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Multiphysics Modeling for Bone Remodeling Simulation: A Methodological Framework

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Abstract: In the present study an object oriented integrative modeling methodology is proposed for the construction of synthetic, computational models of bone-bone environment system that allow its simulation under *in vivo* conditions. The analytical mathematical approach to model and study ordinary materials will be outlined, indicating its limitations when dealing with biomaterials in physiological environments. The proposed object oriented integrative modeling will be explained emphasizing its advantages and possibilities. Finally, the architecture of the "*in vivo*" modeling and simulation software framework is shown, described and explained indicating further work based on this framework.

Key words: Bone remodeling, bone tissue, multiphysics modeling, multiphysics simulation, integrative modeling, object oriented modeling

INTRODUCTION

Tissue engineering is a strategic and dynamic area of research and technological development because it is the organization level where the cell dynamics and physical processes mutually interact to give as result the physiological specificity of organs. Tissue engineering and regenerative medicine constitute two of the main targets in biomedical science research and biotechnology development.

Despite of major advances in bone and skin engineering obtained as the result of in vitro experimentation and using animal models, it has not been possible to standardize both the rapeutic approaches and biomaterials production protocols as a consequence of the complexity of their target biological systems such as bone and skin whose behavior and responses are strongly determined by the simultaneous and concurrent physical, chemical and biological phenomena (Rodrigues *et al*., 2011).

In the present study, it will be discussed the possibilities and limitations of the analytical mathematical approach when used to model and prognostic the performance of a biomaterial implemented at *in vivo* conditions to stimulate and guide regenerative processes. Computer based object oriented integrative modeling is presented as the best alternative and the architecture of the "*in vivo*" modeling and simulation software framework is presented, justified and explained.In addition, further work based on the use of "*in vivo*" will be reported.

Complex system structure of the bone-bone environment system: Bone-bone environment system is a complex system. Although, there is no complete agreement on the definition of a "complex system" in the scientific community, there are some definitions that allow us to derive their defining characteristics and behaviors.

The advances in complex systems journal, a Q1/Q2 journal from world scientific publishing Co. defines a complex system as "the latter (complex systems)" are seen as systems comprised of multiple interacting components or agents. Non-linear feedback processes, stochastic influences, specific conditions for the supply of energy, matter or information may lead to the emergence of new system qualities on the macroscopic scale that cannot be reduced to the dynamics of the agents. Quantitative approaches to the dynamics of complex systems have to consider a broad range of concepts from analytical tools, statistical methods and computer simulations to distributed problem solving, learning and adaptation. This is an interdisciplinary enterprise (Corporation, 2017).

Simon (1995), one of the complexity theory pioneers, defines complex systems as: "a system that can be analyzed into many components having relatively many

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relations among them, so that the behavior of each component depends on the behavior of others". From the contemporary scientific perspective, a complex system such as the earth weather the global financial system, a city, a human organ is a system which presents the following features.

Multiplicity and diversity of components: The system is composed by a multiplicity of diverse object classes including subsystems and autonomous (sometimes intelligent) agents.

Hierarchy: The system is hierarchically structured and the different levels in its hierarchy may be determined by composition relations ("is component of") and/or behavior relations ("its behavior is affected by").

Decomposability, nonlinearity: The system cannot be understood by a direct process of analysis and synthesis because many of its identity features and behaviors emerge from the connectivity between components (synergy). In the colloquial language this is called "non-linearity": the system's features and behaviors cannot be obtained from the addition (superposition) of the individual features and behaviors of its components.

Emergent events and phenomena: Global system behavior is determined or strongly altered by events and processes occurring at basic composition levels (atomic, molecular, cellular, individual, local micro-weather, etc.) possibly being these emergent processes the roots of randomness.

Contingency and dynamical bifurcation: A dynamical bifurcation occurs when a small perturbation switches the dynamical behavior of the system to a radically different one. As is conceived by Frauenfelder and Wolynes (1994) "contingency" is "the dependence of the present state on the vagaries of its past history". Bifurcations and contingency are closely related giving as a result the impossibility to prepare a system in such way that follow a predetermined behavior: uncontrollability without feedback.

In the case of bone tissue and its environment, the studied system is composed by other complex systems: cell populations their extra cellular matrix and external stimulus such as mechanical stress and strain, thermal processes, chemical reactions and the presence of microorganisms such as bacteria and fungi (Rodrigues *et al*., 2011).

Given the fact that the process analysis-synthesis is unavoidablein the human knowledge construction process, the alternative for complex systems is the contemporarily so-called process of "integrative modeling and simulation" in which the system's components are modeled in isolation but integrated into a hypothetical system by creating scenarios from hypothesis about connections whose validity is verified by contrasting simulation experiment results with observed data from the real system (Sayama, 2015).

When dealing with a complex material such as biological tissue or a smart material, the macroscopic or global superposition of the knowledge concerning each component or class of components is inadequate to explain their most outstanding features: autopoiesis, self-regulation and self-adaptation. These features are the result of the interplay between emergent phenomena produced by a diversity of component objects, some of them autonomous agents which form part of a hierarchically organized structure: a complex system (Sayama, 2015).

As a result of their unique features: diversity of components, emergence and contingency, complex systems cannot be globally modeled by an enumerable set of deterministic laws expressed by mathematical functions, therefore, the idea of a single set of governing equations (algebraic, differential, integral or a combination of them) is not satisfactory for complex systems modeling (Fritzson, 2014).

In the early stage of complex systems science, statistical physics has been used as an alternative. Given that the probability function associated to the states of a system is relevant for its mathematical modeling, ergodicity is a fundamental hypothesis in statistical physics as the partition function (essential to the construction of probability density function) relies in the correspondence between the probability of finding the system in a given state and its associated energy level (Thirring, 1996).

In the case of a system having autonomous agents (such as biological cells) between its components their autonomyproduces an ergodicity breaking making inappropriate the hypothesis that they may be considered as identical particles and consequently to associate them a partition function.

As an example, in the case of biological cells, their autonomy stems in the fact that each cell have a redundant set of "programs", its genotype which codifies a corresponding set of possible adaptation, regulation or response behaviors. Depending on the values of many factors: physical and chemical conditions globally called "epigenome", the cell will execute just one program which will trigger the production of one specific protein and consequently, realizing just one specific behavior. Given this non-deterministic nature of complex systems (even in

the probabilistic sense), there isn't a single response to each of the many research questions involved in a complex problem "solution" (management) or a complex product design such as a smart material including biomaterials or biological materials. This diversity of possible ways of actions forces us to design strategies based upon the prognostic of a complex system behavior in response to a multiplicity of inputs and scenarios.

MATERIALS AND METHODS

Mathematical and computational modeling of the bone-environment system dynamics: In the research field of bone tissue remodeling, a high quantity and diversity of scientific papers continually reports advances in mathematical modeling of specific biological and physical processes each of them occurring at a particular space scale and having as focus a specific disciplinary perspective: bioinformatics, biochemistry, mechanobiology, transport phenomena, etc., however, given the fact that all these aspects of bone remodeling are strongly interdependent without a holistic theory or integrated computational framework, it is impossible to aboard common emergent events which trigger global physiological processes impeding accurate predictions and prognostics leading to successful therapies, materials and devices (Rodrigues *et al*., 2011).

In addition to the high specificity of available mathematical and computational models and consequently, its rigidity and low capacity of adaptation to real multiscale and multi-phenomena scenarios, the experimental studies are inspired and designed mainly by surficial (top level of organization) observations quantified by macroscopic variables leading in many cases to cognitive redundancy andunder supported decisions connected to high risk.

These particular phenomenon models are based in a diversity of heterogeneous modeling and simulation paradigms: finite element method (Vivas *et al*., 2015; Mishnaevsky *et al*., 2014) lattice Boltzmann method (Shu *et al*., 2005) theory of chaos and dynamical systems (Hirsch *et al*., 2004) Forrester's dynamics of systems (Shiflet and Shiflet, 2014) mathematical analysis, topology, statistical physics, statistical and data based empirical models and artificial intelligence methods such as knowledge engineering, cellular automata, neural networks, genetic algorithms, fuzzy logic, etc.

RESULTS AND DISCUSSION

***In vivo* a software framework for the hybrid integrative modeling of the bone-environment system:** The deep epistemological impact of object oriented methods and their suitability for the modeling of complex systems has been overshadowed by the misleading idea that they are the same thing as object oriented programming, OOP. Despite the importance of OOP as a paradigm for not "reinventing the wheel" in software engineering and its contributions to parallel programming, OOP may be surpassed as programming methodology by other methodologies such as functional programming or other hybrid ones. In opposition to OOP as a tool suited for machine understanding and information processing efficiency, object oriented methods, OOM such as object oriented analysis and design are ideal for human understandability, communication and mainly for transdisciplinary research knowledge synthesis.

In the transdisciplinary field of biomedical engineering and in particular, in tissue engineering, object oriented methods provide language, methods and tools for the task of integrative modeling.

As an example, in the remaining part of this study the architecture of the "*in vivo*" modeling and simulation software framework, a development project in execution, will be displayed and explained using its UML class diagram (Dennis *et al*., 2015).

***In vivo* architecture:** The "*in vivo*" framework has been designed to facilitate the simulation of tissue growth and remodeling in the simultaneous presence of mechanical loading and transport phenomena. The system is hierarchically organized and at a first level of organization is composed by a "physiological system model", a "simulation engine" and a system of "input-output interfaces" as shows in Fig. 1.

Figure 2 shows the hierarchical structure of physiological model component. In the universe of discourse of the *in vivo* framework, the physiological system under study is conceived as the interaction between an integrated set of objects, globally called a "tissue" and its environment represented in the framework as a set of boundary conditions for the tissue.

In a first stage the framework is intended to simulate the basic phenomenology of the physics-biology interplay and not to serve as a clinical tool and for this reason, the macroscopic topology may be specified as a simple shape such as a cylinder or a rectangular prism. In more general situations, it will not be difficult to introduce a DICOM file as the descriptor of both, the macroscopic shape of the tissue under simulation and the initial microscopic distribution of solid, liquid and gas phases (Fernandez *et al*., 2015).

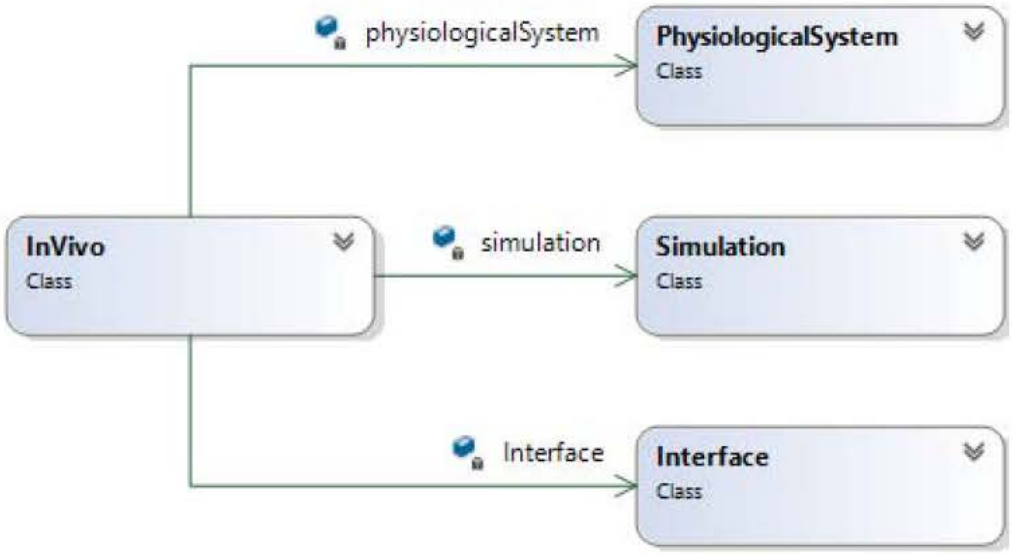

Fig. 1: System of input and output interface

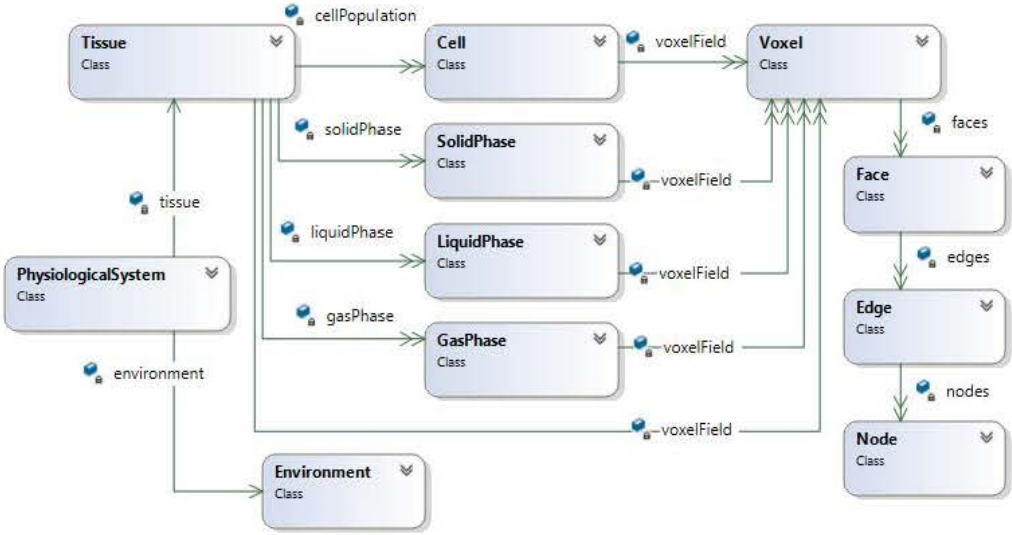

Fig. 2: Hierarchical structure of phyiological model

The spatial reference in the tissue model is attained by using a voxel field (Mishnaevsky, 2012; Mishnaevsky *et al*., 2014) which in the simpler case, corresponds to a cubic lattice where the size of a unit cell determines the resolution of the space discretization to be used by any of the implemented simulation engines: finite element, lattice boltzmann, particle based or monte carlo. At third level, the lowest structural level of the model, there is the voxel class and its components: face, edge and node classes.

As shown in Fig. 3a-d node class objects keep the information about position and shape, each edge object will give account of the mechanical state of the voxel which it belong face objects will allow to evaluate voxel shape and give the necessary information for visual rendering of the microscopic structure state and voxel class objects deal with fluid and thermal system's state. At the first level components of the tissue, second level for the physiological system are the objects belonging to the following subsystem classes.

A set of cell populations, Fig. 4 where each cell population is represented by a cell automata (Velasquez, 2014; Deutsch and Dormann, 2004). A given automaton occupies a contiguous set of voxels in the voxel

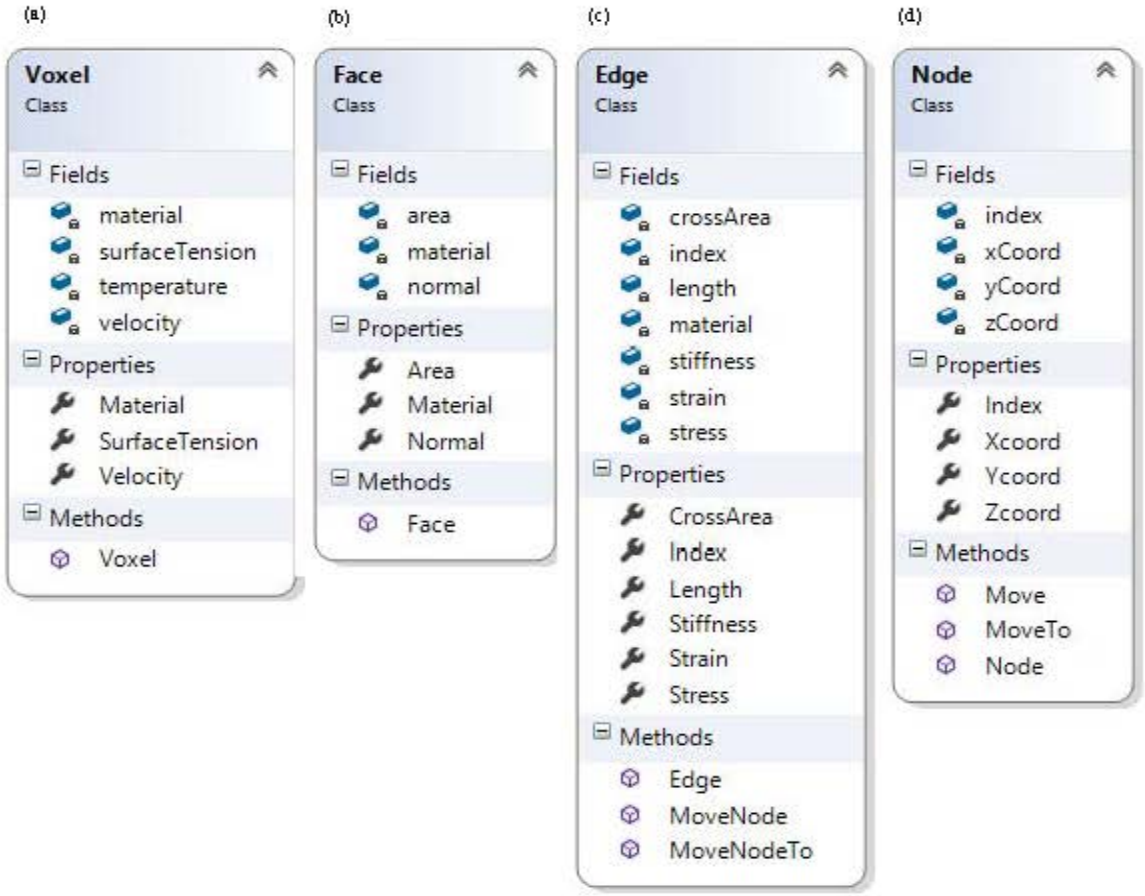

Fig. 3: Node class objects: a) voxel; b) face; c) edge and d) Node

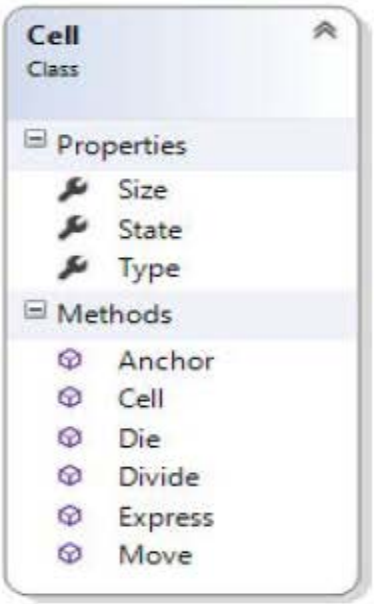

Fig. 4: Cell population

field representing a single cell whose type, fibroblast, osteocyte, osteoclast, osteoblast, stem cell is specified by an attribute variable and its fundamental behaviors will be determined by a small set of rules such as displacement, adherence, differentiation, division, death and expression. Figure 4 shows the single cell class structure.

The second level of organization in the physiological model corresponds to a set of solid phases composed by contiguous voxels as shown in Fig. 5a-c.

The voxel field in each material phase, be it solid, liquid or gas is just a subset of the main voxel field where each voxel is referenced by its index. In addition, the macroscopic states and dynamics of these material phases may be computed from the individual voxels at the microscopic scale.

The second component in the *in vivo* framework is the simulation subsystem, corresponding the "Simulation" class in the diagram, Fig. 6 have two components: an instance of the "Scenario" class where all the initial conditions and the tissue's boundary

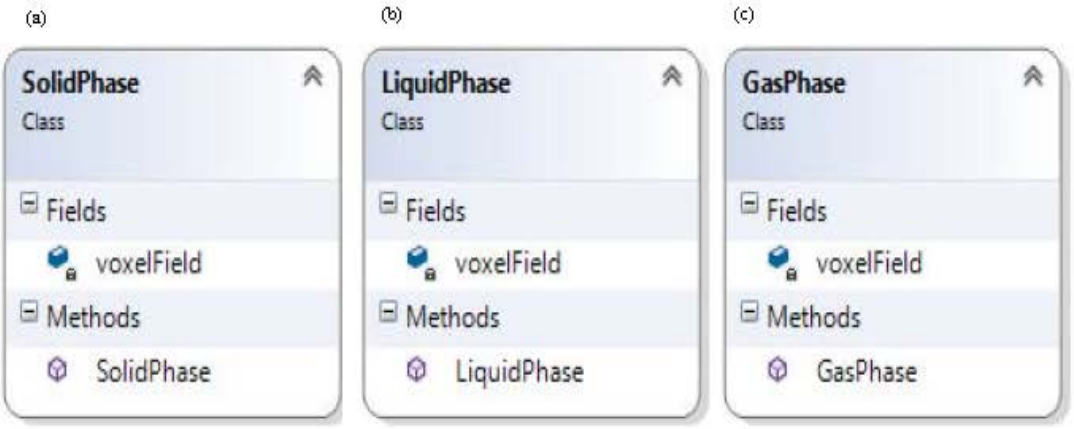

Fig. 5: The second level of organization in the physiological model: a) solid phase; b) liquid phase and c) gas phase

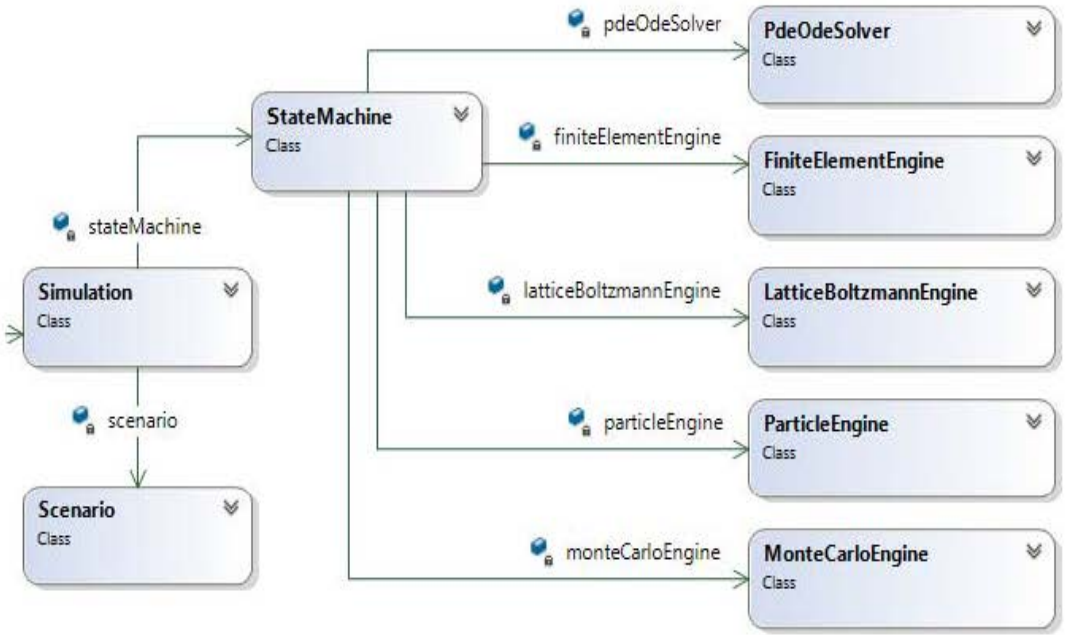

Fig. 6: The simulation subsystem

conditions, the "environment" are specified. Additionally, in the "Scenario" class, the space and time metrics is specified.

A set of state machines, each in charge of the generation of the solid, liquid and gas phases states and the states of the cell populations. Each state is computed by the corresponding "state machine engine" in a time step of the main time loop in a simulation trial.

The "PdeOdeSolver" takes in charge the generation of the dynamical states corresponding to those components obeying ordinary or partial differential equations. The "FiniteElemenEngine" instances compute the mechanical state for the solid phases at each time step. The "LatticeBoltzmannEngine" and "Particle Engine" engines allow the generation of the fluid phases states and finally, the "MonteCarloEngine" may act as a general stochastic events generator, especially for thermodynamics and gas phases.

Finally, a system of input-output interfaces (Fig. 7) will be implemented in order to request the user all the system's and scenario definition parameters and an output subsystem, the "Execute Experiment" class in the diagram will include all the resources to visualize in a controlled way the simulations output corresponding to scalar and vector fields, 3D visualizations and the generation of the necessary XY plots.

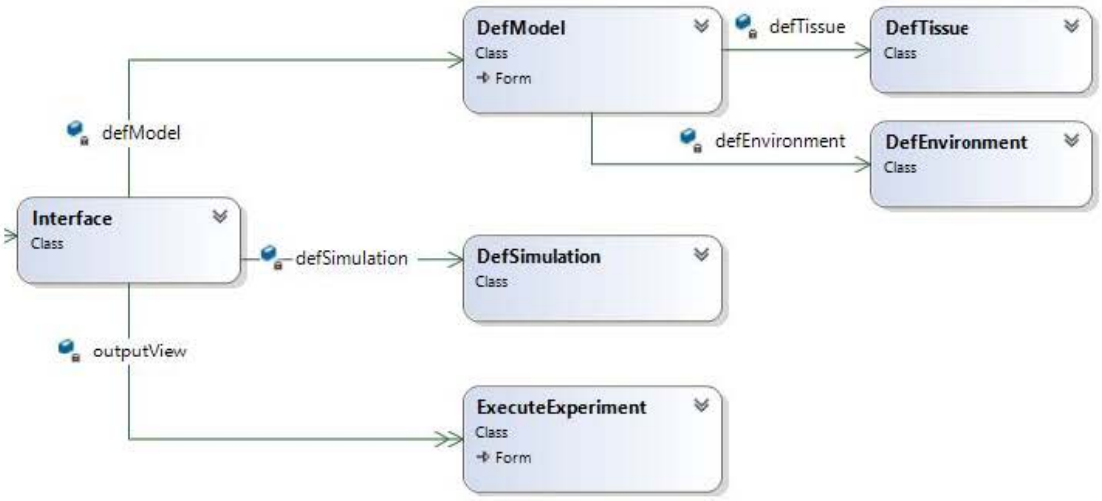

Fig. 7: The execution experiment

CONCLUSION

The complex system structure of the bone-bone environment system has been discussed. The heterogeneity and disconnected nature of the available knowledge: physical, chemical and biological about the hierarchical organization and interaction of bone-environment subsystem components was discussed.

It was explained and justified the impossibility to mathematically model the bone-environment interaction dynamics in order to explore and support strategies for bone regeneration and bone remodeling control.

A software framework for the hybrid integrative modeling of the bone-environment system that allow its multiphysics simulation was designed and explained. Further work strategies based on complex systems science concepts and complex systems engineering methods are proposed.

RECOMMENDATIONS

As a software engineering project, the next steps in the *in vivo* system life cycle are implementation, testing and maintenance. The implementation phase will be realized by the use of compatible software development tools such As visual studio, python and its many extensions and unity. Testing will be done by comparing results obtained by simulation using *in vivo* with results from a clinical study chosen from the related literature. Considering maintenance, it will be done thanks to the high modularity of object oriented methods: the *in vivo* system is designed to be an evolutionary platform which will allow the straightforward modification, change o addition of models an knowledge about any component of the bone-bone environment system.

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