American Review of Mathematics and Statistics
December 2015, Vol. 3, No. 2, pp. 69-82
ISSN: 2374-2348 (Print), 2374-2356 (Online)

Published by American Research Institute for Policy Development
DOI: 10.15640/arms.v3n2a9
URL: http://dx.doi.org/10.15640/arms.v3n2a9

Comparative Assessment of Simulation Tools for Biochemical Networks

GökçeTuncer[1] & Vilda Purutçuoğlu[2]

Abstract

There have recently been many simulation tools developed by researchers for observing the dynamics of biochemical networks. These tools have mainly designed for the stochastic and deterministic simulations and some of them also support the inference of the model parameters under deterministic modellings. Therefore, they are known as the simulation softwares for biochemical systems. Although these tools aim the same purpose in the application, they have their own advantages and disadvantages. Hereby, in this study, to help the users for choosing the most suitable simulation tools for their purposes, we initially present the widely implemented ones, namely, Cellware, COPASI, Dizzy, Dynetica, E-CELL, GENESIS, Jarnac/JDesigner, Systems Biology Toolbox and Virtual Cellsoftwares, and then, compare them according to our selected attributes. For the comparison criteria, we define the theme, user-friendliness, platforms supported, language of the software, capacity in the simulation, inference, visualization and the Systems Biology Markup Language. Finally, we suggest certain tools for academic and non-academic users by taking into account their plausible major attributes for the selection.

Keyword: Simulation tools, biochemical networks, comparison criteria, system biology.

1. Introduction

Recently, many researchers have started to deal with the dynamical behavior of biochemical networks. Thereby, they apply computational tools for the deterministic or stochastic simulations and analyses of the systems. In these network tools, most of the algorithms are based on the deterministic computations such as the deterministic simulation, modelling and the inference of the model parameters, which are majorly found by optimization approaches. The main concern in these methods is to describe the biochemical systems via a set of ordinary differential equations (ODEs) in which each equation accounts for the rate of changes in the concentration of the species. In these models, the estimates of the model parameters, which are the rate of changes in each ODE, are calculated by using exact or numerical methods. These methods detect the simultaneous equilibrium in all ODEs (Bower and Bolouri, 2001).

On the other hand, if the random nature of the system is one of the main features in its activation, this system can be presented by the stochastic models, such as the Langevin or diffusion models(Wilkinson, 2006), and be generated by the stochastic simulation algorithms such as the Gillespie (Gillespie, 1977) or the next reaction methods (Gibson and Bruck, 2000). Accordingly, the associated model parameters can be mainly inferred by the Bayesian approaches, optimization or numerical methods (Bower and Bolouri, 2001; Wilkinson, 2006; Lawrence et al., 2010). In stochastic models, it is considered that a random error term, which describes the stochasticity under low concentrations of species, comes from the Brownian motion (Bower and Bolouri, 2001; Wilkinson, 2006; Lawrence et al., 2010). In these models, the parameters of interest are the stochastic reaction rate constants (Wilkinson, 2006; Lawrence et al., 2010) which denote the speed of the reaction under the given numbers of molecules of the species.

[1] Department of Statistics, Middle East Technical University, 06800, Ankara, Turkey
[2] Department of Statistics, Middle East Technical University, 06800, Ankara, Turkey

Finally, the biochemical systems can indicate a mixed feature if both deterministic and stochastic events are crucial for the description in the activation of the system. Under such cases, the researchers should combine both modelling types in order to get realistic solutions (Wilkinson, 2006).

Hereby, in our study, we focus on the most well-known simulation tools of biochemical networks, namely, Cellware, COPASI, Dizzy, Dynetica, E-CELL, GENESIS, and Jarnac together with JDesigner, Systems Biology Toolbox and Virtual Cell. All of these tools can simulate the systems deterministically, but mostly, can also make stochastic simulations and rarely can support hybrid simulation approaches, which consider both deterministic and stochastic calculations in turn for a system (Wilkinson, 2006). Such an overview of the tools has been also presented in the study of Kurnaz (2005) with four tools (Systems Biology Toolbox, Jarnac, Virtual Cell and E-CELL). In this study, we extent it by adding current toolboxes as well. Furthermore, we propose certain criteria in order to classify the tools with respect to their efficiencies in the application. Accordingly, in the organization of our study; we give a brief information about each tool and the supported simulation methods in Section 2. In Section 3, we compare them based on some attributes in order to distinguish their superiorities and deficiencies. Then we suggest certain tools by considering the plausible attributes for academic and non-academic users in Section 4. Finally, we summarize our findings in Section 5.

1. Major Simulation Tools

In the literature, there are a number of methods suggested for the simulation of different dimensional systems. Here, we consider only the most well-known ones as they are not only capable of the generation of systems, but also the inference of the model parameters and the visualization of biochemical systems under various sizes. Thereby, we represent the Cellware, COPASI, Dizzy, Dynetica, E-CELL, GENESIS, and Jarnac together with JDesigner, Systems Biology Toolbox and Virtual Cell tools, below, in order. Table 1 presents their web links. In our description, the numbers in parantheses (.) written in the title of the subsections show the version of the associated tools.

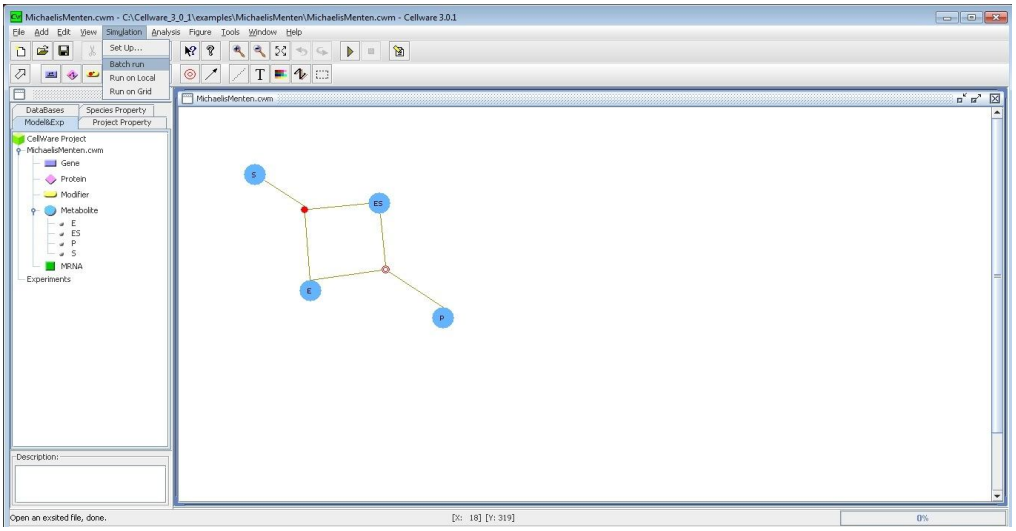
Table 1: The web links of the simulationtools

Tool	Web link
Cellware	http://www.bii.a-star.edu.sg/achievements/applications/cellware/
COPASI	http://copasi.org/
Dizzy	http://magnet.systemsbiology.net/software/Dizzy/
Dynetica	http://people.duke.edu/~you/Dynetica_page.htm
E-CELL	http://www.e-cell.org/
GENESIS/Kinetikit	http://genesis-sim.org/
Jarnac/JDesigner	http://sbw.kgi.edu/software/jarnac.htm
Systems Biology Toolbox	http://www.sbtoolbox.org/
Virtual Cell	http://vcell.org/vcell_software/login.html

2.1 Cellware (3.0.1)

Cellware (Dhar et al., 2004; System Biology Group, 2005) is a multi-algorithmic simulation tool developed for modeling and simulating deterministic and stochastic events in a cell. The tool can handle the immense diversity of the cell by supporting different simulation methods.With this tool, the users can apply the Euler Forward or Backward method, Trapezoidal method, Explicit 4th order Runge-Kutta method, Rosenbrock method andthe Adams-Bashforth method for the deterministic representation of the systems (Jeffrey, 2000). On the other hand, for the stochastic simulation, Cellware supports the Gillespie direct method (Gillespie, 1977), the Gibson next reaction method (Gibson and Bruck, 2000)and the explicit time-step (τ-leap) method (Gillespie, 2001). This tool can also perform the StochODE method which is a hybrid stochastic simulation approach. On the other side, for the inference of model parameters, Cellware applies the Particle SWARM algorithm based on a deterministic calculation (Gillespie, 2001). Finally, the tool has a user-friendly diagrammatic graphical user interface which can be seen in Figure. 1.

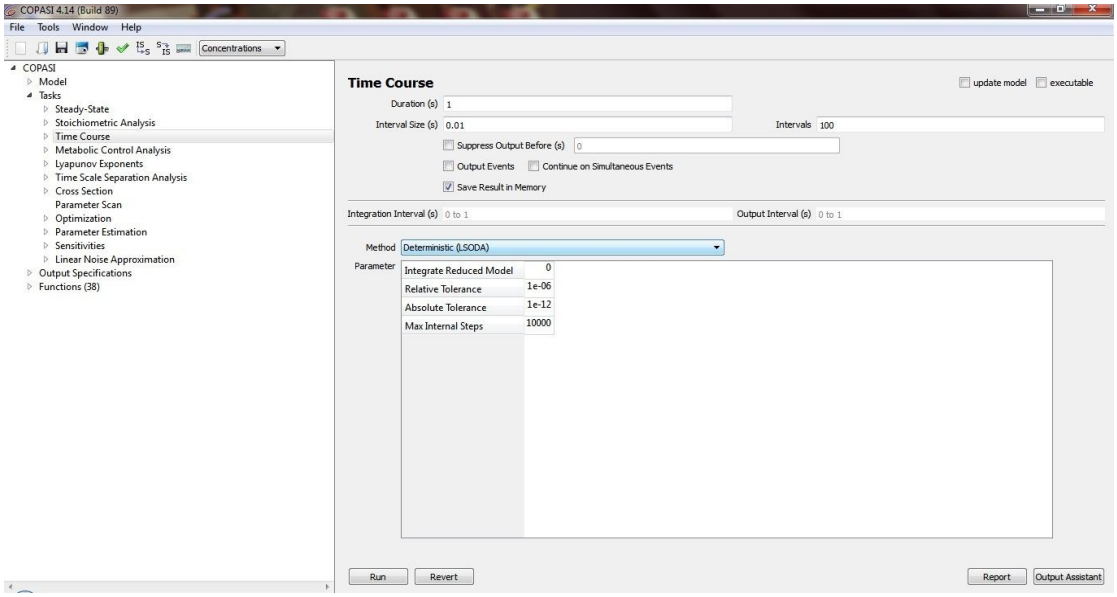
Figure 1: The user interface of Cellware in the Mac OS platform.



2.2 COPASI - a Complex Pathway Simulator (4.14 - Build 89)

COPASI (Hoops et al., 2006) is a user-friendly simulation tool which supports the diverse simulation and analyzes the genomic data. In deterministic simulations, COPASI appliesthe Livermore Solver (LSODA) method (Radhakrishnan and Hindmarsh, 1993) and in stochastic simulations, similar to Cellware, it implements the Gillespie direct method, the next reaction method (Gibson-Bruck), the time-step (τ-leap) and adaptive time-step (τ-leap) methods. Moreover, the tool offers hybrid methods by using the LSODA or Runge-Kutta methods combined with stochastic algorithms. For inference, the tool presents abundant deterministic approaches, namely,the differential evolution, evolutionary strategy (SRES), evolutionary programming and genetic algorithm by using the stochastic ranking, Hooke and Jeeves, Levenberg-Marquardt, Nelder-Mead, particle swarm, praxis, random search, scatter search, simulated annealing, steepest descent and the truncated Newton methods (COPASI Development Team, 2010). Moreover, COPASI has diverse analyses' methods such as the metabolic control, bifurcation and the sensitivity analyses and has a friendly dialog in the user interface as shown in Figure 2.

Figure 2. The user interface of COPASI in the Microsoft platform.



2.3 Dizzy (1.11.4)

Dizzy (Ramsey et al., 2005) is a simple textual simulation tool for modeling the homogeneous kinetics of the integrated large-scale genetic, metabolic and the signaling networks. It presents both deterministic and stochastic algorithms together with a modular simulation design, reusable modeling elements, complex kinetic rate laws, multi-step reaction processes, spatial compartmentalization and estimationsunder the steady state noises.
For deterministic simulations, the researchers can choose a method among the 5th order Runge-Kutta approach with a fixed step-size or an adaptive step-size controller, the 5/4 Dormand-Prince ODE solver approach with an adaptive step-size controller and the implicit-explicit ODE solver approach with the doubling step. On the other hand, for stochastic simulations, we can apply the Gibson-Bruck method and the Gillespie direct method as the exact stochastic simulation algorithms and perform the Gillespie time-step method as the approximate stochastic simulation algorithm (Ramsey, 2006). Lastly, Dizzy has a simple and textual user interface as presented in Figure 3.

2.4 Dynetica (1.2 beta)

Dynetica (You et al., 2003) is another common and simple modeling interface which is designed for the construction, visualization and the analysis of kinetic models of biological systems. This tool offers the 4th order Runge-Kutta method and the Runge-Kutta Fehlberg method, for deterministic calculations. On the other side, it uses the Gillespie direct method, the optimized direct method and the first reaction methods (Gillespie, 1992) in the exact simulation of the complex systems. It is also possible to conduct the sensitivity analyses via this tool (You, 2002). Finally, Dynetica offers a basic and diagrammatic user interface as displayed in Figure 4.

Figure 3: The graphical user interface of Dizzy in the Microsoft platform.

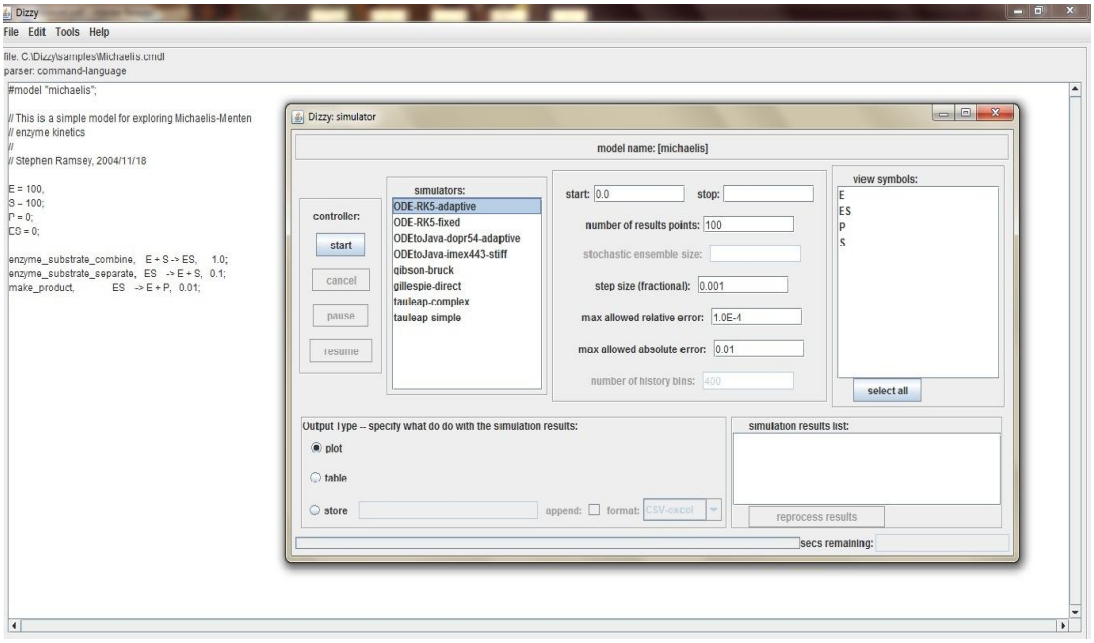
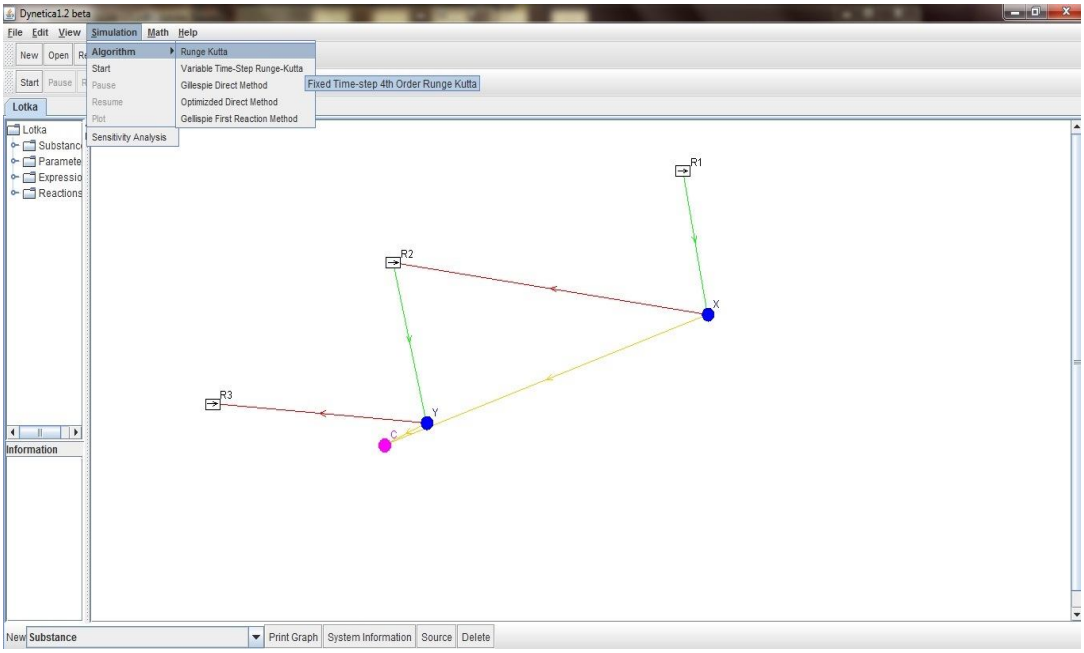


Figure 4: The user interface of Dynetica in the Microsoft platform.



2.5 E-CELL (3)

In the E-CELL tool (Tomita et al., 1999), the researcher can model and simulate the biochemical networks and genetic processes with the functions of proteins, their interactions with DNA and cellular metabolicactivations. In the calculation, the tool supports the Euler method and the Runge-Kutta method for deterministic simulations similar to other tools. It can also run the Gillespie algorithm, the Gibson-Bruck algorithm for stochastic simulations. Moreover, we can apply a discrete-time simulator and a hybrid as well as dynamic/static pathway simulator in the computations (Tomita et al., 1999; Takahashi et al., 2003a; Takahashi et al., 2003b). On the other hand, E-CELL is capable of performing the analyses of the metabolic control and the bifurcation.

2.6 GENESIS – the General Neural Simulation System (2.4beta)

Although GENESIS (Bower et al., 2003) is designed as a software platform for the simulation of neuronal systems, its applications can be broadened by using Kinetikit (Bower et al., 1998) which is generally applied for the simulation of biological signaling pathways. In the deterministic calculation via Kinetikit, GENESIS can perform the exponential Euler method and the Runge-Kutta method. On the other side, it can run the Gillespie direct algorithm, the first reaction algorithm and the Gibson-Bruck algorithm for the stochastic simulations. The tool also supports the mixed stochastic methods under hybrid approaches.

In inference of the deterministic model parameters, GENESIS presents the parallel genetic algorithms and the parallel simulated annealing method (Collins and Jefferson, 1991; Azencott, 1992). Additionally, it has an efficient script language even for the description of large systems in the sense that merely few lines can be sufficient enough for the representation. Moreover, the users can modify the findings of the current simulations and can extend the graphical user interface. The underlying object-oriented design and the scripting language can be seen as the greatest strengths of this tool (Bower et al., 2003). As the disadvantage, GENESIS only works on the UNIX-based systems with the X-Window System, including Linux, OS/X and Windows with Cygwin.

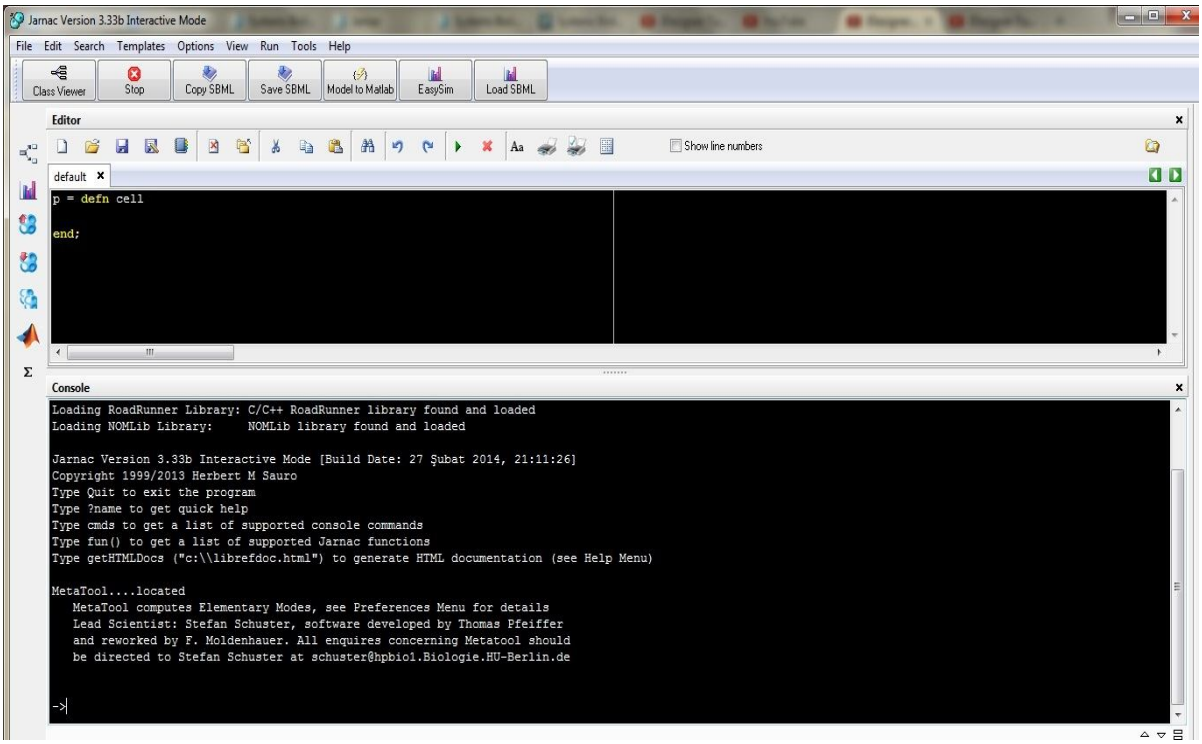
2.7 Jarnac/JDesigner (3.33b/3.1.2)

Jarnac (Sauro et al., 2003) whose user interface is shown in Figure 5, is an advance script language to define and manipulate cellular system models, particularly, gene or metabolic networks and signal transduction pathways.

On the other hand, JDesigner (Sauro et al., 2003; Sauro et al., 2012) whose user interface is seen in Figure 6, can be performed with Jarnac to describe the reactions, specifying the reactants with its diagrammatic graphical interface and to simplify the application of Jarnac on itself.

For the simulation, Jarnac includes the CVODE integrator and the LSODA integrator as the deterministic method and the Gillespie algorithm as the stochastic simulation method. Moreover, we can conduct several analyses such as steady-state analyses (NLEQ solver), simple stability analyses (eigenvalues analyses), matrix arithmetic (using the IMSL library), metabolic control analyses (all steady-state control coefficients and elasticizes)and metabolic structural analyses with this tool (Sauro et al., 2012).

Figure 5: The user interface of Jarnac.



2.8 Systems Biology Toolbox for MATLAB (2)

Systems Biology Toolbox (Schmidt and Jirstrand, 2006) is presented as a toolbox for MATLAB in order to analyze and simulate biological and biochemical systems. The tool also offers the network identification, sensitivity and the bifurcation analyses. Moreover, the researchers can extend the application of the tool by writing required scripts in MATLAB. In the calculations, the toolbox presents the Runge-Kutta, Adams, NDFs (BDFs), Rosenbrock, Trapezoidal TRBDF2 and the BDFs methods for deterministic simulations. Additionally, it presents the Gillespie method for exact stochastic simulations and the Binomial τ -leap (also called as Binomial time-step) and the Poisson τ -leap (also called as Poisson time-step) algorithms for approximate stochastic simulations. Furthermore, the tool has a nonlinear solver based on the Newton iterations, local and global optimization functions based on the Nelder-Mead downhill simplex and the simulated annealing approaches for the parameter estimation (Schmidt, 2015). Finally, the toolbox works with MATLAB as shown in Figure 7. Moreover, it has a textual interface. Since it does not have a design tool, it can be combined with JDesigner.

Figure 6: The user interface of JDesigner.

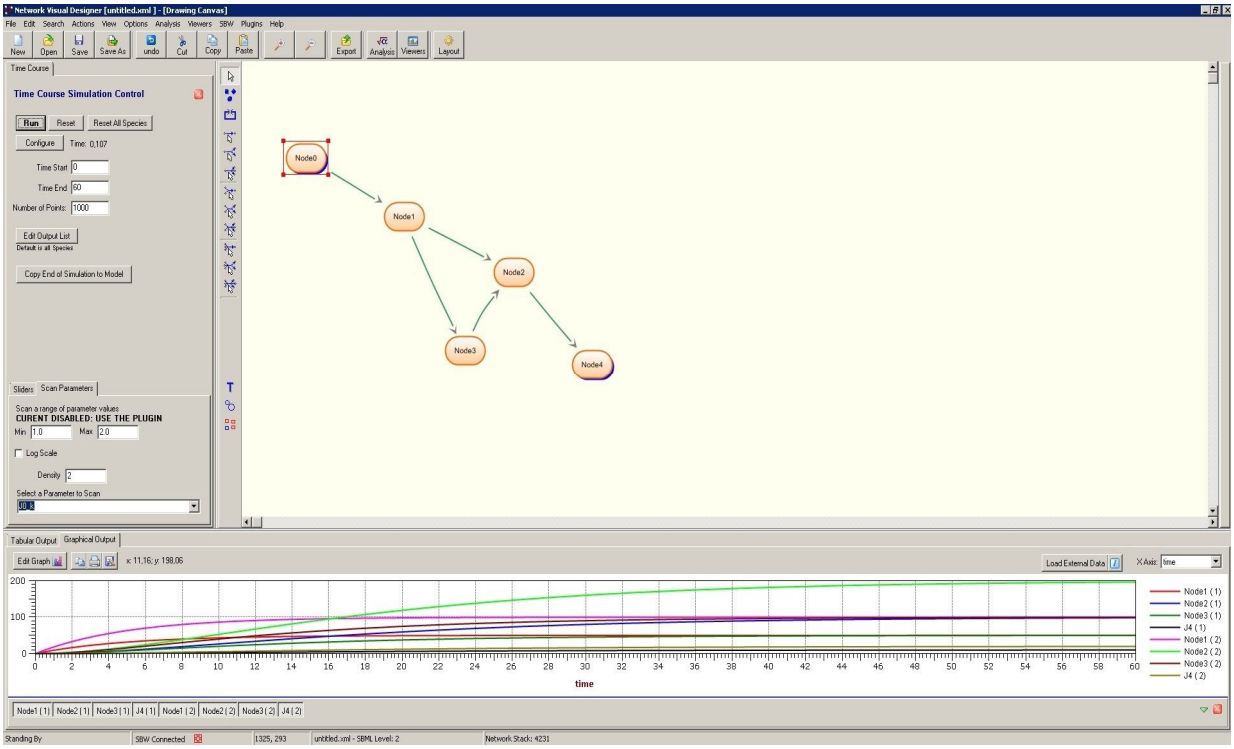
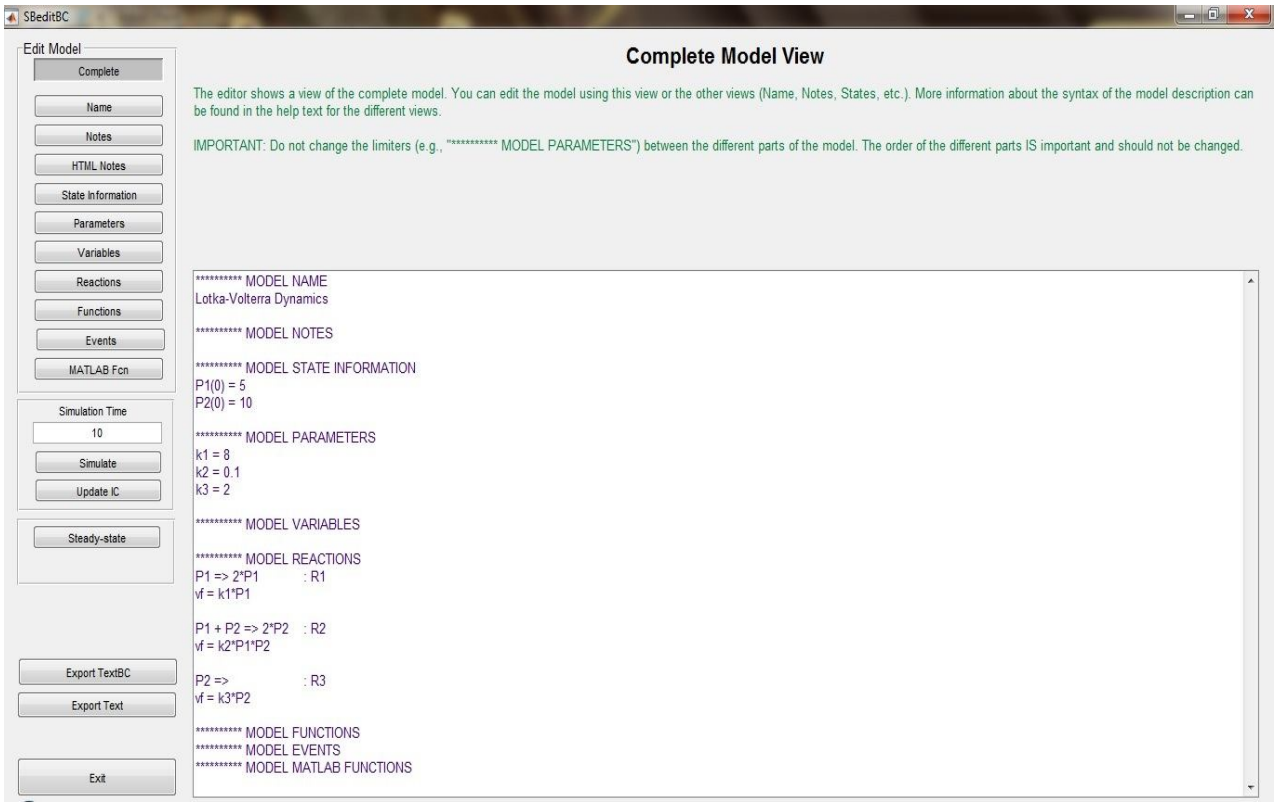


Figure 7. The user interface of Systems Biology Toolbox for MATLAB.



2.9 Virtual Cell (5.3 beta)

Virtual Cell (Loew et al., 2001) is a web-based simulation tool for the modeling and the simulation of the cell biology. The tool is created for a wide range of scientists, from experimental cell biologists to theoretical biophysicists (Loew et al., 2001). For the calculations, Virtual Cell has an extensive library in the sense that for the deterministic simulations, the forward Euler under the first order and the fixed time step, Runge-Kutta under the second order and the fixed time step, Runge-Kutta under the fourth order and the fixed time step, Adams-Moulton under the fifth order and the fixed time step, Runge-Kutta-Fehlberg under the fifth order and the variable time step, IDA under the variable order and the variable-time step, CVODE under the variable order and the variable-time step, combined stiff solver CVODE/IDA can be are applicable. Likewise, for the stochastic simulations, the Gibson-Bruck next reaction stochastic method is supported. Furthermore, the tool performs the Gibson and Milstein as well as adaptive Gibson and Milstein methods as the hybrid simulation approaches. On the other side, it applies the particle swarm optimization algorithm with a simulated annealing based on the local search engine (LPEPSO-SA) in inference of the deterministic model parameters (Virtual Cell Version 5.2. Tutorial 1 and 2, 2015). Moreover, the tool supports almost all optimization methods of COPASI. In Figure 8, an example of the user interface is presented.

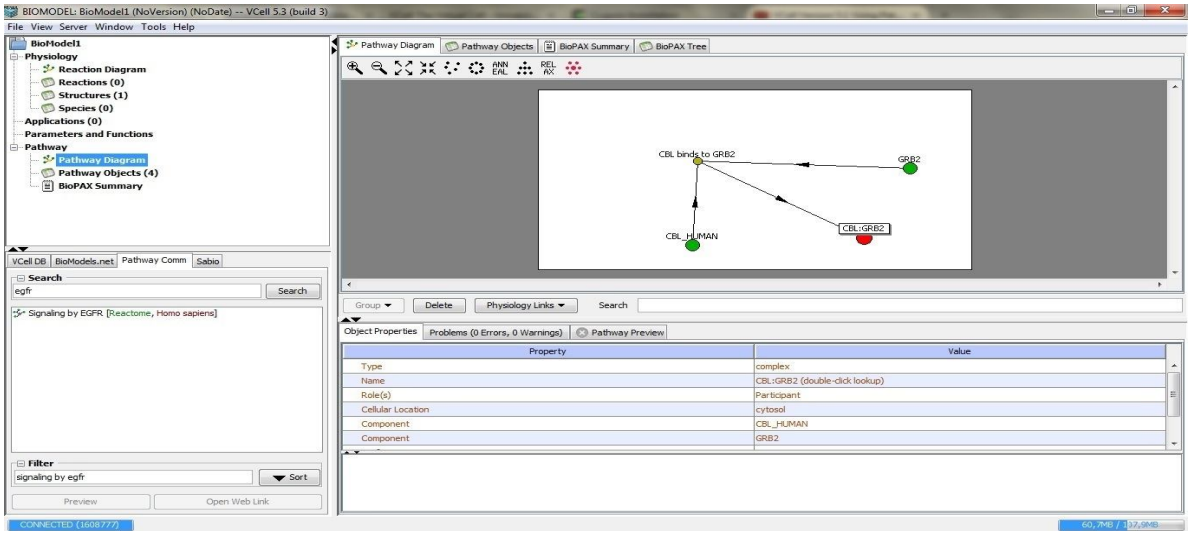
3 Comparison Criteria for the Simulation Tools

All the underlying simulation tools indicate diversities in their capacities, supported algorithms and the information about their applications. Hence, in order to evaluate and compare them, we define several criteria, namely, the theme, user-friendliness, supported platforms, capabilityof simulation, calculation for the parameter estimation, compatibility of the Systems Biology Markup Language (SBML)(Hucka et al., 2003) and the capability of the visualization. Here, we initially present the detailed description of each attribute as below and then categorize each tool with respect to these criteria.

3.1 Theme

Although all of the tools are capable of simulating biochemical networks, some of the tools are specialized in certain areas. For instance, Cellware and Virtual Cell are more preferable to simulate biochemical reactions in a cell, whereas, GENESIS can be chosen for the simulation of neuronal systems. In Table 2, we represent the themes of each tool for the comparison.

Figure 8. The user interface of Virtual Cell.



3.2 User-Friendliness

One of the most important concept is how easy to apply the software. This is mainly related with the user interface and the available documentation of the tool. There are three main types of graphical user interfaces for the model definition. These are the textual, diagrammatic and dialog interfaces. In the textual interface, the model is described in a textual form.

On the other hand, in the diagrammatic interface, the user draws diagrams instead of writing chemical equations. Lastly, in the dialog interface, we can enter the chemical equations and the rate expressions and finally, can define the compartments by filling dialog boxes.

Hereby, for instance, if the researcher prefers to write the reactions manually when the size of networks is small, he/she may apply the simulation tools having textual interfaces such as Dizzy, GENESIS, Jarnac or Systems Biology Toolboxfor MATLAB. On the other side, if he/she does not write equations manually, the diagrammatic interface may be selected, as implemented in Cellware, Dynetica, JDesigner or Virtual Celll or the dialog interface may be chosen as performed in COPASI or E-CELL. The difference of the diagrammatic interface over the dialog ones is the ability of the visualization of the network graphically and its interpretation in the tool. Whereas in this study, we further investigate the capacity of the visualization separately as a distinct criterion in the comparison. In Table 3, we show the graphical user interface of each tool.

Finally, for the user-friendliness, the documentation of the tool can be an important criterion. Among the tools, all of them have tutorials and manuals. But COPASI offers the most comprehensive documentation.

3.3 Platforms Supported

The platforms supported by the tool can be thought as an another criterion for the selection of the appropriate tool. Among alternatives, only GENESIS is available on the Unix-based systems while the remainings can work on several platforms as presented in Table 3.

3.4 Language of the Software

The language of the software typically becomes crucial when the researchers consider to extend the current utility of the tools by adding new algorithms or improving the available ones and to develop new applicationsin the current version of the tools. But, this feature can be also effective for the computational time of the algorithms. Hereby, from the comparison of the tools with respect to the programming language, we observe that most of tools apply either C++, which is a compiled language, or Java, which is an interpreted language. The former is more advantageous than the latter since it increases the machine instructions at runtime, resulting in a faster speed, in particular, during the calculation of high dimensional systems. Among the selected tools, COPASI, E-CELL, GENESIS (via C) and Virtual Cell are based on the C++ codes that are compiled and the remainings are based on the Java codes (apart from System Biology Toolbox which uses MATLAB) that are interpreted. We also present this classification in Table 3.

Table 2: The themes of the simulation tools

Tool	Theme
Cellware	Biochemical Reactions in a Cell
COPASI	Biochemical Networks and Their Dynamics
Dizzy	Genetic, Metabolic and Signaling Networks
Dynetica	Biological and Genetic Networks
E-CELL	Biochemical and Genetic Processes
GENESIS/Kinetikit	Biochemical Networks and Neuronal Systems
Jarnac/JDesigner	Biochemical Networks
Systems Biology Toolbox	Biological and Biochemical Networks
Virtual Cell	Cell Biology

3.5 Simulation Capacity in Simulation

It is important for a tool to have several simulation options for the user. In this sense, it can be said that COPASI and Virtual Cell are particularly more comprehensive and Cellware is moderately comprehensive among alternatives. However, in the tools having textual interfaces as Dizzy, GENESIS, Jarnac or Systems Biology Toolbox for MATLAB, it is possible for the user to write further simulation methods and to extend the implementation of the tools.

For instance, in a biochemical system, if the state is exposed to external abrupt changes, the underlying network can be represented by impulsive differential equations. Under such conditions, the user can define an impulsive function accompanying with a simulation method if the calculation is performed under the MATLAB tool. In Table 4, we list the capacities of all tools in simulations and parameter estimations.

3.6 Capacity in Inference

In the concept of the parameter estimation, different tools present distinct methods. Among alternatives, COPASI can be considered as the most comprehensive tool for the parameter estimation mostly based on the optimization approaches which can be also seen in Table 4. However, the tools having the textual interfaces also enable us to write our optimization functions for the inference of parameters. Specifically, Dizzy, GENESIS, Jarnac or Systems Biology Toolbox in MATLAB can support this flexibility in calculations.

3.7 Compatibility of the Systems Biology Markup Language

The Systems Biology Markup Language (SBML) is a free representative XML-based format for interchanging different biological processes. By means of this format, the users do not need to rewrite models when they pass from one program to another. Furthermore, it enables us to get a standard representation of networks within the environments of different softwares. Apart from GENESIS, all tools support to directly read or write SBML files in computations.

Table 3: The user interface, supported platforms and the type of programming languages (compiled and interpreted) of the tools

Tool	User Interface	Platform Supported	Compiled Language	Interpreted Language
Cellware	Diagrammatic	Windows, Linux, Macintosh		X
COPASI	Dialog	Windows, Linux, Macintosh, Sun Solaris	X	
Dizzy	Textual	Windows, Linux, Macintosh		X
Dynetica	Diagrammatic	Windows, Linux, Macintosh		X
E-CELL	Dialog	Windows, Linux	X	
GENESIS/Kinetikit	Text/ Diagrammatic	Linux, OS/X and Windows with Cygwin	X	
Jarnac/JDesigner	Text/ Diagrammatic	Windows, Linux, Macintosh		X
Systems Biology Toolbox	Text	Windows, Linux, Macintosh		X
Virtual Cell	Diagrammatic	Windows, Linux, Macintosh	X	

Table 4: The number of deterministic and stochastic simulation methods as well as the number of hybrid simulation and parameter estimation methods available in the tools

Tool	Number of Deterministic Simulation Methods	Number of Stochastic Simulation Methods	Number of Hybrid Methods	Number of Parameter Estimation Methods
Cellware	6	3	1	1
COPASI	1	4	2	15
Dizzy	4	4	Not Supported	Not Supported
Dynetica	2	3	Not Supported	Not Supported
E-CELL	2	2	1	2
GENESIS/Kinetikit	2	3	1	2
Jarnac /JDesigner	2	1	Not Supported	Not Supported
Systems Biology Toolbox	7	3	Not Supported	4
Virtual Cell	8	1	2	13

3.8 Capacity in Visualization

The capacity in the visualization is an important criterion since it enables researchers to see the dynamics of the systems like the detection of stable or unstable states. Dizzy only provides a simple plot which shows the changes in simulated values over time. Cellware and Dynetica has again basic plotting capabilities such as plotting the changes in simulation results versus time and phases. On the other hand, Jarnac supports the userplots by coding. In GENESIS, the users can alsoextend the main plotting capabilities of the tool. Additionally, E-CELL has a flexible graph drawer/editor and allows bifurcation analyses. COPASI has a flexible and user-friendly output assistant which is able to create the plots. It is also possible to draw bifurcation graphs by this tool. Lastly, Systems Biology Toolbox and Virtual Cell have a similar template for plotting the time series data. However, the former is more comprehensive since it also allows drawing bifurcation graphs and benefits the general graphical capabilities of MATLAB. In Table 5, the capacity of each tool is summarized for simplicity.

Table 5. The capacity of the simulation tools in visualization.

Tool	Basic Plots	Bifurcation Plots	Advanced Plotting
Cellware	Yes	No	No
COPASI	Yes	Yes	Yes
Dizzy	Yes	No	No
Dynetica	Yes	No	No
E-CELL	Yes	Yes	Yes
GENESIS/Kinetikit	Yes	No	Yes
Jarnac /JDesigner	Yes	No	Yes
Systems Biology Toolbox	Yes	Yes	Yes
Virtual Cell	Yes	No	Yes

4 Results

In this part, we divide the possible user-type into two groups, namely, academic and nonacademic users, based on the most plausible criteria in previous sections for the selection of the appropriate tool. Hereby, we choose the plausible three attributes for each group which can be seen in Table 6. For the academic users, the capacities in simulation, inference and visualization, which offer a variaty of methods, can be more essential than other attributes. Because they are more concentrated on the steps of the algorithms, rather than the practical application of the tools. On the other hand, for the non-academic users, the user-friendliness, the supported platform and the capacity in the visualization are more suitable among alternatives due to the fact that their main interests are not the computational procedures of the tools. On the contrary, they deal with the simplicty in the application under the default algorithms proposed by the tools.

From this assessment, we consider that Systems Biology Toolbox and COPASI can be a good choice for academicians. On the other side, Cellware, COPASI and Virtual Cell can be a more appropriate choice for non-academic users. Besides, if the researcher's intent to apply a collaboratively additive tool, Virtual Cell can be even better choice since it is an internet-based simulation server. Moreover, Systems Biology Toolbox and Cellware can be applied if the users prefer to perform different simulation algorithms for comparative findings. Furthermore, the software having textual interfaces can be more suitable when the researchers need distinct simulation algorithms such as algorithms for impulses in the system.

On the other side, from the application of all these tools in toy systems, we observe that there is almost no difference in the accuracies of simulated systems (Tuncer, 2015). The slight changes in results are caused by the default algorithms in inference of the deterministic modelling from each tool. Because they are based on solving the ordinary differential equations that are computed by distinct optimization methods. On the other side, we observe that there is a difference in the computational demand of the tools, in particular, when the dimensions of the systems increase. As we discussed under the programming language, we observe that the tools supported by C++ are faster than others since they use the compiled language. We detect the same conclusions when we compare the tools under impulses in the system as well (Tuncer, 2015; Tuncer and Purutçuoğlu, 2015).

Table 6: The most plausible important attributes for each user-type

Attribute	Academic User	Non-academic User
Theme		
User-Friendliness		X
Platform Supported		X
Software Language		
Simulation Capability	X	
Inference Capability	X	
SBML Compatibility		
Visualization Capability	X	X

5. Conclusion

Recently, a number of tools is developed for simulating the dynamic behavior of the biochemical networks. Although most of these tools have similar aim, they can be separated from each otherby their supported algorithms and capabilities. In this study, we have compared the most well-known simulation tools, namely, Cellware, COPASI, Dizzy, Dynetica, E-CELL, GENESIS, Jarnac/JDesigner, Systems Biology Toolbox and Virtual Cell according to our proposal attributes.

In this assessment, we consider that understanding the skills of each tool can be helpful for the researchers to select the most appropriate toolbox for their analyses of the biological/biochemical systems. But this selection can vary with respect to the background of the researchers. Therefore, in our analyses, we aim to evaluate the necessity of each attribute regarding the non-academic and academic users. This division can be further extended by different types of users such as doctors and engineers. Additionally, this study enables us to detect the undeveloped parts of each tool and from this assessment; we observe that the listed tools do not offer any choice for the stochastic inference of the systems even though they comprehensibly support it for deterministic models. Indeed, such calculations can be partially applicable by developing new codes based on the maximum likelihood estimator or fast Bayesian algorithms like the Gibbs sampling for small and moderately large systems.

Acknowledgement

The authors would like to thank the AGEP grant (Project No: BAP-08-11-2014-007) of the Middle East Technical University for the support.

References

Azencott, R.(1992). Simulated annealing: parallelization techniques. New York: Wiley Press.

Bower, J. M., &Bolouri, H. (2001).Computational modelling of genetic and biochemical networks, Cambridge: MIT Press.

Bower, J. M., &Beeman, D. (1998). The book of GENESIS. New York: Springer.

Bower, J. M., Beeman, D., &Hucka, M. (2003). The GENESIS simulation system.InM.A.Arbib (Ed), Handbook of brain theory and neural networks.(pp. 475-478). Cambridge: MIT Press.

Collins, R. J. & Jefferson, D. R. (1991). Selection in massively parallel genetic algorithms, Proceedings of the 4th International Conference on Genetic Algorithms, 249-256.

COPASI Development Team. (2010). COPASI Documentation Version 4.6 (Build 32). [Online] Available: http://copasi.org/Support/Change_History/COPASI_4_6_Build_32/ (September 2, 2015).

Dhar, P., Meng T. C., Somani, S., Ye, L., Sairam, A., Chitre, M., Hao, Z., & Sakharkar, K. (2004). Cellware-a multi-algorithmic software for computational systems biology, Bioinformatics, 20 (8), 1319-1321.

Gibson, M. A., & Bruck, J. (2000). Efficient exact stochastic simulation of chemical systems with many species and many channels. Journal of Physical Chemistry A, 104 (9), 1876-1889.

Gillespie, D. T. (1977). Exact stochastic simulation of coupled chemical reactions, Journal of Physical Chemistry, 81, 2340-2361.

Gillespie, D. T. (1992). A rigorous derivation of the chemical master equation, Physica A, 188, 404- 425.

Gillespie, D. T. (2001). Approximate accelerated stochastic simulation of chemically reacting systems, Journal of Chemical Physics, 115 (4), 1716-1733.

Hoops, S., Sahle, S., Gauges, R., Lee, C., Pahle, J., Simus, N., Singhall, M., Xu, L., Mendes, P.,& Kummer, U. (2006). COPASI-a complex pathway simulator, Bioinformatics, 22 (24), 3067-3074.

Hucka, M., Finney, A., Sauro, H. M., Bolouri, H., Doyle, et al. (2003). The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models, Bioinformatics, 19 (4), 524-531.

Jeffrey, A. (2000). Handbook of mathematical formulas and integrals . (3rd ed.). Academic Press.

Kennedy, J., &Eberhard, R. C. (1995). Particle swarm optimization.Proceeding of the IEEE International Conference on Neural Networks, 4, 1942-1948.

Kurnaz, I. A. (2005). Biochemical modelling tools and applications to metabolic engineering. TurkishJournal of Biochemistry, 30 (2), 200-207.

Lawrence, N. D., Girolami, M., Rattray, M., &Sanguinetti, G. (2010). .Learning and inference in computations systems biology. Cambridge: MIT Press.

Loew, L. M., &Schaff, J. C. (2001). The Virtual Cell: a software environment for computational cell biology, Trends in Biotechnology, 19 (10), 401-406.

Radhakrishnan, K., &Hindmarsh, A. C. Description and use of LSODA, the Livermore solver for ordinary differential equations, LLNL report UCRL-ID-113855, (December 1993).

Sauro, H. M., &Fell, D. A. (2003).Jarnac: a system for interactive metabolic analysis in animating the cellular map. Proceedings of the 9th International Meeting on BioThermoKinetics, 19 (13), 294-295.

Sauro, H. M. (2012). An introduction to biochemical modeling using JDesigner and Jarnac.Seattle: AmbrosiusPublising.

Schmidt, H., & Jirstrand, M. (2006). Systems Biology Toolbox for MATLAB: a computational platform for research in systems biology, Bioinformatics, 22 (4), 514-515.

Schmidt, H.(2015). Tutorial on the BPOP package: Efficient support for model based drug development from mechanistic models to complex trial simulations.

Systems Biology Group, (2005). Cellware Manual version 3.0.Bioinformatics Institute, Singapore.

Ramsey, S., Orrell, D., &Bolouri, H. (2005).Dizzy: stochastic simulation of large-scale genetic regulatory networks, Journal of Bioinformatics and Computational Biology, 3 (2), 415-436.

Ramsey, S. (2006). Dizzy User Manual version 1.11. [Online] Available: http://magnet.systemsbiology.net/software/Dizzy/docs/UserManual.html (September 2, 2015).

Takahashi, K., Ishikawa, N., Sadamoto, Y., Sasamoto, H., Ohta, S., Shiozawa, A., Miyoshi, F., Naito, Y., Nakayama, Y., & Tomita, M. (2003a). E-Cell 2: multi-platform E-Cell simulation system, Bioinformatics, 19(13), 1727-1729.

Takahashi, K., Sakurada, T., Kaizu, K, Kitayama, T., Arjunan, S. et al., (2003b). E-CELL System Version 3: A Software Platform for Integrative Computational Biology, Genome Informatics Series, 19 (13), 294-295.

Tomita, M., Hashimoto, K., Takahashi, K., Shimizu, T. S., Matsuzaki, Y., Miyoshi, F., Saito, K., Tanida, S., Yugi, K., Venter, J. C., &Hutchison, C. A. (1999). E-CELL: software environment for whole-cell simulation, Bioinformatics, 15 (1), 72-84.

Tuncer, G. (2015). Comparison of the simulation tools for the deterministic modeling of biochemical network. Master Thesis. Department of Statistics, Middle East Technical University.

Tuncer, G., &Purutçuoğlu, V. (2015). Application of impulsive deterministic simulation of biochemical networks via simulation tools, Proceedings of the Jangjeon Mathematical Society (Accepted in publication).

Virtual Cell Version 5.2.(2015). Tutorial 1 and 2. [Online] Available: http://vcell.org/vcell_software/user_guide.html?current=four (September 2, 2015).

You, L. (2002).Dynetica User Guide (version 0.1beta). [Online] Available: http://people.duke.edu/~you/Dynetica/DyneticaUserGuide.htm (September 2, 2015).

You, L., Hoonlor, A., &Yin, J. (2003). Modeling biological systems using Dynetica-a simulator of dynamic networks, Bioinformatics, 19(3), 435-436.

Wilkinson, D. (2006). Stochastic modelling for systems biology. New York:Chapman and Hall/CRC Press.