Towards a unified approach in the modeling of fibrosis: A review with research perspectives

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Abstract

Pathological fibrosis is the result of a failure in the wound healing process. The comprehension and the related modeling of the different mechanisms that trigger fibrosis is a challenge of many researchers that work in the field of medicine and biology. The modern scientific analysis of a phenomenon generally consists of three major approaches: theoretical, experimental, and computational. Different theoretical tools coming from mathematics and physics have been proposed for the modeling of the physiological and pathological fibrosis. However a complete framework is missing and the development of a general theory is required. This review aims at finding a unified approach in the modeling of fibrosis diseases that takes into account the different phenomena occurring at each level: molecular, cellular and tissue. Specifically by means of a critical analysis of the different models that have been proposed in the mathematical, computational and physical biology, from molecular to tissue scales, a multiscale approach is proposed, an approach that has been strongly recommended by top level biologists in the past decades.

Key words: Complexity, wound healing, therapeutics, multiscale, ODE and PDE, Kinetic theory, agents

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1. Introduction and motivations of the review

The modeling of complex phenomena in physics and life sciences systems is an hot theme of the last and this century. The complex phenomena emerging in physical/biological systems is the consequence of nonlinear interactions occurring among the elementary elements that constitute the system, e.g. molecules, cells, tissues, animals, humans, see the book [1]. The comprehension and the related modeling of the different mechanisms that have as result a physical/biological phenomenon is a challenge of many researchers that work in the field of the applied sciences. The great interest comes from the fact that emerging phenomena in complex system are not obvious from the analysis of the properties of the individual parts, indeed these phenomena are consequence of nonlinear collective interactions, see, among others, [2–4].

The modern scientific analysis of a phenomenon generally consists of three major approaches: theoretical, experimental, and computational. In particular, various biological systems have been considered by researchers that work in the field of the mathematical, computational and physical biology, e.g. tumor growth under the immune system surveillance [5–7], soft tissues growth [8–14], and recently fibroproliferative disorders such as the pathological fibrosis, see the review paper [15] and reference cited therein.

Recently the different mechanisms that trigger physiological and pathological fibrosis have gained much attention. Fibrosis is the result of a failure in the wound healing process characterized by the formation of excess fibrous connective tissue in an organ or tissue. Different organs and tissues can be affected by fibrosis, e.g. lungs (idiopathic pulmonary fibrosis, cystic fibrosis), liver (cirrhosis), heart (post-myocardial infarction, endomyocardial fibrosis/hypereosinophilic syndrome), kidney (renal fibrosis), brain, skin (scleroderma, nephrogenic systemic fibrosis), joints (arthrofibrosis), bone marrow (myelofibrosis). In particular the organs, in the fibrotic pro-

cess, become stiff and cannot perform correctly functions essential to life and health, leading to organ failure and death. The fibrotic progression is characterized by the development of fibroproliferative wound healing. This type of abnormal healing can be regarded as pathologically excessive responses to wounding in terms of cells profiles and their inflammatory growth factor mediators. The mechanisms which are responsible of fibrosis and its disease comprise many phenomena occurring at different scales, among others, atomic, molecular (nucleotides, DNA helix), organelle (chromatine, cell nucleous), cellular and tissue scales. In particular molecular scale is devoted to the dynamics of genes, the cellular scale deals with the cell-cell interactions (epithelial and endothelial cells, platelets, fibroblasts/myofibroblasts, inflammatory cells such as macrophages, neutrophils), and the tissue scale is concerned with the dynamics of tissue including invasion, angiogenesis, morphology and shape.

The major causes of fibrosis include tissue damage (postoperative, burns, liver cirrhosis), infections and autoimmune diseases, foreign material (silicone implants, e.g., silicone mammary implants, gastric banding), spontaneous (Dupuytren's contracture, Peyronie's disease), tumors (tumor stroma, fibroma). Biological insight into the pathogenesis, progression and possible regression of fibrosis is lacking and many issues are still open. Different theoretical tools coming from computational, mathematical and physical biology have been proposed for the modeling of physiological and pathological fibrosis. However a complete framework that takes into account the different mechanisms occurring at different scales is missing and the development of a general theoretical framework is required. Specifically the fibrosis-modeling methods present in the literature can be grouped into two main approaches (see Fig. 1):

- Top-down approach. The system is broken down to gain insight into its compositional subsystems. In this approach an overview of the system is formulated, specifying but not detailing any first-level subsystems. Each subsystem is then refined in yet greater detail, sometimes in many additional subsystem levels, until the entire specification is reduced to base elements. This approach solves the problems through a large number of entities. This approach does not emphasize the microscopic entities explicitly, but estimate the behavior in macroscopic level, exemplified by Ordinary Differential Equation (ODE) and Partial Differential Equation (PDE). The ODE and PDE-based models are all population-based, and the spatiality and topology which both depend on individual interactions are, in general, ignored.

- Bottom-up approach. The individual base elements of the system are firstly specified in great detail then linked together to form larger subsystems, which then in turn are linked, sometimes in many levels, until a complete top-level system is formed. This approach is the piecing together of systems to give rise to more complex systems, thus making the original systems sub-systems of the emergent system. It is based on the synthesis of a complex from the activities on a lower system level; it emphasizes the microscopic level. This approach requires greater computational power in order to simulate a large number of significant entities in real world. From the model built by this approach, we can observe the interactions between entities specifically and study how they contribute to the emergence of global property. Cellular automata and (Multi)Agent-based methods are the most used bottom-up ones.

This review aims at finding a unified approach in the modeling of fibrosis diseases that takes into account the different phenomena occurring at each level: molecular, cellular and tissue. Specifically by means of a critical analysis of the different models that have been proposed in the mathematical, computational and physical biology from molecular to tissue scales, a multiscale approach is proposed. Meanwhile, the contents of the present review aims at answering the following questions: How many approaches can be used to model fibrosis diseases? What are

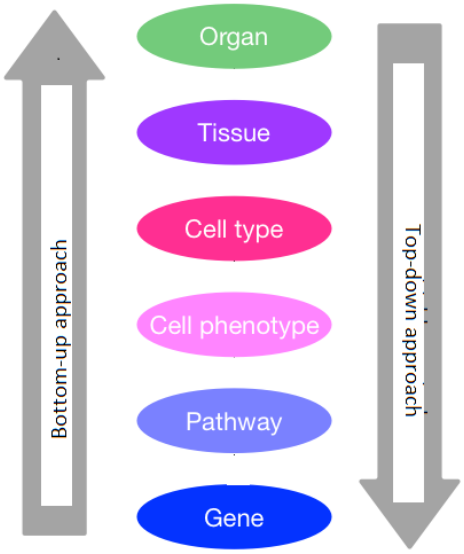

Fig. 1. The top-down and bottom-up approaches for a biological system.

the advantages and disadvantages of the existing models for pathological fibrosis?

The present review is proposed by using a common style of presentation: A survey on the main biological phenomena occurring at a certain level, the related description of the main existing approaches employed at that scale, the review of some specific models, followed by a brief comment on the results of the simulations. The contents are not limited to a survey of existing models. Several indications concerning research perspectives are given in the whole paper and in the last sections focusing on the methodology and applications, respectively.

The review is organized in eight more sections that follow this introduction. Specifically:

- Section 2 introduces the notion of fibrosis and the main diseases. Specifically, after a concise presentation of the wound healing process, the general phenomena that generate fibrosis are discussed. The existing therapeutics strategy are also mentioned into the section. It is worth precising that the section does not claim to be exhaustive from the biological point of view, therefore the interested reader to a deeper understanding of the phenomenon is referred to the pertinent bibliography that is cited into the section.

- Section 3 highlights some conceptual aspects of the known modeling approaches. The aim is to introduce the not-specialized reader to the main concepts and techniques which distinguish the different applied sciences that are involved in the modeling of biological systems. In particular motivations and scopes of biomathematics, bioinformatics, biomechanics and biophysics modeling are debated into the section, including also the possible interplay towards the definition of a multidisciplinary and multiscale approach for the treatment of pathological fibrosis.

- Section 4 deals with a summary of the phenomena that trigger the onset of a fibrosis disease at molecular/genetic level. In particular the section is a survey of the main models that have been proposed taking into account the molecular responsible actors. Specifically the section contains an overview of the most famous top-down approach, namely the ordinary differential equation-based model, and the most famous bottom-up approach, namely the (multi)agent-based model. The above mentioned approaches will be introduced at tutorial level.

- Section 5 is concerned with the cellular phenomena that are responsible of pathological fibrosis. Specifically cellular interactions have been modeled by employing top-down models with structured variables. The most recent proposed approach is also discussed into this section: Thermostatted kinetic theory for active particles. This mathematical theory is based on the main assumption that systems under consideration are composed by a large number of individuals, called active particles, whose microscopic state includes not only the classical mechanical variables, but also a continuous variable, called activity, which models the function or purpose expressed by individuals.

- Section 6 is devoted to the modeling of the last outcome of fibrosis, namely the tissue. The main properties of a fibrotic tissue are reviewed within this section. In this context, the response of fibrotic tissues to mechanical stress allows to understand many behaviours of fibres including clinical pain. The main modeling approach proposed at this scale is based on the theory of finite elasticity applied to biological tissues.

- Section 7 contains a critical analysis on the different modeling approaches reviewed into the present review paper. Specifically advantages and disadvantages of the various modeling methods are discussed. The main aim is to distinguish at each scale the most appropriate framework in order to guide the researchers towards a suitable choice of the modeling approach.

- Section 8, unlike the previous ones, treats research perspectives from the biological and modeling viewpoint. In particular some open questions are posed in view of the development of a multidisciplinary interaction.

- Section 9 concludes the review by suggesting the definition of a unified multiscale approach which allows to link the dynamics at a certain scale with the dynamics occurring at lower and higher scales.

As already mentioned, the main scope of this review is to analyze the different models that have been proposed in the pertinent literature and at different levels, from molecular to tissue, in order to propose a multiscale approach, an approach that has been strongly recommended by top level biologists in the past decades. The presentation of a suitable multiscale framework as general as possible, which acts as background paradigm for the derivation of specific models for fibrosis diseases, is thus the final goal.

2. The fibrosis process

This section is concerned with the biological description of the main processes occurring in fibrosis including the onset of the related pathologies. As already mentioned into the introduction, this section does not claim to be exhausted from the biological viewpoint. Indeed the description will be limited to the main phases that are involved into the process, the surgery, histology and the existing therapeutic actions including the new frontiers of nano-medicine. The contents of this section takes advantage of the description that has been made in the book [16]

2.1. *The repair process*

The understanding of the fibrosis process requires the knowledge of the response of the human body to injury: Wound healing process. Wound healing, or wound repair, is an intricate process by which the skin or other organ, repairs itself after injury. In normal skin, the epidermis (outermost layer) and dermis (inner or deeper layer) exist in a steady-stated equilibrium, forming a protective barrier against the external environment. Once the protective barrier is broken, the normal (physiologic) process of wound healing is immediately put into motion. The process results characterized by four sequential, partially overlapping, phases: hemostasis (stopping of the bleeding, that is not considered a phase by some authors), inflammation, proliferation, and maturation (remodeling), see Fig. 2. The sequence of these phases is an essential condition for the successful completion of the healing process, see Fig. 3. The four phases are characterized by a vascular, cellular, humoral reaction. Hemostasis is characterized by vasoconstriction; coagulation cascade is initiated by interaction of coagulation factor FVII with TF; Von Willebrand factor helps platelets bind at wound sites, where they activate and degranulate. During the inflammation phase an enhanced blood vessel permeability occurs, due to release of histamine and other factors; inflammatory cells infiltrate (PMN, macrophages) and kill any microbes accompanying the injury; leukocytes produce cytokines, chemokines, and growth factors, some of which (IL-1beta, TGF-beta, TNF) recruit fibroblasts. The proliferation phase induces fibroblasts activation, which secrete ECM components (type III collagen, fibronectin); formation of granulation tissue (fibroblasts, inflammatory cells, new blood vessels, fibronectin, hyaluronan, collagen, endothelial cells) and epithelialization. The remodeling phase is characterized by wound contraction via myofibroblasts at the edges; type III collagen is replaced by Type I, and fibers are rearranged and crosslinked. Remodeling will continue for weeks to months. In particular during the remodeling phase there is a generalized reduction of blood vessels, fibroblast apoptosis occurs resulting in a normal looking scar; humoral factors play a subordinate role with respect to the mechanical reaction (the mechanical stretch and strain). The modeling of tissue in this phase is primarily determined through mechanical forces and no longer through growth. The cycle of healing and repair is self-regulating. However, the process is susceptible to interruption or failure leading to the formation of chronic non-healing wounds. It is worth stressing that effective healing is usually characterized by a dominant Th1 response, whereas a predominant Th2 response and an increase in Th17 cells lead to chronic inflammation, which can ultimately result in fibrosis [17].

2.2. *The fibrosis diseases*

The term fibrosis, or scar formation, refers to excessive deposition of collagenous and non-collagenous extracellular matrix (ECM) components in organs and tissues as a consequence of proliferation and activation of fibroblasts and myofibroblasts. Myofibroblasts can develop from both fibroblasts and nonfibroblastic cells by transdifferentiation triggered by proinflammatory and profibrotic cytokines produced by cells of the innate and adaptive immune systems. The pathological condition is characterized by excessive production and accumulation of collagen, loss of tissue architecture, and organ failure. Different cells are involved in this process, among others bone marrow-derived circulating fibrocytes, endothelial cells, resident fibroblasts, epithelial cells, pericytes. Fibrosis diseases are always related to the inflammatory processes, and in particular during the inflammatory phase, both innate (neutrophils for bacterial infections, eosinophils for parasite infections, monocytes/macrophages, mast cells, and lymphoid cells in-

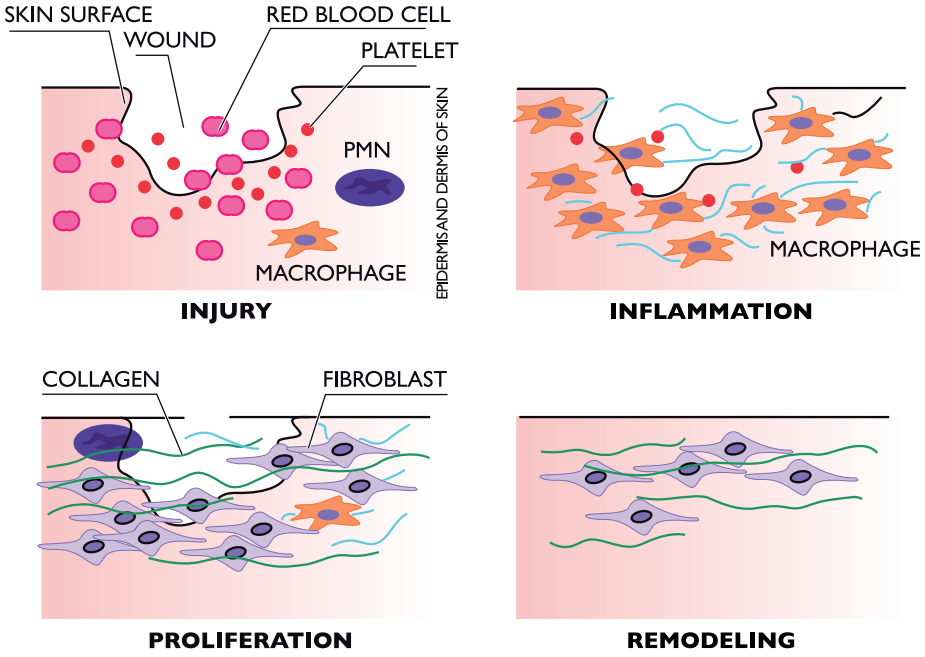

Fig. 2. The phases of cutaneous wound healing.

cluding natural killer cells) and adaptive immune mechanisms are operative. The process is initiated when immune system cells such as macrophages release soluble factors (TNF-α and IL-1) that stimulate fibroblasts and induce overproduction of ECM proteins. The most well characterized pro-fibrotic mediator is TGF-beta, CTGF, platelet-derived growth factor (PDGF), and Interleukin-4 (IL-4). These initiate signal transduction pathways such as the AKT/mTOR [18] and SMAD [19] pathways that ultimately lead to the proliferation and activation of fibroblasts, which deposit extracellular matrix into the surrounding connective tissue. In contrast, antifibrotic effects are exerted by interferon (IFN)-γ produced by activated NK cells.

As already mentioned into the introduction, pathological fibrosis develops as a consequence of tissue damage, primary inflammatory diseases, fibrotic alterations induced by foreign body implants, and tumor-associated fibrotic changes. Specifically:

- Heart fibrosis [20] can occur in response to left ventricular pressure-overload, which leads to cardiac hypertrophy and necrosis. Alternatively it could occur in response to myocardial infarction, inflammation, and myocyte death.

- Systemic scleroderma - skin [21] is the consequence of autoimmune disease of the skin and, in some cases, of the internal organs; arteriole endothelial and smooth muscle cell apoptosis, followed by inflammation and fibrosis.

- Liver cirrhosis [22] develops as a result of chronic liver disease (alcoholic, fatty liver disease, autoimmune disease, or hepatitis virus, etc.), or idiopathic.

- Renal fibrosis [23] is the final result of most kinds of CKD, leading to end-stage kidney failure;

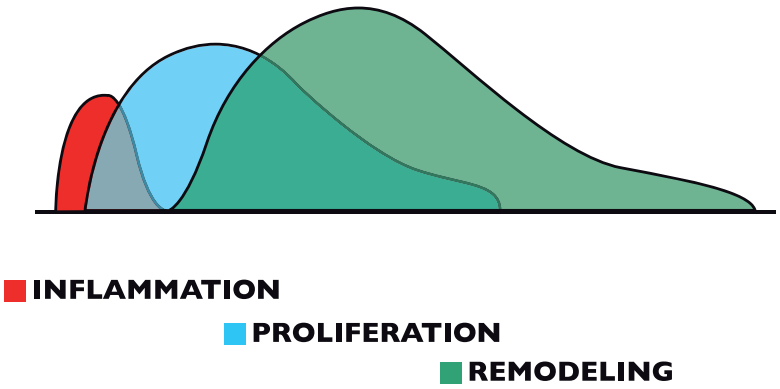

Fig. 3. Overlapping in the sequence of phases of normal wound healing.

myofibroblast accumulation, increased matrix deposition, tubular cell death, loss of peritubular and glomerular capillaries.

- Pulmonary fibrosis [24] is idiopathic or result of injury or disease, including: Inhalation of particulates and gases, smoking, infections, drugs (bleomycin, amiodarone, etc.).

2.3. *A particular fibrosis: Capsule around implants*

This section focuses on the capsular tissue around mammary implants and its excessive contracture. Capsule is the natural protection of some organs, e.g. kidney, knees. This fibrous tissue is a vital cover for any mechanical displacement or stresses. For mammary implant, capsule seems to be a spontaneous reaction to its introduction into the body and is helpful to fix it in the breast. However the capsular tissue can stiffen and extend, becoming extremely painful and aesthetic only few months post-implantation.

The structures of the network of fibers depends on the stage of pathology: Roughly parallel fibers or cross-linked network. The fibers are not isolated, they range into bundles, themselves being embedded into the extra-cellular matrix of the tissue. In addition the fibroblasts which actively make the collagen fibers as the pathology proceeds, construct a complementary network of F-actin which is connected to the bundle in an helicoidal fashion at least in Grade III [25]. Moreover, such tissues contain active cells such as myo-fibroblasts (also detected in large wounds) which exert a contractile stress on the tissues. Angiogenesis proceeds and fibrotic tissues are vascularized and swell. The dynamics of the network is not limited to the biological activities, it is also a consequence of the loading exerted on the tissue or appearing at small scales. For instance a simple thin cuboid (shape of surgical capsular tissues) in tension may experience breakdown, remodeling and sometimes domain separation for moderate values of the traction as observed on fabrics [26]. These domains remain unexplained but change the macroscopic deformation. All these possible processes hide the true constitutive law in tension, requiring a multiplicity of experiments which is not always possible to perform or analyze without complementary modeling studies. For compression, it is even worse because of the macroscopic buckling of the sample. The orientation of the bundles in tissues coming from surgery is not always known. A recent

paper on a polymer brush under compression by a virtual piston [27] performed with molecular-dynamics simulations shows a bifurcation in compression due to a symmetry breaking of the main orientation of quasi-parallel fibers. This proves that both processes tension/compression are absolutely not symmetrical and must be studied independently.

2.4. *Nano-therapeutic strategies*

The fibrotic tissue limits the transport of drugs and the best solution remains surgery. Recently, new strategies for the treatment of fibrosis diseases have been developed, in direction of nanomedicine. Indeed nanomedicine has given a lot of hopes in the treatment of solid tumors but the promise has not been realized on humans up to now [28]. The use of nanomedicine for the treatment of pathological fibrosis is under investigation, e.g. for liver and pancreas [29–31]. Progress has been made in the modeling of the transport of nanoparticles via blood vessels [32], on their ability to reach specific cells by targeting receptors, on the choice on nano-particles (shape, size) and on the estimation of the amount of drug necessary to better target the cells to eliminate. The theoretical challenge is to model this nanomedicine strategy to the geometry of the capsular tissue (different from the tumor trauma) around the implants taking properly its biomechanical state according its pathologic state.

In the treatment of various pathologies, the application of nanoparticles (which are drug carriers) has emerged as a rapidly evolving area for the safe delivery of drug with minor side effects - Encapsulated by the nanoparticles, the clearance rate of the small molecular drug can be effectively reduced and the aim to targeted cells can be realized by the surface chemistry of the particles. Basically, the drug targets on five possible issues: 1) the inhibition of collagen synthesis, 2) the interruption of matrix deposition, 3) the stimulation of matrix degradation, 4) the anti-fibroblastic proliferation, or 5) the induction of fibroblast death.

However, as in the conventional treatment of the fibrotic liver and the other pathologies, most of the drugs which are highly effective in animal models, turns out to be ineffective to humans. This is because of the calibration of drug concentrations resulting from these models, insufficient for a correct accumulation around the target cells in humans. Given a dose of nanomedicine, from the loading spot (oral uptake, intravenous injection, etc.), unless the therapeutics are injected locally, they will be passively transported by the circulation system through which they can pass through the capillary bed of the targeted area. It is worth stressing that in the application of nanomedicine the onset of anomalous transport strongly depends on the dimension of pores [36,37]. Therefore in order to reach the targeted cells, they have to first extravasate from the local vasculature and then penetrate the interstitium. Each step is highly sensitive to the local microenvironment of the targeted area. However, the blood/lymphatic circulation dysfunctions may also contribute to better retention in the study of nano-therapeutics. If it is the case for the capsular microenvironment, it will need similar investigations as it is done in the tumors [33–35].

3. Biomathematics, bioinformatics, biomechanics and biophysics modeling

The understanding of fibrosis diseases at each stage and level requires the definition of a research field where different scholars coming from different research fields have to be involved. Indeed physiological and pathological fibrosis are concerned with molecules, cells and tissues. Therefore in order to reach a comprensible and complete framework, the mechanics and physics of cells and tissues needs to be understood, bearing in mind that the support of mathematical and

computational methods and models are required.
Recently four research fields have acquired a great interest into the study of complex biological phenomena that occur at different levels: Biomathematics, bioinformatics, biomechanics and biophysics.

3.1. *The interplay among the different approaches*

The application of mathematics to biology has recently attracted much attention considering in particular the recent developement in the genoma analysis [38], the onset of complex and irregular behaviour in various biological systems (humans, animals, plants, organs, cells, see [39–41], the analysis of big data [42].

Biomathematics (or mathematical biology) aims at the representation, treatment and modeling of a biological system by employing equations (algebraic and differential) and theoretical tools. Different research fields are part of mathematical biology, however ecology and evolutionary biology have recently attracted much attention [43]. Differently from biology, in mathematical biology the term "model" usually refers to the equation (or system of equations) whose analytical or numerical solution describes the time evolution of the biological system. The definition of assumptions and parameters are the input of the model. Deterministic and stochastic processes are often involved in the derivation of the evolution equations. In the deterministic modeling difference equations (DE), ordinary differential equations (ODE), partial differential equations (PDE), cellular automata (CA) are involved. Master equations, dynamic Monte Carlo method, Fokker-Planck equation usually describe the stochastic counterpart.

Bioinformatics aims at understanding biological systems by combining computer science, statistics, mathematics, and engineering. Bioinformatics has been used for in silico analysis of biological queries using mathematical and statistical techniques [44]. Bioinformatics and computational biology have similar aims and approaches, but they differ in scale: bioinformatics organizes and analyzes basic biological data, whereas computational biology builds theoretical models of biological systems, just as mathematical biology does with mathematical models.

Biomechanics aims at studying biological systems by means of the methods of mechanics [45], with special attention to their movement and structure. The analysis of biological systems is performed by employing engineering sciences, especially biomedical engineering. In particular continuum mechanics, mechanism analysis, structural analysis, kinematics and dynamics constitutes the main methods of biomechanics. Recently the application of biomechanics have increased for what concerns animal locomotion, orthopedic biomechanics, occupational biomechanics, implant (medicine), sports biomechanics, injury biomechanics. Specifically sports biomechanics deals with human movement in order to gain a greater understanding of athletic performance and to reduce sport injuries as well. Mechanical engineering, electrical engineering, computer science, are common methods used in sports biomechanics [46]. The mechanical analysis of biomaterials and biofluids is part of biomechanics, in particular the analysis is usually carried forth with the continuum mechanics. This assumption breaks down when the length scales of interest approach the order of the micro structural details of the material. Mechanical deformation of hard tissues (wood, shell and bone) may be analysed with the theory of linear elasticity. On the other hand, soft tissues (skin, tendon, muscle and cartilage) usually undergo large deformations and thus their analysis rely on the finite strain theory and computer simulations. Biofluid mechanics is the study of both gas and liquid fluid flows in or around biological organisms, e.g. blood flow in the human cardiovascular system that can be modelled by the

Navier-Stokes equations. It is worth stressing that biomechanical principles has been also developed to embryogenesis (animals) [47], bacteria [48], morphogenesis of plants and plant organs [49,50]. Biotribology is a study of friction, wear and lubrication of biological systems especially human joints such as hips and knees, e.g. femoral and tibial components of knee implant routinely rub against each other during daily activity such as walking or stair climbing [51]. Computational biomechanics lies in its ability to determine the endo-anatomical response of an anatomy, without being subject to ethical restrictions thus finite element method has become an established alternative to in vivo surgical assessment [52].

Biophysics aims at studying biological systems by means of methods of physics [53] but covering all scales of biological organization, from molecular to organismic and populations. In particular molecular biophysics typically addresses biological questions similar to those in biochemistry and molecular biology, but more quantitatively, seeking to find the physical underpinnings of biomolecular phenomena. Scientists in this field conduct research concerned with understanding the interactions between the various systems of a cell, including the interactions between DNA, RNA and protein biosynthesis, as well as how these interactions are regulated. Molecular biophysicists usually consider complex biological events as systems of interacting entities which can be understood through statistical mechanics, thermodynamics and chemical kinetics.

Bearing all above in mind, the interplay among the different scientists working in biomathematics, bioinformatics, biomechanics and biophysics is required in order to obtain a complete description of a biological system, and in particular for pathological fibrosis. In particular it is becoming increasingly common for biophysicists to apply the models and experimental techniques derived from physics, as well as mathematics and statistics, to larger systems such as tissues, organs, populations and ecosystems.

3.2. *The multiscale problem*

As already mentioned in the previous subsection, the description of a biological system can be pursued with a different framework thus allowing the modeling of a phenomenon at a specific scale. However in order to obtain a complete description of a biological system, the modeling at different scales is an important issue. The hard problem is the link between the different phenomena that occur at different scales, usually molecular (microscopic), cellular (mesoscopic), and tissue (macroscopic). The microscopic level is devoted to molecular interactions and intracellular events and processes such as gene expression and signal transduction; the mesoscopic scale refers to cellular processes such as differentiation, proliferation, apoptosis, as well as cell movement and extracellular phenomena; the macroscopic scale involves processes such as tissue homeostasis, organ function and systemic circulation. Timescales associated with these processes span from femtoseconds to minutes and years [55].

The modeling at each level (scale) is usually performed as follows [56]:

- Microscopic (molecular) scale ($10^{-9} - 10^{-7}$m): Ordinary differential equations, partial differential equations, stochastic differential equations (SDEs), master equation, boolean network modelling, graph theory logical, rule-based models;

- Mesoscopic (cellular) scale ($10^{-6} - 10^{-4}$m): Ordinary differential equations, delay differential equations (DDEs), age-structured models, stochastic differential equations, reaction-diffusion equations, boolean network modelling, cellular automata, agent-based models, potts models, lattice gas, lattice Boltzmann;

- Macroscopic (tissue) scale ($10^{-3} - 10^{0}$m): Ordinary differential equations, partial differential equations, lattice-based models, continuum mechanics, mechano-biological framework, agent-based models, lattice Boltzman.

The multiscale problem consist of integrating the mathematical and computational description of processes operating at variable spatial, temporal and organizational levels [54]. The modeling of many biological system requires a multiscale approach: immune system [56], neural systems [57], tumour growth [58], epidermal wound healing [59,60], tissue engineering [61].

Recently mathematical multiscale approaches for biological systems have been proposed. The approaches consist in linking mathematical frameworks to lower and upper scales by means of hydrodynamic limits with the aim to derive macroscopic tissue equations based on the underlying description at the microscopic scale, see, among others, papers [62–68].

4. Modeling at microscopic scale

This section deals with the literature referring to the microscopic (molecular)-scale-modeling of fibrosis. As already mentioned in the previous section, at this level of observation of a biological system, different modeling frameworks have been proposed. This section, after a brief description of the main phenomena occurring in fibrosis at microscopic level, focuses on the ODE-based models and the agent-based models.

4.1. *An overview on the phenomena at molecular scale*

The past decade of research in fibrosis has produced a wealth of information about the underlying defect responsible for the disease. In particular the study conducted at genetic level has provided important information about the genomic location of the gene causing fibrosis. Further analysis at genetic level has shown that although there is a single mutation that accounts for most of fibrosis, there are other lesions within the gene that can cause disease as well [69].

Important investigations have been developeed in cystic fibrosis [70–73]. Located on chromosome 7 (band q31-32), the cystic fibrosis gene encompasses 250 kilobases and is made up of 27 exons. Approximately 200 disease-causing mutations have been identified in the cystic fibrosis gene, see the review paper [70]. Important molecular mechanics have been identified in renal fibrosis, which is the common final outcome of almost all progressive chronic kidney diseases, see the review papers [74,75]. Alcohol and non-alcohol liver fibrosis is also consequence of molecular outcome, see [76]. Gene expression is also responsible of lung (pulmonary) fibrosis, see the review papers [77,78].

It is worth stressing that at this scale, the literature is very limited. Thus a major effort is required to researchers working in the field of pathological fibrosis.

4.2. *ODE-based models*

The modeling of fibrosis diseases at molecular scale has been pursued by employing mathematical models derived into the framework of the most famous top-down approach: ODE-based model. Models within the ODE framework views the molecules as homogeneous and ignores the spatial structure. The interactions are performed through ordinary differential equation based on parameters, populations and subpopulations. Numerical solutions of ODE-base model can be

obtained by using standard integration packages available in C, FORTRAN, MATHEMATICA MATLAB.

ODE-based models have been used to model cell growth, cell proliferation and the competition with the immune system, mainly due to their mathematical simplicity; see the review [79] and the reference therein. The complexity of the model grows with the increasing number of cell populations. This would mean dividing the cell population into more subpopulations, each of which is dedicated to one cell state, modeled by a single differential equation. Cell division, as well as cell differentiation and cell maturation, are not instantaneous processes but take a finite time to occur. In some cases the durations of the cell processes can be ignored but, in principle, they should be included in the model so that it is consistent with the cell growth kinetics. When ODE-based models are used, the delays can be modeled directly (see [80] and therein references) or can be modeled indirectly, for example, by a special choice of parameter values or by introducing intermediate phases into the cell division model. Thus, avoiding the explicit modeling of the delays yields a mathematically less complex model and, even if models often involve nonlinearities that make the analytical solution especially difficult, it is sometimes possible to find an analytical solution, steady states, stability conditions and threshold expression to an ODE-based model for relatively simple systems or when simplifying assumptions are made [81].

The evolution of populations modeled with the ODE-based model has in common the characteristic that the description at a certain time depends on the description at the same time. However the phenomena that occur at a certain time are strictly related to the behavior of the system at a previous time. Recently time delay has been inserted into mathematical models for the biological and economical systems, see, among others, the review paper [101], papers [83–92] and the references cited therein.

As already mentioned, the root cause of cystic fibrosis is the loss-of-function mutations in the CFTR gene product, an anion-selective channel. Trans-epithelial potential difference measurements are routinely carried out on nasal epithelia of cystic fibrosis patients in the clinic. In [93] a quantitative mathematical model of human nasal epithelial ion transport has been proposed. In particular the authors have shown that while the loss of CFTR permeability hyperpolarises trans-epithelial potential difference and also increases amiloride-sensitive trans-epithelial potential difference, these effects are too small to account for the magnitude of change observed in cystic fibrosis epithelia. The study provides quantitative predictions for the complex relationships between ionic permeabilities and nasal trans-epithelial potential difference, giving insights into the physiology of cystic fibrosis disease that have important implications for its therapy. Cystic fibrosis lung disease is characterized by liquid hyperabsorption, airway surface dehydration, and impaired mucociliary clearance. In [94] the authors present a compartment-based mathematical model of the airway that extends the resolution of functional imaging data. Specifically the model is a system of mechanism-motivated ordinary differential equations that allows to describe the mucociliary clearance and absorption of aerosolized radiolabeled particle and small molecules probes from human subjects with and without cystic fibrosis. Accordingly to the results, the authors postulate that patients with cystic fibrosis have regions of airway with diminished mucociliary clearance function that can be recruited with hypertonic saline treatment.

For what concerns renal and liver fibrosis, the modeling with ODE-based model is appearing very limited. Recently a mathematical model has been proposed for multiple myeloma as consequence of damage to the kidney by tubulointerstitial fibrosis. Specifically in [95] the authors model the interaction between cells in the proximal tubule of the kidney and free light chains produced by the myeloma monoclonal protein. In particular for liver fibrosis a validated ODE-based model reveals hepatobiliary transfer rates for Gd-EOB-DTPA using human DCE-MRI data

[96]. In [97] a ODE-based model with delay has been investigated for the acute inflammatory response to trauma. In [98] an ODE-based model has been proposed, which takes into account the main geometrical (size, shape, insertion angle) and chemical (coating surface) properties of the implant. The aim is to predict the thickness of the fibrotic capsule when the inflammatory reaction stabilizes. This tool allows to evaluate different hypothetical solutions for accounting the tissue-electrode mismatch.

The interested reader in long-dated ODE-based models for fibrosis-related diseases is referred to papers [99–103] and the references cited therein.

4.3. *Agent-based models*

The agent-based model (ABM) is a computational approach paradigm which aims at looking a phenomena as dynamical systems of interacting agents. An agent is a discrete entity (people, groups, organizations, social insects, swarms, plants, robots) with its own goals and behaviors; the agent has the capability to adapt and modify its behaviors. The agents are diverse and heterogeneous. Accordingly, in order to define an agent-based model we need to define a set of agents, a set of agent relationships and a framework for simulating agent behaviors and interactions. Unlike other modeling approaches, agent-based modeling begins and ends with the agent perspective. This approach can be considered as the natural extension of the Ising model [104] or cellular automata-like models [105].

In comparison with variable-based approaches using structural equations (that will be treated in the next section), or system-based approaches using differential equations, agent-based simulation offers the possibility of modeling individual heterogeneity, representing explicitly agent decision rules, and situating agents in a geographical or another type of space. Agent-based models are of value in most branches of social science: urban models [106], opinion dynamics [107], consumer behavior [108], industrial networks [109], electricity markets [110], immunology [111,112].

The modeling of pathological fibrosis by means of the agent-based framework has been also developed. In this context agent-based models have proposed to integrate local interactions to recapitulate overall dynamic changes in the referent biological system, thereby facilitating the generation of mechanistic hypotheses regarding emergent spatial or temporal patterns that often result in biological systems. In [113] an agent-based model of liver tissue has been developed in order to computationally examine the consequence of liver inflammation. The model is based on literature-derived rules describing molecular and histopathological aspects of inflammation and fibrosis in a section of chemically injured liver. Hepatocytes are modeled as agents within hexagonal lobules. Injury triggers an inflammatory reaction, which leads to activation of local Kupffer cells and recruitment of monocytes from circulation. Portal fibroblasts and hepatic stellate cells are activated locally by the products of inflammation. The ABM exhibits key histopathological features observed in liver sections from rats treated with carbon tetrachloride. In [114] an ABM has been proposed to examine the response of an abstracted population of inflammatory cells (nominally macrophages, but possibly including other inflammatory cells such as lymphocytes) and cells involved in remodeling (nominally fibroblasts) to particulate exposure. The model focused on a limited number of relevant interactions, specifically those among macrophages, fibroblasts, a pro-inflammatory cytokine (TNF-α), an anti-inflammatory cytokine (TGF-$\beta 1$), collagen deposition, and tissue damage. The role of stem cells in the tissue regeneration is an important issue. An agent-based computational model has been proposed in [115] to

investigate the regeneration of the chronic chagasic cardiomyopathy after bone marrow stem cell transplantation. The model includes inflammatory cell, fibrosis area, cardiomyocyte, proinflammatory cytokine tumor necrosis factor-α, Trypanosoma cruzi parasite and bone marrow stem cell.

Further agent-based models where the role of fibrosis is taken into account can be found in [116,117]. The reader interested in a detailed description of other agent-based models for fibrosis-related diseases is referred to papers [118–126] and the references cited therein.

5. Modeling at mesoscopic scale

This section is concerned with the main phenomena that occurs in fibrosis at the cellular level. Specifically, after a brief introduction of the main actors that trigger pathological fibrosis at cellular scale, the section deals with the mathematical models with internal structures. Subsequently the thermostatted kinetic theory for active particles is reviewed and the models for pathological fibrosis derived within this framework are discussed.

5.1. *An overview on the phenomena at cellular scale*

The cellular mechanisms fulfill an important issue in fibrogenesis [127]. Indeed cellular interactions are responsible of the last product at the macroscopic scale: the fibrotic tissue. The main cellular mediator of fibrosis is the myofibroblast, which when activated serves as the primary collagen-producing cell. Myofibroblasts are derived from epithelial cells in a process called epithelial-mesenchymal transition (EMT), see [128,129]. In particular EMT-derived myofibroblasts participate with resident mesenchymal cells in the reparative process [130]. Moreover conserved pathogen-associated to molecular patterns (PAMPs) found on bacteria, viruses, fungi and multicellular parasites help maintain myofibroblasts at a heightened state of activation thus allowing many fibrotic disorders, see the review paper [131].

Innate and adaptive immune mechanisms regulate myofibroblast activity, indeed B cells are responsible of fibroblast growth factors by producing autoanti-bodies or by secreting IL-6 [132]; Th2-type cytokines are also involved in the mechanism of fibrosis [133,134]. Chemokines are leukocyte chemoattractants that cooperate with profibrotic cytokines in the development of fibrosis by recruiting myofibroblasts, macrophages and other key effector cells to sites of tissue injury, see, amomg others, [135]. However fibrosis is not always characterized by persistent inflammation, see the studies of schistosomiasis-induced liver fibrosis [133].

It is worth stressing that it is not clear whether in advanced fibrosis, normal tissue architecture can be restored completely; if fibrosis is sufficiently advanced, reversal is no longer possible. Cell-based therapies using adult bone marrow-derived progenitor/stem cell technologies might also prove highly successful for the treatment of fibrosis [136–138]. Since fibrocytes and EMT-derived myofibroblasts produce a variety of factors that are involved in the fibrotic process recruitment and/or activation could provide a unique therapeutic approach to treat a variety of fibrotic diseases. There is a growing list of novel mediators and pathways that could be exploited in the development of antifibrotic drugs. The most difficult obstacle is to design effective clinical trials with well-defined clinical endpoints.

5.2. *Models with internal structure*

In the last century, models with internal structure have been proposed in order to take into account the spatial/aging dependence of the various components involved in the onset of complex phenomena, see, among others, papers [139–143] and the references cited therein. The microscopic state of each component thus includes another variable, called the structure variable. Bearing all above in mind the corresponding theoretical framework consist of partial integro-differential equations or reaction-diffusion equations. In the definition of these models, it is essential the analysis of the domain in which the equations are valid, the initial values of all variables across the domain, and the boundary conditions imposed at the boundary of the domain. Usually boundary conditions models a constant source or sink of the quantity (Dirichlet conditions), or the flux of a quantity across the boundary (Neumann conditions). Special solutions include steady state solutions (independent of the time variable t), self-similar solutions (invariant under a rescaling of the spatial x and time t variables), and traveling wave solution. Numerical solutions are obtained transforming the system into a system of algebraic equations by finite difference methods (the derivative is approximated by finite differences) or finite element methods (the model is rewritten into a variational form formulated as integrals over appropriate test functions with compact support).

Since physiological/pathological fibrosis is an age-dependent process [144,145], the applicability of models with internal structure appears suitable. Most existing models with internal structures for fibrosis focus on the repair of the epithelial layer [146] and the remodeling of the fibrotic tissue [147]. Repair of the epithelial layer is a combination of two processes: migration of epithelial cells and cell proliferation.

The reaction-diffusion equation commonly employed is the Fisher-Kolmogorov equation with proliferation given by a logistic term [148,149]. The role of growth factors has been considered in [150–152] by means of two nonlinear reaction-diffusion equations that track epithelial cell density and the epidermal growth factor (EGF). Further developments have been considered in [153–158] for including the impact of increased mitotic and migratory activity due to an EGF, the effects of cell density-dependent diffusion, the role of key chemicals in determining the quality of healing (see also the review papers [159,160]).

Recently a mathematical model of renal interstitial fibrosis have been proposed in [161]. The model aims at monitoring the effect of treatment by anti-fibrotic drugs that are currently being used, or undergoing clinical trials, in non-renal fibrosis. In [162] a mathematical model for idiopathic pulmonary fibrosis have been derived. The model is based on the interactions among cells and proteins that are involved in the progression of the disease. Two phenotypes of macrophages are considered: monocyte-derived inflammatory macrophages and anti-inflammatory alveolar macrophages. The lung geometry is also taken into account by introducing a periodically arranged cubes with smaller cubes representing the air space of alveoli. Simulations are in agreement with available lung tissue data of human patients [163]. Javierre et al. [164] analyzed the roles of diffusion, closure rate, and wound geometry on healing kinetics and concluded that healing is always initiated at regions with high curvatures.

The role of diffuse fibrosis on wave propagation, arrhythmogenesis, and arrhythmia mechanism in human ventricular tissue has been elucidated in [165]. In particular the model shows that diffuse fibrosis slows down wave propagation and increases tissue vulnerability to wave break and spiral wave formation. The authors of paper [166] have developed a mathematical model in the maintenance of alveolar epithelial integrity as related to the genesis of pulmonary em-

physema and fibrosis. The model reveals a close relationship between alveolar emphysema and fibrosis and EMT in lungs affected by chronic obstructive pulmonary disease.

In order to mimic diffuse fibrosis in the human ventricular tissue, a mathematical model has been developed in [167]. The model takes into account fiber rotation, transmural heterogeneity, myocytes, and fibroblasts. The model is able to capture a large variety of nonequilibrium states, temporally periodic, quasiperiodic, chaotic, and quiescent.

5.3. *The thermostatted kinetic theory*

Recently the thermostatted kinetic theory has been proposed as a new paradigm for the modeling of complex biological systems composed by a large number of entities [168]. This framework is based on a new system biology approach that looks at the entities composing the system for their ability to express a specific strategy or function. In this context the entities are called active particles and their microscopic state is composed by space, velocity and activity variables (dependent variables). Coupled to the classical mechanical variables, the activity variable takes into account the activity express by the entities. The system is thus divided into different subsystems, called functional subsystems, each of them composed by heterogeneous entities expressing the same activity. The representation of the system is statistical and is obtained by introducing a distribution function (independent variable) on the microscopic state for each functional subsystem. Moments of the distribution function allows to define macroscopic quantities (density, momentum, energy). The distribution function is solution of an evolution equation which is obtained by equating the time derivative of the distribution function to the inlet and outlet flows of active particles. The flows are obtained by considering changing on the magnitude of the activity variable (increase of cell-heterogeneity, reaching of high values of activity), proliferative/destructive events (birth and death of cells) and mutations (onset of a new cells), see Fig. 4. Thus the inlet and outlet flow are composed by conservative-number-density and nonconservative-number-density interactions. The distribution function is thus solution of an evolution equation which is composed by conservative and nonconservative operators. The operators are derived by considering the definition of parameters (functions) which represent interaction rates among the particles. In particular stochastic operators take care of changing into the spatial and velocity variable. Specifically the velocity variable fulfils a jump process, e.g. Poisson process, and the evolution of space variable is linear in velocity transport. Open questions in this context relate to the choice of turning kernels in the integral operators, a realistic modeling of the turning rates, and the wellposedness in less regular function spaces, under less restrictions on the data.

The (known) action of external agents can be introduced at the same scale of the particles (open systems) by defining the agents as an outer functional subsystem which interacts with the particles of the inner functional subsystems. Moreover the external action can be introduced as an external force field which acts on the whole system. In order to ensure the existence and reaching of nonequilibrium stationary state **??**, the external force field is coupled to an operator, called thermostat, which acts as a damping operator [171]. The whole framework consists of a system of nonlinear integro-differential equations with quadratic nonlinearities (mathematical model). By implementing numerical schemes, the numerical solution of the model depicts the evolution of the system. It is worth stressing that stochasticity is also at the base of the definition of interactions rates, in fact stochastic game theory is employed for instance in the definition of changing into the magnitude of the activity variable. Stochastic games are thus responsible

of microscopic interactions whereas changing into the distribution function are responsible of cellular interactions.

The dynamics at tissue scale is obtained by employing asymptotic methods of the kinetic theory. Classically different kinds of scalings lead to different kinds of equations: parabolic and hyperbolic [172–181]. Specifically by defining a rescaling of time and space variables (low-field or high-field scaling), and under suitable technical assumptions, macroscopic equations typically of the mechanics continuum approach are derived. In particular parabolic asymptotic limit of rescaled kinetic equations leads to a drift-diffusion-type system in which the diffusion processes dominate the behaviour of the solutions [182,183] and the references therein. In the high-field (or hyperbolic) limit, the influence of the diffusion terms is of lower (or equal) order of magnitude in comparison with those of other convective or interaction terms and the models consist of linear or nonlinear hyperbolic equations for the local density [184–186].

It is worth stressing that the models derived within the framework of the thermostatted kinetic theory for active particles share the same guideline of the models with internal structure.

The thermostatted kinetic theory for active particles has been recently proposed for the modeling of fibrosis diseases and more specifically for keloid formation [187,188]. Keloid is a fibrosis diseases that forms during a protracted wound healing process characterized by increased deposition of extracellular matrix by mutated fibroblast cells [189,190] which eventually undergo a somatic mutation in the tumor suppressor p53, and in addition to the inherited predisposition, generate cells (keloid) which have a high potential proliferation rate and an ability to escape apoptosis [191,192]. A viral hypothesis has been also made for keloid formation [193].

Bearing all above in mind, a kinetic for active particles-based model has been proposed in [194] and further analyzed in [195]. Specifically the model is developed assuming that the keloid formation involves four interacting functional subsystems: Normal-fibroblast cells, activated viruses, keloid fibroblast cells, malignant cells and immune system cells. According to medical hypotheses is assumed that viruses and the genetic susceptibility of patients are the main causes that trigger the genesis. A sensitivity analysis on some of the parameters has been performed showing that the model is able to depict the main emerging phenomena that are typical of the formation process of this disease, including the possibility to develop malignant effects and the immune system competition.

Recently a thermostatted kinetic model for keloid formation and the introduction of specific therapy has been considered in [196]. Employing a computational analysis, the effects of three different external forces miming therapeutic actions are analyzed: A vaccine for the virus, the PUVA therapy for the keloid and a vaccine for the cancer. The results are in agreement with the evidence that the sole action of the immune system is not sufficient to obtain a total depletion of keloid thus requiring the definition of a therapy. However the sole good action against keloid is the surgery.

Bearing all above in mind, the thermostatted kinetic theory for active particles can be considered as a new theoretical framework that appears suitable to model many complex biological system and especially fibrosis diseases. Indeed the possibility to consider birth/death process and mutation by introducing rates that have biological meaning, allows to tune these rates directly with experiments. However many issues need to be explored thus the various opening problems offer a good platform for reasearchers working in the applied sciences [197].

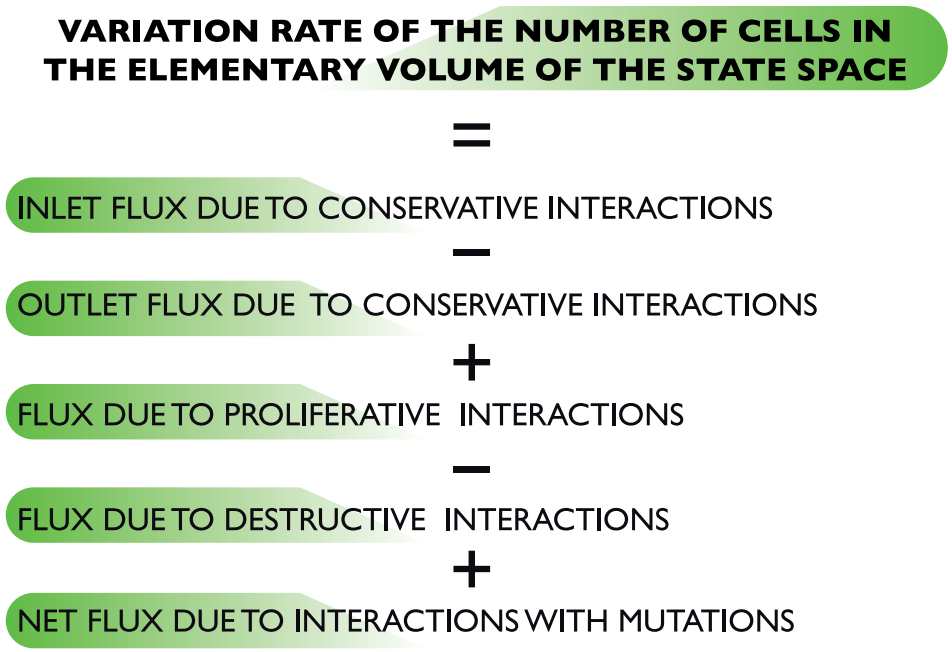

Fig. 4. Inlet and outlet flows of active particles in thermostatted kinetic models.

6. Modeling at macroscopic scale

This section is devoted to the modeling of fibrosis at tissue (macroscopic) level. The macroscopic models have been derived by mass conservation and mechanical force balance. The section, after the biological description of the main mechanical properties of the fibrotic tissue, is concerned with the coarse-grained modeling and the definition of constitutive laws for the fibrous collagen.

6.1. *An overview on the phenomena at tissue scale*

The fibrous connective tissue appears high-strength, slightly stretchy and consists mainly of collagen, a protein which is known for providing strength and stability. The two other main components of the fibrous connective tissue are water and polysaccharides, which are complex strands of carbohydrates. The primary purpose of fibrous connective tissue is to provide support and shock absorption to the bones and organs. Increased deposition of the fibrillar collagens I and III is typical of tissue fibrosis, and these collagens add stiffness to tissues.

The understanding of mechanical force and mechanotransduction in fibrosis is the key to understand the basic pathophysiological mechanisms of fibrotic diseases as well as developing new therapies. Forces result from cell-generated tension, fluid flow, stretch, and hydrostatic/osmotic pressure. The mechanical force regulates the phenotype and proliferation of myofibroblasts and other cells in damaged tissues, the activation of growth factors, the structure and mechanics of

the matrix, and, potentially, tissue patterning [198]. In particular myofibroblast activation due to mechanical forces has been proved for skin [199], heart [200], lung [201], liver [202], and kidney [203].

The mechanical forces that act in fibrosis are highly varied: tensile/compressive forces (perpendicular to the surface of an object) generated in response to tissue stiffness and fibrotic tissue growth, and shear forces (parallel to the surface) by fluid flow through the vasculature, ducts, and interstitium. These forces exert stresses (force normalized to the area over which it acts). However the above mentioned forces are not the only force that causes precursor cells to become myofibroblastic and fibrogenic, for instance hydrostatic pressure induces myofibroblastic activation [204]. It is important to note that there are important differences between signaling from mechanical and chemical stimuli, see [205].

It is worth stressing that the experimental study of the mechanics role in the large-scale architectural remodeling associated with fibrosis appears relatively limited [238].

6.2. *Coarse-grained modeling*

The coarse-grained approach is a way to extend molecular modeling and bridge it with experimental techniques. The system is represented with a reduced (in comparison with an all-atom description) number of degrees of freedom. Due to the reduction in the degrees of freedom and elimination of fine interaction details, the simulation of a coarse-grained system requires less resources and goes faster than that for the same system in all-atom representation. The coarse-graining approach has been proposed for various biological systems, especially for biomolecular simulations and in genetic. A coarse-grained approach has been proposed in [206] for the modeling of nucleic acids; the results have demonstrated a good quality in maintaining the nucleic acid hairpin structures, in reproducing the dynamics of backbone atoms of nucleic acids, and in describing the hydrogen-bonding interactions between nucleic acid base pairs. In [207] the coarse-grained approach has been developped for modeling RNA 3-D structures. The reader interested to further models derived within this framework is referred to the review papers [208–211].

The employment of the coarse-grained approach for the analysis of a fibrous disease aims at determining the mechanical properties of a fibrotic tissue by analyzing the dynamics of the constituents and making a statistical average in order to establish constitutive laws. This purely analytical work evaluates the energy of the system from the elementary bundles or from connected pairs in interaction with a matrix, the cross-linking breakage and the re-connection [212]. Such treatments are able to introduce temporal transformation of the network and viscoelasticity, internal rearrangements and large structure formation. Usually the Hamiltonian of one bundle is simple, however stochasticity, defects, localized active forces need to be introduced and finally averaged. This modeling has the scope to explain physically the nonlinear behavior of constitutive laws from the microscopic interactions, to explain time scale for dynamics and relaxation. This is the standard activity of statistical physics of soft matter as initiated by P.G Gennes for polymer physics [213].

It is worth pointing out that, even if the literature on the modeling of fibrosis within the coarse-grained framework appears very limited, the applicability of this modeling approach can be considered as an interesting research perspective. Indeed the coarse-grained paradigm appears to be the more appropriate framework for the modeling of fibrosis considering the recent developments in the fibers of cytoskeleton [214–216].

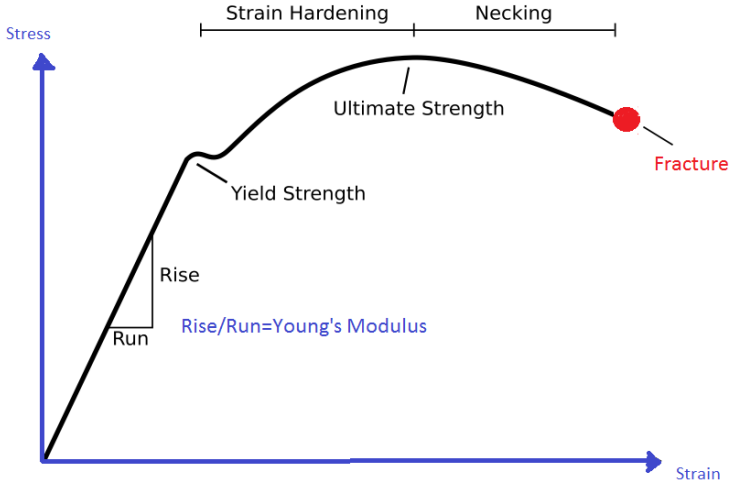

Fig. 5. Stress vs. strain diagram indicating the various stages of deformation.

6.3. *Constitutive laws for fibrous collagen network*

A constitutive law is a relation among physical quantities of a specific material or substance. The origin of a constitute law is related to the response of that material to external applied fields or forces. A constitutive law can be simply phenomenological or can be derived from first principles. The first constitutive law deals with the case of linear elastic materials and dates back to Robert Hooke (stress-strain relation or Hooke's law). In the mechanical properties of matter the constitutive laws usually refer to the following quantities (see Fig. 5): Stress, strain, elastic modulus (Young, Shear, Bulk), compressibility, see [217] and the section reference.

It is important to mention that accurate constitutive laws are necessary for stress evaluation, especially for soft tissues. Contrary to the linear elasticity Hooke law, there is no universal relationship between the stress and strain, and in particular for anisotropic soft tissues. The biomechanics approach is based on the definition of invariants, which are mathematical scalars constructed from the strain deformation tensor that do not modify in the change of coordinates. The elastic energy is obtained by means of these invariants (one or two for homogeneous matter but with an increasing number as the direction of anisotropy increases). It is worth stressing that most of the Young moduli of biological tissues have never been evaluated. Moreover the neglecting of one invariant in a nonlinear treatment may induce wrong predictions or fail to recover an important feature. In the anisotropic material case, the state-of-the-art is very limited; the case of the heart [218,239] and arteries [220] have been studied in details. Few models have been proposed, and the most famous is the Hopzafel-Gasser-Ogden model [221]. These models are valid in tension (ignore simply compression) and only the homogeneous part is considered. The generalization of the above mentioned model for breast tissues will be a fundamental contribution to the elasticity of soft tissues.

The right coverage of the wound is an important step for avoiding the onset of pathological

fibrosis. The wound closure requires that the epithelial cells migrate collectively and in synchrony [222–224]. Therefore it is not surprising that most of the models of the pertinent literature refers to this phenomenon (and in particular observed *in vitro*). Specifically several mechanisms of closure have been proposed: a leader cell mechanism [225], cooperative traction force mechanism [226], steered migration mechanism [227], differential adhesion hypothesis [228], and differential interface tension hypothesis [229]. The authors of [230] have studied the wound closure in Madin-Darby canine kidney epithelial cell layers and established that submarginal cells exhibit protrusive and migratory behavior similar to that of marginal cells. In [231], the wound made in an epithelium of human cancerous melanocytes, does not exhibit this leader cell mechanism but exhibits a diffuse and noisy border. The results of [232] show that the fibroblast growth factor leads to directed migration of leader cells but do not control cell migration and coordination of the follower cells. Various models describe migrating cells using reaction-diffusion equations for cell density. The model proposed in [146,233] reproduces not only wound closure dynamics but also the irregular, undulating, progression of the edge of the layer typical for scratch-wound assays, without the need to specify leader cells. The model proposed in [234] predicts how ischemic conditions may impair wound closure. The results of [235] show low migration speed at high and low integrin concentrations and high velocity at medium concentrations; the model is only appropriate in situations in which the wound has a simple geometry with two long parallel wound edges. The model [235] is concerned with the closure of a wound and the expansion of a cell colony. In [236] the cell sheet is represented as a compressible inviscid fluid, and therefore individual cells are not distinguishable.

Differently from the above mentioned models, cell proliferation has been assumed for the wound closure in [147,237]; cell proliferation limits the irregularity of the wound frontier. The interested reader to further macroscopic continuous models for both the physiological and pathological fibrosis is referred to the review paper [15].

Recently a biophysical and biomechanical investigation of the growth of collagenous tissue owing to inflammation has been proposed in [238]. Specifically the authors of [238] deals with the capsular contracture, which is the excessive fibrosis around the implant that leads to a high re-operation rate [25]. The elasticity of the tissue is derived from uniaxial traction experiments to propose the best modeling of capsular tissue. After the definition of constitutive laws for capsular tissues, full calculations of the stresses has been achieved and the implant deformation predicted. It is worth to point out that in vivo, there is no exterior loading but one part of the stresses comes from the growth process itself, constrained by two borders: the implant surface and the outer soft layer. It consists of a 3 layers or shells problem of elasticity, not completely trivial to achieve but the calculation can be done mostly analytically in cylindrical first and spherical geometries [240]. Observation of implants once they are excised from a patient proves that the stresses are above the shape stability of these materials: they are completely crumpled, suggesting extremely large compressive stresses and explaining the dolor of the patient. It is clear that the growth tissue is above the stability of the initial geometry and bifurcates making first ripples at the implant surface and after evolving towards plastic deformations. The mechanical model can predict the loose of stability of the implant surface due to the growth in conjunction with active cells contained in the tissue as a function of the capsule thickness and the two shear modulus ratios: implant/capsule, implant/healthy tissue for a 3 layer combination. Such analysis [239] gives an estimation of the stresses, an evaluation of the growth arrest due to homeostasis. The calculation is based on the multiplicative decomposition gradient [240,241].

7. A critical analysis on the different modeling approaches

The present review paper has been devoted to various models for physiological and pathological fibrosis in the attempt to understand the qualitative and quantitative aspects of the complex processes which trigger its formation. Differently from the biological sciences, the term "model" here refers to the definition of a theoretical structure based on assumptions and parameters which allows to obtain the description of fibrosis. On one hand, the contents has been mainly addressed to the existing theoretical/modeling structures, on the other hand the biological aspects of fibrosis are reviewed into the whole paper and at each scale of observation; the specialized reader in the biological description of fibrosis can take advantage of this review considering that also many review papers of researchers coming from biology, immunology and medicine are cited.

The reviewed models have been derived following different theoretical frameworks coming from biomathematics, bioinformatics, biomechanics and biophysics and at different scales (molecular, cellular, tissue). As mentioned in the previous sections, the models differ substantially in scope, but the modeling principles are related and can be applied to multiple biological systems. In particular at each scale, several approaches can be considered and an overlap among them can exist depending on the definition of actors of the phenomenon. The choice of a specific model type depends on the information desired. Specifically certain models are appropriate at molecular or at cellular level, while other models are more beneficial on a tissue level.

At present each modeling framework revised in the present paper requires some assumptions which limit the global description of the phenomenon. ODE-based models are constrained to deal with the time evolution of a population consisting of identical entities. Therefore a mathematical model derived within this framework consists of a limited number of populations (equations) in order to control the numerical cost of their numerical simulations. In particular also the number of parameters increase with the number of equations. Systems of ODEs do not automatically reflect compartmentalization, transport and diffusion of molecular species unless explicitly specified. Similarly agent-based models require the definition of many rules in order to take into account the heterogeneity of the biological system but differently from an ODE-based model, it is not possible to obtain analytical results for the asymptotic behaviour; thus only the numerical simulations are feasible. Bearing all in mind, the two above mentioned approaches appear suitable for the modeling of complex biological systems where the heterogeneity of the constituting elements is low. Moreover the applicability of these models relies on the good knowledge of the all microscopic components and the degree of their interactions. The reader is also referred to the review papers [242,243]. It is worth stressing that one of the most striking features of agent-based modeling is its ability to visualize emergent phenomena, i.e. the generation of patterns brought forth by complex interactions of the individual system components. Moreover agent-based models are flexible and can easily be adapted to new constraints. Finally agent-based modeling provides a framework for tuning the complexity of an individual agent or group of agents by elaborating on their behavior, degree of rationality, interaction rules, or ability to learn and evolve.

The introduction of a structural variable appears more convenient to reduce complexity. Indeed the structural variable can take care of the heterogeneity of the elements. However a high number of actors with different degree of heterogeneity can restrict also this approach. From the mathematical point of view, the introduction of the structural variable implies the derivation of a model that includes beyond the time derivative also the derivative with respect to the structure variable thus complicating the analytical and numerical analysis. Indeed PDE solvers are even more computationally intensive than ODE solvers. In contrast to the general framework with

internal structure, the thermostatted kinetic theory for active particles (that can be considered as a generalized model with internal structure) has the advantage that can take into account the modeling of nonequilibrium steady states that are typical of the biological systems [168,170].

The methods of deriving constitutive laws for biological tissue, or more specifically the applicability of the mechanical continuum approach, appear more suitable al tissue level. However some aspects of continuum mechanics must be adjusted to address the unusual behavior of living materials. For example, unlike other materials that elastically snap back to their original shape after being stretched and released, growing tissues do not return to their original shape. The kinematic equations therefore need to account for reversible elastic and irreversible growth deformations. The precise definition of growth, and hence the exact form of this irreversible deformation, generally differs depending on tissue type and can ideally be tied to changes on the cellular or even molecular level. Finally the equations modeling this growth process are highly non-linear, reflecting the complex geometries and heterogeneous materials involved [244,245].

It is worth stressing that the main objective of a theoretical modeling consists in showing the large time behavior of the solutions based on the bifurcation parameters that have a role on the two asymptotic trends: blow up of fibrosis related to inhibition of the immune system, and, alternatively activation of the immune system with progressive inhibition of fibrosis.

8. Research perspectives and open problems

The definition of powerful approaches to biology and medicine are already revolutionizing the understanding of the physiological and pathological fibrosis by bringing new quantitative level of fundamental understanding of the processes and by enhancing countless applications. The desire to look at a biological system as a whole, with the complexity of interactions among its components, is associated with significant challenges but will also bring enormous rewards.

The main research perspectives include the creation of enabling mathematical, computational and experimental methodologies. It should be a requirement for good modeling practice to make data and models available at the time of publication in a form where others can reproduce the modeling results. The rewards from the integration of novel computational and experimental techniques would be a new level of understanding of the biology and the ability to design more efficient medical treatments. The applications include advances in drug discovery and therapeutic applications, better diagnostic tools, new and improved surgical procedures and medical devices.

Bearing all above in mind, the following open questions are proposed to scholars that work in the field of pathological fibrosis:

- To what extent are immune cells and factors involved in driving fibrosis? Can they be effective therapeutic targets?

- What are the cellular origins of myofibroblasts in various fibrotic settings? Is epithelial to mesenchymal transition a significant source of myofibroblasts?

- What are the root causes of idiopathic fibroses? Can we identify further genetic or environmental causes, in addition to those already identified?

- What role might the microbiome play in either disrupting a normal wound healing response and causing fibrosis, or in promoting normal wound healing?

- Can we identify noninvasive biomarkers for liver fibrosis that might help catch the disease early and stratify patients for improved treatment?

- Is reversal of fibrosis feasible?

The possible answers to the above question will benefit of a multidisciplinary collaboration between scholars of the biological sciences and of the applied sciences. Several other open problems can be found in the review paper [246].

It is worth pointing out that in order to give an answer to the above open questions, some theoretical aspects of the different reviewed frameworks need to be investigated. In particular the thermostatted kinetic theory needs to be generalized for taking into account systems where the individual behavior is not linear and can be characterized by thresholds, if-then rules or nonlinear coupling [197,247].

9. Toward a unified multiscale approach

An interesting and challenging research perspective consists in the development of a unified multiscale approach for fibrosis, or more in general for complex biological systems. It is a fascinating objective considering that the scientific community looks intensely at a rigorous formalization of biological sciences by methods of the applied sciences, similarly to what happened in the past centuries to the interaction between mathematical and physical sciences. Multiscale modeling have been considered for fluids and solids [248], for polymer materials [249], for simulations of macromolecules [250], for nonequilibrium plasma [251]. The reader is also referred to the review [252].

The models proposed in this review paper generate problems, which demand further analysis and refinements. Biologists can take advantage of their interactions with the applied sciences. In fact, still pursuing their interest for experimental research, they can focus the experimental analysis on the tuning of models by identification of the parameters of the various models we have presented in the preceding sections. Their identification can be achieved by looking at the dynamics of the interaction at the molecular and cellular scale and between these two scales.

Particularly interesting is the multiscale aspect of biological phenomena. For instance the passage from the molecular to the cellular scale needs the assessment of the clustering of genes that produce certain phenomena at the cellular scale. Subsequently, the analysis can be focused on the measurements of gene expression that generate, related to different intensity, emerging phenomena, expression of biological functions, at the cellular scale.

A robust multiscale approach represents a challenging and highly attractive objective. The passage from an approach valid in the field of the applied sciences to a theory valid also in the field of biology can be achieved by a deep insight into biological sciences to obtain the above mentioned models by a theoretical rather than phenomenological approach. Experiments, possibly new ones still to be designed, and the multiscale approach can march together to pursue this objective. At present this objective is a challenging target that will ask for a great deal of research activity in the next decades.

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