Bone Remodelling: A Complex Automata-Based Model Running in BioShape

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Abstract. Bone remodelling, as many biological phenomena, is inherently multi-scale, i.e. it is characterised by interactions involving different scales at the same time. At this aim, we exploit the *Complex Automata* paradigm and the BioShape 3D spatial simulator respectively (i) for describing the bone remodelling process in terms of a 2-scale aggregation of *uniform Cellular Automata* coupled by a *well-established* composition pattern, and (ii) for executing them in a *uniform* and integrated way in terms of shapes equipped with perception and movement capabilities.

On the one hand, the proposed model confirms the high expressiveness degree of Complex Automata to describe multi-scale phenomena. On the other hand, the possibility of executing such a model in BioShape highlights the existence of a general mapping - from Complex Automata into the BioShape native modelling paradigm - also enforced by the fact that both approaches result to be suitable for handling different scales in a uniform way, for including spatial information and for bypassing inter-scale homogenization problems.

1 Introduction

Nowadays, it is possible to observe biological systems in great detail: with a light microscope one can distinguish the compartments of a human cell, and with an electron microscope one can even see very small details such as proteins. At the same time, models for describing and simulating biological systems have comparable resolution regimes and work on different spatial and temporal scales: in the microscopic approach, molecular dynamics and Monte Carlo methods describe systems at the level of atoms or proteins while, in the macroscopic regime, continuum-based simulations model complete biological assemblies (but do not describe any explicit molecular information). Actually, a characteristic of biological complexity is the *intimate connection* that exists between different length scales. For instance, subtle changes in molecular structure as a consequence of a single gene mutation can lead to catastrophic failure at the organ level, such as heart failure from re-entrant arrhythmias that lead to ventricular fibrillation. But information flows equally in the reverse direction: mechanoreceptors at the cell level sense the mechanical load on the musculoskeletal system and influence gene expression via signal transduction pathways.

S. Bandini et al. (Eds.): ACRI 2010, LNCS 6350, pp. 116–127, 2010.

1.1 A Case Study: The Bone Remodelling Process

Old bone is continuously replaced by new tissue. This ensures that the mechanical integrity of the bone is maintained, but it causes no global changes in morphology: Frost defined this as *remodelling* [1]. Such a phenomenon can be considered "multi-scale" (see Fig. 1) since macroscopic behaviour and microstructure strongly influence each other.

Bone remodelling at tissutal scale. Two macroscopically different bone tissue types are distinguished: the *cortical* one - which is a rather dense tissue although it is penetrated by blood vessels through a network of canaliculi - and the *trabecular* one - which is porous and primarily found near joint surfaces, at the end of long bones and within vertebrae.

On a macroscopic level, remodelling might be regulated by mechanical loading, allowing bone to adapt its structure in response to the mechanical demands. It is well-known that trabeculae tend to align with maximum stresses in many bones and greatly increase their load-carrying capacity without increasing mass, thus improving structural efficiency; mechanical stress also improves bone strength by influencing collagen alignment as new bone is being formed. Cortical bone tissue located in regions subject to predominantly tensile stresses has a higher percentage of collagen fibers aligned along the bone long axis. In regions of predominant compressive stresses, fibers are more likely to be aligned transverse to the long axis.

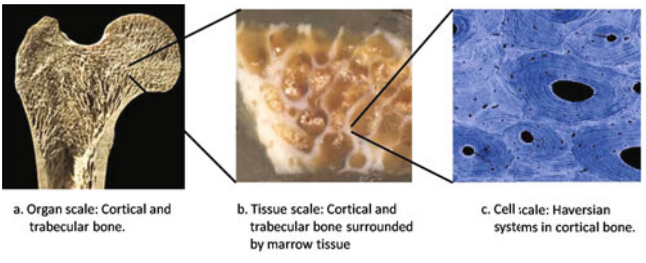

Fig. 1. Multiscale view of a human femur

Bone remodelling at cellular scale[1]**.** Two main kinds of cells, namely *osteoclasts* (O_c) and *osteoblasts* (O_b), closely collaborate in the remodelling process in what is called a *Basic Multicellular Unit* (BMU). The organization of the BMUs in cortical and trabecular bone differs, but these differences are mainly morphological rather than biological.

The remodelling process begins at a quiescent bone surface (either cortical or trabecular) with the appearance of O_cs, which attach to the bone tissue matrix, form a ruffled border, create an isolated microenvironment, acidify it and dissolve the organic and inorganic matrices of the bone.

Briefly after this resorptive process stops, O_bs appear at the same surface site, deposit osteoid and mineralize it. Some O_bs are encapsulated in the osteoid

[1] For a more detailed description, see `http://courses.washington.edu/bonephys/physremod.html`.

matrix and differentiate to *osteocytes* (O_y). Remaining O_bs continue to synthesize bone until they eventually stop and transform to quiescent *lining cells* (L_c) that completely cover the newly formed bone surface and connect with the O_ys in the bone matrix through a network of canaliculi.

1.2 Motivations and Contribution of the Paper

The need of a multi-scale modelling approach. Bone remodelling was always subject of extensive studies in many fields of research: much of this research is based on reduction - i.e. isolating the various components to unravel their individual behaviour - without taking into account how mechanical forces are translated to structural adaptation of the internal cellular architecture [2,3,4,5], while other approaches relate density changes in bone directly to local strain magnitudes, abstracting from the underlying cellular processes (i.e. morphology and metabolic activity) [6,7,8,9].

Being bone remodelling an inherently multi-scale process, it is reasonable to bet on multi-scale modelling approaches [10,11,12], i.e. modelling approaches linking phenomena, models and information between various scales. To support this conjecture, it suffices to consider that the actual knowledge about this biological process shows several gaps *at different resolution degrees*:

- *(Tissue level)* There are some questions as to whether the orientation of collagen fibers in bone occurs through functional adaptation as the bone is being remodelled or is under genetic influence during development.
- *(Cell level)* BMU existence indicates that a coupling mechanism must exist between formation and resorption (i.e. among O_bs and O_cs). However the nature of this coupling mechanism is not known.
- *(Cell-Tissue level)* It is not so clear how mechanical forces can be expressed in cell activity and whether they are enough to explain remodelling. The current concept is that the bone architecture is also controlled by local regulators and hormones (mainly insulin-like growth factors, cytokines interleukin-1, interleukin-6 and RANKL) and that both local mechanical and metabolic signals are detected from O_ys. Whether this is true remains to be proven.

Homogenization and uniformity. Indeed, a multi-scale model is not necessarily more "faithful" than a single-scale one only because it is multi-scale. It is well-known that a multi-scale model can be more or less "faithful" according to what "single-scale" models are taken into account (for each scale) and how they are "homogenized" (i.e. integrated). Homogenization is in fact a very delicate and complex task - when "single-scale" models are heterogeneous, as well as when the biological systems to model admit different homogenization techniques - which can lead to loss of information between scales. As a consequence, a high uniformity degree among "single-scale" components implies the possibility of defining well-established homogenization rules and increasing the "faithfulness" of a multi-scale model in the whole.

Space and geometry. It is also well-known that the possibility of expressing spatial information is another important element which can add "faithfulness" to a biological model (not only multi-scale).

Consider, for instance, the microtubules: not only they have a specific geometry, but their polarity arises from the geometry of their tubulin components. Cytoplasm (of even the simplest cell) and enzymes are another excellent examples. The first contains many distinct compartments, each with its own specific protein set; even within a single compartment, localization of molecules can be influenced in many different ways, such as by anchoring to structures like the plasma membrane or the cytoskeleton. The latter, acting in the same pathway, are often found co-localised; as the product of one reaction is the substrate for the next reaction along the pathway, this co-localisation increases substrate availability and concomitantly enhances catalytic activity, by giving rise to increased local concentration of substrates.

Contribution of the paper. On the basis of the above observations, we exploit at the same time *Complex Automata* (CxA) [13] paradigm and BioShape[2] [14] 3D spatial simulator: the first for defining cellular and tissutal scale of bone remodelling as *uniform Cellular Automata* (CA) and aggregating them by a well-established composition pattern (see Section 2), while the latter for simulating, in a *uniform* and integrated way, both CAs in terms of shapes, equipped with perception and movement capabilities (see Section 3).

In particular, we deliberately approximate the biological process taking into account only mechanical stimuli and ignoring metabolic ones (see Subsection 2.1). This approximation does not deeply influence the tissutal scale, where the associated CA only models a lattice of BMUs; on the contrary, it is quite evident at cellular scale, where each single BMU is in turn described as a CA of O_ys, avoiding an explicit local regulator and hormone representation. If, on the one hand, the assumed approximation could influence the multi-scale model "faithfulness" w.r.t. the real phenomenon, on the other hand it does not influence the validity of the proposed crossing approach (modelling in CxA and simulating in BioShape) and the underlying mapping, being both CxA and BioShape able to describe and handle spatial lattices.

Although CxA paradigm was already equipped with its own execution environment [15] and BioShape with its native modelling language [16], the proposed crossing approach - here tested for a specific biological process - aims just to be the first step to state an expressiveness study between CxA and BioShape (see Section 4). In fact, the possibility of modelling bone remodelling as a CxA and executing it in a shape-based fashion in BioShape aims to highlight the existence of a *more general* encoding from CxA into BioShape. This conjecture is enforced by the fact that both approaches (i) are based on uniform single-scale models, (ii) rely on a Lattice Boltzmann Model-like time step scheme, (iii) can express spatial information and (iv) can bypass inter-scale homogenization problems.

[2] `http://cosy.cs.unicam.it/bioshape`

2 The Complex Automata Modelling Paradigm

The Complex Automata (CxA) [13] paradigm has been recently introduced for modelling multi-scale systems and, in particular, the process of development of stenosis in a stented coronary artery [17].

CxA building blocks are single-scale *Cellular Automata* (CA) (i) representing processes operating on different spatio-temporal scales, (ii) characterized by a uniform Lattice Boltzmann Model-like (LBM) update rule - and, as a consequence, execution flow (see Fig. 2 (b)) - (iii) mutually interacting across the scales by well-defined composition patterns[3] (see Fig. 3).

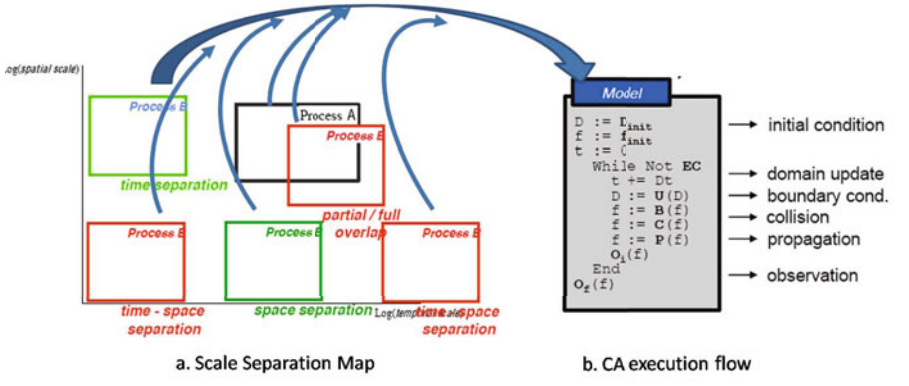

Fig. 2. a) Scale Separation Map; b) CA execution flow.

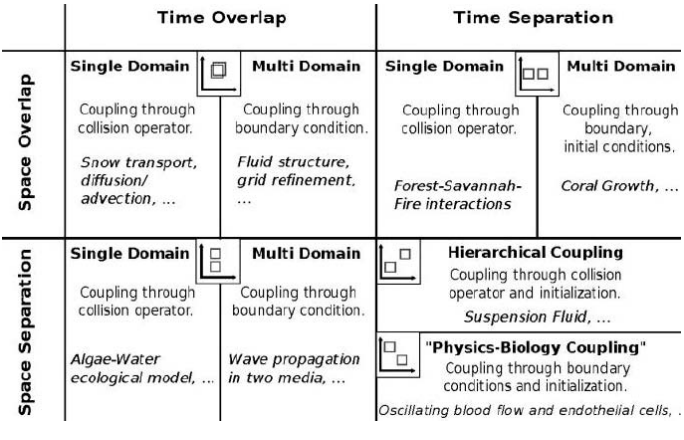

Fig. 3. SSM and Composition patterns

[3] Due to the lack of space, composition patterns are not discussed here and we refer to [18] for further details.

More in detail, the update rule of any CA is uniformly defined as a composition of three operators: *boundary condition* $B[\cdot]$ and *collision* $C[\cdot]$, both depending on external parameters, and *propagation* P, depending on the topology of the domain. Given a CA, (i) the B operator is needed to specify the values of the variable that are defined by its external environment (in the case of a LBM fluid simulation, the missing density distributions at the wall), (ii) the C operator represents the state update for each cell, and (iii) the P operator sends the local states of each cell to the neighbors that need it, assuming an underlying topology of interconnection.

Being the update rule of any CA uniformly defined, such composition patterns only depend on the CA spatio-temporal "positions" in a *Scale SeparationMap* (SSM), where each CA is represented as an area according to its spatial and temporal scales (see Fig. 2 (a)). Formally:

Definition 1. A CxA $\mathcal{A}$ is a graph (V, E), where V - the set of vertices - and E - the set of edges - are defined as follows:

- $V = \{C_k \stackrel{\text{def}}{=} \langle(\Delta x_k, \Delta t_k, X_k, T_k), \mathbb{S}_k, \Phi_k, s_k^0, u_k\rangle | \, C_k \text{ is a CA}\}$ where $\forall C_k \in V$,
  - $(\Delta x_k, \Delta t_k, X_k, T_k)$ denotes the spatio-temporal domain of C_k, i.e. Δx_k is the cell spatial size, X_k is the space region size, Δt_k is the time step and T_k is the end of the simulated time interval of C_k;
  - $\mathbb{S}_k$ denote the set of states;
  - $s_k^0 \in \mathbb{S}_k$ is the initial state;
  - u_k is a field collecting the external data of C_k;
  - Φ_k is the update rule encoded in LBM style as follows

$$s_k^{n_k+\Delta t_k} = P \circ C[u_k^C][s_k^{n_k}] \circ B[u_k^B]$$

  where $s_k^{n_k}, s_k^{n_k+\Delta t_k} \in \mathbb{S}_k$ denote resp. the state of C_k obtained as the numerical solution at the n_k-th time step and the one at the $(n_k + 1)$-th time step.
- $E = \{E_{hk} | E_{hk}$ is a *composition pattern* between C_h and $C_k\}$.

Finally, the numerical outcome of each C_k is denoted by $s^{T_k} \in \mathbb{S}_k$.

2.1 Multi-scale Trabecular Bone Remodelling in CxA

Assuming that O_ys act as mechano-sensors, the model - for simplicity proposed in 2D - consists of a CA, whose cells are in turn CAs: the "macro" CA (denoted by C_1) models a portion of trabecular bone as a lattice of BMUs (macroscopic slow process), while each "micro" CA (denoted by $C_{(i,2)}$, where i corresponds to the cell i in C_1) models a single BMU as a lattice of O_ys and their surrounding mineralized tissue (microscopic fast process).

A similar grid-based micro-macro spatial decoupling can be found in [19], where a discrete, agent-based stochastic model for studying the behavior of limb

bud precartilage mesenchymal cells in vitro is proposed. The model employs a multiscale spatial organization for cells and molecules as a two-dimensional discrete pixel grid. The coarsest resolution spatial scale (the cellular level) is the base spatial scale, and the molecular one is an integer ratio size of that base grid. Each molecule is considered to have a spatial extent of just one pixel, and each type of molecule has its own spatial grid independent of the other molecule types, so any number of molecule types can be defined, each with their own scale relative to the base spatial scale.

In our case, the "macro" cell size is linearly determined from the "micro" cell one, which is in turn derived from the O_ys estimated density in bone. Assuming that a cubic millimeter of fully mineralized tissue contains 16000 O_ys, then a 3D lattice representing this unit volume should contain 25 ($\approx 16000^{1/3}$) cells in each side. Therefore, a cubic millimeter of bone could be modeled as a 3D lattice of 25^3 cells, matching with the data reported in [20]. As a consequence, a 2D cell lattice with a thickness of 1/25 mm can be structured in 25^2 cells, matching also with the data presented in [21].

The "macro" neighborhood layout can be defined either as the simplest 2D Von Neumann neighborhood (4 cells) or as the 2D Moore one (8 cells), depending on how "local" we consider the remodelling process on a trabecular region (i.e., in other terms, how "local" we consider the propagation of remodelling activation state among BMUs). The "micro" neighborhood layout can be defined as the 2D Moore neighborhood.

Micro execution flow. The state of each cell j in $C_{(i,2)}$ at a time $t_{(i,2)}$ is defined by its mass fraction $m^j_{(i,2)}(t_{(i,2)})$, varying from 0 (bone marrow) to 1 (fully mineralized). The mechanical stimulus $F^j_{(i,2)}(t_{(i,2)}) = U^j_{(i,2)}(t_{(i,2)})/m^j_{(i,2)}(t_{(i,2)})$ - being $U^j_{(i,2)}(t_{(i,2)})$ the strain energy density of j at time $t_{(i,2)}$ - is calculated by the *Meshless Cell Method* [12] (MCM). Each cell j modifies its mass according to the error signal $e^j_{(i,2)}(t_{(i,2)})$ between the mechanical stimulus and the internal equilibrium state, determined by the condition $e^j_{(i,2)}(t_{(i,2)}) = 0$; when this condition does not hold, a local collision formula[4] modifies the mass fraction $(m^j_{(i,2)}(t_{(i,2)} + \Delta t_{(i,2)}))$ to restore the equilibrium condition. Consequently, the change in mass modifies the stress/strain field in the bone and, therefore, the stimulus operating on j. This processes continues until the error signal is zero or no possible mass change can be made. The convergence is satisfied when the change in density is small: if there is no convergence, the process continues with a new MCM analysis.

Macro execution flow. Similarly to the micro execution flow, the state of each cell i in C_1 is defined by the apparent density $m^i_1(t_1)$, which can vary from 0 (void) to 1 (fully mineralized tissue). An homogeneous apparent density distribution for any i corresponds to an isotropic material, while intermediate values represent trabecular architecture.

[4] The formula can be selected from the approaches presented in [22].

A global MCM analysis evaluates the stress field $F_1^i(t_1)$ on i at a time t_1, so defining the loading conditions operating on each i. We know that i modifies the microstructure by processes of formation/resorption (corresponding to $s^{T_{(i,2)}}$, see below); this process results in formation and adaptation of trabeculae. Hence, the global MCM analysis is performed over the resulting structure to update the stress field until there is no change in the relative densities and there is no change in the stress field.

Micro-Macro composition pattern. Each $C_{(i,2)}$ is linked to C_1 by the "micro-macro" composition pattern, defined in Fig. 3 and maximized in Fig. 4. More in detail, C_1 takes input from explicit simulations of $C_{(i,2)}$ on each lattice site i at each time step Δt_1, while each $C_{(i,2)}$ runs to completion, assuming that all $C_{(i,2)}$ are much faster than the macroscopic process and therefore are in quasi-equilibrium on the macroscopic time scale.

A close inspection of this coupling template shows indeed that upon each C_1's iteration each $C_{(i,2)}$ executes a complete simulation, taking input from C_1. In turn, each $C_{(i,2)}$'s output ($s^{T_{(i,2)}}$) is fed into the C_1's collision operator.

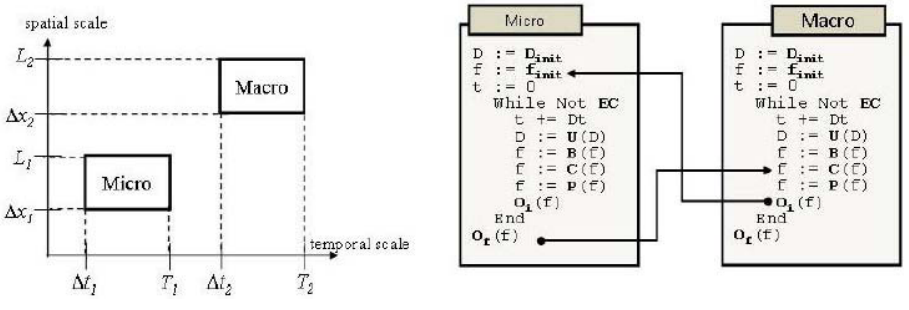

Fig. 4. Micro-Macro composition pattern

3 The BioShape Modelling and Simulation Environment

BioShape[5] is a spatial 3D simulator which has been engineered in the perspective to be a *uniform*, *particle-based*, *space-oriented* multi-scale modelling and execution environment.

BioShape's modelling approach treats biological entities of any size as geometric *shapes*, equipped with perception, interaction and movement capabilities. The behaviour of every shape, i.e. the way it interacts with other shapes and with the environment, is formally defined through a process algebra (namely, the *Shape Calculus* [16]). Every entity has associated its physical movement law: this approach guarantees granularity in entities management as everyone is treated uniformly but independently from the other ones.

Scale-independence property just follows by the uniform way biological entities of any size are treated. As a consequence, homogenization between single scales

[5] A complete description of BioShape can be found in [14].

simply reduces to mappings between homogeneous representations at different granularity (i.e. zoom resolution) of the same biological system.

Time is simulated as a sequence of fixed time intervals called *time frames*; specific events - namely *perceptions* and *collisions* - occur during any time frame according to a well-established LBM-like sequence.

3.1 Multi-scale Trabecular Bone Remodelling in BioShape

BioShape can import and execute the CxA model described in Section 2 without substantial arrangements, since "micro" and "macro" CAs (i) can be encoded using a small subset of primitive (namely shapes, perception- and collision-driven interaction, communication and internal calculus), being simple spatial lattices, as well as (ii) can be easily homogenized, being homogeneous representations of the same process at different zoom resolution (micro-macro). Moreover, the BioShape software architecture has been already engineered from the perspective of supporting massive parallel computations[6], a computational approach which is intrinsic to the CA paradigm and, as an immediate consequence, to the CxA one.

The CxA model of bone remodelling can be also executed in BioShape to provide a graphical simulation of the phenomenon at tissutal level. More in detail, the whole 2D trabecular tissue body can be visualized as a grid of square shapes in the fully mineralised part of the bone and in the fully fluid part (resp. full/green squares and void/black squares in Fig. 5 (B)). The bone *surface* can be represented also by squares, but decomposed using, as usual in visual graphics, five basic shapes able to "discretize" the trabecular surface (green shapes in Fig. 5 (C)).

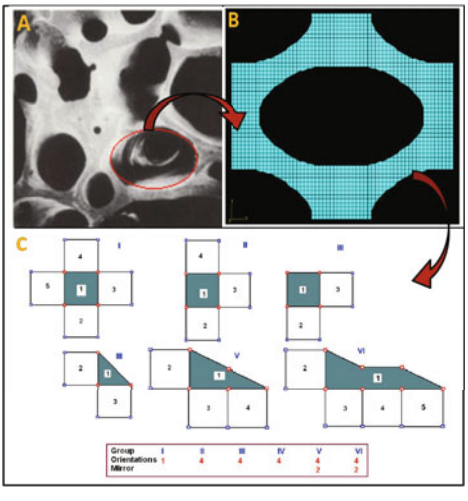

Fig. 5. Trabeculae (A). 2D grid (B). Surface shapes (C).

The basic surface shapes are square, rectangle (1:2 aspect ratio), truncated square, two right angled triangles (side ratio of 1:1 and 1:2), and a trapezium glued with a rectangle and a triangle. They are grouped into 6 element families. Allowing for rotations and mirror images of these groups, only 29 stiffness matrices need to be defined, thus we can always find a good

[6] The current version is based on the UNICAM agent-based Java framework Hermes [23], a middleware supporting distributed applications and mobile computing. Currently, a porting on a Multiple Instruction Multiple Data (MIMD) architecture with message passing is under development.

representation of the border avoiding the need of a re-shaping primitive, which is not yet available in the current version of the simulator.

Each void/full/surface shape in the cell i has an associated mineralisation density. As a consequence, its dynamics is determined by the CxA model execution: in particular, a variation from $s_1^{n_1}$ to $s_1^{n_1+\Delta t_1}$ involving i determines the replacement of the shape in i with another void/full/surface shape - that one associated with the new density value.

4 Conclusion and Future Work

The CxA paradigm has been here taken into account to propose a uniform multi-scale model for the bone remodelling process. Such a model has been then imported and executed in BioShape.

Scale-independence property, ability of expressing spatial information and LBM-like time frame scheme are altogether elements which heavily draw up both modelling approaches. However, if on the one hand the CxA here proposed for bone remodelling confirms the high degree of expressiveness and flexibility of the CxA paradigm, on the other hand the possibility in BioShape to associate to each shape *its own* physical movement law (which can be different from that one associated to a neighbour) could make BioShape more expressive than a CxA. As a consequence, a formal investigation on the expressive power of the above modelling approaches seems reasonable.

We are also exploiting BioShape alone for defining a multi-scale model for bone remodelling where local regulators, O_bs, O_cs and their relative precursors, namely *pre-osteoblasts* (P_b) and *pre-osteoclasts* (P_c), are explicitly modelled as particles at cellular scale. The implementation of such a model in BioShape is quite natural, as it involves shapes that either move possibly attracted by biochemical signals or stand still. Also the composition of O_cs from P_cs is a primitive supported by the simulator. This is a promising approach, already exploited in [24], where basic simulation algorithms of the Celada-Seiden model for the immune response process are presented in terms of operations on abstract particle types, and where new algorithms for diffusion, proliferation and cell-cell interaction are defined as discrete versions of established continuous models.

We plan to tune and validate the new particle-based cellular model taking into account experimental data as well as those produced by the CxA-based model here proposed and by some available continuum-based descriptions [2,3,4,5,6,7,8,9]. We also plan to realize such tuning and validation procedures in the opposite direction.

Our believe is that particle-based tissutal and cellular views of bone remodelling turn to be helpful (i) to better understand the blurry synergy between mechanical and metabolic factors triggering bone remodelling, both in qualitative and in quantitative terms, and (ii) to develop a coherent theory for the phenomenon as modulated by mechanical forces and metabolic factors in a uniform way.

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