Space, Geometry, Motion and Interactions in Modeling Biological Systems: the BioSHAPE Approach

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Abstract

We present BioShape, a modeling and simulation environment for biological systems at different scales. The basic assumption is that the system is modeled using autonomous entities that have a physical shape, move in a geometrical 3D space and can interact in different ways. The modeled biological phenomenon will be observed and analyzed as the emerging behavior of the entities’ behaviors in the in-silico experiment (simulation) that is set up. We show several application areas of our approach at different levels: molecular, cellular and tissue. Moreover, we show that different levels can be specified uniformly within BioShape, making it a powerful multiscale environment.

1 Introduction

In a near future, Systems Biology will profoundly affect healthcare and medical science. The ultimate aim is to design and test “in-silico” drugs giving rise to individualized medicines that will take into account physiology and genetic profiles [12]. This implies the existence of detailed digital models of each human organ and, possibly, of the whole human body. The advantages of performing in-silico experiments by simulating a model, instead of arranging expensive in-vivo or in-vitro experiments, are evident. But of course the models should be as faithful as possible to the real system.
The molecular level is surely the scale at which biological systems have been studied more intensively in the perspective of Systems Biology, so far. Within this field, Takahashi et al. underline, in [15], the importance of considering space when modelling cellular phenomena and in particular biochemical signal cascades. They also highlight that macromolecular crowding in a limited space can also deeply affect biochemical reactions in the cell. Since physical concepts like space occupancy, intra-cellular movement, contacts (collisions) and shape transformation determine biomolecular interactions and therefore cell life, there is the need to provide physical characteristics (shape, mass, size, position) to entities. They can be collocated in the continuum space, autonomously move and interact with their spatial neighbour/colliding entities, react accordingly to their specified behaviour to reproduce the emerging behaviour observable in in-vivo and in-vitro experiments as well as at a higher scale of the same model.

Using a particle-based approach (i.e. there are specific actors that represent individuals) and adding geometric information (e.g. space, shape) to a model not only makes it more faithful and close to real biological systems (at any scale), but also gives the possibility to represent different levels of the same biological system in a uniform way. This characteristic results to be very useful in the construction of multiscale models and many biological phenomena are inherently multiscale, i.e. they are characterized by interactions involving different scales at the same time.

2 The BioShape simulation environment

The main idea guiding our work over the past recent years is that at every level of representation, being it organ, tissue, cellular or molecular, it is always possible to model the system using the same concepts: individual, moving entities that interact in the 3D space by binding to form complex entities or just by transforming into different entities by a concept of “reaction”. The idea of a geometric particle-based environment for simulation started, in our group, some years ago [9, 8] in the context of the simulation of biochemical reactions without using the classical approach of Ordinary Differential Equations. The same idea has then evolved towards the realization of a simulator prototype, called BioShape [1], that embodies spatial 3D information and shape-based interactive entities. Some recent works [3, 5, 7] give evidence of the advantages and of the feasibility of this approach, ap-
Figure 1: An example of a simulated space with entities of different shapes moving at their own directions.

During the development of BioShape, several questions arose about how 3D shapes should be considered, how motion should be associated to them and, most importantly, what kind of interactions should be considered among entities in order to reproduce typical scenarios of biological (but not only limited to them) systems at any scale. We found several solutions about the possible representation of 3D shapes and their movement in a space, mainly in the computer game world. In this and in related fields, the problem of reproducing/simulating virtual physical environments has been intensively studied and a lot of libraries and tools exist to manage space and to deal with the unavoidable problem of collision detection and collision response. We mainly refer to [11, 14] and to references therein for a first glance in this rich and articulated world. However, the possibility to import good techniques for managing the virtual environment solved only half of the problem. The specification of the behaviour of the autonomous entities, and the modalities on which this behaviours should be based, represented another difficult question to address.

BioShape embodies an agent-based technology [10] that realizes the abstraction of autonomous agents. Autonomous agents are entities that can be programmed to fulfill any behaviour. This means that the main language of
specification is a programming language. On the one hand this is a very flexible and powerful way for expressing entities’ behaviours, but on the other hand it implies that a user of the environment must have programming competences. This is not always the case, as the intended user is someone that typically has a biological/biomedical background. Thus, there is the need of defining a more abstract language in order to enable the users to focus only on the specification of the biological interactions and abstract away from the technical details of programming. This consideration led us to the definition of a basic language that we called Shape Calculus [4, 2, 3]. The Shape Calculus is a formal calculus that gives a very precise characterization of the environment in which our simulations should run, with all the advantages that a formal semantics brings to the development of the simulator itself. It is not the final language that we intend to embed in the BioShape environment, but it is intended as the first core of basic operators on which a graphical component-oriented language (to be designed) will be translated.

Fig. 1 shows a potential configuration during a BioShape simulation. Shapes can be either basic (spheres, cylinders, cones and polyhedra) or composed ones (glued on a certain touching common surface) resulting from the binding of basic or composed shapes. By composition we can approximate any kind of complex shape with arbitrary precision (with increasing computational cost). For instance, Fig. 2 shows how a complex molecule such as the hexokinase enzyme, involved in the first reaction of the glycolysis pathway, can be represented in BioShape.

Binding of shapes can be used to represent complex formation and then

![Figure 2: The shape of the Hexokinase enzyme with a possible approximation using a combination of polyhedra.](image-url)
Figure 3: A scenario representing the simulation of the first reaction of the glycolysis pathway.

reactions. A binding can occur only if two entities collide. Every entity has a mass and is equipped with a personalized motion law (that, anyway, can be also a general one, for instance in presence of an attraction field, or in case of Brownian motion) that can specify both translation and rotation motion. The simulation evolves along time moving the entities according to the velocity vectors given by their motion laws. BioShape embeds a collision detection algorithm that stops the spatio-temporal evolution of the system whenever a collision between at least two entities occur. This situation can evolve into different ways: if the shapes that are colliding are not “compatible”, the collision is resolved as a bounce, changing the velocities of the involved shapes accordingly to the laws for conservation of linear momentum and kinetic energy. The other possibility is that the shapes are “compatible” and thus bind, forming a new unique shape that will move as a unique body whose velocity is determined by the law for conservation of linear momentum. Compatibility is defined using active sites: every entity exposes a set of active sites that are pairs of a name and a certain portion of the surface of the entity’s shape. Two colliding shapes are compatible only if the collision surface is on an active site of both of them and these two active sites have the same name. Fig. 3 shows a scenario in which the first reaction of glycolysis is simulated. The Hexokinase enzyme has two active sites, \( (\text{glc}, Y_{hg}) \) and \( (\text{atp}, X_{ha}) \), on which a glucose (GLC) molecule and an ATP molecule can bind, respectively; GLC and ATP expose active sites of the same names on their
Figure 4: BMU shape-based scenario on the left. A real BMU on the right.

whole surface. In this way we have that Hexokinase-GLC, Hexokinase-ATP and Hexokinase-GLC-ATP complexes can be formed. In the last case a reaction occurs, represented by a split event, in which the previously established bounds are broken and three new entities are formed: an Hexokinase, equal to the original one, a Glucose-6-phosphate (G6P) and an ADP. Note that the shapes of G6P and ADP can be the same of GLC and ATP (or can loose some pieces), but in any case they will have a different behavior.

Within BioShape also non-physical entities can be defined. For instance, grouped entities can represent some particular molecular species that we do not want to explicitly represent either to save computational cost or because we can assume that they are always available at each place (e.g. water molecules or some ions). In this case, the datum that we manage is only an aggregated one, e.g. the total number of the grouped entities, or their concentration. Also other entities representing chemical or electrical gradients can be defined. Moreover, the bind-split interaction, that is collision-driven, is not the only kind of interaction that can be represented in BioShape. Non-collision-driven interactions between physical or non-physical entities are possible. For instance, perception-based interactions can be set between entities that are close enough and that, thus, perceive each other along a given perception radius. In this case the interaction becomes a message exchange or a protocol between two or more involved entities.

Fig. 4 shows another possible scenario of simulation, this time at a cellular level. Here the shapes represent both cells involved in the bone remodelling
phenomenon in a Bone Multicellular Unit (BMU) and portions of mineralized tissue. In this case study [5] the multiscale capabilities of BioShape are pointed out. We specified also a tissue-level model in addition to the cellular-level one (the BMU). Both levels of the same phenomenon are runnable, simultaneously, in the same simulation. In this case coupling functions have to be defined in order to specify how the two (or more) levels of abstraction interact in space and time.

These multiscale capabilities are not yet fully embedded in the simulator, which is being continuously upgraded in order to embed more and more functionalities. We refer to the official web page [1] for technical information and for the current status of the implementation.

References


