Interactive Biotechnology: Design Rules for Integrating Biological Matter into Digital Games

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ABSTRACT
In recent years, playful interactions with biological materials, including live organisms, have been increasingly explored and implemented. Such biotic games are motivated and enabled by biotechnological advances and their increasing presence in everyday life constitute a form of human-biology interactions (HBI). Here we systematically discuss the design space for "digital-biology hybrid" games, summarize current best-practice design rules based on recent works, and point to technologies that will enable others to design and utilize similar games to advance this field. In particular, we show how augmentation with overlaid digital objects provides a rich design space, we emphasize the advantages when working with microorganisms and light based stimuli, and we suggest using biotic processing units (BPUs) as the fundamental hardware architecture. In analogy to the history of digital games, we make some predictions on the future evolution of biotic games as the underlying core technologies become readily accessible to practitioners and consumers. We envision that broadening the development of playful interactive biotechnology will benefit game culture, education, citizen science, and arts.

Keywords
User Interfaces, Computers, Education, Human-Biology Interaction (HBI), Human-Computer Interaction (HCI), Tangible Microscopy, Biotic Game, Biotic Processing Unit, Microscopy, Alternative Computation, Augmented Reality, Interspecies Collaboration.

I) INTRODUCTION: HUMAN BIOLOGY INTERACTION, BIOTIC GAMES
Biotechnology and the modern life sciences are expected to dramatically transform our society in the near future in a similar way information technology has transformed our society within the last few decades (Goonatilake et al. 2013). These new technologies provide novel ways for humans to interact with their environment, computers, and each other and will also lead to innovations for playful activities and games. By including biological matter into these interactions, "biotic video games" have been established and allow humans to interact with live microorganisms via computer interfaces (Riedel-Kruse et al. 2011). Players supply physical stimuli to microbes that react and respond in return. The control and observations might be mediated by an electronic interface such as a computer and a screen. For additional augmentation, virtual objects, as commonly found in traditional electronic video games, can be overlaid onto these systems. Hence, such a biotic video game constitutes a digital-biology-hybrid, leading to a three-way interaction between the human (H), biological (B), and digital worlds (D) (Fig. 1). This motivates the

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Figure 1: Biological processes (living micro-organisms) can be integrated into digital games. The three constituents (human players (H), biological matter (B), and digital layer (D)) may interact pairwise with each other. This paper explores the design space of such systems from technical and artistic viewpoints. H, B, D notation is used throughout the paper.

concept of human-biology interaction (HBI) (Lee et al. 2015), in analogy to traditional human-computer interaction (HCI) (Carroll 2009).

Foremost, we believe that these games should be designed and played for their intrinsic value and enjoyment. Beyond that, a number of applications spring to mind, in particular where a pure digital implementation (simulation) of the equivalent game might be technologically infeasible or not as effective to achieve the intended outcome. Examples: (1) Games can be used for education to teach biology (Egenfeldt-Nielsen 2005). It is frequently found that students' interest is higher when experimenting with a real system rather than the corresponding simulation (Chien et al. 2015). (2) Citizen science games motivate people to participate in life science research and make relevant discoveries (Lee et al. 2014). Such discoveries can only be made when interacting with the real biological substrate as a simulation would capture at best the current state of knowledge. (3) Even if the underlying biophysics were completely understood for a particular phenomenon, exact real-time simulations might be computationally inaccessible, such as solving the Navier-Stokes equations for hundreds of cells (Elgeti et al. 2015). (4) Given the fact that biotechnology increasingly affects our daily lives on a societal scale (Goonatilake et al. 2013), it is also important for everyone to get a first hand experience with these technologies. These games can provide a means for informal education (Riedel-Kruse et al. 2011). (5) Finally, the fact that consumer devices like smartphones will soon likely include technology for diverse diagnostic purposes (Ozcan 2014), the platform technologies enabling HBI and biotic games will be available. Consequently, games will be designed for this technology – in the same way digital games emerged through advancements of computer technology (Lowood 2009).

In this paper, we will first characterize some of the existing digital-biology-hybrid games, and uncover interesting and relevant engineering and design challenges as well as opportunities. We report heuristic design rules that should facilitate future development of the technology and lower the entry barrier to designing these systems, i.e., allowing game designers, researchers, and other practitioners to enter the field. We also draw motivation from fields such as augmented reality (Koutromanos et al. 2015) and the technological history of early computers, game consoles, home computers, and arcade video game cabinets (Guins 2015, Huhtamo 2005, Guins 2014, Lowood 2009). We focus on systems that (1) use low-cost, high-throughput, microscopic biological materials, e.g. single cells and molecules; (2) can be operated through digital input-output interfaces such as a biotic processing unit (BPU) (Riedel-Kruse et al. 2011, Hossain et al. 2015); and (3) can be overlaid with digital objects, which significantly aids game and application design. Future HBI systems will greatly benefit from the recent biotechnological advances in handling, manipulating, and measuring biological materials at small scales with high throughput (Whitesides 2006, Melin and Quake 2007).

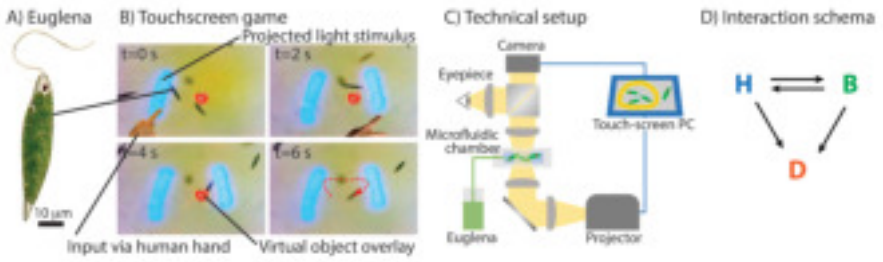

Figure 2: Example of a biotic game. A) Euglena cell. **B)** Human player interacts with freely swimming Euglena by drawing patterns on a touch-screen that are projected as blue light onto these cells thereby by eliciting photophobic responses. The game objective is to influence the cell's swimming path (red dashed line) to collect an overlaid virtual object (apple). **C)** The hardware forms a closed loop of a touch screen tablet, LCD projector, microfluidic chamber (housing Euglena cells), and microscope camera. **D)** From an interaction perspective, the human (H) sees and stimulates the biological cells (B), but does not directly control any virtual objects (D) although can see them, similarly between B and D.

II) EXISTING WORK: DIVERSITY, OPPORTUNITIES, CHALLENGES

Let us start by considering *TrapIt!,* an illustrative example of a biotic game and the technology behind it (Fig. 2) (Lee et al. 2015). Single-celled organisms (*Euglena gracilis*) (Fig. 2A) are housed in a microfluidic chamber and are displayed in real time on a touch screen (Fig. 2B,C). The player can draw patterns on the screen that are projected microscopically as a light pattern onto the chamber and the cells. These cells have a photophobic response, i.e., when they swim into this light, they turn around. One mini-game implemented on this platform is "Apple," where the player tries to direct these cells towards digital objects that are virtually overlaid on the screen. Computerized tracking of the cells enables detection of when the goal is achieved, i.e., the Euglena cell and the apple are on the same position on the screen. There is also a countdown on the apple, providing a time limit to the player to achieve this task. These interactions take place in real time, and a game takes 1 minute involving multiple successive apples. The virtual objects are influenced by the biology, but do not influence the biology. Other games and applications can be designed on this platform by changing the virtual overlay ("the skin") and the logic of the interaction, e.g., another mini-game Box tasks the player with corraling many cells inside a digital box overlaid on the screen (Lee et al. 2015). The original motivation for the *TrapIt!* project had been to enable hands-on life science museum exhibits as they are typically less interactive than their mechanical and electronic counterparts (Hamilton et al. 1995, Salmi and Kreinberg 2001, Salmi 2002), and *TrapIt!* was successful as it lead to prolonged engagement of multiple minutes (Lee et al. 2015).

Casting a wider net, we find that various live organisms and biological samples have been integrated into games recently by different research groups for various purposes (Fig. 3): The Euglena setup described above can also be presented without any digital objects overlaid, enabling free play (Fig. 3A) (Lee et al. 2015). Euglena have been used in setups which allow for simpler light stimulation from four cardinal directions in the plane. This setup can be used for student projects in instrumentation classes and maker spaces (Fig. 3B) (Cira et al. 2015). Other microorganisms have been used as well, such as Paramecia

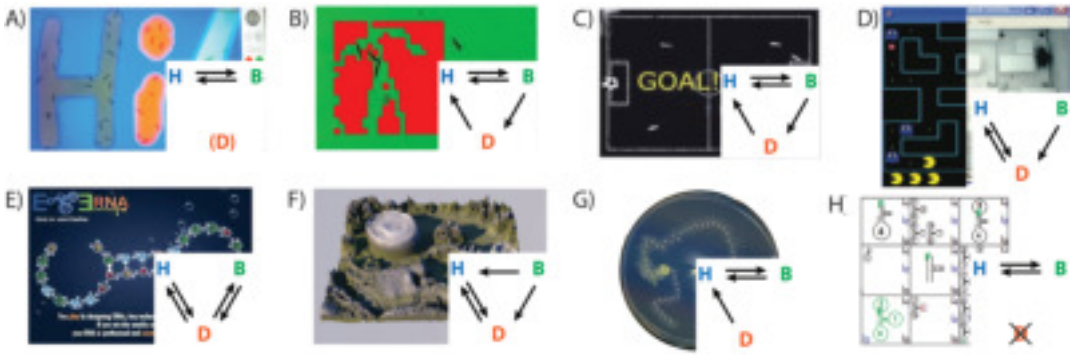

Figure 3: Games that include various biological matter, stimuli, and interaction interfaces. A) Euglena touchscreen setup as in Fig. 2 with no digital overlay. **B)** Euglena game with directional light stimuli via joystick. **C)** Paramecia soccer with electric stimuli via joystick. **D)** Cricket motions are used to animate ghosts in *PacMan* games. **E)** RNA game utilizes RNA synthesis in a cloud lab. **F**) Pre-recorded images from mold and bacteria cultures provide the landscape for digital games. **G)** Web interaction with slime molds using chemical stimuli. **H)** DNA-based *Tic-Tac-Toe* using pipette and visual inspection without any digital computers involved. **The inset graphs** represent the interactions between the human, biology, and digital layers.

that can be electrically stimulated to play a soccer game (Fig. 3C) (Riedel-Kruse et al. 2011). Macroscopic animals (crickets) have been integrated into *PacMan* (Fig. 3D) (van Eck and Lamers 2006). In the citizen-science platform *EteRNA* (Fig. 3E) (Lee et al. 2014) users solve puzzles related to the folding of RNA molecules, and player designs are experimentally tested in a cloud (i.e. online and remote) lab. The results are returned to players within a few days. In contrast, the citizen science game *FoldIt* (concerned with protein folding) (Cooper et al. 2010) does not provide experimental feedback, although biological facts established and recorded prior to the game drive the game mechanics. Static biological images of live organisms that were acquired prior to a game have been used to evolve game terrains that virtual in-game characters interact with (Fig. 3F) (van Eck and Lamers 2015). Another cloud lab enabled free play with slime molds (Physarum) chemotaxis for educational purposes, and the students were able to receive experimental feedback within minutes (Fig. 3G) (Hossain et al. 2015). Lastly, to demonstrate the power of biotechnology (rather than to be actually played), a *Tic-Tac-Toe* game has been implemented on a DNA computer (Fig. 3H) (Stojanovic and Stefanovic 2003); note that in this case no digital computer is involved, instead pipetting liquids and visual inspection of their color changes provide the interaction. For further HBI examples see also (Riedel-Kruse et al. 2011, van Eck and Lamers 2013, Gerber et al. 2016); the accompanying movies in many of these publications are also illustrative.

The variety of this previous work not only illustrates the broad design space for interactive biotechnology and its potential applications, but also reveals several practical challenges for developing this technology as well as designing games. For example: (1) Many of these systems require significant preparation and back-end logistics to run. However, some interactions come closer to the plug-and-play experience of digital video games, e.g., Euglena cells can be cultured for weeks in a closed micro-aquarium (Fig.

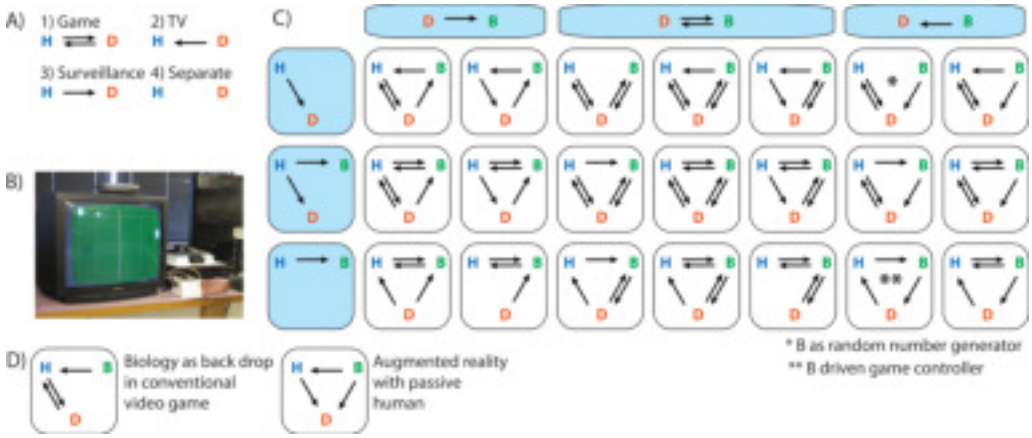

Figure 4: The design space of Human-Biology-Digital interactions. A) The HCI design space for traditional digital media. **B)** Early video games were often media hybrids, such as using transparency overlays on the Odyssey. **C)** Illustration of the 21 design options (out of 64 total) for HBI where H affects at least one of either B or D, H receives feedback from both B and D (although potentially only indirectly), and B and D interact with each other at least one way. *: Biology as random number generator in conventional video game. **: Biology mediated game controller in conventional video game. **D)** Examples of meaningful interactions that fall outside C) but are of interest as well.

2A,B). (2) Some games use macroscopic organisms like crickets (Fig. 3D), raising logistical as well as ethical questions (Harvey et al. 2014), while simpler microorganisms or even molecules avoid these issues (Fig. 3A-C,E-H). (3) For some games, the connection between human input and physical stimulus is directly implemented in hardware (Fig. 3B,C), while others have a software layer in between (Figs. 2,3A,E) and hence provide more flexibility to the game designer to shape the interactions. (4) Some games are augmented with overlaid digital objects (Fig. 3B-E,G), while others even lack digital interfaces at all, e.g., pipetting colored liquids provide input and output (Fig. 3H).

In the following sections we formulate practical guidelines for designing such biotic games, choosing suitable biological materials, and engineering the relevant hardware.

III) DESIGN SPACE OF HUMAN-BIOLOGY-DIGITAL INTERACTIONS

The design space for HBI is vast and compelling as the three involved constituents – human, biology, and digital – generate 64 (4^3) possible interaction schemas (Fig. 4). We find it illustrative to contrast this to conventional HCI where the two constituents (the human and the digital layer) generate only four (4^1) possible interaction schemas (Fig. 4A; note that X actuating Y is the same as Y sensing X): 1) In a traditional video game, the human influences and sees virtual objects; 2) movies are watched passively; 3) surveillance camera records human activity but the human remains unaffected; and 4) no interactions between human and the virtual. Only 1) is truly interactive, hence, this design space is rather restricted falling into specific, well-known applications.

It is curious to note that early video games were actually hybrids between different media. For example the first commercial videogame console Odyssey (Magnavox),

augmented video games with themed (although static) transparencies attached to a TV screen (Fig. 4B) (and other physical components were included such as dice) (Lowood 2009), while the underlying mechanic always involved a simple digital block that could be moved across the screen. Many early video games were implemented using custom electronic logic chips rather than software and many mechano-electronic arcade systems were hybrids. Eventually, microprocessors became sufficiently powerful and cheap, and starting with the Fairchild System F (1976) and the Atari VCS (1977) only microprocessors were used (Guins 2015, Huhtamo 2005, Lowood 2009), and it became convenient for game designers to implement everything in software. Hence the hybrid nature of these early video games enabled offsetting limits of the technology, but also provided its own charm and shaped the player's experience.

Analyzing all 64 possibilities of this combined HCI/HBI design space in depths is beyond this paper, but we provide an illustrative exploration. We note 21 arrangements (Fig. 4C) of special interest as they fulfill three criteria for meaningful interaction between human (H), digital (D), and biology (B). First, they shall involve direct human stimulation of at least one other component (biology or digital), i.e., there must be H→D, or H⇆D, or H→B. Second, there should be at least one-directional communication between biology and digital, i.e., there must be B←D, or B⇆D, or B→D. Third, the human experiences (at least indirectly) both the biology and the digital, i.e., there must be a path form both B and D back to H. To illustrate some applications of these 21 arrangements, consider a random number generator based on biological properties that can be provided for a traditional video game (Fig. 4C*); or the characters in a traditional video game "behave naturally" as they are driven by biological objects, which are (unknowingly) stimulated by the player (Fig. 4C**). But some possibilities outside these 21 arrangements have interesting applications as well (Fig. 4D), e.g., biology can provide a non-interactive backdrop in a conventional video game, or digital objects augment the biology with the human passively watching. In conclusion, the design space for these digital-biology hybrids is significantly larger than that for pure digital video games. This provides new design opportunities for digital games, eases the design for biotic games, and in the future programmable biotechnology may become sufficiently powerful and expressive to stand on its own, i.e., digital objects may not be needed.

IV) KEY TECHNOLOGIES FOR HUMAN-BIOLOGY-INTERACTION

A key challenge in designing robust, user-friendly, and cost-effective games lies in the combination of a diverse and interdisciplinary set of skills required, such as biology, electronics and hardware, programming, and game design. Recent advances in automation, throughput, monitoring, and cost give a broad range of people access to life sciences and biotechnology (Fig. 5) (Riedel-Kruse et al. 2011). These continuing advances can be harnessed to address these considerations and will enable the future use of a wider range of microorganisms and stimuli in biotic games. Microfluidic devices (Whitesides 2006) aid the automated manipulation of fluids and biological content at small scales. Analogies between microfluidic valves and circuits vs. electronic transistors and integrated circuits have been made: exponential increases in procedural power and reductions in cost are occurring (Riedel-Kruse et al. 2011). Additional automation of liquid handling and culturing can make the biological response even more robust and consistent, but implementing this automation complicates the design of the biotic gaming platform. Also, emerging cloud lab technologies (Hossain et al. 2015), (Lee et al. 2014), akin to cloud computation, provide laymen access to these technologies.

Single-celled microorganisms (Figs. 2A, 3A-C) are particularly advantageous as large numbers can be maintained in small spaces, and advances in high-throughput instrument

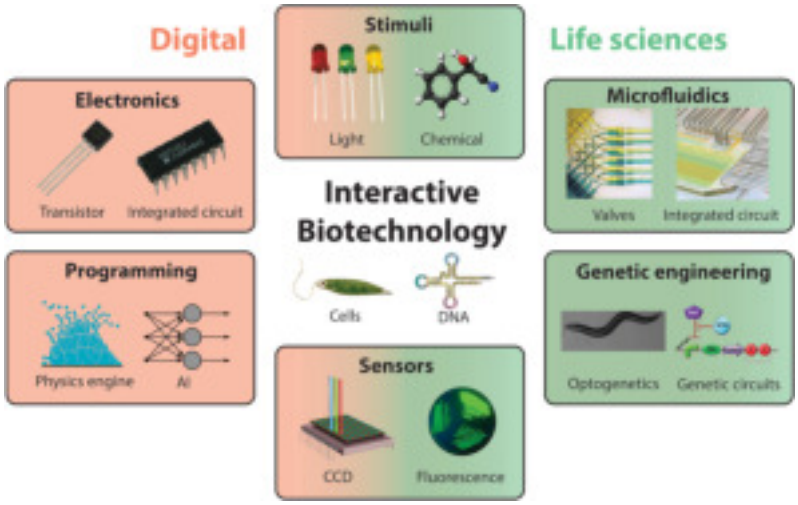

Figure 5: Technological advancements in the digital and life sciences enable interactive biotechnology and biotic games. Electronics and microfluidic techniques have matured analogously from individual transistors respectively valves to complex integrated circuits. Programming of software as well as genetic engineering steadily increase in their power and allow integrating digital objects and living matter into game play. Both stimuli and sensors have become specific, high resolution, and accessible and allow precise actuation and observation of living matter.

automation and miniaturization (Whitesides 2006), (Balagaddé et al. 2005), (Melin and Quake 2007) make these organisms easier and cheaper to work with than macroscopic plants or animals. For example, the visible area in the Euglena setup (Fig. 2C) is <1 mm^2; hence, one projector operating over 1 cm^2 could operate in principle 100 games in parallel. However, if the biological material becomes too small, the requirements and costs for optics increase, ultimately reaching the resolution limit of light microscopy, requiring other physical principles of measurement and visualization. For example, molecular RNA structures are manipulated in the *EteRNA* game (Fig. 3E), where the secondary RNA folding structure is detected via gel electrophoresis (involving manual labor at the backend) and results are presented to the player as digital representations of the gels, not as photographs of the RNA molecules themselves.

Light as a stimulus is particularly advantageous as it is easy to control and administer (e.g. with a consumer grade pocket projector (Lee et al. 2015)). Light does not linger (like chemical stimuli), and projecting a light image already enables significant programmability of stimulus, e.g., consider moving light objects coupled to real time tracking of cells (Lee et al. 2015). Of course, the organisms must display specific responses to light, such as phototaxis seen in Euglena. Also, optogenetics (Deisseroth 2011), which consists of genetically modifying cellular functions in various organisms to respond to light, will enable an endless range of organismal behaviors to be controllable by light stimuli in the future. For example, cell mobility can be genetically altered to respond to external light stimuli (Bacchus and Fussenegger 2012). Potential concerns of whether specific genetically modified organisms should be used outside biolabs (Harvey et al. 2014) can be addressed with cloud lab technology (Fig. 3E,G) (Hossain et al. 2015).

Other photoresponsive organisms that may be suitable for digital biotic games using light stimuli include Chlamydomonas, a widely used model organism (Polin et al. 2009), cyanobacteria (Westrick et al. 2010), and Volvox (Short et al. 2006). For example, Volvox is a multicellular ball ~200 μm in diameter that exhibits phototaxis. Volvox swims more slowly than Euglena but is visible to the (trained) naked eye; hence, the relationship between the macroscopic world and the microscopic world may be clearer from interactions. Another interesting microecosystem that is stable over months consists of *Escherichia coli*, Chlamydomonas, and Tetrahymena (Hekstra and Leibler 2012).

Stimuli other than light can also be explored for use in biotic games. Euglena and many other microorganisms are known to respond to many stimuli, such as gravity (Wager 1911), electric or magnetic fields (Tanimoto et al. 2000), and chemicals (carbon dioxide, ethanol, hydrogen peroxide) (Ozasa et al. 2013).

V) BIOTIC PROCESSING UNITS (BPU)

In order to make HBI systems operable for both the game designer and the player, it is important that the corresponding instruments operate with the convenience of existing game engines (Gregory 2009). We term such an instrument a biotic processing unit (BPU) (Fig. 6) (Riedel-Kruse et al. 2011, Hossain et al. 2015). A BPU is a device that houses biological material as well as physical actuators and sensors and furthermore communicates via digital input/output channels with other computers. The previously discussed *TrapIt!* setup (Fig. 2) fulfills these criteria: a web camera and projector are used for sensing and actuation and the Euglena cells are cultured semi-automatically in a reservoir and automatically supplied to the interrogation chamber when needed, enabling automatic operation for days. Note that the organisms essentially become a component of the BPU, although different biological materials could be added to a given BPU. A BPU allows the game designer to treat the biological component with the same convenience and abstraction as other electronic components such as GPUs, or a physics engine.

For a BPU, the standard notion of "Turing complete computation" does not hold, instead it is domain specific regarding a certain subset of biological experiments that can be executed. And a BPU does not necessarily need to be fully automated. In the case of *EteRNA* (Fig. 3E), experiments are executed at the backend by a combination of automated and manual labor over a few days. Nevertheless, the biological experiments are executed through a digital input/output interface from the player's and game designer's point of view. Overall, the operating cost, turnaround time, flexibility of

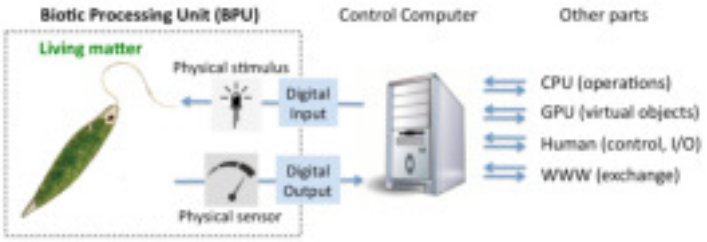

Figure 6: Concept and actual implementation of a biotic processing unit (BPU). BPUs holds the biological material, include physical stimuli and measurement components, and have digital input and output channels. A control computer facilitates between the BPU and human, furthermore animates the virtual game objects. Hence the BPU can be effectively treated as a conventional physics engine or as an electronic chip.

programmability, and throughput of any given BPU are important to consider. For example, projected 2D light fields, as in the *TrapIt!* museum exhibit (Fig. 2, 3A), allow much richer stimulus combinations than four single LEDs placed on the four sides of the apparatus do (Fig. 3B). These design considerations are of particular interest when designing novel BPU hardware in the future.

VI) PRACTICAL RULES FOR DESIGNING BIOTIC GAMES

Designing good games is a challenge in itself (Schell 2008), but the design of biotic games carries additional challenges due to the biological matter in these platforms. Biological systems experience inherent variability over time, such as changes in cell density, speed, response time to external stimuli, and morphological variability among cells. In contrast to conventional video games, the designer cannot rely on deterministic and programmable behavior, yet at the same time has to deliver a consistent and robust game experience (within the bounds defined by the designer – but ultimately judged by the player). In the following we report and illustrate a first set of design lessons that emerged through previous work (section II). (Here we only focus on lessons that can be considered new and specific for biotic games – not repeating lessons on game design in general.) While this list of rules and examples will likely grow in the future, it should already provide a set of "lenses" for the game design process (Schell 2008).

a) Choose a robust and programmable BPU and biological material

Utilizing small biological material (single cells, organic molecules) that can be housed, stimulated, and measured for extended periods of time (multiple days) with minimal intervention and low cost is key. Additional abstraction of the biotic hardware into a BPU enables game design with convenience similar to current game and physics engines (Fig. 6). The Euglena based light interactions, which we discussed previously (Fig. 2, 3A,B), provide a sturdy and amenable starting point.

b) Matching human and microbiological length and time scales

The intrinsic speed of the biological process and the magnification of the system should match the human response time and scale. In contrast to traditional video games, the speed of a given character (a cell) in a biotic game usually cannot be changed by the game designer (although future biotechnology will likely enable to do so; Fig. 5). However, the magnification power of the microscope and the amount of zoom when projecting the organisms onto a screen can be manipulated (Fig. 7A). For example, Euglena cells are ~50-100 μm long and swim ~50-100 μm/s, moving approximately one body length per second (Fig. 2). Magnifying them as 10-cm objects on a 25-cm screen results in objects that are displayed on the screen for just a few seconds, suddenly and unpredictably entering and exiting the field of view. In contrast, a magnification of 5 mm onto a 100-cm screen makes the cells slow and easy to follow (Fig. 7A). The effective "on-screen" magnification is the combination of optical/digital magnification and screen size. The on-screen magnification can also put constraints on use input if the screen serves as input device. For example, when a user draws on a touchscreen to capture a highly magnified cell (Fig. 7A), the effective cell movements may become so fast that the human hand cannot match it. Hence, zooming-in makes biological objects appear faster. These biophysical constraints can be graphed (Fig. 7B), providing guidelines for the designer regarding the on-screen magnification. Figure 7B for example allows to readout an onscreen length: Euglena are 50-100 micrometer in length; projection to the secondary y-axis indicates the size on the screen (here 5 cm). Applying a different magnification and thus shifting the right macroscopic y-axis vertically (red arrows), provides a valuable design feature. For example, the cells move faster on the screen when a higher

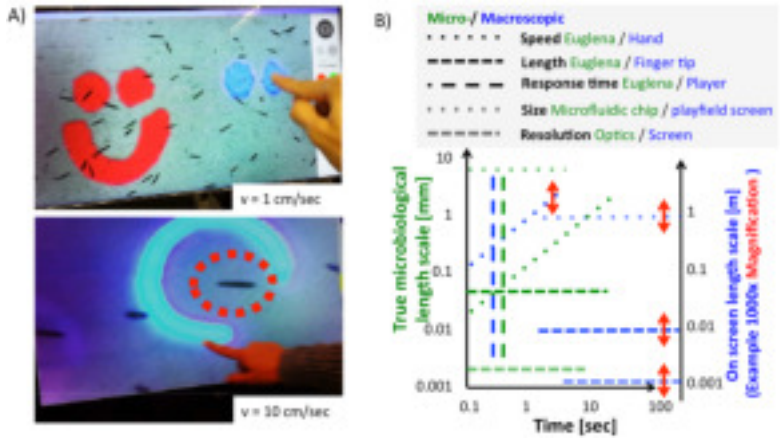

Figure 7: Time and length scales of the underlying biophysical phenomena set the range of possible game and user interaction speeds, while adjustments of on-screen magnification enables tuning. A) Illustration of different apparent Euglena speed using different optical magnification and screen size. **B)** Graphical representation of relevant length and time scales. For example, the speed of the human hand is still larger than Euglena velocity; Euglena stays on screen significantly longer than the human reaction time; or the screen resolution matches the limit of the optical setup. Red arrows indicate variables the designer can change with magnification.

magnification is chosen. At one point they are too fast to be caught by the player as the player's reaction time is too slow. The game designer must select a magnification that corresponds to a game speed neither too slow (potentially boring), nor too fast (impossible to play). Very high magnification can be also interesting, as the player might be able to stimulate and observe sub-cellular parts of the organisms only.

c) Hardware and software solutions to counter biological variability

Continuous stimulus control (rather than on-off switch) can enhance the robustness of play. For example, some Euglena-based systems (Fig. 3B) use an analog joystick to control the intensity of the light stimulus compared to a digital on/off switch of the galvanotactic stimulus in the Paramecia-based system (Fig. 3C). Cells can vary in their responses to the stimulus over different days, e.g., sometimes align with the maximum intensity of light, while other times this intensity prompts the cells to spin on the spot (Lee et al. 2015). Hence an analog joystick provides the opportunity for the experienced player to tune the intensity of the stimulus to elicit particular behavioral responses.

Overlaying virtual objects facilitates game design. Currently, the diversity of biological organisms and stimuli suited for biotic games remains somewhat limited. Overlaying virtual objects provides design opportunities for integrating a narrative into gameplay and enables important adjustments to game dynamics. The properties of these virtual objects are much easier to change by the designer on the virtual level than on the biology level. In principle, virtual objects could be even dynamically adapted to the state of the organisms. For example, the number of swimming microorganisms in the field of view (Fig. 2) naturally varies. If the goal of a biotic game is to guide one of these

microorganisms into a virtual goal, then the size of that goal could be dynamically changed depending on cell numbers to keep the probability of hitting the goal constant.

Players should be able to choose a particular biological object on the screen that interests them. When many cells are visible onscreen, some cells may move and respond in ways that are more desirable. Providing the player with the opportunity to select a "good" cell allows for more robustness against biological variability. For example, *TrapIt!* (Fig. 2) enables players to select and interact with a specific cell, in contrast to the paramecium game (Fig. 3C) where players interact with the entire swarm of cells.

Simulations are useful for game prototyping. Prototyping in different media is a general principle of game design, just like the usage of paper prototypes during the development of electronic games (Schell 2008). This principle applies to biotic games as well, as simulations can allow developers to test specific cases and conditions which may be difficult to recreate on demand with a BPU. Although many media may be useful for this task, computer simulations provide a good starting point. These simulations require a biophysical model of the biological process of interest, but simple agent-based simulations of similar responses to stimuli are often sufficient. For example, simple simulation of Euglena behavior and corresponding games could be implemented in the children programming language Scratch (Resnick et al. 2009).

d) Bringing biology and technology forward to the player

The biological features of interest should be highlighted to the player. While early biotic games such as the paramecium game (Fig. 3C) depicted cells only as white speckles, it is beneficial to provide colorful subcellular details as in *TrapIt!* (Fig. 2). The resolution is ultimately limited by the limits of optical microscopy and organism speed as discussed above. The biological features of interest extend beyond static visuals and can include motion, species interactions, or growth, e.g., for Physarum (Fig. 3G), the time scale of interaction is over days to highlight the growth and motion of the organism.

The underlying biology and biotechnology should be transparent to the player. While electronic video games can be perceived as pure and abstract simulations, it is critical that the "realness" of biological interactions is conveyed to the players, otherwise the player may confuse the system with a pure simulation. This realness is the major advantage of HBI versus standard simulations of biological behavior (Chien et al. 2015, Lee et al. 2015). This transparency can be achieved through tutorials, by making the underlying technology visible and understandable, or when microscopy is involved, by providing an eyepiece in addition to the camera. These affordances were demonstrated with the *TrapIt!* exhibit (Fig. 2). For online systems (Fig. 3G) an external camera (in addition to the microscope camera) can provide an external view onto the setup. But there may be cases of HBI in which attention should not be drawn to the realness of the system, for example when using the biology as a random variable generator (Fig. 4C).

The system should answer the design question of "Why not just simulate?" Biotic games should highlight deliverables that cannot be achieved through electronic versions alone, as electronic simulations are typically much easier to achieve than HBI systems. A simple yet powerful motivation is curiosity. This motivation is clear for research-directed games such as *EteRNA* (Fig. 3E), where the biological output is directly needed for discovery. For educational games, interacting with the real substance may heighten player interest and attention compared to simulations; the knowledge that the biological behavior is not simulated but real may significantly change the player's experience and attribution of relevance (Chien et al. 2015, Lee et al. 2015).

e) Design aspects of ethics and safety

Ethical and biosafety considerations must be addressed. A scale of ethical issues (Harvey et al. 2014) emerges for HBI systems that involve living matter, especially macroscopic organisms (Fig. 3D,A,E). We suggest embracing the philosophical view that the player manipulates a physical stimulus to which a cell may or may not respond, rather than manipulating the cell itself, i.e., the player interacts with the biology rather than manipulates it. Four minimal ethical recommendations were established recently (No Pain; Engage with the public; Respect the player; Respect the organism (Harvey et al. 2014)) and highlight the benefits of using non-sentient single-celled organisms and organic molecules. While many organisms are safe to use, the safety of players and bystanders must be guaranteed. Organisms with a track record of educational use, such as Paramecia and Euglena, are suitable. Alternatively, sealing the organisms into closed systems (BPUs, Fig. 6) promotes biosafety, as does remote experimentation (Fig. 3E,G).

f) Considering audience and application

The audience, outcome, complexity, and replay value of the game should be considered. Is the game intended to be a 5-min experience that will be played once by school children for a playful demonstration? Or should the game engage the player for hours, yielding a reliable game experience? This distinction significantly impacts the requirements for automation and system reliability. For example, it may determine whether the underlying technology should be plug and play or should be prepared by a biology teacher or other provider before a class/gaming session. Note that the provider and the player are not necessarily the same person, e.g., teacher versus student.

HBI design should strive for richness in observable biological behavior, i.e., a large discovery space. In general, images and movies of biological content can be very information rich and interesting to the player, e.g., Euglena cells change their shape and exhibit meandering motion providing significant opportunity for discovery in an educational setting. Citizen-science discovery games like *EteRNA* (Fig. 3E) require very large biological search and outcome spaces. For *EteRNA* in particular, these spaces are essentially limitless, as many combinatorial RNA sequences can be searched.

VII) PREDICTING FUTURE DEVELOPMENTS

Comparing the recent histories of computing (Pichover 2011) and (molecular) biotechnology (Hausmann 2013) reveals multiple parallels, overall suggesting a 50-year lag between these fields (Fig. 8): The foundations of quantum mechanics (such as the discovery and explanation of the photoelectric effect and development of the quantum hypothesis) can be paralleled to those of molecular biology (identification of DNA as the carrier of genetic information and solving it's structure). There were "Golden Years" that led to the accumulation of wider and deeper scientific understanding in both disciplines, followed by key engineering inventions such as transistors, switches, and integrated circuits (Streetman 2000) for universal execution of logic in computing and fluid manipulation in the life-sciences (Unger 2000). Universal DNA computing (Adleman 1994) and synthetic biology (Andrianantoandro et al. 2006) may also be viewed as analogous to electronic circuits. Eventually, games emerged in both fields (*Tennis for Two* (Lowood 2009) and biological examples shown in Fig. 3).

Extrapolating forward, these analogies suggest that in 5~10 years we could expect the equivalent of the commercial console and home-computer revolution that occurred in the mid to late 1970s, when computing technology became widely available for hobby and home use, commercialization starting in 1972 with Pong (arcade) and Odyssey (home) (Lowood 2009) (Fig. 8). This scenario is not far fetched for biotechnology, given the

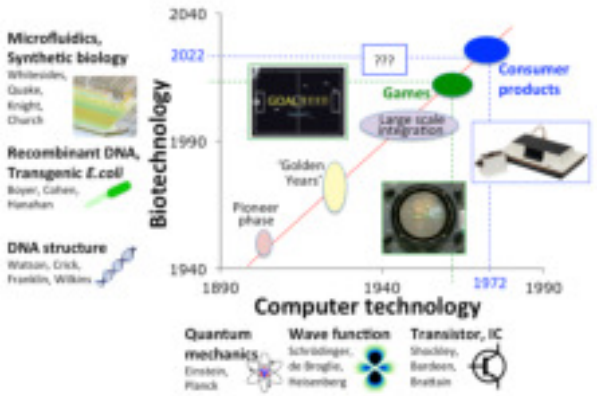

Figure 8: Extrapolating into the future of interactive biotechnology from the past of interactive electronics. Parallels between electronic and biological engineering suggest a 50-year lag that is also apparent for game development. Mean and error bars represent the distribution of multiple scientific advancements and technological breakthroughs for any given category.

expected development of consumer-grade diagnostic devices for smartphones (Ozcan 2014), which could be the "killer applications" equivalent to spreadsheets and word processing in computing. Biotic digital games could also be disseminated through cloud laboratories (Fig. 3E,G). Note that much of this home-computer revolution was also driven by "edutainment", parental expectations of the educational benefits of emerging computer technology and the desire of children to play computer games; ultimately, both parties got what they wished for (Mertens 2006, Ito 2012); hence biotic games could be an economic driver for medical technology (Riedel-Kruse et al. 2011).

The same way electronic video games have significantly evolved and many game genres have emerged (many of which lacked counterparts in the pre-electronic age), we can also speculate about the future genres of biotic games. Here are a few developments and genres that we expect to encounter in the coming years: (1) Many existing game genres (electronic and others) will be "ported over" and adapted to the HBI space. This porting is exemplified by a paramecium-based soccer game or the cricket based *PacMan* (Fig. 3C,D). (2) All game functions, including scoring, will be physically implemented at the microscopic scale, i.e., digital overlays are not needed. For example, could cells self-arrange to produce text that relays game instructions to the player on screen? (3) Genetically modified organisms will be designed and incorporated, up to the point that organisms are made ("programmed") for a particular game. Optogenetics (Deisseroth 2011) in particular provides powerful ways to manipulate, stimulate, and suppress biological reactions, and would integrate well with light-based spatiotemporal control. (4) Games will utilize directed evolution, which would allow players evolve, synthesize, and culture specimens with specific properties and towards real-world applications (Packer et al. 2015). Note that cloud lab technology (Hossain et al. 2015) can physically contain and separate organisms of concern while still enabling interactions.

VIII) DISCUSSION

We believe that the following key technological features are within reach and will greatly facilitate the wide availability of HBI-based platforms to game designers and players: (1) Plug-and-play robustness of the platform components. Despite the reliance on variable

biological components, the system should be as reliable and user friendly (for the designer and the player) as a conventional computer, (2) A big design space, which allows for open exploration. (3) An affordable consumer product, self-assembly kit, or cloud-based lab that has a low entry barrier regarding cost and expertise. (4) Visual and other intrinsic appeal that makes the games stand out from their electronic counterparts. (5) Entertaining games will provide value for education and research. Current systems as discussed (Figs. 2, 3A,B) begin to reach these goals. The current hardware (electronics, camera, optics) of such a system (Fig. 2C) could be priced for a consumer mass-market product that is far cheaper than the first home computers in today's prices (Lowood 2009). Multiple educational applications and dissemination possibilities via self-builder kits, cloud labs, and museum exhibits have been successfully demonstrated (Fig. 3).

As the technologies mentioned above are becoming readily available, game designers, artists, citizen scientists, and others can now get involved with HBI in the following four ways: (1) The simplest starting point for new contributors may be simulations of biological systems. These simulations are not HBI in the strictest sense but provide a good starting point for game prototyping. (2) For interactive experiments, Euglena and light stimuli are well suited for beginners (Figs. 2, 3A,B). (3) Engaging with existing academic or commercial cloud-based labs for biology experimentation (Fig. 3E,G) (Hossain, et al. 2015) may provide a robust platform, but considerations should be given to cost, experimental turn-around time, overall limitations to experimental throughput, and how versatile the design space is. We expect that these systems and the underlying technologies will continue to become more accessible. (4) The highest level of complexity is the development of new instruments and organisms (i.e. new BPUs, Figs. 5 and 6). Good control over and expertise with a particular biological system, as existing in many life-science labs, constitutes an important foundation for exploration. It would therefore be advantageous for bioengineers and game designers to team up.

IX) CONCLUSION

We have provided an overview of existing projects that integrate biological materials with electronic game play, and we summarized a number design rules for such systems. We conclude that systems based on single-celled microorganisms integrated within BPUs provide strong advantages over other designs in terms of the game design and experience, cost, throughput, biosafety, and ethical considerations. Some designs are very accessible to DIY enthusiasts and inexpensive, thus rendering them suitable to initial explorations, while other setups allow more versatile interactions with the biological world. After drawing analogies from the history of digital video games, we expect this new field to mature technologically and from a consumer' perspective within the next 5-10 years. After a transition phase with digital-biological hybrids, also games with pure biological interactions should become available. Overall, we envision that digital biotic games will connect players from distinct strata of society and with differing levels of scientific fluency with the microscopic biological world and biotechnology, which increasingly impacts our daily lives in many ways and on many scales.

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