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Pascal Ballet[1]

[1] University of Brest – Laboratory of Medical Information Processing (LaTIM – INSERM UMR 1101) – UFR Médecine – IBRBS – 22 avenue Camille Desmoulins – 29238 Brest Cedex 3 – FRANCE – Contact: pascal.ballet@univ-brest.fr – Website: http://virtulab.univ-brest.fr

Abstract

New biomedical advances at cellular level give the possibility to develop more and more accurate computational models of cells. Moreover, the increasing power of graphical processor units allows the simulation of millions of interacting virtual cells. This paper summarizes efforts made to create multicellular simulators, their attended benefits and their inevitable drawbacks. In particular, it presents the new software SimCells that simulate the dynamics of multicellular systems using a graphically programmable multiagent system. A fully functional example of the tumoral and blood vessel co-development is also detailed.

Introduction

The biomedical field at cellular scale is a very active field of research, dealing with data from simple molecules up to entire organisms. It works both on the fundamental comprehension of the living and on the design of treatments against complex diseases. Although numerous entities are in interaction at very different scales and inside heterogeneous environment in cellular systems, many data coming from biological experiments can be integrated in computational systems to explain how the real system works. The creation of such systems is made through a long and difficult process entailing interdisciplinary knowledge, computer science and mathematical skills, rigor and creativity. It also demands high computational power which can be found in massively parallel processors.

Creativity is a hard and fragile dynamic process, especially during the development of models on complex living systems which usually are non-linear and counter-intuitive. Advanced software can contribute to this creativity by giving intuitive and computational tools. Graphical designing tools enable researchers to focus on their models instead of how they implement it. Computational tools resolve the models and verify their validity. Moreover, they can organize huge amount of data inside formal paradigms which can be easily understood and shared.

The modelling and simulation of cellular systems, both at molecular level and at multicellular scale has already been initiated in the early ages of computers with the works of Alan Turing on the chemical basis of morphogenesis and those of John Von Neumann on cellular automata. Moreover, computer aided design has been used since the 1950's in numerous fields of science and technology like mathematics, molecular modelling, car or plane design. Although computer scientists have been interested in modelling multicellular systems, this field has encountered many difficulties both theoretical, due to partial cell comprehension, and practical, with the limitation of computational power.

Despite the development of many fundamental algorithms and programs for the modelling of multicellular systems, most of them have been limited to prototypes and dedicated to specific problems.

This work presents the recent efforts to develop fully integrated software, that help biologists to create models of multicellular systems. An attention is given to systems with many interacting entities capable of self-assembly.

This paper begins with some objectives, expected benefits and the inevitable drawbacks of such software. Then the contemporary contexts of cellular biology, computer science and computational biology are presented. Next, different algorithmic approaches are shown. Afterwards, two advanced software are described. Finally, a SimCells simulation of the angiogenesis process is detailed.

Objectives

The comprehension of living cell is still incomplete and computational approaches can participate in their study. This help can be divided into four short term and two long term objectives.

Short-term objectives

1. simulation of complex cellular systems to improve the understanding and control of those systems
2. formalization of knowledge which can reduce ambiguities inside biological models
3. integration of diverse scientific knowledge to improve the realism of models
4. dissemination of knowledge which could accelerate the rhythm of discoveries by sharing models and simulations
5. the training of students in biology, enabling them to deal with complex systems.

Long-term objectives

1. computer aided design of tissues and organs for medical applications to contribute on their replacement or restoration
2. computer aided design of tissues and organisms for industrial applications to create materials, systems or computers based on multicellular systems 1.

These objectives lead to benefits that irrigate science and technology even before their completion.
They are briefly described in the following section.

Benefits

The study of multicellular systems using computers is interesting both scientifically and technically and it can also have important implications in society.

Scientifically, it serves the comprehension of fundamental mechanisms governing cells, from single-cell behaviors to embryogenesis of a whole organism, including tissue formation and organs morphogenesis.

Technically, it requires enhancement of computational models, from algorithms to graphical user interface. In return, it can improve the field of computer science.

As regards the implications in society, computation of multicellular systems could help medical researchers to discover new medical treatments. It could also be used, in some cases, as an alternative to animal testing both for research and teaching.

Moreover, the creation of computational models imitating multicellular systems involves many areas of science such as biology and medicine, computer science and computational biology, physics and complex systems, mathematics and pedagogy and may lead to think how to reorganize scientific fields by encouraging interdisciplinary that induces discoveries.

Despite these benefits, it is necessary to clarify the limits of this approach in order not to over-estimate its potential.

Drawbacks, limitations and difficulties

Modelling and simulation of multicellular systems have to deal with many problems. Some are shown below.

Modelling problems

Any model contains approximations, bias and gaps that inevitably denatures the real system.
For example, a model contains what is known on a real system but not what is unknown2: *in fine*, *in-vivo* or *in-vitro* experiments could be necessary. Even what is supposed to be known must be carefully questioned because data coming from experiments are of various kinds, have different experimental conditions and possess margin of error. A model is only valid under certain conditions. It generally has limited predictive capabilities, especially with non-linear systems. Furthermore, a biological system can be described by two or more different models. Living systems are non-optimal, so their models cannot be discriminated by simply using the principle of parsimony.

Models can contain false or obsolete knowledge and can slow down the discoveries by propagating non-relevant data, mechanisms and behaviors.
Creating a computational model of multicellular systems requires either a modeler to have an interdisciplinary expertise or specialists to work closely together. In both cases, the time needed for the construction of the model is greatly increased.
A model can be difficult to use because it has no simple algebraic solution, it does not fit any existing computational approaches or because it demands

too much computation time. More problems related to simulation are described in the next section.

Simulation problems

Multicellular systems are intrinsically multiscale. Spatial scales start from the size of water molecules, 3×10^{-10} meter up to the size of Sequoia trees that can nearly reach 10^2 meters [1]. Between a molecule of water and a giant sequoia, there are about 12 orders of magnitude which cannot be simulated yet and probably not for a while.
In terms of time, the same problem occurs. The time of a water molecule to reorganize with its neighborhood molecules is about 10^{-12} second and the oldest living tree is close to 5×10^3 years old [2], which corresponds to 15 orders of magnitude. Again, this cannot be simulated using today's computers.
During a simulation, calculation approximations are possible, especially when working with floating-point numbers because of truncation.
A simulation is based on an implementation of a model and it does not always reflect accurately the model itself. Topology and geometry of computational objects and environments strongly affect simulation results. For example, a cell can be modelled as a solid sphere in a continuous environment or as a cube with integer coordinates and size inside a 3D matrix. An underestimated problem concerns the use of advanced software that may reduce the critical mind of those who use them. It should be remembered that models and simulations are only approximations of the real system, especially for students.
Nevertheless, benefits are more important than drawbacks and computational models and simulations contribute to the construction of knowledge in a broad sense.

Properties and control of cells

Living cells are usually seen as the structural and functional basic unit of life. Encyclopaedia Britannica defines the cell as the basic membrane-bound unit that contains the fundamental molecules of life and of which all living things are composed [3]. All known living organisms, in their huge diversity 1, are made of cells, from unicellular organisms to humans 2. Since their discovery by Robert Hooke in the middle of the 17th century 3, they have been one of the most studied scientific objects. Cells have numerous forms 4, functions 5, behaviors 6, interactions 7 and organizations 8 but are based on very similar structures and mechanisms 9. In terms of evolution, the first cell is dated 3.5 billion years old [4]. Multicellular systems are more recent and the oldest one known is 2.1 billion-year-old [5].

A multicellular system is made of interacting cells that can express numerous shapes and functions.
Furthermore, many scales can be observed, starting from tissues that involve several cells, to organs which realize essential functionalities, up-to whole organisms that constitute societies and ecosystems. Every known life kingdom possesses multicellular structures: animal cells (for instance caenorhabditis elegans), plant cells (oak), bacteria (Nostoc for example), fungal cells (Penicillium), protista (without specialized tissues like algae Seaweeds) or archaea (see Methanosarcina acetivorans for instance). Most of them also can perform cellular recognition, a key mechanism that enables the distinction between self and non-self, even on primitive organisms like Porifera [6] [7].
When studying such living structures, many properties can be observed that are biological, mechanical, chemical, thermodynamic, morphological, etc. Therefore, multicellular systems can be modelled with many different theories or approaches. Each of them corresponds to a specific point of view on real multicellular systems which are, by now, too complex to be fully understandable with a single approach.
Numerous and fundamental advances in the understanding and control of cells have been made recently, both at molecular and cellular levels. In 2002, Sydney Brenner, H. Robert Horvitz and John E. Sulston obtained the Nobel Prize for their work on genetic regulation of organ development and programmed cell death, describing seminal mechanisms occurring during organism development. Another important work, made in 2006, involves Shinya Yamanaka's team who has artificially generated a pluripotent stem cell from an adult somatic cell. Qualitative and quantitative improvements have been made to this work since this date. About two years later, in 2008, Doris Taylor and her research team built the first beating bioartificial heart using a tissue scaffold from a rat heart and heart cells from newborn rats. More recently, in 2010, Thomas Vierbuchen et al. were able to directly convert fibroblasts into functional neurons, without passing through the stage of stem

cell. Also, in 2010, Craig Venter and his team created a bacterial cell controlled by a chemically synthesized genome, that although controversial, is paving the way for the construction of artificial organisms. In 2011, Mototsugu Eiraku et al. showed that embryonic stem cells derived into retinal epithelium self-organize to spontaneously form hemispherical epithelial vesicles corresponding to the optic cup. Besides the fact that such researches lead to a better understanding of cells, they also enable the creation of tissues and organs able to replace those of patients from their own cells, avoiding immune rejection and replacing cells that normally do not easily regenerate by themselves like neurons, retina or cardiac cells. The engineering of tissues and organs is still in its infancy 10, but the examples we have at our disposal show that they are about to revolutionize medicine and probably many other areas.

A key point we can extract from works in biology is that some mechanisms governing multicellular structures are based on rules that can be written in the form of algorithm. Moreover, these mechanisms, though often based on microscopic stochastic phenomena, are reproducible, giving them a strong macroscopic determinism. Given these data, we see that algorithms can be developed to reproduce and therefore to explore some of these phenomena using computers. This is facilitated by recent advances in multicore processors whose computing power overcomes the limitations due to stagnating clock frequencies of processors. Recent advances in quantum computing suggest that it could be possible to drastically improve the speed of some algorithms [8].

Finally, let us note the importance of philosophy and epistemology at the border of biology and computation. These includes the works of Maturana and Varela [9] on the autopoietic principle, or those of Jean-Jacques Kupiec with its ontophylogenetics theory [10] which gave useful formalisms to deal with multicellular systems.

Computer science context

Since the beginning of computers in the 1940s, scientists have tried to reproduce living cells in computers. One of the first try has been made by John von Neumann with the concept of cellular automata 11. This has been completed by the reaction-diffusion approach introduced by Alan Turing in 1952. Although computer power was limited at that time, the concepts and their results launched new scientific fields like artificial life and computational biology. This led to many developments, more and more precise, following the fast evolution of computing power.

Two of the most interesting research areas for our work is the multiagent approach [11] where multiple interacting agents evolve in virtual environments and where different models can be executed inside a same simulation. The second interesting approach is called artificial life [12]. It aims to imitate living things, and furthermore to explore life-as-it-might-be.

Advances in software architecture, algorithms and graphical user interface are also important in a context of interdisciplinary researches. A software should be flexible enough to integrate new ideas and new data that are not initially foreseen, and it should be usable by a large spectrum of persons, from end-user to expert in software development.

Another important point is the modelling of multiscale problems which are legion in biology.

Despite the difficulties of simulating these systems, several works have been made. For example, Jean-Louis Deneubourg in 1989 focused on examples where microscopic pheromones guide the collective behaviors of agents [13]. The multiagent architecture of Jacques Ferber showed agents made of agents [14]. Generally, multiscale simulations necessitate powerful processors when the number of entities is high.

Today, the power of computers continues to grow exponentially even though clock speed of microprocessors has stabilized below 5 GHz 12. The means chosen to overcome this limitation is the use of multicore microprocessors. The first multicore processor called POWER4, was made in 2001 by IBM. 13 The first general public multicore processor was the Intel Pentium D in 2005 just followed by the AMD Athlon 64 x2 in 2006 14. Today, the graphics cards have the highest computing power through their massively parallel architecture. They are programmable thanks to general purpose language close the C language like Cuda [15] or OpenCL [16].

The third point is the interactions between human and computer. The maturity of multi-touch, three-dimensional screens, virtual or modified reality and the recent development of screens with tactile sensations, such as friction or roughness, improve the immersion in virtual environments and can help user to create multicellular simulations.

These advances in computer sciences and technologies, are largely used to develop models in the field of computational biology.

Modeling and computational biology context

Computational biology is a vast interdisciplinary field of science where mathematical and algorithmic approaches are applied to biology.
If we focus around the cellular scales, we can see that many scientific approaches can be applied to model biological properties, interactions or mechanisms. These approaches can be chemistry, thermodynamics, classic or quantum mechanics, statistic or individual based modelling, genetic or epigenetic, etc.
There also exists numerous ways to represent cellular systems. Any biological object can be modelled as a single and simple entity or as a complex dynamical multi-entity and self-assembled system.
Furthermore, their environment can be omitted, viewed as static or modelled as a dynamic system.
To model cellular systems, there are two principal methods. The first focuses on individual biological objects like molecules or organels and isolate them. This method is called reductionism, for which a complex system is divided into simpler sub-systems or objects. The second method does the opposite by putting together individual biological objects. This method is called integrative biology, where simple sub-systems or objects are combined to explain the functioning of a bigger system.
An important difficulty is the development of theories able to integrate these scattered data. This development has already begun inside the integrative computational biology field, also called system biology. For Denis Noble, "Systems biology is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programs, but different. It means changing our philosophy, in the full sense of the term".
The best tool we got to work on the complex is, by far, the human brain. However, when the quantity of data is important, when the diversity of behaviors, properties, structures, parameters and scales become overwhelming, the help of computer can be decisive. This computational assistance can apply both when the data are scattered, to gather them in a comprehensive way, or when the theories are well established, to explore their potential and make predictions.
The computer has become what Jol de Rosnay called in 1975 a macroscop, a tool to investigate the infinitely complex, by analogy with the microscope that explores the infinitely small and the telescope which observes the infinitely large [17].
We briefly see in the next section that each scale of modelling has its own methods, theories, tools and objectives, making the development of multiscale computational models difficult.

- *Molecular scale (from 10^{-9} to 10^{-8} m)*

A molecule can be seen either as a whole or made of atoms. It can be modelled by using quantum mechanics or Newtonian theories. At this scale, a classical method is the computation of molecular binding, also called molecular docking where the best-fit location and orientation of a ligand that binds a protein is calculated. This method principally aims at the rational design of drugs [18]. Overviews of docking methods can be seen in [19] and [20]. Software to compute docking have also been developed like Arguslab [21] or AutoDock [22].

- *Macromolecular scale (from 10^{-8} to 10^{-6} m)*

A macromolecule can be modelled either using interacting molecules or as a single entity. A common objective consists in the computation of protein folding to determine the tertiary structure (3-dimensional structure) of a protein using its primary sequence of amino acids. An overview of simulations can be seen in [23]. We can quote some software like Folding at home [24] made to understand protein folding, misfolding and related diseases, using personal computers across the world. Another software called ProteinShop was developed for an interactive protein manipulation [25].
Another example at molecular scale deals with the simulation of lipid membrane. Some methods can be seen in [26] and, as for software, we have GROMACS for example, which is able to treat hundreds to millions of particles [27]. A more macroscopic model has been made to reproduce the behavior of the inner mitochondrial membrane [28].

- *Cell scale (from 10^{-7} to 10^{-5} m)*

At the cellular scale, like the previous levels studied above, a cell can be seen as a single irreducible unit or as a system made of interacting parts. At this

scale level, an important research concerns the cell metabolism. It can be simulated by using very different methods from the ones seen just before.
One of the first work was published in 1964 on metabolic control mechanisms [29]. At this scale, biological regulatory network like genetic regulatory network can be applied to model gene interactions and to help biologists to understand and predict emergent cellular behaviors [30] [31].
Software with advanced graphical user interface have been produced like GEPASI [32] which works on biochemical systems, or like Virtual Cell [33] which treats two or three dimensional biochemical problems or finally, like E-Cell [34] that enables precise whole cell simulations with activation or knock-out of genes.

- *Multicellular scale (from 10^{-6} to 10^{-3} m)*

We move up now to the scale of several interacting cells which is our main subject of interest. A multicellular tissue, organ or organism can be abstracted thanks to interacting single cell models or thanks to more global tissue models. Several computational approaches can be used to model and simulate multicellular systems. The more common are briefly presented below.

Algorithmic approaches

Reaction-diffusion

A seminal research started with the work of Alan Turing on the Chemical Basis of Morphogenesis in 1952 which gave birth to the reaction-diffusion field of science. This field was improved by many researchers like Hanz Meinhardt and J. D. Murray. Although this approach focuses on molecular mechanisms, its scale of observation is close to 10?6 m. It consists in a macroscopic model of interacting and moving molecules and is particularly relevant and useful for the multicellular scale.
The next section describes one of the first integrated software developed to simulate multicellular system. This software, called CompuCell3, is based on the Cellular Potts Model for modelling cells and uses a reaction-diffusion system to model molecules.

Ising system

One of the first system that can reproduce self-organized system and which can be easily simulated with a computer is the Ising model, solved in 1925 by Ernst Ising [35]. It consists in a mathematical model of ferromagnetism with discrete variables, called spins, which are located in a lattice and interact with their nearest neighbors. It reproduces phase-transition occurring in real substances.

Cellular Potts Model

An evolution of the Ising and Pott systems is the Cellular Pott's Model (CPM). It was created in 1992 by James Glazier and Francois Graner [36]. It enables the simulation of multicellular systems by taking into account surface and volume energies for each cell and contact energy between cells.
It is used in many ways today, for example to simulate embryogenesis [37], morphogenesis [38] or angiogenesis [39].

Cellular automata

A classic approach is the cellular automaton, which was designed in the 1940s by John von Neumann and Stanislaw Ulam [40]. It was initially used to study self-reproducible systems. In this approach, a cell is represented by a value located in a matrix. It was used to create a simple but expressive system called the Game of Life in the middle of the 1960's by John Conway where simple local rules, leading the birth or death of cells, enables complex emerging behaviors [41]. This approach is also interesting to reproduce many different physical systems [42]. However, programming complex biological systems with this paradigm is not easy because the design of rules are not intuitive. The multiagent approach is more relevant in an interdisciplinary context.

Multiagent systems (MAS) and Individual Based Modelling (IBM)

An Individual Based Modelling 19 is required when each entity has to be distinguished from others. It is also useful when there are too few entities so that they cannot be summarized by a continuous value. Moreover, it is interesting when local behaviors are known whereas the global behavior is not. furthermore, this modelling is appropriate when the bottom-up emergent properties are preferred to more directive top-down approaches.
Many examples have been developed in MAS. For instance, they were used in 1990 to simulate immune responses thanks to the work of Philip E. Seiden and Franco Celada [43]. This individual based

approach can also be combined with global approaches like in the simulation of the earliest stages of embryogenesis in a multicellular organism or brain [44] or for the simulation of the angiogenesis in cancer development made in 2005 by A. Stéphanou, S.R. McDougall, A.R.A. Anderson and M.A.J. Chaplain [45].

Mass-spring systems

A cell membrane can be seen as a mass-spring system [46], eventually combined with a multiagent systems to improve the expressivity of simulations [47]. Such approach has also been developed by Szymon Stoma et al. to simulate a plant morphogenesis thanks to a mass-spring system [48].

Voronoi diagram

When simulating numerous interacting cells using a mass-spring system, the computation of interacting cell is essential. It can be done by calculating a Delaunay-Voronoi tessellation, as used in the embryomorphic model developed by R. Doursat [49].

Other approaches

Fleisher made a model and a simulator where cells can bind and are able to secrete chemoattractants and chemorepellents to generate patterns of virtual proto-organisms [50]. Laforge et al. developed an approach based on an equilibrium between the auto-stabilization of stochastic gene expression and the interdependence of cells for proliferation to model embryogenesis and cancer [51]. Another model of morphogenesis in cellular systems is related to the study of the cell reorganization during in-vitro wound healing [52].
Other approaches are currently developed and can be seen in the book [53].

Software examples

To complete this paper, this section deals with two fully integrated software designed to reproduce multicellular systems.

CompuCell3D (see figure 1)

- *Description*

CompuCell3D is a free open-source software based on the Cellular Potts Model where cells are modelled thanks to several matrix sites that represent their surface and volume. In this approach, cells also interact with each other thanks to adhering properties and chemical signals. The software enables the simulation of cellular and multicellular systems using parallel devices.

- *Key features*

This software uses an original approach, invented by their authors in 1992, which is relevant for the simulation of many different multicellular systems from cell sorting to organism morphogenesis. This system can also be connected with other matrix-based systems like fluid mechanics based on Navier-Stoke to achieve simulations involving, for example, blood coagulation or blood circulation.

- *Computational model*

In this approach, a molecule is a simple value in a matrix. A cell, which is more detailed than a molecule, is a dynamic set of matrix sites. A membrane is simply defined as cell site borders in contact with other cell sites belonging to other cells. We can notice that many cellular behaviors are simulated like migration, division, differentiation and apoptosis.

- *Biological scale*

The usual scales go from 1 micrometer square (or cube when in 3D) for a cell site to 1 millimeter square (or cube) for a whole simulation.

- *Computational method*

The shape and the size of a cell depend on its target surface and volume. Annex developments have been done, like one enabling the design of a target shape for each cell type [54]. We can note that about 30 plugins can be added to the simulator like Chemotaxis, Mitosis or Secretion.

- *Graphical user interface*

The graphical user interface enables the user to manage the execution of simulations, view the evolution of the system and see the cellular types used. The XML file describing a simulation must be made outside the interface.

- *Programming language*

Two approaches are possible. The first is the use of an XML file to describe a simulation. The second one, which is more powerful, is the use of the

Python language to explicit models and simulations. Developers can create their own plugins using the C language.

- *Documentation*

The web site of Compucell3D offers a useful quick start guide, including tutorials and exercises. Two detailed documents are also dedicated to bio-modelers. The first explains the general objectives, the theoretical and algorithmic point of view and contains advanced examples made with Compucell3D. The second describes how to use Python to develop models and simulations. Moreover, a paper explaining how to create plugins in C language is downloadable for developers.

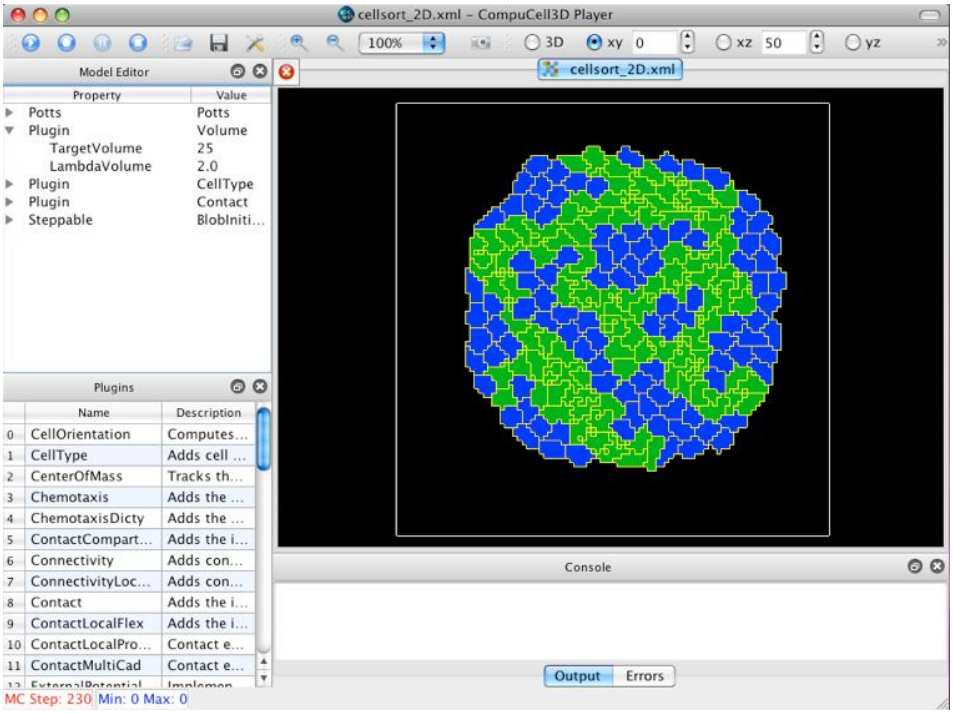


Figure 1: Graphical user interface of the integrated software CompuCell3D.

SimCells (see Figure 2)

- *Description*

SimCells is a free software based on a multiagent system where deformable and interacting cells are modelled inside matrices. The user can create different kind of multicellular systems by using a simple graphical language.

- *Key features*

This software uses an original approach, developed for multicore devices. All steps of modeling are graphically made thanks to an advanced graphical user interface, letting non-developers to create their own simulations.

- *Computational model*

Like for CompuCell3D, many cellular behaviors can be simulated like migration, chemotaxis, division, differentiation, apoptosis, membrane deformation and adhesion.

- *Biological scale*

SimCells uses a multiscale approach with cells, bricks, molecules and fields.

- *Computational method*

It uses recent Graphical Processor Unit (GPU). The number of simulated cells depends on the power of the graphical processor unit (GPU) used. It can be about one million with a premium GPU in 2018.

- *Graphical user interface*

The graphical user interface enables the user to manage the execution of simulations, view the evolution of the system, create cells, design the initial state, view and export simulation results.

- *Programming language*

The creation of cellular behaviors is made by a graphical language under the form of *Conditions Then Actions*. Each entity (a cell, brick or molecule) carries its own behaviors. The number of entities is not limited, and they can be explicitly named (like Lymphocyte, Antigen, etc).

- *Documentation*

The web site of SimCells gives a user guide explaining the different entities specificities, how to program them and how to export results and video.

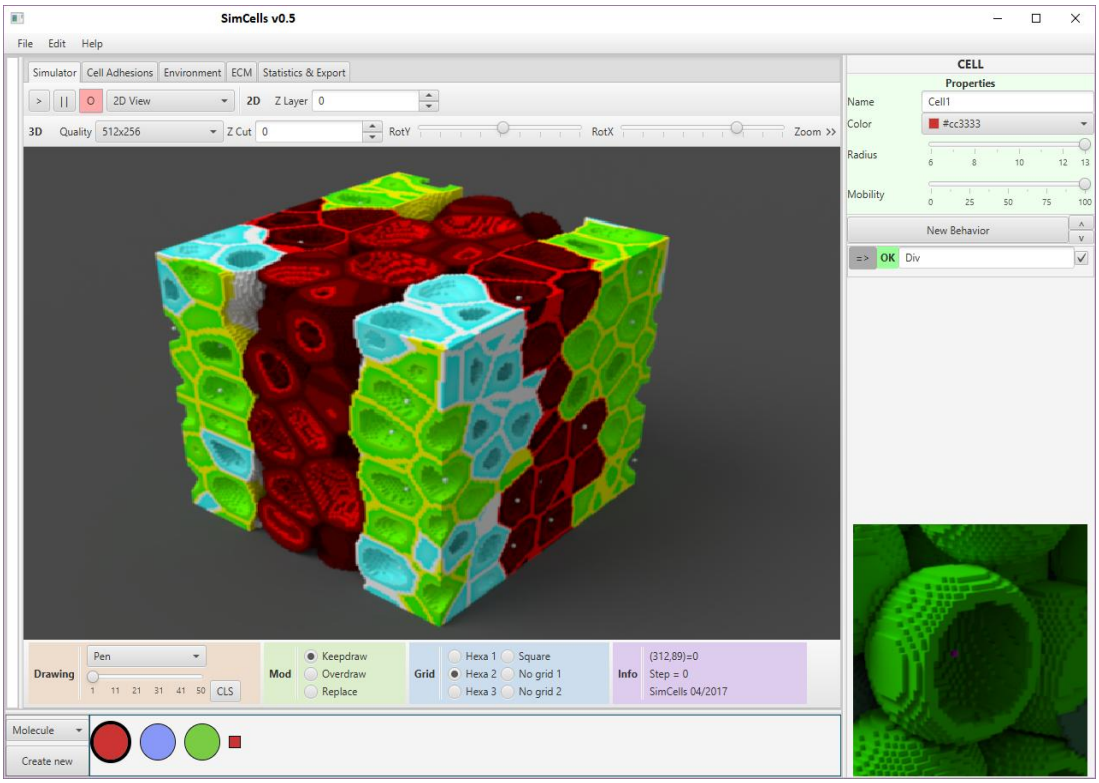


Figure 2: Graphical user interface of the advanced software SimCells.

Timeline of multicellular simulation

This section presents a brief history of software built to simulate multicellular systems. A time line of different models and approaches is shown on the table 1. It covers the period from 1965 up to now. A third time line focuses on advanced software made to simulate multicellular systems. It can be seen on the table 2.

Dates	Computational systems	Authors	Models/Archi
1965	Game of life	J. Conway	SC/CA
1991	Cellular Potts Model	Glazier and Graner	CC/CPM
1992	ImmSim	Seiden and Celada	SC/xCA
1993	Morphogenesis testbed	K. Fleisher	SC/ISS
1994	Cell Programming Language	P. Agarwal	O/O
1997	MAS for Immune Response	P. Ballet	MAS
1997	Bacteria colony growth	E. Ben-Jaob	O/MAS
1998	Cell Cicatrisation	P. Dugnolle	SC/ISS
1998	BacSim	JU. Kreft	O/O
1999	Dictyostelium Model	Stan Mare	CC/CPM
2002	Cytomechanics of cell	A. Stéphanou and P. Tracqui	O/O
2004	Smoldyn	S. Andrews	SC/xCA
2004	HCell	P. Amar	SC/xCA
2004	Flame and Flame GPU	Walker DC and al.	O/O
2004	Modeling embryogenesis and cancer	Kupiec and al.	SC/xCA
2005	A single-cell based model to tumor growth	Drasdo and al.	O/O

[a] The underlying models are abbreviated as follow: SC=Simple Cell, CC=Complex Cell, DE=Differential Equation, O=Other.
[b] The underlying architectures are abbreviated as follow: CA=Cellular Automata, xCA=extended Cellular Automata, MAS=MultiAgent System, CPM=Cellular Potts Model, ISS=Interacting Solid Spheres, MSS=Mass-Spring System, O=Other.
[c] See next works in the next table.

Table 1.1: brief history of computational systems for multi-cellular simulation [a b c].

Dates	Computational systems	Authors	Models/Archi
2006	french flag	G. Beurier et al.	SC/MAS
2006	Organically grown architectures	R. Doursat	CC/O
2006	FlexCell	P. Ballet and P. Tracqui	CC/MAS
2007	Geometric model of Deformation	P. Tracqui	CC/DE
2007	Multiscale model of Thrombus	Zhiliang X	CC/CPM
2007	Hybrid Multiscale Model of Tumor	A. R.A. Anderson	O/O
2007	Emergent tissue organization	T. Beyer	O/O
2007	Individual Viscoelastic Cells	KA. Rejniak	O/O
2006	Plant Morphogenesis	Dupuy	O/O
2008	MorphoBlocs	P. Ballet	SC/MAS
2010	MorphoPotts	S. Tripodi	CC/CPM
2010	Evolving virtual embryogenesis	R. Thenius	O/O
2010	Autoregulated growth	M. Dauschan	O/O
2010	Delaunay object dynamics for Tissues	T. Beyer	O/O
2011	JBioDyn	P. Ballet	SC/MAS
2011	PreBioDyn	N. Glade and P. Ballet	SC/MAS
2011	GEcoBioDyn	N. Glade and P. Ballet	SC/MAS
2011	GPU Cell	P. Ballet	SC/xCA

[a] See previous work in the previous table.

Table 1.2: brief history of computational systems for multi-cellular simulation [a].

Dates	Advanced Software	Authors	Model/Archi
1992	ImmSim	Seiden and Celada	SC/xCA
1998	BacSim	JU. Kreft	O/O
1999	NetLogo	Wilensky	O/MAS
1999	SimunA	P. Ballet	SC/MAS
2000	HematoSim	P. Ballet	SC/MAS
2000	Cellular Automata Viewer	Rennard	SC/CA
2001	MGS	J-L. Giavitto	CC/O
2003	SimBioDyn	P. Ballet	CS/MAS+MSS
2004	Smoldyn	S. Andrews	SC/xCA
2004	HCell	P. Amar	SC/MAS
2004	Flame and Flame GPU	Walker DC and al.	O/O
2007	netBioDyn	P. Ballet	SC/MAS
2007	CompuCell3D	Glazier and Graner	CS/CPM
2008	BSim	Stephen Reid	O/O
2017	SimCells	P. Ballet	O/O

[a] An advanced software is based on a computational model (Game of Life or CPM for example). It has a graphical user interface, can import, export, load and save simulations and can export or draw the simulation results.

Table 2: advanced software for multi-cellular simulation [a].

SimCells example

The growth of a cancerous tumor and its blood vessel network is a multicellular self-regulated mechanism. Its comprehension is complex because it involves a feedback loop: the tumor is guiding the angiogenesis, and at the same time, the blood vessels supply the cancerous cells with nutriments and oxygen.

A way of studying the dynamics of this system consists in building a computational multiagent simulation that can i) exhibit fundamental processes occurring over time, ii) make forecasts on how the tumor could evolve in the future and iii) give clues about how to control the tumor development.

A multiagent simulation, based on the software SimCells, is described hereafter.

Virtual agents' description

The simulation is made of three principal agents: *cancerous cells*, *blood vessel* and *tip cells* (see figure 3). Moreover, three diffusing fields are required: the *supply field*, (field 3) generated by the blood vessel, the *vascular growth field* (field 1) generated by cancerous cells and the *matter consumption field* (field 2) generated by the growing blood vessels.

Two other agents are used to reproduce inert tissue that can be found close to tumors: bones and healthy tissue.

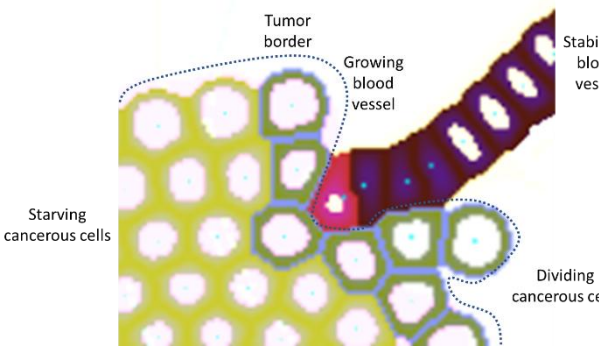


Figure 3: main agents of the simulation.

- *Cancerous cells*

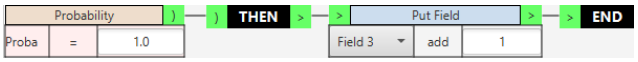
They have two states: *starvation*, when they are too far from a blood vessel and *dividing* when they are supplied by blood vessels.

- *Blood vessels*

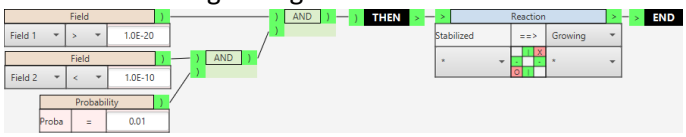
A blood vessel agent has two states: *stabilized*, when mature and not evolving anymore and *growing* when developing towards the tumor.

Stabilized vessels have 2 behaviors:

Supply: at each simulation time step, each blood vessel agent produces a diffusing field 3 (supply field).

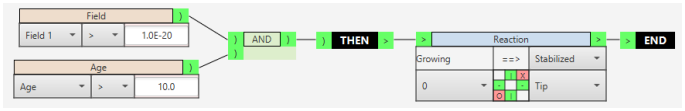


Angiogenesis: at each time step, on a probability of 0.01 and when the field 1 (vascular growth field) is greater than a threshold and when the field 2 (matter consumption field) is lower than another threshold, then the stabilized blood vessel become a growing blood vessel.



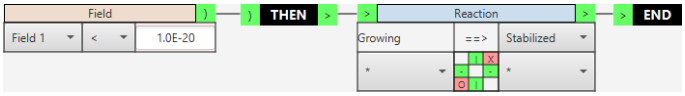
Growing vessels have 4 behaviors:

Stabilization / Progression:



Supply:

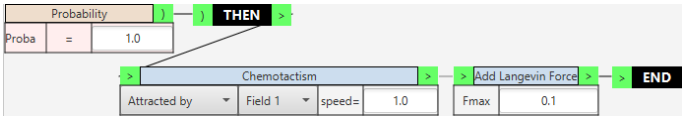
Stabilization:



Matter consumption:

- *Tip cells*

Their main behavior consists in orienting towards the positive gradient of the vascular growth field:



Simulation results

A 2D simulation is performed in a 1024x512 matrix. The initial state contains a single vertical blood vessel and a tiny round tumor with about 50 cancerous cells. The figure 4 shows the early stages of angiogenesis. At about 7000 simulation steps, the tumor reaches a bone (see figure 5). The simulation ended after 27000 simulation steps (see figure 6). At this time, all the available space is occupied by the tumor and its blood

vessel network, showing the robustness of this co-developing system.

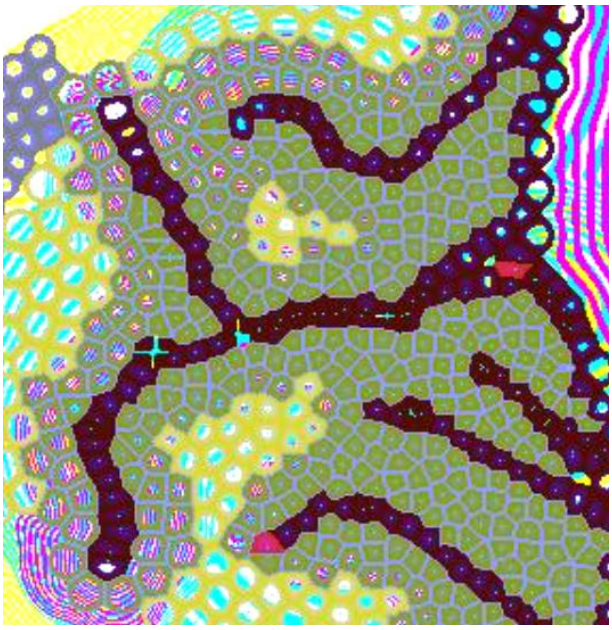


Figure 4: simulation after 1950 simulation steps. The main blood vessel (on the right), has new developing branches (from left to right).

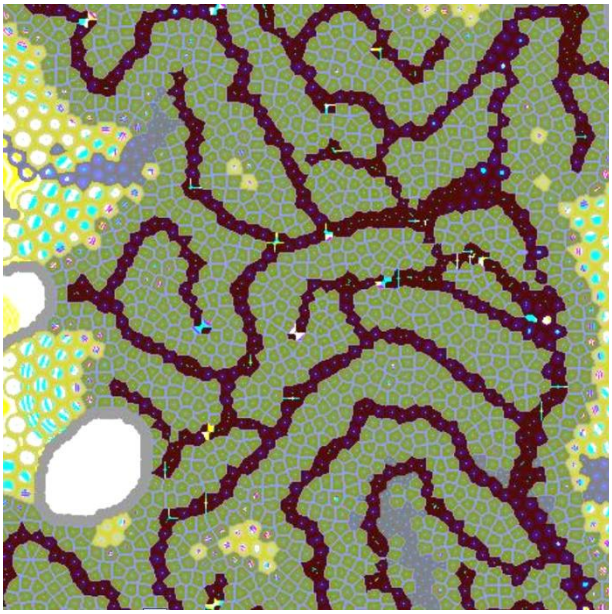


Figure 5: simulation at 6930 steps. The tumor continues to grow, inducing the co-development of the blood vessel network. Round gray agents, on the left, represent bones. Grey cells, at the upper-left and bottom-right, represent inert tissues compressed by cancerous cells.

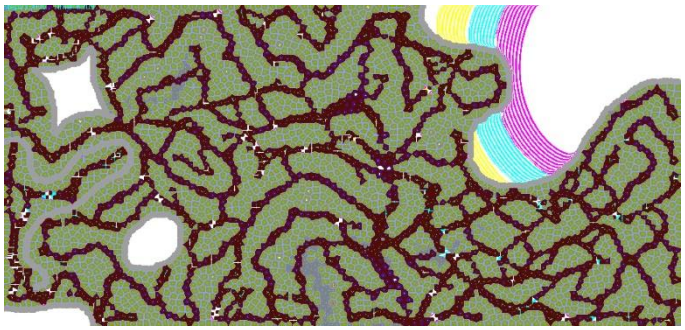


Figure 6: final simulation state at 27030 steps. All available space is occupied by dividing cancerous cells and stabilized blood vessels.

The simulation can also be executed in a 3D environment of size 126x126x126, but the size of the environment must be reduced (see Figure 5) due to memory size of the graphical card. The early stage of the simulation is shown on the figure 7.

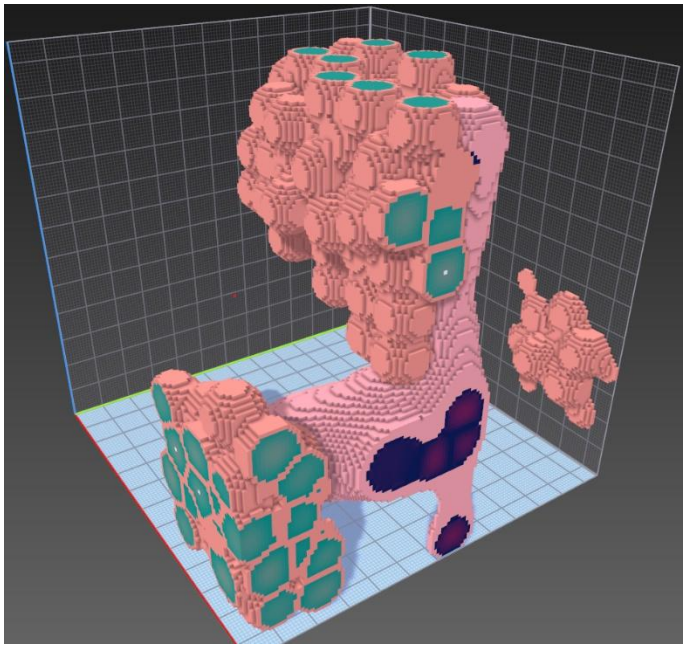


Figure 7: same simulation in a 3D environment.

Conclusion

The biomedical field at cellular scale and computer science are independently and together in deep change, opening new ways in the control of the living at the cellular scale.
In this context, computer aided design of large and dynamic multicellular tissues becomes possible. Computer scientists and biologists can cooperate in a complex interdisciplinary field thanks to advanced software, sharing common formal computing languages.

The software, like SimCells, use specific graphical interfaces to exploit computational models in a simple way, keeping creativity of the user at a high level.

The simulation of numerous interacting cells can use multicore devices to drastically decrease the computational time.

Interdisciplinary in science, although hard to implement, is a requirement for the development of multicellular simulators. More scientists and engineers at the interface of different sciences should be formed to be the spearhead of these new advances.

More generally, it will help to support biology and medicine towards more predictive, quantitative and individualized levels.

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