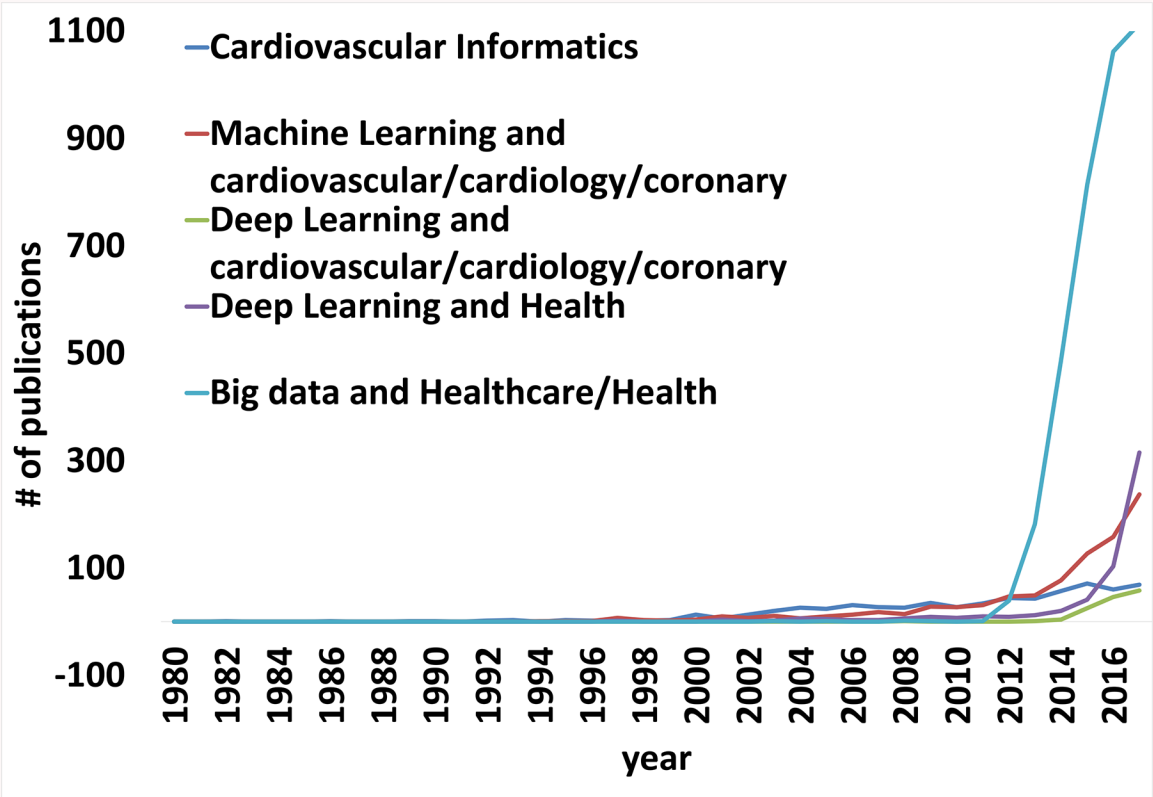

Fig. 4:
Distribution of published studies, within the last 37 years employing cardiovascular informatics, machine learning and cardiovascular or cardiology or coronary, deep learning and cardiovascular or cardiology or coronary, deep learning and health. Source: scopus.com.

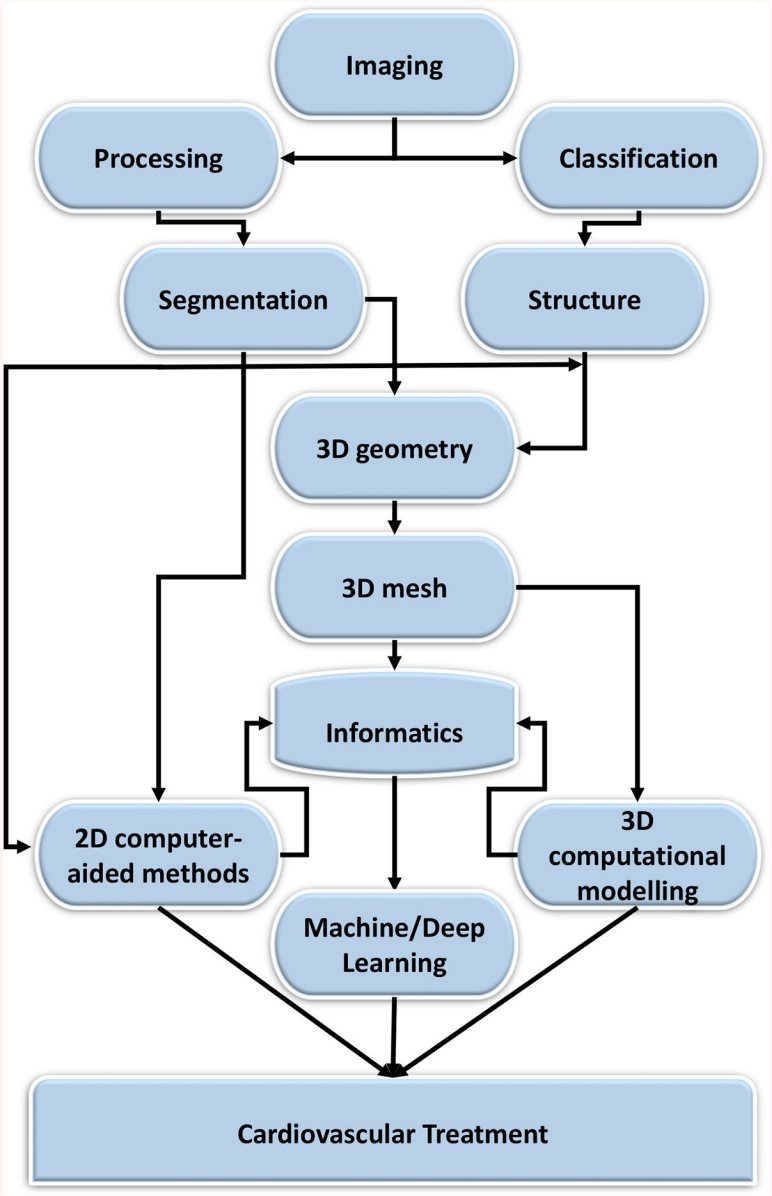

Fig. 5:
Scheme presenting the perspective of cardiovascular treatment according to this manuscript.

TABLE I:

STATISTICAL RELATION USING REGRESSION ANALYSIS BETWEEN THE NUMBER OF PUBLISHED STUDIES BASED ON SEVERAL SEARCH TERMS * AS PRESENTED IN Fig. 3.

r	stl	st2	st3	st4
stl	l	0.98	0.99	0.97
st2	0.98	l	0.99	0.96
st3	0.99	0.99	l	0.96
st4	0.97	0.97	0.96	1

* Search term (st) - st1: Shear stress and atherosclerosis, st2: Computerized method, st3: Atherogenesis/Plaque development, st4: Imaging atherosclerosis

TABLE II:

STATISTICAL RELATION USING REGRESSION ANALYSIS BETWEEN THE NUMBER OF PUBLISHED STUDIES BASED ON SEVERAL SEARCH TERMS * AS PRESENTED IN Fig. 4.

r	st5	st6	st7	st8	st9
st5	1	0.84	0.66	0.59	0.77
st6	0.84	1	0.94	0.89	0.96
st7	0.66	0.94	1	0.91	0.95
st8	0.59	0.89	0.91	1	0.81
st9	0.77	0.96	0.95	0.81	1

* Search term (st) - st5: Cardiovascular Informatics, st6: Machine Learning and cardiovascular/cardiology/coronary, st7: Deep Learning and cardiovascular/cardiology/coronary, st8: Deep Learning and Health, st9: Big data and Healthcare/Health