Chapter 11
Life-Science Experiments Online: Technological Frameworks and Educational Use Cases

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Abstract We review remote (or "cloud") lab technologies for life-science experimentation. Compared to other remote labs such as for physics, a particular challenge arises from the variability and stability of biological materials. We describe and compare four biology cloud labs that demonstrate different user interaction modes, i.e., real-time and turn-based interactive, programmed, and augmented batch, respectively, and furthermore regard their underlying hard and software architecture, biological content ("bio-ware") (i.e., microswimmer phototaxis, slime mold chemotaxis, bacterial growth under antibiotics, RNA folding), and various other features such as the time required for one experiment or scalability to large user numbers. While we generally focus on educational use cases, research applications are included as well. General design rules for biology cloud experimentation labs are derived; open questions regarding future technology and opportunities for wide deployment are discussed. We hope that this review enables stakeholders from the life sciences, engineering, and education to join this relevant and exciting field.

Keywords Biology · Life sciences · Remote experimentation · Online experimentation · Cloud lab · Education · Biotic processing unit (BPU)

11.1 Introduction

Being able to perform versatile biology experiments online has many applications for research and education. Many access barriers to life-science experimentation exist for academic and commercial research, mainly due to professional training needs, cost of equipment purchase and operation, and safety considerations (Sia and

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Fig. 11.1 Biology cloud experimentation labs enable remote users (scientists and students) to conveniently carry out life-science experiments online

Owens 2015). Remote operation of biology experiments in the cloud (Fig. 11.1) has been suggested to help lower these barriers (Hossain et al. 2015, 2016). Since biological investigations are diverse—unlike general-purpose computing, there is no clear foundation (e.g., binary 1s and 0s) for executing all types of experiments—different types of back-end instruments and online architectures are needed to address the duration of an experiment, the response time of the biological material, and the frequency of user interactions.

Multiple approaches to implement biology cloud labs have been developed but only rather recently (i.e., over the past ~4 years): We previously developed two interactive biology cloud lab architectures that were real-time (Hossain et al. 2016) and turn-based (Hossain et al. 2015); commercial and academic entities developed noninteractive biology cloud labs where experiments can be programmed (Riedel-Kruse 2017; Transcriptics 2015; Klavins 2017), and online citizen science games have been deployed that provide the user with experimental feedback (EteRNA) (Lee et al. 2014). All these labs have been used in educational contexts to various extends.

These four approaches can be categorized based on their directness and flexibility of the user interactions, which is enabled and constrained by the underlying architecture: (1) "Real-time interaction" enables direct experimentation and adaptive user input on the sub-second time scale, while the experiment is running (Hossain et al. 2016). This is suited for biological phenomena with response times on the scale of seconds. Experiment duration is typically short (minutes), and a user obtains sole and direct control of a single instrument for a time period on the scale of minutes (although both requirements could be relaxed, in principle). (2) "Turn-based interaction" also enables direct experimentation and adaptive user input, while the experiment is running, but now on more discrete time scale, e.g., every few minutes (Hossain et al. 2015). The biological response time of interest is significantly longer than 1 s, and no real-time interaction is required. Experiment duration might be multiple hours, and experiments of multiple users can be multiplexed and parallelized on a single machine or on multiple machines (again, these requirements can be relaxed). (3) "Programmed batch" enables code-based instruction of one or multiple instruments to execute a more complex series of experiments. Here, all instructions are completely predefined before the experiment starts (Riedel-Kruse 2017; Transcriptics 2015; Klavins 2017), and no interaction or adaptions during the experiment are possible. This approach is particularly geared toward academic and industrial research, where robots shuttle biological samples between fully automated pieces of equipment, thereby enabling highly complex experiments on the scale of hours. (4) "Augmented batch" enables the user to focus on higher level experimental design tasks while abstracting away the particularities of controlling an instrument. This is particularly useful for citizen science games (Lee et al. 2014) that provide experimental feedback to online players. (Note that these four examples provided here do not map exclusively onto these four categories, e.g., interactive labs can be used for batch processing (Hossain et al. 2016), or pre-programmable labs could be converted into turn-based ones (Riedel-Kruse 2017) depending on the exact hardware setup. Furthermore, these approaches can be categorized along other dimensions, and we will discuss throughout the paper.)

The goal of this paper is to provide an overview of these existing biology cloud labs with a particular focus on educational uses, although we also consider professional and citizen science. We highlight their architectures, practical implementation, and user testing of these approaches; detailed descriptions of these studies can be found in the original publications (Hossain et al. 2015, 2016; Riedel-Kruse 2017; Lee et al. 2014). We also briefly mention purely virtual approaches, i.e., simulations of biology experiments (de Jong et al. 2013; Heradio et al. 2016). We provide a systematic comparison between these four approaches (Table 11.1), and we discuss open questions for future larger-scale deployment and for increasing the availability of distinct experimentation types.

11.2 Background and Motivation

Cloud labs are poised to help solve significant educational challenges. Familiarity with advanced scientific practices and "authentic inquiry" (Chinn and Malhotra 2002; Pedaste et al. 2015; States 2013) are imperative for K-12 and college education (Next Generation Science Standards, NGSS; States 2013; Bybee 2013) but are difficult to achieve in real-world classrooms given logistics and cost (Chinn and Malhotra 2002; Wellington 2007). In addition to traditional physical hands-on labs, virtual and remote labs have been successfully deployed recently, particularly in engineering and physics (de Jong et al. 2013; Heradio et al. 2016). User studies have shown that hands-on, remote, and virtual modalities each have distinct advantages given educational goals and situational contexts, but ultimately, the question is how to best use these approaches synergistically (de Jong et al. 2013; Heradio et al. 2016; Wieman et al. 2008; Bonde et al. 2014; Sauter et al. 2013). Remote experiments in the life sciences have been lacking compared to these other disciplines, in particular due to the added challenges and necessary logistics for keeping biological materials healthy and readily available for extended periods of time.

Modern biotechnology and life sciences are poised to provide solutions to these challenges. Of particular importance are liquid-handling robotics (Kong et al. 2012)

Table 11.1 Comparison of four biology cloud labs

User instruction mode	Real-time interaction	Turn-based interaction	Programmed batch	Augmented batch	
Biological substrate	*Euglena gracilis*	*Physarum polycephalum*	*Escherichia coli*	RNA	t3.1
User controlled variable (stimulus)	Light	Food solution	Antibiotics	Nucleotide sequence	t3.2
Raw output data	Image sequence of *Euglena* in microfluidic chip	Image sequence of Petri dish with *Physarum*	Optical density of bacterial population	Single-nucleotide-resolution chemical reactivity measurements	t3.3
Processed data output	Cell tracks	Binarized image	Growth curves	Graphical display of secondary RNA structure	t3.4
Interactive experimentation?	Yes (real-time)	Yes (turn-based)	No	No	t3.5
# Experiments per run per BPU	1	6	96	10,000	t3.6
# BPUs in cluster	6	3	1	1 (incl. manual labor)	t3.7
Duration of one experimental run	~1 min	~48 h	~24 h	~1 month	t3.8
# Exp. in 24 h	~5000	~10	~100	~0.1	t3.9
Cost per experiment	~US $0.01	~US $10	~US $1	~US $0.2	t3.10
Maximum frequency of updated user input	600/run	~250/run	1/run	1/run	t3.11
	(10/s)	(6/h)	(1/day)	(1/month)	
Actual # of updates users made per run	~5/run	~3/run	1/run	1/run	t3.12
# perceived available choices per update	~16	~400	~10	$\sim 4^{100}$	t3.13
# choices per experiment	>1000	>100	~10	$\sim 4^{100}$	t3.14
Dimensionality of experimental design space	~100	~5	~1	$\sim 4^{100}$	t3.15
Extendability to other experiments	Medium	Low	Very high	Low	t3.16

and integrated microfluidic devices (Balagaddé et al. 2005; Melin and Quake, 2007) that incorporate sensing and actuation devices, achieving very complex liquid handling (often at high throughput) to fully automate sophisticated life-science experiments (Fig. 11.2). These technologies are increasingly impacting our society through their academic and industrial use, will potentially also soon lead to devices

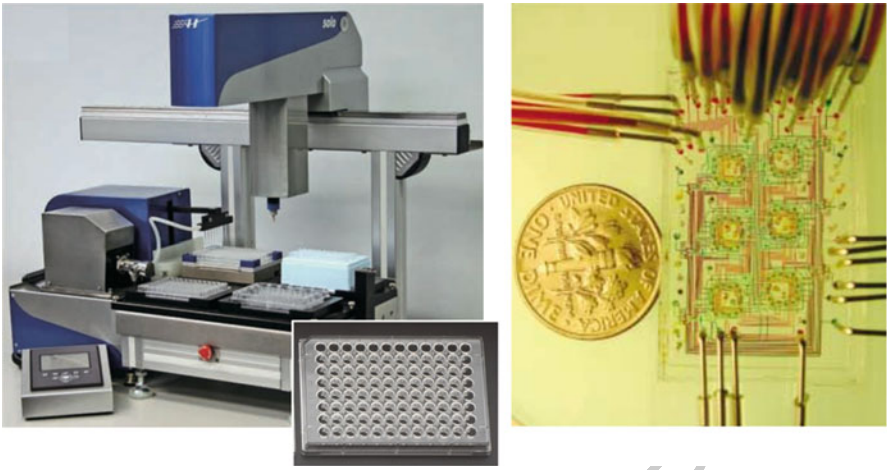

Fig. 11.2 Automation and cost reduction in life-science experiments via (left) liquid-handling robotics and (right) microfluidics. (Images adapted from Kong et al. (2012) and Balagaddé et al. (2005))

of personal use, and may ultimately transform our daily lives as radically as modern computing technology has done previously (Riedel-Kruse et al. 2011; Gerber et al. 2016). Hence, the life sciences and associated technologies should also be put at the forefront of formal and informal education in order enable modern citizens to navigate these new realities.

These new technologies and new educational needs both enable and motivate the field of interactive biology (Riedel-Kruse et al. 2011; Gerber et al. 2016), in which human users interact with microscopic organisms and processes in real time. In addition to cloud labs (Hossain et al. 2015, 2016), these interactive technologies have been implemented as biotic games (Riedel-Kruse et al. 2011, self-builder smartphone kits (Kim et al. 2016), and interactive museum exhibits (Lee et al. 2015). College-level device classes have been deployed around such interactive biology and game project themes (Cira et al. 2015), and we expect future synergy as students build interactive biology devices and put them online as remote labs (Hossain et al. 2016). User studies associated with these previous projects often identified standout features of a real biological system compared to pure simulation (Hossain et al. 2015, 2016), although ultimately we believe that both real and simulations should be combined synergistically for better educational outcomes. Advantages of real biology labs include the chance of genuine discovery and also illustrating biological noise and variability (Hossain et al. 2015, 2016).

To aid the design of instruments suitable for biological cloud labs (and interactive biology in general), we previously introduced the conceptual abstraction of biotic processing units (BPUs) (Hossain et al. 2015; Riedel-Kruse et al. 2011; Hossain and Riedel-Kruse 2017; Lam et al. 2017). BPUs are instruments that have both sensors and actuators that interface with the biological material, with standardized digital input/out channels for instructions and data transfer as well as standardized biological input/output channels for handling the biological material (and potentially even moving biological materials between different BPUs).

When setting up a biology cloud lab, several design specifications must be considered depending on the deployment needs. In particular, in order to enable K-12 and college education, the following features have been identified previously as particularly valuable (Hossain et al. 2016): The system must (1) enable the types of inquiry mandated (which would be very different for professional science vs. educational K-12 purposes); (2) have a low entry barrier and be usable even at the K-12 level; (3) be real-time interactive; (4) have a fast turnaround time (within minutes); (5) be fault tolerant against biological variability and failure; (6) scale to millions of users worldwide from a design as well as economic viewpoint; (7) have a sufficiently large exploration and discovery space; and (8) generalize to many other experiment types easily. For research purposes, additional requirements do apply, such as high fidelity and reproducibility of the results, furthermore significant versatility of instruments, and biological materials that can be processed.

11.3 System 1: Real-Time Interaction (*Euglena* Phototaxis, Light)

This system was developed with the goal to allow direct, real-time interactivity with microbiological systems—at cost and scale (Hossain et al. 2016) (Fig. 11.3). This goal required a short overall experimental duration (at the scale of minutes) and full automation to enable 24/7 access without much manual labor at the back end.

11.3.1 Architecture

On this platform, a single user becomes—for a limited amount of time—the sole actuator of a remotely placed piece of equipment (BPU). The user management system was implemented as a real-time queue. The primary new affordance of this platform is a direct and closed interactive feedback loop between the user and the biological system, but submitting fully preprogrammed batch experiments that are executed serially at a later time is also possible.

The BPU for this implementation consisted of a simple microfluidic chip (Whitesides 2006) housing the phototactic single-celled organism *Euglena gracilis* (Fig. 11.3a, b) (Barsanti et al. 2012). The chamber on this chip is a square (approximately 1 mm long, 1 mm wide, and 150 µm high) and has an inlet and outlet for fluid and organism exchange. These organisms are imaged from above via a webcam microscope. On each of the four sides of the chip, an LED shines light of varying intensity onto the chip and where this intensity can be controlled by the user.

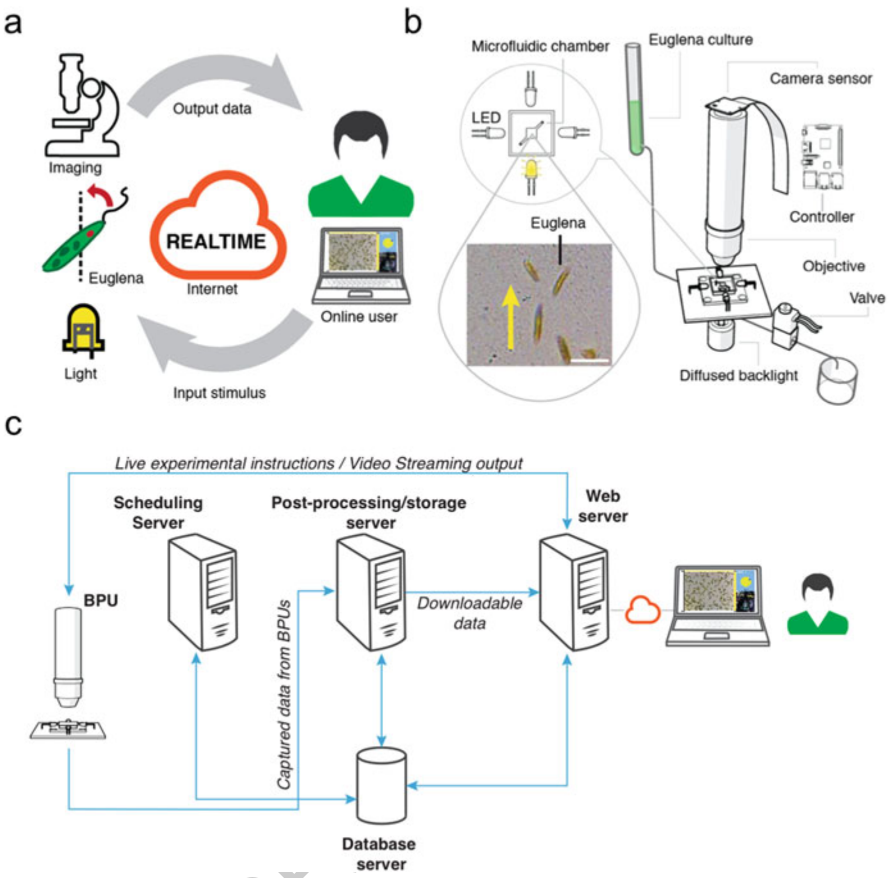

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Fig. 11.3 Real-time biology online lab architecture for light-based interaction with photoresponsive microorganisms. (**a**) Online users send light stimuli to *Euglena* and observe the response in real time. (**b**) Back-end hardware. *Euglena* are replenished automatically from an upstream reservoir. Scale bar, 50 µm. (**c**) System architecture. (Images adapted from Hossain et al. (2016))

Euglena responded to these stimuli by swimming away from high light intensities (Barsanti et al. 2012). Many more subtle responses to light are detectable in this system, such as cells spinning around their own axes. *Euglena* cells respond to a change in light conditions on the time scale of seconds, making them particularly attractive for interactive experiments for students and even children.

A cluster of six such BPUs was set up, each of which was controlled by its own microcomputer to control the LEDs, to stream live video, to post-process data, and to communicate with the central server. The task scheduling concepts of high-performance computing. The work of Etsion and Tsafrir (2005) was adopted to design the central server. This server assigns BPUs and remote users according to a non-exclusive group allocation policy, handles distinct BPU types, routes

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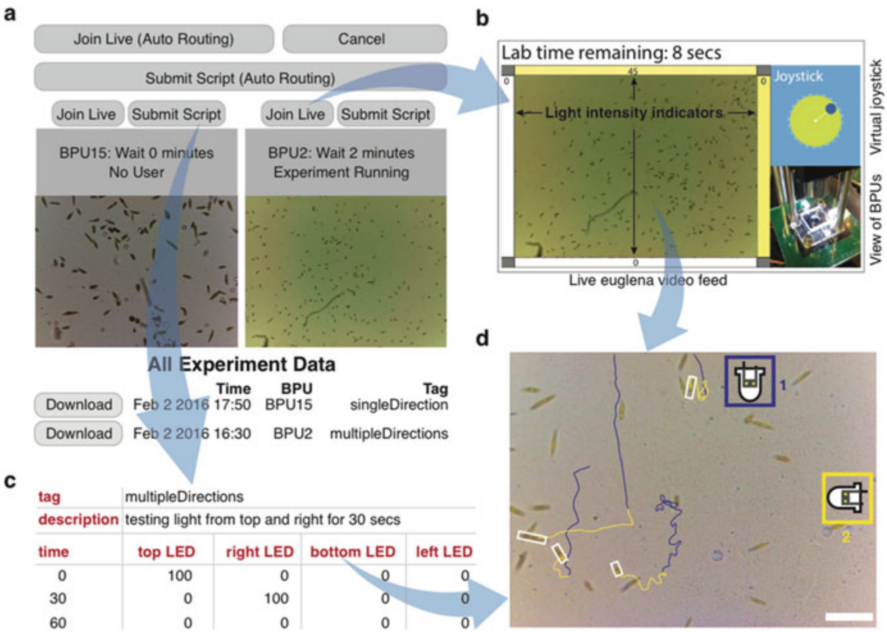

Fig. 11.4 The *Euglena* cloud lab. (**a**) Landing webpage. (**b**) Live mode, with a virtual joystick to control the intensities of the four LEDs. (**c**) Example of preprogrammed instructions for batch mode. (**d**) Example of the cellular response to a light stimulus sequence from top to right (blue, yellow). Scale bar, 100 μm. (Images adapted from Hossain et al. (2016))

experiments to the best-suited BPU, and optimizes wait time through load balancing. A webserver including databases then connects to the user on the client side.

Users perform real-time exploratory as well as preprogrammed experiments that are executed at a later time, and users can download the data for analysis (Fig. 11.4). The user controls the intensity and direction of the two-dimensional light stimulus via a simple online joystick.

A particular affordance of this BPU and organism is the opportunity to implement a low-cost, fully automated cloud lab. *Euglena* cultures are typically stable over long periods (multiple weeks) without much care given appropriate growth medium and light for photosynthesis. The microfluidic chip is connected to an external *Euglena* culture, and hence fresh *Euglena* can be automatically exchanged into the culture via an automated valve whenever needed, typically every few days, yielding a fully automated platform that requires <15 min maintenance once each week per BPU. Another important feature is an automonitoring framework in which each BPU runs an experiment automatically every hour, thereby determining the density of cells as well as their velocity and responsiveness to light. If these parameters are outside the desired regime, then the system attempts to correct itself by autoflushing fresh organisms into the chip. If the system still is not appropriate, then lab personnel are notified to service the BPU. Given that there are multiple BPUs in the cluster, remote users have a very high chance (>99%) of finding at least one functional BPU available at any time; the webserver then also routes users to a "good" BPU. Such automonitoring and self-correcting schemes are essential for delivering cloud labs containing variable, fragile biological materials at low cost and high scale.

11.3.2 Deployment in K-12 Education and Assessment

This platform has been used and tested in multiple middle schools (Hossain et al. 2016). During one study, the cloud lab was projected to the front of a class (27 students, seventh and eighth grade; Fig. 11.5 left), so that all students could do the experiments together. Students then analyzed their data in pairs on their own computer and finally engaged with a virtual modeling environment (see also details in Sect. 11.7, Fig. 11.16) to fit parameters. In another study, 34 students (eighth grade; Fig. 11.5 right) working individually or in pairs used the iLab (Harward et al. 2008) batch interface to submit instructions for light stimuli. The system ran experiments for these students, and the students received movies for analysis. Students chose a diverse set of designs: some explored light intensity, some tuned the light direction, and other students were less systematic.

In both middle-school deployments, it became clear that students liked the activities overall, that the students felt empowered, and that there was a positive educational outcome. While it is possible to introduce the system in one or two class sessions, there should be sufficient time for each student to understand the system and to run multiple experiments. Due to restrictions on class time, firewall restrictions, and the number of available setups, it was not always possible to let each student run as many experiments as desired. In general, it appeared that five to ten experiments lasting 1 min each would be ideal for each pair of students.

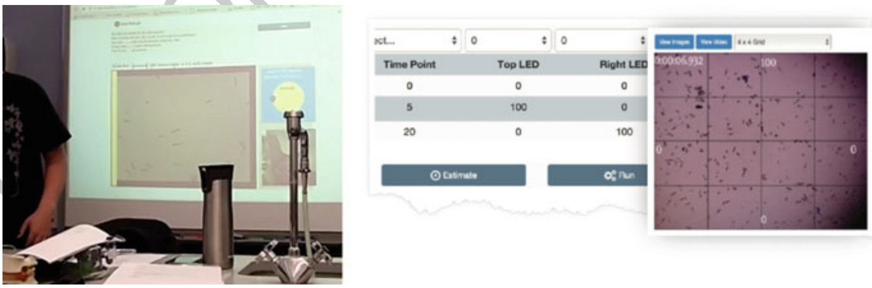

Fig. 11.5 Middle-school deployment of the *Euglena* cloud lab. Left, projection of the setup to the front of the class. Right, *Euglena* cloud lab use through the iLab platform via batch mode. (Images adapted from Hossain et al. (2016))

11.3.3 Deployment in College Education and Assessment

It was also tested whether university students taking a professor-led theory-based biophysics class could successfully carry out experiments and sophisticated quantitative data analysis from home in a self-paced manner on this platform (Fig. 11.6) (Hossain et al. 2016). Over 14 days, ten students, working individually, completed a homework project focusing on concepts regarding microswimmers, diffusion, and low Reynolds number hydrodynamics (Purcell 1997). Using the live mode (Fig. 11.4b), students explored *Euglena* light response behavior and made cells swim along geometric paths (Fig. 11.6a). Students were able to self-discover semiquantitative relationships, e.g., reporting that the "fraction of *Euglena* participating in the directed motion seems to increase as you hold the joystick longer, and depending on the intensity of the light." They performed back-of-the-envelope analyses of *Euglena* size (∼50 μm), speed (∼50 μm/s), and drag and propulsion forces (∼10 pN) (Purcell 1997), experimentally confirming lecture content. Students then analyzed self-generated large-scale batch data (Fig. 11.6b) in MATLAB to test two hypotheses: (1) Do *Euglena* behave like passive Brownian particles? (2) Does the population-averaged velocity differ between dark and light conditions? These results demonstrate that even 1 min experiments provide students with rich experimental data including hundreds of auto-traced cells, supporting sophisticated statistical analysis. The logged data also revealed that students accessed the system at their own convenience at day and at night and that they engaged in different modes of experimentation.

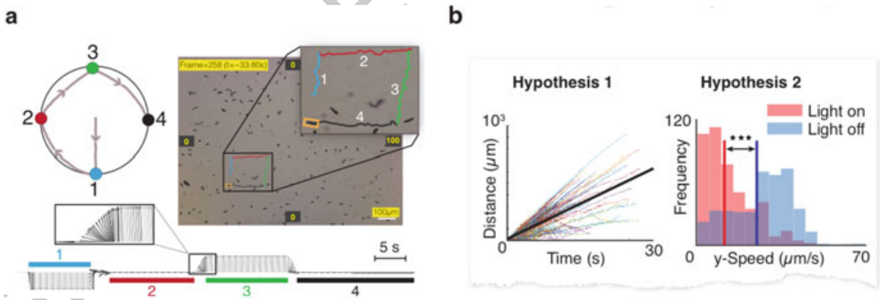

Fig. 11.6 User studies in middle school and college demonstrate the utility of the platform for face-to-face and online education. (**a**) University students performed exploratory joystick-based experiments from home. (**b**) Automatically generated large-scale data (hundreds of cells) using batch mode allowed students to investigate two hypotheses. Left: Are *Euglena* active or passive particles? Right: Does the population-averaged swimming speed depend on light conditions? (Images adapted from Hossain et al. (2016))

11.3.4 Deployment in a MOOC Setting and Assessment

An open online course was developed around this *Euglena* online lab and deployed via the Open edX platform (Hossain et al. 2017). This online course with a remote biology lab engaged >300 remote learners worldwide (Fig. 11.7 left) in the scientific practices of experimentation, modeling, and data analysis to investigate phototaxis of a microorganism. Participants typically took 2–6 h to complete the course during a 1-week period. The course was reoffered weekly, which allowed to respond to user feedback and to iterate on the course content. Overall, >2300 experiments were run by these participants.

In contrast to the deployments on this platform described earlier, here students were completely autonomous in their actions, although the course itself was significantly scaffolded. In addition to the previously offered activities, this online course incorporated data handling via Google Sheets (Fig. 11.7 right), which was more amenable than MATLAB, especially since even middle schools are increasingly using Google Sheets. Online users were asked to execute a final open research project (a voluntary option in order to not overburden the students within a 1-week period). Twenty-one students engaged in their own research projects, for example, exploring how *Euglena*'s response depends on light intensity or duration of the applied light. These students made discoveries that appear in the literature (e.g., how *Euglena* sometimes "freeze" for ~1 s if the light intensity increases very suddenly (Ozasa et al. 2014)). Thus, users on such a platform can engage in realistic scientific inquiry and make genuine discoveries.

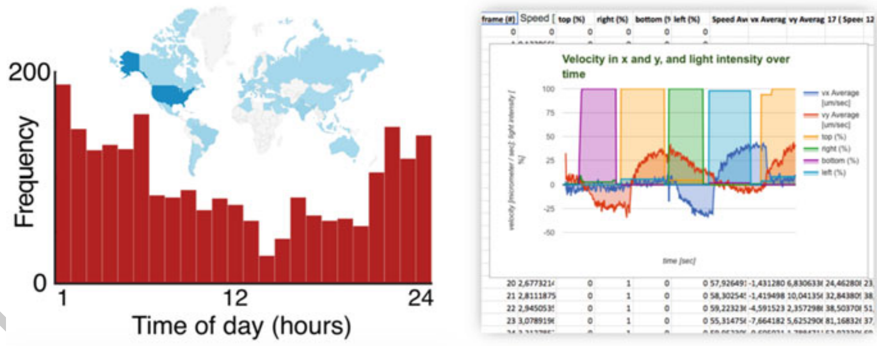

Fig. 11.7 MOOC-scale deployment of the *Euglena* cloud lab. Left: System access pattern. Inset, density of traffic sources by location. Right: Students exported data into Google Sheets, where relationships could be plotted easily. (Images adapted from Hossain et al. (2017))

11.3.5 Reflections and Next Steps

These deployments and user studies have shown that this *Euglena*-based platform enjoys high educational affordances by enabling students to go through the major components of the scientific inquiry paradigm, that the challenge level can be adapted to specific educational needs (middle school to advanced college), that the experimentation and discovery space is sufficiently rich, that the students and teachers overall like these activities, and that the experiment duration and associated costs are such that large-scale deployment seems feasible. Students performed scientific practices and engaged in inquiry-based learning within a short time span without logistical effort, which was impossible before. Our findings also suggest that classrooms could be flipped in the future, with the students operating the lab as homework (Fig. 11.8). This should be a reference to Fig. 11.7 (NOT 11.8)

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The experimental throughput and cost of such a *Euglena*-based platform scale to massive user numbers and diverse curricular demands, from middle school to college to MOOCs. There are >15 million high-school students in the USA alone, and hundreds of millions of users in developing countries and remote locations could access such platforms via increasingly ubiquitous smartphones (Ozcan 2014). It was estimated that implementing lesson plans in which ~1 million students each run five to ten experiments per year could be achieved with ~250 BPUs, a modest back-end footprint of ~10 m^2, and standard 1 Gb/s internet connectivity. Importantly, each experiment would cost less than 1 US cent; hence, cloud lab access for all students in a class (34 students, 10 experiments each) would be less than one live *Euglena* sample (~US $7 plus shipping).

Given the generality of the BPU paradigm, other biological specimens, stimuli, and experimental frameworks are amenable to this cloud lab framework. The platform already supports complex investigations of microswimmers and microecologies that are of current interest to the biophysics community (Romensky

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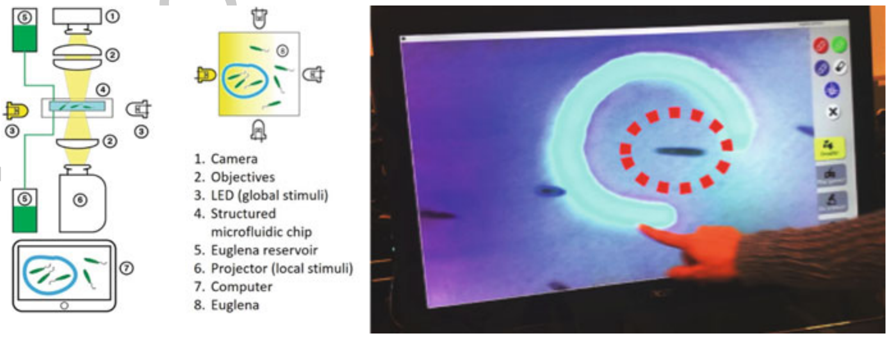

Fig. 11.8 Expanding the *Euglena* cloud lab. Left: Setup to projects light patterns onto a microfluidic chamber housing light-responsive *Euglena* cells. Right: Patterns drawn by user onto a touchscreen are projected onto phototactic *Euglena* that accumulate in colored regions. (Images adapted from Lee et al. (2015))

et al. 2015; Goldstein 2015). Image data are information-rich (e.g., this platform unexpectedly captured cell-division events); combined with a rich stimulus space, many phenomena can be identified and systematically studied. Projector-based setups for *Euglena* (Lee et al. 2015) enable a much richer set of spatiotemporal stimuli, including the use of colors and more complex "mazes" for *Euglena* (Lam et al. 2017). The communication and data protocols are not domain-specific; hence, this platform is expandable beyond *Euglena* and light stimuli to a general class of increasingly automated and low-cost/high-throughput experiments, such as those involving valve switching in microfluidic devices (Balagaddé et al. 2005) and cloud chemistry (Skilton et al. 2015).

The obvious next step is to deploy the current *Euglena*-based platform in more classrooms, particularly in a teacher-autonomous fashion in which the teacher creates the desired lesson plans, and where all students have enough time and opportunity to operate the platform by themselves. The first studies along these lines are currently under way. In order to achieve this goal, the platform must also be scaled up from the current 6 to 20 online microscopes to enable all student pairs in a typical classroom to work concurrently.

It would also be important to synergistically complement these online activities with local hands-on activities, e.g., observing *Euglena* directly through a hands-on microscope. Further, the modeling and simulation aspects should be extended, such as demonstrated previously with the programming language Scratch (Resnick et al. 2009; Kim et al. 2016). Having students build their own interactive microscopes (Cira et al. 2015; Kim et al. 2016), which could even be put online in the long run, and empowering students to self-publish their experiments are other future objectives.

Notably, since these experiments are controlled with a Raspberry Pi, a camera, and a simple electronic board, other experiments outside biology, such as a physics pendulum, could be amenable to investigation. Conversely, given that the back-end experiments are kept sufficiently modular, integration into other cloud lab frameworks is possible (Heradio et al. 2016).

11.4 System 2: Turn-Based Interaction (Slime Mold Chemotaxis, Food)

This biology cloud lab architecture was motivated by the idea of enabling real-time interaction between a remote user and a biological organism in a turn-based manner. This interaction was intended to be visually intuitive, with the back-end hardware being so simple that it could potentially be reproduced by students as a mini-cloud.

11.4.1 Architecture

The architecture of this cloud lab is optimized to allow multiple users to share multiple instruments (BPUs), each of which carries out multiple biology experiments in parallel (Fig. 11.9) (Balagaddé et al. 2005). In order to enable turn-based interactivity, an underlying batch processing framework was developed. Batch processing is increasingly common in the life sciences, including usage of high-throughput hardware in which each machine typically handles only a specific type of experiment with a specific set of instructions—many experiments can be executed in parallel. Each BPU has its own controller and operates synchronously on its own clock while querying the central database for updated instructions and for sending the biological measurements back to the database. Multiple users access their experiments remotely in an asynchronous manner, sending instructions and checking for experimental updates at arbitrary times. This architecture enables collaborative experimentation and optimal user distribution among BPUs. Users are assigned their experiment slot prior to the experiment run, and they can change the experimental instructions multiple times throughout the run. Hence, this architecture coordinates asynchronous user actions with synchronous equipment cycles to optimally utilize parallelized equipment.

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This should be a reference to Fig. 11.7 (NOT 11.8)

As a specific demonstration, an experimental paradigm was developed for studying the spatiotemporal chemotactic response of the slime mold *Physarum polycephalum* to an oatmeal solution food trail (Fig. 11.9) (Hossain et al. 2015). *Physarum* is a single-celled, multi-nuclei, cytoplasmic organism that forms active and dynamic tube networks to search for food (Alim et al. 2013; Tero et al. 2010; Adamatzky 2010). Food trails of liquid oatmeal that are pipetted onto the agar surface stimulate the growth and behavior of the organism, offering a scientifically interesting as well as educational relevant experimental paradigm with high-dimensional input and output spaces.

For this implementation, liquid handling-imaging robots (BPUs) were developed from Lego Mindstorms (Fig. 11.9) (Hossain et al. 2015; Gerber et al. 2017); each of three such robots could run six experiments in parallel. The organism was housed in an open Petri dish, which was imaged from below and chemically stimulated from above via dispensing droplets of nutrient solution. The BPUs communicated with a Python-based webserver. The front-end user interface (UI) (Fig. 11.10) enabled remote users to select a specific experiment (either one that is currently running or one that had already finished and was archived). The experimental interaction consisted of users graphically determining where and when liquid food stimuli would be administered by the robot onto the Petri dish (Fig. 11.10b, c). Before the experiment, a lab technician prepared fresh Petri dishes with *Physarum*. The BPU then administered new stimuli (as determined by the remote user) and obtained images every 10 min over an experiment that typically lasted 24 or 48 h. At the end of the experiment, all data were archived, and the dishes and *Physarum* were discarded.

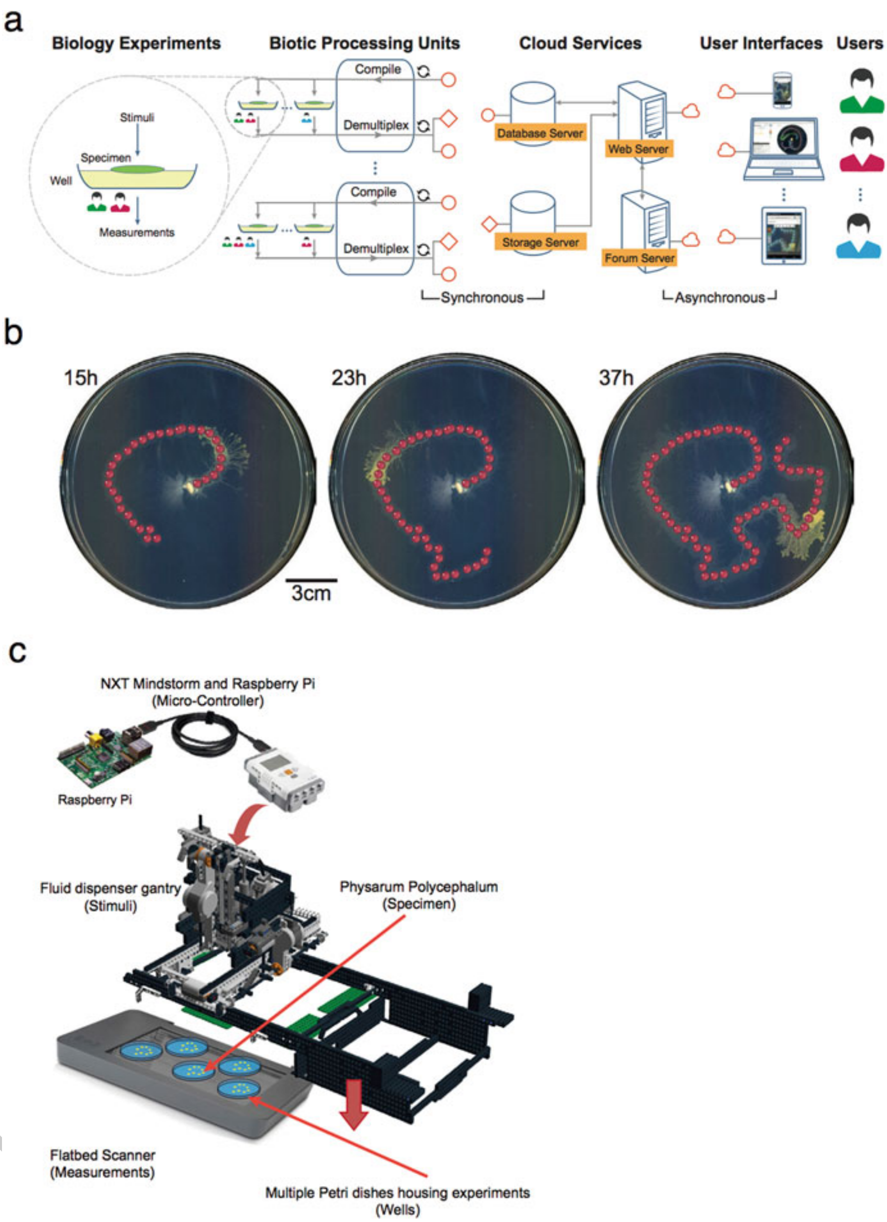

Fig. 11.9 Experiments and hardware for interaction with a slime mold. (**a**) A turn-based cloud lab allows multiple asynchronous users to share equipment for synchronous experimentation. (**b**) The spatiotemporal chemotactic growth response of *Physarum* (yellow) to an oatmeal solution trail (red). (**c**) BPU consisting of a Lego pipetting robot and a flatbed scanner. (Images adapted from Hossain et al. (2015))

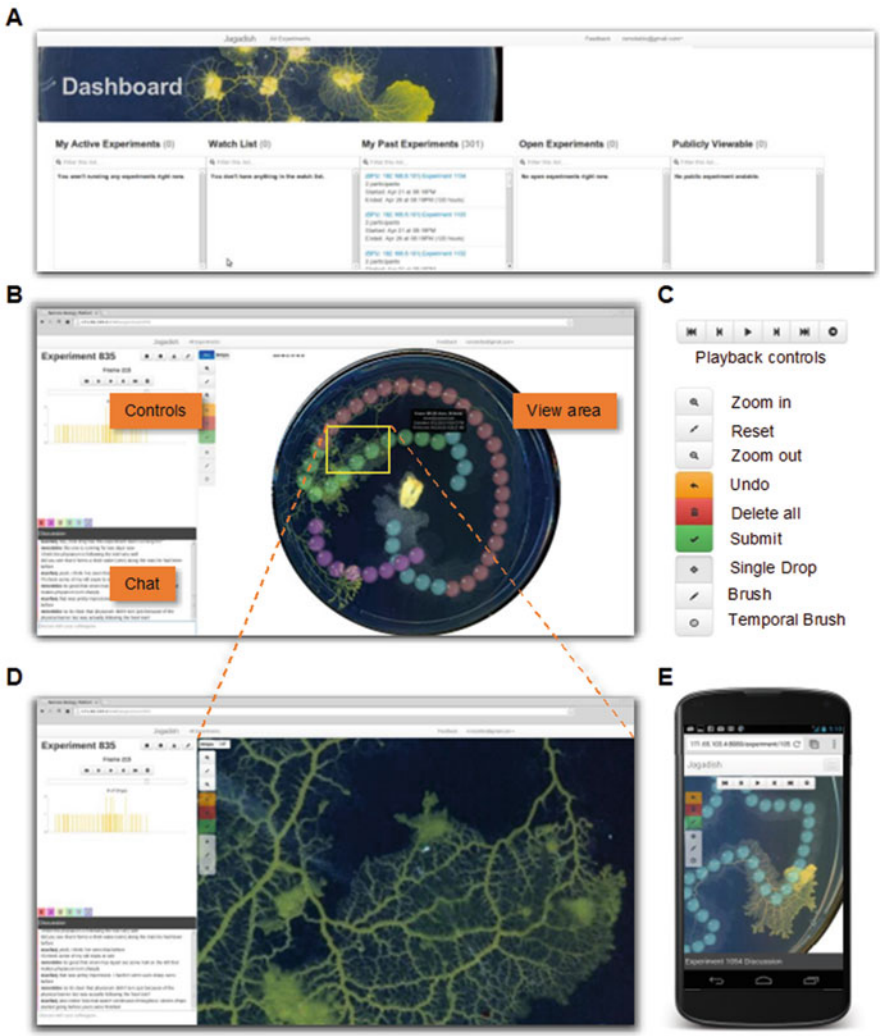

Fig. 11.10 UIs for the *Physarum* cloud lab. Users (**a**) choose a current or past experiments, (**b, c**) dictate the position and timing of chemical stimuli, and (**d**) scroll and zoom through existing image data. (**e**) Experiments are operable from multiple platforms, including smartphones. (Images adapted from Hossain et al. (2015))

11.4.2 Deployment in College Education and Assessment

This *Physarum*-based system was tested in a 10-week lecture-based graduate-level biophysics class at a university. Four students had access to the cloud experimentation platform throughout the course and performed ~20 experiments each. The students typically logged in two to three times during the run of each experiment. Throughout the course, the students progressed from guided work to free exploration to self-motivated experiments that led to a final course project. Students reported interesting observations in their experimental data and then developed a biophysical model (which was the learning objective of the course) to explain various aspects of their experimental data.

This user study revealed that the system was fully stable for the 10-week period. Students self-reported that they liked the online experimentation system and that it was a valuable addition to the otherwise theory-based class. Students also expressed that using real biology experiments (rather than simulations) significantly increased their motivation to explore these biological specimens. The analysis of all user actions revealed differences in student behavior, for example, how much of the previous experimental data was analyzed before conducting the next experiment. Thus, this study highlights the potential of biology cloud labs for educational use as well as for learning analytics (Romero and Ventura 2010).

As a final class project, the students were tasked to engage in the relevant parts of genuine scientific practice: exploration, making observations, formulating hypotheses, designing experiments, and developing a biophysical model. During this project, two students made interesting observations on how the network structure of *Physarum* depends on the overall size of the organism, as well as how the shape of the organisms (number of branches and length distribution of branches) dynamically changes over time (Fig. 11.11). One (nonbiology) student was particularly struck by his observation that organisms with smaller masses had fewer branches (Fig. 11.11i), which seemingly went against the notion of "self-similarity across scales" in fractals that had been discussed earlier in the course. The corresponding phenomena had not been described in the literature. The students then collected more data and iteratively developed and improved a biophysical model capturing these phenomena (Fig. 11.11ii–iv). These students are currently in the process of submitting a full research paper detailing their biophysical model (Cira and Riedel-Kruse 2017). Thus, biology cloud labs also show potential to be used for genuine research, enabling students to perform deep inquiry over the internet.

11.4.3 Reflections, Lessons Learned, and Next Steps

A major challenge of this particular implementation was the back-end logistics supporting these experiments. For example, approximately 30–60 min was always required for a lab technician to prepare all fresh biological material before starting the next round of experiments. Further, the overall footprint of the platform (a server rack filled with three BPUs executing 18 experiments in parallel over 48 h) does not easily scale to very large numbers of remote users in multiple institutions. Nonetheless, this platform would be beneficial as a local cloud lab within a school, for example, and where the chosen Lego Mindstorms implementation would allow students to build and modify their own instruments (Danahy et al. 2014; Gerber et al. 2017). Swapping out the hardware (BPUs) for more professional, higher-throughput

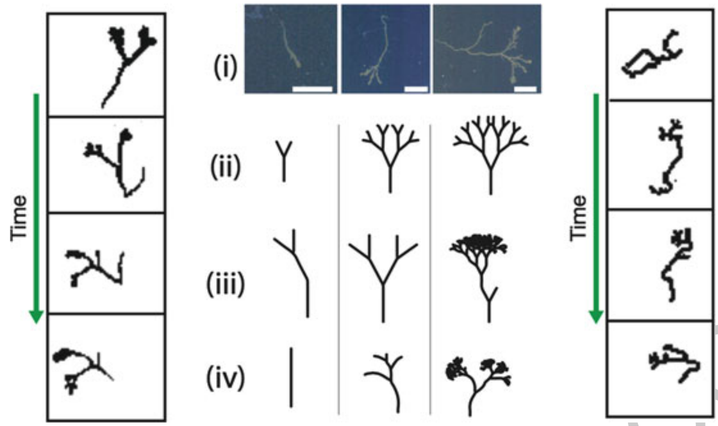

Fig. 11.11 Experimentation (left) and modeling (right) by graduate students using this cloud lab. Middle: Iterative modeling motivated by the cloud lab. (*i*) Image data reveal size-dependent network structures. Scale bars, 3 mm. (*ii*) Static symmetric bifurcation model. (*iii*) Static random bifurcation model. (*iv*) Dynamic growth-retraction model. Right: Time sequence of the model in (*iv*), compare to the sequence at left (Images adapted from Hossain et al. 2015)

instruments would allow the execution of different types of experiments at much larger scale and lower cost.

The cost and back-end logistics per experiment were significant and could be estimated as follows (assuming this type of system would be deployed at much larger scale). A BPU costs approximately US $500 in parts, and each BPU houses six experiments, with three runs per week for 1 year, leading to 50*3*6 = ∼1000 experiments. Additional costs include lab personnel to maintain *Physarum* colonies, prepare the agar plates, and prepare each experimental run, which is estimated at 2 h per week or ∼US $100 in labor cost/week. Lab space would cost ∼US $10/experiment. This estimate does not include the initial development of the platform.

Overall, this system successfully supported students in their learning activities, enabled the introduction of an experimental component into a theory-based class, and empowered nonbiologist students to carry out biology experiments in depth, effectively lowering access barriers.

11.5 System 3: Programmed Batch (Bacterial Growth, Antibiotics)

The computational cloud and time-sharing paradigms (Fox 2011) have recently inspired the development and deployment of biology cloud experimentation labs for research, such as commercial platforms that can execute experiments semiautomatically (Transcriptic, Emerald Cloud Lab) (Sia and Owens 2015; Riedel-Kruse 2017; Transcriptics 2015; Hayden 2004). These commercial platforms provide a large suite of instruments and reagents, with the ultimate vision of enabling the automated execution of any academic or industrial experiment, in particular when it comes to molecular and cell biology.

Here we also point to "Aquarium" (Klavins 2017), an academic "Laboratory Operating System" where online users can choose from prespecified laboratory protocols and experimental workflows via an online web interface; these experiments are then executed (in large part by manual labor, i.e., undergraduate technicians that can be easily trained), enabling students and researchers to build, e.g., transgenic strains online.

These platforms are different from the ones described earlier in this article as they are not interactive during the experiment. Instead, all experimental instructions must be provided before the start of the experiment. The experiments have turnaround times on the scale of days or more. None of these labs had been used for education previously; hence, a collaboration with the company Transcriptic was initiated to test one of these platforms with students. These investigations are described in detail in Riedel-Kruse (2017).

11.5.1 Architecture

Transcriptic has been developing a "Workcell" platform in which a robot shuttles biological specimens, for example, contained in 96-well plates, between experimental instruments such as liquid-handling robots, imaging devices, and incubators (Fig. 11.12). Experiments can be fully programmed in Python. This overall framework is under constant development; for example, some experimental steps are still executed by hand but will eventually be automated. Hence, the general vision and roadmap to full and flexible cloud experiment automation is clear.

11.5.2 Deployment in College Education and Assessment

To test the platform's educational potential, bacterial growth under the influence of antibiotics was chosen given its relevance for college level classes the relative ease of implementation on the existing platform (Riedel-Kruse 2017). Initially, bacteria were loaded into 96-well plates. Each student could claim 6 wells on that plate, allowing 15 students to work at once, leaving a few wells as controls. Prior to the start of the experiment, students defined the concentration of antibiotics in each well, leading to different growth rates over ~8 h (Fig. 11.13). Every 20 min, the amount of bacteria in a dish was measured via spectrophotometry. This cloud lab did not allow for interactive experimentation, i.e., users were not able to add antibiotics throughout the experiment, but this could be added to this framework in the future.

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Fig. 11.12 Transcriptic Workcell, a custom robotic cellular and molecular biology laboratory. (Image adapted from https://www.transcriptic.com/)

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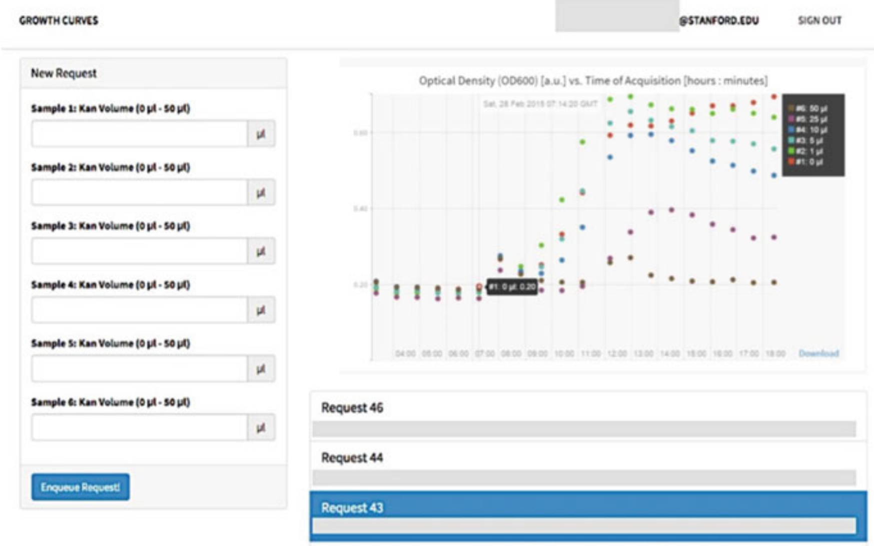

Fig. 11.13 Customized Transcriptic UI for educational deployment. Left: Six antibiotic amounts can be submitted. Right: Batch of data at the end of the experiment (time and optical density appear on the x and y axes, respectively). (Images adapted from Riedel-Kruse (2017))

A user study was run where 13 students could run 6 wells over 6 successive rounds of experimentation (36 experiments in total). It was found that one to two this figure will be printed in b/w

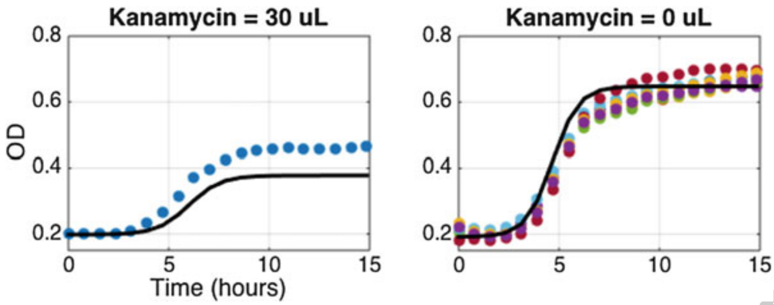

Fig. 11.14 Student-generated data (dots) and fit to models (solid lines) of two antibiotic concentrations. (Images adapted from Barsanti et al. (2012))

AQ5

This reference is wrong - it should be "Riedel-Kruse 2017"

rounds were needed to familiarize the students with the platform. Students then chose one of many growth models that had been discussed previously in class and fit their data to that model in MATLAB. Unfortunately, mutations arose in some of the bacteria over successive experiments, and there were some other technical issues, leading to not fully consistent results between experiments that made it more challenging for the students to interpret their data. These technical challenges were due to the early stage of platform development at the time but were later rectified by the company with updated equipment and protocols (~~Fig. 11.14~~).

AQ6

11.5.3 Reflections and Next Steps

Overall, the activities were successful and allowed students to design and run their own experiments, collect their data, and post-process the data. The exploration space available to the students was rather low dimensional compared to the cloud labs discussed earlier. The student's only option was to choose one of six antibiotic concentrations (they explored only a one-dimensional space). The concentration was determined before the experiment started—there was no interactivity during the experimental run. Further, the data consisted of zero-dimensional measurements points, which is much less information rich than the image data in the other cloud labs, rendering the experience more abstract than a classic experiment.

Based on Transcriptic's business model, the cost of these of experiments was ~US \$70 per 96-well plate. This cost depends on the experiment type and is likely to decrease in the future given advancements in the technology. This platform would also offer a much higher variety of experimental types due to the diverse set of instruments in the Workcell. The 96-well experiment suggests that high-throughput experiments could be virtually partitioned between many users. The challenges encountered due to early-phase technology also suggested opportunities for students to confront the real messiness of biological experiments in an educational context, at the same time point to the importance of stability and robustness of cloud labs, which is a particular challenge for biological systems.

In conclusion, commercial cloud labs are on the rise and afford interesting opportunities to run very complex life-science experiments in the cloud. The cost per student, in the range of US $30 (6 wells, 6 experiments), is not cheap, but in a reasonable range for lab classes. Given existing technologies (robotics, range of instruments, underlying scripting language), future opportunities should open up to pool the experiments of many more students (e.g., using 1536-well plates), enabling higher-dimensional experimentation (e.g., choosing from multiple antibiotics) as well as interactivity (allowing users to change experimental parameters such as antibiotic concentration throughout the run based on current experimental results). To achieve these goals, corresponding UIs must be developed that also account for educational requirements. From the company's perspective, enough students must use such a system to support the initial investment. Alternatively, the educational value of this platform could begin with graduate-level research, and as these platforms become less expensive and user friendly, their usage could expand even into K-12 education.

11.6 System 4: Augmented Batch (RNA Folding, Nucleotide Sequence)

A fourth set of biology cloud labs relates to citizen science games such as Foldit (Cooper et al. 2010) and EteRNA (Lee et al. 2014). Both games enabled tens of thousands of online players to participate in research by solving puzzles regarding protein and RNA folding, respectively. EteRNA is special in that it additionally provided experimental feedback for a smaller subset of (more expert) players. Foldit was primarily virtual but has also been used in projects where player suggestions were experimentally tested (Eiben et al. 2012). It should be noted that for these projects, the experimental work at the back-end was not fully automated. Instead, there was significant hands-on work by lab scientists—which does not matter much from the remote user's perspective.

11.6.1 Architecture

The EteRNA platform revolves around the scientific question of how a particular RNA folds into its secondary structure based on its primary RNA structure (its nucleotide sequence). Here, the online user is provided with a gamified graphical UI displaying an RNA strand with the four nucleotides marked by letter (CGAU) and color (Fig. 11.15). The user can change individual nucleotides and then instruct the computer to calculate the currently predicted folding structure due to the base

Fig. 11.15 EteRNA lets players explore the relationship between RNA sequence and secondary structure. (Image adapted from Lee et al. (2014))

pairing based on lowest energy considerations. Users are guided through a number of puzzles of increasing difficulty. After users have gained sufficient understanding of the platform and the RNA folding features by solving ~120 puzzles, they are allowed to participate in the lab.

Lab participation means that users are asked to come up with nucleotide sequence that will fold into a desired target shape and which will then be tested experimentally. For any given lab puzzle, each user makes her suggestion, and then based on certain criteria, the most promising designs are chosen to be tested experimentally. At the time of the first major deployment (Lee et al. 2014), the experimental throughput was only eight designs per week and carried out in significant part by manual labor; throughput has improved since then to ~10,000 designs per month through parallelized microfluidic chip technology (Bida and Das 2012; Seetin et al. 2014) but still operated in part manually. The particular RNA sequences are synthesized, and the nucleotide base pairings are assessed via single-nucleotide-resolution chemical reactivity measurements (SHAPE) (Lee et al. 2014). The experimental results (secondary structure and base pairing) are conveyed back to the user with single-nucleotide resolution through an in-game visualization that is similar to the original design interface (Fig. 11.15).

11.6.2 Citizen Science (and Educational) Deployment

During the first major deployment, >37,000 players experimented with this platform (Lee et al. 2014). During each weekly round, players submitted their proposals for designs to be tested, of which eight were chosen to be synthesized and tested experimentally. Over successive iterations, the designs suggested by the best players eventually consistently outperformed current RNA prediction algorithms, enabling the development of better prediction algorithms that took into account the new rules that players had identified. This development demonstrates the power of citizen science, in particular when coupled with experimental feedback.

So far, EteRNA has not been formally used nor assessed for formal education, to our knowledge. However, Nova Labs (http://www.pbs.org/wgbh/nova/) created a version of the simulation to support students learning about RNA in middle and high schools, and we are aware of many K-12 and college instructors who use EteRNA with their students.

11.6.3 Reflections and Next Steps

The costs for any experiment are due to labor and reagents, which for EteRNA were estimated to be ∼US $2.000 per month or ∼US $0.2 per design. The experimental design space of the platform is arguably very large since each position of the RNA strand of given length N can be any of four nucleotides (4^N, where N is already given for a given lab, but could modified). The virtual part of the platform has been deployed in various educational settings (unpublished results and personal communication by Prof. Das).

It is interesting to note that "designing an experiment" through a highly augmented user interface (including game elements) rather than operating or instructing a scientific instrument directly. These citizen science projects (EteRNA and Foldit) clearly demonstrate a very different avenue by which non-experts can be empowered to do experiments and participate in research. The success of these projects certainly motivates more fully automated and versatile cloud lab designs in the future.

11.7 Virtual Biology Cloud Labs and Interactive Simulations/Models

Although it is not the primary goal of this article to extensively address virtual biology labs, we would like to mention a few approaches (Fig. 11.16). (1) For the *Euglena* online lab discussed in Sect. 11.3, a modeling environment had been co-deployed (Hossain et al. 2016) that primarily allows students to perform parameter fitting. (2) Modeling environments like Scratch (Resnick et al. 2009) have been explored to enable students to program simple models of cellular behavior (Kim et al. 2016). (3) Other groups have developed gamified laboratories (such as Labster) that fully animate all lab components (Bonde et al. 2014). A number of other life-science simulations exist, for example, as part of the PhET project (Wieman et al. 2008). We note that both real and virtual labs have their distinct advantages and limitations, e.g., less cost at scale, and "running every experiment within seconds" in virtual labs versus the potential for novel discoveries or changes in student motivation in a real labs. Ideally, both approaches would be deployed synergistically (de Jong et al. 2013).

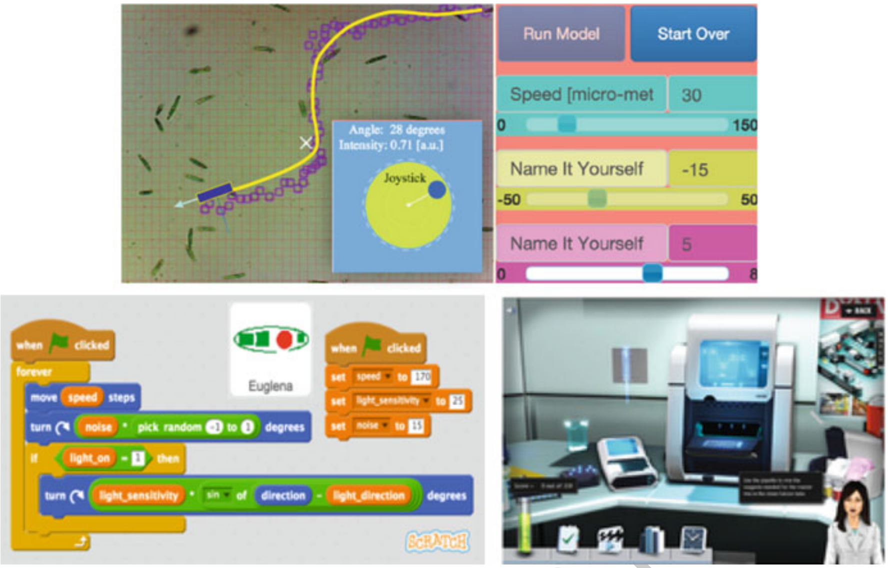

Fig. 11.16 Examples of virtual biology labs and simulations. Top: Middle-school students modeling *Euglena* phototaxis. Bottom left: Modeling *Euglena* behavior in Scratch. Bottom right: Gamified laboratory (Labster). (Images adapted from Bonde et al. (2014))

11.8 Lessons: Performance Metrics for "Interesting" Cloud Labs

Given that now a small but distinct and versatile number of biology cloud labs exist, we are in the fortunate situation to be able to compare these labs (Table 11.1) and to extract overarching themes and generalizable rules. A significant portion of these insights would also apply to cloud labs outside the life sciences.

The four cloud-lab architectures we presented are all rather different from a conceptual point of view. (1) The *Euglena* lab allows a single user to "own" an instrument for a short period of time. The experiment is real-time interactive, and biological responses are apparent within seconds. The low-cost and short experiment duration make this approach scalable. Parallelization is achieved by deploying multiple BPUs. (2) The *Physarum* lab shows how multiple experiments that belong to different users are executed in parallel on a single instrument. These experiments are interactive—the user makes changes while the experiment is running, but there is a delay of a few minutes. The individual user does not have direct control of this instrument. (3) The Transcriptic experiment is parallelized but not interactive during the run at all. Given that the Workcell moves samples between instruments automatically, it allows for essentially infinitely complex experiments (all other platforms described here are confined to a specific experiment type). (4) EteRNA is also parallelized, noninteractive, and provides feedback on the scale of weeks; the UI abstracts the process of experimental design into a game, although it eventually becomes scientific research for the dedicated user. Each of these platforms could be extended in the future. We expect that all four approaches will have their place in education in the future, depending on particular applications.

Table 11.1 provides a comparison of the four labs, many features of which could also be regarded as performance metrics. Which of these features are relevant depends on the given application, but considering all of them in the planning phase of developing a new biology cloud lab is recommended. For example, one can ask how much a single experiment costs, how many experiments can be run per unit of time, or how complex each experiment is, i.e., how many choices does it provide to the user and how large the corresponding response (or discovery) space is. The numbers in this table are largely estimate, and other criteria might be considered in the future—overall we hope that this overview illustrates how to think about this performance issue. A more detailed analysis will also be published in the future (Hossain et al. 2017).

In the following, we discuss these and other considerations in more detail:

1. *The size of the exploration space.* How many parameters can an experimenter change and how many distinct experiments can be run? For example, we found that the *Euglena* experiments allowed for changes in light intensity and direction on a 10-ms time scale. For simplicity, assuming a 1-min experiment with 0.1 s resolution, four LEDs with ten intensity settings would generate an astronomical amount of measurements $(10^4)^{600}$ distinct experimental sequences. In contrast, the Transcriptic experiments allowed users to choose among ∼10 antibiotic concentrations before the start of the experiment.
2. *The size of the discovery space.* Despite a large exploration space, many experimental designs can have equivalent outcomes. Hence, we need to ask how many experimental outcomes ("discoveries") are possible. For example, if *Euglena* essentially reorients to the light stimulus on a 10-s time scale, once the user has discovered that behavior, he is done. In reality, image data may capture a much richer range of responses to different light intensities, yielding a larger and more complex discovery space. For example, *Euglena* displays many subtle changes in behavior due to light stimuli; it even changes its shape due to strong light. In general, it will be challenging to quantify the discovery space completely, as exhaustive exploration is usually not practical. Choices should be made whether to provide the user with the information-rich, raw data (e.g., raw movies of *Euglena* behavior) versus processed and information-reduced data (e.g., a table with positional information for the cells).
3. *Combined exploration/discovery space.* Combining both the input and output possibilities for an experiment would quantify how "interesting" a platform is. For example, in the MOOC deployment (Hossain et al. 2017), online learners were asked to propose their own investigations. Approximately, 10 dependent and 10 independent variables were identified, implying ∼100 experimental investigations that could be executed, which for an educational setting is certainly very interesting. We also refer to the paradigm of low floor, high

ceiling, wide walls (Resnick and Silverman 2005), which describes how easy it is to engage in a particular platform, but also how diverse and complex an investigation can become. For example, in order to enable "authentic inquiry" in the classroom (Chinn and Malhotra 2002), this amount of freedom is desired.

4. *Biological variability as a challenge.* For all four architectures, biological variability requires significant consideration. On the one hand, keeping the user experience and experimental outcomes consistent (within defined bounds) is important, and not always easy. Significant layers of automonitoring, self-correction, and controls can be deployed, as, for example, in the *Euglena* lab (and which could still be improved). We therefore also recommend that each instrument provides the user with quality measures for their experiments (such controls are good practice for experimentation in general). Even when a system has been stable for months, biology may still hold surprises, such as mutations.
5. *Biological variability as an opportunity.* On the other hand, this variability provides interesting phenomena that are absent from more deterministic physics labs, potentially making the experiments more interesting and "lifelike." Variability and noise in biological systems are active areas of research (Elowitz et al. 2002). Students must be prepared to encounter variability, which can be exploited to great educational effect. In either case, this variability needs to be delivered within the proper educational context.
6. *The benefits of "living" labs.* Why not just simulate? Unlike pure simulations, live biological organisms are highly complex systems with emergent, unpredictable properties, providing educational opportunities for novel discoveries. Student feedback captured this aspect, for example, with "It was fun to play around with real organisms . . . " (Hossain et al. 2016). Implementations should also aim to harness this unpredictability and to convey it to the user. We note that simulations and experimentation should be used in synergy. Cloud labs should also utilize and feature the "realisms," e.g., information-rich image data (as in the *Physarum* lab) may be more enticing and interesting than a processed graph of single-point measurements (as in the bacterial growth lab). The entire instrumentation architecture should be conveyed so that the user can understand it and feel agency. Real labs also provide students to be confronted with experimental noise, anomalous data, and even failed experiments. Interacting with living matter can also provoke ethical discourse that does not arise from simulation alone, which again could be put to good use in an educational context (Cira et al. 2015; Harvey et al. 2014).
7. *Potential safety and ethical issues.* The safety aspect should be considered. Although remote experimentation can generally be considered much safer than hands-on experimentation, remote users could potentially cause harm, e.g., by hacking the system or generating dangerous biological material. Compared to other science disciplines, biological experiments are special given that particular biological organisms or types of experiment may fall under ethical

regulations, e.g., animal rights. Additionally, users and bystanders may voice their own concerns about what kinds of experiments with a given organism are in good taste. Ethical analysis of biotic games (Harvey et al. 2014) has provided some general guidelines and insights, even though the value of an "educational experiment" is likely considered of higher priority than "game play."

8. *Time for executing one experiment (and time of one user interaction).* A lower time limit exists for any given biological process based on how fast the experiment can be executed. For example, the effect of antibiotics on bacterial populations can only be detected after hours, while *Euglena* responses due to light are apparent within seconds. Note that these time limits can be pushed to some extent by using instruments with higher spatial or temporal resolution, e.g., the effect of antibiotics on bacterial cells can be observed within <1 h when imaging individual cells directly (Kong et al. 2012).
9. *Time required for experiment reset.* The biological and instrument downtime between experiments needs to be considered. In the case of the *Euglena* lab, after the light stimuli have been turned off, the *Euglena* go back to their prior state on the scale of 15–60 s. In the case of the *Physarum* lab, all biological material must be replenished for each new experimental run. One should also discriminate between the time it takes for the biological material to reset and some other downtime of the instrument, such as processing the last rounds of image data. Additional downtime results from instrument and biology maintenance.
10. *Experimental throughput.* Many of these issues ultimately point to how many experiments can be run in a given time. Experimental throughput can be increased by shortening the duration of a given experiment (including the necessary downtime between experiments), by parallelizing the number of experiments on a given instrument (BPU), by increasing the number of instruments in a cluster, and by replicating these BPU clusters at different sites.
11. *Number of experiments and time required for user familiarization with the platform.* When deploying the experiment, students generally should do five to ten experiments on a platform to allow for familiarization with the experiment, to explore, and to collect controlled data. Even if the platform allows many experiments in parallel, the student should have the opportunity for iterative, successive operations. Hence, it should be determined how many experiments are minimally required to promote a meaningful experience on the platform. If the experiments are expensive, then training experiences (as in EteRNA) could lower the load on the physical cloud lab.
12. *Logistics and automonitoring.* A major challenge compared to other online platforms (such as remote operation of physics experiments) is the maintenance required for biological material. Accordingly, choices must be made at the start of the project to account for these logistics and—if possible—to make use of specimens and hardware that minimize these challenges. The implementation of automation and automonitoring is crucial and has been significantly achieved with the *Euglena* cloud lab. Working with biological material and protocols that show consistent behavior is important. Back-up instruments should also be

considered. The increasing advances and cost reductions in biotechnological automation (including high-throughput machines) will enable increasingly more robust platforms, including commercial ones, in the future.

13. *Cost per experiment (and the business model).* The total cost of any individual experiment (or a set of experiments that would provide a coherent investigation) should be considered. These costs are driven by consumables, maintenance, and service, as well as by the initial development efforts. The numbers from Transcriptic may be the most reliable information currently available, as they have an underlying business model. These numbers can be in flux, and as technology improves and the concept becomes more common, costs will certainly go down. Generally, a benchmark for comparison is the cost of a similar experiment in a conventional, hands-on setting. As a relevant comparison, shipment of living organisms from a school supply company starts at ∼US \$20 for ∼20 students; consumables for more sophisticated biology experiments can easily go well above US \$100.
14. *Complexity and investment for initial setup, flexibility for future adaptions, and ease of replication by others.* Significant effort is required to initially set up a platform. In the simplest case, remote screen sharing is a very fast and easy way to enable remote biology experimentation and to prototype a platform. How easily this platform can be operated and modified for other experimental types is another important consideration. In that sense, the Workcell approach is inherently much more flexible. Open source code and building instructions could foster incentives for others to replicate and innovate. We also expect that general operation and data handling standards for cloud labs will emerge.

Conclusions on Specifications: The importance of each of these properties depends on the application. Providing a fast and simple biology experiment to millions of high-school students (e.g., to enable students to experience *Euglena* phototaxis) has a very different requirement than providing a community of hundreds of scientists with a platform to execute complex, versatile, and highly precise experiments (as a company like Transcriptic may seek to achieve).

11.9 Next Steps and Open Research Questions

The educational effectiveness of the presented platforms has been demonstrated to varying extents, but undoubtedly all platforms deserve more assessment through wider student and teacher participation as well as controlled studies. The individual studies for these cloud labs indicate learning gains, especially as self-reported by students, but more systematic pre- and posttests are warranted. The *Euglena* and *Physarum* cloud labs enabled students to perform biology experiments at a level of sophistication that is absent from presential and online education. Empowering students to perform inquiry-based practices in which they construct knowledge like professional scientists is a major achievement of these biology cloud labs.

We see several important avenues for future research and development on these biology cloud labs.

1. Refining and testing course content for specific learner groups on the existing platforms, such as middle- and high-school biology students, ultimately paving the way for usage by several thousands or millions of students
2. Including other relevant scientific practices, such as collaborative teamwork and model building
3. Having participants implement more complex projects all the way to geographically distributed team projects
4. Utilizing these platforms for deeper analysis using learning analytics to aid instructors and educational researchers
5. Extending these platforms to other experiment types (other stimuli, other organisms, and distinct types of microbiology experiments)
6. Updating BPU performance protocols, for example, to achieve automatic LED brightness adjustment for optimal negative phototaxis and feedback to users on "current instrument quality"
7. Exploring optimal UIs and scripting languages for online experiments and data handling
8. Open standards that enable easier setup and modifications of biological cloud labs
9. Ultimately bringing experts from different areas closer together, especially bioengineers, software engineers, researchers into human-computer interactions, and educators

11.10 Conclusions

We have presented four distinct user interaction modes and architectures for biology cloud labs and discussed the importance of biological variability, automonitoring, and domain-specific BPUs. These best practices could also be implemented for cloud labs in other engineering disciplines (Heradio et al. 2016) in which labs are currently mostly oriented toward single users and single devices. We primarily focused on educational use cases, but emerging high-end research cloud labs were included in our discussion. We conclude that the requirements and approaches for such goals are very different but will be complementary and synergistic in the long run.

Biological cloud (or remote) labs are particularly challenging, as the long-term robustness of the biological matter requires additional manual work or automation to provide a consistent experience. On the other hand, complex biological phenomena—especially when utilizing information-rich image data—constitute very rich discovery spaces. Enabling students to perform inquiry-based practices in which students construct knowledge like professional scientists is another major achievement of these biology cloud labs. Given that at least four biology cloud labs have been successfully tested with hundreds of students (tens of thousands for EteRNA), we are confident that biology cloud labs are feasible and useful.

Deploying biology cloud labs in education could help solve significant educational challenges and simultaneously provide economies of scale to help these technologies to mature. With the more than 15 million high-school students in the USA alone as well as the rise of MOOCs, education will be an important driver of the development of biology cloud labs. Curricula are usually offered repeatedly, allowing technologies to be developed iteratively and tested with many users. These cloud labs provide a cost-effective and practical means to implement inquiry-based learning and ultimately to accomplish the visions of NGSS (Bybee 2013) and the National Research Council (2012).

Critically, the data-logging capabilities of any cloud system constitute a unique opportunity to delve into how learners explore biological experiments that typically have a great deal of natural variability. Learning outcomes can be thoroughly investigated, e.g., in the context of bifocal modeling (Blikstein et al. 2012), when real experiments are juxtaposed with modeling. Several studies have indicated that combining reality (with variability and noise) and modeling (typically clean data) is more beneficial for learning content than either strategy in isolation (Heradio et al. 2016; Blikstein et al. 2012). Moreover, there are indications that students typically explore experiments in novel ways when data are shared with other students. These affordances could be further investigated in a quantifiable manner by implementing data-sharing capabilities in the application layer of our cloud lab.

Biological cloud labs open many interesting avenues for human-computer interactions but require carefully designed UIs. Some experimentation styles benefit from visual programming, while others may benefit from textual descriptions. Biotic games (Riedel-Kruse et al. 2011; Lee et al. 2015; Kim et al. 2016) are another interesting application of BPUs that may foster interest in biology in a playful manner through gamification. Excitingly, games could be implemented in the top UI layer of biology cloud labs. Phone-based internet-of-things instrumentation and diagnostics provide another paradigm for distributed instrumentation (Ozcan 2014).

In summary, we foresee that the iterative development and deployment of biology cloud labs in educational contexts will greatly benefit education and facilitate the development of individual BPU clusters (one experiment type at a time). Certainly, not all experiments can be carried out this way, but with cloud labs, a significant portion of standard biological experiments can likely be implemented much more cost-effectively and without complex logistics. Hence, an investigator (student or professional scientist) can concentrate on experimental design and data analysis, rather than on logistics and the hands-on skills required of a successful experimenter. We expect that there will be synergy between educational and scientific research performed in centralized facilities. We look forward to a future that fosters interdisciplinary participation and democratization of biology experimentation through cloud labs.

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References

Adamatzky, A. (2010). Routing Physarum with repellents. *The European Physical Journal E, Soft Matter, 31*(4), 403–410.

Alim, K., Amselem, G., Peaudecerf, F., Brenner, M. P., & Pringle, A. (2013). Random network peristalsis in Physarum polycephalum organizes fluid flows across an individual. *Proceedings of the National Academy of Sciences, 110*(30), 13306–13311.

Balagaddé, F. K., You, L., Hansen, C. L., Arnold, F. H., & Quake, S. R. (2005). Long-term monitoring of bacteria undergoing programmed population control in a microchemostat. *Science, 309*(57310), 137–140.

Barsanti, L., Evangelista, V., Passarelli, V., Frassanito, A. M., & Gualtieri, P. (2012). Fundamental questions and concepts about photoreception and the case of Euglena gracilis. *Integrative Biology, 4*(1), 22–36.

Bida, J. P., & Das, R. (2012). Squaring theory with practice in RNA design. *Current Opinion in Structural Biology, 22*(4), 457–466.

Blikstein, P., Fuhrmann, T., & Greene, D. (2012). Bifocal modeling: Mixing real and virtual labs for advanced science learning. In *Proceedings of the 11th International Conference on Interaction Design and Children,* Germany, June 12–15.

Bonde, M. T., Makransky, G., Wandall, J., Larsen, M. V., Morsing, M., Jarmer, H., & Sommer, M. O. A. (2014). Improving biotech education through gamified laboratory simulations. *Nature Biotechnology, 32*(7), 694–697.

Bybee, R. W. (2013). The next generation science standards and the life sciences. *Science & Children, 50*(6), 7–14.

Chinn, C. A., & Malhotra, B. A. (2002). Epistemologically authentic inquiry in schools: A theoretical framework for evaluating inquiry tasks. *Science Education, 86*(2), 175–218.

Cira, N. J., Chung, A. M., Denisin, A. K., Rensi, S., Sanchez, G. N., Quake, S. R., & Riedel-Kruse, I. H. (2015). A biotic game design project for integrated life science and engineering education. *PLoS Biology, 13*(3), e1002110–e1002118.

Cira, N., Ma, E., & Riedel-Kruse, I. H. (2017). Network dynamics of slime molds, *in preparation*.

Cooper, S., Khatib, F., Treuille, A., Barbero, J., Lee, J., Beenen, M., Leaver-Fay, A., Baker, D., Popović, Z., & Players, F. (2010). Predicting protein structures with a multiplayer online game. *Nature, 466*(7307), 756–760.

Danahy, E., Wang, E., Brockman, J., Carberry, A., Shapiro, B., & Rogers, C. B. (2014). LEGO-based robotics in higher education: 15 years of student creativity. *International Journal of Advanced Robotic Systems, 11*(27), 1–15.

de Jong, T., Linn, M. C., & Zacharia, Z. C. (2013). Physical and virtual laboratories in science and engineering education. *Science, 340*(6130), 305–308.

Eiben, C. B., Siegel, J. B., Bale, J. B., Cooper, S., Khatib, F., Shen, B. W., Players, F., Stoddard, B. L., Popović, Z., & Baker, D. (2012). Increased Diels-Alderase activity through backbone remodeling guided by Foldit players. *Nature Biotechnology, 30*(2), 190–192.

Elowitz, M. B., Levine, A. J., Siggia, E. D., & Swain, P. S. (2002). Stochastic gene expression in a single cell. *Science, 297*(5584), 1183–1186.

Etsion, Y., & Tsafrir, D. (2005). A short survey of commercial cluster batch schedulers. *The Hebrew University of Jerusalem, 13*, 44221.

Fox, A. (2011). Cloud computing – What's in it for me as a scientist? *Science, 331*(6016), 406–407.

Gerber, L. C., Kim, H., & Riedel-Kruse, I. H. (2016). Interactive biotechnology: Design rules for integrating biological matter into digital games. In *Proceedings of the First International Joint Conference of DiGRA and FDG*. Dundee, Scotland, UK.

Gerber, L. C., Calasanz-Kaiser, A., Hyman, L., Voitiuk, K., Patil, U., & Riedel-Kruse, I. H. (2017). Liquid-handling Lego robots and experiments for STEM education and research. *PLoS Biology, 15*(3), e2001413–e2001419.

Goldstein, R. E. (2015). Green algae as model organisms for biological fluid dynamics. *Annual Review of Fluid Mechanics, 47*(1), 343–375.

Harvey, H., Havard, M., Magnus, D., Cho, M. K., & Riedel-Kruse, I. H. (2014). Innocent fun or 'Microslavery'? *Hastings Center Report, 44*(6), 38–46.

Harward, V. J., del Alamo, J. A., Lerman, S. R., Bailey, P. H., Carpenter, J., DeLong, K., Felknor, C., Hardison, J., Harrison, B., Jabbour, I., Long, P. D., Mao, T., Naamani, L., Northridge, J., Schulz, M., Talavera, Varadharajan, C., Wang, S., Yehia, K., Zbib, R., & Zych, D. (2008). The iLab shared architecture: A web services infrastructure to build communities of internet accessible laboratories. *Proceedings of the IEEE, 96*(6), 931–950.

Hayden, E. C. (2004). The automated lab. *Nature, 516*(7529), 131–132.

Heradio, R., de la Torre, L., Galan, D., Cabrerizo, F. J., Herrera-Viedma, E., & Dormido, S. (2016). Virtual and remote labs in education: A bibliometric analysis. *Computers & Education, 98*(C), 14–38.

Hossain, Z., & Riedel-Kruse, I. H. (2017). Concept and characterization of biotic processing units (BPUs), *in preparation*.

Hossain, Z., Blikstein, P., Riedel-Kruse, I. H., Jin, X., Bumbacher, E., Chung, A. M., Koo, S., Shapiro, J. D., Truong, C. Y., Choi, S., & Orloff, N. D. (2015). Interactive cloud experimentation for biology. In *Presented at the the 33rd Annual ACM Conference* (pp. 3681–3690). New York

Hossain, Z., Bumbacher, E., Chung, A. M., Kim, H., Litton, C., Pradhan, S., Walter, A., Jona, K., Blikstein, P., & Riedel-Kruse, I. H. (2016). A real-time interactive, scalable biology cloud experimentation platform. *Nature Biotechnology, 34*(12), 1293–1298.

Hossain, Z., Bumbacher, E., Blikstein, P., & Riedel-Kruse, I. H. (2017). Authentic science inquiry learning at scale enabled by an interactive biology cloud experimentation lab. In *Proceedings of the first ACM conference on learning scale conference*. ACM.

Kim, H., Gerber, L. C., Chiu, D., Lee, S. A., Cira, N. J., Xia, S. Y., & Riedel-Kruse, I. H. (2016). LudusScope: Accessible interactive smartphone microscopy for life-science education. *PLoS One, 11*(10), e0162602–e0162616.

Klavins, E. (2017). The aquarium project. Retrieved from http://klavinslab.org/aquarium.html

Kong, F., Yuan, L., Zheng, Y. F., & Chen, W. (2012). Automatic liquid handling for life science: A critical review of the current state of the art. *Journal Laboratory Automation, 17*(3), 169–185.

Lam, A. T., Samuel-Gama, K. G., Griffin, J., Loeun, M., Gerber, L. C., Hossain, Z., Cira, N. J., Lee, S. A., & Riedel-Kruse, I. H. (2017). Device and programming abstractions for spatiotemporal control of active micro-particle swarms. *Lab on a Chip, 15*(10), 351.

Lee, J., Kladwang, W., Lee, M., Cantu, D., Azizyan, M., Kim, H., Limpaecher, A., Yoon, S., Treuille, A., Das, R., & EteRNA Participants. (2014). RNA design rules from a massive open laboratory. *Proceedings of the National Academy of Sciences, 111*(6), 2122–2127.

Lee, S. A., Bumbacher, E., Chung, A. Cira, N. J., Walker, B., Park, J. Y., Starr, B., Blikstein, P., & Riedel-Kruse, I. H. (2015). Trap it!. Presented at the *33rd Annual ACM Conference* (pp. 2593–2602). New York.

Melin, J., & Quake, S. R. (2007). Microfluidic large-scale integration: The evolution of design rules for biological automation. *Annual Review of Biophysics and Biomolecular Structure, 36*, 213–231.

National Academies Press. (2012). *Committee on a Conceptual Framework for New K-12 Science Education Standards, Board on Science Education, National Research Council, A Framework for K-12 Science Education: Practices, crosscutting concepts, and core ideas*. Washington, DC: National Academies Press.

Ozasa, K., Lee, J., Song, S., & Maeda, M. (2014). Transient freezing behavior in photophobic responses of Euglena gracilis investigated in a microfluidic device. *Plant and Cell Physiology, 55*(10), 1704–1712.

Ozcan, A. (2014). Mobile phones democratize and cultivate next-generation imaging, diagnostics and measurement tools. *Lab on a Chip, 14*(17), 3187–3188.

Pedaste, M., Mäeots, M., Siiman, L. A., de Jong, T., van Riesen, S. A. N., Kamp, E. T., Manoli, C. C., Zacharia, Z. C., & Tsourlidaki, E. (2015). Phases of inquiry-based learning: Definitions and the inquiry cycle. *Educational Research Review, 14*(C), 47–61.

Purcell, E. (1997). Life at low Reynolds number. *American Journal of Physics, 45*(3), 11.

Resnick, M., & Silverman, B. (2005). Some reflections on designing construction kits for kids. In *Wearable computers, the IEEE international symposium on* (pp. 1–6), March.

Resnick, M., Silverman, B., Kafai, Y., Maloney, J., Monroy-Hernández, A., Rusk, N., Eastmond, E., Brennan, K., Millner, A., Rosenbaum, E., & Silver, J. (2009). Scratch: Programming for all. *Communications of the ACM, 52*(11), 60.

Riedel-Kruse, I. H. (2017). Incorporating a commercial biology cloud lab into online education. In *Proceedings of the International Conference on Remote Engineering and Virtual Instrumentation*. New York.

Riedel-Kruse, I. H., Chung, A. M., Dura, B., Hamilton, A. L., & Lee, B. C. (2011). Design, engineering and utility of biotic games. *Lab on a Chip, 11*(1), 4–22.

Romensky, M., Scholz, D., & Lobaskin, V. (2015). Hysteretic dynamics of active particles in a periodic orienting field. *Journal of the Royal Society Interface, 12*(108), 20150015–20150015.

Romero, C., & Ventura, S. (2010). Educational data mining: A review of the state of the art. *IEEE Transactions Systems, Man, and Cybernetics Part C, 40*(6), 601–618.

Sauter, M., Uttal, D. H., Rapp, D. N., Downing, M., & Jona, K. (2013). Getting real: The authenticity of remote labs and simulations for science learning. *Distance Education, 34*(1), 37–47.

Seetin, M. G., Kladwang, W., Bida, J. P., & Das, R. (2014). Massively parallel RNA chemical mapping with a reduced bias MAP-seq protocol. *Methods in Molecular Biology, 1086*(6), 95–117.

Sia, S. K., & Owens, M. P. (2015). Share and share alike. *Nature Biotechnology, 33*(12), 1224–1228.

Skilton, R. A., Bourne, R. A., Amara, Z., Horvath, R., Jin, J., Scully, M. J., Streng, E., Tang, S. L. Y., Summers, P. A., Wang, J., Pérez, E., Asfaw, N., Aydos, G. L. P., Dupont, J., Comak, G., George, M. W., & Poliakoff, M. (2015). Remote-controlled experiments with cloud chemistry. *Nature Chemistry, 7*(1), 1–5.

States, N. L. (2013). *Next generation science standards: For states, by states*. Washington, DC: The National Academies Press.

Tero, A., Takagi, S., Saigusa, T., Ito, K., Bebber, D. P., Fricker, M. D., Yumiki, K., Kobayashi, R., & Nakagaki, T. (2010). Rules for biologically inspired adaptive network design. *Science, 327*(5964), 439–442.

Transcriptics. (2015). *Discovery biology on demand*. Retrieved from https://www.transcriptic.com

Wellington, J. (2007). America's lab report: Investigations in high school science. *Science Education, 91*(3), 514–515.

Whitesides, G. M. (2006). The origins and the future of microfluidics. *Nature, 442*(7101), 368–373.

Wieman, C. E., Adams, W. K., & Perkins, K. K. (2008). PHYSICS: PhET: Simulations that enhance learning. *Science, 322*(5902), 682–683.

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