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Biomechanical modelling in nanomedicine: multiscale approaches and future challenges

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Abstract

Nanomedicine is the branch of nanotechnology devoted to the miniaturization of devices and to the functionalization of processes for the diagnosis and the design of tools of clinical use. In the perspective to develop patient-specific treatments and effective therapies against currently incurable diseases, biomechanical modelling plays a key role in enabling their translation to clinical practice. Establishing a dynamic interaction with experiments, a modelling approach is expected to allow investigating problems with lower economic burden, evaluating a larger range of conditions. Since biological systems have a wide range of typical characteristic length and time scales, a multiscale modelling approach is necessary both for providing a proper description of the biological complexity at the single scales, and for keeping the largest amount of functional interdependence among them. This work starts with a survey both of the common frameworks for modelling a biological system, at scales from atoms to a continuous distribution of matter, and of the available multiscale methods that link the different levels of investigation. In the following, we define an original approach for dealing with the specific case of transport and diffusion of nanoparticles and/or drug-delivery carriers from the systemic circulation to a target tissue microstructure. Using a macro-micro viewpoint, we discuss the existing multiscale approaches and we propose few original strategies for overcoming their limitations in bridging scales. In conclusion, we highlight and critically discuss the future challenges of multiscale modelling for achieving the long-term objective to assist the nanomedical research in proposing more accurate clinical approaches for improved medical benefit.

Keywords: Multiscale modelling, Biological systems, Transport, Nanoparticles, Nanomedicine

1 Introduction

Nanomedicine is the branch of nanotechnology devoted to facilitate medical diagnosis and to improve therapeutic methodologies [106, 107]. According to the Forward Look Report on Nanomedicine published by the European Science Foundation, nanomedicine aims at "ensuring the comprehensive monitoring, control, construction, repair, defence and improvement of all human biological systems, working from the molecular level and using engineered devices and nanostructures to achieve medical benefits, ultimately" [8]. A pioneering definition of nanotechnology has been given by Feynman as the possibility to make smaller and smaller machine tools down to the atomic level [56]. This vision perfectly applies to nanomedicine, where miniaturization of medical tools pushes medicine towards more accurate, controllable and reliable protocols [60], with the long term purpose of facing the challenges of chronic diseases and improving the efficiency of the healthcare [126]. Nanomedicine does not only study the role of a specific molecule that acts in some process in a living system, but it also aims to address the whole set of issues behind pathologies [133]. For example, the design process of a nanomolecule for targeted delivery requires the evaluation of the complex biochemical and biophysical interactions present in a biological system. The increasing impact of nanomedicine in our daily life can be understood by looking at either the incidence of the main diseases over the world population (see, for example [150]) and the growing trend in investments for nanotechnology [57, 50].

A comprehensive list of fields of interest in nanomedicine has been illustrated by Freitas Jr [62]; he took into account 96 categories, ranging from nanostructured materials and functionalized surfaces to DNA manipulation and molecular motors. This number is even more impressive if one considers that one of the earliest therapeutic applications of nanomedicine was presented by Desai et al [44] in 1998. Until few years ago, three quarters of research studies and 59% of the patents in the field of nanomedicine could be classified as drug-delivery systems; other applications included nanoscale therapies, in-vivo imaging agents, in-vitro diagnostics sensors, biomaterials and active implants [50]. The success of nanoparticles for therapeutic goals resides in the flexibility of their design according to different shape and size, suitably tuned to interact with biological systems at different scales on the basis of different mechanical, magnetic and optical properties. The classification provided by Sivasankar and Kumar [136] divides nanoparticles into nanotubes, nanowires, nanocrystals, ceramic or metal nanoparticles and nanorobots. A further class is constituted by synthetic and biopolymeric materials, which are particularly attractive as degradable nano-carriers [115].

Regarding the particular case of cancer, Ozecelikkale et al [120] stressed the importance of the multiscale and multiphysics aspects of nanoparticle-tumour interaction in nanomedicine design, rather than the sole mechanical transport. The rationale behind such complex interactions was discussed by Albanese et al [1]: they illustrated how size, shape and functionalization are connected. As a consequence, growing interest is currently shown for multifuctional nanoparticles, as reviewed by Bao et al [14]. Surface functionalized nanoparticles was also investigated by Hondow et al [76], opening to the field of nanoparticles used for tracking and imaging [19, 96, 160].

Three keywords are crucial in order to understand the purposes and the methods of nanomedicine for targeted-delivery: theranostics, pharmacokinetics/pharmacodynamics and nanotoxicology.

- Theranostics is the combination of diagnosis of pathology and its consequent targeted therapy [157]; it is intrinsically patient-specific, requiring functionalized treatments [141].

- Pharmacokinetics aims at understanding how nanoparticles or drug-carriers distribute among organs in a global sense, whilst pharmacodynamics addresses the processes acting locally, in the specific site [25]. Joint application of these two disciplines makes it possible to evaluate how nanovectors distribute, penetrate and interact with their micro-environment.

- Nanotoxicology deals with the toxic impact of nanomaterials. Parallel to the increasing use of nanomedicines, to assess the negative effects of the presence, evolution and degradation of nanoparticles in a biological system has become a matter of primary importance [66, 117].

Most of the literature in nanomedicine illustrates experimental results. Nevertheless, mathematical modelling is a promising tool for the future development of this research field. Although experiments are fundamental to understand the potential offered by materials or technologies, the *in vitro* and *in vivo* studies are expensive both in terms of time and costs. By using mathematical models, instead, a quantitative understanding of system behaviour and of the efficiency of techniques can be rapidly obtained and the results from simulations can be used to guide experiments and improve the overall clinical effectiveness [61, 124]. After a proper validation, a mathematical model can be used to investigate *in silico* a range of conditions wider than the ones allowed by experiments. An example are the data on pathological situations: they are of fundamental importance while they are often difficult to obtain and manage *in vivo*.

The aim of this survey is to provide a description of the mechanical modelling approaches used in biological problems with a particular focus on nanomedicine in applications for targeted delivery for which a multiscale "top-down" description is proposed. In Section 2, the intrinsic multiscale nature of biological systems is highlighted. In Section 3, classical methodologies to model a biological problem at given characteristic length and/or time scales are presented. In Section 4, the example of transport of nanoparticles in porous media is considered to build a multiscale mathematical approach. Finally, the limitations of current approaches and the future trends in nanomedicine modelling are examined in Section 5.

2 Multiscale nature of biological systems

A biological system can be defined as a set of integrated components which interact and mutually depend on each other by the means of biological processes. Biological systems work over a wide range of characteristic length- and time-scales (Fig. 1): the largest scale is the one at which the macroscopic function is explicated, whereas the lowest scale is the one at which the elementary blocks can be separately recognized. A certain number of mesoscopic levels, instead, can be identified as the bridges between these two limits [130]. A generic biological

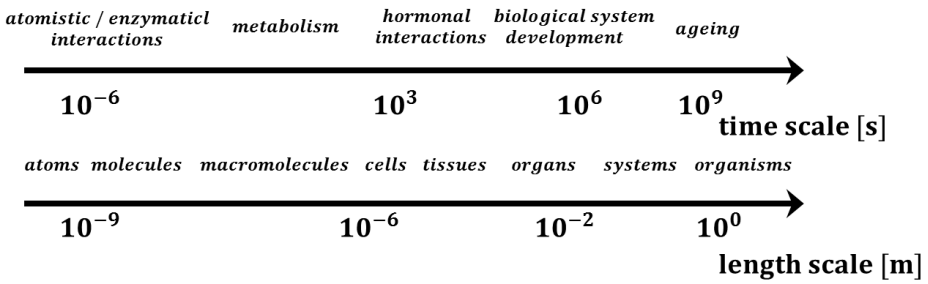

Figure 1: Multiscale nature of biological systems: building components and underlying biological processes can be identified in a wide range of length and time scales

system can be defined looking at its function, its form and its material properties; within the same biological system, as a consequence of the hierarchical structure [26, 15, 139], these aspects can differ if different characteristic scales are considered and the overall behaviour is not the simple superposition of the single lower scale ones [135].

Focusing on the topic of this article, the multiscale nature of biological system is briefly explained by using two examples: the cardiovascular system, through which nanoparticles are driven into the body, and a solid tumour, one of the most common clinical targets for nanoparticles. In the circulatory system, the heart pumps blood from the left ventricle, a chamber with a volume of a few cubic centimetres (cm^3), working in a range of $55 - 200$ beats per minute. From the aorta, the largest arterial vessel (diameter $\sim 3cm$), the vascular system branches out in smaller and smaller vessels in order to reach all the peripheral districts: arteries (cm), arterioles (mm) and arterial capillaries (μm). At this stage, red blood cells and nutrients transported in the network perfuse into the intracellular space through the capillary walls and biochemical reactions occur due to macromolecule exchanges (nm - μs). On the way back, venous capillaries, venules and veins close the system again into the heart. Blood itself is a multiscale system: at different characteristic lengths (i.e. different vessel diameters), blood constituents, of dimensions of the order of a few μm, interact with each other and with the vessel walls in different ways, whilst different time-scales regulate the balance between mechanical, chemical and electrical forces.

A solid tumour can be defined as a growing population of abnormal cells which invades the mesenchyme of the primary site and, finally, metastasizes in a distant site [33]. During its development, tumour achieves six capabilities, in an order depending on the tumour type: self-sufficiency in growth signals; insensitivity to anti-growth signals; evading apoptosis; limitless replicative potential; sustained angiogenesis; tissue invasion and metastasis [73]. Such properties can be related to the typical characteristic scales of the tumour structure: at lengths of hundreds of nm or μm and times of μs, electrochemical interactions among tumour cells and enzymes and/or molecules occur; the development of new microstructures, such as newborn blood vessels, becomes important when the system is analysed at typical scales of cm and s; the migration of tumour cells in the circulatory system and the creation of metastasis affects at the larger length scale of the circulatory system. However, the multiscale nature of a pathologic system has its further peculiar characteristics; considering angiogenesis, for example, the cancerous circulatory system is less organized and regular than the healthy vascular network [68]. Tumour blood vessels have a leakier and more permeable endothelium

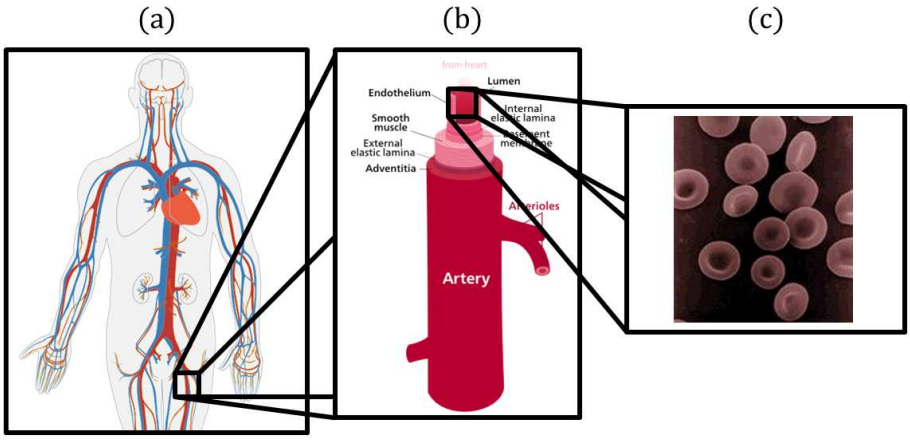

Figure 2: Different length- and time-scales within the human circulatory system: (a) whole circulatory tree at the macroscale; (b) small artery structure at the mesoscale; (c) capillary with red blood cells at the microscale (images taken from http://en.wikipedia.org/wiki/)

than healthy ones and an impaired lymphatic system, which result in high interstitial fluid pressures [113], which also depend on the stromal structure [154].

Mathematical modelling in nanomedicine for targeted delivery can not be limited to the sole design of nanoparticles: on the contrary, it requires analysis of the biological phenomena at nanoscale (i.e. protein folding or molecule / cell membrane interaction) and the different levels of multiphysics interplay. In the following Section, we provide a survey on the theoretical approaches and methods for investigating a biological phenomenon at its particular single-scale, which can constitute the building blocks of larger multiscale model. Although the presented modelling frameworks have a general validity beyond the particular field presented in this review, they have been extensively used in nanomedicine in many applications.

3 Single-scale models

Understanding the functional relationships between the macroscopic properties and microscopic features of biological systems is one of the most important challenges for modelling purposes. Different classes of methods are required when investigating the system properties at different length- or time-scales, as schematically depicted in Fig. 3.

A major partition can be operated between phenomenological and nanostructural approaches. In the former, the laws that regulate a phenomenon are extracted by empirical observations and are not derived from theoretical arguments. A great disadvantage is that the resulting model has lumped parameters, which are often difficult to interpret and identify. The latter, instead, starts from microstructural models of a single part of the system under investigation and the overall behaviour is obtained through integration (uplift) of the single parts using a number of functional interdependence rules. A list of fundamental properties for materials in nanomedicine and biomaterials can be identified: structural, mechanical, surface, transport, optical, magnetic, rheological [83]. Furthermore, biological systems possess two additional peculiar properties which differentiate them from inert matter: growth, i.e.

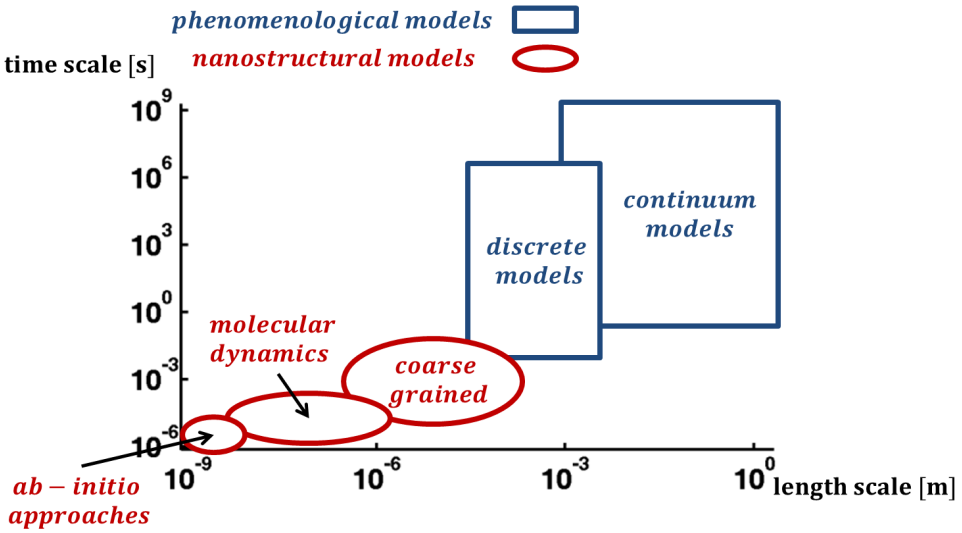

Figure 3: A classification of methods to be used for modelling biological systems in terms of their characteristic length- and time-scales

variations of mass, and remodelling, i.e. rearrangements of the microstructure [142].

3.1 Ab-initio approaches

The atomistic scale can be considered as a universal platform where different scientific disciplines interact: chemistry, studying the chemical bonds; physics, studying the properties of atoms; material science, analysing how the mechanical, electrical and/or thermal properties concur to determine the material structural properties [23]. Ab-initio methods (ABM) are entirely based on theory from first principles or natural laws without averaging nor approximations: this means that the properties of the single atom and the interactions with the surrounding particles have to be taken into account from the point of view of quantum mechanics [111]. The limit of these all-atoms simulations is the maximum dimension of a model, restricted to few hundreds of atoms: in fact, simulations of problems with characteristic lengths larger than tens of nm or times larger than the μs become computationally too expensive. Several applications have been proposed in a nanomedical context: for example, Merkle and Freitas [104] used an ABM for investigating the building process of diamondoid structures acting as nanorobots, with the long-time purpose to use them as targeted drug delivery vectors. The goal to improve the nanoparticle's cell selectivity was also present in the work of Shah et al [132] where Brownian motion and adhesion kinetic theories are coupled to assess the effects of the nanoparticle shape, the ligand density and the shear rate on the adhesion probability to vascular wall.

3.2 Molecular dynamics

The theory of molecular dynamics (MD) dates back to the work of Alder and Wainwright [3]. In this technique, one generates the atomic trajectories of a multi-particles system by numerical integration of Newton's law for given initial and boundary conditions and inter-

atomic potentials [95]. The key feature of this approach is the requirement of basic hypotheses for the interatomic interactions [121], which are introduced to identify the single components of a multi-body model. Such interactions, which can be extracted from experiments or ab-initio electronic calculations, define both the advantages and the limitations of the model [70]. Indeed, if the interactions within a body are imposed, they are inputs and they cannot be investigated by the simulation itself; nevertheless, the size of the simulation can increase up to a length scale of $100nm$ and time scale longer than μs. A widespread application of this technique is the investigation of the behaviour of biological macromolecules [87]. An extensive review of the application of this method in the description of protein folding was provided by Dobson et al [47], whilst de Groot and Groot and Grubmuller [40] presented a real time simulation of water permeation through human aquaporin-1 with atomic resolution. By coupling MD with Monte Carlo methods (MCM) [72], Muller and Albe [110] investigated the ordering kinetics in FePt nanoparticle, evaluating how the free surfaces, the bulk vacancies and the mutual interactions drive the disorder-order transition; Wang et al [155] analyzed the targeting properties of ligand-tethered polymer nanoparticles, including the effect of different parameters, such as the number of tethered polymer chains, the tether length, the core size, the receptor density and the receptor binding specificity.

3.3 Coarse graining

Investigating the interactions at the characteristic length of a living cell (μm) and characteristic time of μs is of fundamental importance in biological systems. Notwithstanding the increase in computational power of modern clusters, these kinds of problems cannot be tackled using atomistic approaches: therefore, coarse grained models (CG) are extensively employed [147]. As in MD, a CG model is characterized by a two-step procedure: first, the overall system is partitioned in structural units and, second, the interactions between single units are defined. The structural units in a CG model are larger than in MD, leading to a problem with fewer degrees of freedom [108]. As stated by Izvekov and Voth [80], interactions (or potentials) to be considered at this level have lower transferability than in the case of atomistic analysis, because they results from larger spatial and temporal averages, thus leading to a greater sensitivity on the imposed thermodynamic conditions in simulations. Nevertheless, this approach is unavoidable for defining a bridge toward macroscale analysis [83]. The use of CG models was presented in the work of Bahar [11] with the purpose of modelling large-scale and long-time conformational motions of proteins, assuming a bead-and-spring model as the basic unit. The importance of the proper choice of the potentials is highlighted, for example, in the work of Tirion [145] where a single-parameter potential has been proved to be suitable for studying protein dynamics. Moreover, Ramachandran et al [125] proposed a coarse grained model to study the DNA translocation in chemical modified nanopores, investigating how the surface probe density and the type of interaction potentials could affect the DNA transport in experimental tests.

3.4 Discrete (cell) models

In discrete models (DM), the spatial unit is a cell and its interactions with the surrounding environment (including the other cells) define the dynamics of the system [97]. Two large classes of DM are identified: in lattice-based DM (e.g. cellular automata), the cell's possible

positions are restricted on a regular mesh (structured or unstructured); in the lattice-free DM, such a constraint is absent. Both of them require deterministic or probabilistic interaction rules among cells. If the former is computationally less expensive but requires a rigorous preliminary analysis on the mesh structure, that should not affect the solution, the latter can be used in a wider range of situations [97]. Each cell is typically modelled as a three-component vector, describing its position, its velocity and the internal variables, possibly extracted from larger scale continuous equations [16]. An extensive review on the application of cellular automation (CA) approach in modelling biological cells was provided by Alber et al [2]: CA is attractive in the field of nanomedicine models whenever its key feature, the modelled cell, exactly matches a fundamental mesoscopic structure of a biological system. Therefore, cell aggregation is one of the most successful applications. A review on the application of Potts models (PM) in cellular modelling was due by Scianna and Preziosi [131]; they provide a novel approach to link the mesoscopic cell inner variables with the microscopic properties, instead of using a priori assumptions. PM was also used by Turner ans Sherratt [148] to study cell proliferation, and tumour cell invasion in particular, by making use of an Hamiltonian formulation that takes into account for both growth and mechanical deformations, demonstrating that the cell-medium adhesion plays a more important role than the cell-cell adhesion. Finally, a widely used discrete model for fluid dynamics problems is the lattice Boltzmann method (LBM), as in case of modelling the viscous flow in large distensible blood vessels [54].

3.5 Continuous models

The hypothesis underlying the concept of a continuous model (CM) is that the matter continuously fills the spatial domain under analysis: this assumption applies successfully at length scales much larger than the interatomic distances. Mathematically, this means that the problem can be analysed in terms of partial differential equations describing the temporal and spatial evolution of averaged quantities [16, 149]. Continuum biomechanics investigates the structural constitutive laws of biological systems, which typically show non-linearity in stress-strain elastic response [32], viscoelasticity [159, 144], and anisotropy [29, 119]. A single-phase material can be described looking at both its structural, chemical, thermal and optical properties and the mathematical relations used to evaluate their effects. In case of biological system, the phenomena of growth and remodelling are of primary importance. The volumetric growth can described using a multiplicative decomposition of the deformation gradient [129, 102], which relies on the concept of a virtual natural state. The stress-dependent remodelling laws can be formulated using thermodynamical principles [45, 5, 27] and can take into account the characteristic size effects in biological tissues [98]. Cowin [35] and Ambrosi et al [4] recently proposed extensive reviews of the continuous approaches in modelling these two phenomena in soft tissues, whilst their importance in orchestrating the emergence of shape in living matter is a matter of open debate [31, 28].

Whenever the interaction between the components of a biological system cannot be neglected, the use of multiphase models becomes relevant. In this framework, a crucial issue is the definition of reference volume element (RVE) [48, 86], the smallest volume over which an average can be made that will yield a value representative of the whole. The particular case of interaction between solid and fluid phases is widely observed among biological materials, from cells [105] to tissues, e.g. tumours [114] or bone tissue [93, 98], and suitable approaches are the poroelastic mixture models. A poroelastic material with time-dependent

properties is composed by a solid (elastic) skeleton whose pores are filled by a viscous fluid; suitable volume integrations of the fields of the single phases define a new biphasic material with averaged properties. This method is based on the so-called effective medium approach and the momentum exchange among phases at the microscale leads to the introduction of a coupling term in the constitutive equations accounting for the mutual stress between the phases. In the mixture theory, a soft hydrated tissue is considered as a material with two or more constituting phases, independent and uncompounded with each other [37], and the averaging is weighted on the phase-densities of the basic constituents. As it often happens at long time-scales, phases exchange mass and a suitable mass source law must be supplied for each phase. The dynamics of nutrients or growth inhibitors is usually taken into account in terms of reaction-diffusion equations of nutrients or growth inhibitors [7, 30, 79]. Mixture theories based on mesoscopic averaging lead to systems of partial differential equations with a mathematical structure similar to balance equations of single phase continuum mechanics, while accounting for micro-structural complexity; however the rationale to supply constitutive equations relations for partial stress and boundary conditions for each phase are sometimes obscure [6].

The proper choice of the parameters in CM is more delicate than in mesoscopic models, as they clearly depend on both the physical material constants and the geometry at the microscale [13] in an averaged sense. Under suitable assumptions, some multiscale methods provide rigorous tools to relate material properties at different scales.

4 Multiscale approaches in nanomedicine

4.1 Multiscale analysis in biological systems

On the basis of the schematic definitions given in Section 3, we can resume that ABM, MD and MCM are suitable methods for the description of microscopic phenomena; CG and DM refer to the mesoscopic level, whilst CM are well established techniques to model the macroscopic aspects. The aim of a multiscale approach is to bridge together models and methods which pertain to different characteristic length- and time-scales, with the purpose of obtaining a more comprehensive description of the macroscopic phenomena from microscopic bases [78]. Generally speaking, a multiscale analysis can be developed by using three different viewpoints: in a "bottom-up" approach, the study begins at the smallest scale and the results obtained are used as input conditions for larger scales; in a "top-down" approach, the study begins at the largest scale, where a continuum hypothesis is valid, and the results are used as boundary conditions for the underlying microscopic mechanisms; in a "middle-out" approach, the study begins at an intermediate scale and the results can be used to analyse both larger and smaller lengths or times [38].

The choice among these approaches typically depends on the available information on the physics of the phenomenon; nevertheless, all of them must face with the difficulties related to the "integrating-out" processes, which define the collection of rules to be used for linking the scales among them [111]. Ayton et al [10] introduced a classification for these processes, distinguishing between serial and parallel approaches. In the former case, different resolution models are developed in sequence and the information passing unidirectionally. In the latter, models at different scales are concurrently developed and the information flow can be bidirectional. Within this classification, some of the common approaches available in literature are

briefly described.

Homogenization techniques are widely used in multiscale modelling and they usually deduce mathematical relations between micro- and macro-fields using a multiscale expansion of the relevant physical fields. Effective properties are then extracted on the basis of assumptions of linearity and periodic or very slowly varying microstructure, in principle without even need of physical measurements [77]. Generally speaking, all homogenization techniques produce properties at the macroscale as averages of microscale conditions [89]. Applying the *rule of mixtures* [127, 152], the macroscopic properties are calculated through a weighted average of the properties of the single constituents: therefore, the concept of volume fraction becomes central in this approach. In the *effective methods approximation* [52], material properties to be used at macroscale are computed by solving analytical boundary value problems in simple representative domains. Considering *asymptotic expansion methods* [138], instead, the macroscale behaviour is obtained by expanding the macroscopic fields and the constitutive equations in terms of the characteristic, separable scales of the problem; therefore, the homogenized equations among macroscale fields are regulated and derived from properties at the microscale. Thus, the key feature of this approach is the proper choice of the relations between the scales, reflecting the medium structure: as a consequence, asymptotic expansion can be applied only when the microscopic domain shows a certain regularity [134].

An additional class of multiscale methods is based on the *averaged field theory*, using the idea that relationships holding at macroscale must be function of certain averages of the microscopic fields [77]. This approach fails in case of long-range fluctuations at the microscopic scales, in which case it cannot be properly applied [94] and requires a more general self-consistent theoretical framework. For example, a biological system can be described as a loop between larger and smaller levels of organization (i.e. scales) in which the relations among them are not simply derived from averages, as shown by Malo et al [99] for modelling cell proliferation.

Furthermore, the class of *micro-macro methods* is extensively considered in the multiscale modelling for biological tissue, whose purpose is to compute a material property to be used in a larger model by developing an additional relation holding at a smaller scale. The result at the smaller scale is not required to be valid for the whole macroscopic domain but it is representative only of the particular microscopic domain [89, 137]. Therefore, this approach is well-suited in all the cases in which the macroscopic system contains isolated and localized defects or singularities [158], albeit more complex microstructures can also be taken into account.

4.2 Multiscale models of nanoparticles transport in living materials

The investigation of the transport properties of nanoparticles and/or drug-delivery carriers in living tissues is one of the most active and evolving branches in nanomedicine [82]. This fundamental knowledge is of utmost importance to design novel therapeutic options for clinical practice, e.g. patient-specific treatments. In the biomechanical literature many works focus on the determination of the biological characteristics at a particular scale, while they are based on simplifying hypotheses on the material parameters to link different scales. Often a comprehensive work investigation of the whole multiscale problem from the nanometric scale to the macroscopic biological system is lacking, mainly because of the wideness of the problem itself. In this Section, we make a survey of some relevant multiscale approaches to study

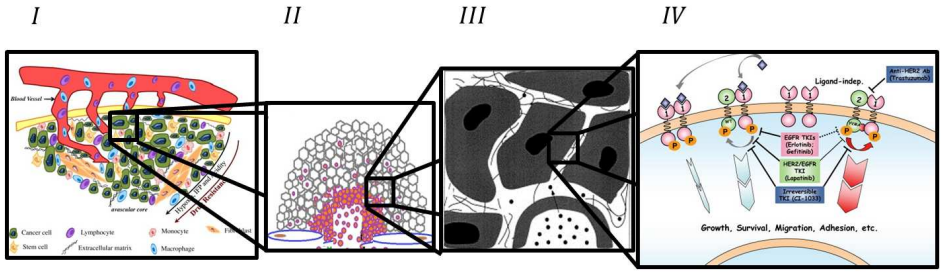

Figure 4: Multiscale analysis of a living tissue modelled as a porous medium. Four levels are highlighted. (I) Tissue scale (Reprinted from [39], with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]); blood flows inside blood vessels that are embedded into a solid structure constituted by cells (i.e., healthy cells, tumorous cells and antibodies) and extracellular matrix. (II) Extravascular space (Reprinted from [65], with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]); once blood (represented in red) crosses the vessel wall, it perfuses among the structures (represented in white) of the extravascular space. (III) Cellular level (Reprinted from [64], with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]); the blood constituents (natural or artificial nanoparticles) can be analysed separately and they are advected by the blood flow while diffusing in the space among cells and interacting with them. (IV) Subcellular level (Reprinted from [156], with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]); the biochemical interactions between a nanoparticle and a cell influence the cell's life driving towards phenomena like growth, survival, migration, adhesion or apoptosis

transport properties in living materials. In order to take into account for the different length- and time-scales, we suggest a "top-down" approach composed by four levels of investigation, based on the organization of the single components of the tissue and the biological mechanisms that regulate the transport properties within living matter.

(i) The tissue scale (cm - tens of s), where the structured heterogeneities within the living material can be recognized separately;

(ii) The extravascular space (mm - s), in which the blood transfer occurs from the capillary network to the extra-cellular matter and the cells;

(iii) The cellular level (μm - ms), in which nanoparticles/nanovectors diffuse and are advected by the flow or uptaken by the cells, behaving like a suspension within a fluid domain;

(iv) The subcellular level (up to hundreds of nm - μs), where the biochemical interactions, such as the particles uptaking or cells regulation, become the dominant processes.

4.2.1 The continuum level

At a tissue level (i), the poroelastic theory due to Biot [20] applies well to the average macroscopic properties of a living material composed by a solid skeleton with pores filled by an interstitial fluid. Considering a macroscopic RVE of volume Ω and boundary Γ, the equilib-

rium equations in quasi-static conditions can be written as:

$$\begin{cases} \nabla \cdot \boldsymbol{\sigma} = \mathbf{F}_{ext} & \text{in } \Omega \\ \boldsymbol{\sigma}\mathbf{n} = \mathbf{f}_{ext} & \text{on } \Gamma \end{cases} \tag{1}$$

where $\boldsymbol{\sigma}$ is the effective Cauchy stress tensor, $\mathbf{n}$ is the normal to the boundary Γ, $\mathbf{F}_{ext}$ and $\mathbf{f}_{ext}$ are external body and traction forces, respectively. Under assumptions of isotropy, small strains and hydrostatic fluid stresses, the constitutive equation for the stress reads:

$$\boldsymbol{\sigma} = \mu_{eff}[\nabla\mathbf{u} + (\nabla\mathbf{u})^T] + \lambda_{eff}(\nabla \cdot \mathbf{u})\mathbf{I} - \alpha p\mathbf{I} \tag{2}$$

where $\mathbf{u}$ is the displacement, μ_{eff} and λ_{eff} are the effective Lamé constants of the material (typically depending on the solid volume fraction), $\boldsymbol{I}$ is the unit-second order tensor, p is the fluid pressure and α is the isotropic effective stress coefficient. A wide class of constitutive equations coupling the pore pressure and the solid matrix can be found in Cowin and Doty [36]. Such a constitutive equation can be generalized to nonlinear solid and fluid components and an effective strain energy function for the material can be defined through a proper homogenization process [116]. Assuming a Newtonian fluid filling the pores, the fluid velocity $\mathbf{v}$ is governed by Darcy's law:

$$\mathbf{v} = -\mathbf{K}\nabla p \tag{3}$$

where $\mathbf{K}$ is the permeability tensor, possibly taking into account anisotropy effects in the microscale porosity. As the size of red blood cells is comparable to the diameter of microvessels, the blood flow in small vessels is better described by a shear-thinning model [153], as follows

$$\tau = H|\dot{\gamma}|^n sgn\,(\dot{\gamma}) \tag{4}$$

where the relation between fluid shear stress τ and shear rate $\dot{\gamma}$ depends on two material parameters H and n ($n < 1$). According to Bonfiglio et al [21] and Tosco et al [146], Darcy's law in this case should be rewritten as:

$$\mathbf{v} = -K_{eff}|\boldsymbol{\nabla} p|^{(1/n)-1}\boldsymbol{\nabla} p \tag{5}$$

where K_{eff} is a phenomenological parameter depending on the permeability tensor and the porosity (i.e. as the ratio between the volume fractions of fluid and overall domains). The set of governing equations is closed by imposing the mass balance for the fluid, leading:

$$\nabla \cdot \mathbf{v} = \frac{1}{2}\alpha\frac{\partial}{\partial t}\left(\nabla\mathbf{u} + \mathbf{u}^T\right) + \frac{1}{M}\frac{\partial p}{\partial t} \tag{6}$$

where the right-hand side represents the variation of the fluid content, which is related to the Biot-Willis coefficients α and M. Such parameters describe the dilatation properties of the porous material, with $\alpha = 1$ and $1/M = 0$ being the incompressible limit. In the poroelastic framework, the entries of the permeability tensor are unknowns parameters and a multiscale strategy is required for their proper definition because they depend on the microstructure of the material. For a laminar fluid flow over a granular bed of solid, the Kozeny-Carman equation can be employed, defining a functional relationship for the permeability depending on the porosity of the material and the ratio between the wet surface area and the reference volume [24, 90]. In biological materials, the permeability can be also influenced by the applied

strains [92], and different phenomenological laws have been considered depending on the microstructure of the tissue under consideration [91, 103] Alternatively, a direct micro-macro approach can be used for the determination of the permeability if the spatial distribution of voids is known for each mesoscopic domain composing the RVE, e.g. by using imaging techniques, as done by Guo [71]. Another interesting application concerns materials in which the voids are distributed according to a fractal rule: in this case an analytical relation links the permeability to the typical fractal dimensions of the voids [34] . This is an attractive approach for modelling solid tumour, whose vasculature generated by angiogenesis has been found to have a fractal structure [12, 128].

The tissue (i) and the vascular (ii) scales can be linked performing a homogenized approach based on the asymptotic expansion method, as recently proposed by Shipley and Chapman [134] and extended by Penta et al [122, 123]. The poroelastic RVE is composed by two separated domains where different physical laws apply: Ω_F is the fluid domain (the vasculature) and Ω_E is the porous extravascular domain, so that $\Omega = \Omega_F \cup \Omega_E$. The microscopic domains and the interface Γ_{FE}, are depicted in Fig. 5 in the case of the capillary vassels network in healthy liver lobule. The extravascular domain is modelled as a porous medium:

$$\nabla \cdot \mathbf{u}_E = 0 \quad \text{in } \Omega_{\mathrm{E}} \tag{7}$$

$$\mathbf{u}_E = -\frac{k_E}{\mu_F} \nabla p_E \quad \text{in } \Omega_{\mathrm{E}} \tag{8}$$

where equation (7) accounts for the mass conservation and equation (8) is Darcy's law with isotropic permeability k_E and fluid viscosity μ_F, $\mathbf{u}_E$ and p_E being the fluid velocity and pressure fields, respectively, in the extracellular medium. Conversely, in the fluid domain a Newtonian fluid flows according to:

$$\nabla \cdot \mathbf{u}_F = 0 \quad \text{in } \Omega_{\mathrm{F}} \tag{9}$$

$$\rho_F \left(\frac{\partial \mathbf{u}_F}{\partial t} + (\mathbf{u}_F \cdot \nabla)\, \mathbf{u}_F \right) = -\nabla p_F + \mu_F \nabla^2 \mathbf{u}_F \quad \text{in } \Omega_{\mathrm{F}} \tag{10}$$

where equation (10) is the Navier-Stokes equation for a fluid with density ρ_F, with $\mathbf{u}_F$ and p_F being the fluid velocity and pressure fields, respectively, in the vascular domain. At the interface Γ_{FE} between the two domains, two interface conditions are required to close the set of governing equations. The mass exchange at the interface can be implemented by using Starling's equation of filtration that, in a general framework, reads:

$$\mathbf{u}_F \cdot \mathbf{n} = \mathbf{u}_E \cdot \mathbf{n} = L_p \left[p_F - p_E - \sigma_T \left(\pi_F - \pi_E \right) \right] \quad on\ \Gamma_{FE} \tag{11}$$

where $\mathbf{n}$ is the outward pointing normal to the fluid surface, L_p the hydraulic conductivity of vessels wall (the interface in this case), σ_T the osmotic reflection parameter, π_F and π_E are the osmotic pressures in fluid and extravascular domains, respectively. Furthermore, a slip condition at interface between a Newtonian fluid and the porous medium must be supplied [85]:

$$\left[(\mathbf{n} \cdot \nabla)\, \mathbf{u}_F \right] \cdot \boldsymbol{\tau} = -\frac{q}{\sqrt{k_E}} \mathbf{u}_F \cdot \boldsymbol{\tau} \quad \text{on } \Gamma_{\mathrm{FE}} \tag{12}$$

where $\boldsymbol{\tau}$ is any unit vector tangential to Γ_{FE} and q is a dimensionless parameter which characterizes the slipping properties of the interface.

If the Reynolds number of the flow is low enough, the nonlinear advection terms in equation (10), may be neglected. Furthermore, if the exact representation of the boundary layers near the vessel walls is not the main interest in the model, then the interface conditions in equation (11) and (12) may be reduced to simply imposing continuity of the normal velocity and normal traction as in Discacciati et al [46] In this case, the model (7) - (10) may be manipulated to define a "fictitious domain" formulation where the the equation to be solved in both Ω_F and Ω_E has the same form, while the different flow properties in different regions are represented by varying the equation coefficients. The main step in this procedure consists of reformulating the constitutive relations in (8) and (10) according to the Brinkman model [22] as

$$\nabla p = -\frac{\mu_{Br}}{k_{Br}}\mathbf{u} + \mu_{Br}\nabla^2\mathbf{u} \tag{13}$$

Here the permeability k_{Br} and the viscosity μ_{Br} are discontinuous at the vessel walls and their values are such that $\frac{k_{Br}}{\mu_{Br}} = \frac{k_E}{\mu_E}$ in Ω_E and $\frac{k_{Br}}{\mu_{Br}} = \frac{k_F}{\mu_F}$ in Ω_F where k_E, k_F, μ_E and μ_F indicates the permeability of the extravascular domain, the permeability of the fluid domain, the viscosity of the extravascular domain and the viscosity of the fluid domain. Using such modified constitutive relations the equations (7) - (10) may be rewritten in the unified form

$$\nabla \cdot \mathbf{u} = 0 \qquad \text{in } \Omega_F \cup \Omega_E. \tag{14}$$

$$\nabla p = -\frac{\mu_{Br}}{k_{Br}}\mathbf{u} + \mu_{Br}\nabla^2\mathbf{u} \qquad \text{in } \Omega_F \cup \Omega_E. \tag{15}$$

It is shown in Angot et al [9] that equations (14) and (15) are a "good approximation" of equations (7) - (10). Furthermore, in the limit when the ratio of the permeability in the extravascular region to that in the vessels tends to infinity, then the solution to equations (14) and (15) converges to the solution of a Stokes flow model set in Ω_F with no-slip conditions at the boundary walls. This latter fact has been exploited in the literature fluid flow around obstacles [88, 9]. The stable numerical treatment of equations (14) and (15) in cases where the coefficients display large discontinuities requires the use of suitable numerical methods the study of which has been of interest both in the context of the literature on finite elements [101] and isogeometric methods [53].

4.2.2 Homogenization technique in multiscale analysis

Let us now assume that a strong separation between the lengths that characterize the structure of such a domain: a macroscopic one L, typical of Ω, and a microscopic one d, typical of the subdomains Ω_F and Ω_E, such that:

$$\epsilon = \frac{d}{L} << 1 \tag{16}$$

Accordingly, let us introduce the spatial position vectors in the microscale $\mathbf{X}$ and in the macroscale $\mathbf{x}$, that are related by

$$\mathbf{x} = \epsilon\mathbf{X} \tag{17}$$

Assuming that all fields depend, in principle, on both the independent variables ($\mathbf{X}$ and $\mathbf{x}$), one can perform a series expansions of the physical fields as follows

$$\mathbf{u} = \mathbf{u}^{(0)}(\mathbf{x}, \mathbf{X}) + \epsilon\mathbf{u}^{(1)}(\mathbf{x}, \mathbf{X}) + \epsilon^2\mathbf{u}^{(2)}(\mathbf{x}, \mathbf{X}) + ... \tag{18}$$

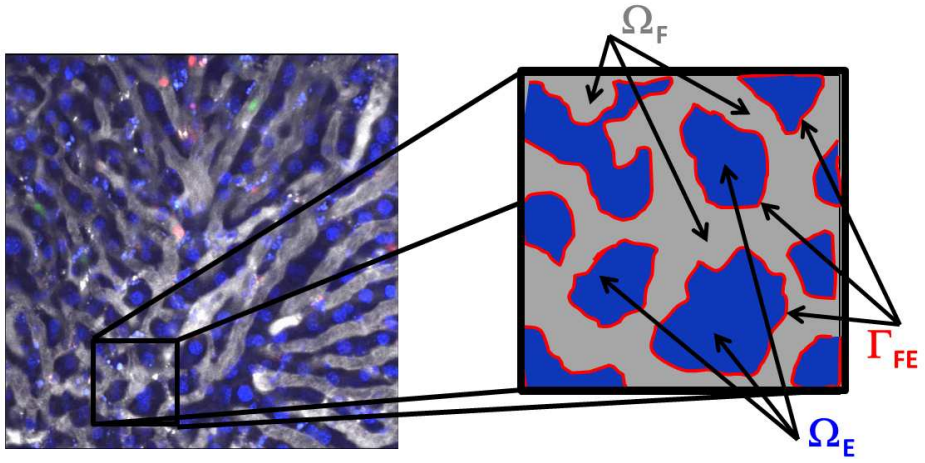

Figure 5: Microstructural organization inside a liver lobule: (left) micrography (area of $250x250\mu m$) showing the capillary vessels as gray domains and the nuclei of the hepatocytes as blue dots; (right) scheme of the representative volume unit, indicating the fluid and extravascular domains $\Omega_F$and Ω_E, respectively, together with their interface Γ_{FE}. The micrography frame is a courtesy of M. Iannacone and L. Sironi, Ospedale San Raffaele, Milan

$$p = p^{(0)}(\mathbf{x}, \mathbf{X}) + \epsilon p^{(1)}(\mathbf{x}, \mathbf{X}) + \epsilon^2 p^{(2)}(\mathbf{x}, \mathbf{X}) + ... \tag{19}$$

After lengthy manipulations, under the hypothesis of periodicity in $\mathbf{X}$, Darcy's law can be derived for the extracellular domain, relating the averaged leading order macroscale velocity $\left\langle \mathbf{u}_E^{(0)} \right\rangle_E$ to the leading order macroscale pressure $p_E^{(0)}(\mathbf{x})$, constant on the microscale, as follows:

$$\left\langle \mathbf{u}_E^{(0)} \right\rangle_E = -\frac{k_E}{d^2} \mathbf{E} \cdot \nabla_x p_E^{(0)}(\mathbf{x}) \tag{20}$$

The same result is found for the fluid domain where the averaged leading order macroscale velocity $\left\langle \mathbf{u}_F^{(0)} \right\rangle_F$ is related to the leading order macroscale pressure $p_F^{(0)}(\mathbf{x})$, constant on the microscale, as follows:

$$\left\langle \mathbf{u}_F^{(0)} \right\rangle_F = -\mathbf{G} \cdot \nabla_x p_F^{(0)}(\mathbf{x}) \tag{21}$$

In equations (20) and (21), tensors $\mathbf{E}$ and $\mathbf{G}$ depend on proper averaging of microscale quantities only, and can be obtained by solving the corresponding adjoint problems [123].

4.2.3 Multiscale model of circulation using lumped elements

If a given amount of nanoparticles is injected in the systemic circulation, the concentration of nanoparticles in the circulatory system up to the target organ is dictated by the transport properties of the flow in the vessels. The available literature in this field is large. For example, Formaggia et al [58] studied how to couple three dimensional, one dimensional and zero-dimensional models of different vascular districts, using a geometrical multiscale model. An application of this approach was presented by Malossi et al [100], where the fluid structure model in a three-dimensional aorta is coupled with six one-dimensional elements representing the surrounding vessels. A comprehensive multiscale model of the drug pharmacodynamics

from organ to cells has been presented by Tang et al [143]. The drug concentration $C_i(t)$ in *i-th* organ and $C_B(t)$ in the blood can be obtained by solving the coupled differential equations:

$$\frac{dC_i}{dt} = -k_{iB}C_i + k_{Bi}C_B - k_{i,loss}C_i \tag{22}$$

$$\frac{dC_B}{dt} = -\left(\sum_{i=1}^{n} k_{Bi}\right) C_B + \left(\sum_{i=1}^{n} k_{iB}\right) C_i - k_{B,loss}C_B \tag{23}$$

where k_{iB} is the transfer coefficient from *i-th* organ to blood, k_{Bi} the transfer coefficient from blood to *i-th* organ, $k_{i,loss}$ the rate of elimination in *i-th* organ and $k_{B,loss}$ the rate of elimination in blood. The initial concentration at the *i-th* organ is assumed null, $C_i(0) = 0$; whereas the initial condition for blood drug concentration $C_B(0)$ is imposed according to the subministration dose and method.

4.2.4 Nanoparticle transport and diffusion

Solving for the velocity fields in Equations (17) and (18), the transport properties in the intravascular space (ii) can be modelled using a reaction-advection-diffusion differential equation, derived from the classical colloid filtration theory. If the number of nanoparticles is sufficiently large that a concentration field can be defined, it obeys the equation:

$$\frac{\partial C_E}{\partial t} + \nabla \cdot (\mathbf{u}_E C_E) = \nabla \cdot [D \nabla C_E] - k_f C_E \tag{24}$$

where C_E is the molar concentration of the particles in the extravascular domain, D the diffusion coefficient, k_f is the absorption rate coefficient of the particles, e.g. by the target cellular matter, which are functions of the particles properties (e.g. size, shape, electric conductivity), of the local velocity and of the porous structure. Two conditions are to be enforced at the interface Γ_{FE}; some examples [81, 134] are e.g.

$$C_E = C_i \tag{25}$$

$$(C_E \mathbf{u}_E - D \nabla C_E) \cdot \mathbf{n} = r\,(C_E - C_i) \tag{26}$$

$$\beta C_E = C_i \tag{27}$$

Equation (25) imposes the continuity of the local concentration across the interface; equation (26) assumes that the concentration jump depends on the permeability of the wall (i.e. membrane law); and in equation (27) the concentration depends on the solubility of nanoparticle in domain under investigation, where C_i is the local concentration of the nanoparticles in the *i-th* organ from equations (22) and (23), r is the permeability of the interface with respect to the nanoparticle typology and β is the interface solubility of the nanoparticle typology.

In order to take into account for the transport properties at cellular scale, the material parameters D and k_f can be computed using analytical correlations or mathematical models based on the cellular scale (iii). The diffusion coefficient D can be calculated in one of the forms suggested for intercellular, porous domains in biomaterials [59, 69] , such as:

$$D = D_0 \frac{k_B T}{6\pi\mu a} \frac{L(\lambda)}{F\tau(\lambda)} \tag{28}$$

where D_0 is the diffusion coefficient of the nanoparticle in an unbounded fluid domain, k_B the Boltzmann's constant, T the absolute temperature, $F > 1$ a shape factor, $L(\lambda)$ a factor related to the steric reduction of diffusivity, $\tau(\lambda)$ the tortuosity, $\lambda = a\ r_p$ where a is the particle radius and r_p the effective pore radius. In order to define k_f, Su et al [140] proposed a direct micro - macro approach, based on the Brownian motion of a nanoparticle in a fluid. Accordingly, the random forces $\mathbf{R}(t)$ and torques $\mathbf{T}(t)$, acting on a nanometric particle of general shape, have to be consistent with the fluctuation-dissipation theorem, reading [109]:

$$\langle \mathbf{R}_i(t) \rangle = 0, \qquad \langle \mathbf{T}_i(t) \rangle = 0 \tag{29}$$

$$\left\langle \mathbf{R}_i(t)\mathbf{R}_j(t') \right\rangle = 2k_B T \beta_t \delta_{ij} \delta(t-t')\boldsymbol{I}, \left\langle \mathbf{T}_i(t)\mathbf{T}_j(t') \right\rangle = 2k_B T \beta_r \delta_{ij} \delta(t-t')\boldsymbol{I} \tag{30}$$

where δ_{ij} is the Kronecker delta, $\delta(t-t')$ is the Dirac delta function, β_t and β_r are the translational and rotational friction coefficients of nanoparticles, respectively, depending on the particles shape [132]. The motion of the particle flow and the colloidal filtration in porous media can be typically modelled by using the Happel's sphere-in-cell model [74], where a spherical particle flows within a porous structure composed by spherical cells; such a theory holds under the hypotheses of particles much smaller than the chemically inert cells, and a dilute, laminar flow. Neglecting their mutual interactions, the nanoparticles follow a Brownian motion and they are subjected to van der Waals attractive force, electrostatic double layer force, hydrodynamic drag force, lift force, buoyancy force, Basset force, and Magnus force, if they are nearby the cell surface [112]. In case of nanometrical particles, inertial forces can be neglected and the trajectory of the *j-th* nanoparticle can be modelled by the stochastic Langevin equation:

$$d\mathbf{r}_j = \left(\frac{D}{k_B T} \sum_k \mathbf{F}_k^j + \mathbf{u}_E \right) \Delta t + (\Delta \mathbf{r})_j^B \tag{31}$$

where $\mathbf{r}_j$ is the displacement vector, $\sum_k \mathbf{F}_j$ is the summation of the forces acting on the *j-th* nanoparticle and $(\Delta \mathbf{r})_j^B$ is the Brownian displacement. A model composed by a large number of nanoparticles and a solid phase composed by a single sphere was considered by Su et al [140] and a trajectory can be computed for each nanoparticle by integrating equation (31) using the time integration interval Δt. Accordingly, the parameter k_f is calculated by computing the number of nanoparticles that have a trajectory falling on the sphere.

Finally, the investigation of transport properties can be moved at the subcellular level (iv) where a complex interplay between extracellular environment and cellular functions occurs [49], it is possible to investigate the relation between the local concentration of drugs or growth factors and the number of receptors on the cell membrane for evaluating the characteristics of cell proliferation[51]. Similarly, a discrete lattice MCM has been proposed by Jiang et al [84] to determine the rule of cell duplication in function of the local concentrations of the available chemicals. The importance of size and shape effects in regulating the distribution of injected nanoparticles among the different districts has been experimentally pointed out by Decuzzi et al [43]. The theory proposed by Decuzzi et al [41, 42] can be used to study the specific interactions between a cell and a nanoparticle in order to evaluate the dynamics of the uptaking process, depending on the particle volume and its aspect ratio. In these works, moving from the theory developed by Freund and Lin [63] to determine the adhesion of a cell over an infinite plane substrate, the authors evaluated the cell wrapping around a cylindrical particle as a function of the binding energy factor, the molecular bond surface density, the

density of the receptor molecules and the mobility of receptors over the membrane, for different geometries.

5 Towards bridging scales: limitations and future perspectives

In this work, we have shown how mathematics can assist nanomedicine by modelling the mechanical behaviour of biological systems, considering both the single length- and time-scales of investigation and the possible functional connections among them. Although clinicians are very interested in the advantages apparent in using models, their impact in nanomedicine is far to be of current use for real applications in diagnosis and therapeutics: indeed, the state-of-the art in multiscale models of biological systems still presents serious limitations and a number of challenges must be faced for obtaining more effective approaches in future.

A major difficulty that occurs in developing a reliable model at a particular scale is how to take into account the sensitivity of the biological systems on the great number of biochemical factors and signals that are continuously exchanged, while preserving the apparent robustness with respect to certain perturbations in the environment and components [17]. Multiscale approaches aim at deriving the governing parameters at a particular scale by developing larger or smaller scale models, so that the system behaviour strongly depends on the interconnection rules between the scales. Consequently, there exists a fundamental trade-off between the accuracy of the biological system description and the insight that the model is able to provide. This is a particularly harsh limitation in nanomedicine, where the transfer of knowledge from the nanometric scale to the tissue level is of utmost importance for delivering effective therapeutic actions in clinical practice [161]. Indeed, we focused on the nanoparticle delivery in porous systems to show how multiscale mathematical models can be employed to provide a more accurate description of the microscopic processes in a biological system. Nevertheless, the achieved results can be just considered as a starting point, and the improvement of multiscale techniques appears as one of the most challenging research fields in the next future [18]

We share with Ferrari [55] the vision that mathematical modelling in nanomedicine will serve as a compass for guiding the clinicians through the unbearable complexity of the nanometric systems, providing tools for identifying the key mechanisms of a given phenomenon and guiding the technological innovation towards conquering bottlenecks in the fight against disease. Although much effort is directed towards achieving a greater accuracy in bridging scales, this should be accompanied by a deeper understanding of the underlying phenomena at the meso- and micro-scales, where the complexity of biological systems reaches the highest level. The development of novel experimental techniques will provide an enormous quantity of new data at smaller and smaller scales of investigation, which the modeller should accurately analyse for determining the level of approximation at which the nanomedical phenomenon must be described. This step becomes fundamental in the absence of any a-priori knowledge of the systems properties, and it requires the development of an interactive, interdisciplinary research where the model is informed by extant data and continuously revised by new experimental information [67].

If most of the current approaches test the appropriateness of the model with respect to the observable system features which it is able to reproduce, much work must be done to test the robustness and reliability. Having this goal in mind, there is the stringent necessity to

move from deterministic models, where the dynamics of the whole system is insensitive to small fluctuations of the individual biological events, to a probabilistic approach, which takes into account the intrinsic uncertainty and variability of the biological phenomena. This work highlights how this mandatory request in multiscale approaches reflects not only the need to model the single scales but also the connection mechanisms among them.

In order to be predictive, the modelling approach should be tested through a multi-step process including:

- validation, i.e. investigation of the accuracy with which a model is able to reproduce particular physical events of interest,
- calibration, i.e. determination of the model parameters for the specific physical environment in which such events take place, and
- uncertainty quantification, i.e. developing measures of the uncertainty in predicted particular quantities of interest. [75].

In practice, after that validation and calibration are performed using different solution domains and boundary/initial conditions, generally in a hierarchy of descending complexity, the propagation of uncertainty must be traced in every step of the processes and ultimately quantified for the variables of interest [118]. In the field of nanomedicine, all these concepts are crucial: the extent of new biological data forces the existent models to be revalued or developed again, the variability of the biological system's responses enlarges the confidence under which the models hold, and the uncertainty quantification checks the model's predictivity.

In conclusion, we are convinced that taking up these challenges will significantly help the nanomedical research in proposing more accurate, controllable and reliable clinical approaches to achieve a greater level of medical benefit. The integration of applied mathematics, statistics, biology and computer science has the potential to drive progress towards the creation of fit-for-purpose and responsive multiscale modelling and simulation, with the ultimate goal to lead to quantitative predictions to be used in clinical practice [151]. Increasing the modelling complexity of a biological system is an unavoidable but necessary task to deliver minimally invasive, patient-specific therapeutic options. This is a tremendously ambitious but certainly not an unachievable goal.

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