

Visualization of Biological Processes Described by Models of Apoptosis

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Abstract: Visualization of biochemical processes is important for understanding various phenomena in living organisms. One of the famous biological processes is apoptosis. Apoptosis or programmed cell death plays an important role in many physiological states and diseases. Detection of apoptotic cells, tracing the development of apoptosis, drug development and regulation of apoptosis are an important parts of basic research in medicine. A large number of models have been developed that are based on differential equations of chemical kinetics, and can be expressed in a uniform notation using some XML-based languages. Here we briefly discuss the simulation and visual presentation models of apoptosis. We review modelling languages, such as SBML, FieldML and CellML and briefly describe the simulation environments and software libraries for these languages (SBMLeditor, libSBML, SBMLToolbox, MGSmodeller, OpenCell). These tools can display models schematically and output results in the form of graphs showing time dependencies of component concentrations. However, at the present time we have not software that could represent the result of modelling in a form animation especially in the form of three dimensional models. We discuss approaches to visualization of biological processes described by apoptosis models by using descriptive as well as quantitative models. The quantitative method was implemented by using a three-dimensional visualization of molecular biology processes modelled by chemical kinetic equations. The quantitative parameters in our visualization scheme are determined based on kinetic equations governing the participating components, so our visualization is not only qualitative but also quantitative. The descriptive method was presented as a game developed by using a game engine and video clips. As case studies we presented examples of visualization obtained by using various methods.

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1. Introduction

The visualization of biological data is the part of bioinformatics that concentrates on issues of applying the computer graphics in various fields of life sciences. Only a partial list of problems is to be solved in this area including the visualization of the genome, macromolecular structures, phylogeny, dentition, microscopy, and magnetic resonance visualization data. Software visualization systems are also diverse, ranging from simple and straightforward to complex integrated software solutions. Visualization is widely used for educational purposes. However, different methods of modeling are used for the disclosure of essence of the processes, the laws of functioning and the description of systems. The modeling of biological systems is one of the most important tasks of systemic biology and bioinformatics. The computational biology develops algorithms, data structures and methods for visualization and modeling biological systems. The methods of computer modeling and appropriate XML-based modeling languages are often used in solving problems. One of them is the problem of modeling and visualization of the apoptosis process.

Apoptosis plays a significant role in many physiological states and diseases [1], e.g. in understanding the development of cancer and cardiovascular diseases. Generally accepted standards of modelling are SBML [2], BioPax and CellML [3]. There are also comparatively new projects, which include FieldML [4,5] - the language that describes the spaces (fields), which is used to describe the human body. In spite of the existing progress, the problem of visualizing biochemical processes and models is not resolved completely. Therefore we propose both qualitative and also quantitative approaches to visualization of apoptosis models. To implement some kinds of visualization, we developed videos and software based on the game engine and C#. To support the process, the database of three-dimensional forms of model molecular complexes was created. This work is a brief and apparently incomplete overview of languages and environments for modelling the biological processes that are used and could be used to describe apoptosis. There is also an analysis of the approaches to the creation of a system of visualization of apoptosis models.

The work consists of six basic parts.

The second part is a brief overview of languages and tools of computational biology that are used for modelling of apoptosis. We review some popular languages such as CellML, SBML, FieldML and programming tools designed for editing and debugging models.

The third part describes some CellML models and approaches to visualization of apoptosis.

In the fourth, fifth and sixth parts we analyze the approaches to the creation of systems that could visualize apoptosis models. We present examples of implementation and briefly discuss the advantages and disadvantages of the approaches. Three basic ways of visualization are reviewed:

- Creating animations (video clips) or static visualizations of the process by using a descriptive (qualitative) model.

- Developing a system for converting descriptive models with a limited set of parameters into visual representations (picture, photography and video).

- Developing a system for visualization of biological models by using modeling languages such as CellML

In conclusion we briefly review the difficulties and disadvantages of implementations.

To avoid confusion, we would like to note that this paper does not address the visualization of apoptosis of living organisms by means of invasive and non-invasive methods, which are another big and promising field of practical research. We present approaches only to visualization of apoptosis models.

2. The languages and tools for modelling biological processes

There are several popular languages for describing biological processes: SBML, CellML, FieldML. These languages lie in the basis of several frameworks considered below.

The SBML language is focused on representation of chemical reactions in the form of processes. The processes in this case are caused by the actions of participants. Such an approach is typical also for the other types of processes. Moreover, the language supports mathematical functions and discrete processes, thus it can be used not only for modelling of biochemical processes. Enhanced Petri nets is used as the mathematical basis of this tool of representing biochemical reactions [6]. Moreover, the language supports mathematical functions and discrete processes, thus it can be used not only for the modelling of biochemical processes. One of the models of apoptosis process on the basis of SBML is given in [7], where MatLab is used as a simulation tool. A huge number of models are annotated in BioModels Database (<http://www.ebi.ac.uk/biomodels/>) [8].

CellML is an XML-based markup language for describing mathematical models. It is originally created for biology. Although the language reminds of SBML, it is aimed at a wider class of models, not only in the field of biochemistry. The first specifications of CellML were released in 2001. CellML is currently popular as a compact format to describe the computational models [9]. CellML has a modular structure that facilitates the description of complex interconnected cell models. A variety of tools exists for the CellML and SBML model creation and modification (editors) as well as for their debugging and verification (validators).

CellDesigner is a structured diagram editor for drawing gene-regulatory and biochemical networks. It stores a diagram using the SBML and supports browsing and modifying these models. Let's briefly review this tools.

SBMLeditor is a relatively simple, low-level editor for SBML files. It allows of manipulating the elements of SBML and saving the file with the actions. SBMLeditor also allows of creating and editing annotations, in accordance with the SBML specifications [10].

CellDesigner is a structured diagram editor for drawing gene-regulatory and biochemical networks. It stores a diagram using the SBML and it can browse and modify these models [11].

libSBML is a free programming library, with an open source reading, writing, manipulation, transfer and checking SBML files and data streams. This is an API (application programming interface) which can be inserted into your own applications. It is supported by many programming languages and operating systems, such as C++, Java, Python, MATLAB, C#, Ruby, Perl, Octave [12, 13].

SBMLToolbox. is built on the basis of libSBML and provides a set of basic functions that allow of using SBML models in MATLAB and Octave. SBMLToolbox provides functions for creating and testing models, manipulating and modeling these models by using ordinary differential equations solvers. SBMLToolbox translates SBML models to / from the structure of MATLAB, called MATLAB_SBML [14]. It provides tools for working with these organizations as a part of the MATLAB or Octave. LibSBML allows importing and exporting these structures to / from SBML files. The toolbar should not be considered a complete platform of biology tools for MATLAB, it provides the ability to access SBML from MATLAB and actually serves as a starting point from which users can develop their own applications.

SBML converters – there are a lot of converters that allow of converting from/to SBML to BioPax 2 and 3, XPP and Octave [2].

MGSmodeller is a system designed for the creation, calculation and analysis of molecular genetic systems (IGU). It contains the following modules: "designer / modeler", "model calculations", "inverse problem", "optimal control". The versatility of the system is based on the capabilities of each module. The "designer / modeler" module allows to create and edit models by using the original and is developed by the authors' specification standard for «SiBML» models. Syntactic and semantic analyses for language modeling are implemented in this system. Mathematical models in MGSmodeller are reconstructed in the format and rules of the standard SibML within the universal chemical-kinetic approach [15, 16]. The analysis of simulation results are produced by MGSmodeller, Matlab and Gnuplot. Compilation units and numerical study are implemented in FORTRAN. Module annotations and editing SibML language, as well as post-processing of the results are realized in Java language [17]. The MGSmodeller system also includes: tools for constructing IGU models, tools for preparing models for the calculation of dynamics, solution of reverse and optimal control problems.

OpenCell (Physiome) is a framework for working with CellML models. It provides a uniform way of working with CellML documents, including the creation of new models, editing of existing models, and running simulations [18]. Its main features:

- Integration of CellML models that include ordinary differential equations.
- CellML 1.0 and CellML 1.1 support, which allows of building complex models by importing one model to another.
- Ability to work in a variety of operating systems, Linux, Windows and Mac OS.
- Ability to build and edit graphics.
- Support of draft specifications metadata modeling and graphics.
- The project is open (Open Source).

Although the processes of apoptosis were originally manifested at the cellular level, they affect the organs and tissues of the body. Thereby it is appropriate to consider the means of human body modeling.

One of the comparatively new projects in the field of human body modeling is FieldML [4] - the language that describes the spaces (fields). Its concept is described in [4], and supported by the project [5]. This modeling language is developed as a standard for modeling and sharing descriptions of fields using a wide range of computational methods. This language includes a set of operators to determine the generalized fields as functions of other

fields, ranging from the primary domain of the field, including a set of discrete objects and a coordinate system. It is extensible because of the ability to add new operators and to arbitrarily combine them in expressions. As a result, it is well-suited for the description of biological materials and organ systems [6]. In general, it is a declarative language for representing hierarchical models that use generalized mathematical fields. Also FieldML can be used to represent dynamic 3D models and fields in the area of computational models of cells, tissues and organs.

A key feature of FieldML format is the separation of large amounts of data described in XML. This makes it more efficient for a partial reading and for the assessment of the compatibility description of the fields before the merger of the existing data in the memory. The second important feature is that the language and its components are open source. The FieldML language is based on CMISS software (www.cmiss.org) that is designed for modeling fields of finite elements. CMISS uses fields to model most of the variables, including the geometric properties, material properties and other dependent variables. To visualize the models, it is necessary to install special plug-in ZINC viewer (<http://www.cmiss.org/ReleaseCenter/zinc/releases/0.7.0.0>). Despite the fact that the FieldML language is not complete and not accepted as standard (current version 0.2), there are examples of its successful application that demonstrate the capabilities of this campaign in the modeling and visualization of the human body. Examples of applying FieldML are shown in [19], where the computational mechanics of the heart is demonstrated, and the use of basic functions with the observed distribution of the fibers is illustrated.

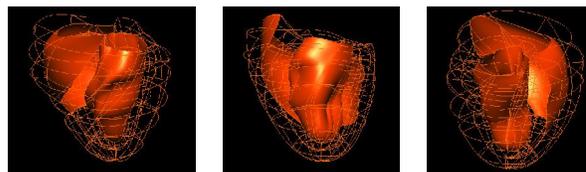


Figure 1. Different views of the model by using ZINC plug-in

The ventricular model (Figure 2) is based on the theory of finite deformation of anisotropic and inhomogeneous material properties and accurate representation of the geometry of the ventricles.

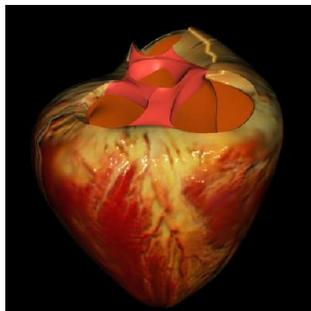


Figure 2. Ventricular model [19]

Other models may represent tissue structure, diffusion of proteins and other biomedical components, documented in the anatomy etc.

3. Visualization of apoptosis and models based on CellML

Currently, there is a significant number of sources that use models constructed on the basis of CellML. See, for example <http://models.cellml.org/cellml>. This repository shows the possibilities of the language in representing wide categories of molecular biology models. Some of the models are devoted to the analysis of the impact of various factors on the process of apoptosis. There are about 27 papers describing apoptosis in a form of mathematical models.

Authors of the article [20] presented a mathematical model which includes TNF-initiated survival and apoptotic cascades. The model describes the known protein-protein interaction that is determined experimentally. Using the tumor cells as a hypothetical model, the interactions between the components of survival and apoptosis were researched. The model is capable of predicting the viability of cells in condition of DNA damage within the duration of the stimulus TNF- α .

The work [21] proposes a mathematical model to simulate the effects of nitric oxide (NO) on apoptosis. Biochemical apoptosis in combination with NO-related reactions is described with ordinary differential equations using the mass action kinetics. In the absence of NO, the model predicts either cell survival or apoptosis (bistable behavior) with changes in the early apoptotic response times depending on the strength of extracellular stimuli. These models also describe transient effects of apoptosis, the duration of which can be up to an hour, despite the possible pursuit of antiapoptotic state. The calculations indicate the importance of the exact timing of NO production and external stimulation to identify potential pro-or anti-apoptotic roles of NO.

In the paper [22] the authors proposed a mathematical model for mitochondria-dependent

apoptosis. This study based on mathematical modelling confirms the authors' assertion that the cooperativity in apoptosome formation is critical for determining the healthy responses to apoptotic stimuli, and also helps to identify the role of Bax, Bcl-2 and MPTP in relation to apoptosome formation.

All of these models are illustrated by the schemas and diagrams that show details of simulation. Note, that one of the first approaches to visualizing CellML models was proposed in [23]. This article considers the framework that combines visual languages and CellML ontologies to support the visualization of mathematical models. Nevertheless, it would be very useful to see the changes in proteins, cells and tissues of organs that are described in the models. The combination of modeling and visualization makes an appropriate visual representation that can improve our understanding of occurring processes. Therefore we need to visualize the biological process described by models. There are three potential ways of visualization:

- Creating animations (video clips) or static visualizations of the process by using a descriptive (qualitative) model.
- Developing a system for converting descriptive models with a limited set of parameters into a visual representation (picture, photography and video).
- Developing a system for visualization of biomodels created by using modelling languages such as CellML

A brief analysis of the capabilities of each approach and results is given below.

4. Creating animations or static visualizations of the process by using a qualitative model

This line of investigation was realized during the first phase of the research. The following videos were developed (Figures 3-6):

- Apoptosis & necrosis.
- Myocardial tissues of a rat with the coronary artery disease. A video clip created from photos.
- The protein function scheme of anti-apoptotic hsp70 warm shock.
- An animated scheme of apoptosis.

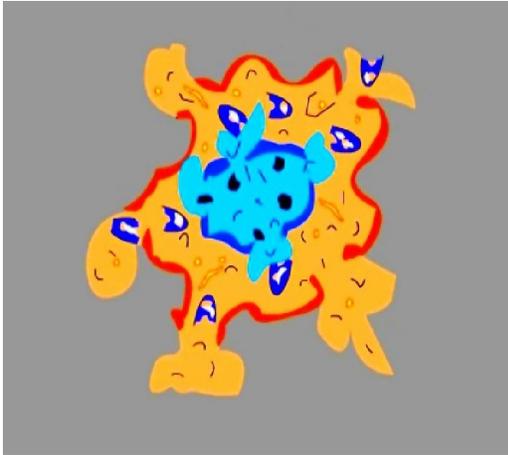


Figure 3. Apoptosis via necrosis. Comparative video.



Figure 4. Myocardial tissues of a rat with the coronary artery disease.

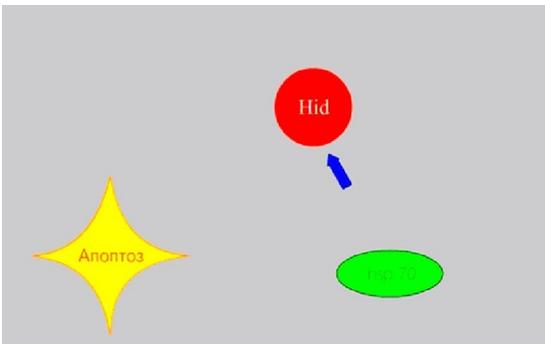


Figure 5. The protein function scheme of anti-apoptotic hsp70 warm shock.

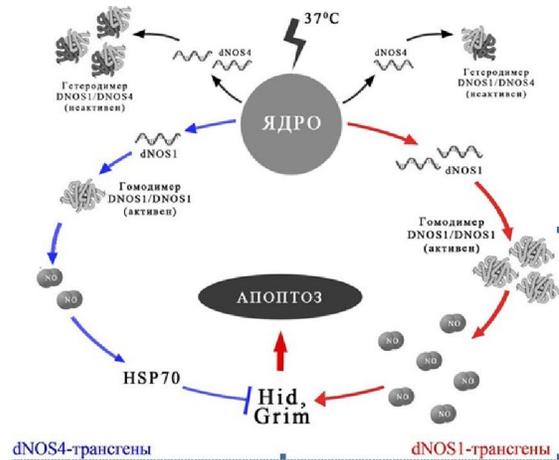


Figure 6. Animated scheme of apoptosis.

This approach has merits and demerits:

Advantage – the simplest approach in realization.

Disadvantage – absence of variability, disability of process modeling.

5. Developing a system for converting descriptive models with a limited set of parameters into visual representation

To realize this approach a set of video clips or images (display images) should be created. Each of these video clips corresponds to its set of parameters. The interface should allow to input the parameters and to check the limitations. The system should select the video clip or image with the parameters closest to the input one. This approach is possible due to the fact that many available models are descriptive, and if it is planned to use them mainly for educational purposes. In addition, it is possible to create a system to select the most appropriate representation as described in accordance with the input parameters. There are several aspects to solve the problem:

- Creating a set of images and videos.
- Developing the database for saving video clips and parameters of appropriate processes.
- Creating a system of selection of the most suitable images or videos that correspond to the input parameters.
- Creating an interface system, which should analyze the input parameters, check them and show them on the screen.

The system is illustrated by Fig. 7, where User is a system user (player, student, doctor);

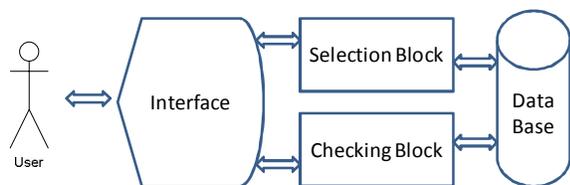


Figure 7. Simple visualization system.

Interface is a block that works with the user, implements receipt of model parameters and its visualization; The selection block selects the model suitable for the parameters input by the user; Database is a system database that stores a set of images, parameters and appropriate restrictions. The block of checking is the block that controls input parameters.

This approach was realized by creating a simple game based on the model of bistability of apoptosis proposed in [22]. The game was created by using the Game Maker game engine. Figures 8 and 9 show the stages of apoptosis in the game.



Figure 8. The beginning of the apoptosis process in the game.

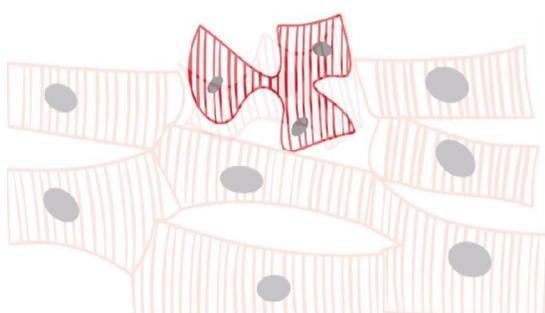


Figure 9. Cell destruction as a part of apoptosis process.

As mentioned above, the method has advantages and disadvantages:

Advantage – simplicity in realization.

Disadvantage – absence of variability, reduced abilities of process modeling.

6. Development of a system for visualization biological models created by using modelling languages

The system should convert the changes of parameters in a model that is created by one of the modeling languages into changes of visual objects. This approach seems the most promising, but also the most difficult because of a lack of a comprehensive mathematical model of apoptosis as well as the complexity of the system. At present, the modelling environment can be created to display the model schematically [23].

To create full 2-D and 3-D graphical models that are close to photographic images and the ability to react to changes of the parameters will require a significant effort. The first step is to create the game that shows processes at the molecules level. These processes are described in the models and can be represented as result of simulation. To realize this approach we developed parser-visualizator that reads output file of simulation and creates 3D-models [24].

Our method creates three-dimensional visualization of the molecular biology processes modeled by chemical kinetic equations. The quantitative parameters are determined from kinetic equations governing the participating components. Fig. 10 illustrates this approach.

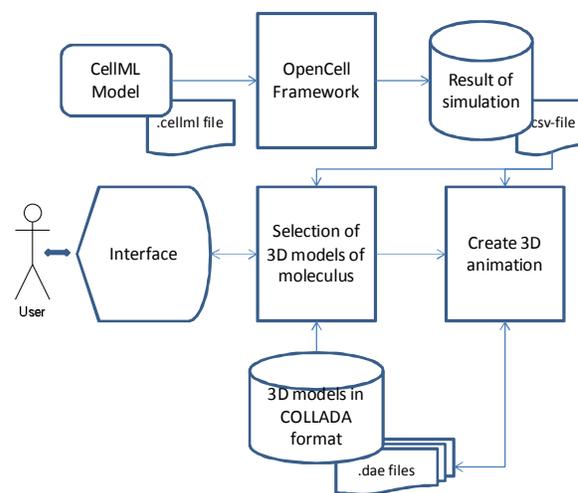


Figure 10. The scheme of parser-visualizator.

The Framework OpenCell reads the .cellml file that describes the model. The result of simulation is saved in a .csv file. Parser can obtain all needed information from this file. The User chooses molecules by using a simple interfacing form. Then, if the selected molecules have graphical representation in the COLLADA format, they will be shown in a graphical window. In the window the user can see the Brownian movement of the molecules.

The number of molecules corresponds to concentration of proteins at the moments of the model time. Fig. 11 shows the screenshot of the window.

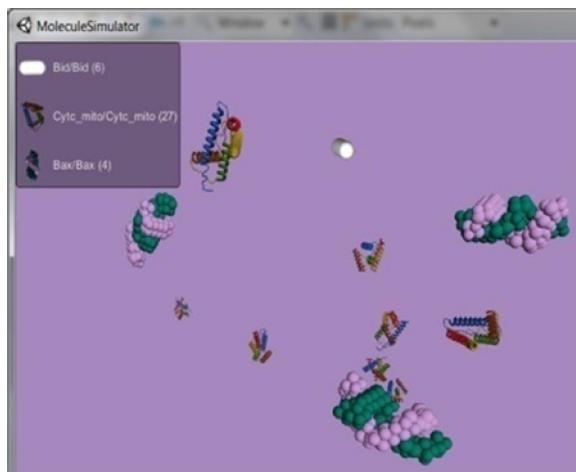


Figure 11. Animation of Brownian movement of proteins.

An advantage of these approaches is the possibility to create visualization that corresponds to the model parameters.

A disadvantage is the necessity to store a huge amount of 3D-models of proteins.

Of course we should note that the possibilities of the approach is limited by a model and expressiveness of the modeling language.

7. Conclusion

Biological processes that occur in human body are complex for modelling and understanding and not fully studied. A living organism is the most complex natural object for research. In this context, visualization of the processes is a normal way for understanding and analysing them to improve the quality of their studying.

Despite the relative abundance of methods and tools for modeling that were briefly discussed in this paper (SBMLeditor, libSBML, SBMLToolbox, MGSmodeller, OpenCell) today there are no full-featured environments providing not only modeling but also for a graphical display of two-and three-dimensional models of biological processes.

There are several approaches to creating a visualization system of apoptosis models, each of them has its own advantages and disadvantages:

First. Creation of animated (video clips) or static images of processes by using the descriptive (qualitative) model. It is plain that absence of variability is a natural feature of this method. Therefore we can use results for illustration only.

Second. The system of converting descriptive models into visual models (video clips, games). Of course, all descriptive models are characterized by a fundamental disadvantage. Their abilities of process modelling are very limited.

Third. The system of converting changes of the model parameters into a visual object model. This way seems to be the most promising, but also the most difficult, especially if we want to create a three-dimensional realistic model.

Literary sources indicate a huge interest of researchers in apoptosis modeling using the language CellML. Use of CellML as a data source for the graphic model of the process is obviously natural.

Software products like OpenCell can solve models defined in CellML. However, their output in the form of graphs shows only time dependences of component concentrations. This gives a quantitative description but doesn't provide for a rich visual presentation. We propose a method for three-dimensional visualization of molecular biology processes modelled by chemical kinetic equations. The developed program works with any molecular shapes stored in COLLADA format and simulates the Brownian movement of the proteins and changing of their concentration.

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