BioGraphr: Science Games on a Biotic Computer

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ABSTRACT
The advancement of biotechnology enables novel types of interaction devices, alternative computers, and games. Design principles for effective human interactions on these technologies is still largely unexplored. Here we present the BioGraphr, an interactive tabletop gaming system that enables playful experience and interaction with millions of microorganisms at the millimeter scale: Light patterns (images) are projected into a mini-aquarium containing phototactic (i.e. respond to light) Euglena cells, which then arrange into complex dynamic bioconvection patterns within seconds. We characterized the bio-computational properties of the BioGraphr, designed biotic games, and explored novel interactive scientific and artistic activities. Responses by test players indicate fun and meaningful gameplay and emphasize how learning about microscopic biology can be naturally coupled to a "bio-computational" substrate. We derived general human-computer interaction design lessons for games on biological machines. The BioGraphr is accessible for DIY, museums as well as formal science education as its low-cost version is easy to reproduce, and Euglena cell cultures are long term stable.

Keywords
User Interfaces, Human-Biology Interaction (HBI), Interactive Biotechnology, Tangible Microscopy, Biotic Game, Biotic Processing Unit, Alternative Computation, Education.

INTRODUCTION, MOTIVATION, AND GOALS
We are currently witnessing a biotechnology revolution that is enabling novel human-interaction devices and alternative computing architectures that are inspired by or directly utilize biological processes (Whitesides 2006; Trietsch 2011; Pepperkok 2006; Kong 2012). Several such "human-biology interaction" (HBI) (Lee 2015) devices have been developed and successfully tested: Examples include cloud-based biology labs (Hossain 2015), biotic games (Riedel-Kruse 2011), museum exhibits (Lee, 2015), and citizen science (Lee 2014), all of which merge biology, computers, and users on various levels. All of these systems incorporate playful approaches, as games are regarded to have high educational potential, and serve as good test cases for human-computer interaction (HCI) research in general (Block 2012; Bilda 2011; Brody 2009; Horn 2009; Yannier 2015). The challenges with systems that include living biological material are overall robustness, longevity and responsiveness of the biological substrate, and accessibility including costs. The previous work primarily focused at the level of individual cells (Cira 2015; Riedel-Kruse 2011; Lee 2015), here we investigate how these challenges can be addressed and the opportunities that exist at the centimeter-scale level involving large numbers of cells.

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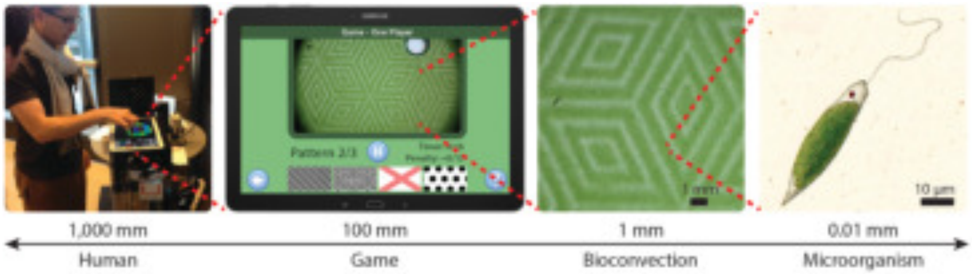

Figure 1: The BioGraphr uses millions of living organisms (Euglena) in its core. These cells form collective patterns when stimulated with light, and enables games, scientific observations, and artistic expression. Video: https://youtu.be/bYDcjVkCVSc

To build a robust and accessible biotic gaming system, we designed the BioGraphr, a biotic computer that utilizes the collective behavior of over one million *Euglena gracilis* (Euglena) cells (Fig. 1): The phototactic behavior of these microorganisms (Hill 2000; Machemer-Röhnisch 1999) generates striking patterns when illuminated with homogenous or structured images of light. These patterns are a form of bioconvection, i.e., the "motion of large numbers of small organisms in a fluid" (Shoji 2014). Bioconvection inside the BioGraphr constitutes a non-trivial computational transformation that bears analogies to edge detection and photographic processing (Fig. 1). In contrast to conventional electronic computers, here the information processing is carried out by millions of living cells that actively move in 3D space in response to external stimuli; these cells also interact with each other via shading and hydrodynamic effects at the local and global scales (Shoji 2014). We turned this biophysical process into a practical and robust human-interaction device via a touch-screen tablet with an integrated camera and an external projector to image and stimulate the cells housed in a mini-aquarium. Hence, a closed feedback loop is established between the human user and the microorganisms that reaches across multiple length scales (Fig. 1).

In terms of interaction design, that major challenge with this HBI system is the novel and largely unexplored quality of the interaction (Gerber 2016), as an additional layer of conceptual complexity is introduced. Figure 2 shows an expanded Mechanics, Dynamics, and Aesthetics model (Hunicke 2004) that includes a biological layer (on both the designer and player sides) in addition to the digital layer. Both layers can be designed, but given the current state of the technology, this is more easily achieved at the digital level than at the biological level. The opportunity and challenge for the game designer is to develop a combined set of digital and biological game rules that lead to a "natural lens" for the player to experience the biological content.

We designed and tested games to exam the affordances of the BioGraphr and to elucidate general principles for HBI design; furthermore we sought to foster informal science education and to explore applications for scientific inquiry and artistic expression (Ramey-Gassert 1994; Alberts 2010; Podolefsky 2012). Games motivate players to explore and learn the "laws" of the game world (Johnson 2015). We therefore reasoned that games on the BioGraphr lead to direct benefits for biology education, such as via direct knowledge acquisition or via preparation for future learning (Bransford 1999; Preist 2015). This rationale is consistent with results from augmented reality systems (de Souza 2006; Billinghurst 2015) that expand the educational potential of digital technologies (Banister 2010; Lenhart 2008) with benefits like increased motivation and engagement (Pivec 2007; Prensky 2005).

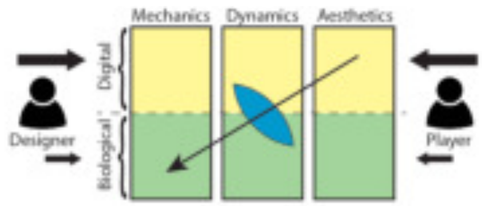

Figure 2: Extended *Mechanics, Dynamics, Aesthetics model* for human-biology interaction A successful game design focuses (blue lens) the player's experience on aspects of the underlying "biological mechanics."

The BioGraphr can be seen as a tabletop system given its form factor and interaction quality. It has come a long way from first-generation HCI-enabling technologies such as the balopticon (an early optical projection system) that were successfully used in training programs of the Army and Navy by projecting pictures in the classroom in the 19^{th} century (Watson 1879). In second-generation HCI-enabling technology, the interaction took place on tablets and mobile phones (Casey 2008; Lee 2004). We view the BioGraphr as a third-generation tabletop technology based on interactive, horizontal tabletops; we added HBI to the tradition of sensing and display technologies (Kunz 2010). While applications such as SandCanvas (Kazi 2011) and BricoSketch (Tsandilas 2015) focus on artistic and process-improvement tools, BioGraphr can be situated in the educational, artistic, and computational domains.

This paper is structured along five goals: (1) to design a robust and practical device (the BioGraphr) that enables human interaction with the emergent bioconvection patterns of millions of cells; (2) to characterize this biotic computation, revealing constraints and opportunities for interactive application; (3) to design meaningful games and other applications for the BioGraphr; (4) to assess user responses to the system and its applications, in particular regarding whether the games are perceived as fun and provide meaningful play; and (5) to test for educational opportunities, e.g., whether players can infer novel biological knowledge through play. We conclude with lessons learned and future perspectives including wider dissemination pathways.

1) DESIGN OF THE BIOGRAPHR

Bioware: Underlying biological principles. We developed the BioGraphr, which uses the single-celled photosynthetic organism *Euglena gracilis* (Carolina, #5867092) in its core. Euglena is a microorganism that is commonly found in freshwater ponds (Fig. 3). Euglena has been used widely in educational settings due to its robustness, safety (Littleford 1960), and relatively large size (~50 µm in length), which allow students to study them with conventional light microscopy. They are phototactic, meaning that they orient themselves and swim in response to light. Phototaxis is achieved by a photosensitive organelle (the eyespot) coupled to a motile flagellum at its anterior pole (Fig. 3a), which propels them forward. In nature, these cells need to experience optimal light conditions in which there is sufficient light for photosynthesis but not so much to overheat the cells or to cause ultraviolet damage. Hence, positive and negative phototaxis at distinct light levels ensures that cells remain 2~4 cm below the surface of natural habitats such as ponds. Here, we used relatively strong light to induce the cells to swim away from the light source. This photophobic response can be observed within seconds, therefore allowing real-time interactions with human users (Lee 2015). At larger-scale, this photo response leads to bioconvection patterns (Fig. 3b,c, right) given sufficiently high cell densities: If a strong light source is placed below the organisms, all cells swim upward and agglomerate at the surface, where they form patches of very high density as

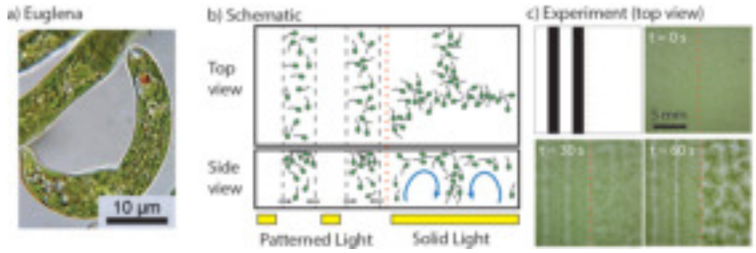

Figure 3: The BioGraphr utilizes the collective patterns that emerge from millions of phototactic microorganisms in response to light. a) Single-celled Euglena. b) Schematic of emerging spatiotemporal Euglena patterns. Light projected from below stimulates cells to swim to darker regions. Fluid with a high density of cells may sink, leading to circulating bioconvection patterns. c) Euglena pattern formation.

they shade each other (Shoji 2014). As the cells are slightly denser than the surrounding water, the fluid as a whole becomes denser at the top. Eventually the top fluid becomes unstable and sinks down at a higher speed than the Euglena can swim upward, at the same time the less-dense fluid containing fewer Euglena is dragged upward. The resulting vertical convection rolls look phenomenological similar to thermal convection rolls (Batchelor 2000), but in this case the energy is generated by the cells. These macroscopic patterns become visible within seconds after the strong light is turned on due to the swimming speed of Euglena (~0.1 mm/s (Machemer-Röhnisch 1999)) and the depth (3 mm) of the micro-aquarium. The overall light intensity in the BioGraphr is not harmful to the organisms; cells in the mini-aquarium remained responsive for weeks without significant accumulation of dead cells or decline in system response.

Hardware and software. The main components are an LCD DLP projector (IncrediSonic Pico Mini) that projects light onto the micro-aquarium containing Euglena (Fig. 4a) and an unmodified Samsung tablet (Galaxy Tab Pro 12.2, Android 4.4) for image acquisition (back camera) and user interaction. The aquarium (Fig. 4a) was prepared from two acrylic disks and one acrylic ring with diameters and heights of 3 cm and 3 mm, respectively. A suspension of Euglena (Fig.4b) containing approximately one million cells was injected through a small hole that was drilled into the side of the ring. No sealing was applied. This aquarium remained functional (and the Euglena remained alive) for ~4 weeks when maintained at a natural day/night cycle. For homogeneous specimen illumination, the projector was placed directly under the Euglena (Fig. 4c,d) and a physical servo-shutter was used to controls whether light from the projector reached the Euglena. This shutter is controlled by an application on the tablet that communicates with an Arduino UNO via Bluetooth. The tablet wirelessly sends the patterns over Google Chromecast to the projector. The projected light patterns have a resolution of <100 µm at the site where the Euglena are housed. Conceptually, this linear forward loop (projector, biological material, camera) represents a Biotic Processing Unit (BPU) (Riedel-Kruse 2011; Hossain 2015). Hence, a closed feedback loop between human user and biological material is established in which the user stimulates the cells with light and observes them at the same time. A basic but functional version was made from Lego pieces to demonstrate easy replication and dissemination (Fig. 11b.c).

In operation, the projector shines a light pattern onto the mini-aquarium. Just before the application takes a picture (typically every 4 s), a signal to close the servo-shutter (to block the light pattern) is sent to the Arduino controller. After the image is taken, the shutter opens again and allows the light pattern to reach the aquarium. We used the

Figure 4: The BioGraphr consists of a projector, a tablet with an integrated camera, and a micro-aquarium with Euglena cells. a) The micro-aquarium contains about one million Euglena cells. b) Placing the mini-aquarium under a microscope reveals individual Euglena as well as bioconvection patterns. c,d) Setup of the BioGraphr. e) Slider to insert Euglena and observation port. f) View through the objective.

physical shutter (instead of just setting the pattern to black) as its use led to better images with a more homogeneous background and minimal glare. In live mode the users see the camera feed without any pictures being stored; the shutter may be opened or closed at any time manually to project the patterns or observe the Euglena with no distortion from the projector lamp. The graphical user interface and the hardware control for imaging and projection are written in Android Studio. For easy manipulation the micro- aquarium sits on a slider (Fig. 4e,f).

We also included several design features that allow users to better understand the inner workings of the setup and to nurture a curiosity about biology. To observe the organisms by eye and with the external microscope, the micro-aquarium can be taken out of the BioGraphr (Fig. 4a). This is important as before a new game, the cells must be "reset" (gently shaken to redistribute the cells and to erase the previous pattern). Being able to remove the micro-aquarium also empowers the user to experience the biological matter more physically. The user may observe the aquarium outside the BioGraphr or live in the system through the eyepiece and beam-splitter (Fig. 4e). Additional features such as transparent casing and integrated observation port allow live observation of the BPU.

2) PERFORMANCE OF THE BIOGRAPHR

We characterized the bioconvection behaviors in the BioGraphr as a form of dynamic computation. An input light pattern is transformed into an output Euglena pattern over time (Figs. 3c, 5). This transformation is non-trivial in the sense that it is not simply an identity transformation and this computation can be loosely compared to the neuronal processing of images in the human visual pathway (Posner 1989), where images projected onto the retina are transformed into complex spike patterns in distinct neuronal layers. Characterizing this computation is important for understanding the affordances and limitations of any human interaction (game play) and is intriguing intellectually.

To characterize the response to spatial light stimuli, we projected stripe patterns with different widths. Small stripes (0.5 mm) led to clear domains in which Euglena agglomerated in dark areas and the stimulus pattern was imprinted on the Euglena population (Fig. 5a). For large stripes (3 mm), agglomeration initially occurred in dark areas as well as at the edges of the micro-aquarium (Fig. 5b,c); the Euglena density inside the dark areas (the center of the stripes) decreased over time (* in Fig. 5b,c). Smearing occurred in bright areas due to circulating bioconvection. Hence, the Euglena response initially reflected the edges and centers of the input light stripes, then transitioned into a pure edge detector, and eventually was replaced by vertically circulating bioconvection.

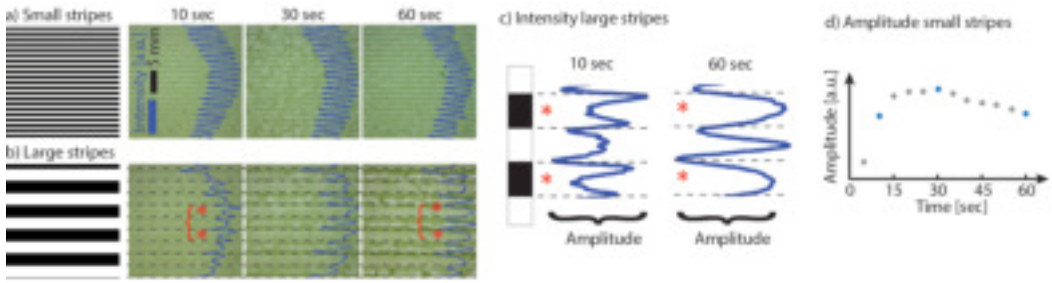

Figure 5: Euglena bioconvection response to light represents a non-trivial computational process. a) Small stripes (0.5 mm) projected onto an initially homogenous Euglena solution prompt the formation of a "photograph" over time. Regions of bright light lead to low Euglena density, and vice versa. Blue lines: Euglena density averaged vertically over the image. b) Large stripes (3 mm) form patterns that function like an edge detector. Secondary peaks initially develop inside bright regions (*). c) Enlarged signal from large stripes. d) Amplitude evolution of the pattern in (a), showing fast the emergence of the pattern and its later decay.

To characterize the dynamic behavior of this system, homogenous white light was projected. Circulating bioconvection patterns began to form after 5-10 s (Fig. 3c, right). These patterns fluctuated over time and remained alike for at least 10 min. After the light was switched off or the shutter was closed, the patterns disappeared within 30-40 s (data not shown.) Figure 5a,d shows the temporal evolution with the patterning amplitudes increasing fast initially, and then becoming smaller again.

While a full white (100% intensity, ~12,000 lux) projection pattern induced strong vertically circulating bioconvection patterns after only 30 s, it required 40 s at 80% brightness. At 60% brightness, only weak circulating bioconvection patterns formed after >3 min. Lower intensities did not result in any circulating bioconvection patterns (data not shown.) Similar effects were observed for different colors (Fig. 6a): pure white stripes (on black background) resulted in the fastest appearance of circulating bioconvection (~10 s), while green and red stripes (on black backgrounds) required more time (40 s, and 60 s, respectively). Colors and intensities can therefore be used to fine-tune the temporal patterning aspects of the BioGraphr.

Finally, we assessed the effect of projecting multiple patterns serially as well as the effect of switching frequency on bioconvection pattern formation. We alternately projected a large stripe pattern (3 mm) and its exact inverted pattern at various frequencies. For switching at 10 Hz, no matching stripes were formed by the Euglena, but vivid circulating bioconvection patterns emerged after 30 s, as observed for pure white light. At 2 Hz, Euglena underwent simple bioconvection and agglomerated in thin stripes (1 mm) at the borders of the projected stripes. Similar observations were made 0.2 Hz, while for switching times >2 min, the Euglena had enough time to move and agglomerate in the dark areas, thus matching the projected patterns in Figure 5b and exhibiting some circulating bioconvection. Alternating between distinct patterns led to direct superposition or more complex patterns, depending on the switching rate (Fig. 6c). When the last pattern was projected for longer times, it dominated the Euglena behavior, with interference from circulating bioconvection.

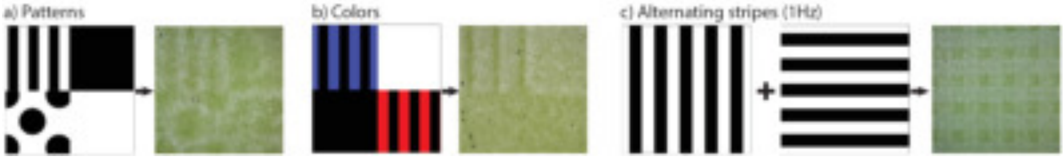

Figure 6: Euglena responses after 30 s of light stimulus. a) 4-in-1 patterns demonstrate responses due to light intensity and spatial structures. Complex patterns and fine tiling can be "photographed." b) 4-in-1 patterns demonstrate patterning responses to color. c) Superposition of two patterns projected alternately at 1 Hz, leading to near-linear superposition.

Comparing multiple instances of pattern formation on different days revealed some quantitative variations in the biological response, but the overall qualitative behavior of Euglena in the BioGraphr is very robust, certainly sufficient for the present gaming and educational applications. Such "noisy features" are normal for analog and alternative computing paradigms (Nagpal 2004) and can highlight the biology to the user.

In conclusion, this biotic computer transforms light patterns into emergent Euglena patterns in a reproducible manner, as one would expect from a computational device. The resulting Euglena patterns are path-dependent and usually are not simple linear superimpositions; this history dependency also implies that patterns are not commutative in general. We determined optimal space and time regimes for meaningful HBI: patterns in the millimeter range are replicated by the microorganisms within seconds to minutes, circulating bioconvection patterns are formed in large bright areas, and the order of projected patterns affects the output (Figs. 5, 6). With these bio-computational characteristics in hand, we carried out rational game design. Awareness of these characteristics also underpinned the development of play strategies (see user tests below).

3) INTERACTIVE HUMAN-BIOLOGY APPLICATIONS

Activity overview menu. We developed multiple interactive human-biology experiences (Figs. 7-9) for the BioGraphr. On the starting menu the user sees a live view of the Euglena, which are magnified through the camera by ~4x; individual Euglena cells are not resolved on the screen. Users choose from the main menu games, science experiments, and exploratory activities (Fig. 7a-d). The game category has a submenu (not shown) allowing selection of one- or two-player games, each with multiple levels of difficulty.

Scientific explorations and artistic expression. The Exploration tab shows a live view of the Euglena pattern (Fig. 7d) and is intended for free exploration of the biological responses to patterns and colors. The user selects pre-made patterns or colors to draw free-hand expressive patterns on top of the displayed Euglena. To enhance the view of the Euglena, the drawn images can be toggled on/off the image, while always being projected onto the Euglena. This open interface allows the user to obtain familiarity with the spatial and temporal responses of the cells to the light stimuli in real time, rather than still images (Fig. 7). In order to highlight the general biological response to patterns and colors, we integrated a simple and directed Science tab (Fig. 7c). Two experiments (Fig. 6a,b) with four predefined patterns within a single image enable side-by-side comparisons of the effect of projecting different colors or different patterns.

One-player and two-player games. We explored various game ideas on this platform and eventually determined that a pattern-guessing game lends itself to single and multiplayer games that optimally utilize the features of the biotic computer. These types

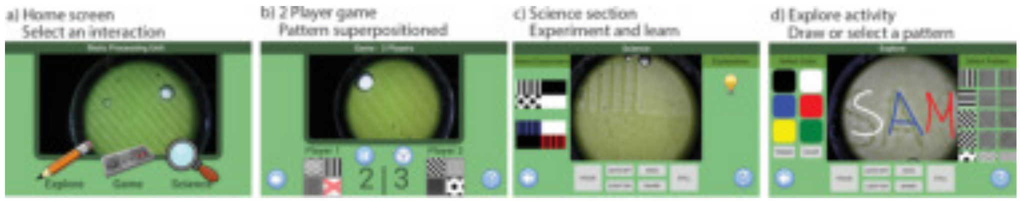

Figure 7: Screenshots of user interface: a) Home screen. b) Two-player game. c) Science tab. d) Explore tab: Colorful patterns drawn by hand over the live view are projected onto the Euglena. Here, the cells respond to white and blue light but not to red light. Note that the drawing was intentionally misaligned and scaled to illustrate the underlying pattern formation.

of games also make it easy to create game levels of differing difficulty without the need for complex automated image analysis.

We sought to develop a one-player game that would last ~1 min and could be easily adjusted in difficulty (Figs. 1, 8). The computer randomly selects one pattern that is projected onto the Euglena, and the player is presented with a choice of four possible patterns. The player now needs to guess from this selection the pattern that is projected. Selecting the correct pattern advances the player to the next round, where a new pattern is randomly selected and projected; selecting the wrong pattern results in a time penalty of 10 s and the player must keep guessing. The game ends after three rounds. The game score is based on total time, including a time penalty for wrong guesses. To achieve high scores, a strategy combining speed, risk, and experience is required.

In the two-player game (Figs. 7b, 9), each player is presented with four random patterns to from which to choose. Both players may see all eight patterns. Each player secretly selects one of his four patterns (by blocking the opponent's view). The players press start, which swaps the four displayed patterns; each player now chooses from one of the four choices initially presented to their opponent. Both patterns are projected simultaneously and the resulting bioconvection pattern is a complex superposition due to the effects of two patterns. Every 4 seconds, the shutter is closed to acquire an image that is shown to the players. The players now guess which pattern the opponent picked and select the matching pattern. If the guess is correct, the player earns 1 point and the round ends. If the guess is incorrect, the player loses 1 point, the incorrectly guessed pattern is crossed out, and the round continues until one player guesses correctly. Multiple rounds are played until one player reaches 5 points to win the match. This game also has a psychological element: "You think that I will choose this pattern because it is hard, therefore I will do something else". Compared to the one-player game, the players actively select here the projected patterns and thereby directly affect Euglena behavior.

4) USER INTERACTION TESTS

User study goals, design, and logistics

The goals of the following user interactions were to: (1) understand the general affordances of the BioGraphr and how users respond to it; (2) determine whether the activities, especially the games, are perceived as "fun" and interesting, and whether meaningful game play emerges; (3) establish whether the games have a learning curve; (4) identify how game difficulty can be adjusted; and (5) determine whether game play leads to inferences and learning about the underlying biology. We sought to identify general design principles for HBI in general from these interactions.

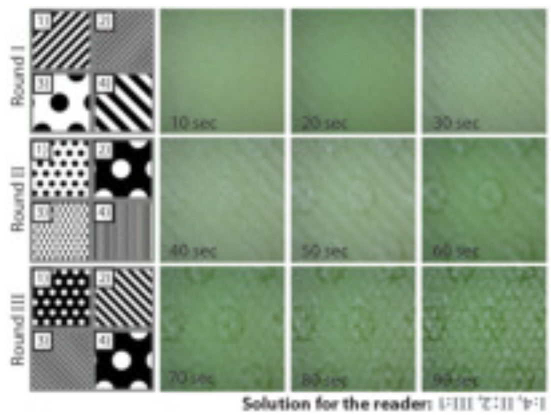

Figure 8: In this one-player game, the player observes Euglena patterns as they change over time. The user must guess which of four randomly generated image patterns (left panels 1-4) is projected. A game consists of three consecutive rounds. As the Euglena are not reset between rounds, the patterns blend. The reader is prompted to guess the correct answers.

First, through multiple informal pre-studies with 11 lab members, we collected feedback during the iterative design process. Second, we set up the BioGraphr at various sites on a university campus for multiple days for general testing and allowing the participants to interact in an open fashion. 43 university students, postdocs, and staff participated, whereof 26 provided formal feedback and 17 were timed in at least one activity. Third, we ran a single elimination tournament within the lab in 2-player game mode with 8 participants from our lab. Forth, we tested if our setup was able to convey biological knowledge (15 participants again from the university). Finally, we set up the BioGraphr in a local science museum, drawing a diverse population of participants that included over 15 individuals or groups ages ranging from ~5 to ~50. Participants were introduced to the system, assessed with pre- and post-quizzes about Euglena, phototaxis, and bioconvection, and asked whether they had previously played a biotic game. We also requested verbal feedback and took notes on participants' comments. Typically, one researcher mediated the setup, and the other conducted interviews and took notes. Playing a single game required ~1 min. The typical overall interaction time with the setup was 1-5 min, some participants who used the "Explore tab" (Fig. 7) stayed >10 min.

i) Public responses and overall acceptance

Based on our observations and feedback received, all participants were comfortable using a tablet as a gaming device even as the BioGraphr's appearance (Figs. 4,7), including the Euglena, projector, and the noisy shutter were novel to them. Typically, we facilitated the first game round and reset the micro-aquarium. After that, participants played and reset the cells independently and no participant expressed difficulty in switching between tabs and applications (Fig. 7). Most participants had not heard about Euglena or bioconvection before and many expressed fascination after being provided with the biological explanations. The view through the microscope eyepiece helped to increase the participants' understanding of how tiny the cells are and how fast they swim. Participants understood that these were live organisms and seemed to understand what phototaxis is.

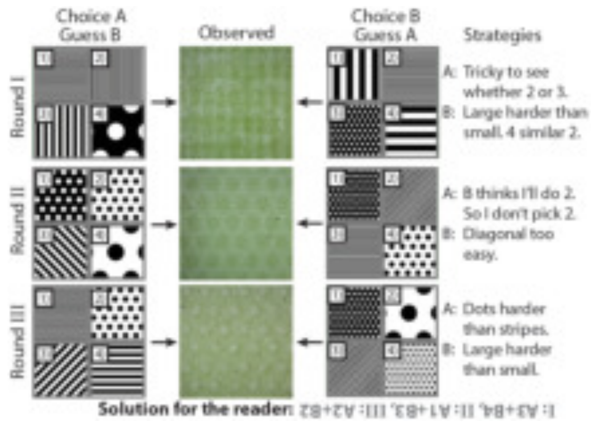

Figure 9: In the two-player game each player secretly chooses a pattern (out of 4 options) that will be projected. Both selections are superimposed and lead to complex Euglena patterns. The player who first guesses the opponents pattern correctly scores one point; wrong guesses are penalized. More subtle "psychological" strategies start to emerge among players. Note: Euglena are "reset" between rounds, hence only patterns from the same round blend into each other. The reader is again invited to guess the correct answer for both players.

Several common themes emerged from the comments and interviews (Table 1). None of the participants had seen something similar or played biotic games before. Many participants expressed positive surprise, fascination about gaming and learning with live microorganisms and felt that the system was novel. The participants immersed quickly in the games and it appeared that they reflected on the underlying biological basis only in between and after the interaction. We conclude that the BioGraphr and its apps captured participants' attention and are easy and convenient to use.

Concept and Technology: BPU, projector, optics, Euglena.	**Scientific Observations:** Biology, dynamics of responses, effect of patterns and light.	**HCI:** Wish for implementation.	**Games:** Response time, interactions between players, strategies, bystander's comments.	**Expansion:** Interest in BPU. Replicate system.
"What does the Arduino do?" "Are there any lenses?"	*"It forms stripes!" "I can see them!" "They move so fast!" "Red same as blue?"*	*"You can control them." "What else could you do?" "Can it solve problems?"*	*"I win!" / "I beat you!" "It's so fast" "Stripes are easy." "The first pattern is easier." "I know it!" "Try this pattern"*	*"Want to do my experiments." "Where do you get Euglena?"*

Table 1: Comments collected during user studies organized in individual categories.

ii) Emergence of game strategies and meaningful play

In order to understand how participants interact with the BioGraphr and how they compete against each other, we observed several hundred games. When asked "How did you like the overall activity?" participants responded with 4.7 (SD = 0.5; n = 10) on a five-point Likert scale. While playing, many participants recognized that pattern guessing became harder the longer they waited, and therefore devised the strategy of guessing sooner and risking a penalty rather than waiting too long. Taking too much time resulted in a "burnt-in" pattern, making the subsequent pattern more difficult to guess. The best scores were achieved when a participant waited 1-3 frames (4-12 s) for each pattern. A typical full game with three guesses lasted <60 seconds.

The two-player game (Figs. 7b, 9) received positive feedback, and participants enjoyed it. We observed competitive behavior (*"I beat you!"*) and participants appeared to be easily immersed in the game. We also ran an elimination tournament with eight participants, i.e., 7 matches total, until one player got 5 points (on average, each match lasted eight rounds). To develop a winning strategy, the participants needed to realize that some patterns are easier to recognize than others. Many participants indicated that stripe patterns are easier to guess than dot patterns, and small patterns are easier to guess than large patterns. Therefore, participants often selected large dot patterns for their opponents to choose. Looking at the itemized times for small, medium, and large patterns (50 each), there was a trend that it took users longer to recognize medium patterns (14.4 ± 4.7 s) than large (12.0 ± 4.1 s) and small (11.9 ± 4.2 s) patterns ("±" indicates SD in this paper; difference is not significant). Interestingly, no participant indicated that medium patterns were tricky, although some identified large patterns as hard while others stated that small patterns were hard. Secondary psychological strategies emerged when participants noticed this behavior and discussed it. Some participants tried guessing their opponent's choices without even looking at the Euglena's response, as they "knew" what their opponent was likely to select. The development of game strategies implies engagement in the games, which we therefore consider to be successful from a game design perspective.

iii) Repeated game play improves playing skills

In order to quantify the improvements in scoring over time, we timed players in multiple single games. We asked 10 participants to play 5 single-player games each (Fig. 8). Each game consisted of 3 projected patterns with 4 patterns displayed to guess from. Based on these observations and verbal feedback, we found evidence that participants became more skilled during the game by recognizing specific features of the game mechanics, including those due to the underlying biological dynamics. We found a significant improvement ($p < 0.001$) from game 1 to game 5 (which showed identical patterns) as measured both in terms of time (38.8 ± 8.3 s down to 30.3 ± 3.7 s) and the number of errors (9 down to 2 total). From this analysis, we conclude that participants acquire skills while playing and that the game is neither trivially simple nor unnecessarily difficult.

iv) Biological properties allow tuning of game challenge

We sought to characterize "biological knobs" that affect game difficulty in order to enable more rational game design. In line with individual user feedback, typically the first pattern within each game was guessed faster and fewer mistakes were made. Pooling all data form the 10 participants playing 5 single-player games each, lead to the following results: In each round the 1st patterns were guessed significantly faster than the 2nd and 3rd patterns (12.3 ± 0.14 s, 13.4 ± 0.53 s, 14.8 ± 0.38 s; $p < 0.05$). Also significantly fewer mistakes were made in the 1st pattern compared to the 2nd or 3rd (7, 26, 19; $p < 0.05$). We attribute this observation to two facts. First, Euglena react more rapidly from a perfectly dispersed state. Second, the superposition of later patterns on a previous pattern makes it more difficult to recognize the new pattern. Therefore, the average guessing times increase within a game from pattern 1 to 2 and from pattern 2 to 3.

Additional adjustments to the level difficulty can be achieved by changing the intensity of the light or the image acquisition rate. Presenting a player with images that are updated more frequently forces the player to pay closer attention to subtle changes in Euglena behavior. Using these observations, the biophysical dynamics underlying the game can be actively exploited to tune game challenge.

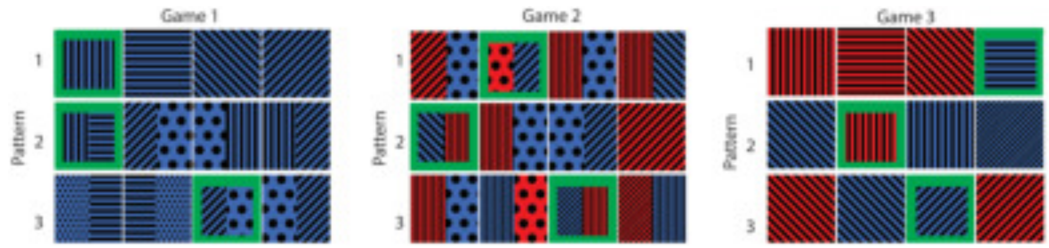

Figure 10: All patterns used in the color learning game with highlighted solutions in green. Each of the 3 games consists of 3 consecutive patterns.

v) Game enables players to infer and discover biological properties

To further investigate whether participants can learn and make inference about biology during game play, we established the following implicit learning goal: "The Euglena eye spot is less sensitive to red light than to blue light" (Fig. 6b). Novice participants were initially told that "Euglena respond to light" while explaining the setup – but no explicit mention of colors was made at all. Over three one-player games (three consecutive patterns each), the participant was confronted with patterns of red and blue light (Fig. 10). These patterns were the same for all participants and predefined such to guide and test the participants towards this learning goal. To increase the information learned from each pattern, split-screen patterns were also used. Some of these patterns included two areas with different patterns and colors (Fig. 10). In the first game, only blue patterns were used to teach the participants that Euglena respond to blue light. In the second game, bi-color split-screen patterns were used; the participants observed that cellular responses only occurred in the areas of blue light. In the third game, the participants needed to have grasped the relationship between light color and cellular response in order to pass the level. Overall, responses to patterns of red light took much longer to develop, which participants noticed easily (example quote: *"So they don't react to red!"*). Afterward, when asked about the color sensitivity of the Euglena eyespot, 14/15 participants (93%) succeeded in this task, indicating scientific learning through gaming and observation. These results demonstrate the potential for coupling educational content to game play on the BioGraphr; future game design and user studies should explore how to make this coupling more effective.

5) DISSEMINATION TO MUSEUMS AND CHILDREN

Presenting the BioGraphr in a local science museum as a guided game exhibit (Fig. 11a) revealed interest among visitors. Families with children and groups of school children interacted with the system, played the games (*"Oh that is a fun game!", "This is really hard"*), showed curiosity (*"So why do they respond to light?"*), and expressed fascination (*"This is the best Arduino project I have ever seen."*). Children became excited when looking through the eyepiece of the BioGraphr, but such a strong response did not occur when they looked at the tablet itself as it was less obvious that the interactive content was living. We also noticed that it took multiple visitors some time to grasp that they were interacting with live cells and that actual patterns of light were projected. Overall we consider the BioGraphr as very promising for a public informal learning space, but especially for an unsupervised exhibit the design should be improved to make it apparent to the user much quicker that the content is alive, especially given the typically short dwell times for museum exhibits (Boisvert 1995; Horn 2012).

In order to enable wide dissemination of the BioGraphr, for example to schools and children's rooms, we stripped the setup to its bare components (projector, micro-aquarium, and tablet) and built a Lego version, which was also displayed in the museum (Fig. 11b). While the core operation principle remains the same with the Lego version, the acquired images lack some quality, as the projector's lamp will always be visible on screen (directly or as glare) even when turned to black. Instead of a mini-aquarium, a conventional 35 mm-diameter Petri dish can be used. Placing a Lego figure (Fig. 11c) may convey the concept of "very small organisms", children were particularly excited (*"Oh Lego - I want to build it!"*), and it seemed to help children grasp that there are living organisms in the BioGraphr and that they are small (*"This is a fish tank for Lego!"*). To what extent this scaling analogy helps children understand these concepts, and what age ranges are most suitable for this type of education, needs further investigations. As demonstrated previously for other media (Resnick 2009), educational synergy could be realized when children build these interactive devices themselves.

DISCUSSION AND FUTURE WORK

Based on this work, we add the following recommendations and insights to previously established design lessons for HBI (Lee 2015, Gerber 2016) and biotic games:

(1) Utilizing a biological phenomenon that relies on millions of cells rather than a few individual ones (Lee 2015) significantly increases the robustness of the activity and also lowers the technological requirements. For example, circulating bioconvection is observable without a microscope and the pattern is recognizable despite air bubbles or other contamination inside the micro-aquarium (air bubbles are even desirable, as they help mixing). Euglena are well suited to biotic games and biotic computing as they are responsive, safe and easy to use for children (Littleford 1960), and usable for weeks.

(2) Our game design avoided the need for computerized image processing, which can be computationally expensive. Instead, the game questions always revolved around the image that was projected, which is "known" by the computer to allow scoring. Technically, all image processing was off-loaded to the human users and Euglena. This practice eases the adaption of the BioGraphr and should facilitate its dissemination.

(3) A shutter that updates images every few seconds (rather than a live view) makes it harder for users to realize the underlying biology. We expect that seeing the development of a pattern without being able see the individual cells complicates the recognition of the living nature of the medium. Here the shutter was necessary for image quality as well as to hide the light stimulus pattern from the player. Improved hardware and game design is desired to allow players to directly experience the movement of the living cells.

(4) The speed of pattern formation and Euglena resolution turned out to be important aspects of game design. Refreshed images every 4 seconds worked well. If images are refreshed slower, interest may be lost, while at higher frame rates, details may be ignored.

(5) Game and level design facilitate fosters excitement about biology. While in two-player games scoring was essential for engagement and retention, single players seemed

Figure 11: BioGraphr in a science museum. a) Visitors interacting with a regular microscope and BioGraphr. b) Lego BioGraphr. c) Placing a micro-aquarium next to a Lego figure conveys the concept of "very small organisms" to children.

to engage more with the underlying science when they did not chase high scores and rush through levels. We attribute this difference to more focused interactions.

(6) We demonstrated that discovering and learning about biological content (i.e., the effects of blue versus red light on the eyespot) can be inferred by players through game play without any explicit additional information. Here the split-screen for direct comparison of responses turned out to be important. Short times between observation and logical conclusion likely maximize these effects.

We envision the use of the BioGraphr and other biotic computers in schools as DIY kits as well as in public spaces such as museums, with potential for formal and informal education that is similar to that of these systems' electronic counterparts (Alberts 2010; Schweingruber 2010). These activities also fit well with formal learning content, such as the Next Generation Science Standards in the USA, which emphasize biology and scientific investigations in middle schools (Stage 2013). Code and building instructions are open source for replication and further development.

On a more philosophical note, some readers may still ask: Is this really a computer or just a biophysical process? We argue that the same question could be asked about the visual pathway in humans (Posner 1989) or tissue morphogenesis during embryonic development (Stark 2013). Especially for the HCI community, we believe it is worthwhile to frequently ask "what is computation?" (Comer 1989), realizing that for algorithm to work, it must be implemented on a dynamical physical substrate. Interestingly, the time delayed Euglena bioconvection patterns also have some correspondence to the oscilloscope afterglow in *Tennis for Two* (Lowood 2009).

CONCLUSION

Here we presented the BioGraphr, a new HBI device that utilizes the collective bioconvection patterns of millions of cells, thereby enabling immersive game play and other activities at the multi-cell scale. A key feature of the BioGraphr is its plug-and-play robustness despite its reliance on live cells. Pattern-matching games were successful and entertaining activities. The setup is ready to include more complex image analysis of bioconvection patterns, to expand its overall design space to develop other games and applications, and to further explore its potential for formal and informal education.

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REFERENCES

Alberts, B. 2010. "Prioritizing Science Education." *Science* 328, 5977: 405-405.

Banister, S. 2010. "Integrating the iPod Touch in K–12 Education: Visions and Vices." *Computers in the Schools* 27, 2: 121-31.

Batchelor, G.K. 2000. *An Introduction to Fluid Dynamics*. Cambridge University Press.

Bilda, Z., Edmonds, E., and Candy, L. 2008. "Designing for creative engagement." *Design Studies* 29, 6, 525-40.

Billinghurst, M., Clark A., and Lee G. 2015. "A Survey of Augmented Reality." *Foundations and Trends in Human-Computer Interaction* 8 (2-3). Now Inc.: 272-73.

Block, F., Horn, M.S., Phillips, B.C., Diamond, J., Evans E.M., and Shen, C. 2012. "The DeepTree Exhibit: Visualizing the Tree of Life to Facilitate Informal Learning." *Vis. Comp. Graphics, IEEE Transactions on* 18, 12: 2789-98.

Boisvert, D.L. and Slez B.J. 1995. "The Relationship Between Exhibit Characteristics and Learning-Associated Behaviors in a Science Museum Discovery Space."

Science Education 79, 5: 503-18.
Bransford, J.D. and Schwartz D.L. 1999. “Rethinking Transfer: a Simple Proposal with Multiple Implications.” *Review of Research in Education* 24: 61.
Brody, M., Bangert A., and Dillon J. 2009. “Assessing Learning in Informal Science Contexts.” *Commissioned Paper by the National Research Council for Science Learning in Informal Environments Committee.*
Casey, C.J., Lau D.L., and Hassebrook L.G. 2008. *Structured Light Illumination Methods for Continuous Motion Hand and Face-Computer Interaction*. Human Computer Interaction: New Developments, Kikuo Asai (Ed.)
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.
Comer, D.E, Gries, D., Mulder, M.C., Tucker, A., Turner, A.J., and Young, P.R. 1989. “Computing as a Discipline.” *ACM* 32, 1: 9-23.
de Souza A. and Delacruz G.C. 2006. “Hybrid Reality Games Reframed: Potential Uses in Educational Contexts.” *Games and Culture* 1, 3: 231-51.
Gerber, L.C., Kim, H., Riedel-Kruse, I.H. 2016. "Interactive Biotechnology: Design Rules for Integrating Biological Matter into Digital Games." DiGRA/FDG.
Hill, N.A. and Plumpton L.A. 2000. “Control Strategies for the Polarotactic Orientation of the Microorganism Euglena Gracilis.” *J. of Theoretical Biology* 203, 4: 357-65.
Horn, M.S., et al. 2009. *Comparing the Use of Tangible and Graphical Programming Languages for Informal Science Education*. *The SIGCHI Conference*. ACM.
Horn, M.,Solovey, E.T., Crouser, R.J., and Jacob, R.J.K. 2012. *Of BATs and APEs: an Interactive Tabletop Game for Natural History Museums*. ACM.
Hossain, Z., Jin, K., Bumbacher, E.W, Chung, A.M,, Koo, S., Shapiro, J.D., Truong, C.Y, Choi, S., Orloff, N.D., Blikstein, P. Riedel-Kruse, I.H.. 2015. *Interactive Cloud Experimentation for Biology: an Online Education Case Study*. ACM.
Hunicke, R., LeBlanc M., Zubek R. 2004. “MDA: a Formal Approach to Game Design and Game Research.” *Proc. AAAI Workshop on Challenges in Game*, AAAI Press.
Johnson, D., Nacke L., Wyeth P. 2015. “All About That Base: Differing Player Experiences in Video Game Genres and the Unique Case of MOBA Games.” *School of Electrical Engineering & Computer Science.* ACM, New York, USA.
Kazi, R.H., Chua, K.C., Zhao, S., Davis, R.C., Low, K.L. 2011. *SandCanvas: a Multi-Touch Art Medium Inspired by Sand Animation*. *The 2011 Annual Conference*. ACM, New York, USA.
Kong, F., Yuan, L., Zheng, Y.F., and Chen, W. 2012. “Automatic Liquid Handling for Life Science a Critical Review of the Current State of the Art.” *J. Lab. Auto.* 17 (3). SAGE Publications: 169-85.
Kunz, A. and Fjeld M. 2010. “From Table–System to Tabletop: Integrating Technology Into Interactive Surfaces.” In *Tabletops - Horizontal Interactive Displays*, edited by Müller-Tomfelde C., 51-69. Springer London.
Lee, J., Kladwang, W., Lee, M, and Das, R.2014. “RNA Design Rules From a Massive Open Laboratory.” *PNAS* 111, 6: 2122–27.
Lee, J.C., Dietz, P.H., Maynes-Aminzade, D., Raskar, R., and Hudson, S.E. 2004. *Automatic Projector Calibration with Embedded Light Sensors*. ACM.
Lee, S.A., Chung A.M., Cira N., and Riedel-Kruse I.H. 2015. *Tangible Interactive Microbiology for Informal Science Education*. *The 9th Intern. Conf.*. ACM, USA.
Lee, S.A., Bumbacher, E., Chung, A.M., Cira, N., Walker, B., Park, J.Y., Starr, B., Blikstein, P, and Riedel-Kruse, I.H. 2015. *Trap It!: a Playful Human-Biology Interaction for a Museum Installation*. *The 33rd Annual ACM Conference*. ACM.
Lenhart, A. 2008. *Teens, Video Games, and Civics.* Washington, DC: Pew Internet;

American Life Project.
Littleford, R.A. 1960. “Culture of Protozoa in the Classroom.” *The American Biology Teacher* 22, 9: 551-59.
Lowood, H. 2009. “Videogames in Computer Space: the Complex History of Pong.” *IEEE Annals of the History of Computing*.
Machemer-Röhnisch, S., Nagel, U., and Machemer, H. 1999. “A Gravity-Induced Regulation of Swimming Speed in Euglena Gracilis.” *Journal of Comparative Physiology A* 185, 6. Springer: 517-27.
Nagpal, R. and Mamei M. 2004. “Engineering Amorphous Computing Systems.” *Methodologies and Software Engineering for Agent Systems*, 11:303-20. Multiagent Systems, Artificial Societies, and Simulated Organizations. Boston, Springer US.
Pepperkok, R. and Ellenberg J. 2006. “High-Throughput Fluorescence Microscopy for Systems Biology.” *Nature Reviews Molecular Cell Biology* 7, 9: 690-96.
Pivec, M. 2007. “Editorial: Play and Learn: Potentials of Game-Based Learning.” *British Journal of Educational Technology* 38, 3: 1-7.
Podolefsky, N. 2012. “Learning Science Through Computer Games and Simulations.” *Studies in Science Education* 48, 2: 237-40.
Posner, M.I. and Petersen S.E. 1989. “The Attention System of the Human Brain,”. *Annu. Rev. Neurosci*. 13: 25-42.
Preist, C. and Jones R. 2015. *The Use of Games as Extrinisic Motivation in Education*. *The 33rd Annual ACM Conference*. ACM, New York, USA.
Prensky, M. 2005. “Computer Games and Learning: Digital Game-Based Learning.” *Handbook of Computer Game Studies*.
Ramey-Gassert, L. and Walberg H.J. 1994. “Reexamining Connections: Museums as Science Learning Environments.” *Science Education* 78, 4: 345-63.
Resnick, M., Berg, R., Eisenberg, M. 2009. “Beyond Black Boxes: Bringing Transparency and Aesthetics Back to Scientific Investigation.” *The Journal of the Learning Sciences* 9, 1: 7-30.
Riedel-Kruse, I.H., Chung, A.M., Dura, B., Hamilton, A., and Lee, B.C. 2011. “Design, Engineering and Utility of Biotic Games.” *Lab on a Chip* 11, 1: 14-22.
Schweingruber, H. and Fenichel M. 2010. Board on Science Education, Div. Behavioral and Social Sciences and Education, National Research Council. *Surrounded by Science: Learning Science in Informal Environments*. National Academies Press.
Shoji E., Hiraku, N., Akinori, A., Makoto, I. 2014. “Localized Bioconvection Patterns and Their Initial State Dependency in Euglena Gracilis Suspensions in an Annular Container.” *Journal of the Physical Society of Japan* 83, 4: 043001.
Stage, E.K., Asturias H., Cheuk T., Daro P.A. 2013. “Opportunities and Challenges in Next Generation Standards.” *Science* 340, 6130: 276-77.
Stark, W.R. 2013. “Amorphous Computing: Examples, Mathematics and Theory.” *Natural Computing* 12, 3: 377-92.
Trietsch, S.J., Hankemeier T., van der Linden H.J. 2011. “Lab-on-a-Chip Technologies for Massive Parallel Data Generation in the Life Sciences: a Review.” *Chemometrics and Intelligent Laboratory Systems* 108, 1: 64-75.
Tsandilas, T., Grammatikou M., Huot S. 2015. *BricoSketch: Mixing Paper and Computer Drawing Tools in Professional Illustration*. *2015 Intern. Conf.* ACM, NY, USA.
Watson H.F. 1879. *Feeding Plants*. *The American Biology Teacher*. Vol. 7. ACM.
Whitesides, G.M. 2006. “The Origins and the Future of Microfluidics.” *Nature* 442, 7101: 368-73.
Yannier, N., Koedinger, K.R., and Hudson, S.E. 2015. *Learning From Mixed-Reality Games: Is Shaking a Tablet as Effective as Physical Observation?* ACM.