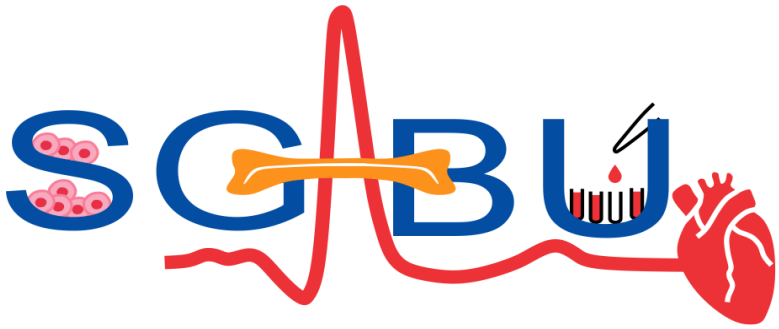

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Disclaimer

Executive summary

This deliverable is part of Work Package 3 (Mobilize knowledge and expand the network) of SGABU, in particular of Task 3.1 (State of the art in multiscale modeling in biomedical engineering). The latter aims at analyzing the current state of the art in the field, in order to provide the basis for the development of an innovative integrated platform, which will serve as modeling method library.

Accordingly, this report can be regarded as a critical literature review on multiscale modeling techniques employed in biomedical engineering, which has led to the following content:

- The report includes in-depth explanations of the very basics of multiscale modeling itself, in order to sharpen the understanding as to which requirements must be fulfilled such that multiscale modeling techniques can be applied at all.
- Continuum micromechanics is introduced as key concept in the context of multiscale modeling, which can be applied for a wide range of different (biomedically relevant) materials.
- Another class of (multiscale) models important for the field of biomedical engineering deal with the biological processes leading to the development of biological tissues over time. Such models are also presented in this report, and the physiologically relevant couplings to the aforementioned mechanical models are pointed out.
- Aiming at covering the whole range of studied observation scales, from the molecule to the macroscopic structure, also (mechanics-based) cell biology models are discussed, again including the important interaction between mechanical forces and biological processes.

Two key aspects are emphasized in this report. Firstly, multiscale modeling should not be considered as universally utilizable concept which merely requires application of existing methods, but requires careful considerations concerning the question which theoretical concept can be employed on which observation scale. Ignoring this question may lead to severe errors in the model predictions. Secondly, integrating biological processes into a multiscale modeling framework is a challenge which has been acknowledged in literature, but which remains to be successfully completed in a broad sense.

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List of Abbreviations

Abbreviation	Explanation
ABM	Agent based modelling
AFM	Atomic force microscopy
BEM	Boundary element method
CA	Cellular automata

CT	Computed Tomography
DEM	Discrete element method
DPD	Discrete particle dynamics
DSMC	Direct simulation Monte Carlo
EFG	Element-free Galerkin
FE	Finite Element
FFT	Fast Fourier Transform
FIB	Focused-ion-beam
HIV	Human immunodeficiency virus
IPM	Immersed particle method
LB	Lattice Boltzmann (method)
LDL	Low-density lipoprotein
MD	Molecular Dynamics
MPCD	Multi-particle collision dynamics method
MPFEM	Moving particle finite element method
MPS	Moving particle semi-implicit (method)
oxLDL	Oxidized low-density lipoprotein
RBC	Red blood cells
RVE	Representative Volume Element
SDM	Stokesian dynamics method
SIR model	Susceptible-Infected-Removed model
SMC	Sequential Monte Carlo
SPH	Smoothed particle hydrodynamics
WBC	White blood cells

1 Introduction

In an interesting, recently published review article, Alber et al. [1] propose the following definition of "multiscale modeling": "Multiscale modeling is a successful strategy to *integrate* multiscale, multiphysics data and uncover mechanisms that explain the emergence of function." In this context, Alber et al. refer to "small-scale" constitutive equations, and "large-scale" conservation laws as the general physical frame in which the multiscale models, being themselves supported by machine learning if necessary, may be developed. Thereby, the small-scale constitutive equations may be adopted from the classical engineering field, by considering elastic, viscoelastic, or elastoplastic behavior. As concerns living materials, the constitutive equations may be more complex, and concerning the "large-scale laws", biological applications may require rethinking "of the underlying kinetics, the balance of mass, and the laws of thermodynamics", and also inclusion of "the biological, chemical, or electrical fields that act as stimuli of this living response".

We here embrace the aforementioned focus on integration of multiscale/multiphysics data, and we share with Alber et al. [1] a deep root in engineering mechanics, as evidenced through their association of small-scale differential equations with classical mechanical behaviors, such as elasticity [2], viscoelasticity [3, 4], and elastoplasticity [5, 6]. Accordingly, we set a primary focus on multiscale mechanics modeling. This choice appears natural, given the importance of mechanics-related aspects in the biomedical field, in particular when focusing on multiscale modeling. However, we wish to complement Alber et al.'s account of the state of the art in multiscale modeling of biomedical materials and systems, by adopting an extended theoretical frame. More specifically, we set our focus not so much on *one* small ("constitutive") versus *one* large ("conservation laws-related") scale, but on the numerous *intermediate* scales, where one type of constitutive behavior is effectively transformed into another type of constitutive behavior. At the same time, we wish to review and discuss how the constitutive behavior at the smallest relevant scale may be either governed by largely invariant ("universal") properties or even by the first principles of physics, in both cases avoiding any empirical parameter fitting. It is this focus on the intermediate scales and corresponding successive scale transitions, which defines the (bio-)mechanical science-related literature reviewed and discussed in the remainder of this document (see Sections 2,3, and 4).

Still, we do not restrict ourselves to multiscale methods for *pure* mechanics, but we also address the exploration of the cross-roads of mechanics/physics and biology, as it is well-known that biologically driven processes may influence mechanical properties, and that, in turn, mechanical loading may influence the biological environment. In this context, the present review is completed by multiscale modeling concepts which, in a theoretically consistent manner, obey both the traditions of mechanics/physics (by employing field theories in mechanics and beyond, interaction/constitutive laws, geometrical compatibility) and of biology (by employing cell population dynamics, cell biology); found in Sections 5 and 6.

2 The representative volume element – "home of a constitutive law"

As a rule, biomedical materials and biological tissues are hierarchically organized, encompassing multiple pore spaces and other organizational patterns at different length scales [7, 8]. Therefore, the *ad hoc* adoption of the material point concept inherent to traditional solid mechanics is not straightforward, and in most cases, very questionable. This suggests prudence and good reasoning whenever using standard continuum mechanics quantities associated with the so-called material point, such as the Cauchy stress tensor (and associated notions of mechanical strength), various types of strain tensors (in particular the Green-Lagrange or the linearized strain tensor), or corresponding stress-strain laws (also referred to as constitutive laws), in the context of highly complex biological and biomedical materials. A good starting point for tackling the corresponding challenges is to resort to well-accepted, theoretically formulated and practically useful concepts which originate from geotechnical engineering, and which actually form the very basis of the scientific field called poromechanics [9] (i.e. mechanics of *porous media,* rather than mechanics of pure solids.)

A conceptual crystallization point in this context is the so-called representative volume element (RVE), which may be traced back to Maurice A. Biot's famous 1941 treatise on consolidation [10] – in Biot's words, a "*phenomenon … whose mechanism is known to be in many cases identical with the process of squeezing water out of an elastic porous medium*". For the appropriate representation of the latter, Biot proposes: *"Consider a small cubic element of the consolidating soil, its sides being parallel with the coordinate axes. This element is taken to be large enough compared to the size of the pores so that it may be treated as homogeneous, and at the same time small enough, compared to the scale of the macroscopic phenomena in which we are interested, so that it may be considered as infinitesimal in the mathematical treatment."*

We see that Biot defines his small element, at the same time, both as a point at the macroscopic scale and as a volumetrically extended (here cubic) entity at the microscopic scale. Explicitly assigning *two scales* to *one and the same element* goes impressively beyond the material point concept of classical solid mechanics, and hence, is not only qualified as the birth of poromechanics, but, from a more general viewpoint, marks the actual starting point of *multiscale modeling* in the engineering sciences – long before this term eventually gained ubiquitous popularity, both in the traditional engineering sciences and beyond – especially so in biomedical engineering.

The concept of such a simple RVE consisting of a solid matrix and a fluid-filled pore space entails a fundamentally new constitutive property linking pore pressure variations, under constant macroscopic strains, to macroscopic RVE-related stresses: the so-called Biot coefficient in the isotropic case [10], or the second-order Biot tensor in the general anisotropic case [11]. Within the RVE-concept, the same type of material property is multiply introduced, namely at different scales: Elastic properties are assigned to the solid matrix at the microscopic scale and to the overall porous medium, i.e. to the entire RVE. As an additional complication, the overall, RVE-related elastic properties depend again on the action of the fluid, with two important limit cases described for the first time by Fritz Gassmann in 1951 [12]: (i) that of empty pores or of pores with pressures governed from outside of the RVE (drained stiffness), and (ii) that of a closed RVE with the fluid being trapped inside the RVE (undrained conditions). Corresponding, meanwhile

classical relations were applied to soils, rocks, and shales, and nurtured important technological progress in geotechnical and petroleum engineering throughout the next four decades. It was not before the late 1990s, that such basic poromechanical relations entered the bioengineering realm. This was largely the merit of Cowin and co-workers, who dealt with the poroelasticity of bone [13, 14], and transferred, very successfully, the consolidation problem into biomechanics, by discussing the role of fluid flow in stimulating biological cells residing in pores, one of the key topics of this review, discussed further below, in Section 5.

Independently of the early poromechanical developments, the idea of a representative volume was embraced by the community dealing with *reinforced* solids. Going beyond the poromechanicians' conceptualization of a fluid pressure at the microscale, the reinforced solids community introduced the entire stress and strain fields at the microscale, thereby establishing, in the 1960s, a new scientific field called composite mechanics or continuum micromechanics. The key concept of the latter is that a macroscopic material point is associated to a full continuum mechanics boundary value problem, formulated on an RVE defined at the microscopic scale. In terms of length scales, this RVE coincides with that of poromechanics. More specifically, the size of the pores is now taken by the size of any type of (solid) inhomogeneities, and the boundary of the RVE is subjected to a microscopic displacement field which is governed by homogeneous macroscopic strains. These boundary conditions readily imply a strain average rule [15, 16]: The spatial average of kinematically compatible microscopic strains is equal to the macroscopic strain. Alternatively, if the boundary of the RVE is subjected to microscopic traction forces which are associated, via Cauchy's fundamental theorem, with one and the same macroscopic stress tensor, the following stress average rule applies: The spatial average of equilibrated microscopic stresses is equal to the macroscopic stress. Accordingly, one of the pioneers in the field, Rodney Hill, writes in 1963 when explaining what he calls "the representative volume" [15]: *"This phrase will be used when referring to a sample that (a) is structurally entirely typical of the whole mixture on average, and (b) contains a sufficient number of inclusions for the apparent overall moduli to be effectively independent of the surface values of traction and displacement, so long as these values are 'macroscopically uniform.' That is, they fluctuate about a mean with a wavelength small compared with the dimensions of the sample, and the effects of such fluctuations become insignificant within a few wavelengths of the surface. The contribution of this surface layer to any average can be made negligible by taking the sample large enough."* Hill has also complemented the stress and strain average rules by a third average rule associated with (rates of) work, standardly referred to as Hill's lemma: The average (rate of) of work (rate) done by equilibriated microstresses on kinematically compatible (rates of) microstrains is identical to (rate of) work done by the macroscopic stresses on the macroscopic strains.

In this context, the following practical question arises: Which ratio between the characteristic length of the RVE and that of the typical inhomogeneity within the RVE is needed to keep the aforementioned fluctuations sufficiently small, i.e. to make homogenization over microheterogeneities admissible and useful? This question had kept the scientific community busy for some time, until Drugan and Willis [17] provided a particularly satisfying answer in 1996, by considering the ergodicity principle and employing ensemble averaging. More precisely, Drugan and Willis consider the RVE as an ergodic system where *"local configurations [of microscopic quantities, such as polarization stresses quantifying the fluctuation of elasticity tensors] occur over any one specimen with the frequency with which they occur over a single neighborhood in an ensemble of specimens."* Hence, the spatial average of microstrains over one material sample representing the small material element in the sense of Biot and Hill becomes equivalent to the

average of the microstrain at one specific microscopic point over an ensemble of very many samples representing the same type of material. Subsequent comparison of the mathematical solution for the stress-strain relations of the homogenized single sample with that of the ensemble averages reveals a surprising result: An RVE exceeding only twice the diameter of spherical reinforcements defining the microheterogeneity size already allows for an accurate prediction of the overall elasticity, as quantified by an error margin of only 5%. Only one year later, this somewhat surprising result was heuristically confirmed by Monte Carlo computations on cubic unit cells hosting very many different disordered arrangements of spheres subjected to periodic boundary conditions [18]. The rather small RVE size also indicates that the boundary of an RVE undergoing homogeneous (i.e. Hill-Hashin) boundary conditions must be carefully chosen: It needs to circumvent local environments with high elasticity fluctuations, as explicitly noted by Dormieux et al. [19] when discussing pores as “zero-stiffness reinforcements".

The aforementioned compact RVE sizes impressively underline the role of continuum (micro-)mechanics as a particularly efficient, robust, and versatile tool for materials with pronounced microscopic organizations, such as biological tissues. However, similar to the situation with poromechanical theories, RVE approaches hardly entered the biomedical field before the 1990s, and it was not before the 2000s, that they started to flourish. In the case of bone, typical examples concern trabecular (spongy) bone with several millimeter RVE size [20-26], cortical bone with several hundred micrometers RVE size [21, 27-38], extravascular bone material with hundred micrometers RVE size [31, 39, 40], extracellular material with tens of micrometers RVE size [28, 31, 35, 37, 39-43], mineralized collagen fibrils [30, 31, 39, 41] and extrafibrillar polycrystals [30, 31, 39, 44], with hundred nanometers RVE size both. The latter two RVE types contain the elementary building blocks of bone, i.e. nanometer-sized hydroxyapatite crystals and crosslinked type I collagen molecules [45]. Notably, when using semi-analytical approaches, as discussed in more detail in Section 3, several of the aforementioned RVEs were straightforwardly combined to multistep homogenization schemes, sometimes referred to as “Russian doll models”, [21, 22, 28, 30, 31, 41-43, 46]. In this case, the microheterogeneities within an RVE are represented by yet smaller RVEs, with the size of the latter being smaller or equal than the aforementioned microheterogeneity size [39]. An illustrative example is seen in Figure 1, featuring the hierarchical organization of cortical bone, from the macroscopic, structural scale down to the scale of single collagen molecules, hydroxyapatite crystals, and fluid-filled pore spaces, together with the corresponding multistep micromechanical representation. Again, the actual realization of homogeneous stress or strain boundary conditions imposed onto a sufficiently RVE may practically imply carefully chosen, somewhat wavy RVE boundaries deviating from Biot’s originally envisioned, simply *cubic,* element, as can be seen from Level 5 shown in Figure 1.

While bone appears as the most intensively studied biological tissue, several other biomedical materials have been studied by RVE approaches as well, including arterial wall tissue [47, 48] or muscle [49].

The general nature and usefulness of the RVE being set now, it is time to continue with connecting microscopic to macroscopic physical quantities, i.e. with scale transition: upscaling and downscaling.

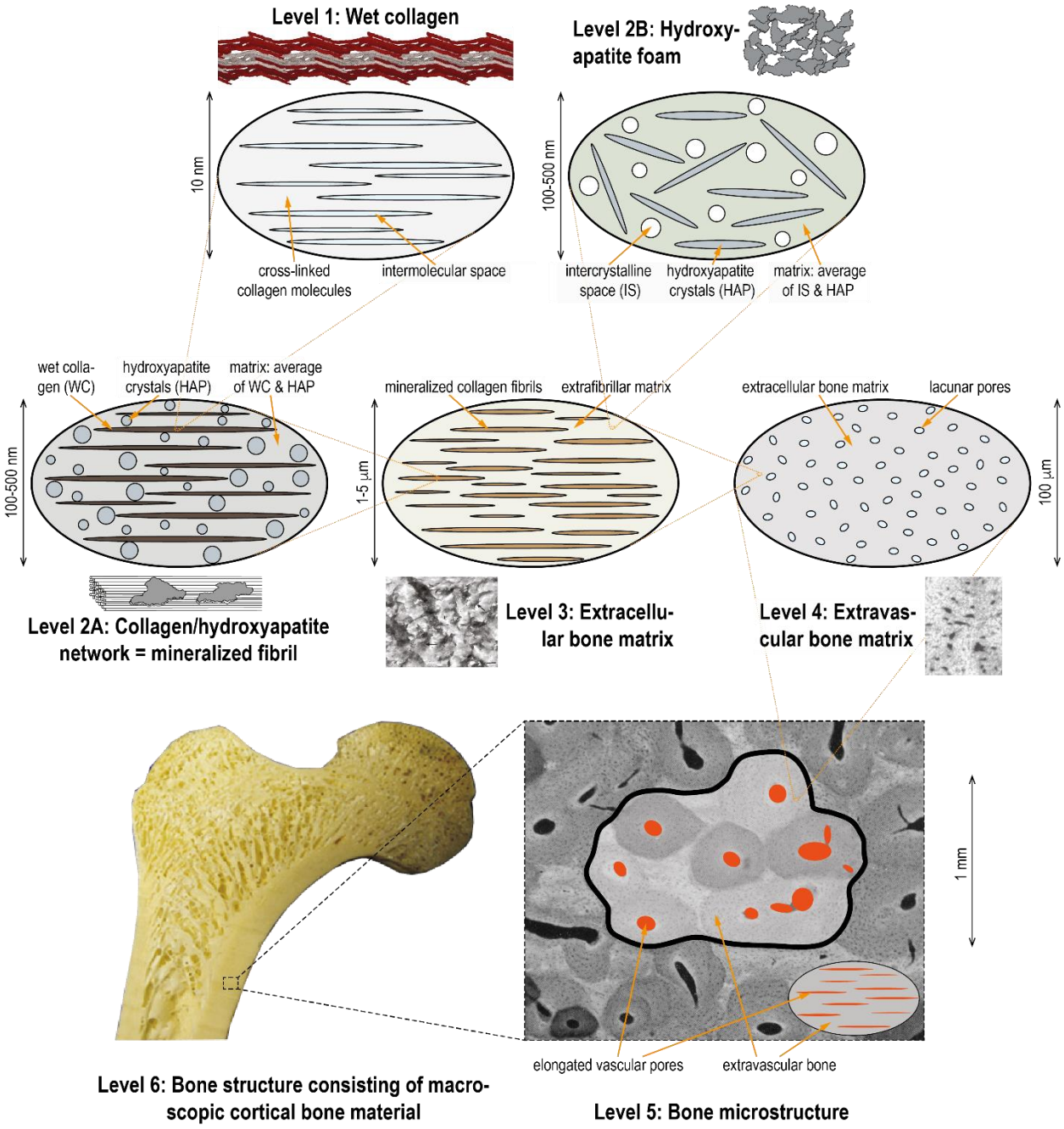


Figure 1: Hierarchical organization of bone (see images and cartoons, respectively), and the corresponding micromechanical representation (elliptic cross sections of the three-dimensional representative volume elements), with indication of the respective characteristic lengths; the micromechanical representation follows from Fritsch et al. [31, 39]. Note that on level 6, the region across which the representative volume is defined is precisely indicated (with the Haversian canals seen in their cross-sectional planes), whereas the respective cartoon is included as well (with the Haversian canals seen in longitudinal orientation). The included images were extracted from/adapted based on [50] (wet collagen), [51] (collagen/hydroxyapatite network), [31] (hydroxyapatite foam), [52] (extracellular bone matrix), [53] (extravascular bone matrix), [54] (macroscopic bone material or bone micro-structure), and [55] (femoral whole bone structure).

3 Scale transition – up/downscaling and homogenization

The quest for efficient and/or accurate solutions for microscopic boundary value problems associated with RVEs has stirred enormous scientific activity, and led to very many applications of standard computational mechanics-based approximation tools, such as the Finite Element (FE) method [56, 57]. In the latter context, periodic boundary conditions are usually prescribed onto a detailed representation of the RVE's microstructure, typically obtained from computed tomography. While appealing from a "ready-to-use" perspective which does not require deeper conceptual scrutiny, such approaches require a "full" description of the microstructure. However, such a description, particularly in 3D, remains virtually inaccessible, as the resolution of images is *per se* limited. Given in addition the high computational demands of numerical approximation schemes for partial differential equations (such as the FE method), the latter are typically restricted to single-step homogenization procedures.

Having, however, set our present review focus on repeated scale transitions across several observation scales, we devote the rest of this section to alternatives for purely numerical solution procedures, namely to analytical or semi-analytical solutions for the boundary value problems defined in the micro-heterogeneous RVEs. As a rule, such solutions rely on the smart use of Green's functions [58-60], i.e. of the solution for the displacement field throughout an infinitely extended homogeneous elastic body subjected to a singular point load of unit intensity. First, the micro-heterogeneous linear elasticity field is equivalently represented as the superposition of a homogeneous elastic field and a field of micro-heterogeneous eigenstresses, so-called polarization stresses. Setting the micro-stress and micro-strain fields of both representations equal to each other delivers the polarization stresses as the tensor product of the micro-heterogeneous deviations of the micro-elasticity field from the properties of the homogeneous elastic body and the micro-strains [61-63]. This opens the way to incorporating solution schemes for the Lippmann-Schwinger equation (which was originally proposed in the framework of quantum mechanics [64]), into the conceptual framework of continuum micromechanics, particularly so in the context of Fast Fourier Transform (FFT) analyses. The latter were pioneered by Moulinec and Suquet in 1998 [65], and continuously refined thereafter [65, 66]. Only very recently, namely in 2019, these elegant solutions have made their way into the image-based micromechanics of cortical bone [34]. Such approaches outperform FE-based homogenization approaches by orders of magnitude in terms of computational efficiency – however, they still rely on "complete" microstructural information. This might be the reason why yet another approach, namely that based on so-called material phases and estimates for homogenized mechanical properties, has gained much more popularity in the theoretical and applied mechanics field; and virtually propelled true multiscale approaches in biomechanics and bioengineering.

The premise for phase-based estimation of RVE-related properties is the explicit awareness that the resolution of the microstructure in infinite completeness is eventually impossible. Accordingly, this resolution is not even aimed at, but the focus is *a priori* set at microstructural features potentially governing the homogenized mechanical behavior of the RVE. Accordingly, within the RVE, homogeneous subdomains are introduced, so-called material phases [16, 67, 68]. Each material phase is characterized by homogeneous mechanical properties (such as one phase elasticity tensor, instead of a micro-elasticity field), by a characteristic shape, and by the volume fraction it occupies within the RVE.

As the first key modeling step in phase-based homogenization, each phase is approximated by a homogeneous ellipsoidal elastic inclusion, and each of those inclusions is embedded into the same type of infinitely extended auxiliary matrix subjected to homogeneous strains at its infinitely remote boundary, see Figure 2. This auxiliary matrix exhibits elastic properties which are different from those of the inclusion. The interest in such auxiliary matrix-inclusion problems arises from the existence of corresponding analytical and semi-analytical solutions. They were provided by Eshelby in 1957 [69] and by Laws in 1977 [70], for inclusions embedded in isotropic and anisotropic matrices, respectively. As was the case with the FFT-solutions described in the last paragraph, also the solutions for Eshelby's matrix-inclusion problems were derived by combining the polarization stress concept with the method of Green's functions. These solutions provide the remarkable result that the strains in the inclusion are actually homogeneous and depend on the inclusion shape, the elastic stiffness contrast between the inhomogeneity and the surrounding matrix, as well as on the remote matrix strains. If the investigated RVE is predominantly made up by a matrix phase in which inclusion phases are dilutely embedded, the RVE-related macroscopic strains can be approximated by the auxiliary matrix, and the macro-to-micro strain transition is already completed. Insertion of the phase strains into the phase-specific linear elastic laws yields phase stresses, and averaging the latter over the RVE eventually gives access to macroscopic stresses; leading to the homogenized elasticity tensor associated with the so-called dilute homogenization scheme. Modeling of "dilute suspensions" can be traced back to Einstein's 1906 treatment of rigid spherical inclusions in a Newtonian viscous fluid [71], and already appears as a broad review topic in Hashin's 1963 report [72].

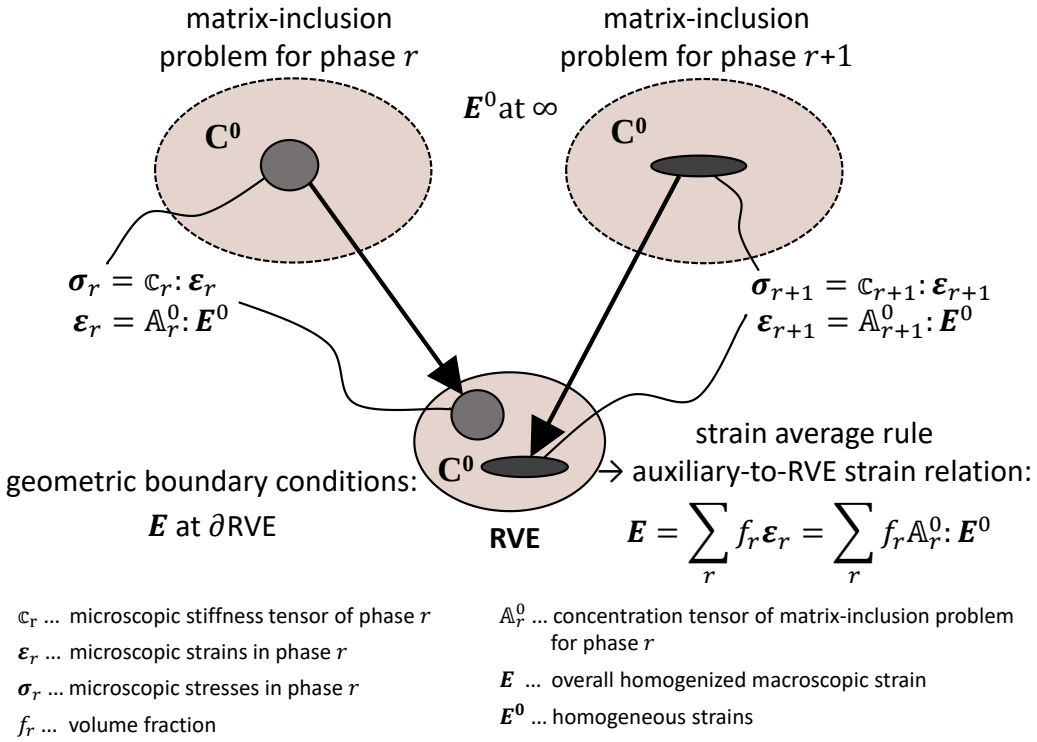


Figure 2: Concept of matrix-inclusion-problem-based homogenization (also called "far-field-homogenization" or "homogenization of media with random microstructures"): several such problems are subjected to the same fictitious far-field strains, and then "superimposed" into a representative volume element (RVE), by means of the strain average rule

However, for the frequently encountered cases where the individual phases are equally dominant in filling the RVE and consequently *interact* with each other, a second key modeling step is necessary, as sketched by Mori and Tanaka [73] in 1973 and rigorously formulated by Benveniste in 1987 [74]: Namely, the matrix-inclusion problems-related phase strains are inserted into the strain average rule, thereby providing a link between the remote auxiliary matrix strains and the macroscopic strains associated with the RVE. This link is then combined with the aforementioned solutions for the matrix-inclusion problems, yielding relations between phase strains and RVE-related macroscopic strains. The latter relations are multi-linear, and hence expressed by so-called strain concentration or downscaling tensors of fourth order. Use of the phase-to-RVE strain relations in the phase-specific microscopic linear elastic law, and subsequent averaging of corresponding micro-stresses over the RVE yields the macroscopic (homogenized) RVE-related elasticity tensor, as an analytical or semi-analytical tensor function involving the elastic properties of the phases, their shapes, their volume fractions and the stiffness of the auxiliary matrix. Choice of the latter completes the elasticity upscaling problem, with two main options: Choosing the matrix as an individual phase with given stiffness and volume fraction leads to the so-called Mori-Tanaka scheme [73], which is appropriate for matrix-inclusion composites. The second option is to assign the homogenized elastic properties and a zero volume fraction to the matrix. This leads to an implicit equation for the homogenized elastic properties. Its iterative solution is called self-consistent scheme. This scheme is appropriate for polycrystalline materials where all phases are in intimate mutual contact. Self-consistent schemes in the context of continuum mechanics can be traced back to the 1950s and 1960s [72, 75, 76]. However, they effectively entered bioengineering only in the early 2000s, in the context of modeling the porous polycrystals (or mineral foams) [77] and the mineralized collagen fibrils [31] present in the ultrastructure of bone. From that time on, also the Mori-Tanaka homogenization scheme was successfully applied to various levels across the hierarchical organization of bone, namely for the representation of wet collagen (Level 1 in Figure 1), of the extracellular bone matrix (Level 3 in Figure 1), of the extravascular bone matrix (Level 5 in Figure 1), and of the macroscopic bone material (Level 6 in Figure 1). Naturally, such micromechanical representations need to undergo careful experimental validation (as discussed in Section 4).

Bioengineering applications were a major driving force for developing Eshelby problem-based homogenization schemes for material properties beyond the elastic regime. The corresponding classical extension is that from elasticity to viscoelasticity, i.e. to assigning Boltzmann-type linear viscoelastic behavior to the material phases which *per se* remain fixed throughout time. In the Laplace-Carson space, such a linear viscoelastic behavior appears as a succession of formally linear elastic material behaviors, for each of which the classical Eshelby problem-based homogenization schemes described in the two preceding paragraphs can be employed, as explained in detail by Laws and McLaughlin in 1977 [78]. Effective application of this type of theory in bioengineering took place only in 2014 [79], with assigning viscoelastic properties to the hydrated extrafibrillar mineral crystals in the ultrastructure of bone, in order to explain hydration- and mineralization-dependent creep of macroscopic bone material. In this context, the computational endeavors really start when back-transforming the homogenized properties into the time domain, e.g, by means of the Gaver-Wynn-Rho algorithm [80].

Another straightforward extension beyond elastic homogenization concerned perfectly brittle materials where failure at the microscopic level is directly associated with overall macroscopic failure of the RVE. Accordingly, the insertion of the phase stress-to-RVE stress relation (expressed by fourth-order stress concentration tensors) into a microscopic failure criterion directly yields a macroscopic failure criterion,

which considers not only the strength properties of the weakest phase, but also the mechanical interaction of phases, driven by their shape, arrangement, and elastic stiffness contrast. However, when comparing the evaluation of corresponding mathematical formulations with experiments (see Section 4), the representation of the RVE's microstructure in terms of a finite number of phases generally turns out as a too crude approximation. As a remedy, the RVE may be represented by infinitely many non-spherical phases being oriented in all space directions and labelled by polar and azimuthal angles [81]. Corresponding two-dimensional integrals over the unit sphere are then solved by appropriate approximation schemes such as Stroud's formulae [82]. This type of multiscale modeling has provided unprecedented insight into the strength characteristics of man-made hydroxyapatite biomaterials [83] – and more generally, of a large number of ceramic material systems [84, 85].

However, what really broadens the application range of Eshelby-problem based homogenization, is the explicit introduction of eigenstresses and eigenstrains in the true physical sense; i.e. the introduction of strains and/or stresses which are fully independent of elastic, i.e. non-dissipative, phenomena. In the context of biomedical materials, two types of such eigen-quantities are of particular interest: plastic strains associated with ductile behavior, and pore pressures arising from fluids entering and leaving the various pore spaces found throughout the materials' hierarchical organization. Important averaging rules for eigenstresses and eigenstrains go back to Levin's 1967 paper [86] and follow from repeated use of Hill's lemma, as explained in [67, 87]: The macroscopic eigenstress tensor is the average over the RVE, of the tensor contraction between the microscopic eigenstress tensor and the strain concentration tensor; and the macroscopic eigenstrain tensor is the average over the RVE, of the tensor contraction of the microscopic eigenstrain tensor and the stress concentration tensor. The aforementioned eigenstress averaging rule implies a most interesting link between the micromechanics of media with random microstructures and the classical poroelasticity theory of Biot, as lined out in [19]: Considering a two-phase composite consisting of an elastic matrix and a pore space with eigenstresses of the format pore pressure times the second-order unity tensor yields the Biot tensor as the pore space-related strain concentration tensor times the porosity. This has a very important practical implication for the investigation of porous materials: The Biot tensors quantifying the interaction between pore pressure and macroscopic stress under a state free of macroscopic deformation need not be determined from complex poromechanical tests with independent control of pore pressure and macroscopic stress or strain, but can be readily determined once an elasticity homogenization scheme, as the ones discussed further above, has been established. This opportunity has been repeatedly taken in the context of the mathematical modeling of bone, in particular so for the determination of pore pressures in the intermolecular, intercrystalline, lacunar, and vascular pore spaces under various physiologically relevant loading scenarios [40, 88-90]; the latter are of central biological importance, as is further described in Section 5.

When the interest goes beyond "simple" eigenstress or eigenstrain averaging of a two-phase composite with only one phase being eigenstressed, interesting scale transition solutions concerning eigenstrains and eigenstresses can be obtained from the extension of the classical Eshelby-Laws matrix-inclusion problems to eigenstressed matrix-inclusion problems [67]. The solutions of such problems are again based on Green's functions, now in combination with a homogeneous elastic medium and two types of eigenstresses: the classical polarization stress explained further above, and an additional, physically motivated eigenstress, such as a pore pressure or an eigenstress associated with plastic strains. Benveniste's micro-to-macro scale transitions can then be extended to eigenstressed multiphase media, as outlined by Pichler and Hellmich in 2010 [91]: Each phase is represented by an inclusion in an infinite

matrix subjected to remote auxiliary strains; however, now both the inclusion and the matrix exhibit eigenstresses. Insertion of corresponding phase-specific homogeneous strains into the strain average rule yields a relation between the remote auxiliary strains, the RVE-related macroscopic strains, and the eigenstresses in the inclusion and in the matrix, respectively. In order to eventually relate the eigenstresses in the auxiliary matrix to the RVE-related macroscopic eigenstresses, additional use of Levin's theorem is made, finally yielding the so-called concentration-influence relations (originally coined by Dvorak in the early 1990s, as "transformation field analysis" [92-94]): The strains in each phase are not only related to the RVE-related overall macroscopic strains (by the already discussed strain concentration tensor), but also to the eigenstrains in *all other* phases and in the considered phase itself (by means of so-called fourth-order influence tensors). Homogenization of eigenstressed media was particularly helpful for explaining the strength of bone, arising from ductile sliding between hydrated crystals followed by brittle failure of molecular collagen [31]: Therefore, elementary plastic strains fulfilling the flow and consistency rules of classical plasticity [95] were introduced at the level of the hydroxyapatite crystals at Level 2B of Figure 1, and thereafter upscaled up to the level of macroscopic bone material. More recent studies based on the representation of Level 2B of Figure 1have revealed the elastoplastic failure behavior of the cement lines surrounding secondary osteons in Haversian bone from the surrounding bone matrix [44].

Yet further extension of the use of Eshelby problems for scale transitions in complex materials concerns large deformations, the typical biological example being soft tissues. As compared to hard tissues, this challenge has only recently been tackled. First successes with arterial tissues [48] are mainly due to (i) re-formulation the Eshelby problems for velocity gradients (rather than linearized strains), allowing for the derivation of concentration relations between macroscopic strain rates on the one hand, and microscopic strain *and spin* rates, on the other; as well as to (ii) thermodynamically consistent hypoelastic material laws [96, 97] linking objective (i.e. observer-independent) phase properties.

Upscaling of the largest RVE of Figure 5 (level 5: cortical or trabecular bone material) to the whole organ level can be realized by means of computed tomography-derived Finite Element models [98, 99]. Thereby, the CT images give access to (i) the topology of the organ, and (ii), via the average rule for X-ray attenuation coefficients [100, 101], to heterogeneous fields of vascular porosities throughout the organ. When additionally accounting for the invariance over space and time of the organ-specific chemical composition of the bone ultrastructure when averaged over milimeter-sized domains [102-106], and of the correspondingly invariant volume fractions inside the RVEs of the ultrastructure level and below, the aforementioned homogenization schemes provide inhomogeneous mechanical property distributions throughout the FE models. Eventually, this allows for the estimation of patient- and activity-specific safety factors of a load-bearing organ [107]: E.g., mild physiological loading of a lumbar vertebra is associated with a safety factor around 5, see Figure 3.

As a rule, the usefulness of all the aforementioned applications of scale transition techniques to biological and biomedical materials needs to be shown through careful and extensive experimental validation. This is the topic of the next subsection.

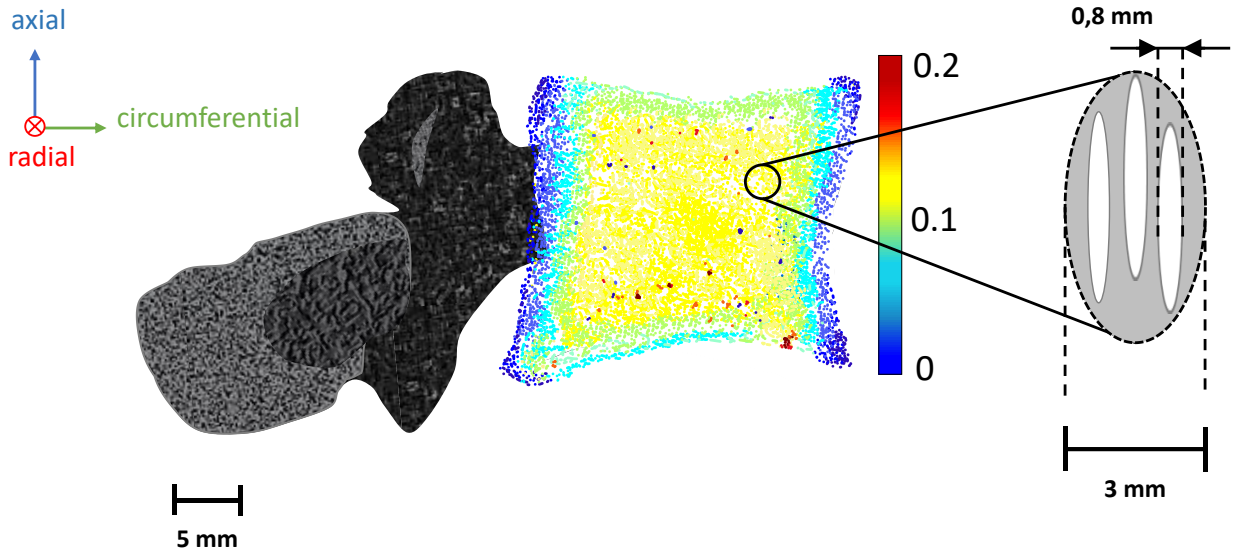


Figure 3: Micromechanics-informed safety assessment of human lumbar vertebra under mild physiological loading, after[107]: color representation of loading degree with respect to ultimate load (100% … elastoplastic failure)

4 Experimental validation – different methods at different scales

According to Popper's famous reasoning on the logic of scientific discovery [108, 109], a hypothesis which the human mind comes up with needs to survive as many statistically and physically different falsification tests as possible, in order to eventually reach, after extensive discussions and debates between the "peers" of a scientific community, the status of a reliable scientific theory. In this spirit, various multiscale micromechanics approaches, as described in Section 3, have been carefully validated by means of biomechanical, biophysical, and biochemical experiments [21, 31, 39, 42, 44, 77, 110]. Typically, such experiments concern (i) "universal" mechanical properties of the elementary components making up any tissue belonging to a particular class of tissues (e.g. in the case of bone tissues: molecular collagen type I, hydroxyapatite, and water with non-collagenous organic); (ii) tissue-specific mechanical properties at any hierarchical level above that of the elementary constituents, tested across the vertebrate animal kingdom; and (iii) tissue-specific compositional information which can be converted into phase volume fractions, phase shapes, and phase interaction patterns at any hierarchical level above that of the elementary constituents, again tested across the vertebrate animal kingdom. In this context, the premier experimental sources for elastic properties are ultrasonic tests and mechanical tests.

In the case of ultrasonic tests, see Figure 4, acoustic signals with a given frequency are sent, along different paths, through the tested material sample. From all the waves traveling along *one* path through the tested sample, the fastest one is associated with elasticity, and the product of the squared velocity of the elastic wave with the sample's mass density gives access to the components of the elasticity tensor [111]. Thereby, the actually tested RVE is determined through the wavelength, the former is five to ten times smaller than the latter [112]. Ultrasonic tests have been very successfully employed for biological and

biomedical material characterization, both at the fundamental level of the elementary constituents of a biological tissue class, and at various levels of hierarchical organization. In the case of bone, the elastic properties of the elementary building block "hydroxyapatite" were determined from ultrasonic tests performed on densely compacted hydroxyapatite powder by Katz and co-workers in the 1970s and 1980s [113-115]: The isotropic Young's modulus and Poisson's ratio amounted to 114 GPa and 0.27, respectively. These numbers were impressively confirmed by *ab initio* density functional theory computations some thirty years later [115]. The elementary component "type I collagen" was elastically characterized by Cusack and Miller in 1979 [116], by means of Brillouin light scattering (i.e. inelastic scattering of light by thermally excited elastic waves). The employed 10 GHz signals refer to wavelengths of 300 to 400 nm, hence characterizing an RVE of some tens of nanometers characteristic length, i.e. to Level 1 in Figure 1. In more detail, Cusack and Miller tested rat tail tendon, which, upon drying, collapses to a material consisting almost exclusively of type I collagen [117, 118] and hence, represents "molecular collagen" phase of the RVE of Level 1 in Figure 1 [39, 42]. This reasoning was further refined [117] by considering xylene imbibition tests [119], showing that dried collagen still exhibits 12% intermolecular porosity in the sense of Level 1 of Figure 1; and most interestingly, hydration-dependent wave velocity changes reported by Cusack and Lees [120] could indeed be traced back to composite material behavior in the sense of the RVE of Level 1 in Figure 1. However, the issue might get trickier once a critical water-to-organic mass ratio of about 0.45 is exceeded: then, conformational changes of the molecular collagen itself are probable to lower its intrinsic elastic stiffness. Anyway, regardless of these refined discussions, the axial normal stiffness of molecular stiffness remains a little higher than 10 GPa. Ultrasonic tests at lower frequencies give access to the larger RVEs of Figure 1 [21, 39, 110]: 10 MHz tests [121-124] refer to the extracellular bone material (Level 3 of Figure 1); 2.25 MHz tests [125-127] refer to the extravascular bone matrix (Level 4 of Figure 1), and 50 kHz tests [128-130] refer to the macroscopic (here trabecular) bone material (Level 5 of Figure 1).

In the case of classical mechanical tests, uniaxial stress states are imposed as homogeneously as possible, to prismatic or cylindrical specimens, and corresponding strains (in load direction and orthogonal to it) are recorded. In order to retrieve elastic properties from such tests, the thermodynamic nature of elasticity needs to be carefully considered [2, 3, 9, 131]: elastic energy is that portion of the internal energy stored in the material which can be back-transformed into efficient mechanical work. This transformation happens once a sample is *unloaded,* and the slopes in corresponding stress-strain curves have given access to the elastic properties to ceramic-polymer-based biomaterials [132, 133] and extracellular bone material (from focused-ion-beam (FIB)-milled single micron-sized pillars compressed by a flat punch [134]), see Figure 4. Still, it is advisable to remember that bone behaves viscoelastically [135], implying that even the unloading portion might not give direct access to elastic properties, as was shown explicitly for cement paste [136].

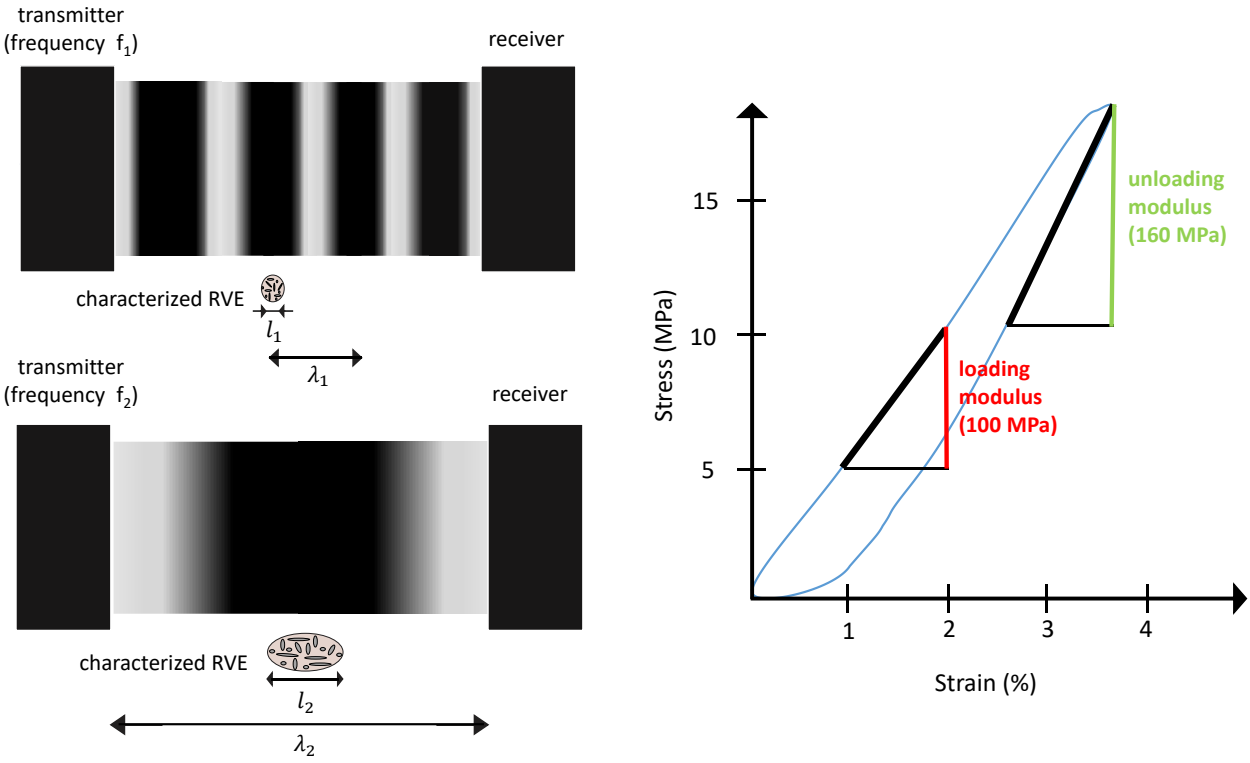


Figure 4: Principles of elasticity testing: (a) ultrasonic wave length controls the size of the elastically tested RVE; (b) elastic energy is associated to delivery of mechanical work by the tested specimen (here ceramic-reinforced polymer biomaterial for implants during unloading [132]

When it comes to strength, there is virtually no alternative to mechanical tests: Accordingly, the strength properties of bone's elementary components (collagen and hydroxyapatite) were inferred from uniaxial mechanical tests where rat tail tendons [137] and samples of densely compacted hydroxyapatite powder [138, 139] have been loaded up to failure. The strength of the extracellular bone material can be gained from micropillar testing [134], the strength of polycrystalline material making up the cement lines around osteons can be accessed through osteon push-out tests [140], and the strength of macroscopic bone materials has been amply tested over the last five decades (at least). In this context, it is advisable to prefer tests where homogeneous stress states prevail in the sample, such as uniaxial tension tests and uniaxial compression tests [141-158]. By example, bending tests deliver much less reliable results as major hypotheses concerning material and structural behavior need to be made. Normally, such hypotheses have been readily borrowed from engineering steel construction – however, as actually evident from abundant chemical and mechanical features, bone is obviously not steel.

In this context, demineralization, decollagenization, and dehydration tests, in combination with weighting tests, Archimedes' principle, and microscopic investigations [52, 159-165] , are the key experimental access to the chemical composition of bone ultrastructure. When additionally considering X-ray and neutron diffraction tests giving access to the distance between collagen molecules, several "universal" rule concerning the composition and microstructure of mineralized collageneous tissues (such as bone) can be derived: (i) upon hydration, the extrafibrillar space grows proportionally to the fibrillar swelling in non-mineralized collagenous tissues [117]; (ii) within the bone ultrastructure, the average extrafibrillar and the average extracollageneous mineral concentration are the same [166]; (iii) the

mineral and collagen volume fractions within the extracellular bone matrix are linearly related to each other [167]; and (iv) tissue shrinkage upon mineralization can be explained from precipitation of mineral from a liquid solution under closed thermodynamic conditions [168]. These rules yield the tissue-specific volume fractions within the lower-scale RVEs depicted in Figure 1, so that the multiscale models can be rigorously validated by independent experiments. On top of that, the RVE representation of bone's ultrastructure has independently been confirmed by an electrodynamics model based on Maxwell's equations [169].

5 Merger with biology: the systems approach

Biology in general is inherently complex. In particular when considering not so much single reactions or processes but rather cascades of several processes, or interacting and/or concurrently occurring reactions or processes which together form whole mechanisms, a potentially large number of different players and factors are involved. In many cases, the interactions between the latter are very specific and selective, and, importantly, highly non-linear. This means, for example, that doubling the amount of a certain substance involved in a biological process (or mechanism) does not necessarily mean that its final outcome is also doubled [170, 171].

In biomedical engineering, understanding (and in further consequence even controlling and predicting) the involved biological mechanisms is obviously a key issue. Traditionally, investigating those mechanisms has been a task dealt with based on experimental studies. A myriad of examples can be found in literature, comprising all conceivable subdisciplines; see, e.g., [172-174]. Interestingly, mathematical models of biological processes were developed, as complements to the aforementioned experimental studies, long before the term "biomedical engineering" was even coined or computers were integral tools in (medical or engineering) workplace environments. Let us mention a few examples. Firstly, both Gompertz [175] and Verhulst [176] came up, independently from each other, with simple population growth models, which later proved useful for the prediction of tumor growth dynamics [177]. Secondly, the development of epidemics has been a promising playground for mathematicians for around 100 years. As early as 1927, Kermack and McKendrick laid the conceptual foundation for the famous SIR models which are still by many considered to be the gold standard in the field [178]. Thirdly, the kinetics of red blood cells and bone marrow stem cells were studied by sets of differential equations by Kirk et al., as documented in their respective paper published in 1968 [179].

Nowadays, owing to the advent of computers in the 1980s and especially in the 1990s, mathematical models can be solved within sophisticated computational environments, allowing for developing and implementing much more complicated models, able to replicate reality in more refined ways. The involved fields include (but are certainly not limited to) the bone metabolism [180-187], tissue engineering [188-190], or the brain [191]. From a methodological point of view, different kinds of mathematical models are standardly used, aiming at understanding and predicting the biological processes in the above-mentioned and other examples, see [192-194] for general overviews. In more detail, atomistic simulations allow for revealing the behaviour of single molecules or chains thereof [195, 196]; the activities of cells due to the binding of ligands to receptors is standardly treated based on differential equations [197]; the collective behaviour of whole transcription networks, involving the interactions between large numbers of proteins

acting as transcription factors and genes, can be modelled by utilizing so-called network motifs [198]; population models, in turn, understand the behaviour of biological systems in terms of the interactions of specific subpopulations, into which the key players involved in the respective system can be grouped [180, 183, 184]; agent-based models allow for tracking the development of single biological entities through imposition of very specific behavioural rules attached to each of those entities (which can be single cells or single living beings) [199, 200]. If the observed behaviour of a biological system is however so complicated that no explicit rules can be formulated whatsoever describing the behaviour of the involved factors, as basis for some kind of (quasi-) deterministic mathematical model, bioinformatics methods can be optionally applied, see deliverable report D3.2 for further details.

When dealing with biological tissues, it is well known that the mechanical loading they are subjected to may have a substantial influence on the biological processes responsible for maintaining their integrities, or even for their sizes and shapes. *Mechanobiological* regulation is the term that has been created to express that regulatory cues are driven not only biologically, but also mechanically [201-205]. The probably most prominent example is bone (tissue) – it is well-known that bones may become thicker and denser upon increased mechanical loading (e.g., due to prolonged physical exercise), whereas they may become thinner and less dense upon decreased mechanical loading (e.g., due to bedrest or exposure to microgravity). In order to take this additional effect into account in mathematical models, models of biological processes need to be coupled to mechanical models. This considerable challenge has been tackled numerous times, mainly by integrating simplified rules which are supposed to reflect the biological behaviour of the respective tissue (in response to the prevailing mechanical loading) into numerical organ models. For the latter, Finite Element models have been and still are the most popular choice [206-209], whereas other modeling techniques, such as unit cell models [210, 211], have been also applied. Also, more refined strategies have been pursued, namely by using mechanical stimuli as regulatory factors of cell population models on the material scale; related works have been reported, e.g., for bone [212-214].

Finally, we want to come back to the very purpose of this review, namely reviewing multiscale models in biomedical engineering. Most of the above-mentioned works relate to single scales, although mechanobiological regulatory processes are inherently of multiscale nature: Mechanical loading is usually applied macroscopically, is somehow transferred to the scale of cellular processes or even below, where corresponding mechanical stimuli influence the occurrence and behaviour of biological factors. Hence, multiscale mechanobiology involves, per se, multiscale (poro-)mechanics, on the one hand, and multiscale systems biology, on the other hand. Multiscale (poro-)mechanics has already been dealt with in the previous sections, and it has been successfully applied in order to estimate mechanical stimuli occurring on the cell scale in response to macroscopically applied mechanical loading; see, e.g., [40, 212, 215, 216], developed for bone tissue in the context of bone remodeling. These examples are based on or inspired by continuum micromechanics as underlying concept. As alternative, so-called numerical homogenization approaches have been used as well [217-219], where numerical models have been implemented on various length scales, allowing for passing information from one scale to the other. As concerns multiscale systems biology models, it is stressed that the multiscale nature of biological processes should not be categorically neglected, especially when studying biological tissues functioning through the interplay of processes and reactions discernible on distinctly different length scales. This concerns in particular multiporous tissues (such as bone tissue), comprising pore spaces on distinctly separated observation scales, see Figure 1. Nevertheless, to date, multiscale systems biology appears to be severely underrepresented in literature. A small number of works (as compared to the mechanics realm) explicitly

acknowledges the need for developing multiscale systems biology modeling approaches [220-225]. However, it is striking that most of the literature available on this topic has been elaborated in terms of opinion, perspective, or discussion papers, where promising modeling concepts were presented theoretically, without actually implementing them. Hence, although it seems generally accepted that accounting for the multiscale nature of biological processes in respective mathematical models is crucial for eventually obtaining reliable model predictions, the corresponding, sufficiently comprehensive, body of literature, is still pending.

Multiscale approaches combining and coupling multiscale mechanics models and multiscale systems biology models, are extremely scarce. Figure 5 shows the modeling concept proposed in [213], aiming at prediction of the progress of the (mechanobiologically regulated) process of bone remodeling on the scale of macroscopic bone tissue. To that end, the authors combined a poromicromechanical model (for quantifying the mechanical stimuli occurring in response to physiological mechanical loading conditions on the cellular scale) and a bone cell population model taking into consideration the type of pore space in which the involved cells and biological factors are residing, as well as the respective hierarchical levels of the pore spaces. Despite comprehensively searching the literature, no other example of a comparable multiscale approach could be found. This deficit definitely points out promising opportunities for future research endeavors. In order to finally reach a stage, where predictive mathematical models are actually being applied in biomedical engineering practice, it seems key to lay a major emphasis on filling this gap.

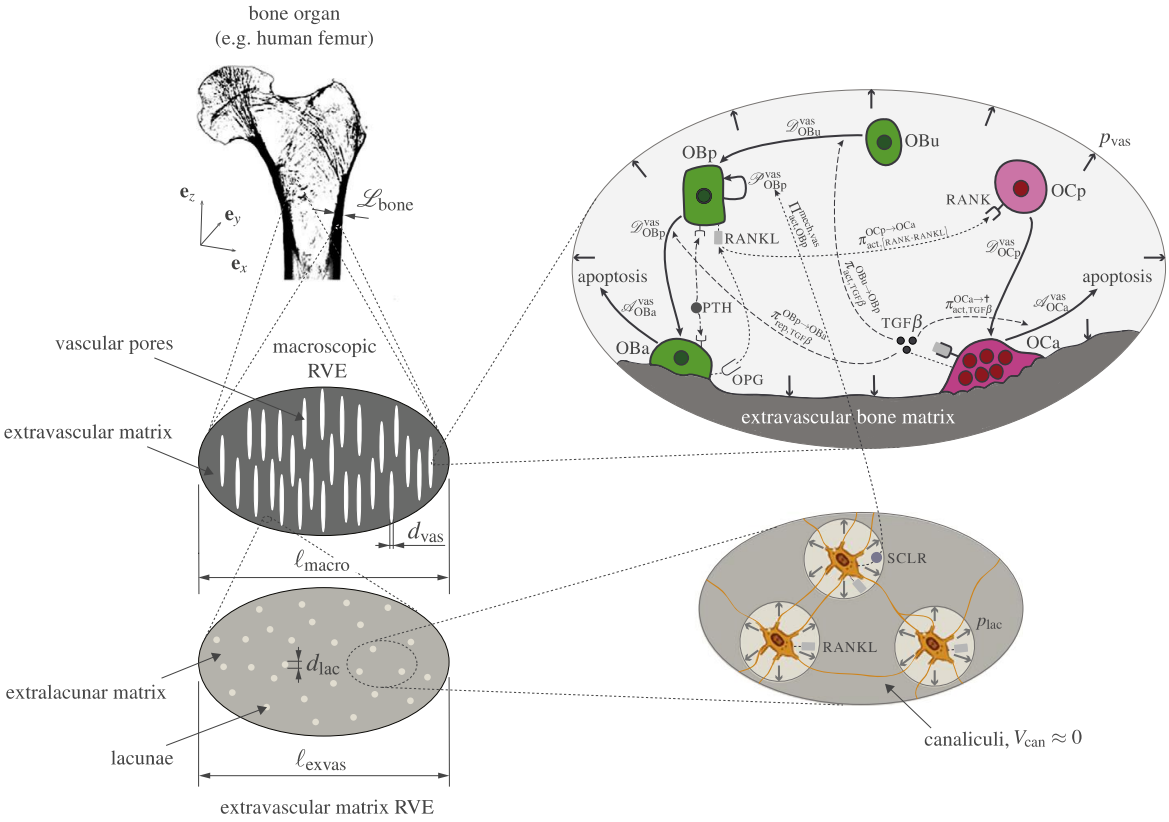
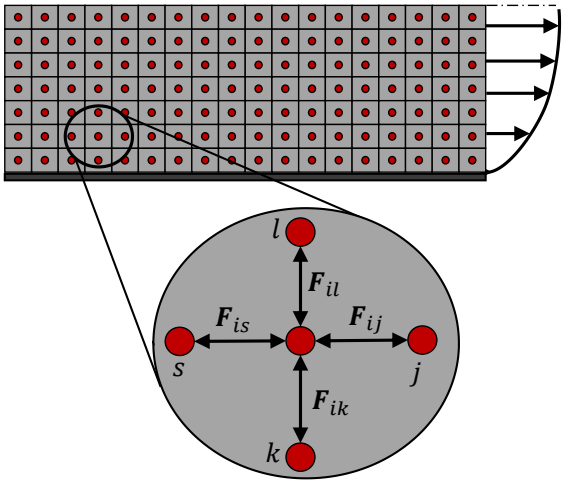


Figure 5: The multiscale model proposed by Pastrama et al. [216] comprises coupling of a multiscale poromicromechanics model of bone (utilized for calculating the hydrostatic pressure in the pore spaces hosting the bone cells as mechanical stimulus) and a multiscale bone cell population model of bone remodeling, using the micromechanically derived pore-scale pressures as regulatory factors.

Another class of modeling technologies targeting populations of biological cells or macromolecules considers such biological entities as discrete particles. In this review, the focus is on particle-based methods for multiscale modeling dealing with blood flow and atherosclerosis. On the one hand, blood contains species characterized by different phases and different material properties, such as plasma, red blood cells, white blood cells, and platelets. Thereby, the blood constituents are responding to biomechanical and chemical stimuli in order adapt their functions and configurations to their environment. All of these processes have to be taken into consideration in the modeling process. In atherosclerosis, on the other hand, low-density lipoprotein (LDL) macromolecules enter through leaky junctions into the intima. LDL transport through the endothelium may occur either through vesicles, taking up LDL from lumen by receptor-mediated endocytosis, or via leaky junctions, being with endothelial cells in a state of apoptosis [226]. Notably, some molecules making up LDL are known to easily oxidized. This is necessary for the interaction of LDL with respective receptors. Without going into the related biological details more comprehensively, the below elaborated overview of particle-based techniques demonstrates how the above-introduced processes and mechanisms are considered in the context of (multiscale) modeling approaches.

Particle-based method within a Lagrangian framework introduce flow as the motion of the cellular components. Within this conceptual framework, the response of the cellular components in the blood can be computed under physiological and pathological flow conditions. The individual red blood cells (RBC) are standardly modeled as a soft shell capsules whose content is a very viscous fluid, whereas white blood cells (WBC) have a more complex internal structure. Platelets are usually modeled by means of the discrete element method (DEM) [227]. The so-called Stokesian dynamics method (SDM) allows for separately analyzing the fluid mechanics behavior of the considered entities [228]. Plasma, in turn, is often modeled by means of moving particle semi-implicit methods (MPS) [229] or smoothed particle hydrodynamics (SPH) methods [230].

Traditional continuum-based models can be used to simulate mass transport in general, and in particular the transport of LDL, the proliferation of macrophages, or the growth of foam cells, including the LDL interaction with monocytes. A major drawback of this type of models is that blood is treated as a homogeneous medium so that the model is notable to describe the behavior of individual blood constituents. Hence, it is not possible for such models to consider that blood is a highly complex mixture of chemically and electrostatically active cells suspended in an electrolytic fluid with active proteins and organic substances [231]. Especially in microvascular vessels, blood flow is not observed as a homogeneous fluid flow, but it is rather a motion of RBCs, lubricated by the rest of the colloidal suspension. To study the fundamental nature of LDL oxidation, penetration and macrophages growing, it would be desirable to use the so-called Lagrangian approach, tracking individual oxidized LDL in the sequence of the process. Although the obvious advantages of the discrete approach over the traditional continuum methods may have long been recognized, it was not technically feasible until recently. Facilitated by rapid increases in computer power, Lagrangian computational approaches have been the subject of extensive research, with advances such that they became now more applicable to real problems [232, 233]. In a nutshell, the so-called discrete particle dynamics (DPD) method is a discrete modeling technique which involves particles corresponding to coarse-grained entities as molecular clusters and not to individual atoms [234]. This technique is remarkably effective when it comes to simulating hydrodynamics of simple and complex liquids on a mesoscopic scale. [235]. Details on the mathematical implementation of the discrete particle dynamics (DPD) approach can be found, e.g., in [226, 236-239], see also Figure 6. The so-called particle tracking method, in turn, involves numerical simulation of the particles representing the studied fluid until all particles have reached a steady state [240].



$$\boldsymbol{F}_{ij} = \boldsymbol{F}_{ij}^{\text{Conservative}} + \boldsymbol{F}_{ij}^{\text{Dissipative}} + \boldsymbol{F}_{ij}^{\text{Brownian}}$$

$$m_i \dot{\mathbf{v}}_i = \sum_j \left(\boldsymbol{F}_{ij}^{C} + \boldsymbol{F}_{ij}^{\text{D}} + \boldsymbol{F}_{ij}^{\text{B}} \right) + \boldsymbol{F}_i^{\text{ext}}$$

$$\boldsymbol{F}_{ij}^{C} = a_{ij} \left(1 - \frac{r_{ij}}{r_C} \right) \boldsymbol{r}_{ij}^{0}$$

$$\boldsymbol{F}_{ij}^{D} = -\gamma w^{D} (\mathbf{v}_{ij} \cdot \boldsymbol{e}_{ij}) \boldsymbol{r}_{ij}^{0}$$

$$\boldsymbol{F}_{ij}^{R} = \sigma w^{R} \xi_{ij} \boldsymbol{r}_{ij}^{0}$$

$$F_w^a = k_{bw} \left(1 - \frac{L_w}{L_{\max}^{wall}} \right)$$

$\boldsymbol{F}_{ij}^{\text{C}}$ ...	conservative (repulsion) force	$\boldsymbol{r}_{ij}^{0}$ ...	unit vector pointing in direction from "j" to "i"
$\boldsymbol{F}_{ij}^{\text{D}}$ ...	dissipative force	γ ...	friction coefficient
$\boldsymbol{F}_{ij}^{\text{R}}(\boldsymbol{F}_{ij}^{B})$ ...	random force	σ ...	amplitude of the random force
$\boldsymbol{F}_i^{\text{ext}}$ ...	external force exerted on particle "i"	w^{D} ...	weight function for dissipative force
$\boldsymbol{F}_{\boldsymbol{w}}^{\text{a}}$ ...	attractive forces	w^{R} ...	weight function for random force
m_i ...	mass of element particle "i"	ξ_{ij} ...	random number with zero mean and unit variance
$\dot{\mathbf{v}}_{\boldsymbol{i}}$ ...	element particle acceleration	r_c ...	domain of influence if the interaction forces
a_{ij} ...	maximum repulsion force per unit mass	L_w ...	distance of the activated particle from the wall
r_{ij} ...	distance between particles "i" and "j"	L_{max}^{wall} ...	size of the domain from the activated wall

Figure 6:Illustration of the fundamental principle of discrete particle dynamics approaches, including a brief sketch of the related mathematical framework, involving the forces acting onto the considered particles; for further details, see, e.g., [226, 236-239]

Cellular automata (CA) models involve discrete systems consisting of a finite number of cells where each cell can be in specifically defined states. For example, a CA-based disease model may involve cells which can be healthy, infected or dead. At each time step the CA model is described by a state vector providing a mathematical format for the describing the state of each cell. Essentially, the state vector at the subsequent time step is then obtained by applying certain rules reflecting the fundamental behavior of the studied cells. For example, simulating atherosclerosis based on a CA approach is presented in [241] where the authors tested the hypothesis that plaque morphology results from a self-perpetuating propagation process driven by macrophages. The rate of macrophages recruitment is set to be a steeply rising function of the number of macrophages locally present. On this basis (entailing a number of further rules motivated by experimental data) simulation results agreed well with *in vivo* observations of atherosclerosis. Lee et al., on the other hand, developed a model that uses CA to describe the proliferation of migrating contact-inhibited cells [242]. The discrete modelling approach was powerful enough to incorporate all of the essential features of the cell locomotion and division processes, including the complicated dynamic phenomena occurring when cells collide. Furthermore, Benyoussef studied the

evolution of HIV infection using a CA approach, focusing on the influence of the virus on the immune cells in the blood [243].

Lattice Boltzmann (LB) approaches belong to the class of CA-type models. This means that the physical system can be observed in an idealized way, so that space and time are discretized, and the whole domain is made up of a large number of identical cells [235]. A number of particles that move and collide in the discretized time-space domain are observed and the dynamics of these particles are modelled. In LB models a particle distribution function is assigned to every lattice node (representing one particle). Furthermore, propagation functions are defined depending on the state of neighboring cells. All cell states are updated in synchronized fashion, iteratively and in discrete time steps. LD approaches can be easily implemented, yield stable solutions, allow for straightforward consideration of boundary conditions, and provide parallelization in natural manner. For further details concerning the mathematical basis of the LB method, see [244, 245].

A modeling concept which can be regarded to be similar to CA approaches, yet more intricate, are so-called agent-based models (ABM), comprising interacting autonomous agents. Each agent individually assesses its state and makes decisions on the basis of a set of rules. ABM allow for consideration of multiple agents which interact with each other and operate simultaneously The process evolves from the lower (micro) level of systems to a higher (macro) level. As such, a key notion is that simple behavioral rules generate complex responses. Even a simple agent-based model can exhibit complex behavior patterns and provide valuable information about the dynamics of the real-world system that it emulates. Since all entities in atherosclerosis process interacting according to biophysical and biochemical rules, they can be considered as agents. Following natural behavior of molecules and cells sets of rules for each kind of entity in the process can be defined, see, e.g., the work of Deo [246].

This section is concluded by a compact overview of further methods that have been applied for numerical solution of blood flow and atherosclerosis progression, see also [247] for a respective review. Two of the most common ones are Monte Carlo-type simulations and molecular dynamics (MD) methods. Both methods are particle dynamics-based methods and derive (to some extent) from the Boltzmann equation [244]. While they are potentially accurate, they are computationally expensive and are hence restricted to problems with very small physical dimensions. Smoothed particle hydrodynamics (SPH) is a macroscopic, particle-based method, allowing for studying particles immersed in fluids [248, 249]. The suite of available modeling techniques is complemented by other mesh-free methods, which are however less relevant in the field, see [247] for an overview.

6 An emerging field: Mechanics-driven cell biology

We finally turn towards *single* biological cells and their inner structure: Traditional visco-elastic continuum models have been widely used to quantify cell mechanical properties [250]. Such models are convenient to help parameterize the results of mechanical measurements from techniques such as atomic force microscopy (AFM), micropipette aspiration, micro-rheology and parallel plate compression [251]. They offer a straightforward and minimal way to interpret differences between experimental conditions and summarize the results of mechanical measurements. When restricted to the timescale and spatial resolution of a specific measurement, these relatively simple mechanical models are in strikingly good

agreement with observed mechanical behavior. For example, the force-indentation response obtained from an AFM measurement typically corresponds well to Hertz theory for elastic bodies [252]. However, when generalizing mechanical properties across spatial and temporal scales, visco-elastic or poro-elastic constitutive models invariably break down. Instead, living cells appear like glassy materials that exhibit power law rheology when probed across timescales [253-255]. This property has been attributed to the cell's active material properties [256]. At the microscopic scale, the mechanical behavior of a cell is governed by the cytoskeleton, a dynamic reorganizing polymer network that forms mechanically relevant structures at a broad spectrum of characteristic length scales, giving rise to self-similarity and fractals [257]. Furthermore, the cytoskeleton exhibits biphasic rheology, with frequent solid-to-fluid dynamics and even self-organized criticality in active structures such as the lamellipodium [258, 259]. To date, these properties have complicated homogenization attempts to model the mechanical behavior of intracellular material [260]. Indeed, the absence of a clearly defined microscopic (small) length scale prevents the straightforward formulation of 'representative volume elements' in the pursuit of macroscopic constitutive equations. Successful attempts to model the mechanical properties of intracellular material at cellular scale include coarse-grained representations of acto-myosin polymer networks and continuum models based on hydrodynamic theory of active fluids.

Coarse-grained molecular dynamics models of active polymers aim to provide a computationally minimal representation of the network structure formed by the cytoskeleton [261, 262]. Typically, they include as discrete elements the filaments and cross-linkers of acto-myosin or microtubule networks. Contrary to fully resolved Molecular Dynamics, they do not include atomic interactions, but instead are based on coarse-grained approximations of thermal forces, internal mechanics and interaction properties [263]. For example, the mechanical properties of polymers are commonly represented using worm-like chain models, whereas the asymmetry in attachment of myosin motors to actin filaments is modeled using a 'ratchet' potential [264, 265]. Various computational implementations of these discrete coarse-grained elements exist, such as bead-spring models, rod models and finite element representations of fibers [266]. As a whole, this family of models has been very successful in unraveling the mechanics of specific relevant cytoskeletal structures, such as polymerization in the lamellipodium, the attachment membrane or adhesion complexes and the formation of stress fibers [267-269]. Moreover, they are particularly useful in studying artificial cytoskeletal structures, such as reconstituted acto-myosin networks, of which the well-known composition and chemical conditions greatly facilitate mechanistic model formulation [270]. However, the applicability of these models in the context of a biological cell is limited, not only due to computational limitations, restricting the spatio-temporal scale of the domain, but also due to the inability to exhaustively represent the complex environment in intracellular material.

At the other end, hydrodynamic models of active fluids (or active 'gels') are constitutive continuum models that represent a relevant subset of behaviors of intracellular material [271, 272]. In poroviscous theory, pioneered in the context of cells by Dembo and co-workers, the intracellular material is modeled as two coupled interpenetrating fluids, the cytosol and a gel-like cytoskeletal network [273]. By addition of signaling-coupled reaction terms for network assembly and disassembly, these models are able to simulate various cell dynamical processes. Active nematic theory combines the hydrodynamic equations of an active – typically, contractile – fluid with a polar or apolar director field. In doing so, it is able to capture the intrinsic anisotropy of the underlying network and the spontaneous flow as a result of contractile forces generated by myosin activity [274]. Since they are essentially fluid models, these models are generally unable to describe the elastic mechanical response that would be measured in a typical AFM

measurement [275]. However, they provide a very useful tool to help understand the intracellular flows that allow the cell to reorganize itself over longer timescales. For example, simulations using these models have been instrumental in explaining the role of the dynamical organization of actin filaments in furrow formation during development [276, 277]. Furthermore, the emergence of spontaneous cell division and cell motility has been observed in models that combine active nematics with poroviscous theory [278].

To address the shortcomings of these limiting conceptual frameworks, various hybrid modeling approaches have been proposed that combine discrete coarse-grained networks with hydrodynamic continuum equations [279]. These attempts have yielded important insights into specific cell mechanical processes (e.g., blebbing). However, the formulation of a general modeling methodology for describing cell mechanical behavior, based on measurable microscopic parameters and amenable to homogenization for multiscale models, remains a major scientific challenge [275].

A perspective towards overcoming this major challenge recently emerged from a very classical concept in continuum mechanics: the principle of virtual power in its most modern format put forward in 1973 by Paul Germain [280]: This principle is a natural merger of the laws of equilibrium (or motion in case of inertia forces) with the kinematical characteristics of system. Accordingly, it states that the power of internal, external, and inertial forces on arbitrary admissible virtual velocity fields defining the kinematical nature of the considered mechanical system, need always to be zero. Given the current atomistic-to-continuum homogenization challenge, identification of the power performed by equilibrated molecular dynamics-derived atomistic forces in different configurations of the investigated system on virtual velocity fields characterizing macromolecular kinematics in terms of beam-theory-type continuum notions (stretching, twisting, bending) opened a new avenue to study coupled deformation modes in DNA [281]: stretching and twisting of these long double-helical macromolecules are, as a rule, coupled, and the type of coupling depends on the deformational state. This may hold the promise to come up with a new type of structural mechanics which is complex and at the same time stable enough, so as to effectively build up a new, mechanics-driven, addition to the current state-of-the-art in genetics and cell biology. These most probably worthwhile endeavors have been recently coined as „mechanobiome“ research [282].

7 Deviation from the work plan

The due date for the development of the D3.1 – State of the art in the multiscale modelling in biomedical engineering was M4 (January 31st, 2021). A number of SGABU project teams' members were affected by COVID 19 in December and January. Due to this situation, we had a delay in compiling the deliverable. The responsible EU officers were informed about the situation during January.

8 Conclusions and future research directions

This deliverable can be considered as an important basis for the development of the SGABU integrated platform, which will be the key contribution in the later stages of the project. The deliverable clearly showcased that multiscale modeling has become one of the main conceptual pillars when it comes to

developing computational models of materials and structures related to biomedical applications. Some of the main concepts were pointed out and elaborated in unprecedented fashion.

As concerns the mechanical behavior of materials and structures, a wide range of different modeling techniques are readily available, promising reliable results (if employed correctly). However, translation of these engineering science results into the clinical practice remains a steady, but slow process, due to the huge conceptual differences in classical engineering versus medical research and practice. On the other hand, capturing the biological behavior of biological tissues, in terms of their mechanobiologically regulated development over time (which is highly relevant in many different cases), by means of multiscale mathematical models is still very much in its infancy. The latter conclusion clearly points out a very important direction for future research.

9 References

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