Biomechanics in AIMETA

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Abstract This chapter aims at presenting a concise picture of the research in Biomechanics developed by researchers of various disciplinary areas that refer to AIMETA. The research collectors are the international journal Meccanica, published by Springer, and the AIMETA congresses including publications of studies presented therein. This chapter is devoted to studies related to AIMETA activity and mainly refers to the topics from the above-mentioned sources. Final comments and future developments are outlined.

Keywords Biomechanics · Biological tissues · Articular biomechanics · Medical devices · Biological fluid mechanics · Cardiovascular mechanics

1 Introduction, from Mechanics to Biomechanics

Biomechanics is the science that studies the structure and function of biological systems using methods and knowledge of Mechanics.

The birth of Biomechanics can be dated back to the first studies of Aristotle (384–322 BC) and later developed by Galen (129–210), Leonardo da Vinci (1452–1519), Galileo Galilei (1564–1642), and Giovanni Alfonso Borelli (1608–1679), up to a few further advancements through the nineteenth and twentieth centuries. It found in the last 50 years a rebirth of interests that became an exponential growth in the last 20 years. In the 50's of the past century, it was in fact considered a subject for

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technicians rather than a science worthy of the scientific research attention, as it is today in its own right.

The extraordinary development during the recent decades is due to the combination of various factors, such as the development of both computational tools and 3D graphic representation, the improvement of measurement techniques and instruments. It also benefited of the greater attention that today is paid to the centrality of the health and wellness of the human being, which led to the convergence on Biomechanics of various areas of knowledge, from Medicine to the different branches of Engineering, passing through Physics, Materials Science, advanced technologies (Vision, Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Fluoroscopy, 3D printing, etc.), highlighting the strongly interdisciplinary aspect of Biomechanics.

This convergence of knowledge has allowed on the one side to build increasingly refined mathematical models of physical and biological phenomena, and on the other side to develop advanced analysis and synthesis tools, which allow prompt and preventive diagnoses, as well as efficient design methods of medical devices and instruments.

Theoretical and applied Biomechanics developed naturally as a sub-specialty of Mechanics. They started from theoretical and applied interests in various branches of Mechanics holding competencies needed to study problems of biomechanical relevance.

In order to give wide visibility to the activities of Biomechanics in the AIMETA community, the AIMETA Biomechanics Group (GMBA) was established, with the aim of aggregating skills of the different sections and stimulating synergies on Biomechanics issues. It is hardly necessary to emphasize that Italian research in Biomechanics is at the forefront of the international state of the art. Unfortunately, space limits prevent to give an account of all the biomechanical issues developed so we apologize to readers for the inevitable omissions. Priority was given to research originated or presented within the AIMETA activities.

2 Developments Since 70's to Nowadays

2.1 Tissue/Solid Biomechanics

The relevance of bioengineering problems to applied mechanics was recognized by the President of AIMETA in the preface to the proceedings of the II AIMETA conference (Naples 1974). However, it was after the XV AIMETA conference (Taormina 2001), hosting the first mini-symposium on Mechanics of Tissues and Implants [70], that AIMETA conferences became an important forum for discussion and exchange of ideas among different areas of Biomechanics and for identifying potential collaborations to address most challenging biomechanical problems. Contributions ranged from fundamental research to clinical applications, including theoretical, computational, and experimental work, facing problems whose physical dimensions span from the microscopic environment, at the cell-size, across the intermediate scales up to the macroscopic and organ level. Themes ranged from molecular and cell mechanics to cell motility, from mechanics of soft or mineralized biological tissues to growth and remodeling, from organ mechanics to medical devices. Such a variability reflected in a great variety of physical problems and required the development of a similarly wide range of methods and concepts.

The mechanical characteristics of *cells* are highly variable across phenotype and dynamically evolve in response to changes in the microenvironment. Cells behave as both passive and active materials, supporting and transmitting loads and generating forces. In turn, cells sense and respond to chemo-mechanical signals from their environment (e.g., [53]). Their mechanical properties have emerged as potential label-free biomarkers for detecting the presence of an underlying condition or disease (e.g., cell activation, degree of differentiation, or metastatic potential).

Several experimental techniques are available to study cell mechanics. Because a typical cell body is about 10 μm in diameter, to capture a complete picture of mechanical interactions and physical properties of cells, the resolution of the tools utilized in cellular biophysical studies has to be in that order of size or smaller. Traditional methods, such as micropipette aspiration, atomic force microscopy or optical tweezers have limited throughput. Emerging microfluidics-based methods have enabled single-cell mechano-phenotyping at throughput of thousands of cells per second [40]. Information gained from these studies is utilized in computational models that address cell mechanics as a collection of biomechanical and biochemical processes (e.g., [53, 62]). These models are advantageous in explaining experimental observations by providing a framework of underlying cellular mechanisms. They also enable predictive, in silico studies, which would otherwise be difficult or impossible to perform with current experimental approaches.

Several studies investigate *nanoscale structures*, including macromolecules and their aggregates. Proteins constitute the main building blocks of biological systems, and their mechanical vibrations play a pivotal role in biological activity. Lowest-frequency vibration modes are related to protein conformational changes, which are strictly linked to their biological functionality. Scaramozzino et al. [87] present a coarse-grained finite element space truss model suitable for investigating protein vibrations. Based on modal analysis, their model turns out to be an effective tool to investigate protein dynamics, conformational changes and protein stability. Collagen is the main structural protein in the extracellular matrix. Marino and Vairo [51] propose an elasto-damage model for the mechanics of collagen fibrils. They apply a multiscale approach that allows to account for nanoscale mechanisms and to introduce model parameters with a clear biophysical/biochemical meaning. Their model is able to reproduce many well-known experimental features of fibril mechanics.

Mechanical signals received by a cell can originate in the external environment, or they can be the signals from extracellular matrix or neighboring cells. Mechanical signals are transmitted to the appropriate targets inside the cell through biochemical pathways or relayed through the *cytoskeleton*. Various signaling pathways may

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be activated after mechanical signal reception, depending on the type of mechanical stimulus received (whether it be tension/stretch, compression/contraction, or shear/distortion). Mechanical signals may also be transmitted to the nucleus through the cytoskeletal network and affect transcription processes. In his pioneering work, Ingber [41] surmises the cytoskeleton behaves like a tensegrity architecture, i.e., a system of isolated components under compression (microtubules) inside a network of continuous tension (microfilaments and intermediate filaments). Fraldi et al. [32] remove the standard hypothesis of rigid struts in tensegrity structures when used to idealize the cell cytoskeleton mechanical response. Accordingly, they explain some counter-intuitive mechanical behaviors actually exploited by cells for storing/releasing energy, resisting to applied loads and deforming. Focal adhesions operate at the interface between cells and extracellular matrix, as part of the cell mechano-sensing machinery. Fusco et al. [33] investigate how the dynamics of assembly and disassembly of focal adhesions is influenced by the substrate stiffness. Their approach to focal adhesion dynamics characterization is a valuable investigation tool for cell mechano-biology. Vigliotti et al. [92] analyze the response of cells on a bed of micro-posts. They use a homeostatic mechanics framework, enabling quantitative estimates of the stochastic response of cells along with the coupled analysis of cell spreading, contractility and mechano-sensitivity. Their results suggest that the increased foundation stiffness causes both the cell area and the average tractions exerted by cells to increase.

Biological tissues are ensembles of cells and extracellular matrix that together carry out a specific function. The range of mechanical properties exhibited by biological tissues is remarkable, and depends on both composition and structural organization of the constituent materials at nano- and micro-scales and the resulting tissue architecture/geometry at meso- and macro-scales. Understanding the mechanics of these complex materials is very challenging, given the multitude of intricate physical mechanisms that act over a very wide range of spatial and temporal scales. Soft tissues include muscle, tendons, ligaments, blood vessels, etc., and are characterized by abundant extracellular matrix containing collagen, elastin and ground substance. Mineralized tissues fulfill critical load-bearing functions throughout the skeleton, facilitated by hierarchically organized structures that are optimized to provide high stiffness and/or excellent resistance to fracture. Tissues have evolved over millions of years into complex and diverse shapes under the forces of natural selection. Evolution has also provided tissues with the capability to adapt to their specific environments during growth and to remodel and regenerate if they are damaged [20, 71].

Bone is a mineralized heterogeneous material with microstructural features. Fatemi et al. [28] use generalized continuum mechanics theories to account for the influence of microstructure-related scale effects on the macroscopic properties of bone. Falcinelli et al. [27] describe healthy bone and metastatic tissue using a linearly poroelastic approach, proposing a strategy for the quantification of fracture risk in metastatic femurs.

The anisotropic, non-linear elastic behavior of *soft biological tissues* may be accounted for by the hypothesis of hyperelasticity, using Fung-type potentials. Federico et al. [29] derive a necessary and sufficient condition for the strict convexity of such potentials, providing a clear physical meaning for the involved parameters and their relationship with the small-strain elastic moduli. Maceri et al. [50] study the mechanical response of soft collagenous tissues with regular fiber arrangement, using a nanoscale model and a two-step micro–macro homogenization technique. Entropic mechanisms and stretching effects occurring in collagen molecules are accounted for at the nanoscale. The model is based on few parameters, directly related to histological and morphological evidences. It is applied to tendon, periodontal ligament and aortic media, and is used to simulate some physio-pathological mechanisms.

The constitutive behavior of biological tissues is generally *time-dependent*. Vena et al. [91] present a constitutive model of the nonlinear viscoelastic behavior of ligaments, as a generalization of the quasi-linear viscoelastic theory. The time-dependent constitutive law assumes that a constituent-based relaxation behavior may be defined through different stress relaxation functions for the isotropic matrix and for the collagen fibers. The model is able to predict the time-dependent response of ligaments described in experimental works. Deseri et al. [24] introduce a hierarchic fractal model to describe bone hereditariness. The rheological behavior of the material is obtained using the Boltzmann–Volterra superposition principle. The power laws describing creep/relaxation of bone tissue are obtained by introducing a fractal description of bone cross-section, with the Hausdorff dimension of the fractal geometry related to the exponent of the power law. A discretization scheme is proposed by Di Paola et al. [25].

Tissues are organized into *organs*. Among the biomechanical studies of different organs, the biomechanics of the *eye* has received significant attention. The human cornea has the shape of a thin shell, originated by the organization of collagen lamellae parallel to the middle surface of the shell. The lamellae, composed of bundles of collagen fibrils, are responsible for the anisotropy of the cornea. Anomalies in the fibril structure may explain the changes in the mechanical behavior of the tissue observed in pathologies such as keratoconus. Pandolfi and Manganiello [63] employ a fiber-matrix constitutive model and propose a numerical model for the cornea that is able to account for its mechanical behavior in healthy conditions or in the presence of keratoconus, opening a promising perspective for the simulation of refractive surgery on anomalous corneas. Romano et al. [79] experimentally assess the differences between highly myopic eyes and emmetropic eyes in the biomechanical response to ex vivo uniaxial tests of the human sclera.

Biomechanical modeling of the *head* is crucial to analysis and simulation of traumatic brain injuries under impact loads, virtual reality and robotic techniques in neurosurgery, design and assessment of helmets and other protective tools. Velardi et al. [90] perform an experimental analysis and present a transversely isotropic hyperelastic model of tensile behavior of brain soft tissue. They adopt a transversely isotropic hyperelastic model and obtain material parameter estimates through tensile tests, accounting for regional and directional differences.

Muscles have the function of producing force and motion, and are responsible for posture, locomotion, as well as movement of internal organs. Phenomena causing muscle contraction range from the subcellular ion dynamics up to the macroscopic excitation–contraction coupling. The multi-physics behavior of muscle tissues fostered a continuous forefront research in Biomechanics. Cherubini et al. [13] present an electromechanical model of myocardium tissue coupling a modified FitzHugh-Nagumo type system with finite elasticity, endowed with the capability of describing muscle contractions. The diffusion process is set in a moving domain, thereby producing a direct influence of the deformation on the electrical activity, thus explaining various mechano-electric effects. Pandolfi et al. [64] develop a constitutive model for stochastically distributed fiber reinforced visco-active tissues, where the behavior of the reinforcement depends on the relative orientation of the electric field. They use their electro-viscous-mechanical material model to simulate peristaltic contractions on a portion of human intestine.

In addition to mechanical function, biological tissues and organs are living objects and present a capability of functional adaptations in response to diverse chemo-mechanical stimuli. Their behavior is governed by *growth and remodeling* responses on time scales from hours to months. Mechano-regulated growth and remodeling plays important roles in morphogenesis, homeostasis, and pathogenesis, including disease progression wherein normal tissue is altered (e.g., aneurysms), organs adapt (e.g., cardiac hypertrophy or dilatation) or abnormal tissue develops (e.g., tumors). Experimental methods and theoretical frameworks provide an increasingly detailed understanding of molecular and cellular mechanisms of growth and remodeling as well as tissue-to-organism level manifestations [2, 3, 21].

Grillo et al. [38] represent a biological tissue by a multi-constituent, fiber-reinforced material, in which two phases are present: fluid and a fiber-reinforced solid. They study growth, mass transfer, and remodeling. Sacco et al. [82] propose a mathematical description of biomass growth that combines poroelastic theory of mixtures and cellular population models. The formulation, potentially applicable to general mechano-biological processes, is used to study the engineered cultivation in bioreactors of articular chondrocytes.

Preziosi and Tosin [72] develop a multiphase modelling framework for the description of mechanical interactions of growing tumors with the host tissue. They account for the interaction forces between cells and a remodeling extracellular matrix, and for the diffusion of nutrients and chemicals relevant for growth, describing the formation of fibrotic tissue. Carotenuto et al. [12] take into account residual stresses that develop to make compatible elastic and inelastic growth-induced deformations. The residual stresses directly influence tumor aggressiveness, nutrients walkway, necrosis and angiogenesis.

Activity and autonomous motion are fundamental in living and engineering systems. The field of *active matter* focuses on the physical aspects of propulsion mechanisms, and on motility-induced emergent collective behavior of a large number of identical agents, whose scale range from nanomotors and microswimmers, to cells, fish, birds, and people. This is an interdisciplinary topic that involves different aspects related to the mechanics of machines, of solids and their interaction with the surrounding fluids.

Inspired by biological microswimmers, various designs of autonomous synthetic nano- and micromachines have been proposed [37]. Swimming, i.e., being able to advance in the absence of external forces by performing cyclic shape changes, is

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particularly demanding at low Reynolds numbers. This is the regime of interest for micro-organisms and micro- or nano-robots. Alouges et al. [1] present a theory for low-Reynolds-number axisymmetric swimmers and a general strategy for the computation of strokes of maximal efficiency. Arroyo et al. [4] study euglenoids, exhibiting an unconventional motility strategy amongst unicellular eukaryotes. That strategy consists of large-amplitude highly concerted deformations of the entire body, mediated by a plastic cell envelope called pellicle. A theory for the pellicle kinematics is devised, providing an understanding of the link between local actuation by pellicle shear and shape control, and suggesting that the pellicle may serve as a model for engineered active surfaces with applications in microfluidics. Gidoni and DeSimone [36] formulate and solve the locomotion problem for a bio-inspired crawler consisting of two active elastic segments, resting on three supports providing directional frictional interactions.

Another example of amazing mechanics taken from Nature is given by spiders' weight lifting. Pugno [73] discusses the smart technique they use, allowing a single spider to lift weights, in principle of any entity, just using a tiny pre-stress of the silk. Such a pre-stress occurs naturally with the weight of the spider itself when it is suspended from a thread. The related mechanism could be of inspiration for engineering solutions of related problems, and may have inspired ancient populations for dragging and lifting weights.

Several pathologic conditions can be effectively treated using *biomedical devices*. As an example, atherosclerosis is characterized by the presence of lesions (called plaques) on the innermost layer of the wall of large and medium-sized arteries. The plaques contain lipids, collagen, inflammatory cells, etc., and can rupture and impede blood flow downstream, leading to life-threatening problems such as heart attack or stroke. Stent therapy is widely adopted to treat atherosclerotic vessel diseases. Intravascular stents are small tube-like structures expanded into stenotic arteries to restore blood flow perfusion to the downstream tissues. The stent is mounted on a catheter and delivered to the site of blockage. The stent expansion and the stress state induced on the vascular wall are crucial for the outcome of the surgical procedure. Indeed, modified mechanical stress state may be in part responsible for the restenosis process. The outcome of artery stenting depends on a proper selection of patients and devices, requiring dedicated tools able to relate the device features with the target vessel. Migliavacca et al. [55] simulate the implantation of a coronary stent by means of a finite element analysis, showing the influence of the geometry on the stent behavior, and, more generally, how finite element analyses could help in stent design to ensure ideal expansion and structural integrity. Auricchio et al. [5] use finite element analysis to evaluate the performance of three self-expanding carotid stent designs, as a first step towards a quantitative assessment of the relation between device geometry and patient-specific carotid artery anatomy. Popliteal artery stenting is used for the endovascular management in peripheral deep artery diseases. The complex kinematics of the artery during leg flexion leads to severe loading conditions, favoring the mechanical failure of the stent. Conti et al. [17] reconstruct by medical image analysis the patient-specific popliteal kinematics during leg flexion, which is exploited to compute the mechanical response of a stent model, virtually implanted in the artery by structural finite element analysis.

Among other cardiac pathologies, aortic stenosis is the narrowing of the exit of the left ventricle of the heart. It may occur at the aortic valve as well as above or below this level, and typically gets worse over time. Percutaneous aortic valve replacement is a minimally invasive procedure introduced to replace the aortic valve through the blood vessels, as opposed to valve replacement by open heart surgery. Its clinical outcomes are related to patient selection, operator skills, and dedicated pre-procedural planning based on accurate medical imaging analysis. Morganti et al. [60] investigate a balloon-expandable valve and propose a simulation strategy to reproduce its implantation using computational tools. They simulate both stent crimping and deployment through balloon inflation. The developed procedure enables to obtain the entire prosthetic device virtually implanted in a patient-specific aortic root created by processing medical images. It allows the evaluation of postoperative prosthesis performance depending on different factors (e.g., device size and prosthesis placement site), in terms of coaptation area, average stress on valve leaflets as well as impact on the aortic root wall.

Three-dimensional (3D) printing is a disruptive technology quickly spreading to healthcare. On one hand, it allows the creation of patient-specific models generated from medical images, which can facilitate the understanding of anatomical details, ease patient counseling and contribute to the education and training of residents [69]. On the other hand, 3D bioprinting, allowing to print engineered 3D scaffold prototypes and to control the distribution of cells, can be used to create realistic in vitro models of tissues and organs, to be used for research purposes or in regenerative medicine.

2.2 Biological Fluid Mechanics

The fluid mechanics in biological systems played an important role in the scientific activity of AIMETA during last decades. Contributions belonging to this subject were present since the first AIMETA conferences in the 70's. Such pioneering studies were still limited to few presentations included in sessions of fluid dynamics. Those making explicit reference to biological flows were principally centered on the non-Newtonian behaviors of blood, whereas several others addressed fundamental aspects, like numerical methods, unsteady flows or irregular geometries, which had a later impact on the advancements of the subjects.

The first mini-symposium dedicated to Biomechanics, in 2001 AIMETA conference, hosted the first few contributions with modern approaches to the study of biological flows in situations of medical interest. A leap forward can be traced then to 2005 conference, in Firenze, which featured a dedicated session within the others in fluid dynamics. Since then, the contributions in biological fluid dynamics were constantly grown. The XIX AIMETA conference, Ancona 2009, represented a further step forward with a thematic lecture in cardiac fluid dynamics [66] and starting from that year, mini-symposia on Biomechanics were present in all following conferences where scientists could find an opportunity to meet and share knowledge and ideas on all aspects of Biomechanics including biological fluid mechanics.

The analysis of *blood flow* in the human circulation represents the principal subject around which the scientific activity centered its focus. Nevertheless, this was not the only one and other important topics, like the fluids inside the eye, gained special attention for their relevance in medical applications.

The circulatory system fulfills the task of carrying blood across the body; in this respect, fluid flow represents a principal actor for many mechanical phenomena that occur therein. Initially, a series of studies were dedicated to understanding how the non-Newtonian behavior of blood alters the solution for flow in regular vessels [22]. At the same time, blood is transported inside a domain surrounded by biological tissues, with both active and passive behaviors; therefore, cardiovascular fluid dynamics cannot be tackled without ensuring a proper account for the dynamics of soft tissues surrounding the vessel. This is a general rule for many applications of biological fluid dynamics, which involve the wider, slightly interdisciplinary topic of fluid–structure-interaction (FSI). FSI introduces a series of complexities both in the experimental settings and in numerical modelling that can be dealt with different approaches. The management of FSI is relatively straightforward when dealing with prosthetic elements whose geometrical and mechanical properties are known and well defined. Differently, biological tissues are subjected to alteration during time challenging laboratory experiment; on the other side, the feasibility of numerical modelling depends on the availability of information about the mechanical properties of the biological tissue. In fact, native tissues are typically non accessible and their properties can be only estimated. In an alternative numerical approach, characteristics on the moving geometry of the surrounding tissues can be recorded by non-invasive medical imaging (CT, MRI, Echocardiography) and these moving boundaries are implemented in the flow dynamical equation in a one-way interaction.

The *fluid dynamics inside the human heart* captured the attention of numerous studies [66]. The diagnosis of heart diseases represents a critical element of clinical cardiology because most cardiac dysfunctions are progressive and present clear symptoms only after the heart has undergone detectable pathological alteration. The recognition of a pathology at its early stage would permit its treatment by means of a non-invasive therapy such as lifestyle changes or by a light pharmacological therapy that can be effective only before the occurrence of irreversible modifications. In such a situation, the dynamics of blood flow takes special relevance as it immediately responds to minor alterations of the surrounding conditions; indeed, there are indications that a careful inspection of cardiac fluid dynamics can be informative to predict the risk of pathology progression [67].

On the methodological side, models for the fluid dynamics inside the heart chambers present the challenges of dealing with the boundaries undergoing large displacements. A straightforward numerical approach is based on the solution of the equation of motion (Navier–Stokes equations) inside a geometry assigned with a prescribed motion; this approach can be appropriate for patient-specific studies when the dynamics of the boundaries can be extracted, for example, from medical images

[67]. On the other hand, this method does not face explicitly the physical phenomena associated with the reciprocal interaction between flow and tissues. More advanced computational techniques have been presented to accurately include FSI behaviors of tissues that, the other way round, can be less reliable for patient-specific studies as the mechanical properties of the tissues cannot be measured in vivo. This shortcoming can be particularly critical for the muscular ventricular walls (the myocardium), which presents a phase with active contraction driven by electrical stimulation. The description of these active phenomena requires a definition of a more complete electro-mechanical model and of the related physiological parameters [93]. These studies demonstrated that the flow inside the left ventricle is characterized by the formation of a vortex structure that dominates the phenomena of blood transit and energetic balances (Fig. 1, left picture). Numerical methods were accompanied by experimental studies. They allow a validation of the numerical approaches and of the findings; more than that, experimental approaches permit to reproduce complex conditions associated with specific geometries, material and interactions between elements, whose detailed mathematical description may be difficult.

The modelling of *blood flow across cardiac valves* deserved special attention in cardiac fluid dynamics because valvular function is intimately involved in different types of cardiac dysfunctions, from valvular insufficiency, to stenosis, to the alterations induced by prosthetic valves and blood mixing [7]. The interaction between blood flow and valvular tissues represents a prototypal challenge of strong FSI because the movement of valvular elements is very rapid, and it is entirely driven by

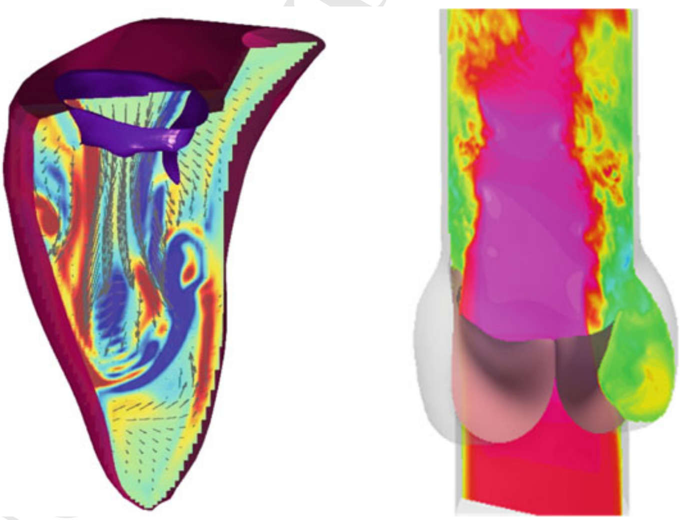

Fig. 1 Left picture: fluid flow in the left ventricle during filling, blood enters through the mitral valve and develops a circulatory pattern inside the chamber. Right picture: flow across the aortic valve at peak systole, velocity is high and although the size of the aorta is relatively small the jet develops a weak level of turbulence. (Credit: Dario Collia, left picture, and Marco Donato de Tullio, right picture, own work, visualizations from computational studies)

the flow. Fluid velocities across the aortic valve reach values above 1 m/s; such figures correspond to a fluid flowing in a transient turbulent regime (Fig. 1, right picture). Although such turbulence is relatively weak with respect to many industrial or environmental fields (Reynolds number is of the order of 10^4), flow is very unsteady, the systolic impulse grows from zero to its peak values and back to zero in about 300 ms. Transient turbulence is regularized during acceleration while it presents a more unstable character during deceleration. This behavior can be dramatically affected by pathologies or after the surgical replacement with prosthetic valves [23]. The mitral valve, at the inlet of the left ventricle, presents a peculiar asymmetric geometry characterized by a large leaflet on one side (anterior side, next to the aortic outlet) and a smaller leaflet on the other. This asymmetry was found to be important for the vortex formation process during ventricular filling; it ensures the development of a circulatory pattern inside the ventricle which is beneficial for an efficient transit of blood [95]. In both valves, the role of physiological FSI is an important topic of research; excessive stresses on the valvular elements induce a mechanical worn out the tissue, while an absence of shear can become prone to calcifications.

Blood flow in large blood vessels represents another central topic of fluid dynamics research because most life-threatening cardiovascular diseases occur in large arteries. The most common pathology is the development of atherosclerosis, which is the deposition of material on the internal vessel wall leading to the progressive narrowing of the lumen (stenosis). As discussed above, stenosis can obstruct the blood from flowing downstream, this induces a reduction/lack of oxygen to tissues supplied by those blood vessels; a phenomenon that can lead to myocardial infarction when the vessels are supplying the heart muscle or to an ictus when supplying a brain region. The interaction between blood flow and arterial walls, principally described in terms of wall shear stress pattern, plays a fundamental role in the genesis and progression of atherosclerosis. Several studies have developed during the years to identify the relationship between geometry and risk of atherosclerosis in sites of clinical relevance. Further applied insights were suggested by the observation that therapeutic procedures are often accompanied by the development of stenosis in neighboring areas due to the alteration of the blood flow therein [56]. Recent years have witnessed significant advances in computational method, which ensure a higher reliability in effective clinical conditions. Such methodological progresses are opening possibilities to achieve, in the next few years, effective definitions of interdisciplinary procedures for personalized cardiovascular care [11, 17].

A different pathology that is common to large arteries is the aneurysm: an excessive, local bulging of the vessel. The arterial wall in the dilated region becomes thinner and weaker, it is then exposed to the risk of rupture and to provoke an internal hemorrhage. The genesis and development of an aneurysm is mainly associated to tissue degeneration, that in many cases can be imputable to genetic predisposition, with the role of fluid dynamics limited to a few specific situations when abnormal high speed flow jet may weaken the tissue in region of impact. Sometimes, fluid dynamics plays a role in its progression or its stability, depending on whether the flow impinges onto the boundary, increases stresses on the weak walls or washes-out inside the dilated region [96].

Congenital cardiac diseases cover a prominent role in cardiovascular fluid dynamics literature, for the importance of addressing details of restorative procedures that are commonly performed at the early phases after birth. These children undergo a series of surgical corrections aiming to rearrange the circulation to overcome the congenital alteration. On some occasions, for the sake of example, the left ventricle is underdeveloped, here surgeries eventually transform the right ventricle in the systemic ventricle and reconstruct surgically a direct connection of the cavae veins to the pulmonary arteries without the right heart in between. Commonly the redesigned circulation requires a careful verification and optimization in several aspects. The pioneering studies developed in the early 2000' [68] underwent continuous improvements following the increasing potential of computational techniques, which are becoming effective for defining optimal therapeutic strategies. Computational techniques in this field featured the introduction of multiscale models. Multiscale models integrate three-dimensional models, that reproduce the site under analysis with high detail, with simpler models of the entire circulation made by one-dimensional and zero-dimensional, lumped-parameter models This approach combines the benefit of accurate simulations with that of taking into account how changes in the site under analysis reflect in the entire circulation [57].

Lumped-parameter *models of the entire circulation* were known since long time and they, too, underwent to progressive refinements during years. In such models, individual elements of the circulation are represented by simple element with analogy to electric circuits integrated with one-dimensional fluid dynamic models of vessel elements [61]. The model sophistication arises here by the complexity of the extended network made of a large number of simple elements which reciprocal influence one on the others. These models permit to verify how acute changes in a specific region of the circulation can have an impact in other, even far, regions and alter global physiological parameters. Such models have the potential to provide clinical information that are otherwise only available through invasive measurements [39].

Biological fluid dynamics extends beyond the cardiovascular systems, although studies of effective theoretical and applied relevance remain limited when compared to cardiovascular fluid mechanics. An exception is the *fluid dynamics inside the human eye*, which had a dedicated special session during AIMETA conference 2011. The ocular chamber contains the vitreous humor: an aqueous viscous fluid that regulates the functions of the eye biomechanics. Its main roles are that of providing nutrients to cornea and lens, and of regulating the intraocular pressure (IOP) through a balance between aqueous production and drainage resistance. It also presents an intrinsic dynamics induced by eye rotations [78]. Models of the vitreous humor have been developed with increasingly reliability during the years [45]. Theoretical results have created a firm ground for the development of studies of applied interest and for supporting actual clinical applications.

2.3 From Articular Joints to Rehabilitation

In the Italian panorama, Mechanics of Machines (MoM) is a vast area that gathers different disciplines ranging from Mechanics Applied to Machines (MaM) to Machine Design (MD) through Mechanical Technology (MT), having as a common language Industrial Drawing (ID).

In the AIMETA community, MoM was represented mainly by both MaM and MD but from 1970 by MaM to an increasing extent, since in 1971 AIAS, the Italian Association for Stress Analysis, was established that attracted most of the MD and ID activities (in 2015 it became the Italian Scientific Society of Mechanical Design and Machine Construction, still maintaining the acronym AIAS). In 1986 the GMA, the Group of MaM, was also established, that collected the activities of MaM, which, however, maintained strong connections with AIMETA too. Indeed, the majority of Biomechanics papers from MoM in AIMETA Congresses and Meccanica Journal come from MaM. Most of them were presented in AIMETA Congresses rather than on Meccanica journal. This result is mainly due to the birth of specific journals in Biomechanics that have significantly attracted the activities of MaM in this specific field. The first papers of Biomechanics from MoM appeared in the XV AIMETA Congress 2001 in Taormina and in the XVI AIMETA Congress 2003 in Ferrara. In the Meccanica journal, from 1996 up to now, 14 papers on Biomechanics appeared from the MoM section, almost all coming from MaM. The first biomechanical paper appeared in 1997 [75], followed by others in 2002, while the first from the MoM section appeared in 2010 [83]. Papers in Biomechanics from MoM are mainly focused on Articular, Computational, Biotribology, Sports, Rehabilitation, Exoskeletons, Medical Devices, Instruments, and Experimental Biomechanics.

Joint Biomechanics studies the *musculoskeletal system* (MSS) consisting of bones, cartilages, muscles, tendons, ligaments, etc. Studies are conducted by both experimental and in silico methods. The basic tools are mathematical models and techniques of analysis of three-dimensional motion, imaging techniques, advanced notions of continuum mechanics [77]. The MSS system is the result of an evolutionary process of millions of years and is a very efficient mechanical system to its purpose. Many studies on the functionality of the MSS of both humans and animals currently inspire the design of mechanical systems that emulate their functional structure to obtain efficient machines [19, 77]. The measurement of movement is based on optical instruments (cameras), which underwent high technological advancements although still often inadequate to detect with high precision the movement of the bones due to the skin movement artifacts and to the problem known as marker occlusion. In [16] the problem is critically analyzed and a solution is proposed that mitigates this drawback. Inertial and magnetometric wearable sensors are now commonly used for measurements that require lower accuracy [77]. The combined use of force platforms and optical systems improves the study of motion (capture motion).

Musculoskeletal models of the human body with rigid elements have been presented in [84] and by the authors of the paper [19] with a few degrees of freedom (DoF), up to 23 DoF [77]. Most of them adopt a muscle Hill-type model

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and solve both the dynamic analysis and the kinetostatic analysis (i.e., given the motion law, find the driving actions to produce it). Several software packages of musculoskeletal models have been presented recently, for instance SIMM, OpenSim, AnyBody, MSMS, etc., to cite a few of the most known. Methods based on continuum mechanics, i.e. on Finite Element (FE) methods, have been developed that take into account elasticity, nonlinear material properties and complex boundary conditions [77]. Despite the great success of these solutions, several unsolved important problems still exist. For instance, the development of predictive musculoskeletal models and, very importantly, a realistic representation of most biological joints still deserve great attention.

In particular, the study of joint Biomechanics is focused on diarthrodial joints, with particular emphasis on the knee [83], hip joint [53, 80, 81], elbow, ankle, shoulder, foot and spine. The problems also concern the phenomena of friction, lubrication [53], wear and roughness of articular surfaces [81], the determination of articular surfaces, their contact areas and deformation, the study through the finite element technique of the infinitesimal and finite deformative states of biphasic materials as well as the distribution of stresses [77, 80]. The literature on the knee, perhaps one of the most important joints for its function and complexity, is impressive. The studies focus on kinematic and kinetostatic analyses, on the etiology and treatment of injuries and diseases (dislocation, arthritis and ligamentous rupture). Here, the key point is the development of mathematical models that analyze femur-tibia and femur-patella-tibia motion [83] as well as the forces transmitted between them. To validate the models, in vivo and in vitro experimental tests of great complexity are required [31]. A further difficulty arises from the fact that mathematical models have singularities whose correct handling requires special attention and experience.

In the last 20 years, specialized books have highlighted the anatomical and theoretical physical mathematical bases necessary for the development of *articular models* [46]. Moreover, numerous papers on robotics and theory of mechanisms [42], that developed precise and efficient techniques to model spatial parallel mechanisms, together with the pioneering papers of O'Connor on joint equivalent mechanisms [97], provided the essential background for more accurate and efficient 3D kinematic and dynamic models of the knee, the ankle and the human lower-limb [15, 65, 83]. These models allowed a deeper understanding of the joints in both natural/passive and loaded motion, and provide a fundamental tool to design prostheses, ortheses and exoskeletons, overcoming the limitations of the trial-and-error approach. An important concept, that is often underemphasized, is that the joints are similar to overconstrained spatial mechanisms: Nature is conservative and has equipped us with redundant constraints to facilitate a failure recovery in case of damage. This concept plays a fundamental role in the design of prostheses and above all in the definition of their positioning with respect to the bones. This is a determining factor for the restoration of the natural motion and balancing of the residual anatomical structures that reflects on the long-term outcome of the intervention/implant [83] to avoid or prolong over time the knee revision arthroplasty.

The limits of measurement techniques and ethical motivations make the accurate survey of the quantities necessary for the models complicated, if not impossible. This imposes the use of indirect techniques and optimization processes that lead to results that are not always satisfactory. New concepts based on the congruence/conformity of articular surfaces [98] (which correlate the shape of surfaces to the temporal history of the load and therefore allow the definition of a relationship between form and movement) integrated with the definition of the three-dimensional models mentioned above, have made it possible to simplify previous patient-specific models reducing the number of parameters to be detected but slightly decreasing the accuracy to the benefit of a much lower computational load [15]. In this context, modern imaging techniques (CT, MRI, dynamic MRI, fluoroscopy, stereophotogrammetry, etc.) play a fundamental role and 3D printing, once the articular surfaces have been defined, allows the construction of patient-specific prostheses, a need that is strongly felt today.

Multibody approach can also be efficiently used to model other complex biological systems. For instance, in [94] a 3D rigid body model of the ossicular chain of the human middle ear is presented that describes the middle ear behavior very well. The model showed to be computationally more efficient than FEM models, and usable also for prosthesis design.

The study of joints also involves *biotribology issues* such that friction, wear, and lubrication. Indeed, tribological principles are of enormous importance in understanding how synovial joints function and fail [80, 81] then, consequently, how important they are in the design of prostheses.

Advanced models can take into account lubrication and wear problems that directly affect the durability of the prosthesis and the definition of the materials. Total knee arthroplasty (TKA) failure is believed to be due from 10 to 18% to wear [43]. In particular, in [80] a hip FEM model was presented that allows a significant reduction of wear tests. The same authors have also studied the influence of the surface roughness on the knee and hip prostheses lifetime. In [81] a detailed hip tribological model under certain kinematic and non-Newtonian unsteady mixed elasto-hydrodynamic conditions is presented and validated by experimental tests. In [53] a hip joint wear mathematical model based on the Cross Shear effect is developed that outlines the influence of the selected wear factor law on the wear prediction. It also highlights, in particular, that the joint geometry influences wear volume more than load.

Analytical methods used within *Sports Biomechanics*, frequently defined as technique analyses sometimes devided into qualitative, quantitative and predictive components, investigate the biomechanical principles of motion and also aim at improving performances. Special attention has been focused on different parts of sport technique. Specifically, pedaling optimal movements and force in cycling have been addressed extensively also for rehabilitation purposes of the lower limbs and the definition of quantitative indicators of both the rehabilitation degree and the quality of the movement [58]. Reliable data collection is of the utmost importance in Sports Biomechanics [47]. In [34] the Biomechanics of the double poling (DP) gesture in cross-country disabled sit-skiers in the field during competition is analyzed. Data were recorded with a high-speed markerless stereophotogrammetric camera system. This study demonstrates the feasibility of a markerless kinematic analysis of sporty gestures. The same authors also presented a review showing that human postures can be efficiently analyzed through inertial sensors (IMU) directly worn on the subject body. The recent trend is to move from imagine data collection to markerless systems (IMU, etc.) whose accuracy is, however, still to be clearly established [14].

Rehabilitation engineering (RE) aims at improving the quality of life of people with disabilities and reduce the care burden of families and society. With the increase of the society well-being and the development of technologies, especially those associated with robotics, RE will have a huge development in the coming years. The aim of the RE is to design devices (orthoses, prosthetic limbs, haptic mechanisms, exoskeletons) for rehabilitation dedicated to the restoration of lost functions as well as systems to assist workers to perform heavy duty works. It therefore becomes essential to know the biomechanics of the human body and the movement and forces transmitted between the human body and the devices. Human–machine interfaces are also of great importance for the success of the devices themselves.

The synthesis of the mechanisms (prostheses, orthoses, exoskeletons), the core of the device, becomes fundamental and it is therefore very useful to resort to the most advanced synthesis techniques, available today and efficiently usable by the great computation power at relative low cost. Motor rehabilitation of upper limbs of patients that suffered from stroke showed that early robotic training, i.e., during acute or subacute phase, can improve motor learning more than chronic-phase training. In [52] a new subacute-phase randomized controlled trial by means of a cable driven robot arm is proposed. The new protocol showed to be as efficient as other ones from the literature, then it can be used in addition and in substitution of them. In [86] a passive exoskeleton for upper-limb rehabilitation of patients who suffered from a stroke is presented. The mechanism is simple, low cost and can be used by the patient at home. Despite being not actuated the system shows remarkable back-drivability within the upper limb workspace. A very ambitious target is to realize upper limb prostheses controlled by brain computer interface (BCI) signals [48]. In addition to the complexity of the mechanical design, whose models are non-linear systems, also complex advanced control techniques are required to get patient comfort.

Since the 60 s of the last century, but especially in the last twenty years there has been a remarkable development of exoskeletons, more of lower-limb devices than of the upper-limb ones since the former are easier to design and control. In [30] techniques are proposed for the ankle motion analysis and the more precise definition of the instantaneous axis of motion, based on stereophotogrammetry and markers properly attached to the skin that limit the effect of the skin artifact. The proposed methodology showed to be an effective tool to customize hinged ankle foot orthoses and other devices interacting with the human joint functionality. A pneumatic interactive lower-limb rehabilitation orthosis is proposed in [8]. In [44] a lower leg exoskeleton with 10 DoF controlled by pneumatic actuators for gait rehabilitation of patients with gait disfunctions is presented. An adaptive fuzzy controller compensates for the dry friction influence in real time.

Hand exoskeletons represent a complementary (distal) part of the upper-arm exoskeletons. Mechanical design and actuation are the most challenging problems [26]. Selection of DoF vs design and control complexity is one basic issue. How to assist the finger motion is again challenging. Indeed, different concepts can be adopted [89] to guide the fingers and to control the motion according to whether the finger are included into the mechanism links or are left apart, or only the last phalanges are moved to drive the fingers to perform the desired trajectory. Electromyography (EMG) signals can also be used to control the hand exoskeleton [48]. Very advanced hand exoskeletons are presented in [9, 18, 49, 85]. Artificial muscles that mimic the muscle human behavior are a very interesting topic, which still deserves attention for the promising features it can provide to actuated rehabilitation mechanisms [88],

Improving *medical device* efficiency and designing new devices is vital for the patients and the healthcare system. The impressive development of new technologies and fabrication processes (for instance 3D printing) gave a tremendous impetus to the design of safer, more usable and cheaper medical devices. Important areas involved in this evolution are surgery, cardiovascular devices and technology, sensor devices, and testing machines [10]. A test bench for measurements on cardiac valves by taking into account the blood characteristics is reported in [59]. A soft robotic gripper for manipulation in minimally invasive surgery (MIS) in reported in [74], while in [35] the overall architecture of a modular soft mechatronic manipulator for MIS is presented.

Experimental Biomechanics aims at collecting data to find relationships between variables and parameters in order to validate mathematical models or find empirical correspondence between input and output with the purpose to understand the biomechanical problem under investigation/study. Research on new materials, their physical and mechanical properties, as well as their compatibility with biological materials is a vast and growing area of interest that involves experiments. An original experimental approach to classify children with cerebral palsy is presented in [76]. An experimental method is presented in [6] to estimate the inertial parameters of the upper limbs during handcycling. In [31] a new test rig for static and dynamic evaluation of diarthrodial joints based on a cable-driven parallel manipulator loading system is presented.

3 Discussion and Perspective

A large amount of scientific research has been produced during last few decades in the field of Biomechanics; nevertheless, more challenges were identified and research is expected to proceed with an accelerating pace during next years.

Biomechanics represents applications of mechanics to living organisms, each one with its own specific details and peculiarities. In this respect, the rapid evolution of technology makes individual information more and more accessible, and the possibility of sharing huge amounts of data, due to the enormous evolution of communication means during last years, will allow the creation of simple and reproducible protocols that can be used effectively in a clinical setting. Along this line, the development of reliable predictive Biomechanics models, easily usable at a clinical level, is still an open problem of great importance for the implications it would have on diagnostics, rehabilitation, therapy and surgery.

An important aspect of the interaction among tissues, that lies sometimes outside the strict definition of Biomechanics, stands in the reaction of living tissues to mechanical solicitations, like stress in solids or wall shear stress of blood flow on the tissue. This aspect is central in the remodeling of tissues like muscles and bones, in vascular development, and for the adaptive response of the heart chambers that can lead to heart failure. Progresses along this topic require to improve the comprehension of how large-scale metrics and processes are sensed at the cellular level (mechano-sensing), what they stimulate and how these stimuli are translated into changes (mechano-transduction) that reflect back at the organ level. This is a fascinating field that requires a cross-fertilization between researches from distant disciplines. This point is crucial to fulfil the need of developing robust predictive models.

Models capable of suggesting the pathological progression can benefit the accelerating availability of data. Improving data collection/measurement techniques with safe and non-invasive tools can rapidly improve nonlinear mathematical models in solids, fluids and haptic exoskeleton devices, which require the use of advanced nonlinear control techniques. However, an increase of the amount of data requires development of physics-based techniques, including physics-guided machine learning, of synthesis and optimization, made possible by recent theoretical developments and the continuous and growing potential of computational tools. At the same time, the availability of numerical models based on individual patient's information will be able to support the development of personalized treatments by using virtual therapeutic tools capable of reproducing the outcome of different therapeutic options and select the optimal solution. Indeed, thanks to the pioneering studies of the last decades in the field of cardiac surgery, it is now possible to reproduce the fluid dynamics, the pressure and wall shear stress patterns in patients with several diseases and anticipate the post-operative state. This represents an embryonal stage of virtual surgery capabilities that research in Biomechanics can help to let it become mature.

A general target for the future is the creation of systems that are simple, more robust, more accurate, personalized to the patient and, possibly, cheaper. This applies to diagnostic methods fed by information extracted by imaging and biological testing and to the development models for personalized therapeutic procedures.

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