Steel and bone:
Mesoscale modeling and middle-out strategies in physics and biology

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Abstract

Mesoscale modeling is often considered merely as a practical strategy used when information on lower-scale details is lacking, or when there is a need to make models cognitively or computationally tractable. Without dismissing the importance of practical constraints for modeling choices, we argue that mesoscale models should not just be considered as abbreviations or placeholders for more "complete" models. Because many systems exhibit different behaviors at various spatial and temporal scales, bottom-up approaches are almost always doomed to fail. Mesoscale models capture aspects of multi-scale systems that cannot be parameterized by simple averaging of lower-scale details. To understand the behavior of multi-scale systems, it is essential to identify mesoscale parameters that "code for" lower-scale details in a way that relate phenomena intermediate between microscopic and macroscopic features. We illustrate this point using examples of modeling of multi-scale systems in materials science (steel) and biology (bone), where identification of material parameters such as stiffness or strain is a central step. The examples illustrate important aspects of a so-called "middle-out" modeling strategy. Rather than attempting to model the system bottom-up, one starts at intermediate (mesoscopic) scales where systems exhibit behaviors distinct from those at the atomic and continuum scales. One then seeks to upscale and downscale to gain a more complete understanding of the multi-scale systems. The cases highlight how parameterization of lower-scale details not only enables tractable modeling but is also central to understanding functional and organizational features of multi-scale systems.

Keywords: Mesoscale models; Reductionism; Multi-scale modeling; Middle-out approach; Homogenization

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1. Introduction

Oppenheim and Putnam (1958) famously expected a unity of science to emerge from gradual microreduction of higher-level models and theories to more fundamental ones. Although this view is largely dismissed by contemporary philosophers of science, lower-scale models are often taken to better lay foundations for the long-term development of scientific explanations (Epstein and Forber 2013).[3] Against such assumptions, the ubiquity of meso- or macroscale models in science appears to be in need of explanation. A commonly held view is that meso- and macroscale models reflect the existence of practical limitations, such as the lack of lower-scale details needed to develop microfoundational models. Similarly, it has been suggested that researchers' cognitive constraints may be the "principal reason for limiting model-scales to mid-size mesoscopic models" (MacLeod and Nersessian 2018 p. 24). While we agree on the importance of minding practical constraints for model choices in science, we take issue with the unquestioned background assumption that a "bottom-up" strategy would be epistemically preferable.[4]

Our aim is to clarify central aspects of mesoscale and multi-scale modeling that challenge microfoundationalist assumptions. By multi-scale modeling, we refer to modeling of systems that exhibit different behaviors at various spatial and temporal scales and therefore require the combining different types of mathematical models. Previous analyses of multi-scale modeling have similarly questioned reductionist views in physics (Batterman 2012; Massimi 2018), biology (Gross and Green 2017; Lesne 2013), and nanoscience (Bursten 2015). We add to these accounts by clarifying a distinctive features of multi-scale modeling, compared to hierarchical modeling (Bokulich, in preparation),[5] namely that model inputs go in both directions (Sabet et al. 2016). In

[3] Epstein and Forber (2013) critically discuss the merits of common assumptions about microfoundational models, but primarily consider the role of higher-level models and parameters as means to tweak parameters to improve model fit. For a discussion of microfoundationalist vs. macroscale models, see also (Neal, in preparation).

[4] MacLeod and Nersessian (2018) seem to indicate this when highlighting that the representations in mesoscale models "do not capture accurately the control structures of biological networks" as they are "highly abstract and simplified representations of systems that likely have a loose relationship with underlying system mechanisms" (p. 17). Whereas mechanistic details indeed are important for some predictive purposes (as in their example), predictability and explanatory power often do not rest on getting the lower-scale details right (Batterman 2002). We therefore aim to clarify the importance of identifying mesoscale features and parameters that – within certain boundaries – are relatively insensitive to lower-scale changes.

[5] A central assumption in hierarchy theory is that many complex systems are hierarchically organized in a way that makes higher-scale levels independent of some lower-scale details. A hierarchy of dynamically uncoupled models can hence be constructed through considerations of which lower-level details are necessary to include when upscaling from lower to higher scales.

such contexts, researchers often adopt a *middle-out approach* where modeling starts at intermediate (mesoscopic) scales, i.e., at a scale between the highest and lowest scale of analysis (Noble 2008). One then seeks to upscale and downscale to gain a more complete understanding of the multi-scale system. Thus, we clarify how the *mesoscale*, rather than the lowest scale of analysis, is often the most useful starting point and, hence, "more fundamental" in this context.

It is important to note that the conception of a mesoscale is not an absolute. What counts as "meso" depends upon the phenomenon one is studying and the research question of interest.[6] By "mesoscale," we mean a scale in between a microscale, say a molecular representation of a fluid, and an macroscale, such as that which describes the fluid as a continuum. Whereas parameterization of lower-scale details is often taken to be conducted primarily to enable tractable modeling, we see upscaling and downscaling as central to understanding organizational and functional features of multi-scale systems. Moreover, we stress that many behaviors of scientific interest simply cannot be studied purely bottom-up. Materials scientists Stoneham & Harding (2003, p. 82) put this as follows: "For many properties and systems, materials behavior [sic] is dominated by mesostructures. The key ideas are not those emphasized in the well-known macroscopic and atomistic approaches". In the context of the life sciences, modelers similarly emphasize that "[l]iving matter operates at an intermediate or mesoscale" (Benítez et al. 2018, p. 4). These quotes point to the philosophically intriguing suggestion that some properties of multi-scale systems cannot be accounted for at lower or upper scales.

Multi-scale models have been employed for many years in physics and engineering, but they are increasingly also used to model active materials in biology, and we therefore examine and compare cases from physics and biology to highlight similarities and differences. Currently, most multi-scale models in the life sciences target cardiovascular and musculoskeletal systems, as there is a pressing medical need to understand complex medical problems such as heart failure and osteoporosis beyond the molecular level (Bassingthwaighte et al. 2009; Qu et al. 2011; Sabet et al. 2016).[7] We use the examples of steel and bone to highlight how modelers in the two contexts employ similar strategies to deal with the challenge of bridging between scales. However, we also contrast the examples later to highlight additional modeling challenges in the context of active

[6] We have more to say about this below.

[7] As we shall see in Section 3, modeling of active materials that change over time often requires the use of computer simulations. These integrate inputs from mathematical models describing different processes at different spatial and temporal scales (Gross and Green 2017; Varenne 2018).

materials. The examples illustrate fascinating aspects of multi-scale modeling that so far have not received much attention from philosophers.

We first provide some background for understanding the need for multi-scale and "middle-out" approaches (Section 2). We then examine strategies used in multi-scale modeling of a steel beam (Section 3.1) and bone (Section 3.2). Both examples demonstrate the central role of material parameters in relating the behaviors of continuum models to models at molecular scales. Section 4 analyses additional modeling challenges for homogenization in the latter case, due to the status of bone as an active anisotropic material with a complex, varied, and adaptive microstructure. We end the paper with concluding remarks on the philosophical implications of mesoscale modeling and homogenization strategies (Section 5).

2. The tyranny of scales and middle-out approaches

The limitations of modeling multi-scale systems from lower-scale "fundamental theories" appear in physics and engineering as well as biology. Already in 1969, the Nobel laureate in physics, Julian Schwinger, clarified such limitations in a Stanley H. Klosk lecture. Schwinger (1969) argued for an *engineering approach* to particle theory. He contrasts this to an approach based on a fundamental theory. Although "fundamentality" of theories is often taken to imply having higher explanatory status or importance (a view discussed in Chang 2015), Schwinger highlights that even if fundamental theories were or are available, they may not be the best means to describe phenomena at higher scales. An important reason is that many phenomena of interest for scientific analysis can neither be conceptualized, nor are literally "visible", at the lowest scale of analysis. Instead, mesoscales often provide the right variables for scientific modeling problems.

As we shall see in Sections 3 and 4, many multi-scale systems such as a steel beam or bone exhibit different structures and properties at different spatial scales. Because different physical factors dominate at different scales, different mathematical models are required to account for behaviors characteristic of phenomena at different scales. This presents serious modeling challenges. To design materials such as certain types of steel, material scientists must try to deal with physical phenomena across 10+ orders of magnitude in spatial scales. This challenge is sometimes referred to as the tyranny of scales problem (Oden 2006; Batterman 2012). Models at different scales rely on different – and often conflicting – theoretical frameworks (Wilson 2012). In many contexts, the difficulty of bridging between scales make modelers focus only on a specific

scale of analysis. In fact, a review in *Nature* suggests that choosing the most relevant scale is often a more useful approach than to try to connect atomic and continuum scale models (Stoneham & Harding 2003).[8] But despite this challenge, many multi-scale models are currently being developed in physics and increasingly also in the biomedical sciences.[9] Our aim is to clarify what may be gained by taking this approach and what kind of modeling strategies are used for this purpose.

A key motivation for the attempt to bridge the gap between scales is that many properties of natural systems can only be fully understood if one can demonstrate their connections to behaviors at other scales. The aim of multi-scale modeling is not only to account for system behaviors at multiple scales, but to use model outputs at one scale as model inputs at another scale (see also Green & Batterman 2017; Gross & Green 2017; Lesne 2013). Often, however, this is a difficult task due to the tyranny of scales problem. Multi-scale modeling in both physics and biology typically requires that continuum behaviors at large (e.g., tissue) scales couple to discrete models of lower-scale (e.g., molecular) structures. These types of models rely on fundamentally different mathematical frameworks (e.g., partial vs. ordinary differential equations, respectively).

Mesoscopic models and parameters often provide the bridges that connect features of relevance for understanding system behaviors at different scales. The characteristic of such models is akin to what Schwinger, in the context of physics, called "intermediate theories":

> The fundamental theory is too complicated, generally too remote from the phenomena that you want to describe. Instead, there is always an intermediate theory, a phenomenological theory, which is designed to deal directly with the phenomena, and therefore makes use of the language of observation. On the other hand, it is a genuine theory, and employs abstract concepts that can make contact with the fundamental theory.

[8] Stoneham & Harding (2003:77) highlight that the attempt to span length scales often results in the "worst of both regimes", and that a simpler strategy will often suffice. Although their article offers resistance to the aim of "bridging" between scales, the article supports our argument that the mesoscopic features are critical for many phenomena of practical and scientific interests (and that starting from a lower-scale models is often not feasible or strategic). We agree with this and hope that our examples will shine further light on why mesoscales are often the most relevant starting point of analysis.

[9] The number of publications on multi-scale modeling in medicine is growing rapidly. A recent search for the term 'multiscale' in the PubMed database (03-05-2020) gave 10861 hits (among these 3682 with `multiscale' in the title). In March 2016, the numbers were 5457 and 2180, respectively (Bhattacharya & Viceconti 2017).

> The true role of the fundamental theory is not to confront the raw data, but to explain the relatively few parameters of the phenomenological theory in terms of which the great mass of raw data has been organized. (Schwinger 1969, p. 19)

Thus, the aim of an intermediate theory (or phenomenological or mesoscale model) is to relate fundamental principles or theories to empirical relationships (e.g., experimental data), but never to attempt to model all possible details of the system. Schwinger here emphasizes that an intermediate theory "looks in both directions":

> The engineer's intermediate phenomenological theory looks in both directions. It can be connected to the fundamental theory at one end, and at the other it is applied to the experimental data. (Schwinger 1969, p. 19)

Similarly, systems biologists Sydney Brenner and Denis Noble refer to a "middle-out" modeling strategy used to link processes at different spatial scales in biology. Noble explains why this strategy does not run into the same problems as a bottom-up approach:

> The reason is that this way we can select what we are interested in. As we reach down towards lower levels, we can rely on our higher-level analysis to identify just those features of the lower-level mechanisms that are relevant, and we ignore the rest. The lower levels are seen through the filter of the higher level. This allows us to highlight what is important in the otherwise overwhelming mass of data. It greatly reduces the amount of information that we must carry over from one level of analysis to the other. (Noble 2006, p. 81)

In a later publication, Noble emphasizes that multiple models are needed because the equations used are scale-dependent:

> The central feature from the viewpoint of biological modelling can be appreciated by noting that the equations for structure and for the way in which elements move and interact in that structure in biology necessarily depend on the resolution at which it is represented. Unless we represent everything at the molecular level which, as argued above, is impossible

> (and fortunately unnecessary as well), the differential equations should be scale-dependent. (Noble 2011, p. 62)

Noble here highlights that attempting to model multi-scale systems in detail "bottom-up" would not only be practically intractable, but also impossible and unnecessary. Like Schwinger, Noble emphasizes that the most useful strategy to handle this complexity is to approach the problem like an engineer, i.e., at the scale of relevance for a specific problem (see also Noble 2017).[10]

"Middle" or "intermediate" strategies in both contexts refer to employing mesoscale models to connect important features that – because of the tyranny of scales problem – must be captured via different theoretical frameworks. In practice, this is done by linking model parameters at the intermediate scale to those at higher and lower scales. As noted in the introduction, the term "mesoscale" does not refer to an absolute scale, but it depends on the phenomenon of interest. Multi-scale modeling of the human heart or developing embryos, for examples, consider the scale of cells (μm) as the mesoscale (Noble 2006; Merks and Glazier 2005). In our example of modeling of human bones, cells instead make up the lowest scale while visible bone structures (at the scale of mm or cm) constitute the mesoscale (Sections 3.2 and 4). Similarly, the number of scales or "levels" deemed important can and will differ depending on specific modeling problems.[11] Thus, "mesoscale" refers to a scale of focus where modelers aim to connect selected aspects of lower and higher scale models in an *intermediate* model or a set of effective parameters, as described below.

In materials science, mesoscale structures are largely responsible for stable properties of materials at continuum or macroscopic scales. Such stability can be understood primarily by paying attention to geometric and topological features at the mesoscales. These include symmetry considerations and, most importantly, correlational details that are contained in features of representative volume elements (RVEs) and order parameters.[12] A key task in multi-scale modeling is therefore to identify mesoscale parameters that "code for" lower-scale details in ways that link model parameters at the intermediate scale to those at higher and lower scales. A goal is to determine values (or at least optimal ranges of values) for material parameters (such as Young's modulus for elasticity) that appear in the continuum equations of materials science. As these

[10] "An engineer also selects the level and detail of simulation he needs according to the problem he is tackling. It is not necessary to understand all the molecules in order to model and construct a bridge, for example" (Noble 2006, p. 81).
[11] For example, the literature on multiscale modeling of bone distinguishes between three (Cristofolini et al. 2008), five (Sabet et al. 2016) or even 8 spatial scales (Richie et al. 2009).
[12] A detailed discussion of representative volume elements will be provided in section 3. For now, simply think of them as mesoscale regions that statistically represent the features of composite systems taken to be important at that scale.

equations treat materials as continua[13], the goal is to find an effective (continuum) analog that will exhibit the behaviors of the actual material that is heterogeneous at lower scales.

The mathematical theory behind this kind of upscaling is called "homogenization theory" --- in effect, it aims to take an actual heterogeneous composite material and then to find a fictitious homogeneous (continuum) system that will exhibit the same behaviors. This theory can explain why the continuum equations, despite getting all the lower scale details wrong, can nevertheless be successful (Batterman 2018). Moreover, it demonstrates the relative autonomy of the upper scale behavior from the lower scale details.[14] Simple volume averaging from lower-scale details only works when dealing with homogenous systems with uncomplicated limit behaviors, such an ideal gas. Whereas one can upscale (or reduce) the continuum thermodynamic behavior of an ideal gas from (or to) a detailed micro-description of its molecules, this simple approach fails as soon as we consider systems that are heterogenous at lower scales. In the following, we examine examples of how simple averaging often completely fails to account for geometric and topological mesoscale features of steel and bone that are actually most important for determining upper-scale behavior. Instead, homogenization strategies are adopted which involve the identification of RVEs and material parameters at the mesoscale. It is also striking to note that similar strategies are employed in multi-scale modeling of inactive and active materials.

3. Middle-out modeling strategies in physics and biology

A general challenge in materials science is to link (discrete/atomic/molecular) models of microscopic structures to models characterizing macroscale (continuum) properties. The examples considered below reveal how similar strategies for modeling and homogenization are employed in modeling of the two materials, but also how models from materials science and physics must be adapted and developed to account for biological phenomena.

3.1. Steel

When we encounter steel on an everyday basis, at the scales of train tracks or bridges, it appears homogeneous. But if we zoom in, e.g., by using x-ray diffraction or atomic force microscopy, a

[13] The equations treat systems as continuous blobs with no structure all the way down to the infinitesimal. Of course, materials are composed of atoms, and have mesoscale structures that those equations completely ignore.
[14] For another discussion of this autonomy and the idea of relatively autonomous levels of reality see (Chibbaro, et al. 2014).

different picture emerges (Figure 1). At the atomic length scale, steel is a structured lattice of carbon and iron atoms. Features of interest at this scale include ionic bonding strength and other chemical factors influencing the stability of crystalline lattice structures. At the mesoscale, a host of inhomogeneities appear, such as small cracks, grain boundaries, and distinct phases such as martensite and pearlite. As mentioned above, homogenization theory starts with structures at mesoscales and tries to upscale to determine values for relevant (elastic) material parameters.

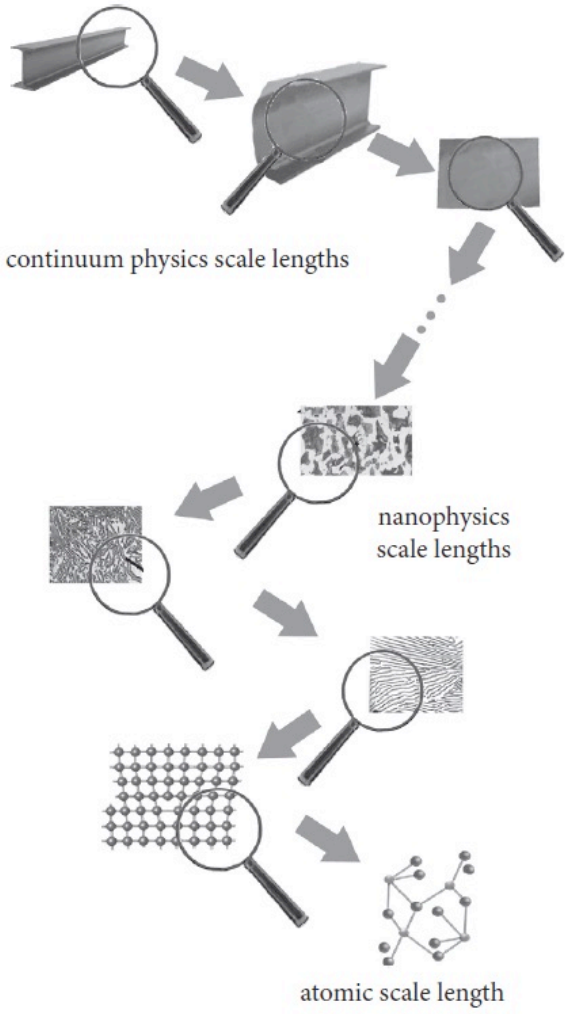

Figure 1. The structure of steel at different scales. Source: Batterman (2012).

A reductionist/fundamentalist perspective, however, would insist that since steel is composed of nothing but its atomic constituents, a detailed microscale description should suffice for the prediction of the macroscale properties of steel, including values for material parameters. This is not the case. A model at the lowest scale (just as an upper-scale continuum model) would not be

able to see the microstructures – the voids, cracks, grain boundaries, etc. – that exist at intermediate scales. Accordingly, a direct bottom-up approach to steel would arrive at wrong estimates for the elastic properties of steel, because the relevant parameters cannot be estimated at the smallest scale (Batterman 2012; Phillips 2001). Moreover, a model incorporating as many microscale details as possible would be explanatorily irrelevant to many engineering applications dealing with upper-scale continuum behaviors.

At large length scales, the elastic behavior of steel can be approximated by Hooke's law describing a linear relation between applied force and compression/extension of a spring. When generalized to elastic solids, the law describes a linear approximation of a material's elasticity, within certain limits of deformations and length scales.[15] Hooke's law describes strain (deformation) as linearly proportional to the applied stress. An important phenomenological parameter capturing the proportionality of stress and strain is Young's modulus, E, which is also called the elastic modulus. Young's modulus parameterizes the *stiffness* of a material, understood as the resistance to deformation in response to applied force. As we shall see in Section 3.2, Young's modulus is also a central material parameter in multi-scale modeling of bone and other biological materials.

Materials such as steel in bridge constructions are often stretched or compressed in multiple directions, making a single vector insufficient to describe the strain state. Instead of a single "proportionality factor", it is often necessary to introduce a stress tensor σ (called the Cauchy stress tensor, replacing F in Hooke's law) and a strain tensor ε. The analogue of Hooke's law for continuous media then becomes (expressed in matrix format):

$$(1)\ [\sigma] = [c][\varepsilon],$$

where c is a fourth-order elasticity (or stiffness) tensor. The latter is described as a matrix of real numbers denoting the possible stretch and shear parameters.[16] Whereas the strain and stress tensors are largely independent of the composition and state of specific materials, the elasticity tensor codes

[15] This is a rather extreme assumption. For example, it rules out the possibility of the buckling/failure of the beam. A full-on approach would start with the Navier-Cauchy equations. Nevertheless, our purpose here is to focus on the role of the material parameters as the right variables that reflect lower scale details in the relevant representative volume element. (See below for details.) In addition, in the next section on bone, accounting for fracture is of extreme importance.

[16] Shear refers to situations where applied stress results in internal structures sliding past one another. Shear is particularly important in materials with network structures such as bone where shearing of internal structure protects the overall structure from breaking up to certain limits (see below).

for properties that are dependent on the microstructure of the material (and often also on thermodynamic features such as temperature). Young's modulus is defined as the slope of a curve denoting the relation between stress and strain of a material.

How should we understand material parameters such as Young's modulus? Typically one determines its values for different materials via tabletop experiments. However, one must also recognize that material parameters reflect lower scale structures in the material—structures that are neither observable at continuum scales nor at atomic/lattice scales. The important features responsible for the values for the material parameters are mesoscale features.

There is a close analogy here with the proper understanding of order parameters in the context of condensed matter physics. Consider, for example, the parameter that characterizes the behavior of a lattice of magnetic moments or spins (a simple model for a magnet). Above a certain (critical) temperature the thermal energy randomizes the directions of the spins and the lattice exhibits no net magnetization M. As the temperature cools to the critical temperature there is an abrupt shift from zero net magnetization to a positive value for $|M|$. This is called spontaneous symmetry breaking. Above the critical temperature there is complete rotational symmetry (no preferred direction); below the critical temperature that symmetry is broken and a preferred direction in space spontaneously appears.

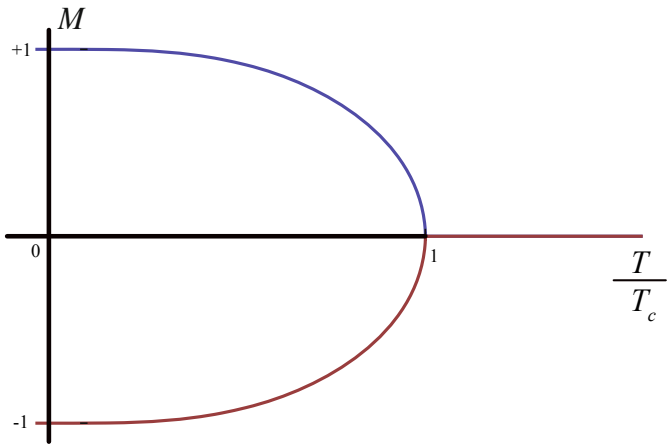

Figure 2. Magnetic Order Parameter; After Selinger (2015).

The physicist Michael Fisher says that:

> "[t]o assert that there exists an order parameter in essence says: 'I may not understand the microscopic phenomena at all' (as was historically, the case for superfluid helium), 'but I recognize that there is a microscopic level and I believe it should have certain general,

> overall properties as regards locality and symmetry: those then serve to govern the most characteristic behavior on scales greater than atomic.
>
> Significantly, in my view, Landau's introduction of the order parameter exposed a novel and unexpected *foliation* or level in our understanding of the physical world. Traditionally, one characterizes statistical mechanics as directly linking the *microscopic* world of nuclei and atoms (on length scales of 10^{-13} to 10^{-8} cm) to the *macroscopic* world of say, millimeters to meters. But the order parameter, as a dynamic, fluctuating object in many cases intervenes on an intermediate or *mesoscopic* level characterized by scales of tens or hundreds of angstroms up to microns (say, $10^{-6.5}$ to $10^{-3.5}$ cm). (Fisher 1998, p. 654)

In the context of steel we should think of material parameters as reflecting mesoscale structures significantly above the atomic scale and significantly below the continuum scale. We can learn about these structures by introducing the concept of a Representative Volume Element (RVE). An RVE can be understood as the smallest volume of a material that at the macroscale can be modeled "statistically", i.e., as a representative for a volume within a heterogenous continuum.[17]

The left side of figure 3 shows how a *material point* at the macroscale continuum level of a material at the same time can be described as a heterogenous microstructure at a lower scale, containing voids, inclusions, cracks, and grain boundaries. The RVE should be sufficient small to allow for a separation of behavior at the two scales (such that properties of the heterogenous structure can be smoothed) but large enough to capture representative collective effects of the microscale elements.

There are actually three length scales here. There is the continuum or macroscale, D, by which the neighborhood of the material point is characterized. There is a microscale, d, that represents the smallest microstructures (typically shapes and boundaries) believed to directly influence the overall responses to stresses and strains imposed upon the neighborhood surrounding the material point. Finally, there is the atomic/lattice scale, ∂. The following relation holds between these length scales: $\partial << d << D$.

[17] A classical definition of the RVE is "a sample that (a) is structurally entirely typical of the whole mixture on average, and (b) contains a sufficient number of inclusions for the effective overall moduli to be effectively independent of the surface values of traction and displacement, so long as these values are *macroscopically uniform*" (Hill 1963).

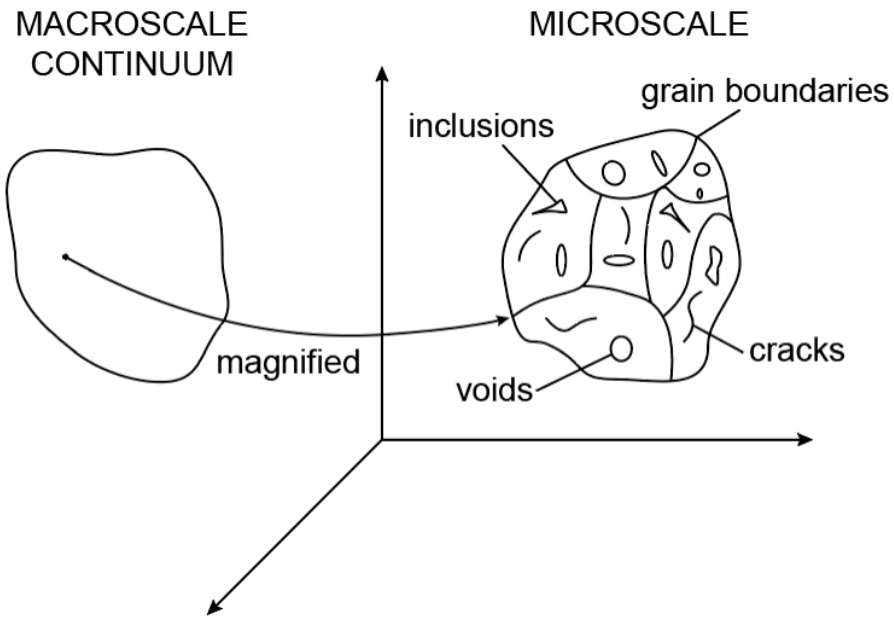

Figure 3. Schematic of an RVE. After: Nemat-Nasser and Hori, 1999.

One can represent the mesoscale structures (characteristic length *d*) using correlation functions. For example, we might want to know the volume fractions of a two-component material consisting of a good heat conductor and an insulator. A one-point (degenerate) correlation function represents the probability of finding conductive material at a given location in the RVE. Suppose the probability is *p*. The volume fraction of the conductor in the RVE is *p* and the volume fraction of the insulator will be 1-*p.* We can consider a two-point correlation function, C_r, that provides information about the probability of finding the same type of material at either end of a line segment of length *r*.[18] This can generalize to *n*-point correlation functions. In addition, one needs correlation functions that enable the representation of boundaries between the materials, etc.

Upon characterizing the relevant RVE for one's material (the railroad track), it is sometimes possible to upscale to determine a range of values for the material parameter(s) that figure in the continuum equations for the bending of beams (*c in* equation (1) above). As mentioned, homogenization provides a rigorous method for upscaling by finding a *fictitious homogeneous* material that will yield the identical behavior of the actual heterogenous composite. Thus, this fictitious material with its upscaled value for Young's modulus (or *c*) will exhibit the same bending

[18] Think of randomly dropping line segments of length *r* throughout the RVE and seeing if the endpoints are in the same material phase.

behavior as the actual railroad track.[19] This homogenization, taking as input details about the structure in the RVE, demonstrates that the continuum behavior of the material is *relatively autonomous* from the actual details of the atomic lattice structure. The important aspects of upper scale behavior described by the values of the material parameters encode mesoscale structures at the level of the RVE.

Computational homogenization strategies are employed when the relevant macroscale constitutive equations are unknown or when material parameters are difficult to estimate experimentally, e.g., because the material contains complex heterogenous microstructures (see Section 3.2). The modeling strategy operates in both directions (up and down). Computational homogenization is used to represent up-scaled parameter estimations, whereas finite element methods (see below) are often used to discretize macro-level parameter values into boundary conditions at the mesoscale. The boundary conditions can in such cases be considered as macro-level inputs to boundary value problems at lower scales. Solving boundary value problems for each periodic microstructure allows for model-based inference of the material parameters in the macroscale models or equations (Gitman 2006). Common to both analytical and computational homogenization strategies is the aim of accounting for relevant mechanical properties of microstructures by encoding such microscale details into a few effective parameters.

In summary, the steel example illustrates Schwinger's point that fundamental theories or models are often "too remote from the phenomena you want to describe" (Schwinger 1969, p. 19). A "fundamental" model based on the lowest scale would at the same time contain too much and too little information. It would include many (atomic) details that are explanatory irrelevant while failing to include information about those mesoscale structures that are of relevance to macroscale behaviors. Examining steel only at the macroscale is also insufficient, as the macroscale models require the specification of values for material parameters. These parameters, we have argued, code for material properties of the heterogeneous structures at the mesoscale. In the following, we examine how the challenges of multi-scale modeling are addressed in the context of multi-scale modeling of bone fracture and strength.

[19] Of course, the actual railroad track is heterogeneous at lower scales. The aim of homogenization is to show that there could be an equivalent homogeneous system that will exhibit the same behavior as the actual system. Since the continuum equations do not recognize any heterogeneities, this is required to explain why those equations actually work to describe the behavior of the actual system. We are not reifying the "fictitious" homogeneous system.

3.2. Bone

Bone, like steel, exhibits different properties at different length scales. At the macroscale (whole bone), bone looks like a relatively homogenous and dense structure. But if we break a bone and study the microstructural constituents (e.g., with a magnifying glass), very complex hierarchical and heterogenous structures appear. Figure 4 shows the upper part of a human femur, which consists of two distinct tissues defined at the mesoscale, called trabecular bone and cortical bone. As we clarify below, the characteristics and distribution of these structures have important implications for the physiological properties of bone – and for modeling behaviors of medical relevance, such as fractures and osteoporosis.

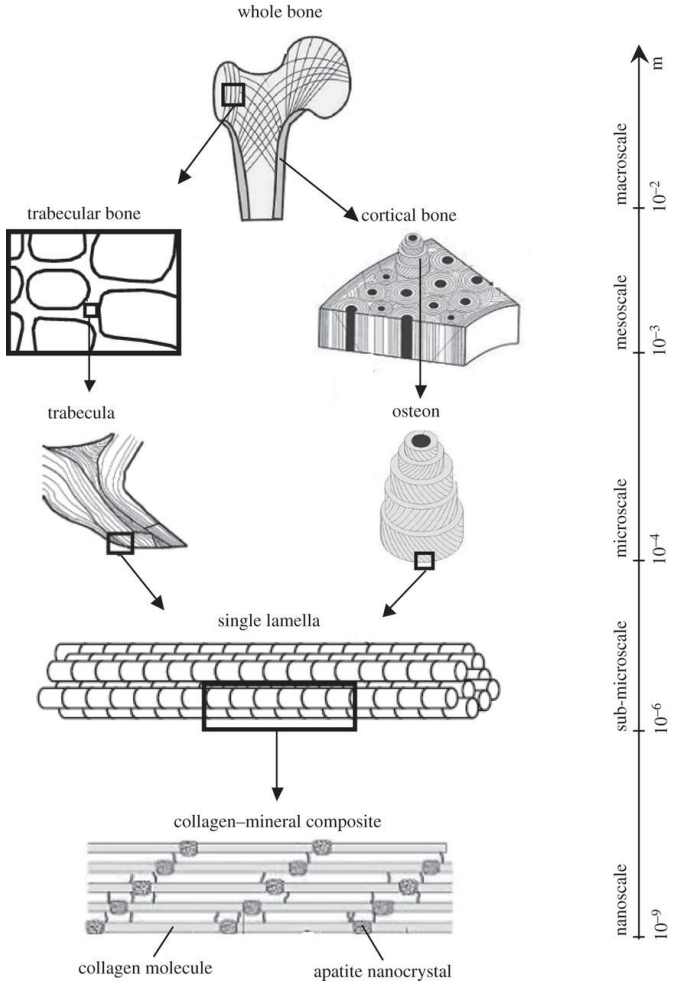

Figure 4. Bone structure at different spatial scales[20]. Figure republished with permission of The Royal Society (U.K.), from (Sabet et al. 2016), permission conveyed through the Copyright Clearance Center.

[20] Note that in this figure the mesoscale is *identified* to be 10^{-3} meters. This is just for the particular modeling problem at hand. In general, as noted earlier, mesoscales are determined to be relevant scales between micro and macro scales for a given phenomenon.

Cortical bone (or compact bone) makes up the dense, hard shell of bone and accounts for about 80% of the total weight of vertebral bones. This type of bone contributes greatly to the stiffness of the material. Cortical bone consists of concentric cylinders, called osteons, embedded in the interstitial bone and separated by cement lines. Bone at this scale also exhibits other complex structures such as a network of blood vessels that is central to bone metabolism. *Trabecular bone* fills the interior and ends of long bone and consists of struts called trabeculae that form a three-dimensional network with a spongy appearance (hence, it is often called spongy bone). The network structure is essential for load distribution and energy absorption. The combination of the rigid cortical bone and the open and porous structure of trabecular bone allows for bone to be surprisingly fracture-resistant compared to the weight of the material.

At the microscale, the geometry of the meso-structures of the two bone types disappear and bone displays the structure of crystal sheets called lamella. The lamellas can, at the nanoscale, be described as a lattice-like fibril consisting of appetite crystals, collagen, and water. As with the steel example, details on the lowest-scale constituents are insufficient to account for the material properties of macrostructures, because the complex geometries are not visible at lower scales.[21] Modeling choices are in part guided by practical considerations, e.g., of whether it is possible to measure material parameters experimentally at the mesoscale (rather than through complex upscaling procedures), and by theoretical considerations about the most relevant starting point for investigating specific properties.

As in the steel example, an important step is to develop a continuum model of the elastic properties of bone in a way that considers the relevant microstructural features at the mesoscale. As mentioned, determination of material parameters (such as Young's modulus) is central for upscaling models from lower to higher scales.[22] In the context of bone, it is necessary to take into account the differences in bone-material density (BMD) of cortical and trabecular bone. Figure 5 illustrates how the mechanical behavior of bones are experimentally determined by compressive load application. Young's modulus and other constants for the constitutive equations can be defined via stress-strain

[21] A few models do start at the lowest scales displayed on Figure 4. For instance, a five-step homogenization procedure has been used to show that volume fraction of different constituents at the microscale can be used to predict bone stiffness, and that the elastic properties of the basic constituents of bone are universal (Fritsch and Hellmich 2007). As clarified below, it is however necessary to account for higher-scale microstructures to predict fracture risk, which is influenced by many other features than material stiffness. Moreover, the employment of RVEs and advanced homogenization strategies clarify the validity of phenomenological models and connections between scales.

[22] Another example from biology is multi-scale modeling of morphogenesis, where Young's modulus and tensor fields represent factors that influence degrees of motion of the viscous epithelial structures of the developing embryo (Davidson 2012; Green & Batterman 2017).

curves generated for the different tissue specimens, and as evident from the figure, the curves (and the material parameters) differ greatly for the two bone types.

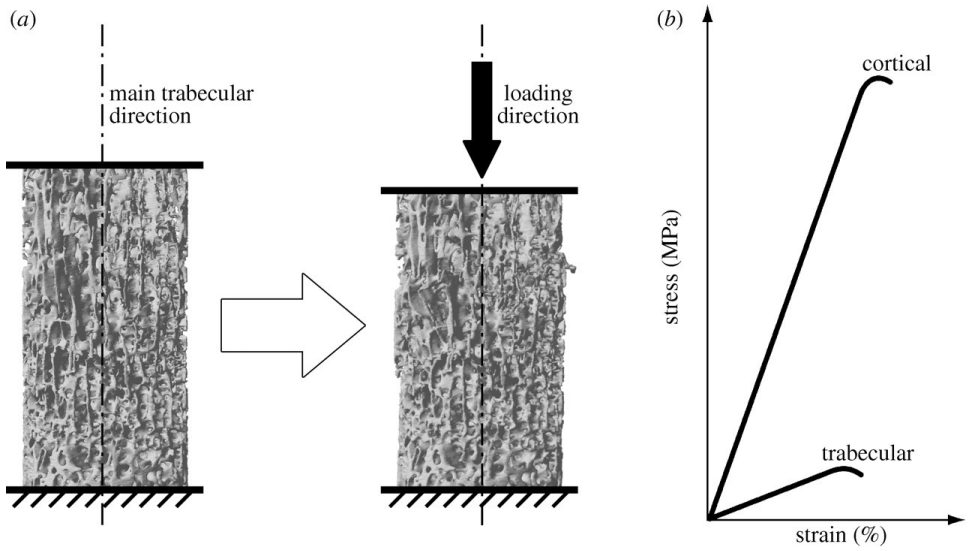

Figure 5. Illustration of approaches to determine the constants for the constitutive equations for bone tissue models. Figure republished with permission of The Royal Society (U.K.), from (Cristofolini et al. 2008), permission conveyed through the Copyright Clearance Center.

Estimation of stiffness from BMD of cortical and trabecular bone is, however, insufficient to predict fracture risk. A large part of the age-related increase in bone deterioration and fracture risk has been found to be independent of changes in BMD (Sabet et al. 2016). Models at the lowest scale are limited when the aim is to account for macroscale behaviors such as plasticity and toughness.[23] This requires consideration of processes at higher scales, such as intermolecular sliding and dissipation of elastic energy through microstructures (Richie et al. 2009). [24] Similarly, microcracks appearing at the mesoscale are essential for many toughening mechanisms, such as crack bridging and crack deflection, and need to be studied at larger length scales (Ibid p. 44). Accounting for the higher-scale *distribution* of tissue types is also essential. For instance, fractures

[23] Whereas *stiffness* is a measure of a material's resistance to deformation in response to an applied force, *toughness* is a measure of the capacity of a material to absorb energy without breaking. Toughness is quantified as the area under a stress-strain curve.

[24] Another interesting example is how epithelial branching in the context of mammary organogenesis is not only determined by the stiffness of the extracellular matrix but also by the local and differential organization of collagen fibers (Barnes et al. 2014; Montévil et al. 2016). We would like to thank an anonymous reviewer for bringing this example to our attention.

are common at the femoral "neck" which consists primarily of trabecular bone, surrounded by a thin cortical shell (see Figure 4).[25]

It is increasingly acknowledged that many age-related changes in bone are only visible at higher scales. Among these are stiffening of the interstitial bone tissue, changes in the thickness of cement lines between osteons (an important site for microcrack initiation), as well as structural changes in the trabecular network (Doblaré et al. 2004).

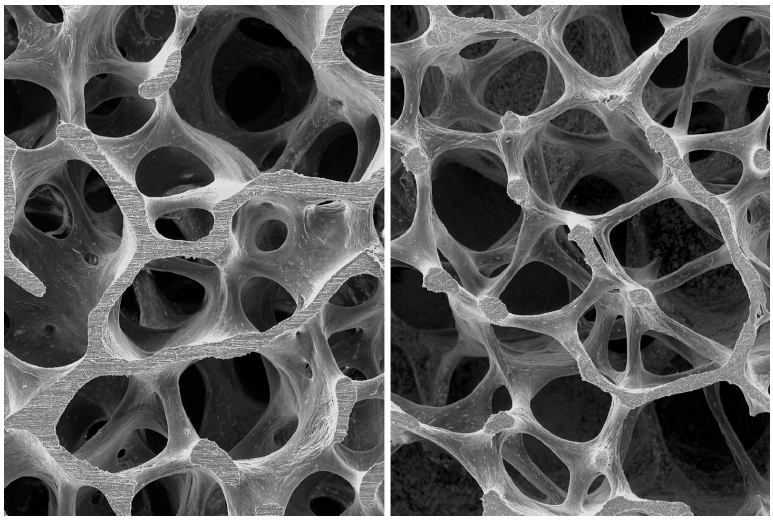

Figure 6. Spongy bone structure of a 21-year old male (left) compared to a 65-year old female (right). Each image is 3mm across. A decrease in the density and diameter of struts are often observed as a person ages, especially among postmenopausal women (Ritchie et al. 2009) (Figure courtesy of James C. Weaver.)

Figure 6 displays a comparison of the spongy bone structure of a 21-year old male and a 65-year old female. Even if the overall BMD remained the same in the two cases, the more open topology of the local trabeculae network of the 65-year old female would be expected to make the bone more prone to fracture (Ritchie et al. 2009). Recent studies estimate the increased bone fracture risk with aging is mostly due to changes in trabecular bone structure (Thurner et al. 2007; Sabet et al. 2016).

Fragility and resistance to bone fracture are capacities that manifest differently at different temporal and spatial scales, and changes at different scales often influence processes at higher or lower scales. As in the steel case, molecular details at the lowest scale are often irrelevant for modeling of meso- and macroscale behaviors. But because bone, unlike steel, is an *active* material, molecular processes for repair and renewal of bone are capable of influencing macroscale

[25] Elastic moduli have been show to differ for the femur neck, femur midshaft, and femur head (Novitskaya et al. 2011). Generally, experimental values for elastic moduli of bone are dependent on features such as porosity (or bone type), mineralization, age, trabecular architecture (see Section 4), but unfortunately also on the testing method and sampling size. The development of predictive models of bone fracture and strength is therefore a hard problem in biology.

behaviors. These processes are collectively called *bone remodeling* and make bone structures change and adapt to changes in load conditions. For instance, molecular mechanisms can alter the cross-linking of collagen proteins and thereby change the macroscopic path of crack propagation.[26] It is therefore often necessary to employ middle-out strategies that start with mesoscale structures and "look both ways" (up and down) to tissues and molecular remodeling mechanisms.

3.2.1. Modeling bone "from the middle and out"

In the following, we examine a middle-out modeling strategy that is motivated by the wish to understand health problems such as osteoporosis, where bone fractures can occur without traumatic events. Many researchers point out that reductionist strategies are limited in addressing such questions because the problem is inherently multi-scale. For instance, Cristofolini, Viceconti, and colleagues argue that the reductionist strategy "has not translated into a better understanding of skeletal fragility as seen in clinical practice" and that "as the event of interest (the fracture) occurs at the organ level, it is wiser to start from this scale, and then drill up, down and across other levels and subsystems" (Cristofolini et al. 2008, p. 3321).

In their modeling approach they explicitly adopt the middle-out strategy highlighted by Noble (2006). As discussed in Section 2, what is defined as the "mesoscale" depends on the problem of interest. Noble's cardiac models treat the cell level as the mesoscale, whereas the trabecular and cortical structures are considered mesoscale in modeling of bone as described above. In the following, we examine strategies to model and predict bone fractures, which require taking into account even higher scales that impact load distributions. In this framework, bone represents an intermediate scale between the upper level of the human body as a whole and the lower levels of tissues and cells.

Figure 7 provides a schematic view of this approach, centering on the development of an intermediate bone model at the organ level as the starting point. The aim of the *organ model* is to be able to replicate and predict how femoral fractures arise in certain bone regions in response to applied loads (external forces or stress) that propagate throughout the hierarchical structure of bone (Cristofolini et al. 2008). The organ model is a finite-element (FE) mesh representing the

[26] The cross-link density is higher in bones of older individuals. This lowers the ability of bone to dissipate elastically stored energy from an applied load before breaking (Ritchie et al. 2009).

geometrical features and tissue types of the femur.[27] The FE mesh estimates the spatial distribution of the mineral density of the bone at the organ level, based on imaging data from *in vivo* CT scans of patients. The model incorporates model outputs from two lower-scale models (tissue model and cell model) as well as an upper-scale model (body model). We describe the features of each of these below.

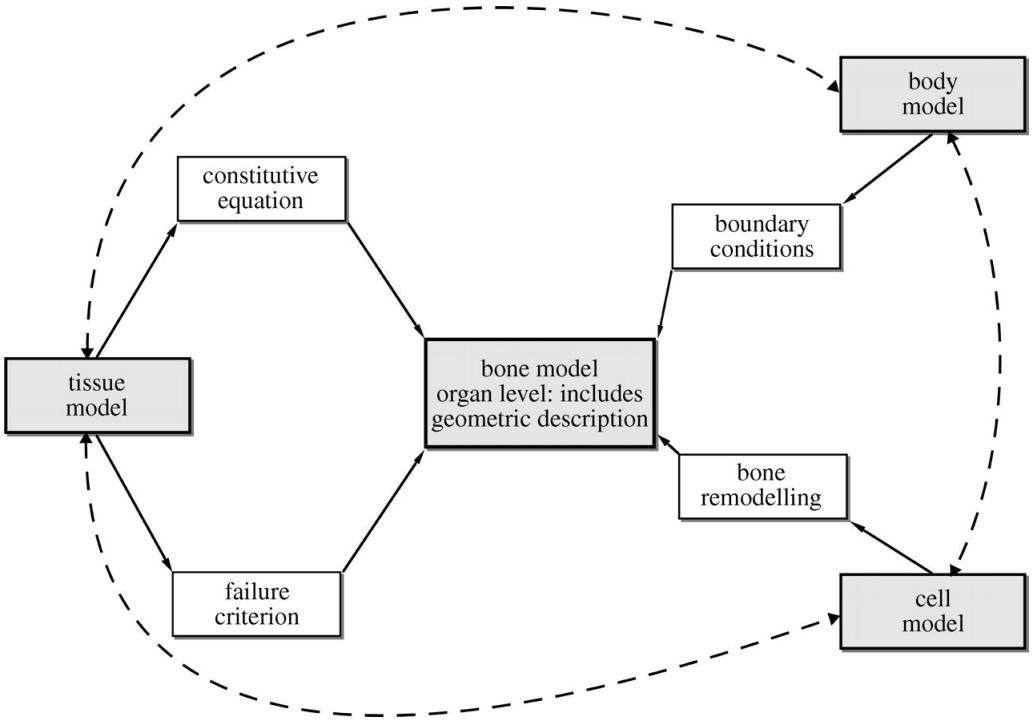

Figure 7. Factors involved in developing a multi-scale model of the human femur. The solid lines illustrate inputs from models at higher and lower scales that are required for the organ level model. Dashed lines illustrate how model inputs travel across models targeting behaviors at different levels. Figure republished with permission of The Royal Society (U.K.), from (Cristofolini et al. 2008), permission conveyed through the Copyright Clearance Center.

The *tissue model* provides information on the quality, chemical composition and structure of trabecular and cortical bone as described above.[28] In practice, the tissue model parameterizes the complex bone morphology and biochemical composition into an elastic constitutive equation to be

[27] Finite element methods refer to computational discretization strategies commonly used to find approximate solutions for complex mathematical problems and (like here) to develop 2D or 3D models of systems. A finite element mesh consists of a number of finite element subunits representing a block of the material (or a subdivision of a mathematical problem). As clarified in Section 4, development of FE models often involves complex homogenization strategies. For other studies using FEM to predict bone behavior, see (Sabet et al. 2016) and references therein.

[28] Thus, the tissue model is considered as a mesoscale model from the perspective of the organ model, whereas the organ model is the intermediate model from the perspective of the whole body model. This underscores Noble's point that the term "mesoscale" is relative to the modeling task at hand.

applied at the organ level. The equation describes the tissue deformation (strain) in response to stress induced by external forces. This involves defining Young's modulus for the two bone tissue types (as illustrated in Figure 5 above). The two models are connected by modeling bone as discrete RVEs at the size of 2 mm^2, where CT data are used as inputs to the constitutive equation. This modeling step thus relates the mechanical properties of the bone tissues (tissue scale) to the spatially distributed variations in mineral density (organ scale).

The tissue model further provides information on the *failure criterion*, which quantifies the threshold leading to bone fracture. Because the failure criterion accounts for correlations between bone tissue structures and microcracks, this involves identification of further constants and boundary conditions. Employment of a simple failure criterion would only allow for prediction of the ultimate force at fracture. To determine the propagation of force and microcracks through tissues and bone segments, the modeler must determine realistic boundary conditions in terms of subject-specific musculoskeletal loads. This includes information not only on ultimate strength but also *yield strength*, defined via stress-strain curves as the limit (i.e., failure) of elastic behavior. In this case, the failure criterion is based on *in vitro* experiments studying femoral neck fractures under physiologically realistic loading conditions. Predicted values for bone strains and fracture risk under specific loading conditions were here validated against controlled experiments using strain gauges as well as epidemiological data.

The tissue model implicitly assumes that the properties of bone are constant and homogenous. A *cell model* is therefore required to account for additional challenges arising when bone structures – as *active materials* – change over time. As highlighted above, bone is a dynamic system that modifies its own structure over time through bone metabolism, including adaptive changes in response to load and activity levels, as well as long-term changes such as growth and aging. Cristofolini, Viceconti et al. (2008) therefore proposes to extend the model network "downwards" by also including a cell model that can be coupled to the organ model through iterative time-dependent simulations. The model updates morphological and biochemical structure of the collagen fiber mesh over a remodeling cycle of 197 days. This step is explicitly presented by the authors as work in progress and as a framework for future modeling procedures.[29]

[29] Coupling of cellular and continuum scales is a persistent challenge, and most approaches to date rely on hierarchical modeling strategies that selectively use inputs from lower-scale model but do not fully integrate these in a multiscale model where inputs go in both directions (up and down) (Sabet et al. 2016). Section 4 offers insights to some advances in multiscale modeling since the publication of this model.

At the highest scale, a *body model* presents the joint forces and loading conditions acting on the whole structure during different motor tasks and perturbations. This model consists of physical parameters estimated for 9 body segments and 84 muscles. The body-level model provides boundary conditions (musculoskeletal loads) for the FE mesh at organ level. Cristofolini, Viceconti et al. emphasize that: "in order to predict the risk that a given patient will suffer a low-energy fracture in the coming years, a multi-scale approach is needed. Such risk cannot be addressed at a single scale: the risk of overloading is defined at the body level and the risk of fracture at the organ level" (Cristofolini et al. 2008, p. 3321). Thus, central concepts are also in this context scale-specific.

The centrality of the organ model exemplifies the aim of developing an intermediate (or mesoscale) model following a middle-out modeling strategy, rather than a reductionist or bottom-up approach. The FE mesh not only balances practical tradeoffs between numerical accuracy and computational/experimental limitations, but also bridges between quite different modeling strategies appropriate for phenomena at different scales. As with steel, the challenge is to describe continuum behaviors at the macroscale while also accounting for relevant microstructural inhomogeneities. The FE mesh at the same time allows for a discretization of the continuum model to account for different bone structures and remodeling processes, and further offers a quite coarse-grained picture where many microscale details are ignored.

4. Modeling of bone as an active material

The previous section not only illustrates many similarities between modeling of steel and bone, but it also notes how additional challenges arise when modeling *active materials*. In this section, we unpack such challenges further and highlight additional complexities.

Temporal dimension. Microstructures change over time in active materials, and the material parameters and boundary conditions must be repeatedly estimated and updated in simulations to capture the evolution of the material structures. As we have seen in section 3.2, bone remodeling can redistribute bone material in response to applied load, growth, and aging, which can result in new bone morphologies with different material properties. The modeling task is not only complicated by the need to account for temporal changes, but also by complex feedback relations between different processes at different scales. For instance, simulations of the formation of high density layers in bone, e.g. in response to externally applied load, need to be integrated with models

describing internal and external bone remodeling (bulk and surface growth), and each of these models must account for how parameters at different spatial scales develop over time (Ganghoffer & Goda 2018b).

Anisotropy. The model system described in Section 3.2 assumed that the material properties of bone (like steel) are isotropic, i.e., that the strength of the material is largely independent of direction in space. But bone, like wood, is far more difficult to break in the transverse direction than to split in the longitudinal direction (Sabet et al. 2016). To explain the anisotropic properties of bone, material parameters must thus not only code for differences between the two tissue types but also for architectural features that affect crack paths. When aiming to account for anisotropy, modelers therefore have to estimate additional elastic constants and parameter values for strain tensors that differ for vertical, axial, and horizontal struts in the trabecular bone structures. Thus, more complicated upscaling strategies are required to account for the geometry of anisotropic materials (Ganghoffer & Goda 2018c). The coupled stress components can be combined in a simulation to account for how anisotropic properties also change over time in response to the temporal changes in the overall bone morphology described above (Ganghoffer & Goda 2018a). While this is a difficult task, it allows for simulations of how increased cross-link density of collagen can accumulate from small damages over time resulting in a lesser ability to dissipate energy before breaking. This is important for medical purposes, because bone can become more prone to fracture as a result of adaptation to previous damage or changes in loading conditions (e.g., extensive lifting or inactivity).

Tendon mechanics. As described in Section 3.2, a body model is often needed to provide boundary conditions for intermediate models of bone. The body model describes the joint forces and loading conditions during a fall or when undergoing motor tasks. Inputs to such a model involve tendon mechanics, i.e., how external forces influence not only the bone structure but on larger body structures composed of different tissue types (muscles, ligaments, tendons, etc.). Modeling procedures of tendon mechanics are often similar to the strategies described above and start at an intermediate level where the specific phenomena in focus are observable. For instance, Maceri et al. (2012) also start at the mesoscale and determine parameters at the tendon scale from homogenization of properties at lower scales (e.g., fiber aspect ratio, fiber curvature, and fiber tangent modulus).

Structural diversity of bone. Section 3 highlighted the need to account for the geometry of the overall bone structure as well as the different material properties of cortical and trabecular bone.

For some modeling problems it is also relevant to account for structural heterogeneity of cortical (dense) bone, such as the role of osteons and cement lines in crack propagation. Again, the approach is typically one of attempting to bridge between scales by accounting first for mesoscale properties. For instance, Mischinski and Ural (2013) develop a macroscale model based on the mechanical properties of microstructures (studied via FE simulations developed from imaging data). Thus, while the strategies in the biological example exemplify middle-out techniques akin to the steel example, the development of predictive models of multi-scale active materials requires more mesoscale models and more complex homogenization schemes.

Despite advances in multi-scale modeling of bone and other biological structures, there remain many open questions and challenges (Bhattacharya & Viceconti 2017). One question concerns whether the central assumption of separation of spatial and temporal scales is justified in all biological contexts. This issue is crucial for determining how many realizations of a mesoscale structures have to be constructed for adequate upscaling (Stoneham & Harding 2003). Sabet et al. (2016) highlight that the assumption of scale separation often is safer in physical contexts such as the steel beam, where the microstructure grain size is about 10^5 times smaller than the beam length. In biological contexts, the difference is often only a few orders of magnitude, or less, and with complex feedback-relations across levels.

Biological variation also provides a challenge for generalization of models in the biomedical context. For instance, Cristofolini, Viceconti et al. (2008) highlight that the clinical impact of bone models could be improved by development of stratified tissue-level models that account for how material parameters for bone structures depend on various clinically relevant contexts. Specifically, they suggest that an atlas of tissue models could be developed for representative population properties such as age, sex, pathology, and anatomical sites. The need for such an atlas raises an interesting question about the size of possible RVEs (and at higher scales universality classes) for biological materials, compared to materials in physics. In some biological contexts, the very existence of a justified representative volume element is debated (Sabet et al. 2016).

Despite this complexity, sensitivity analyses performed to evaluate the consequences of modeling assumptions (e.g., about RVEs) often show that mesoscale model outcomes are robust to a range of change in lower-scale parameters and that homogenization strategies are appropriate also in biological contexts (Bhattacharya & Viceconti 2017; Bhattacharya et al. 2019). Despite the overwhelming complexity of multi-scale biological systems, multi-scale *in silico* models of the human bone have been found to be clinically useful (Viseconti and Dall'Ara 2019). This

applicability is difficult to explain from a reductionist perspective, given that these models necessarily ignore and idealize many lower-scale details. Accordingly, the relative autonomy of meso- and macroscale in both physics and the life sciences should make us question the assumption that predictive utility rests primarily on getting the lower-scale details right.

We have highlighted the importance of finding material parameters, such as those for stiffness or strain, for modeling of steel as well as bone. These parameters code for aspects of lower-scale details without being bottom-up derived (or derivable) from those details. Although more details (and more parameters) are needed to account for biological complexity in the case of fracture prediction in bone, the strategies to tame the tyranny of scales are strikingly similar. Middle-out approaches and homogenization strategies have not yet received much attention from philosophers of science but are topics that can be addressed across the physical and biomedical domains.

5. Concluding remarks

It is often assumed that coarse-grained models describing mesoscale or macroscale features are primarily developed because a more fundamental or more accurate detailed lower-scale model is unavailable. This misses the point that multi-scale systems often display distinct behaviors at different spatial and temporal scales. To capture these behaviors and to see how models of those different behaviors complement and integrate with one another is a daunting scientific undertaking. Yet, because of the tyranny of scales problem, it is a necessary one. A common challenge for multi-scale modeling is to understand the relationship between continuum dynamics at macroscale and material-specific parameters that code for complex and heterogenous structures at lower scales. Mesoscale structures often provide a means for determining such parameters. Were one to focus only on the smallest (atomic) scales one would fail to find the correct variables/parameters to describe the continuum behaviors.

We have argued that the best methodology to tackle this problem is a “middle-out” or “mesoscale first” approach. It is only for the simplest (or better, the most homogeneous) materials that a bottom-up approach is even feasible. The cases examined illustrate that the procedure for taming complexity requires the identification of RVEs that allow for such parameterizations. The RVE defines a mesoscopic level, intermediate between discrete and continuum properties of lower and higher scales. Relations between scales are therefore neither independent nor fully determined

by lower scale "fundamental" details. Identifying the right mesoscale parameters allows researchers to ignore details for purposes of tractability but also provides foundational understanding the main observable aspects of the material systems' behavior.

The fact that many lower-scale details are often unnecessary or even irrelevant when modeling multi-scale systems highlights the (relative) autonomy of upper-scale descriptions. In the context of biology, the relative independence of many lower-scale features also offers important insights to functional robustness. If the functioning of biological systems were determined by fine-tuning of lower-scale parameters, organisms would be very sensitive to changes in, say, gene expression or protein concentrations. But because the influence of such effects is also defined by upper-scale boundary conditions and feedback mechanisms, functional robustness is maintained within certain boundaries (Noble 2012; 2017). Relative autonomy of higher scale phenomena also explains the very possibility of finding stable material parameters for different materials. From a reductionist perspective, it would be difficult to make sense of how the same equations can often be used to describe large classes of materials composed of completely different atomic constituents, and even to model active as well as inactive materials.

In summary, many parameters of relevance for describing macroscale behaviors cannot be inferred from fundamental theories or detailed microscale models in a direct bottom-up fashion. As emphasized by Schwinger more than 50 years ago, a phenomenological model is often more informative than a fundamental theory for solving practical problems in engineering. Similarly, maximally detailed models of the lowest scales would not reveal the medically relevant properties of bone fracture. Homogenization strategies are not only crucial when material parameters cannot be accessed experimentally, but also for providing validation and understanding of phenomenological models. The aim of multi-scale modeling is not just to model behaviors at different scales but also to understand how these are related. For this purpose, middle-out strategies are employed in physics as well as biology and deserve more attention from philosophers of science.

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