ILLUMINATIONS

eSolv, a CellML-based simulation front-end for online teaching

Teun P. de Boer,[1] Sape van der Werf,[2] Bas Hennekam,[2] David P. Nickerson,[3] Alan Garny,[3] Michèle Gerbrands,[2,4] Rianne A. M. Bouwmeester,[1,4] Anne-Petra Rozendal,[2] Ellen Torfs,[2] and Harold V. M. van Rijen[1,4]

[1]*Department of Medical Physiology, Division Heart and Lungs, University Medical Center, Utrecht, The Netherlands;* [2]*Center for Research and Development of Education, Education Center, University Medical Center, Utrecht, The Netherlands;* [3]*The University of Auckland, Auckland, New Zealand; and* [4]*Biomedical Sciences, Education Center, University Medical Center, Utrecht, The Netherlands*

SIMULATION OF PHYSIOLOGICAL processes is a powerful tool to help students integrate and apply the knowledge they gained during traditional forms of teaching (e.g., lectures, textbooks). Several physiology simulation packages are commercially available or custom made and are usually tailored to specific processes or systems. Typical commercial examples are, e.g., SimHeart, SimVessel, SimNerv, SimMuscle, SimNeuron (2), SimBioSys Physiology Laboratories (3); noncommercial examples include ECGSIM (11) and CircAdapt (8). They are typically student proof, which makes them very suitable as a teaching tool. Many of the software packages available require software to be installed locally and administration-intense planning to deploy and use them in university computer classes. Because locally installed software requires specific operating systems and is usually licensed, installation on the devices of students is not always an option. The constraint of most packages is that it holds only one or a limited number of simulated model systems. The model itself, or the parameters that can be modulated by students, is generally not under control of the teacher.

From the research field of physiology, a large source of more than 600 of highly relevant, but complex models from various disciplines, encoded in the CellML format (6) is freely available (7). CellML is an open standard based on the XML markup language and was developed by the Auckland Bioengineering Institute at the University of Auckland (1). The flexibility of these models and tools is extremely useful for researchers, but a serious drawback for use in a teaching context. The models are usually complex, and it is difficult for students to understand all the different parameters of a model and know to what extent a specific parameter can be altered without destabilizing the model. Furthermore, with the available software tools, they are not easy to set up and deploy for teaching purposes.

We, therefore, aimed to combine the best of both the teaching and research simulation worlds and have created a web-based, versatile simulation platform called "eSolv." It can be used on any device, and allows teachers to load any CellML model and define exactly which model parameters are available

to the students, and whether and to what extent these can be manipulated.

MATERIALS AND METHODS

Software development. Using the C# .NET framework, we built a graphical user interface (GUI; called eSolv: http://www.esolv.nl/) that interacts with Csim (5, 10) to run CellML models (both open source). The benefit of running simulations on the server is that computation-intensive models can also be accessed from handheld devices, such as tablets.

Evaluation. eSolv was tested by several groups of students from high school, bachelor and master's students, and biomedical sciences and biomedical PhD students. They all performed our "AxonLab" training, built on several eSolv laboratories and models. This included several laboratories, i.e., action potential, action potential threshold, refractoriness and sodium current, rheobase, Na/K pump, voltage clamp, conductivity, and *m* and *h* parameters (all based on a modified Hodgkin and Huxley squid axon model from https://www.cellml.org). In total, 140 students filled out a digital evaluation form about performance, usability, and perceived instructiveness of eSolv using a five-point Likert scale (1 = strongly disagree to 5 = strongly agree). Data are presented as means ± SD.

RESULTS

The user interface of eSolv is shown in Fig. 1. Model input parameters can be altered using standard GUI elements, such as switches, sliders, radio buttons, or check or text boxes. After defining the parameter values, the user clicks the "Simulate" button, which runs the model and displays the teacher's selected parameter values as line charts. Values in the line chart can be shown using the mouse pointer, which can also drive an animation of a cellular process linked to the parameters shown.

After logging in, teachers can define a "laboratory," add a title and contact name, and upload a model retrieved from the CellML repository (http://models.cellml.org/cellml), or select a previously uploaded model from the library. Subsequently, guided by easy-to-use dialog windows, the time frame and interval of the simulation are set, as well as the output parameters to be displayed. Finally, the input parameters, which can be modified by the student, are configured. Here, the teacher must specify the range of values a given parameter can take; this is to prevent model instability. If useful, a static picture can be included below the simulation to provide background information or instructions to the stu-

Address for reprint requests and other correspondence: T. P. de Boer, Dept. of Medical Physiology, Division Heart and Lungs, University Medical Center Utrecht, Yalelaan 50, 3584CM Utrecht, The Netherlands (e-mail: T.P.deboer@umcutrecht.nl).
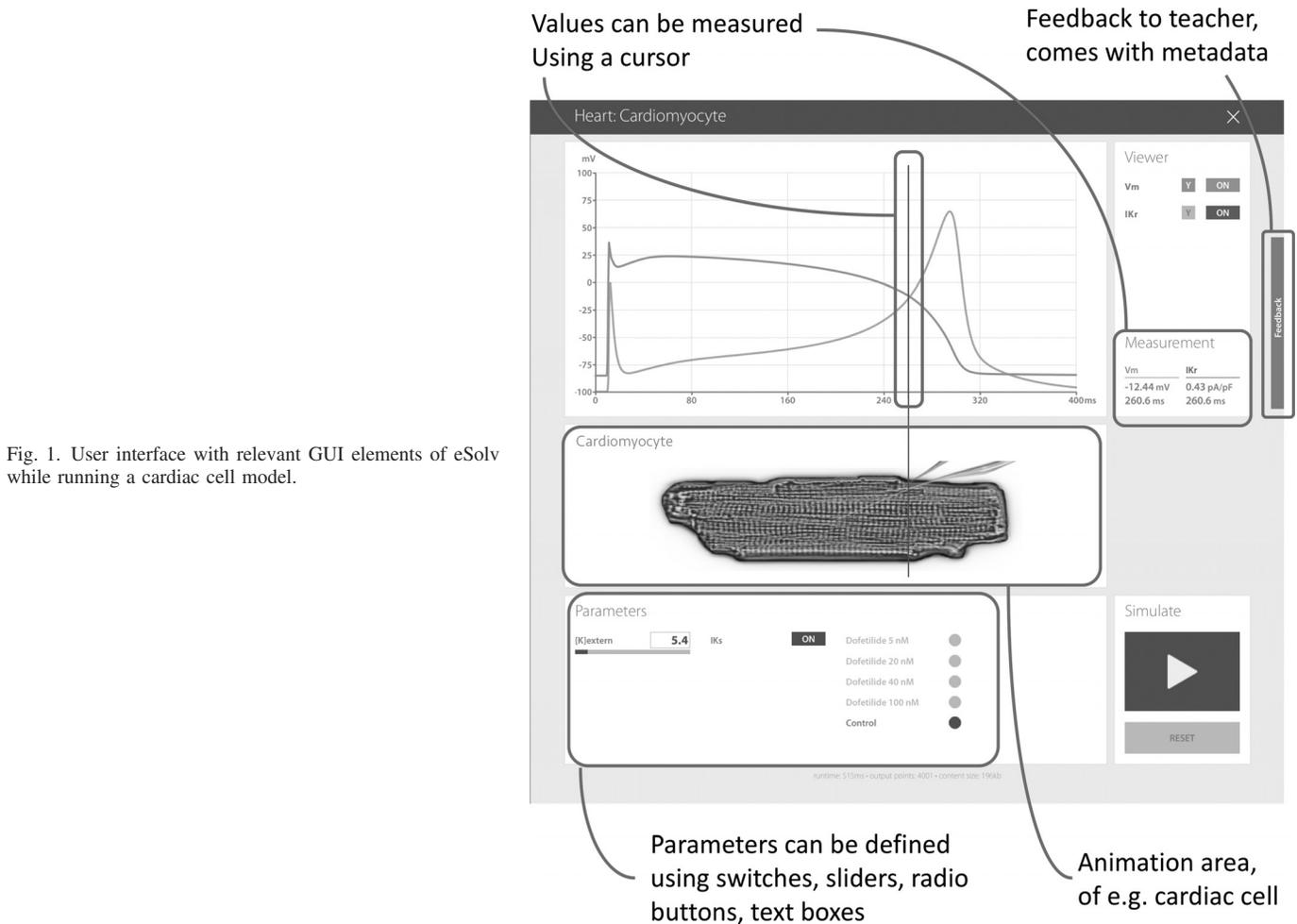
Fig. 1. User interface with relevant GUI elements of eSolv while running a cardiac cell model.

dent. The reset button will restore all settings to their default values. Multiple laboratories can be aggregated on a page with an introductory text, providing an entry point for a specific course.

Our evaluation results showed that the performance of eSolv was found to be good, and it scaled linearly with the number of students. eSolv worked well on all modern browsers on both desktop computers and tablets. Students rated eSolv GUI elements and functions to be very clear (4.0 ± 0.15), with a high level of usability (3.9 ± 0.12) and the simulations as a whole to be very instructive (3.8 ± 0.09).

DISCUSSION

We have developed a CellML-based simulation tool that is very suitable for teaching. Its strong points are as follows. *1*) It is user friendly: it is adaptable to students' levels by allowing the generation of both simple and complex laboratories using the same underlying CellML model. *2*) Many models are freely available. *3*) The simulation platform performs well on all modern browsers and platforms. Current functionality can be extended by including other application-specific animations.

As is true for other approaches relying on computer simulations, it is important that the teacher understand the strengths and caveats of simulations. By building eSolv on the foundation of CellML, teachers can use published and validated

CellML models, which can also be studied in detail by the teacher using the simulation tools developed for researchers [e.g., Chaste (9) or OpenCOR (4)].

The eSolv simulation tool is now being integrated in the (bio)medical curricula of the University Medical Center Utrecht, starting with "AxonLab," in which eSolv is used in combination with an e-module. The e-module provides students with basic knowledge about neural electrophysiology, serves as a practical guide for the more complex neural simulations in eSolv, and gives students direct feedback on their performance.

We would like to encourage our colleagues to have a look at the demo simulations on the eSolv website (http://www.esolv.nl/), and, if interested, request a free teacher account to explore whether eSolv may be suitable for their physiology teaching (http://www.esolv.nl/admin/).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

T.d.B. conceived and designed research; T.d.B. and B.H. performed experiments; T.d.B., R.A.B., and E.T. analyzed data; T.d.B., S.v.d.W., M.G., and A.-P.R. interpreted results of experiments; T.d.B. and H.V.v.R. prepared figures; T.d.B. and H.V.v.R. drafted manuscript; T.d.B., S.v.d.W., B.H., D.P.N., A.G., M.G., R.A.B., A.-P.R., E.T., and H.V.v.R. edited and revised

manuscript; T.d.B., S.v.d.W., B.H., D.P.N., A.G., M.G., R.A.B., A.-P.R., E.T., and H.V.v.R. approved final version of manuscript.

REFERENCES

1. **Beard DA, Britten R, Cooling MT, Garny A, Halstead MD, Hunter PJ, Lawson J, Lloyd CM, Marsh J, Miller A, Nickerson DP, Nielsen PM, Nomura T, Subramanium S, Wimalaratne SM, Yu T.** CellML metadata standards, associated tools and repositories. *Philos Trans A Math Phys. Eng Sci* 367: 1845–1867, 2009. 10.1098/rsta.2008.0310.

2. **Braun HA.** Virtual versus real laboratories in life science education: concepts and experiences. In: *From Guinea Pig to Computer Mouse: Alternative Methods for a Progressive, Humane Education* (2nd Ed.). Leicester, UK: InterNICHE, 2003, p. 81–86.

3. **Cyber-Anatomy, Inc.** *Cyber Physiology - SimBioSys* (Online). http://cyber-anatomy.com/product_CPSBS.php [15 Jul. 2016].

4. **Garny A, Hunter PJ.** OpenCOR: a modular and interoperable approach to computational biology. *Front Physiol* 6: 26, 2015. 10.3389/fphys.2015.00026.

5. **Google Code**. *cellml-simulator* (Online). https://code.google.com/archive/p/cellml-simulator/ [2 Jun 2016].

6. **Lloyd CM, Halstead MD, Nielsen PF.** CellML: its future, present and past. *Prog Biophys Mol Biol* 85: 433–450, 2004. 10.1016/j.pbiomolbio.2004.01.004.

7. **Lloyd CM, Lawson JR, Hunter PJ, Nielsen PF.** The CellML model repository. *Bioinformatics* 24: 2122–2123, 2008. 10.1093/bioinformatics/btn390.

8. **Lumens J.** Creating your own virtual patient with CircAdapt Simulator. *Eur Heart J* 35: 335–337, 2014.

9. **Mirams GR, Arthurs CJ, Bernabeu MO, Bordas R, Cooper J, Corrias A, Davit Y, Dunn S-J, Fletcher AG, Harvey DG, Marsh ME, Osborne JM, Pathmanathan P, Pitt-Francis J, Southern J, Zemzemi N, Gavaghan DJ.** Chaste: an open source C++ library for computational physiology and biology. *PLOS Comput Biol* 9: e1002970, 2013. 10.1371/journal.pcbi.1002970.

10. **Nickerson DP.** *A reboot of CSim to try and better support SED-ML tools and OpenCMISS* (Online). https://github.com/nickerso/csim [2 June 2016].

11. **van Oosterom A, Oostendorp TF, van Dam PM.** Potential applications of the new ECGSIM. *J Electrocardiol* 44: 577–583, 2011. 10.1016/j.jelectrocard.2011.05.006.