Real-time and turn-based biology online experimentation

Zahid Hossain[*#], Alice M. Chung[*], Ingmar H. Riedel-Kruse[*]
Departments of Bioengineering[*] and Computer Science[#]
Stanford University
Stanford, CA 94305, USA
Ingmar@stanford.edu

***Abstract*—Being able to perform versatile biology experiments online would be very beneficial for research and education. Currently no such platforms exist in the life sciences. We have developed two such platforms, which are optimized for biological phenomena at the seconds and hours time scale, respectively: (1) A fully automated real-time biology lab that enables direct online interactions with phototactic microorganisms (euglena) that are long-term stably cultured in a microfluidic chip; (2) A turn-based biology lab that enables the spatio-temporal chemical stimulation of slime molds (physarum) in a petri-dish over multiple days. We compare the utility and affordance of both platforms, especially regarding use in online education.**

***Index Terms*— biology, online experimentation, education, biotic processing unit (BPU).**

I. Introduction

Being able to perform versatile biology experiments online would be very beneficial for research and education. Biological investigations are diverse, and unlike general purpose computing, there exists no clear basis (e.g. binary 1s and 0s) for executing all types of experiments. Different types of biological experiments require different equipment on the back-end as well as different online architectures regarding duration of an experiment, response time of the biological material, and resulting frequency of user interactions. Therefore, we adopted a domain-specific philosophy [1] to design conceptual hardware - Biotic Processing Unit (BPU) - to handle only a specific type of experiment with a specific set of instructions. Swapping out this hardware then allows execution of different types of experiments. The goal then is to design more general architectures of a cloud systems that can exploit and integrate these hardware under a common properties: 1) scalable, 2) time-shared and 3) available at all times, meaning that users can access and run experiments anytime.

We developed two such architectures and implemented corresponding platforms that are optimized for two major categories of biology online experiments (Figs.1,2): Biological phenomena of interest can happen at the time scale of seconds (Fig.1) or hours (Fig.2), and therefore require user input in real time vs. only every few minutes. While in the first case a single user requires direct access to the experiments, in the second case batch processing of many users on parallelized (high-throughput) machines is possible. The goal of this paper is to give an overview of these two architectures, their practical implementation, applications, and aspects of user testing – and compare them. The full technical and user study details are published elsewhere [2], [3].

We are not aware of any fully automated cloud or remote labs for biology, although various educational remote labs exist in other science and engineering disciplines [4], [5], [6]. Few "cloud lab" companies have emerged recently that execute biology experiments in a centralized location [7], [8] . But as of the writing of this manuscript, none enables users to run experiments online interactively (mailing DNA samples to be cloned and mailed back has a very different quality of interactivity than what we provide). But according to these companies' websites interactive experimentation is envisioned for the future, which argues for additional relevance of our present work.

II. Results

A. *Real-time interaction with euglena phototaxis*

The first architecture we developed is optimized to allow direct, real-time interactivity with micro-biological systems. Here a single user becomes for a limited amount of time the sole actuator on a remotely placed piece of equipment (while in principle many users can observe the experiment at the same time). This architecture requires a user management system, for example via a real-time queue or a calendar for pre-scheduling. Submitting fully preprogrammed experiments that are executed serially at a later time is also possible, although here we are primarily interested in a direct and closed interactive feedback loop between user and the biological system.

The specific implementation we developed consists of a simple microfluidic chip [9] housing the phototactic single celled organism *Euglena gracilis* [10]. The chip has the form of a square (approx. 1 mm x 1mm, and 150 µm high), which also has an inlet and outlet for fluid and organism exchange. This square chip then is imaged via a webcam microscope from above to observe the organisms. On each of the four sides of the chip an LED is placed that can shine light stimuli with varying intensity into the chip. Euglena respond to these light stimuli by swimming to the light at very low intensities, and away for very high intensities [10], furthermore there are many other more subtle light responses to be noticed among careful observation, such as the cells spinning around their own axes. Euglena cells respond to a change in light conditions within a second, making them particularly attractive for interactive experiments for children. Euglena cultures are long term stable without any care being needed (4 weeks and more), so we were able to connect the microfluidic chip to an external Euglena culture, and automatically exchanged the culture inside the chip every few hours. This led to a fully automated platform that requires less than 15 minutes maintenance once a week. Users can perform real-time exploratory as well as pre-program experiments that are executed at some later time point, and download the data for analysis. Here the user controls the intensity and direction of the two-dimensional light stimulus via a simple online joystick. All local hardware control was achieved via an Arduino microcontroller. Our web server for streaming video and recording data was written in Node.js, Socket.io and Express web application frame in conjunction with an open source multimedia project, MJPG-streamer. The client side of the framework was written in HTML5 combined with JavaScript.

While the platform is ready and has been tested for many months for long-term robustness, we have not yet undertaken any systematic user studies. The intended first use is as a complement in middle-school biology education. Euglena is commonly found in ponds and widely used in biology education given its rather large cell size (50 µm in length) – enabling the easy observation of subcellular details such as the red eyespot and green chloroplasts being very noticeable organelles – and particularly phototaxis experiments are carried out in schools [11]. During these studies children will be asked to play with the joystick and then observe and describe the Euglena responses. This is closely related to hands-on experiments done in schools, where children put Euglena in complete darkness – except for a small hole on one side of the dish - leading to accumulation of the cells at this region. These existing experiments are much less interactive than what our platform delivers. A typical experiment on our platform lasts 1-5 minutes. Many other phenomena can be studies on our platform in the future, such as Brownian motion, low Reynolds hydrodynamics, and micro-ecology. We will also interview the teacher to assess the utility of this platform from their point of view.

B. Turn-based interaction with slime mold chemotaxis

The second cloud architecture we developed is optimized for allowing multiple users to share multiple machines, each of which can carry out many biology experiments in parallel (Fig.2) [12]. Such batch processing is increasingly common in the life-sciences including usage of high-throughput hardware, where each such machine (BPU) can typically handle only a specific type of experiment with a specific set of instructions but large numbers in parallel. Swapping out this hardware allows execution of different types of experiments. Each BPU has its own controller and operates synchronously on its own clock time while querying the central database for updated

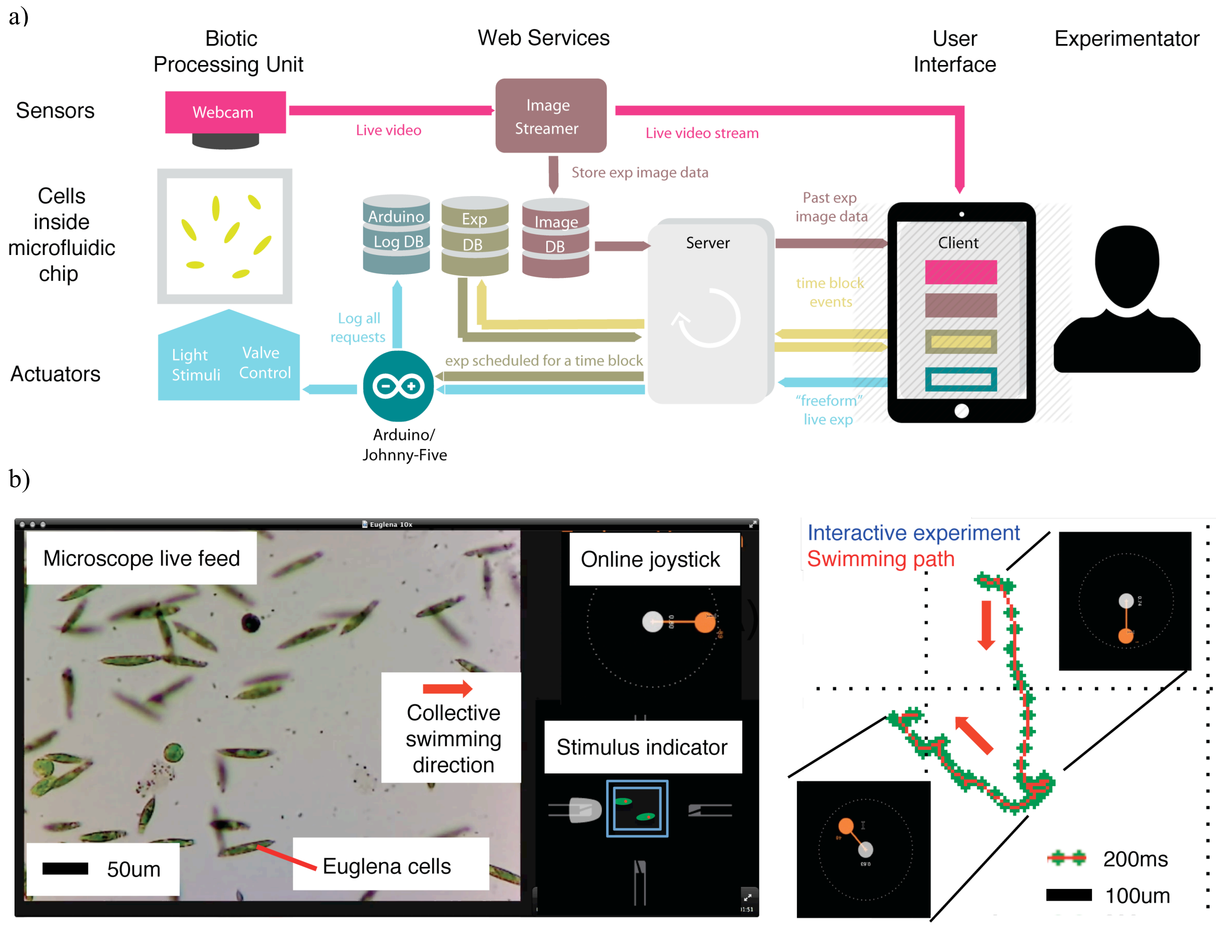

Figure 1: A real-time biology online lab architecture for robust and long-term light based interaction with photo responsive micro-organisms. a) System architecture providing a single user an interactive biology experimentation experience via real-time video streaming and stimulus actuation. b) The user interface enables to influence the swimming behavior of Euglena cells in real time via a two-dimensional analog light stimulus applied via a joystick (right: example of change in swimming path of a single cell upon light stimulus actuated in real time by joystick).

instructions, and sending the biological measurements back to the database. Multiple users can access their experiments remotely in an asynchronous manner, i.e., sending instructions and checking for experimental updates at arbitrary times. This architecture enables collaborative experimentation and optimal user distribution among BPU resources. Users access the system without the need to book a time slot, and they can perform interactive experiments, i.e., change the experimental instructions multiple times throughout the run of the machine. This architecture is optimized to coordinate asynchronous user actions with synchronous equipment cycles to optimally utilize parallelized equipment.

For the specific implementation we developed liquid handling-imaging robots (BPU) made from Lego Mindstorms, where each of three such robots could run six experiments in parallel. Here each experiment (Fig.2b) allowed studying the spatiotemporal chemotactic response of the slime mold *Physarum polycephalum* (yellow) to an oatmeal solution trail (red). Physarum is a single-celled, multi-nuclei, cytoplasmic organism that forms active and dynamic tube networks to search for food [13], [14],[15]. The physarum is housed in an open petri-dish, which is imaged below and chemically stimulated from above. In particular, stimulus food trails of liquid oatmeal that are pipetted onto an agar surface lead to growth behavior of the organism (Fig.2b). This offers a scientifically interesting as well as educational relevant experimental paradigm with high-dimensional input and output spaces.

Each BPU was controlled by a Raspberry Pi communicating with a Phython-based webserver (Pyramid) using MySQL and Node.js for database and chat server. The frontend UI as web application used Bootstrap API and HTML5.

The system was tested in a 10-week lecture based graduate level biophysics class. Here the students had access to the cloud experimentation throughout the course and performed approx. 20 experiments each; 4 students participated. Throughout the course the students progressed from guided, to freely exploratory, and eventually self-motivated experiments leading to a final course project, where the students were tasked to report on interesting observations in their experimental data, and then developed a biophysical model (which was the learning content of the course) that would explain aspects of their experimental physarum data.

This application and user study was successful: The system was fully stable for the 10-week period; the students self-reported that they liked the online experimentation system and that it was a valuable addition to the otherwise theory based class; one student even made a discovery on the platform that is considered novel when compared to the existing literature. The students also expressed that using real biology experiments (rather than simulations) significantly increased their motivation to exploring the biological specimen. We also tracked all user actions, the corresponding analysis revealed differences behavior among student behavior, for example how much of the previous experimental data was analyzed

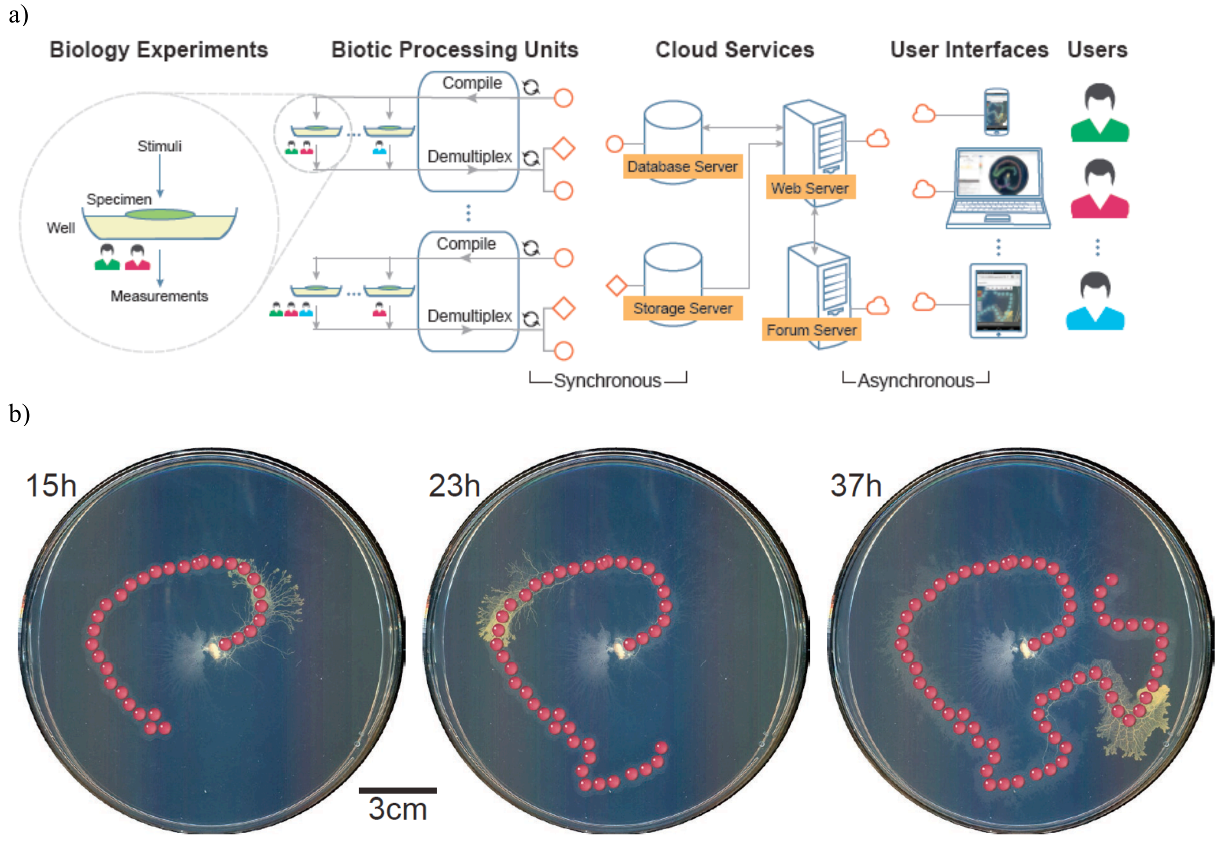

Figure 2: A turn-based cloud lab architecture enables large user numbers to execute biology experiments on shared equipment. a) This cloud experimentation architecture allows multiple asynchronous users to share equipment that runs many interactive biological experiments synchronously. b) The spatiotemporal chemotactic growth response of the slime mold physarum (yellow) to an oatmeal solution trail (red) offers a scientifically interesting experimental paradigm with high-dimensional input/ output spaces.

before conducting the next experiment, indicating the future potential of such biology cloud labs for learning analytics – in particular to understand how students approach experimentation in the life-sciences [16].

III. Conclusions

Both platforms have been tested over multiple months of operation and worked stably. Each platform achieves scale in user number differently: For the real-time platform users sequentially operate the same machine for 1-5 minutes at a time; for the turn-base platform ~20 users carry out multiplexed experiments on the same machine over the course of 2 days. The first is currently geared towards middle and high-school biology education; the later has been successfully used as online component in a college level biophysics theory class.

The main lessons we draw from our results so far: (1) Biology online platforms are technologically feasible and have significant promise for future applications – especially for online education, but likely for research as well. (2) A major challenge compared to other online platforms (such as remote operation of physics experiments) is the maintenance effort of the biological material, i.e., to keep it stable and responsive. Here it is important to make according choices at the start of the project to account for these logistics and – if possible - make use of biological specimen and corresponding hardware that minimize those challenges. The increasing advancement and cost reduction in biotechnological automation (incl. high-throughput machines) will enable many such platforms incl. commercial ones in the future. (3) A key attractiveness of (micro-) biological online experiments is the fact these biological organisms represent highly complex systems with emergent, unpredictable properties, which makes it attractive for education (as well as research), as many unexpected phenomena can be observed and even novel discoveries can be made.

Acknowledgment

This work was supported by Stanford BioX IIP, Stanford VPOL, Stanford MediaX, and NSF Cyberlearning (NSF 1324753).

References

[1] S. J. Trietsch, T. Hankemeier, and H. J. van der Linden, “Chemometrics and Intelligent Laboratory Systems,” *Chemometrics and Intelligent Laboratory Systems*, vol. 108, no. 1, pp. 64–75, 2011.

[2] A. M. Chung, N. Cira, and I. Riedel-Kruse, “An interactive real-time biology cloud lab”, in prep. 2015.

[3] Z. Hossain, X. Jin, E. Baumbacher, A. M. Chung, S. K. J. D. Shapiro, C. Y. Truong, S. Choi, N. D. Orloff, P. Blikstein, and I. H. Riedel-Kruse, “Interactive Cloud Experimentation for Biology: An Online Education Case Study,” *Chi*, Jan. 2015.

[4] G. R. Alves, J. M. Ferreira, D. Muler, H. Erbe, N. Hine, J. B. M. Alves, C. E. Pereira, L. Chiang, O. Herrera, and E. Sucar, “2005 IEEE Conference on Emerging Technologies and Factory Automation,” presented at the 2005 IEEE Conference on Emerging Technologies and Factory Automation, 2005, vol. 2, pp. 1023–1030.

[5] L. Gomes and S. Bogosyan, “Current Trends in Remote Laboratories,” *IEEE Trans. Ind. Electron.*, vol. 56, no. 12, pp. 4744–4756, 2009.

[6] C. Gravier, J. Fayolle, B. Bayard, M. Ates, and J. Lardon, “State of the art about remote laboratories paradigms-foundations of ongoing mutations,” *International Journal of Online Engineering*, vol. 4, no. 1, 2008.

[7] *Emerald Cloud Laboratory*. http://emeraldcloudlab.com

[8] *transcriptics*. https://www.transcriptic.com.

[9] G. M. Whitesides, “The origins and the future of microfluidics.,” *Nature*, vol. 442, no. 7101, pp. 368–373, 2006.

[10] L. Barsanti, V. Evangelista, V. Passarelli, A. M. Frassanito, and P. Gualtieri, “Fundamental questions and concepts about photoreception and the case of Euglena gracilis.,” *Integr. Biol.*, vol. 4, no. 1, pp. 22–36, 2012.

[11] R. A. Littleford, “Culture of Protozoa in the Classroom,” *The American Biology Teacher*, pp. 551–559, 1960.

[12] Z. Hossain, X. Jin, E. Baumbacher, A. M. Chung, S. K. J. D. Shapiro, C. Y. Truong, S. Choi, N. D. Orloff, P. Blikstein, and I. H. Riedel-Kruse, “Interactive Cloud Experimentation for Biology: An Online Education Case Study,” *Chi*, 2015.

[13] K. Alim, G. Amselem, F. Peaudecerf, M. P. Brenner, and A. Pringle, “Random network peristalsis in Physarum polycephalum organizes fluid flows across an individual.,” *Proceedings of the National Academy of Sciences*, vol. 110, no. 33, pp. 13306–13311, 2013.

[14] A. Tero, S. Takagi, T. Saigusa, K. Ito, D. P. Bebber, M. D. Fricker, K. Yumiki, R. Kobayashi, and T. Nakagaki, “Rules for Biologically Inspired Adaptive Network Design,” *Science*, vol. 327, no. 5964, pp. 439–442, 2010.

[15] A. Adamatzky, “Routing Physarum with repellents.,” *Eur Phys J E Soft Matter*, vol. 31, no. 4, pp. 403–410, 2010.

[16] C. Romero and S. Ventura, “Educational Data Mining: A Review of the State of the Art,” *IEEE Trans. Syst., Man, Cybern. C*, vol. 40, no. 6, pp. 601–618, 2010.