A Method of Three-Dimensional Visualization of Molecular Processes of Apoptosis

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Abstract. 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 the differential equations of the chemical kinetics, and can be expressed in a uniform notation using some XML-based languages, such as SBML and CellML. We describe the CellML and the simulation environment OpenCell herein. 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 do not have a software that could represent the results of the modelling in a form of animations as well as in the form of 3-D models. Using descriptive as well as quantitative models we discuss approaches to visualize the biological processes described by the apoptosis models. The quantitative method was implemented using a 3-D visualization of the molecular biological processes modelled by chemical kinetic equations. The quantitative parameters in our visualization scheme are determined based on the kinetic equations governing the participating components, so our visualization is not only qualitative but also quantitative. To implement this visualization, the C# software and a database of 3-D forms that model molecular complexes are developed. We present 3-D visualization of the molecular processes described in the mathematical model for the mitochondria-dependent apoptosis proposed by Bagci et al. [22] as a case study.

Keywords: Apoptosis · Visualization · Chemical kinetics · Molecular biology

L.T. De Paolis and A. Mongelli (Eds.): AVR 2014, LNCS 8853, pp. 103–112, 2014.
DOI: 10.1007/978-3-319-13969-2_8

1 Introduction

Visualization of biomolecular processes is essential for understanding of the biological mechanisms' interaction principles. Chemical composition is not the only factor that determines the interactions between proteins, organelles and other biological molecular complexes. Their shape, i.e. the spatial configuration of the chemical components included in the composition of the macromolecules has significant role. Computer visualization of such interactions will have an important role in understanding the processes and will help to solve the problem of the chemicals' synthesis in order to control the biological processes in the cells; this might lead to the creation of the new medical products. E.g, the diphtheria toxin produced by the Corynebacterium diphtheriae bacteria that is diphtheria pathogenic agent may create pH-dependent pores or channels in the cell membranes. However, the mechanism of the diphtheria toxin permeation through the membrane is currently unknown. In order to answer this question, the understanding of the spatial forms that can be shaped by diphtheria toxin during the interaction with the membrane is required. It is a very difficult to determine experimentally and no one was able to do this yet. This is the reason why the computer modeling and the visualization of the given interaction may cast the light on this problem. The understanding of the mechanisms of the diphtheria toxin penetration through the cellular membrane may lead to the development of the medical products to cure the diphtheria. The study of the diphtheria toxin is also important because this molecule has the same spatial configuration as the Bcl-xL proteing, which has an important role in the process of apoptosis of the mammals' cells including humans [1].

Apoptosis is the process of programmed cell death (PCD) that may occur in multicellular organisms [2]. In contrast to necrosis, which is a form of traumatic cell death that results from acute cellular injury, in general apoptosis confers advantages during an organism's lifecycle.

Despite the chemical composition of the Bcl-xL protein is significantly different from that of the diphtheria toxin the spatial forms of these complexes are very similar and their main functions come to the light during their interactions with the lipid membranes. Besides Bcl-xL the mammal cells' apoptosis is controlled by some other proteins of the Bcl-2 super-family [3-6]. The question of their interaction with mitochondria membranes is opened for all of them for over 20 years as it is very difficult to determine experimentally. Several different hypothesis were proposed [7-9] but it is unknown which one is correct. Computer modelling and visualization may have an important role in the verification of the existing hypothesis as well as in the creation of the new ones and they may lead to the new ideas in conducting the experiments.

The detailed study of the apoptosis process is important as the dysfunction of the apoptosis dynamics leads to the oncological diseases as well as to the neural and endocreanal system diseases. The studies in this field already lead to the creation of the new medical products [10].

In spite of the existing progress, the problem of visualizing biochemical processes and models of apoptosis is not resolved completely. Therefore we propose both qualitative and also quantitative approaches to visualization of apoptosis models in [11].

In the work mentioned above, the languages and tools of computational biology that are used for modeling of apoptosis are considered. Then we described and discussed three possible ways to visualization biological processes and had proposed system for visualization of biomolecular models based on CellML modeling language.

This work contains explanation of the system named as parser-visualizator in details.

2 Basic Features of CellML and OpenCell

There are several popular languages to describe the biological processes: SBML, CellML, FieldML.

One of the popular languages is CellML. It is a compact format to describe the computational models and has a modular structure that facilitates the description of the complex interconnected cell models. Basic features of CellML were described in [12]. The model of the biological processes described by CellML has unique identifier, which can be used to refer to the model. A CellML document can include the elements of one of the following types: units; components; connections; groups; import; or metadata.

- Units are used to measure the quantities. Conversion of one unit to another would be done by CellML framework software.
- Components are the parts of CellML model that are related to one another. Component frequently includes units definitions, variable declarations, equations. Mathematic equations are written using MathML specification.
- Connection establishes mapping between two components, which means that the variables declared in one component might be accessed from another one.
- Groups provide mechanisms to organize components into hierarchies that support geometric containment and logical encapsulation.
- Metadata or data about data can be embedded in the CellML document by using the Resource Description Framework. This type of the information is intended for later usage, for example to search models and components.

A variety of tools exists for the CellML model creation and modification (editors) as well as for their debugging and verification (validators). One of the most famous tools is the OpenCell (Physiome). OpenCell is a framework for working with CellMLmodels (Fig. 1).

It is a uniform way of working with CellML documents including all basic steps of simulation from the creation of new models, editing of existing models and running [13]. OpenCell's main features are:

- Integration of CellML models that includes ordinary differential equations.
- Ability to work in a variety of operating systems, Linux, Windows and Mac OS.
- Ability to build and edit graphics.
- Support of metadata modeling and graphics draft specifications.
- Support of principles of Open Source.

- Based on this possibilities of framework we can create the models in a form of a set of differential equations and obtain results as a list or diagram of proteins concentration that are dependent on the time. By using repository of CellML models users can download and insert some of them into the OpenCell and obtain results from existing ones.

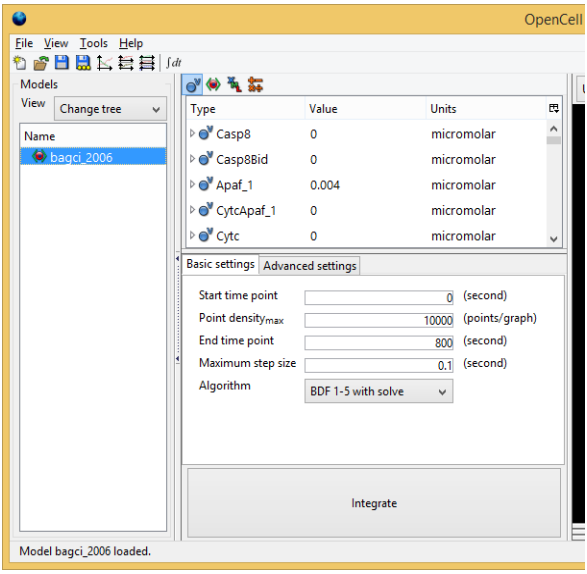

Fig. 1. The screenshot of OpenCell framework

3 Apoptosis Models Based on CellML

There are about 27 papers describing apoptosis in the form of mathematical models constructed on the basis of CellML on the portal http://models.cellml.org/cellml. This repository shows the possibilities of the language to represent wide categories of molecular biological models. The models are devoted to the analysis of the impact of various factors on the process of apoptosis. For example, the mathematical model which includes TNF-initiated survival and apoptotic cascades is presented in the article [14]. The model is capable of predicting the vitality of the cells in condition of DNA damage within the duration of the stimulus TNF-a.

The mathematical model to simulate the effects of nitric oxide (NO) on apoptosis is proposed in [15]. 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 the extracellular stimuli.

The case study of our discussion is the model described in [16]. Authors of this model considered the role of Bax and Bcl-2 synthesis and degradation rates as well as

the number of mitochondrial permeability transition pore (MPTP) in the cell response to apoptotic stimuli. They simulate so-called mitochondria-dependent apoptosis as a bistability process.

The models described in [16] consist of a set of ordinary differential equations (ODEs) and parameters adopted in the model. Part of them are shown below as illustrations.

ODEs:

$d[\text{Apaf-1}] / dt = -J1 + J\text{Apaf-1}$

$d[\text{cyt c} * \text{Apaf-1}] / dt = J1 - 7J1b$

$d[\text{apop}] / dt = J1b - J2 + J4b$

$d[\text{apop} * \text{pro9}] / dt = J2 - J3$

$d[\text{apop} * (\text{pro9})2] / dt = J3 - J3f$

$d[\text{apop} * (\text{casp9})2] / dt = J3f - J4 - J5c - J6b + J6bf$

$d[\text{apop} * \text{casp9}] / dt = J4 + J4b - J5b$

$d[\text{casp9}] / dt = J4 - J4b - J5 - J6 + J6f + J\text{casp9}$

$d[\text{pro9}] / dt = -J2 - J3 + J\text{pro9}$

$d[\text{IAP}] / dt = -J5 - J5b - J5c - J7 + J\text{IAP}$

$d[\text{casp9} * \text{IAP}] / dt = J5$

$d[\text{apop} * \text{casp9} * \text{IAP}] / dt = J5b$

...

Reaction rates (or fluxes):

$J_0' = k_0^+ [\text{casp8}][\text{Bid}] - k_0^- [\text{casp8} * \text{Bid}]$

$J_0^f = k_0^f [\text{casp8} * \text{Bid}]$

$J_1 = k_1^+ [\text{cyt c}][\text{Apaf-1}] - k_1^- [\text{cyt c} * \text{Apaf-1}]$

$J_{1b} = k_{1b}^+ [\text{cyt c} * \text{Apaf-1}]^p - k_{1b}^- [\text{apop}]$

$J_2 = k_2^+ [\text{apop}][\text{pro9}] - k_2^- [\text{apop} * \text{pro9}]$

$J_3 = k_3^+ [\text{apop} * \text{pro9}][\text{pro9}] - k_3 [\text{apop} * (\text{pro9})_2]$

$J_3^f = k_3^f [\text{apop} * (\text{pro9})_2]$

$J_4 = k_4^+ [\text{apop} * (\text{casp9})_2] - k_4^- [\text{apop} * \text{casp9}][\text{casp9}]$

$J_{4b} = k_{4b}^+ [\text{apop} * \text{casp9}] - k_{4b}^- [\text{apop}][\text{casp9}]$

$J_5 = k_5^+ [\text{casp9}][\text{IAP}] - k_5^- [\text{casp9} * \text{IAP}]$

$J_{5b} = k_{5b}^+ [\text{apop} * \text{casp9}][\text{IAP}] - k_{5b}^- [\text{apop} * \text{casp9} * \text{IAP}]$

$J_{5c} = k_{5c}^+ [\text{apop} * (\text{casp9})_2][\text{IAP}] - k_{5c}^- [\text{apop} * (\text{casp9})_2 * \text{IAP}]$

...

Production-degradation rates:

$J_{\text{Apaf-1}} = \Omega_{\text{Apaf-1}} - \mu[\text{Apaf-1}]$

$J_{\text{IAP}} = \Omega_{\text{IAP}} - \mu[\text{IAP}]$

$J_{\text{pro3}} = \Omega_{\text{pro3}} - \mu[\text{pro3}]$

$J_{\text{pro9}} = \Omega_{\text{pro9}} - \mu[\text{pro9}]$

$J_{\text{Bid}} = \Omega_{\text{Bid}} - \mu[\text{Bid}]$

...

All equations shown above were proposed in [16]. The models were described by CellML (Fig. 2).

```
<?xml version="1.0"?>
<!--
This CellML file was generated on 21/08/2009 at 9:19:39 at a.m. using:

COR (0.9.31.1309)
Copyright 2002-2009 Dr Alan Garny
http://cor.physiol.ox.ac.uk/ - cor@physiol.ox.ac.uk

CellML 1.0 was used to generate this model
http://www.cellml.org/
  --><model xmlns="http://www.cellml.org/cellml/1.0#" xmlns:cmeta="http://www.cellml.org/metadata/1.0#" cmet
 <documentation xmlns="http://cellml.org/tmp-documentation">
 <article>
 <section id="sec_status">
  <title>Model Status</title>
  <para>This CellML model is able to run in PCEnv and COR to reproduce published results in the original pap
  </section>
 <sect1 id="sec_structure">
  <title>Model Structure</title>
  <para>ABSTRACT: We propose a mathematical model for mitochondria-dependent apoptosis, in which kinetic coo
  </para>
  <para>The original paper is cited below:</para>
 <para>
  Bistability in Apoptosis: Roles of Bax, Bcl-2 and Mitochondrial Permeability Transition Pores. E.Z. Bagci,
  <ulink url="http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&amp;cmd=Retrieve&amp;dopt=AbstractPlus
  </para>
 <informalfigure float="0" id="fig reaction diagram">
```

Fig. 2. The part of .cellml file that describes model from the [16]

The results (Fig.3) were obtained using OpenCell the .csv (comma separated value) file. The file shows the change of the protein concentrations.

```
time(second),Casp8/Casp8(micromolar),Casp8/Casp8Bid(micromolar),Bid/Bid(micromolar),Apaf_1/Apaf_1(micromolar
0,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.004,0.00
0.00219920946112976,0.004004865752954688,0.003995081401813386,0.004008092582346884,0.004004858312971695,0.00
1.00954602861950 62,0.005575978808382 3494,0.002394422430113 9807,0.006532326272946 62,0.010284202591929916,0.01
2.00954602861950 7,0.006295936102523823,0.001638569014147 4416,0.007531245400186202,0.018361115257353258,0.018
3.00954602861950 8,0.006618415390789018,0.001277216949926359,0.007845254304072501,0.025305910379076733,0.0184
4.00954602861950 9,0.006757586317982871,0.001097858172648 6468,0.007867528463808065,0.030808102973462904,0.018
5.06910074574684 8,0.006814523765704431,0.000997747463550 5866,0.007763277333233 9845,0.035123845626186125,0.01
6.10954602861950 1,0.006829451938561071,0.000940218207803 5618,0.007612692499840367,0.038103992830315 3,0.01884
7.16910074574684 05,0.006825753256298184,0.000900504927308 4257,0.007443404482902 9215,0.040174839401373376,0.0
8.20954602861949 4,0.006813417364251 5825,0.000870265373061 2177,0.007274133660493076,0.041536254341272 96,0.018
9.26910074574683 3,0.006796523228480607,0.000843896462675 8578,0.007103621919553535,0.042456154323233124,0.018
10.30954602861948 6,0.006777694901233297,0.000820354250547 0114,0.006939815158430212,0.043054038104634 21,0.018
11.36910074574682 6,0.006757199474404312,0.000797826239813 4458,0.006777327400615 0755,0.043459199687999 47,0.01
12.40954602861947 9,0.006736220369608 16,0.000776687480142 6781,0.006622181871987278,0.043726915686864 92,0.01895
13.46910074574681 8,0.006714210006341 5375,0.000755943134526 0183,0.006468669052866625,0.043913991966854 66,0.01
14.50954602861947 2,0.006692074011515508,0.000736233364182 8027,0.006322252778722 48,0.044043426935298 564,0.018
15.56910074574681,0.006669062378045569,0.000716774193436359,0.006177455150829092,0.044139630371836 33,0.01895
16.56910074574681 6,0.006646945083233455,0.000698943278678 0145,0.006044686052775 3644,0.044208975916968 02,0.01
17.56910074574683,0.006624463629298691,0.000681610329189 3394,0.005915598938918643,0.044264635872049346,0.018
18.56910074574684 4,0.006601635980776327,0.000664759509808672,0.005790100262832 1435,0.044311165782883945,0.01
19.56910074574686,0.006578477608513845,0.000648377379562 8461,0.005668097199931 03,0.044351551662968 34,0.01896
20.56910074574687 3,0.006555002661772 3625,0.000632451730606 9937,0.005549498009331 33035,0.044387754304659785,0.
21.56910074574688 7,0.006531224550 5910645,0.000616971011838 9723,0.005434212256585462,0.044421065015271 01,0.01
22.56910074574690,0.006507156231194509,0.000601924046968 5663,0.005322150976542997,0.044452337749616 52,0.01896
23.56910074574691 5,0.006482810341739164,0.000587299901034917,0.005213226801756471,0.044482140468653 75,0.0189
24.56910074574693,0.006458199263008047,0.000573087821412494,0.005107354065524492,0.044510853810114694,0.0189
25.56910074574694 4,0.006433335142010071,0.000559277215672 6392,0.005004448882555634,0.044538735427610 21,0.018
```

Fig. 3. The .csv file of results

All of these models are illustrated by the schemas and diagrams that show the details of the simulations.

4 3D Visualization of the CellML Models of Apoptosis

The changes of the modeling parameters are converted by the system into the changes of the visual objects. Due to the lack of the comprehensive mathematical model of the apoptosis and due to the complexity of the system this approach is the most difficult one, however it seems to be the most promising approach on the other hand. Currently the model can be displayed schematically using the modeling environment [17].

The "game" showing the processes at the molecular level is the first step towards the 3-D visualization. The processes described within the models can also be represented as the results of the simulation. 3-D visualization of the molecular biological processes modeled by chemical kinetic equations is created by this method. Kinetic equations governing the participating components determine the quantitative parameters. This approach is illustrated in Fig. 4.

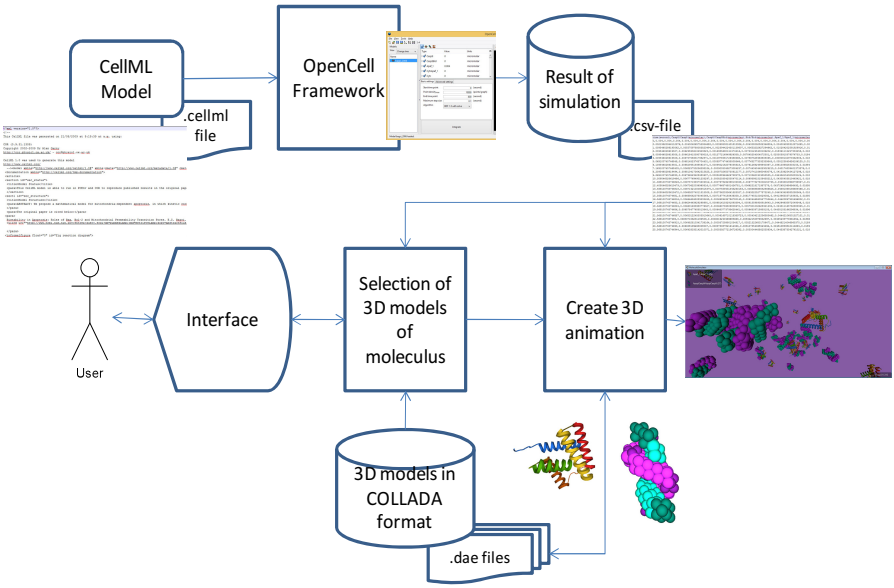

Fig. 4. The parser-visualizator scheme [11]

.cellml file contains the description of the model, which can be opened by the OpenCell Framework. Simulation results are saved in the .csv file that can be obtained along as with the required information from this file by the parser. The user using a simple interfacing form can chooses the necessary molecule. Selected molecules are shown in the graphical window if they are graphically represented in the COLLADA format. The Brownian movement of the molecules can be observed in the window. The number of molecules corresponds to the concentration of proteins during the modeling.

The advantage of these approaches is the possibility to create visualization that corresponds to the modeling parameters.

Of course, there are some hardships in the simulation. For example, in the case of the model taken from [16] the .csv the file contains the concentrations of 31 molecules. It will be difficult to analyze the visualization because of the number of different molecules. Secondly, graphics card requirements will be very high due to the very large number of molecules. Therefore, user must select several molecules to visualize and the number of the selected molecules is limited to 7. Also, user can specify the characteristics of the molecules, if they are known.

Another problem is that the concentrations of the different molecules vary in 1000 and even more times. The solution is to provide logarithmic visualization. Therefore user must specify the type of visualization before it starts.

The third problem is the necessity to use a huge amount of 3D-models of proteins. Therefore the special mechanism is required to access the protein data bank [18].

5 Conclusions

A living organism is the most complex natural object for the research. In this context the visualization of the processes is a normal way for understanding and analysing them to improve the quality of their studies.

Human and other mammal cells' apoptosis is very important and multi-phase process. A lot of phases contain redundant paths and components so that if one fails the other one succeeds.

Despite the relative abundance of the methods and tools for the modeling that were discussed earlier there is no full-featured environment that provides not only the modeling but also the graphical representation of two- and three-dimensional models of the biological processes.

Significant efforts are required to create full 2-D and 3-D graphical models that are close to photographic images as well as to implement the ability to react to the changes of the parameters. The first step is to create the mechanism that shows processes at the molecular levels. So, we propose a method for three-dimensional visualization of molecular biology processes modelled by chemical kinetic equations.

To realize this method we developed parser-visualizator that reads output file from the simulation and creates 3D-models. The developed program works with any molecular shapes stored in COLLADA format and simulates the Brownian movement of the proteins and changes of their concentration.

Note that cell apoptosis in simpler organisms is more simple with a smaller number of redundant paths. However, it is possible to make homologies between the corresponding phases of the apoptosis in all multicellular organisms from the simplest ones to the most complex ones. This is the reason why the study of the apoptosis features in the simpler organisms if important in order to study their correspondence with the more complex ones.

One of the simplest multicellular organisms that has many of its biological processes well studied is Caenorhabditis elegans or C. elegans free-living nematode (roundworm), which is about 1 mm long [19-21].

It has 959 cells and has the simplest neural system, which consists of 302 neurons only and of about 5000 connections between them [22]. During the process of the C. elegan evolution, 131 cell dies exposed to apoptosis. Currently C. elegan is chosen as the first multicellular organism that will be fully modeled using the computers. This is the international project called OpenWorm (http://www.openworm.org/). The participants of the project have already finished the modelling of the neural system of the grown-up C. elegan and the new project Devoworn (http://syntheticdaisies.blogspot.com/2014/06/now-announcing-devoworm-project.html) that is devoted to the C. Elegan evolution and to the process of its cells division from embryo to grown-up organism was started in June 2014. 131 cell are exposed to apoptosis exactly during this process. Computer modelling and the visualization of the apoptosis in C. elegan are planned in the framework of the further studies. In order to perform not only qualitative modelling but quantitative as well the model that describes the dynamics of the components engaged in the process is required, e.g. if this process is described but the system of the equations of the chemical kinetics. Such system of the equation was developed for the apoptosis process in mammals but this was not performed for C. elegans. The development, the quantitative solution and further computer modelling and visualization of the corresponding mathematical model are planned. Despite the fact that C. elegan organism is well studied there still are unsolved problems including the process of its cells apoptosis [23]. E.g., it is unknown whether cytochrome participates in this process as it happens with mammals. We hope that computer modelling and visualization of these processes will help in the studies of this and other similar problems.

Acknowledgements. The work is funded by grant № 1758 GF-OT13 for basic research in the natural sciences of the MES RK Science Committee.

References

1. Muchmore, S.W., Sattler, M., Liang, H., Meadows, R.P., Harlan, J.E., Yoon, H.S., Nettesheim, D., Chang, B.S., Thompson, C.B., Wong, S.-L., Ng, S.-C., Fesik, S.W.: X-ray and NMR structure of human Bcl-xL, an inhibitor of programmedиcell death. Nature **381**(6580), 335–341 (1996)
2. Green, D.R.: Means to an End: Apoptosis and other Cell Death Mechanisms, p. 250. Cold Spring Harbour Laboratory Press, NY (2010)
3. Antonsson, B., Conti, F., Ciavatta, A.M., Montessuit, S., Lewis, S., Martinou, I., Bernasconi, L., Bernard, A., Mermod, J.-J., Mazzei, G., Maundrell, K., Gambale, F., Sadoul, R., Martinou, J.-C.: Inhibition of Bax channel-forming activity by Bcl-2. Science **277**(5324), 370–372 (1997)
4. Minn, A.J., Vélez, P., Schendel, S.L., Liang, H., Muchmore, S.W., Fesik, S.W., Fill, M., Thompson, C.B.: Bcl-x(L) forms an ion channel in synthetic lipid membranes. Nature **385**(6614), 353–357 (1997)
5. Schendel, S.L., Xie, Z., Montal, M.O., Matsuyama, S., Montal, M., Reed, J.C.: Channel formation by antiapoptotic protein Bcl-2. Proc. Natl. Acad. Sci. U.S.A **94**(10), 5113–5118 (1997)

6. Schlesinger, P.H., Gross, A., Yin, X.-M., Yamamoto, K., Saito, M., Waksman, G., Korsmeyer, S.J.: Comparison of the ion channel characteristics of proapoptotic BAX and antiapoptotic BCL-2. Proc. Natl. Acad. Sci. U.S.A. **94**(21), 11357–11362 (1997)
7. Peixoto, P.M., Ryu, S.-Y., Bombrun, A., Antonsson, B., Kinnally, K.W.: MAC inhibitors suppress mitochondrial apoptosis. Biochem. J. **423**(3), 381–387 (2009)
8. Czabotar, P.E., Westphal, D., Dewson, G., Ma, S., Hockings, C., Fairlie, W.D., Lee, E.F., Yao, S., Robin, A.Y., Smith, B.J., Huang, David C.S., Kluck, R.M., Adams, J.M., Colman, P.M.: Bax crystal structures reveal how BH3 domains activate Bax and nucleate its oligomerization to induce apoptosis. Cell **152**(3), 519–531 (2013)
9. Kushnareva, Y., Andreyev, A.Y., Kuwana, T., Newmeyer, D.D.: Bax activation initiates the assembly of a multimeric catalyst that facilitates Bax pore formation in mitochondrial outer membranes. PLoS Biol. **10**(9), e1001394 (2012)
10. Souers, A.J., Leverson, J.D., Boghaert, E.R., Ackler, S.L., Catron, N.D., Chen, J., Dayton, B.D., Ding, H., Enschede, S.H., Fairbrother, W.J., Huang, D.C.S., Hymowitz, S.G., Jin, S., Khaw, S.L., Kovar, P.J., Lam, L.T., Lee, J., Maecker, H.L., Marsh, K.C., Mason, K.D., Mitten, M.J., Nimmer, P.M., Oleksijew, A., Park, C.H., Park, C.-M., Phillips, D.C., Roberts, A.W., Sampath, D., Seymour, J.F., Smith, M.L., Sullivan, G.M., Tahir, S.K., Tse, C., Wendt, M.D., Xiao, Yu., Xue, J.C., Zhang, H., Humerickhouse, R.A., Rosenberg, S.H., Elmore, S.W.: ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat. Med. **19**(2), 202–208 (2013)
11. Muhamedyev, R., Mansharipova, A., Muhamedyeva, E.: Visualization of Biological Processes Described by Models of Apoptosis. Life Science Journal **11**(10), 320–327 (2014). ISSN:1097-8135
12. Garny, A., Nickerson, D.P., Cooper, J., dos Santos, R.W., Miller, A.K., McKeever, S., Nielsen, P.M., Hunter, P.J.: CellML and associated tools and techniques. Phil. Trans. R. Soc. A **2008**, 366 (2008). doi:10.1098/rsta.2008.0094. Published 13 September
13. OpenCell (May 20, 2014). http://www.cellml.org/tools/opencell/
14. Rangamani, P., Sirovich, L.: Survival and apoptotic pathways initiated by TNF-alpha: modeling and predictions. Biotechnology and Bioengineering **97**(5), 1216–1229 (2007)
15. Bagci, E.Z., Vodovotz, Y., Billiar, T.R., Ermentrout, B., Bahar, I.: Computational insights on the competing effects of nitric oxide in regulating apoptosis (2009) (May 20, 2014). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2386238/
16. Bagci, E.Z., Vodovotz, Y., Billiar, T.R., et al.: Bistability in Apoptosis: Roles of Bax, Bcl-2 and Mitochondrial Permeability Transition Pores. Biophysical Journal **90**, 1546–1559 (2006). PubMed ID: 16339882
17. Wimalaratne, S.M., Halstead, M.D.B., Lloyd, C.M., Cooling, M.T., Crampin, E.J., Nielsen, P.F.: A method for visualizing CellML models. Bioinformatics **25**(22), 3012–3019 (2009). doi:10.1093/bioinformatics/btp495
18. Protein Data Bank (2014). http://www.rcsb.org/pdb/home/home.do
19. Brenner, S.: The genetics of Caenorhabditis elegans. Genetics **77**(1), 71–94 (1974)
20. Sulston, J.E., Horvitz, H.R.: Post-embryonic cell lineages of the nematode. Caenorhabditis elegans. Dev. Biol. **56**(1), 110–156 (1977)
21. Sulston, J.E., Schierenberg, E., White, J.G., Thomson, J.N.: The embryonic cell lineage of the nematode Caenorhabditis elegans. Dev. Biol. **100**(1), 64–119 (1983)
22. White, J.G., Southgate, E., Thomson, J.N., Brenner, S.: The structure of the nervous system of the nematode Caenorhabditis elegans. Phil. Trans. R. Soc. Lond. B, Biol. Scien. **314**(1165), 1–340 (1986)
23. Wang, X., Yang, C., Chai, J., Shi, Y., Xue, D.: Mechanisms of AIF-mediated apoptotic DNA degradation in Caenorhabditis elegans. Science **298**(5598), 1587–1892 (2002)