BioShape: a Uniform Multiscale Approach to Biological System Simulation

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Abstract

Many biological phenomena are inherently multiscale, i.e. they are characterised by interactions involving different scales at the same time. Such interactions, even simpler ones, can give rise to emergent properties that only make sense in the context of the system as a whole; at the same time, systems of few interacting components can give rise to complex behaviours that can be missed if all entities, at the different spatial and temporal scales, are not considered.

During the last years a large set of approaches have been developed to provide models and simulation frameworks that can help to better understand the basic and advanced dynamics that regulate biological systems. Confronted with a multiscale system, most of the solutions consisted of a series of different models, each of them best suited for a specific resolution level, that were coupled in some way to guarantee a more faithful simulation.

In this work we present BioShape, a spatial, geometric, three-dimensional, collision/perception driven simulator that results to be "scale-independent". It treats any biological entity as a individual entity having a particular 3D shape, equipped with perception capabilities, moving in the simulation space through a personalised motion law, and colliding with other entities giving rise to bounces or to joined entities. Such a model is naturally uniform as different resolution levels can all be modelled in terms of shapes and interactions among them. The model is also information lose-less since passage from a scale level to another is reduced to a mapping between different granularity instances of the same (shape based) model. To better underline the features provided by BioShape it has been applied in two case studies: an aortic valve and the bone remodelling process that occurs in any skeleton-enabled living being.

1 Introduction

The inherent complexity of biomedical systems is well recognized: they are multiscale, multi-science systems, bridging a wide range of temporal and spatial scales. One of their main characteristics is the intimate connection that exists between different length scales, from the nanometres of molecules to the metre scale of the whole human body. As stated in [7], subtle changes in molecular structure, as a consequence of a single gene mutation, can lead to catastrophic failure at the organ level.

In the past few years a lot of efforts have been put in the creation of integrated unified multiscale models and simulators that can exploit the models available at different resolutions to reach an higher level of simulation faithfulness. With the multiscale approach, a simulation can be carried out at any level of resolution, or different levels can be used for the same problem either *serially* or in *parallel*, as described in [2]. Moreover, information gained at high resolution such as protein-protein, protein-DNA interactions may even be integrated into models at system's level to provide valuable and personalised information.

Coupling (and homogenise) coarser-grain-level and atomistic-level systems involves some degree of bridging of information across various length and time scales and is ultimately one of the most difficult tasks to carry out along with the choice for the "single-scale" models for each scale. As stated in [6], a good way to bypass homogenization problems consists of decomposing biological systems into a hierarchical aggregation of uniform and interacting single-scale models. Furthermore, [9] proved that continuum-based approaches can be successfully replaced by particle-based approaches at different levels. The latter can also be enriched with geometric and spatial information which can have great impact on the simulation accuracy (taking into account phenomena like co-localization [8], and molecular crowding [10].

2 BIOSHAPE simulator

Given the observations above, BIOSHAPE [1], a spatial 3D simulator, has been engineered to provide a uniform, particle-based and geometry-oriented multiscale modelling environment. The simulator is under development and it is currently employed to simulate the bone remodelling case study (see below).

The BIOSHAPE heart is a particle-based model that is scale-independent since it treats **any** biological entity - from macro-molecules such as protein to small molecules such as ions - simply as geometric *shapes*, equipped with perception capabilities and a personalised motion law, moving in the space and interacting with each other. A two-phase collision detection algorithm establishes whether shapes collide in order to possibly interact and bind to construct new shapes.

The scale-independence property is based on the fact that a particle-based and space-oriented model is suited to describe any scale at different spatial granularity and also to express geometric and positional informations. As a consequence, transformation functions between (homogeneous) particle-based representations can be simply defined as mappings between different granularity instances of the same model.

The simulator exploits the *parallel* computing approach to deal with the computational power required to simulate a complex 3D environment. The BIOSHAPE architecture have been engineered with this prospective in mind. The main actors of the simulator are the *coordinators*. A simulation has only one running instance of a *global coordinator* and many instances of *local coordinators*. The former manages the overall simulation, deciding the spatial allocation of the shapes and assigning them to single local coordinators (through load balancing techniques) whereas each local coordinator manages a single computational node involved in the execution (i.e. a cubic portion of the 3D space simulated). The local coordinator deals with movement, perception, communication and collision detection tasks for the simulated elements included in its space, called *entities*. Some entities can be *grouped*, i.e. they represent global simulation constraints (e.g. presence of certain ions in the whole space).

Simulation proceeds by time frames. At the beginning frame, all the communications and all the *perception-driven non-collision-driven* activities are executed. Instead, during the time frame all the activities are related to shape motions and *collisions*, i.e. they are *collision-driven*. In particular, if a collision is found during the simulation frame, an exhaustive search for the exact collision point is executed and the collision resolved, either in elastic or inelastic (join) one. Then, the simulation continues until the end of the current time frame, possibly treating other collisions.

3 Case studies

Let us give a brief description of two case studies developed to show the adaptability of BIOSHAPE to different biological contexts.

Human aortic valve. The aortic valve of a human body can be seen at four different scales: the organ, the tissue, the cell and the molecular scale. At the organ scale the valve can be decomposed into three passive tissue flaps (called leaflets) that react passively to blood pressure. At the tissue scale every leaflet is compound of three different layers consisting of (aligned) collagen or gel. At the cell scale we can distinguish *valvular interstitial cells* (ICs) and *valvular endothelial cells* (ECs) which coat all the blood-facing surfaces. Finally, at the molecular scale, heart valve leaflets are composed of fibrous matrices in which a spongelike matrix of elastin surrounds bundles of collagen fibre (aligned in the plane of the leaflet).

The main mechanical communication from the smaller scale up determines the overall function of the valve: the extensibility and geometric organization of the fibrous molecules determines the tissue stiffness and anisotropy which, along with the tissue-scale geometry, determines the organ-scale motion of the leaflets. There is active communication from the cell scale to the tissue scale, where contraption of the ICs significantly affects tissue stiffness. Similarly, mechanical communication from the larger scales downwards affects active biochemical processes: in the fluid, organ-scale fluid motion applies shears to the ECs while, in the solid, organ-scale motion deforms the tissue, which in turn deforms the ICs. Mechanical signals control gene expression in normal and diseased states of the ECs and ICs.

While molecular scale very often is described in terms of molecular dynamics - thus in terms of particles - organ, tissue and cell scales rely on the theoretical framework provided by continuum mechanics. Specifically, most cell models describe the cell as some combination of fluid and solid enveloped by the cell membrane. Conversely, at the organ and tissue scale, interactions between the valve and blood are modelled through fluid/solid meshes interactions (e.g. through the Arbitrary Lagrange-Eulerian method). However, blood is not a simple fluid but it is compounded of a lot of cellular components which this approach tends to abstract from. Our shape-based model [4] is more expressive, treating every element at every level as a single different entity with a volume, a movement law, perception capabilities and so on.

Tissues are modelled as networks of square elements (nodes) each of them being a particle. During deformation, these particles are allowed to distort in and out of their plane. External forces and specified displacements are treated as input at each node. Internal reactions are calculated for each vertex according to the classic elastic shock laws and assuming that the nodes are connected by (non-) linear springs simulating the elastic properties of the material. The *blood* is composed of objects with different phases and material properties: plasma, red blood cells, white blood cells, and platelets. All of these *single cells* are modelled as connected particles whose connection is fixed so that they can deform but can not be broken, while plasma is modelled by a (in narrow sense) particle method such as Moving Particle Semi-implicit or Smoothed Particle Hydrodynamics. A single cell is viewed as a particle surrounded by a matrix, either fibrosa or ventricularis. The constitutive model for the matrix can be the same as that for the tissue scale.

Transformation functions between two contiguous scales S_1 and S_2 can be defined as relationships between deformations in S_1 and the ones in S_2. Such deformations will be organ motions, tissue deformations and cell deformations respectively at organ, tissue and cell scale. For the sake of efficiency we can consider only those intra-scale deformation that we consider worth noting.

Bone remodelling. It is the continuously replacement of (old) bone tissue by new tissue. This phenomenon ensures that the mechanical integrity of the bone is maintained without causing global changes in bone morphology. It can be considered a multiscale process since macroscopic behaviour and micro-structure strongly influence each other. On a *tissutal scale*, remodelling might be regulated by mechanical loading, allowing bone to adapt its structure in response to the mechanical demands it experiences either by altering the external shape of the bone to suit the loading environment or by altering its internal structure. On the *cellular scale* 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 remodelling process begins at a quiescent bone surface with the appearance of O_cs that attach to the bone tissue, create an isolated micro-environment, 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, thus forming new bone. Some of them are encapsulated in the osteoid matrix and differentiate to osteocytes (O_y) the bone tissue cells. 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. LL_cs are highly interconnected with the O_ys in the bone matrix through a network of canaliculi.

As we can see, the bone remodelling process is a typical multiscale process in which actors from different resolution levels (organ, tissutal and cellular scale) interact to carry out the overall biological process. All the involved entities can be modelled in terms of BIOSHAPE shapes. In particular, we have defined in [3] a two level model (tissue + cell scales). For the sake of simplicity, we use a 2D space. At the tissue level, the 2D bone is defined as a grid of square shapes (cubes, in 3D). The bone surface is represented decomposing it using, as usual in visual graphics, five basic shapes able to discretize the trabecular surface (square, rectangle, truncated square, two right angled triangles (side ratio of 1:1 and 1:2), and a trapezium glued with a rectangle and a triangle). Every shape in the model has a density (of mineralisation) associated. There is a threshold above which the cell is considered mineralised. For each cell a Meshless Cells Method-based system [5] calculates how a tensor field applied to the tissue modifies it over time. The remodelling phenomenon occurs on the surface cells, thus changing the values of the densities over time. Our model couples these changes: at every simulation time frame the values of the densities are re-calculated using results obtained from the cell scale model (BMU model, see below) that uses both internal (systemic) and

external (mechanical) parameters. It gives the new values of the densities according to the bone remodelling that occurred, thus updating the whole tissue configuration.

The BMU model is defined as a rectangular compartment with a plane cutting it initially in half. On the left side we have the mineralized extracellular matrix that can be represented by a regular lattice. A cell of this structure may contain an O_y that is connected to its neighbours with a given geometry. O_ys may be influenced by the deformation tensor field of the tissue obtained from the continuous model defined at the upper scale. L_cs divide the two sides and, when a messengers reach them, they are used to activate the production or to define an attraction field for cells that are loose in the fluid section on the right side, namely precursors of osteoblast and of osteoclasts. The process is simulated as physiologically described above.

As we said, the two models are tightly related and there is a continuous interchange of information between them. At tissue scale, every square has a mechanical charge stimulus associated and mineralization density value that indicate if it can be remodelled (i.e. it is a surface square or not). A set of squares are chosen and the remodelling process is applied on the higher resolution model. At the end of the simulation, the new value for the density is calculated and it is passed to the tissue model that determines how the changes of density modified the mechanical stimuli. Note that cell events occur at a pace of days while tissue timing is in the order of months. Thus, the simulator basic time frame is in the order of a (simulated) day, and when a (simulated) month elapsed also a step of the tissue level is performed.

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