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MATHEMATICAL APPROACH TO BONE TISSUE MODELING

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Abstract. *This paper is dedicated to an overview of the existing approaches and their assumptions in the mathematical modeling of bone tissue and will thus necessarily emphasize future paths of understanding and communicating in this field of science. The understanding of the bone tissue processes, and the possibility of their mathematical modeling is important for several different directions of practical demands, all encompassed in the development of medicine and technology. One aspect of bone tissue modeling is directed towards the bone medicine field that solves acute and chronic problems as computer-assisted orthopedic surgery which requires real-time simulation, disease treatment and improvement of the quality of life. The other aspect is directed towards material science and tissue engineering. On the one hand, we have mathematics and mechanics with their approximations and assumptions and, on the other, we have very complex practical requirements for real-time simulations and in-silico experiments. To meet these two complex fields with efficiency, it is necessary to further explore and better understand all the conditions that influence the feasibility and accuracy of the mathematical models for bone tissue. The first step in this enticing field is to make an overview by categorizing the models into distinct categories from the mathematical attitude to the practical demands. Different practical demands cause different mathematical approaches to modeling. This paper presents, as clearly as possible, the collection of models and approaches according to these practical requirements. Since mathematical methods have their own constraints, we first present the description of mathematical modeling and its challenges and obstacles in biology. As a practical example, the bone cell population model for mechanotransduction of external periodic signals is presented.*

Key words: *Mathematical modeling, Bone remodeling, Mechanobiology, Mechanotransduction, Bone cell population model, Bone multi-scale modeling.*

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1. INTRODUCTION

Close to a hundred and sixty thousand papers are related to “bone tissue modeling” on the Springer Link, with over a hundred and forty thousand in the last fifteen years. Most of them are from the field of medicine, over a hundred thousand, the next are fields of bio-medical science and life science, engineering, with over ten thousand papers, and chemistry. When searching for the key phrase “mathematical models of bone tissue” about nine thousand papers are found, which fits the number published in engineering disciplines. The number is rapidly growing, for instance, in the last year about thirteen thousand papers were published. This is a result of increasing demands but also of technical achievements in interdisciplinary research. Some reasons for such an explosion of interest in the field may be also found in the following facts:

- the explosion of data-rich information sets, due to the genomics revolution, which are difficult to understand without the use of analytical tools,
- the recent development of mathematical tools such as chaos or networks theory to help understand complex, non-linear mechanisms and interactions in tissue processes,
- an increase in computing power which enables calculations and simulations to be performed that were not previously possible and
- an increasing interest for in-silico experimentation due to ethical considerations, risk, unreliability, and other complications involved in human and animal research by in-vivo and in-vitro experiments.

The similar reasoning is given by Podshivalov et al. [1] who state that a significant breakthrough in bone research took place at the end of the 20th century. This breakthrough was made possible by the development of high-resolution medical scanning technology, of computational hardware that is constantly improving and of state-of-the-art computational methods and algorithms. Using these developments, researchers have begun to strive for a better understanding of bone structure and mechanics and to apply this knowledge in designing new medical treatment and procedures, resulting in a constant increase in high quality research in this scientific area [1].

In the present time, when techniques and technology gallop tremendously fast, we still have human operators on devices suffering from different bone pains. This is a principal reason, among others such as aging and degeneration of bone tissue for an increasingly aging population, for tremendous interest in the problems with bone. A small but a vital part of general health is the musculoskeletal health. Musculoskeletal disorders already account for nearly half of all absences from work and sixty percent of permanent work incapacity in Europe. Therefore, effective and application-related research into preventive, prophylactic and regenerative therapies is important.

Scientific understanding of complex bone processes has recently benefited from mathematical and computational modeling. Classical biological studies are focused on observation and experimentation. However, mathematical modeling and computer simulations can provide useful guidance and insightful interpretations for experimental studies, orthopedic surgeries, embedding scaffolds and implants, effect of drugs in patient treatment and so on. Mathematical modeling can also be used to characterize complex bone phenomena, from intercellular signaling to cell division, proliferation, migration and even mutation, from bone remodeling to healing, from tumor growth to cancer metastasis, from osteoarthritis to osteoporosis treatment or else. Mathematics and mathematical modeling can assist in formulating hypotheses and finding the experiments that may differentiate

between different mechanisms, can help in determining which of the assumed mechanisms is likely to be the most important for the observed effects. Finally, and perhaps most importantly, mathematical modeling is a tool for synthesis - the process of combining separate elements in order to form a coherent whole - a tool of inductive reasoning, allowing reconstruction of the bone function as an organ based on the acquired knowledge of elementary processes [2].

In many cases, the quality of a scientific field depends on how well the developed mathematical models agree with the results of repeatable experiments. A lack of agreement between mathematical models and experimental measurements often leads to important advances as better theories are developed. In the case of bone tissue modeling and structural mathematical modeling both fields should benefit. Bone tissue modeling would gain more realistic and accurate models ready to be used for the prediction of treatment and operations, and mathematics would witness the improvement of tools that deal with many different input and output parameters and variables. Also, the results from joining both directions should provide material science with a new path for understanding, producing, simulating and predicting the features of the new generation of biomimetic materials.

This paper outlines how mathematical models can help to improve current understanding of bone biology and discusses examples where mathematical modeling was used to provide new insights into important questions of bone biology. The main concepts of mathematical modeling on different scales are presented first. They are embedded afterwards in different scales of practical demands and their last five-year-results are elucidated. At the end, the view of the state of the art in this field and the direction of future deliberations are presented. The selection of references provided herein was made to present the very contemporary tendencies of application of mathematical and bioengineering bone modeling, but readers should always bear in mind that the field is abundant and that every scientific school has its own “best solution”. The tendency of this review was not to favor some of them, but instead to highlight the modern trends, problems, and certain interesting solutions. Of course, there are so many published studies worth mentioning that are not presented here, because of time and space restrictions, and the interested readers are only versed in the overall domains, thus it remains that they should form an opinion and judgment of their own.

2. MATHEMATICAL MODELING

Using the formulation of a mathematical model as a self-contained set of formulas and/or equations based on an approximate quantitative description of real phenomena and created in the hope that the behavior it predicts will be consistent with the real behavior on which it is based [3], one can notice that the emphasis is on the uncertainty in the connection between the mathematical model and the real-world setting to which it is applied. This emphasis means that modeling requires the theoretical science skills of approximation and validation, and it changes the focus of the mathematical skills from proof and solution to characterization (understanding the broad range of possible behaviors) and simulation (visualizing the behavior in specific examples). The thinking one needs for mathematical modeling is therefore somewhat different from the thinking associated with mathematics per se and more like the thinking associated with theoretical science of interdisciplinary fields. Mathematical solutions provide a wide range of results

but only the practical data could validate which of those results are acceptable. The imperative is to understand the problem as a whole and to validate the model results. At best, a mathematical model can be valid, in the sense of "giving meaningful results under a given set of real-world circumstances" [3]. There are almost certainly quantitative differences between the model and real-world empirical results, and there may be important qualitative differences as well. If the differences are small enough in the given setting, we judge the model to be valid and use it with confidence. The model may work for somewhat different settings as well, but its validity should be checked for the new setting. When the validation is not satisfactory, one must revise the model and try again. Model development is the most critical step in mathematical modeling, generally requiring 50–70% of the project time.

All the models used in biology represent a significant simplification of the reality and depend on specific underlying assumptions. Sometimes it is useful to incorporate subjective information into a mathematical model. This can be done based on intuition, experience, or expert opinion, or based on convenience of mathematical form. In general, model complexity involves a trade-off between simplicity and accuracy of the model. Occam's razor is a principle particularly relevant to modeling; the essential idea being that among models with roughly equal predictive power, the simplest one is the most desirable. While added complexity usually improves the realism of a model, it can make the model difficult to understand and analyze, and can also pose computational problems, including numerical instability. Thus, an experienced researcher with expertise in an interdisciplinary field should possibly create a more complex model and the trick would be to propose a simplification which will make the processes easier to understand but still attempting to imitate it.

When starting modelling we accept a set of specific predictions of how the biological system might behave under certain externally implied conditions. In fact, we make the appropriate assumptions and hypotheses which are the set of physical/chemical/biological processes selected and hypothesized to be critical in the studied phenomenon. Derivation of the hypothesis requires the complexity of real phenomena (biological system) to be reduced and a conceptual (biological) model of a process to be built, which encompasses some logical relationships between the perceived key elements of the whole. Specific hypotheses concerning the elements of the conceptual model can be tested using specific experimental conditions. The experimental outcomes agree or disagree with the stated hypothesis, allowing for the refinement of a conceptual model. In that way, a large collection of individual observations on different aspects of bone regulation is generated. Essentially, these observations can be viewed as single pieces of a large puzzle, the systems behavior of bone. However, without having the overall picture in mind (the conceptual model), these individual pieces cannot be put together in a systematic way. The following step is to translate the accepted biological model into a mathematical one. During this stage, the biological model should provide specificity and precision, which represent the first advantage of using mathematical modeling in biological research - it forces the development of a deeper understanding of biological processes, and consequently more precise formulation of hypotheses. Next, it is necessary to choose the variables and to establish rules between them, after which the estimation of the numerical values of parameters is needed. In the process of modeling the experimental data value of some parameters may be unavailable at the time, so the researcher can estimate the likely range of values from the available experimental data or similar processes or can hypothesize the

values relative to other known values. Importantly, even if absolutely no data exist for the required parameters, and so arbitrary numbers have to be assigned, an advantage of model analysis is that it allows assessment of whether and at which values certain parameters are important for the overall behavior of the model. Such insight can stimulate further experimental studies to measure the most important parameters or can advise that the process is unlikely to be important if the current conceptual model is correct. Thus, the second advantage of mathematical modeling is the ability to identify the important parameters, i.e., those capable of introducing significant changes to the overall behavior of the system.

Mathematical models can be used for different purposes, and the aim of the model plays a large role in determining the type of analysis and the criteria for validation. They describe a system by a set of variables and a set of equations that establish relationships between the variables. Namely, the input data (potential reasons for variation) as the independent variables are functionally related with outputs or outcomes, whose variation is being studied, as the dependent variables. A model of a biological system – a biological model is converted into a system of equations, although the word 'model' is often used synonymously with the system of corresponding equations yet then it stands for a mathematical model. The solution of the equations, by either analytical or numerical means, should describe how the biological system behaves either over time or at equilibrium. There are many different types of equations and the type of behavior that can occur is dependent on both the model and the equations used. As aforementioned, the model often makes assumptions about the system, but the equations may also make assumptions about the nature of what may occur.

In terms of model limitations, it is also important to realize that most problems dealt within bone biology are highly nonlinear and therefore exhibit different types of non-obvious behavior, such as point attractors (for systems reaching a stable equilibrium), periodic attractors (for systems reaching an oscillatory equilibrium), strange attractors (for systems exhibiting chaotic behavior) and bifurcation points (where a small change in model parameters leads to a large, qualitative change in system behavior). Studying complex, non-linear systems often requires advanced analytical and numerical calculation tools, which have limitations and assumptions of their own. Therefore, the success of mathematical modeling strongly depends on the collaborative efforts of biologists and mathematicians (physicists, engineers) engaged in the project.

2.1. Analytical approaches and their practical scales

From a biological perspective bone is present over many biological scales from genetic, intra-cellular, cellular, extra-cellular, tissue, organ and finally to the whole organism. This requires a much deeper understanding of complex processes, feedback mechanisms and “multi-scale’’ phenomena. In mathematical terms, it requires the study of highly nonlinear integrated systems. The biological system characterization is based on the identification of three natural scales; therefore, we distinguish between processes at the intracellular, cellular and tissue scale. Different mathematical techniques and structures correspond to these scales:

The intracellular scale: In response to changes in the external or internal cellular environment, the expression of specific genes and consequently protein synthesis may change. Cascades of biochemical reactions that lead to signal transduction from receptors

located on the cell surface to the cell nucleus are called signaling pathways. These signaling pathways constitute natural regulatory systems that should ensure, on the one hand, cell resistance to random changes in its condition, and on the other, a proper response to external changes. Models at this sub-cellular scale are most often constructed using coupled systems of ordinary differential equations or Boolean networks.

The cellular scale: At the cellular level, the key processes that are modeled are division, differentiation, apoptosis and interactions between cells. These processes are regulated via signaling pathways. Regulatory proteins, whose production is triggered by signaling pathways, initiate or modify the processes of cell division and death. In turn, cell differentiation, both normal and pathological, influences the signaling pathway dynamics, which leads to subsequent changes at the cellular level. Considering the links between cellular models and the models described above at the sub-cellular scale is necessary in order to describe how cells function. Multi-cellular systems, i.e. models at the cellular scale, are usually developed in terms of nonlinear integro-differential equations (of the Boltzman type), the components of the mathematical kinetic theory [4] or individual-based models. At this level, in the bone context, the modeling cell dynamics is the topic of several published papers and here we single out a few of them [5-8]. As all of them deal with the bone remodeling process they are described in more detail in the following section.

The tissue scale: Anomalous processes at the cellular level have led to the development of structures such as osteoporotic bone, for instance, which, in turn, affect the proper functioning of tissue and organs. These changes are observed at the level of whole cell populations. This description is by its very nature phenomenological but allows for a qualitative understanding of the whole system depending on key parameters such as trabecular thickness, osteoclast resorption depth, and activation frequency (understanding the links between these parameters and phenomena occurring at the lower scales is particularly important). At this level a model includes bone micro-architecture. Tissue models usually involve free boundary problems and nonlinear partial differential equations. The choice of proper mathematical methods is usually linked to the precise biological questions we want to address and the type of available data.

The organ level: At this level models are continuum based and describe the variation of bone's apparent density as a function of both biological and external mechanical stimuli.

The organism level: At this level more variable parameters, e.g. age, genetics or hormonal status of the organism, should be included in the description, thus a statistics method should be applied.

Descriptions on different scales seem to be deeply justified because biological processes are inherently multi-scale. For instance, if we consider processes such as diseases, we find that they are present over many biological scales. First symptoms are almost always observed at the clinical (macroscopic) level, but if we look more closely at the origins of those diseases, it is easy to see that a pathological process often begins with intracellular alterations (microscopic level). Therefore, there is a need for new mathematical tools that are suitable to capture such complexities. In the field of bone biology, a plethora of models exist which attempt to replicate and investigate bone's dynamic behavior at different scales. Although informative, these models exist in isolation. Consequently, their interpretation is limited. There are reviews [1, 9] where authors present their overview of the organ-, tissue-, and cell-level models and assesses their ability to reflect bone’s metabolic processes reliably and introduce a framework that integrates those multi-scale modeling approaches.

The preceding subsections have enlightened the main features that a mathematical formalization, namely a general mathematical structure, should retain. In the analysis of the interplay of different scales, namely from molecules to tissues, one might expect that different structures might correspond to each scale. On the other hand, some correlations should exist between them, namely the structure at a certain scale is induced by quantities at the lower and/or upper scale. Therefore, the concept of multiscale should be defined as the passage from the lower to the higher scale. For instance, the dynamics at the scale of cells is induced by the dynamics at the molecular scale, the macro-scale structure of tissues is determined by the dynamics at the scale of cells. Finally, it is worth bringing to the attention of applied mathematicians a feature specific of multi-scale approaches in biology. All living systems evolve in time and are even subject to mutations. This aspect is well understood if we refer to the transfer of the dynamics at the molecular scale to that of cells. The modification of biological expressions at the cellular scale can induce important modifications in macro-scale models. As a matter of fact, macro-scale models of tissues evolve in time and can even undergo changes of type. It is a challenging problem but is far from being solved in a satisfactory way. The approach should arguably use the aforesaid structures as a multi-scale system of equations, namely molecular and cellular, coupled with the nonlinear interactions and solved by an asymptotic approach.

At the end of this section let us refer to the future direction of the analytical approach. An example of a mathematical technique that can be extremely useful in describing many phenomena in biological systems, and that is complementary to those indicated by Ref. [4], are integral terms describing nonlocal interactions. For instance, nonlocal terms might be used to describe the phenomena of intercellular communication. Examples of such intercellular communication are also paracrine signaling, when a cell produces chemical substance signals that are secreted to the extracellular space and induce changes in nearby cells and autocrine signaling when a cell produces chemical messengers that bind to the receptors on the same cell. In both types of signaling, produced chemicals diffuse over a relatively small distance. Another example of a process in which nonlocal interactions are particularly important are the processes in which the cell size is relevant. This refers to models of such phenomena as chemotaxis, cell adhesion or aggregation processes. The nonlocal terms can describe cell size. In some cases, this also ensures that the problem is mathematically well-posed and that the nonlocal models may also be considered at the macroscopic level [10].

2.2. Numerical approach and corresponding applicable scales

As it was mentioned in the previous section the models describing osteoclast/osteoblast (OC/OB) interactions in basic multicellular units (BMUs) will be explained in more detail. Such models, based on nonlinear ordinary differential equations (ODEs), have been developed by several authors representing the power of the analytical approach [5-8], all specific in their own way depending on the demands from practice. These models are complex and elucidate one number of parameters that explain in detail the physiological mechanism of the bone tissue adaptation process. The obtained analytical system of equations needs to be solved, and because of their complexity and the lack of the analytical solutions numerical methods are usually used. One numerical method in wide use is the finite element method (FEM). Biological models that are more phenomenological and often require a relatively small number of parameters are relatively easy to implement in

FE codes. A FEM is characterized by variational formulation, a discretization strategy, one or more solution algorithms and post-processing procedures. Examples of variational formulation are the Galerkin method, the discontinuous Galerkin method, mixed methods, etc. A discretization strategy is understood to mean a clearly defined set of procedures that cover:

(a) the creation of FE meshes,

(b) the definition of basis functions on reference elements (shape functions) and

(c) the mapping of reference elements onto the elements of the mesh.

Examples of discretization strategies are the h-version, p-version, hp-version, x-FEM, isogeometric analysis, etc. Each discretization strategy has certain advantages and disadvantages. A reasonable criterion in selecting a discretization strategy is to realize nearly optimal performance for the broadest set of mathematical models in a model class. There are various numerical solution algorithms that can be classified into two broad categories; direct and iterative solvers. These algorithms are designed to exploit the sparsity of matrices that depend on the choices of variational formulation and discretization strategy. Post-processing procedures are designed for the extraction of the data of interest from the FE solution. In order to meet the requirements of solution verification, postprocessors need to provide for a posteriori error estimation in terms of the quantities of interest. When the errors of approximation are larger than what is considered acceptable, the discretization must be changed either by an automated adaptive process or by an action of the analyst. There are some very efficient postprocessors that provide for the realization of super-convergence. The FEMs have been initially used in the engineering problems calculation, but thanks to their capacity to solve very complex systems they have found application in bone modeling. FE has been used for more than four decades to study and evaluate the mechanical behavior of bone structures [11]. FE methods are attractive because at the macro level the bone exhibits elastic linear behavior for loads in the normal range of regular daily activities. In many published studies, elastic properties of bone are correlated to the bone real density $\rho_{real} = m_{ht}/V_{tot}$ in order to derive an empirical elasticity–density relationship, see [12]:

$$E = C\rho_{app(ash,dry)}^{a} \tag{1}$$

where:

E [GPa] Young's modulus,

$\rho_{app} = m_{ht}/V_{tot}$ [g/cm^3] - apparent bone density

m_{ht} - hydrated tissue mass [g],

V_{tot} - total specimen volume [cm^3],

$\rho_{ash} = m_{ash}/V_{tot}$ [g/cm^3] - ash density,

m_{ash} - ash mass [g],

$\rho_{dry} = m_{dry}/V_{tot}$ [g/cm^3] - dry tissue density,

m_{ash} [g] - dry tissue mass.

Constants C and a have different values for different measurement conditions. Hydrated tissue mass or wet tissue mass is the specimen mass weighted in air after defatting, rehydration and centrifuging on a blotting paper. Dry tissue mass is the specimen mass weighted in air after defatting and drying at moderate temperatures. Ash mass is the specimen weight after defatting and heating in a furnace at a temperature of 500ºC or more for approximately 24 h. Reviewing Eq. (1) from different studies [12], the authors have found over twenty inter-study differences (different values for C and a) in the predicted Young's modulus for cortical and cancellous bones, sorted them out and have presented

the findings tabularly. This large spread in the predicted Young's modulus can partially be explained by the complexity of the experimental techniques needed to obtain the mechanical properties in a highly porous anisotropic material such as bone. Commonly, to determine the mechanical compressive properties, a trabecular bone specimen is cut out of a whole bone and loaded in a material testing machine. By recording the load–displacement curve, the stiffness can be calculated. Over time, different testing set-ups were developed and applied with different specimen boundary conditions (platen-technique, end-caps and other techniques), different specimen size and geometry (cube or cylinder) and the anatomical site from which the specimens were retrieved (femur, tibia, spine and other), all affecting the different parameters in Eq. (1). Furthermore, specimens need to be tested fresh or fresh frozen and in wet conditions since drying and other specimen preservation procedures are known to significantly alter mechanical tissue properties. However, even after normalization with respect to strain rate and densitometric measurement unit [12], they have found out that substantial inter-study differences do exist, and they can only be partially explained by the methodological differences between studies. The values of parameters C and a also depend on different directions, and have bigger values in the axial direction of the long bones, showing that the compressive strength for the cortical and trabecular femoral bone in the axial direction is better than in the transversal (lateral) direction [13].

Initially, computational models in musculoskeletal applications were based on idealized, simplified structures. Today, these models are typically based on image-derived geometries from computed tomography (CT) or magnetic resonance imaging (MRI) and can thus be individualized for the specific patient. Recently, FE analysis has become a frequently used versatile, general purpose simulation tool. Not only does it allow a detailed description of the mechanical load transfer in the analyzed bone, but such simulations have the potential to predict e.g. optimal drug treatment and distribution for individual treatment planning. Advances in silico experiments, modeling bone biology, can help to better understand the long-term risks and outcomes of many different impacts. Most usually FEMs are used to analyze strain and stress fields induced by external loading on bones as organs. Bone's geometrical representation may be obtained from Quantitative computed tomography (QCT) scans, and structure-based models were shown to be appropriate when surface strains are of interest [14, 15]. However, the trabecular architecture of bone is not explicitly modeled in most cases and a homogenized variable that represents the bone apparent density ρ_{app} is used for describing the heterogeneous distribution of porosity and, thus, mechanical properties of bone [16]. Bone is an anisotropic material due to preferred trabecular orientation and anisotropy of the bone tissue itself, and thus the determination of bone's inhomogeneous mechanical properties and their assignment to the FE mesh is yet a major unsolved problem. The mechanical properties of bone depend on composition and structure. However, composition is not constant in living tissues. It changes permanently in terms of the mechanical environment, aging, disease, nutrition and other factors. Many reports try to correlate mechanical properties with composition [12-14, 17-20]. Another assumption of most FE analyses in the literature is the linearity of the constitutive behavior of the bone tissue. This is usually accurate enough, but some authors obtain more accurate results by considering nonlinear material properties for cortical and trabecular bone [18].

The anisotropy of bone could be considered at a tissue level using anisotropic material models which mostly use the bone density distribution as a measure of bone trabecular

architecture. The measurement of the shape and density distribution can be done using imaging modalities and QCT. The shapes of bones are segmented from QCT images using image-processing programs, while the gray values (Hounsfield units - HU) in those images are related to apparent bone density ρ_{app} using linear relationships $\rho_{app} = f(HU)$. The relationship is calibrated using calibration phantoms with known density values. The heterogeneous mechanical properties of bones are then related to bone density through empirical relationships such as in Eq. (1).

The shape and density distribution of bone can be measured [16] using other imaging modalities such as magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA) and ultrasound. As the shape of bone is considered as constant traditionally, density values are the major variables that are predicted using bone tissue adaptation models. The proximal femur consists of cortical (compact) and trabecular or cancellous (cellular) regions. Homogenized mechanical properties of both regions as well as isotropic Young's modulus E were experimentally associated with ρ_{app} or ρ_{ash}. Bone density in turn can be correlated to HUs. The complexity in determining material properties is enhanced by the anisotropic response which is distributed inhomogeneously throughout the bone. The various material properties cannot be obtained from a scalar value (the HU) in CT scans, so simplifications must be applied. For example, an FE study [21] compared the response of the femur when isotropic or orthotropic material properties were assigned under two loading conditions (double-leg standing and single-leg standing) showing that differences between the two material property assignments are small. An alternative approach for obtaining the 3D shape of bones as well as their density distributions is the use of the so-called statistical shape and appearance models [16]. Furthermore, CT scan-based FE models are most accurate when they are generated from CT scan data [22] with the least noise, streak artifact, and beam hardening. As these sources of image degradation increase, the accuracy of the CT scan-derived material properties and geometry decreases, and the reliability of FE models decreases. Thus, in comparison with in vitro-based FE models, in situ-based FE models [19] have an additional source of error that is due to increased noise, streak artifact (e.g., motion, metallic objects, out-of-field, edge gradient effects, high-low frequency interfaces, equipment malfunctions), and beam hardening from the presence of large amounts of soft tissue in the image field. These results demonstrate that using CT scan data obtained in situ instead of in vitro to generate FE models can lead to substantially different predicted results. This effect must be considered when using this technology in vivo.

Finite element (FE) simulations have become a useful tool as well in the field of Orthopedic Surgery and Traumatology, helping surgeons to gain a better understanding of the biomechanics, involved in both healthy and pathological conditions. FE simulation provides information about the biomechanical changes that occur after prosthesis or osteosynthesis implantation, and biological responses of bone to biomechanical changes. It has an additional advantage in predicting the changes in the stress distribution around the specific zones e.g. implanted, fracture and healing zones, allowing the prevention of future pathologies deriving from e.g. unsuitable positioning or shape of the prosthesis [23] or improper healing [13].

FE simulation has facilitated the understanding of how the load is transmitted not only on the bone surface but across the tissue, e.g. after the implantation of a femoral stem, and the prediction of how the stem impacts the bone response in the long-term. Modern high-resolution FE models of cancellous bone can predict apparent yield strength and are often

used to estimate the amount of tissue damage generated by overloads. But FEM has several disadvantages, such as the fact that models are time-consuming to create and verify. The process of acquiring CT images, segmenting the bone from CT images, and converting the segmented model to an FE mesh and their associated mechanical properties is costly, time-consuming, and may need exposure of subjects to high radiation doses.

The type of the selected mesh elements can affect the results [17, 24]. Generally, voxel-based micro-finite element models of trabecular bone, where the micro-finite element models are generated as brick elements from reconstructed bone voxels, have been mostly utilized [20]. However, the voxel-based method requires a very large number of brick elements to establish an accurate representation of the micro-structure of trabecular bone, and therefore, the application of this approach is limited to a very small volume of bone samples. The models could yield numerous errors especially with the voxel element because the element could not reflect the geometry well.

The tetrahedron-based method can be also used to create a smoother representative depiction of the micro-structure of trabecular bone. A number of papers present results from comparison of different element types [17] with the applied 10-node-tetrahedron element type. Over the past two decades, an extensive study on volume mesh generation has been performed. Various methods have been proposed to generate volumetric mesh with high-quality tetrahedron elements. These techniques can be classified into four categories: advancing-front-based, octree-based, Delaunay-refinement-based and lattice-based methods [25].

Furthermore, FEM can also be sensitive to boundary conditions (stress concentrations, local stresses) [23, 24], and sometimes the model needs to be refined repeatedly in order to ensure that the results are reasonably accurate or valid.

FEM obtains approximate solutions and has inherent errors. The difficulties involved in FE simulations of bone remodeling, such as geometric and material complexity which greatly complicates the generation of accurate simulation models, means that the whole procedure is very time consuming. Model order reduction (MOR) is a good alternative for reducing the time needed. The goal of MOR is to construct a low order reduced model to approximate the large-scale original model with a high degree of accuracy, thus reducing the computational cost. It has already been successfully applied in many different fields such as circuit simulation, vibro-acoustics and microelectromechanical systems (MEMS) design and solid or fluid mechanics. For linear systems, many MOR approaches are well established and have proven to be very useful in the case of ordinary differential equations (ODEs). Many accurate models, including bone remodeling simulations, introduce nonlinear equations. A commonly used traditional strategy is to linearize the system first and then perform a MOR on the linear system, but the linearization does not always give a good approximation of the original nonlinear system.

Another popular method is proper orthogonal decomposition (POD) which is widely used in the research of fluid mechanics as well as MEMS. POD is the generalization of the idea of finding a suitable projection base for the reduced model of nonlinear systems as done in the linear case. This projection is generated or estimated through information from data samples of the state-space of the original model. The POD method delivers reduced models, which are more accurate because there is no linearization error. Adapted versions (of the POD) are necessary to achieve a reduction in the simulation time because of the expensive function evaluations. The proper generalized decomposition (PGD) method for numerical solving of multidimensional problems has recently been introduced and widely

used. The mathematical foundations of this recent technique have yet to be rigorously tested. In fact, some crucial aspects at the very root of the method are not fully understood [26]. Thus, nonlinear model reduction in general remains a challenge and research in this area is ongoing.

Various parallel computing techniques have also been proposed in the literature to simulate bone regeneration in tissue engineering [20,23]. These techniques could also be used for bone remodeling simulations. However, their focus is based on improving the multi-scale model rather than accelerating the numerical solution of the bone remodeling problem. The paper [26] studies an approach based on vector extrapolation techniques to reduce the computational time for the numerical simulation of bone remodelling algorithms. Despite the good results of presented numerical methodology, the method does have some limitations. In general, the methodology could be applied for any kind of load, but, in the case of irregular dynamic loading regimes, re-simulation would be necessary in order to improve the density vectors. Furthermore, the presented simplification is an accurate approach for the simulation of bone remodeling in a real 3D femur. However, this approach may not be valid for any kind of bone, where a high variability in the forces could be found.

Furthermore, generating a predictive FE model of biological tissue strains (e.g., physiological-like loading) encounters aspects that are inevitably unclear or vague (numerous uncertainties in quantifying the mechanical loading conditions as well as the overall mechanical properties of bone tissue) and thus might significantly influence the predicted findings [23, 27]. The accuracy of prediction of bone density and the method of assigning material characteristics in the FEM modeling significantly affect the accuracy of the FEM analysis results. This is clearly evident in [23, 28] and in the endeavor of a group of researchers at the University of Niš, Faculty of Mechanical Engineering (MFN), within the project VIHOS (Virtual human osteoarticular system and its application in preclinical and clinical practice, http://vihos.masfak.ni.ac.rs/site/). The author [23] has presented the concept of statically equivalent loads, where the boundary conditions are computed by an inverse simulation from CT–data. The mechanical properties of cortical bone are obtained from a micro–mechanical approach with several stages of homogenization.

There are other numerical alternatives, which can be used for bone remodeling simulations or other bioengineering applications such as the boundary element method, the finite difference method [29], the finite volume method or the meshless method. In the literature there are examples of (semi-)analytical and numerical FE approaches for bone remodeling models [8, 17, 26, 28, 29]. The (semi-)analytical approaches are normally used for convergence results, stability studies and error estimates of different bone remodeling theories. However, the FE method has been frequently used for bone remodeling simulations of real bones, mainly due to its ability to handle complex three-dimensional geometries. Therefore, it is common for bone remodeling theories to be coupled with the FEM.

Application of micro-FE (μFE) analyses could bring some advantages. Based on three-dimensional microstructural imaging, μFE simulations have become feasible using direct conversion of image voxels to either hexahedral or tetrahedral FEs [30]. By resolving the bone microstructure, the complex anisotropic behavior of trabecular bone could be accurately modeled using an isotropic material model. A clear advantage of μFE is the ability to rerun simulations using different types of loading and boundary conditions. Furthermore, stresses and strains can be analyzed locally for individual structures.

However, such simulations, although straightforward, are computationally expensive as they typically contain millions to hundreds of millions of elements. Various methods have been developed to improve computational efficiency [26, 30]. Persistent developments in computer technologies would exceed those problems.

3. DIFFERENT REQUESTS FROM PRACTICE

Mathematics has its own path for the discretization of the problem and for continuing the solutions from PDE and ODE to the visual representation of the solution. A similar attitude to the discretization of biological systems to their inherent parts is obvious. Biological models apply their specific way to the conclusion by using the holistic approach. That is one of the sources of possible cooperation in modeling. The practical demands direct the paths of exploration and collaboration of disparate scientific realms. The recent useful methods applied for different practical demands are presented in what follows.

3.1. Bone remodeling and mechanobiology

Bone remodeling is the continuous process of resorption and formation occurring in the skeleton of vertebrates throughout adult life. Remodeling is accomplished by highly coordinated groups of bone-forming osteoblasts (OBs) and bone-resorbing osteoclasts (OCs) that work together in the so-called “basic multicellular units” (BMUs). Many bone disorders such as osteoporosis, Paget's disease and cancer-related bone diseases can be ascribed to imbalances between resorption and formation, however, exactly how this balance is achieved during normal bone turnover is still unclear. In the last decade, many regulatory factors produced by hormonal glands, tumor cells, immune cells, and mechanosensing bone cells (osteocytes and bone lining cells) influencing different phases of bone remodeling have been identified. Among those factors, the key role of the nuclear factor-kappa β ligand RANKL-RANK-OPG pathway receptor activator (Fig.1) in the development of degenerative bone diseases has been repeatedly demonstrated.

To address the question of how different bone cells interact with each other and the bone microenvironment during remodeling, several models of cell populations have been proposed [31, 32]. These types of models can monitor changes in cell numbers and bone volume over time. These mathematical models have been focused on important questions such as: how does the interplay of different components in the RANK/RANKL/OPG signaling pathway affect bone homeostasis, how can Parathyroid hormone (PTH) both act catabolically and anabolically depending on the type of administration [31], and what are desirable therapeutic strategies for treatment of osteoporosis [32].

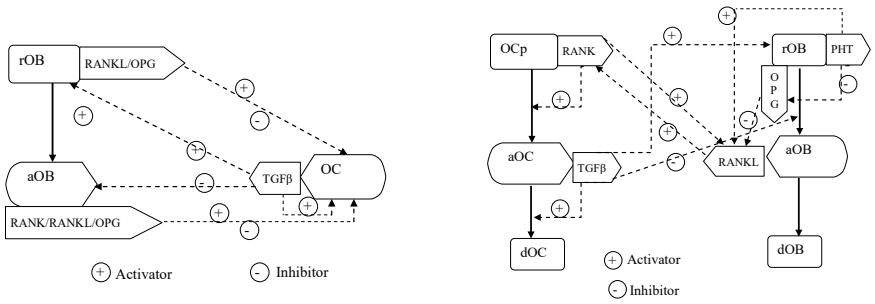

Figure 1. a) The dynamics of responding osteoblasts rOB, active osteoblasts aOB and osteoclasts OC. The feedback mechanism, mediated by the RANK/RANKL/OPG pathway and by TGFβ, is presented by arcs with arrows, as in [32].
b) The process of differentiation of OCs and OBs into three stages of cell maturation is presented with continuous straight arrows. The autocrine and paracrine regulation (presented with dashed arrows) controlled by factors (RANK, RANKL, OPG, TGFβ and PHT) which are attached in the stage of cell when they are expressed, as in [33].

There is experimental evidence that OB cells express RANKL and osteoprotegerin (OPG) differently at different stages of the maturation. The OPG is expressed stronger on active osteoblasts aOBs, while RANKL is expressed stronger on responding osteoblasts rOBs. Also, transforming growth factor β (TGFβ) activates OB differentiation only in the early stage of differentiation. It enlarges the pool of the rOBs by inhibiting further differentiation into aOBs. Therefore, the three-variable model corresponds to the system of three ordinary differential equations (ODEs) in a general normalized form [31, 33]:

$$\frac{dr}{dt} = \alpha_1\big(s(c) - t(r,c)\big)$$
$$\frac{db}{dt} = \alpha_2\big(t(r,c) - u(b)\big)$$
$$\frac{dc}{dt} = \alpha_3\big(v(r,b) - w(c)\big) \qquad (2)$$

where the first members in brackets on the right side represent the gains and the second represent the losses of the population of the representative cell type (where r stands for rOBs, b for OBs and c for OCs). The elasticities of these functions representing the parameters of the stability and bifurcation analyses [33], their interpretation and range are presented in Table 1. α_i, i=1,2,3, are defined as ratios between a flux and a concentration and thus have the dimension of an inverse time and can be interpreted as the inverse lifetime of the representative cell type. Since the average life span of OBs (~3 months) exceeds the life span of OCs (~2 weeks) by a factor close to 6, and since the scale by which time is measured is arbitrary, values for $\alpha_1 = \alpha_2 = 1$ and $\alpha_3 = 6$ have been fixed.

Table1. Parameters used for the stability and bifurcation analysis of Eq. (2) [31, 33]

Parameter	Interpretation	Range
sc	activation of rOB production (via TGFβ)	[0,1]
tc	repression of rOB decay (via TGFβ)	[-1,0]
wc	activation of OC decay (via TGFβ)	[0.5,1.5]
tr	rOB decay linear in r	[1]
vr	action of rOBs on OC (via RANKL/OPG)	[-1,1]
ub	aOB decay linear in b	[1]
vb	action of aOBs on OC (via RANKL/OPG)	[-1,1]

Under physiological conditions and in the absence of external stimuli, the system should reside in a steady state, where the numbers of OCs and OBs remain approximately constant. For the system to remain close to the steady state, the state must be dynamically stable, so that the system is driven back to the steady state after small perturbations. It is also desirable that the stationary densities of OBs and OCs react sensitively to external influences, communicated through the signaling molecules. Mathematically speaking, this means that the system should be robust against fluctuations of the variables, but sensitive to changes in the parameters. The example for the two-variable model of different system dynamics for small changes of parameters was analyzed in [34].

In dynamical systems, the strongest response of steady states to parameter change is often found close to bifurcations—critical thresholds at which the stability to perturbations is lost. Therefore, it is intuitive that there should be some tradeoff between dynamical stability and responsiveness. It is thus possible that the physiological state of the bone remodeling system is characterized by parameter values close to a bifurcation point. The stability and bifurcation analyses of Eq. (2) solutions that have been performed in [33] show that in a parameter space supported by experimental findings the system operates close to a region of instability. The main benefit of this operating is probably that a stronger adaptive response to external changes of the model parameters is possible. Despite the benefits, operating close to a bifurcation also poses risks to the system. A change in the parameters by an external process can shift the system over the bifurcation, so that the stable steady state becomes unstable or ceases to exist [34]. It is therefore reasonable to ask whether certain diseases of bone can be related to bifurcations, leading to qualitatively different dynamical behaviors. This model has not included external effects, but it has been discussed in [35], as will be described later. An intriguing possibility, raised in [2, 32], is that some bone diseases might have their cause not in a shift of the steady-state concentrations, but in a bifurcation, in which the stability of the steady state is lost. Dynamical systems theory has established a large variety of powerful tools for detecting and analyzing bifurcations. If a given disease were found to be related to a bifurcation phenomenon, this arsenal of tools could be utilized for understanding the causes and consequences of the disease.

The next level in spatial sequence of bone modeling is the cellular level. Cells are the living component of bone, and it is the movement and activity of cells that enables bone to adapt to its dynamic environment; hence cells must be considered in any model of engineered bone tissue. The cell dynamics modeling has influenced valuable research [5, 7, 8]. As the dynamics of the bone remodeling process was integral part of the mentioned research, it is described in more detail in what follows.

During bone remodeling BMUs travel at a rate of 20–40 mm/day for 6–12 months, maintaining a cylindrical structure [8]. A mathematical model of BMU has been developed

[8] by describing changes in time and space of the proresorptive cytokine RANKL and its inhibitor OPG concentrations, in osteoclast and osteoblast numbers, and in bone mass. In this study, the authors introduce a spatial extension of the temporal model suggested by Komarova et al. [31] resulting in a novel nonlinear model comprising a system of partial differential equations (PDEs), which describe the role of the RANK/RANKL/OPG pathway in attracting and promoting the BMU, as well as the autocrine and paracrine interactions between osteoclasts and osteoblasts, the main constituents of the unit. The model consists of five state variables: densities of osteoclasts and osteoblasts, concentrations of OPG and RANKL, and the local bone mass. The assumption was that osteocytes surrounding a microfracture produce RANKL, which attracted osteoclasts. OPG and RANKL were produced by osteoblasts and diffused through bone, RANKL was eliminated by binding to OPG and RANK. Osteoblasts were coupled to osteoclasts through paracrine factors. The evolution of the BMU arising from this model was studied using numerical simulations. One of the most important part of remodeling, as it was revealed from the Komarova et al. model [31], is the periodicity of the process as referred in [7, 33-35]. The authors [7] considered a simplified model, similar to [31], in 2003, consisting of three ODEs and introducing delays. As the spatial movement inside the BMU is small, the models based on ODEs can be used. The delays appear because there is a lag in the change of the osteoblast population due to changes in the population of osteoclasts, and vice versa. The properties of the system, including stability and bifurcation, have been studied and it was found that the Delay Differential Equations (DDE) have Hopf bifurcations that give periodic solutions. The numerical solutions have been calculated to illustrate the behavior of the solutions. As expected, the introduction of the delays changes the dynamics of the original model [31]. This research found that the delays destabilize the periodic solutions of the original model. It also found that by starting with values of the parameters for which the model [31] has a stable focus, by increasing the delays it is possible to obtain periodic solutions. As it was concluded by [7] the introduction of delays makes the model more useful to medical researchers and medical doctors who can test whether it is better to increase an autocrine signal or a paracrine one to obtain the desired effect, and to test similar hypotheses.

The Komarova type models are attracting research and drawing attention to their results, which the latest papers [34, 35] prove. In these papers a simplified model of [31] has been considered, in which the autocrine signaling of osteoclast and osteoblast is proportional to their populations. To distinguish the biological model presented in Fig. 1.a, this model also includes the cell death stages, Fig. 1.b. The mathematical model consists of two nonlinear ODEs and a third equation for bone generation, where the difference is made between differentiation rates of the OBs and OCs precursors α_i and the speed of the cells degradation process β_i, i=1,2:

$$\frac{du_i}{dt} = \alpha_i f_i(u_1, u_2) - \beta_i u_i \quad , \quad i = 1,2$$

$$\frac{dz}{dt} = -k_1 v_1 + k_2 v_2 \text{ for } v_i = \begin{Bmatrix} u_i - \overline{u_i}, & if\ u_i > \overline{u_i} \\ 0, & if\ u_i \le \overline{u_i} \end{Bmatrix}, \quad i = 1,2 \tag{3}$$

where u_i are the densities of OCs for $i = 1$ $i = 2$, $f_i(u_1, u_2)$

approximation: $f_1(u_1,u_2)=u_1^{\gamma_{11}}u_2^{\gamma_{21}}$ and $f_2(u_1,u_2)=u_1^{\gamma_{12}}u_2^{\gamma_{22}}$, where γ_{ij} for $i = 1,2$ and $j = 1,2$ are defined by regulators RANK, RANKL, OPG and TGFβ. The third equation, the so-called bone mass equation, describes the activity of bone resorption and formation where z is the total bone mass, k_i are the normalized activities of bone resorption and formation and $\overline{u}_i$ are the steady states for the OCs and OBs.

The structure of the system of Eqs. (2) and (3) seem to be similar but it should be mentioned that for stability and bifurcation analysis of nonlinear systems conclusions differ from the parameters in equations, and not on their structure, whereas there are some general rules coupled with structure. The steady solutions, their nonlinear stability and the existence of positive periodic solutions of a model have been studied and it has been confirmed that the model Eq. (3) has good qualitative features that were observed experimentally, which has been also concluded, among others, in [33] for the system in Eq. (2).

An important feature of the OCs–OBs models [5, 33, 34] is that they are based on the hypothesis of isolated populations, which is not realistic in human biology. Therefore, a new model, suggested by [35], by adding another term which functions as a regulator of the bone remodeling process that includes the external signaling (as the osteocytes activity via the PHT which is an anabolic agent that stimulates the production of OCs), has been proposed. The two types of external signals were observed - the constant impulse and the signaling function type switch that is time dependent. With a nonlinear stability analysis authors have shown that the modified model yields a positive non-oscillatory solution. This behavior of the solution is consistent with the bone remodeling cycle and returns to a quiescent state after three or five months, as in [31]. The authors have given a parametric range as conclusion, based on the nonlinear analysis, where their simplified Komarova's model exhibits periodic solutions. They have introduced external agents to such a model and have analyzed theoretically their effects, finally presenting numerically the behavior of the solutions for the model with and without external agents based on realistic data. The author [36] developed these ideas on the five-variable model that also includes osteocyte (OCy) population dynamics by modeling the mechanobiology of bone remodeling to the periodic external signals. Since the mathematical model of such a complex system is inherently intertwined with noise, the analogue stochastic model was also developed, so that the time series and phase plots for 100 simulations of bone cell dynamics, presented in Fig. 2, reveals interesting phenomena of doubling periods under external stimuli. The yellow sections at the phase plots represent the most visited regions of trajectories over 100 simulations. Making in-silico experiments with a stochastic mathematical model we were in the position to discuss the influence of included oscillatory signals between received and sent signal by osteocytes, and we concluded that the signal with small delays provides the closest matches between the calculated data and biology theory. We also examined the magnitude and frequencies of external signals and justified that the stronger the oscillations, the more the phase plane resembles a loop of doubling periods (∞ shape), yellow sections presented in the phase plans (Fig. 2), indicating the regularity in the cellular communications.

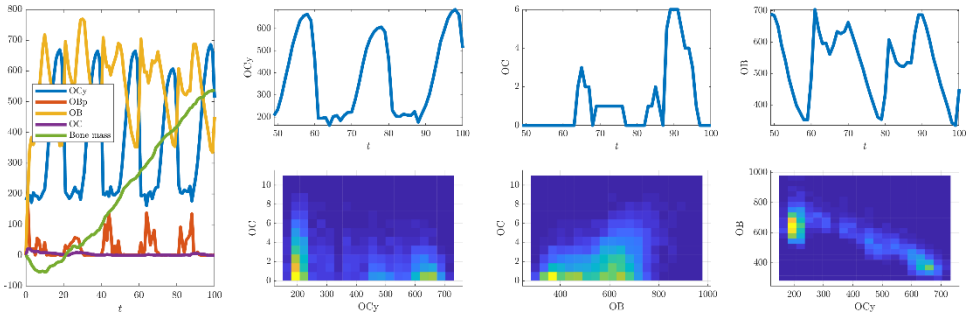

Fig. 2 *B*one tissue active cells periodically excited (left). The three images on the top are OcY, OC and OB concentrations over time, respectively. The bottom 3 images are the phase planes of the two of these variables averaged over 100 simulations.

The group of authors gathered around Buenzli and Pivonka, [5, 6, 37] has made a considerable development of their methods by permanent improvement of their ideas connected with the experimental results, but also by using the contemporary mathematical theories. Recent experimental evidence suggests that OB proliferation plays an important role in the regulation of bone remodeling. The authors in [37] have developed a novel computational (biological) model of bone cell interactions that includes OB proliferation. This model accounts for a catabolic regulatory mechanism of bone remodeling, mediated by the RANK–RANKL–OPG pathway, and a new anabolic regulatory mechanism of bone remodeling, driven by OB proliferation.

As the number of cells, their receptors, inhibitors and inter signaling mechanisms is abundant in the bone remodeling process, as shown previously, one can conclude that the variety of the combinations are still open to be researched and to be elucidated. For instance, the paper [6] reveals an interesting presentation of osteocytes derived from bone-synthesizing cells (OBs) that become buried in the bone matrix during bone deposition. The generation of osteocytes is a complex process that remains incompletely understood. Whilst OB burial determines the density of osteocytes, the expanding network of osteocytes regulates in turn OB activity and OB burial. A spatial-temporal continuous model was proposed [6] in order to investigate the osteoblast-to-osteocyte transition. Paper [35] examines the temporal population model for mechanotransduction of the external periodic signals through a network of communicating OB-OB-OCy cells.

3.2. Biomechanics

Modeling tissue function is the next level that considers bone as an organ with the mechanical function as its major function. Bones support the body weight and act as stiff levers for attachment of the tendons/muscles, thus providing the ability for locomotion. Biomechanics is the discipline applying mechanical principles to study tissue function and it is the focus of this subsection. Biomechanics comprises a variety of engineering fields that include material science, structural engineering, and mechanical engineering, among others. In the last decade the bone biology field has seen a large shift from a purely biochemical view to a coupled biochemical–biomechanical view of bone regulation, which has allowed the application of biomechanics principles to diverse questions such as estimation of material properties of bone, adaptation of bone to mechanical forces and

fracture healing. Analysis of mechanical properties of bone is a major aspect of biomechanics, which is concerned with the investigation of stiffness, strength, toughness and fracture properties of bone tissue. In the recent literature on bone biology the mechanical properties of bone have been associated with the somewhat non-quantifiable term “bone quality” which includes the combination of bone geometry, bone material properties, and bone microstructure. One of the difficulties in applying engineering methodology to assess the mechanical properties of bone is the fact that bone represents a complex material, composed of several different phases including hydroxyapatite, collagen, and non-collagenous compounds, as well as pores. For complex materials, the important step in developing material models is to address the question of how different material phases, such as hydroxyapatite and collagen in bone interact with each other. Such questions can be elegantly addressed within the framework of continuum micromechanics. Using this approach, it was found that mineralized tissues, including bones, at an observation scale of microns, act as open isotropic hydroxyapatite crystal foams which are reinforced unidirectionally by crosslinks between collagen and hydroxyapatite. Based on the information about the relative fractions of mineral and collagen in different bones of different species, the model was able to predict the structural stiffness tensor of different mineralized tissues. In [38] the authors applied this approach to study the diversity of elastic properties of trabecular and cortical bone, and found that within the framework of the model, the elastic properties of different bones are determined by the relative fraction of hydroxyapatite, collagen and water, which themselves were assumed to exhibit only tissue-independent properties.

Another biomechanical issue is related to the ability of bone tissue to adapt to mechanical loading. According to mechanostat theory, bone responds to changes in mechanical loading by appropriately adapting its mass/volume to the mechanical environment. We know that the bone microstructure does not represent random orientations of the rod- and plate-like trabeculae, but that their alignment is very well oriented to withstand the forces of daily loading. According to the theory, bone will be formed in regions with high mechanical strains and removed from unloaded bone structures, hence guiding the tissue structure towards an optimal form that ensures a homogeneous stress distribution. The task of finding an optimal structure based on a given loading scenario is a classical problem of structural optimization, which civil and mechanical engineers have dealt with since the 1970s. The mechanical stimulus that drives bone tissue adaptation is dependent on the large number of muscle and joint reaction forces that change during different physical activities and are different from one person to the other. There is no simple non-invasive way for in vivo measurement of musculoskeletal forces and their distribution as it is in civil or mechanical engineering problems.

Different methods of mechanics are used to elucidate problems of bone modeling. The continuum damage mechanics and theory of crack propagation modeling could be used to explain the osteocyte signal reduction due to microcracks in bone structure [39, 40]. The authors in [40] have used a combined continuum damage mechanics and finite element approach. They have used a preliminary study proposed to simulate the fatigue behavior of cancellous bone based on the assumption that the fatigue behavior of trabecular bone is similar to that of cortical bone. Thus, a bone damage resorption FE model based on the disruption of the inhibitory signal transmitted between osteocytes in bone due to damage accumulation was developed and discussed.

A strain-based stimulus function coupled to a damage-dependent spatial function was proposed to represent the connection between two osteocytes embedded in bone tissue. The signal was transmitted to the bone surface to activate bone resorption. The proposed model was based on the idea that the osteocyte signal reduction is not related to the reduction of the stimulus sensed locally by osteocytes due to damage, but to the difficulties for the signal traveling along a disrupted area due to microcracks that can destroy connections of the intercellular network between osteocytes and bone-lining cells. Study [39] confirms that although linear elastic fracture mechanics is often used in studying the fracture toughness of bone, it may underestimate how tough bone is - since it does not account for the energy spent on plastic deformation. The J integral, a parameter that quantifies both the energies consumed in the elastic and plastic deformations, is presented to accurately describe the toughness of cortical bone. The energy spent in the plastic deformation of the longitudinal fractured and transverse fractured bovine specimens was found to be about 4 times the one spent in elastic deformation. Bone, with its elaborate hierarchical assembly, high amount of organic matter, and water-assisted bonding, was shown to absorb a great amount of energy in plastic deformation before fracture. Therefore, it was suggested in [39] that the J integral method is a better technique in estimating bone toughness for including both the elastic and plastic contributions. Nevertheless, study [30] concluded that prediction of the failure of bone could be further improved, and obtained more directly by describing bone's post-yield, nonlinear behavior. When analyzing the nonlinear properties of bone tissue experimentally, results from four-point bending tests indicate ductile failure modes involving microcrack damage combined with a plasticity component originating from the collagen fibers. Data from such experiments have been incorporated into a model's constitutive law [41] and have been used to define a failure criterion, resulting in nonlinear μFE models. The most frequently used nonlinear material model is a bilinear elastic–plastic model with different Young's moduli for tension and compression, combined with a reduction of the elastic modulus if strains exceed a previously defined yield strain.

The computation time of the nonlinear models was a major concern and limited the size of the analyzed region, as they took about 10 times longer (about 24 h per sample) than the linear simulations (about 2.5 h per sample) on roughly comparable computing clusters. In addition to the bilinear elastic–plastic model, there are more complex nonlinear models, assuming finite-plasticity, strain-rate dependent elastic–plastic behavior or a perfect damage model [41]. While they are typically very versatile and closely match the findings from mechanical tests of the bone ultrastructure, they are often computationally even more expensive. Furthermore, some models have not been yet validated and the determination of required parameters needs further investigation. While current nonlinear models can describe ductile, plastic material behaviors, some experimental observations at micro and nanoscales are yet to be included. Toughening effects due to ligament bridging of microcracks and the role of heterogeneity at the nanoscale are more difficult to model in a constitutive law, as they are intrinsically stochastic, and little is understood about their effects. Simulating the dynamic behavior of bone at the ultrastructural level is even more challenging, as the growth rates of microcracks must be assessed and translated into viscous properties. Furthermore, there is an indication that failure can only be predicted when nonlinear geometric behavior due to large displacements such as buckling and bending of trabeculae is considered.

Poroelasticity is a well-developed theory for the interaction of fluid and solid phases of a fluid-saturated porous medium. It is widely used in geomechanics and has been applied

σ_{ij}, the pore pressure p, the strain in the solid phase ε_{ij}, and the variation in (dimensionless) fluid content ζ. The variation in fluid content ζ is the variation of the fluid volume per unit volume of the porous material due to diffusive fluid mass transport. In the theory of isotropic poroelasticity constitutive stress-strain relations are:

$$\sigma_{ij} + \alpha p \delta_{ij} = 2G\varepsilon_{ij} + \left(\frac{2G\nu}{1-2\nu}\right)\varepsilon_{kk}\delta_{ij} \tag{4}$$

where G and ν are the drained isotropic elastic constants, the shear modulus and the Poisson's ratio of the material, respectively, α is the ratio of the fluid volume gained (or lost) in a material element due to the change of that element volume when loaded under the drained condition, and B is called the compressibility coefficient or Skempton pore pressure coefficient. The relation between the dimensionless fluid content ζ and the stress involves the same parameters:

$$2G\zeta = \alpha\left(\frac{1-2\nu}{1+\nu}\right)\left(\sigma_{kk} + \frac{3p}{B}\right) \tag{5}$$

Coefficients B and α represent aspects of the structural response associated with both the solid and the fluid, α is the ratio of the fluid volume gained (or lost) in a material element due to the volume change of that element when loaded under the drained condition, and ν is a measure of the relative compressibility of the fluid and solid phases. For anisotropic interpretation, the Skempton tensor is $B_{ij} = K_c\left(C^d_{ijqq} - C^m_{ijqq}\right)$, K_c is the composite bulk modulus [42], C^d_{ijqq} and C^m_{ijqq} are interpreted below.

The constitutive equations of poroelasticity, Eq. (4), are completed by the addition of Darcy's law, Eq. (9), to predict flow of fluid through pores in bone. The results of [44] suggest that water content in bone tissue dictates the bulk behavior of bone by altering the interaction between mineral crystals and their surrounding matrix.

Significant differences were observed in the bulk mechanical properties of bone between wet and dry specimens in different loading modes (compression vs. tension). Dry bone specimens were stronger and stiffer than wet bone specimens (Tab. 2) and showed

little post-yield deformation. On the other hand, wet bone specimens exhibited appreciable plastic deformation and failed at much higher strain levels. In addition, considerable differences in mechanical behavior of bone were also observed between tension and compression, showing that the post-yield behavior of wet bone specimens demonstrated a strain hardening effect in tension, but a strain softening effect in compression. Moreover, wet bone specimens showed a greater failure strain in compression than in tension (Table 2).

Table 2. Bulk mechanical properties of bone under wet and dry conditions in tension and compression [44].

	Tension		Compression	
	wet	dry	wet	dry
Elastic modulus E (GPa)	18.6±1.2	24.8±0.7	11.2±1.3	17.7±3.4
Ultimate strength (MPa)	87.6±6.4	127±3.4	106.8±18.8	245±31.5
Failure strain (%)	1.3±0.3	0.6±0.02	16.4±0.91	1.5±0.40

Table.3 Summary of poroelastic constants

Property (units if any)	Cowin, 1999	Steck et al., 2003	Colloca et al., 2014
G_s (GPa) shear modulus of solid	5.5	$G_{longl} = 3.6$, $G_{trans} = 3.3$	
ν drained Poisson's ratio	0.32		
ν_s Poisson's ratio of solid	0.325	0.38 (0.41)	
ν_u undrained Poisson's ratio	0.33		
K (GPa)-drained bulk modulus	12		
K_u (GPa)-undrained bulk modulus	13		
K_s (GPa)-bulk modulus of solid	13.92		13.3
B-compressibility coefficient	0.4		
α -effective stress coefficient	0.14		
E_s (GPa)- Young's modulus of the solid	14.58	$E_{longl} = 17$, $E_{trans} = 11.5$	$E_{longl} = 18$, $E_{trans} = 9$
k (m^2) -specific permeability	$1.5 \cdot 10^{-20}$	$k_{periosteal} = 10^{-15}$ $k_{endosteal} = 2*10^{-12}$	
c x10^{-6} (m^2 s^{-1}) pore fluid pressure diffusion coefficient	0.51		

The retrospective article [45] describes the work on multiscale mechanobiology in context of bone engineering. They have used biosystems engineering, computational modeling and actual experimental approaches to understand bone physiology, in health and disease, and across time (in utero, postnatal growth, maturity, aging and death, as well as evolution) and length scales (a single bone such as the femur, in m; a sample of bone tissue, in mm to cm; a cell and its local environment, in mm; down to the length scale of the cell's own skeleton, the cytoskeleton, in nm). Firstly, they introduced the concept of flow in bone and the three calibers of porosity, matrix, pericellular and vascular porosities, where the

fluid flows. Then they described, in the context of organ–tissue, tissue–cell and cell–molecule length scales, both multiscale computational models and experimental methods to predict flows in bone and to understand the flow of fluid as a means to deliver chemical and mechanical cues in bone. Addressing a number of studies [45] in the context of multiple length and time scales, they referred the importance of appropriate boundary conditions for site specific material parameters, permeability measures and even discussed micro-nano-anatomically correct geometries in the context of model predictions and their value for understanding multiscale mechanobiology of bone. Theoretical framework for study of the interplay between mechanics and transport in bone [45], with governing equations could be presented on a following path:

1a) Theory of Poroelasticity to predict flow in elastic, fluid-filled substrate.

The goal of idealizing bone as an elastic matrix using linear elastic equations (continuum) of Hooke`s law is to predict stress, deformation behavior of structure:

$$\sigma_{ij} = C_{ijkl}\varepsilon_{kl}, \text{ for } i,j,k,l = 1,2,3 \tag{6}$$

where σ_{ij} is the stress second-order tensor, and ε_{ij} is the strain second-order tensor related with displacement u_i as: $\varepsilon_{ij} = \partial u_i/\partial x_j$

The fourth-order tensor C_{ijkl} is a linear map between second-order tensors represented by a matrix of 3×3×3×3 = 81 real numbers, usually called the stiffness tensor or elasticity tensor. In fact, the bone matrix is characterized by a transversely isotropic elasticity tensor and modeled as mineral foam of hydroxyapatite which is "reinforced" predominantly in the longitudinal direction by collagen fibrils, while the transverse stiffness is mainly governed by the mineral concentration. Relevant values for this tensor were introduced in [46] where the average tissue elasticity properties were successfully identified through a coupled approach comprising 10 MHz pulse transmission ultrasound with universal rules governing the composition and the hierarchical mechanical functioning of mineralized tissues, resulting in the following stiffness tensor of extracellular bone tissue:

$$C_{ijkl}^{adult}[GPa] = \begin{pmatrix} c_{1111} & c_{1122} & c_{1133} & 0 & 0 & 0 \\ c_{2211} & c_{2222} & c_{2233} & 0 & 0 & 0 \\ c_{3311} & c_{3322} & c_{33334} & 0 & 0 & 0 \\ 0 & 0 & 0 & 2c_{2323} & 0 & 0 \\ 0 & 0 & 0 & 0 & 2c_{1313} & 0 \\ 0 & 0 & 0 & 0 & 0 & 2c_{1212} \end{pmatrix} = \begin{pmatrix} 12.7 & 6.2 & 6.4 & 0 & 0 & 0 \\ 6.2 & 12.7 & 6.4 & 0 & 0 & 0 \\ 6.4 & 6.4 & 20.2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 7.9 & 0 & 0 \\ 0 & 0 & 0 & 0 & 7.9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 6.5 \end{pmatrix}$$

Although this composition is rather constant in healthy adults, it is known to vary during development and with diseases, e.g. osteogenesis imperfecta. This variation stems from a variation in the bone tissue composition, i.e. from its mineral, collagen, and water contents [36, 46]. The agreement of $c_{1111} = c_{2222}$; $c_{2233} = c_{1133}$ and $c_{2323} = c_{1313}$ indicates the approximate transverse isotropy of the considered human femur specimens, and the micromechanics approaches given by [36] represent good agreement with these symmetries. The authors have studied the three concepts of a micromechanics of bone: the first one was 'collagen–reinforced mineral matrix', where the ultra-structure was considered as mineral foam (with water and non-collagenous organic material in the inter-

crystalline space), serving as a matrix in which the collagen was included; the second was more realistic representations of the organization of collagen within the mineral foam as an interpenetrating network of hydroxyapatite crystals and collagen molecules. Since there are mineral crystals also within the collagen fibrils, they have considered interactions between single collagen molecules and mineral crystals and the third was the combination of both concepts, where mineralized fibrils (mineral–collagen networks) are embedded in a 'pure' mineral foam (without collagen).

The extended version of the constitutive Eq. (6) is the equation used by [41] that includes the pore pressure, thus:

$$\sigma_{ij} = C^{d}_{ijkl}\varepsilon_{kl} + \left(C^{d}_{ijqq} - C^{m}_{ijqq}\right)p \tag{7}$$

Where the drained, the undrained and the matrix elastic compliance constants, denoted by C^{d}_{ijkl}, C^{u}_{ijkl} and C^{m}_{ijkl}, respectively, were developed and presented in Ref. [41] for anisotropic and orthotropic property of the bone material.

Bone fluid interaction is modeled as pores filled with viscous fluid to predict flow velocity $v(x,t)$ with Navier-Stokes equation representing the conservation of momentum, mass and energy:

$$\underbrace{\rho\left[\frac{\partial v}{\partial t}\right.}_{\text{Unsteady acceleration}} \underbrace{+(v*\nabla)v\Big]}_{\text{Convective acceleration}} = \underbrace{-\nabla p}_{\text{Pressure gradient}} \underbrace{+\mu\nabla^{2}v}_{\text{Viscous forces}} \underbrace{+f}_{\text{other body forces}} \tag{8}$$

where ρ is the density, v is the flow velocity, ∇ is the delta operator, p is the pressure, f are the body forces e.g. gravity g

1b) Darcy`s Law to predict flow of fluid through pores in bone:

$$Q = \frac{-\kappa A}{\mu}\left[\frac{p_B - p_A}{L}\right] = \frac{-\kappa}{\mu}\nabla p \tag{9}$$

The total discharge (volumetric flow rate), Q (units of volume per time, e.g., m^3/s) is equal to the product of the intrinsic permeability of the medium, κ (m^2), the cross-sectional area to flow, A (m^2), and the total pressure drop ($p_B - p_A$), (Pa), all divided by the viscosity, μ (Pa·s) and the length (L) over which the pressure drop is taking place. The negative sign is needed because fluid flows from high pressure to low pressure.

2) Diffusion-Convection equation for transport to predict the concentration of solutes in space and time t:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x_i}\left(D_i\frac{\partial C}{\partial x_i} - u_i C\right) + S - KC \tag{10}$$

where $C(x_i,t)$ is the concentration, D_i the diffusion coefficient, u_i the velocity vector component, K the reaction rate and S describes the sources or sinks of the quantity C. For a biological species, $S > 0$ means that a biological reaction is creating more of the species, and $S < 0$ means that a reaction is destroying the species.

An overview of the theory of poroelastic materials can be obtained by considering it as a system of 20 equations in 20 scalar unknowns. The 20 scalar unknowns are the six components of the stress tensor σ_{ij}, the fluid pressure p, the fluid content C, the six components of the strain tensor ε_{ij}, the three components of the displacement vector u_i and the three components of the fluid mass flux vector $Q = [q_i]$. The 10 scalar constitutive equations of poroelasticity are the three scalar equations of Darcy`s law, Eq. (9), the six scalar equations of the strain–stress–pore pressure relation, Eqs. (8) or (6), and the one scalar equation of the fluid content–stress–pore pressure relation, Eq. (7). The other 10 scalar equations that make up the set of 20 equations are the six scalar equations of strain–displacement relations, the three scalar equations of the conservation of linear momentum (also called the stress equations of motion) and the scalar equation of mass conservation. $\partial\zeta/\partial t = q_{k,k} = \rho$, q_k is the fluid mass flow rate in the x_k direction and ρ is the source density, encompassed in the conservation of momentum, mass and energy Eq. (10).

There are both analytical and numerical methods for the solution of poroelastic boundary value problems. These include analytical methods (displacement potentials, method of singularities) and computational methods (finite element and boundary element). Poroelastic FE models provide a platform to understand the interplay between mechanical loading and molecular transport in bone. Taking a two-step approach, *1a* and *1b*, stress and deformation behavior of the bone's solid structure are predicted. Then flow is predicted in the idealized elastic substrate using Darcy's law for fluid flow through pores. To account for the spatial-temporal transport of solutes in the bone fluid, the flow through the micro and nanochannels of bone was predicted [45] using the Navier-Stokes equations, assuming that inertial effects could be ignored. Finally, the diffusion convection transport equation was applied by [47] to predict the concentration of solutes in space and time. FE approaches are also very useful for understanding the relative importance of boundary conditions for flow in bone, where variables can be changed parametrically to predict which boundary conditions will exert the greatest effects on flow behavior [45, 47].

Experimental measurements of actual flow through bone or hindrance to flow serve to validate the theoretical prediction and/or to reject inaccurate models. The models were able to predict and prove among others that the loading mode (pure compression, tension, bending and torsion) exerts a significant effect on the distribution of pore pressures in bone. It was also referred that a hurdle in understanding bone mechano-chemical-transduction was the order of magnitude discrepancy in shear stress magnitudes needed to trigger changes in the baseline of bone cell activity in vitro compared to those calculated for an organ or tissue during physiological loading. Hence, to better understand the nature of cell-scale mechanical signals at a time when imaging resolution was inadequate to observe flow directly, they have developed an additional model to calculate flow in the pericellular space of an atomically correct periosteocytic process flow channels. Studying the effect of model geometry at cell-sub-cell length scale, they have gained an acute appreciation for the balance between building models that are efficient (with respect to computing time) and models that are efficacious. This insight underscored the importance of testing idealizations as part of model validation!

To sum up, depending on the system of interest, bone can be modeled in a variety of ways. Key elements that are common to all models include the function that is to be replaced (which defines the goal of the model), the control volume (an abstract representation of the highly idealized model that aids in reducing the system to one with a

finite, determinate set of variables), governing equations that provide mathematical predictions of model behavior in response to changes in system variables, boundary and initial conditions. The size and boundaries of the model, system or control volume are determined by a variety of factors, including the tissue type and component to be modeled, as well as the length and time scale to be addressed in the system of interest. Depending on the function to be addressed, the time scale of the system may vary from fractions of a second, as in cell signaling, to periods as a month, the time it takes osteoclasts to resorb a cavity and osteoblasts to fill it in with fresh osteoid, to months and years, the time it may take a bone to regain its prior mechanical strength after fracture.

At the end, we can conclude even though mentioned models are generally well developed, there is a lack of well-developed mechanistic models that establish all necessary links with biology. It is interesting to couple the effects of mechanical stimuli with those of biological stimuli. The signaling pathways and the contributions of hormones and growth factors are also of importance. The coupling of bone remodeling and calcium homeostasis should also be considered. There are recent attempts to address these shortcomings and combine system biology approaches with multi-scale mechanical models [48]. However, the problem of developing an adequate mechanistic model of bone tissue adaptation remains open, but we all agree that current and future advances in technology, in particular imaging technology, will aid researchers in pushing the envelope of discovery by enabling in situ measurement of bone material properties (e.g., flow fields and hydraulic permeability, porosity, anisotropy) at multiple length scales.

4. CONCLUSION AND FUTURE DIRECTIONS

In the late 20th and the first decades of the 21st century, the large-scale modern biological achievements were shaped by advances in technologies, material and computational science and all together have found their application in medicine. The current maturity of the field of mathematical modeling of bone tissue can be gauged by the number of review articles addressing the topic in the past thirty years [1, 2, 11, 13, 45, 48] and perspectives for the future development of the field appear just as bright. On the one hand, we have witnessed the emergence of a whole new class of bio-tech studies that are deeply immersed in mathematical and biological science. On the other hand, we are still faced with numerous unclear problems, some of which have been stressed previously. However, the nature of the connection between medical and biological science and mathematics in recent research has begun to change in important ways. The joint efforts of mathematics and biology are becoming more useful in medicine relevant to the life quality improvement. Most outstanding issues remain linked with ambiguities of mathematical results and their discrepancy with experimental results in the modeling of biological tissues. This, of course, opens the next avenues for both improvements in mathematical methods as well as in biological models of tissues, especially bone tissue, but the solutions are squarely in the multidisciplinary approaches of science.

Science is defined by its predictive power. A mature science, such as mathematics, is one where the principles, cause-effect theories, and supporting empirical evidence have accumulated to such an extent that predictions can be made. Thus, mathematical modeling is a superior tool for a) examining whether a complex biological model can describe the observed data; b) identifying the most important aspects of a biological model; c)

predicting an experimental outcome consistent with the biological model; d) augmenting data analysis and e) examining potential changes in the biological model when experimental results differ from the prediction that can account for the difference. In less mature sciences, such as biomechanics, biomathematics or tissue engineering, predictive power is lacking. Knowledge of the underlying cause-effect relationships may be absent or only dimly understood, due to the lack of available parameters to be measured. In the area where the underlying science is more mature, knowledge is often modular. With deeper understanding comes the knowledge about fundamental constituent parts and how those interact. In less mature fields of knowledge, the situation is more complex. There may be a sense of different "pieces", but their boundaries may not be clearly defined, and interactions may not be well understood. Mathematical modeling comes to the forefront with the already proven track record of augmenting experimental analysis, providing new information about the potential mechanisms, and suggesting new hypotheses that allow for a deeper understanding of underlying complexities.

The possibility of in-silico experiments provides the technique to check the proposed models and their approaches. The learning from the failures of these experiments is also needed. Disagreement of what we got and what we expected from the models gives room for improvement, and the failures are the norm, not exceptions. The known pales in comparison to what remains to be discovered. New hypotheses and new findings must be constantly evaluated. Knowing the right answer is far less important than knowing the right experiment to run, which can assist in directing biological experimentation. A unique bridge between biological models and experimental validation, with mathematical modeling and in-silico experiments, is an integral part of modern research in bone tissue. The future advancement of bone biology research will strongly rely on how well experimental and theoretical groups can communicate and collaborate with each other.

Finally, it is necessary to emphasize the role of results visibility, availability and publishing that create the state of the art in contemporary of the field. A scientist who has spent decades researching a particular topic will have accumulated a lot of knowledge about their specialty. Very often, what individual scientists know about the underlying biology of a disease cannot be reduced to precise rules, so data from experiments are subjected to different interpretations. Moreover, what constitutes a strong signal for one researcher may give another pause. Sharing experiences over extended periods of time is important and presentation of results in the contemporary literature is necessary. We hope that this review gives some guidance on how theoretical tools such as mathematical modeling can be used in bone biology research.

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