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BioSim—a biomedical character-based problem solving environment

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Abstract

Understanding and solving biomedical problems requires insight into the complex interactions between the components of biomedical systems by domain and non-domain experts. This is challenging because of the enormous amount of data and knowledge in this domain. Therefore, non-traditional educational tools have been developed such as a biological storytelling system, animations of biomedical processes and concepts, and interactive virtual laboratories. The next-generation problem solving tools need to be more interactive to include users with any background, while remaining sufficiently flexible to target open research problems at any level of abstraction, from the conformational changes of a protein to the interaction of the various biochemical pathways in our body. Here, we present an interactive and visual problem solving environment for the biomedical domain. We designed a biological world model, in which users can explore biological interactions by role-playing "characters" such as cells and molecules or as an observer in a "shielded vessel", both with the option of networked collaboration between simultaneous users. The system architecture of these "characters" contains four main components: (1) bio-behavior is modeled using cellular automata; (2) bio-morphing uses vision-based shape tracking techniques to learn from recordings of real biological dynamics; (3) bio-sensing is based on molecular principles of recognition to identify objects, environmental conditions and progression in a process; (4) bio-dynamics implements mathematical models of cell growth and fluid-dynamic properties of biological solutions. The principles are implemented in a simple world model of the human vascular system and a biomedical problem that involves an infection by Neisseria meningitides where the biological characters are white and red blood cells and Neisseria cells. Our case studies show that the problem solving environment can inspire user's strategic, creative and innovative thinking.

Keywords: Scientific visualization; Biological discovery; Game design; Problem solving; Artificial life; Education

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1. Introduction

Rapid advances in the convergence of Nanotechnology, Biotechnology, Information Technology, and Cognitive Science (NBIC) are believed to have the potential to result in a "comprehensive understanding of the structure and behavior of matter from the nanoscale up to the most complex system" [1]. In biomedicine, high-throughput methodology now allows the accumulation of unprecedented amounts of scientific data, such as genome sequences, gene expression profiles, structural and functional proteomic data. These advances have stirred great hopes for understanding and curing diseases, but the quantity of data demands convergence with information technology to interpret and utilize these data to advance human performance and quality of life [1]. This requires an understanding of the complex interactions between the components of biomedical systems by both domain and non-domain experts. This is particularly challenging in the biomedical domain because of the massive data and knowledge accumulation. Facilitating convergence of NBIC technologies therefore requires a novel problem solving environment (PSE) for the biomedical domain.

A biomedical PSE should be a computer system that provides all the computational facilities needed to immerse into a biomedical problem. It should hide the intricacies of computer modeling of physical phenomena so that the user can concentrate on developing an approach to cure a disease for example. The PSE has to be scientifically accurate and include access to the state-of-the-art in available data, knowledge and technology without requiring the user to bring domain expertise and extensive experience with the technical intricacies of the PSE that would present the user with tiresome activation barriers. Novel approaches are being developed, for example a storytelling system has been presented to fertilize multidisciplinary biomedical problem solving [2]. Furthermore, modern biomedical education makes extensive use of visualization of biomedical processes and concepts, for example the publication of the human genome sequence was accompanied by a CD-ROM that presented genome background as well as DNA sequencing techniques in animations [3]. However, these visualization tools are mostly designed to complement traditional teaching techniques and are not very interactive. More interaction is provided in the "Virtual Cell", a virtual environment in which question-based assignments are given to users in a simulated laboratory [4]. A submarine is launched that immerses the user in the virtual environment of the cell populated by sub-cellular components which the user can investigate. With a toolbox, various cellular processes can be investigated experimentally. The results of these investigations and experimentations allow users to solve the assignments at their own pace and through their own motivation. It was shown that this approach significantly improves authentic learning, in particular for large enrollment general biology classes [5]. At the other end of the spectrum, realistic, fully interactive virtual laboratories have been developed to simulate chemical [6], biomedical [7] and recently nanoscience [8] laboratory experiments. However, in their present form, these systems were not designed to be integrated PSEs because they are targeted to students and researchers for solving very specific problems and therefore contain a large amount of domain specific information. Inexperienced users will not have sufficient insight needed for discovery and solving problems. Insight, i.e. the capability to make non-obvious connections between the complex interactions of the components of these systems, is the main requirement for solving biomedical problems [9]. Such insightful solutions can often be found in an interactive and visual PSE, as demonstrated for example by the fact that despite the modern numerical computing technologies, biophysicists today still use Gedanken experiments for concept development [10]. Although there are many virtual reality 3D molecular models available, biochemists still use hand-made models for intuitive reasoning. It is striking that simple intuitive simulation is still one of the most powerful approaches to creative problem solving.

Since the early days of artificial intelligence, issues of modeling scientific reasoning and its representation, in particular for those connected with everyday knowledge of the behavior of the physical world, have been studied [11]. At least two aspects have been explored: multiple representation and qualitative reasoning. Computation with Multiple Representations (CaMeRa) is a model that simulates human problem solving with multiple representations, including pictures and words [12]. CaMeRa combines a parallel network, used to process the low-level pictorial information, with rule-based processes in higher-level pictorial and verbal reasoning. Furthermore, many AI systems

have been developed to simulate the cognition about physical and biological knowledge. What will happen if we spill a glass of milk on the floor? For humans, the answer is common sense, but understanding this process is non-trivial for computers. To arrive at an exact solution, the computer has to solve a set of non-linear partial differential equations of hydrodynamics that are computationally intractable even for simple boundary conditions [13]. A few studies have focused on the qualitative simulation of physical phenomena. Thus, Gardin uses 2D diagrams to represent physical objects and their interaction [14] and Forbus uses the fuzzy language of "qualitative physics" to model the physical variables [15]. Lower-resolution qualitative models have made significant impact in many fields, including biology. A typical example is the Game of Life, a "Cellular Automaton" [16]. A cellular automaton is an array of identically programmed automata, or "cells", which interact with one another. The state of each cell changes from one generation to the next depending on the state of its immediate neighbors. By building appropriate rules, complex behavior can be simulated, ranging from the motion of fluids to outbreaks of starfish on a coral reef. Even if the line of cells starts with a random arrangement of states, the rules force patterns to emerge in life-like behavior. Empirical studies by Wolfram [17] and others show that even the simple linear automata behave in ways reminiscent of complex biological systems. In light of this discovery, we intend to use simple biological characters to generate dynamic interactions.

Creative problem solving environments have been studied mainly in the management science area. Most recent studies focus on collaborative creativity, stimulus culture, and information flow. For example, "brainstorming" has been viewed as a panacea in corporations since IDEO has promoted the methodology [18]. John Kao's "Jamming" theory [19] uses a jazz jam session as a metaphor to address how to motivate employees at work. Steven Eppinger's Design Information Matrix [20] focuses on representing information flows rather than task flows. According to Constructionism, people do not simply "get an idea"; they construct it. Within the framework of the recently developed "Idea Flow" theory to address the dynamics of creative problem solving [21], it was shown that the bidirectional idea flow is the most efficient interaction pattern in innovation. Feedback can enhance the flow both in terms of effectiveness and efficiency. Multiphysics simulation and knowledge-based innovation heuristics build the bridge between the innovative idea and reality, which will eventually change the landscape of scientific discovery. Open source, open system architecture and virtual communities bring idea flows from the outside. This is the trend of contemporary scientific discovery and system design that not only creates just a product but an inspiration for interaction.

Here we present a computer game as a novel environment for biological problem solving, where it provides a real-time interactive platform for users. The goal of this study is to develop a game-based PSE for users to explore multi-modal interactions inside a biological system. It includes essential biological simulation models for the immune system and the blood system. It allows users to manipulate and to participate in the interactions among the components of the system. The biological characters are simulated by software agents.

2. Prototype

As a test bed for the development of a game-based PSE for biomedical science, we designed a scientific problem that is derived from our ongoing research projects. By applying computational language technologies to the large amounts of whole genome sequence data publicly available, we have identified "genome signatures" that may provide novel approaches to the development of vaccines against pathogenic microorganisms such as Neisseria [22]. The biomedical problem to be explored here is to find treatment for fatal meningitis. In this context, computer scientists without biological background need to understand the basics of the immune system, the blood transport system, recognition of bacteria in the body, and possibilities to fight an infection. Furthermore, the dynamics of an infection need to be understood, in addition to the effectiveness and potential drawbacks of administering antibiotics. Within each of the above topics, there are a multitude of details to know, for example in the blood transport system, the difference between active and passive transport, the points of entry/exit into the tissue, relative dimensions and numbers of different cell types. Insight into all of these aspects that would be required to begin developing a solution against

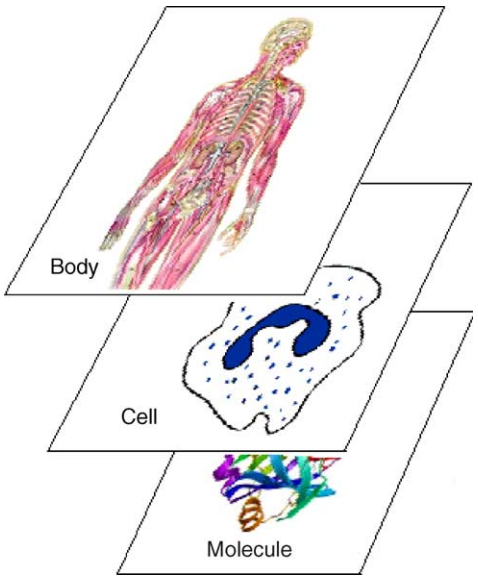

Fig. 1. System hierarchy: the prototype of BioSim involves three levels of hierarchy (see text).

Neisseria infection would require teaching the fundamentals of immunology, anatomy, physiology, microbiology, pharmacology and biochemistry. Thus, traditional teaching tools would offer a high activation barrier. The new idea for the biomedical PSE is to develop an interactive interface modeled after traditional game engines that teaches users without background in biology the understanding of this research problem ranging in hierarchy from atomic to macroscopic scales (Fig. 1). In this hierarchy, the macroscopic level is that of infection of a human body with Neisseria. Fighting the infection requires a molecular level understanding of the processes involved. The goal is to provide the user with the necessary insight to creatively generate and test possible approaches to solving this problem using the PSE.

BioSim version 1.0 is a rapid prototype for this PSE. It is a two-stage game that simulates the journey of red blood cells and white blood cells (macrophages). The goal is to introduce the basic concepts of cellular interaction and the human immune system. The game begins with an animated scene of a blood stream with red and white cells moving passively with the heartbeat. Using a mouse and the arrow keys, the player can take the role of a biological character, for example a macrophage, and navigate inside the blood stream. The game scenario consists of Neisseria cells dividing in the tissue at a certain speed. The macrophages can move actively or passively as specified by the user through the bloodstream and need to find and "squeeze through" the points of exit into the tissue which is only possible at the capillaries. Macrophages can then actively move towards Neisseria and "eat" them. Screen shots of these processes are shown in Fig. 2.

BioSim 1.0 is implemented on PC. Photorealistic 3D models of components of the system were created with 3D Studio Max and exported to Game Studio 3D (an example is shown in Fig. 3). The 3D Modeler of GameStudio 3D was used to create the game scenes, bio-morphed characters and the integration of the world/character dynamics and interactions. C-script, a C-style language, was used to encode the bio-dynamics and bio-sensing behaviors. Game Studio is run under the Windows operation system. It provides capability for either single user or multiple users across the Internet.

2.1. Biological "world model"

In game design, "world models" are similar to the theatre stage or film scene with which actors and characters interact. A world model is often static and large in size. In this project, we developed a comprehensive world model that includes the vascular system with artery, veins and capillaries, as well as tissues (Fig. 2A and B). In this world, the user can fly, walk or run through as one of the biological characters (Fig. 2C and D). In the prototype BioSim 1.0, we have developed two scenes: inside and outside of the capillary. The transition of the scenes is possible by "squeezing" a character actively from the blood stream to the tissue in the capillary regions.

2.2. Biological characters

We have defined the following 3D animated characters that simulate biological behavior: bacteria, macrophages, and red blood cells. To define interactions among characters and between the characters and the world model, we use collision detection (Section 2.4.3). For the stand-alone characters, we apply bio-morphing to assign key frames to them (Section 2.4.2). Bio-morphing is accomplished by digitizing deformed shapes from microscopic images of organisms,

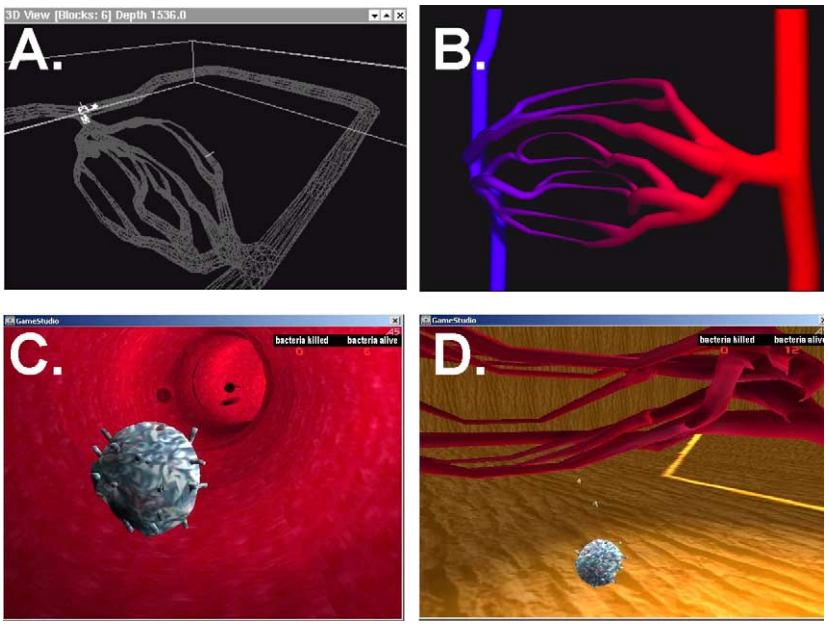

Fig. 2. World model and biological characters implemented in the game. (A) Wireframe model of the vascular system world model; (B) 3D photorealistic model showing arteries and capillaries; (C) the macrophage (white blood cell) is inside the blood stream with red blood cells; (D) after actively moving out of the blood stream, the macrophage approaches bacteria that infected human body tissue.

building wire frames (Fig. 3) and attaching texture and color skins.

2.3. System architecture

The PSE contains three interaction modes: role-play, voyage and networked problem solving.

2.3.1. Role-play

The system allows the user to be a biological character in the game. Cognition Science shows that role-play is an important way to stimulate creative ideas. It enables the user to have an intimate connection to the character. Also, personalization of a biological character makes a game more interactive.

2.3.2. Voyage

The user can navigate through the biological system in the game, either as a character, or using a 'ship', supporting different view angles, e.g. traveling through capillaries and tissues. Voyage allows exploration at the user's chosen leisure, accommodating users with various backgrounds.

2.3.3. Distributed problem solving

The game engine allows users to play the game over the Internet so that large problems can be solved collaboratively or antagonistically, e.g. some users can play macrophages and others can play bacteria. The distributed problem solving enables diverse game strategies and more excitement of the game. The user can also choose between two aims, rather than playing the role of a single biological component only. The user can assume the roles of multiple biological characters, thus studying their individual influence on a particular aim. These aims are to induce an infection with Neisseria and ensure its successful propagation in the human body or to fight the Neisseria infection.

2.4. Biological character library

A biological character is defined as an entity that includes functions, forms, behaviors and interfaces. For example, some of the functions of a macrophage are to locate and destroy bacteria (see below), while the function of a bacterium is to divide and spread. A given character has a sequence of forms in correspondence to its dynamic behaviors. An interface

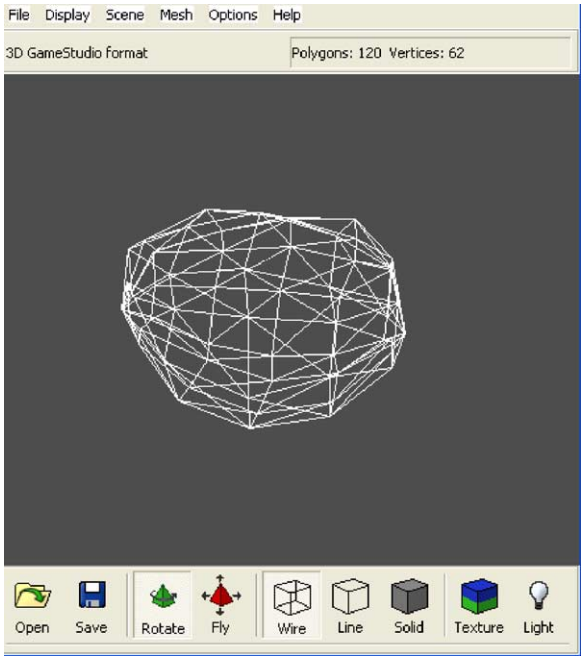

Fig. 3. 3D modeling of biological characters. A wireframe is constructed using sufficient numbers of polygons to allow realistic biomorphing of characters, here a bacterium.

to interact with other entities or the environment is designed.

Example macrophage:

- Functions: locate bacteria | destroy bacteria.
- Behaviors: walk | eat | shrink | kill | die.
- Forms (key-frame sequences): moving | search | squeeze | killing | death.
- Interfaces: collision | chemotaxis (sensing) | tactile (sensing).

The principles describing behaviors, forms and interfaces that are common to all characters are described below.

2.4.1. Behavior

Interaction is the key to computer games, and we believe also to an efficient biomedical PSE. We therefore allow the user to control the behavior of biological characters by realistic and scientifically accurate biointeractions. The transitions of each character are represented by a state machine (Fig. 4A). For example a macrophage's states include the transitions to deform, shrink, eat, walk and die. Each behavior is defined by a set of forms (see Section 2.4.2). We simulate biological processes and character behavior ("bio-dynamics") realistically. For each character, we define its interactive modes, such as motion, reproduction and death. Taking bacteria for example, we use the following rules (Fig. 4B):

Autonomous motion. Given a fixed duration, each bacterium moves a distance x at angle y, where x and y are random values. The distance should not exceed the maximal distance.

Reproduction. Given a predefined duration, each bacterium reproduces a copy of its own which is placed beside its original position. The *Logistic growth model* [23] adequately describes the reproduction process of simple organisms over limited time periods by Eq. (1), where M is the carrying capacity of the population B at time n with growth rate r:

$$B_{n+1} = B_n + rB_n\left(1 - \frac{B_n}{M}\right). \tag{1}$$

Death. If a bacterium's life cycle is over or if other cells eat it, it is removed from the scene.

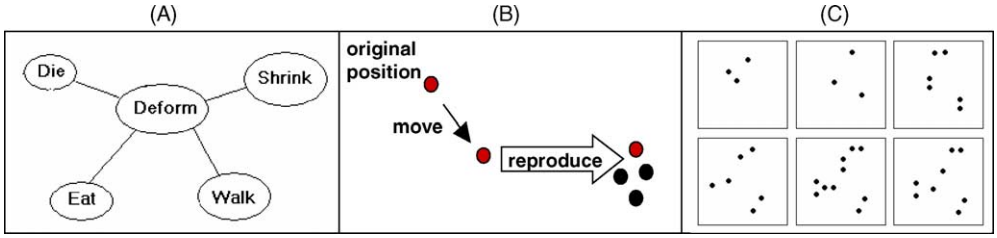

Fig. 4. Examples for character dynamics. (A) State machine for a macrophage; (B) dynamics of an organism modeled by Cellular Automata; (C) example for the time-evolution of bacterial growth and spatial distribution.

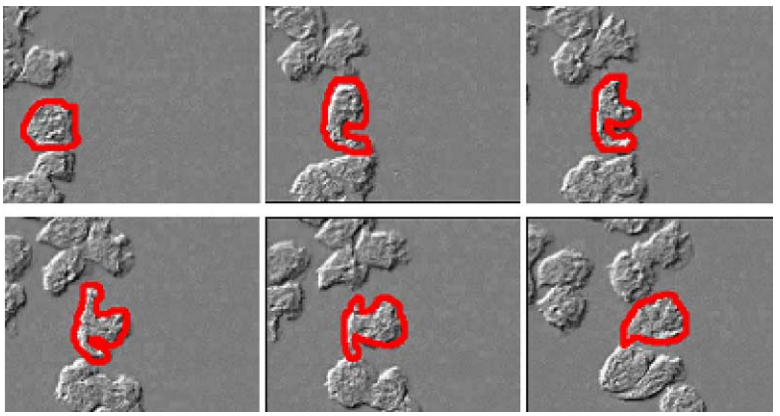

Fig. 5. Realistic and automatic generation of changes in the cellular forms. Cellular images from time-resolved microscopy studies [27] are analyzed using active contour modeling [24] and 3D models are generated.

2.4.2. Form: shape tracking and bio-morphing

To give users precise control and accurate feel of a character's movements, vivid animation sequences are generated for each character. Our approach is to use computer vision-based shape tracking methods to automatically detect the changes in contours of moving cells from microscopy studies. We use active contour tracking models [24], also called snakes, since they are more robust in noisy background typical for biological images than traditional edge detection methods. Active Contour Modeling provides a general algorithm for matching a deformable model to an image by means of energy minimization. The energy function is a weighted combination of internal and external forces. The active contour is defined parametrically as $\mathbf{v}(s) = [x(s), y(s)]$, where $x(s)$, $y(s)$ are x, y coordinates and $s \in [0,1]$. The energy function is

$$E_{\text{snake}} = \int_0^1 E_{\text{snake}}(\mathbf{v}(s))\,\mathrm{d}s = \int_0^1 \{[E_{\text{int}}(\mathbf{v}(s))] + [E_{\text{image}}(\mathbf{v}(s))] + [E_{\text{con}}(\mathbf{v}(s))]\}\,\mathrm{d}s \quad (2)$$

where E_{int} represents the internal energy of the spline due to bending, E_{image} the image forces, and E_{con} the external constraint forces. Usually, $\mathbf{v}(s)$ is approximated as a spline to ensure desirable properties of continuity. Fig. 5 shows an example, the moving patterns of a macrophage. The macrophage area is cropped using the active contour model. Based on the outline frames, we build a 3D model for a character using polygones (as shown in Fig. 3 for a bacterium).

2.4.3. Interface

We have implemented three types of interfaces: collision detection, chemotaxis sensing and tactile control. Collision detection describes how two objects behave when they collide. Chemotaxis sensing describes how an organism senses environmental stimuli. For

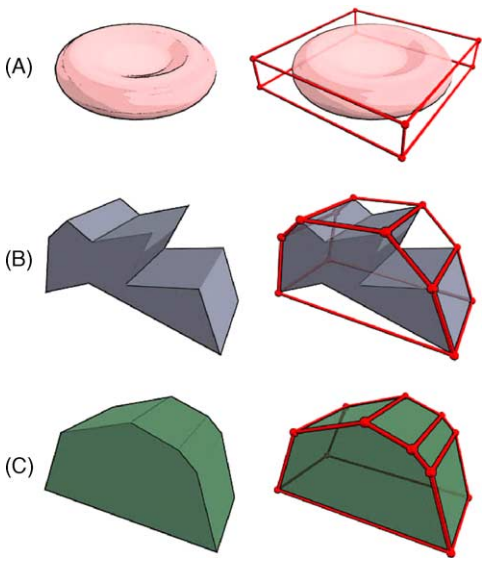

Fig. 6. Collision detection. (A) Boxes surround objects when coarse resolution is sufficient. Polygons are used for higher resolution, but objects may not be concave (B), but must be convex (C).

example, white blood cells can “smell” bacteria and move toward them by chemotaxis. Tactile control adds physical properties to the object. For example, an object can be very ‘sticky’ to the mouse movement, or the object can be very heavy so that the user has to click the left button a few times before its movement happens.

Collision detection is implemented based on the resolution required as a balance between speed and accuracy (Fig. 6): coarse collision detection using boxes is implemented when red blood cells passively move through the blood stream. Tight collision detection using polygons is used when high resolution is necessary, for example during the interaction between bacteria and macrophages. The 3D game studio currently only supports convex map entities. Concave objects (objects that have indents) must be converted to convex map entities. This is challenging in constructing the world model.

To simulate *sensing capabilities*, we define a circular envelope around the character as a sensing region. When the target is inside the region, the character will move towards the target and engage in interactions with it. To enable more complex means of interaction with the biological world, each user is equipped with a ‘ship’ that allows for effective captivation by the environment (Fig. 7, upper left). The ‘ship’ provides a means of transportation (*Voyage*) and action (*Role Playing*). Each activity is determined by availability of “energy points”, which have to be carefully balanced to minimize consumption and maximize effectiveness. The user knows the status of energy points via a control panel, which also provides for the various possibilities

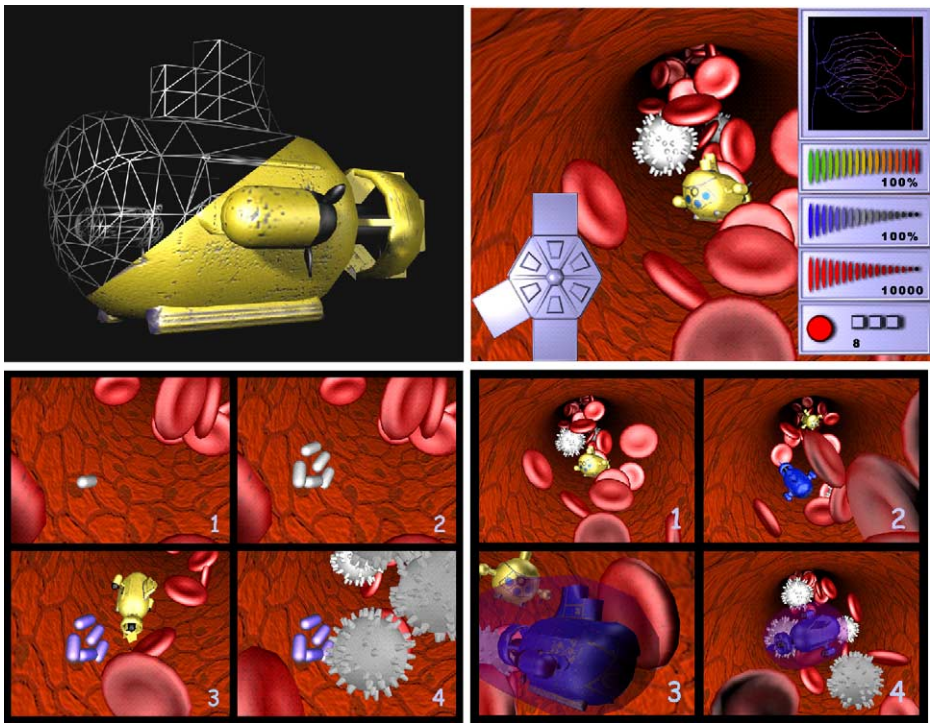

Fig. 7. Captivation of the user by the PSE. A ship provides transportation through the body (upper left). A control panel inside the ship has sensing and action capabilities (upper right). Marking of bacteria with histamines (lower left). Bacteria that have not been marked can divide undisturbed (1, 2). When the ship approaches the bacteria (3), the histamine sensor identifies the bacterial infection and the user can mark them (in the game this is indicated by a change in color). After marking, the user can attract macrophages that will “eat” the bacteria (4). In future implementations of the game, internet connectivity will allow multiple users to participate in collaboration or as antagonists in a single game. Since ships are not-self, the human immune system would identify them as such. Therefore, one ship can mark another ship using immune system tools, i.e. antibodies (lower right). This is represented by the halo of one of the ships. Once labeled with antibodies, the user can again direct macrophages to “eat” this ship.

of action (Fig. 7, upper right). For example, in a state of high energy, the user can afford to travel actively with the ship to a point of infection. However, in a state of low energy, the user would choose to travel passively with the blood stream. This will allow the user to further develop decision-making skills in a biological PSE. In the future, there will also be additional bio-sensing capabilities available through the control panel, for example a histamine sensor (Fig. 7, lower left) and mechanisms of the immune system to distinguish self from non-self (Fig. 7, lower right). This will allow introduction of molecular level information, for example the user will need to use molecular docking of the immune system's antibody structures to those of the bacterial surface structures. This will train users to view protein structures and understand the mechanisms of complementarities of two structures. The player seeking to evade the immune system would need to develop strategies to evade antibody marking, e.g. through surface mutation. Thinking about possible strategies from each point of view will allow the user to gain deep insight into the factors controlling the health of the organism, from the molecular to the macroscopic level, ultimately aiding in the development of novel solutions for biomedical problems such as the Neisseria infection.

3. Problem solving with BioSim

3.1. Supporting strategic thinking in users

We conducted experiments in the effectiveness of the game to raise an awareness of the important issues in biomedical research on users with no background. The ideal group at this stage of implementation of the game is young children, for two reasons. One, children are unbiased and without background. Second, children learn optimally when the material to be learned is presented to them in an accurate way to avoid the build-up of incorrect models by implicit learning [25]. Implicit learning of correct biomedical concepts by children therefore requires the same fundamental issue of scientific accuracy as other users will require once the game reaches the stage of providing a PSE for users with any background. We tested BioSim 1.0 on 14 children at KinderCare, Cranberry, PA, on 9 August 2002 and 25 February 2003. We let 4- and 5-year-old children play with the game on a laptop and focused our attention on strategic aspects and active questioning.

Two strategies were quantified, the speed of macrophage movement towards the bacteria (Fig. 8, left) and the use of antibiotics in aiding the killing of the bacteria (Fig. 8, right). All children learnt quickly to shift from fast pace chasing to slow pace chasing so that their capture rate was improved. We then tested a more challenging concept, that of usage of antibiotics to aid the killing of the bacteria. We included the ability of bacteria to develop resistance in our growth model. Thus, the children had to discover that antibiotics at some stage in the game no longer inhibit bacterial growth. This was only observed by a single 5-year-old, all other children kept on administering antibiotics despite energy consumption and lack of effect (Fig. 8, right). These types of quantitative assessment of strategic behavior of users open novel ways to analyze learning of problem solving skills

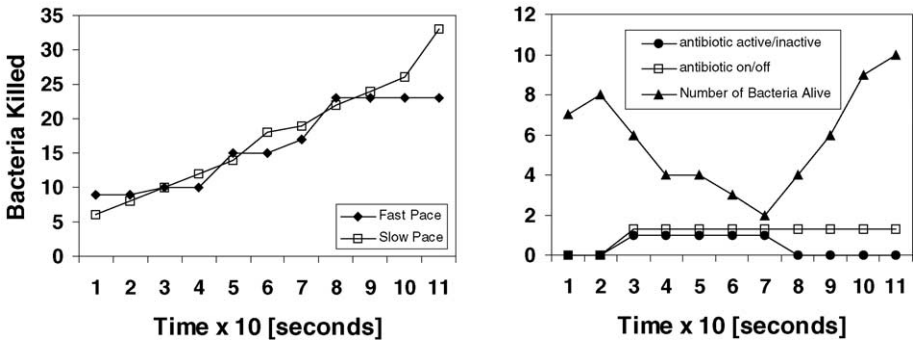

Fig. 8. Strategies against bacterial infection that can be explored in the game, speed of macrophage movement (left) and use of antibiotics (right). The fast pace strategy often leads to missing targets. The slow pace strategy gains steady capture rate. The use of antibiotics can be limited by gradual development of bacterial resistance. At that point, administration of drug does not inhibit bacterial growth.

Table 1
Comparison of the reactions of two groups of children to the game

Observation	4-Year-old	5-Year-old
Asked relevant questions	0	4
Controlled the game successfully	2	5
Described bacterial growth behavior	1	5
Described macrophage behavior	2	6

The children in the first group were 4 years old, those in the other were 5 years old. Each group consisted of 7 children, and the total number of children tested was 14.

that would not be possible with conventional teaching methods.

3.2. Supporting creative thinking in users

To assess learning in children, we asked questions such as "How does the macrophage get out of the capillary?" or "How do you kill bacteria?" The children used intuitive metaphors, for example the analogy of "vacuum" and "crash into" to describe how the macrophage attacks bacteria. This shows that the players are very sensitive to the intimate design details of the game, which opens a window for game developers to *encode* very subtle knowledge about complex biological interactions. Finally, we tested the game-induced stimulation of questioning and creative thinking in the children. The results are summarized in Table 1. The 5-year-old children asked several meaningful questions, for example: "Are bacteria germs?", "Where do the white cells go?", "What's a red cell?", "Where do the bacteria live?", "Is the macrophage good or bad?". Overall, 4-year-old children asked fewer questions, and most of their questions were not relevant, for example, "Do you have other games?", "I don't want my head eaten off". These observations suggest that there may be a turning point between ages 4 and 5 where a PSE can become effective. Studying

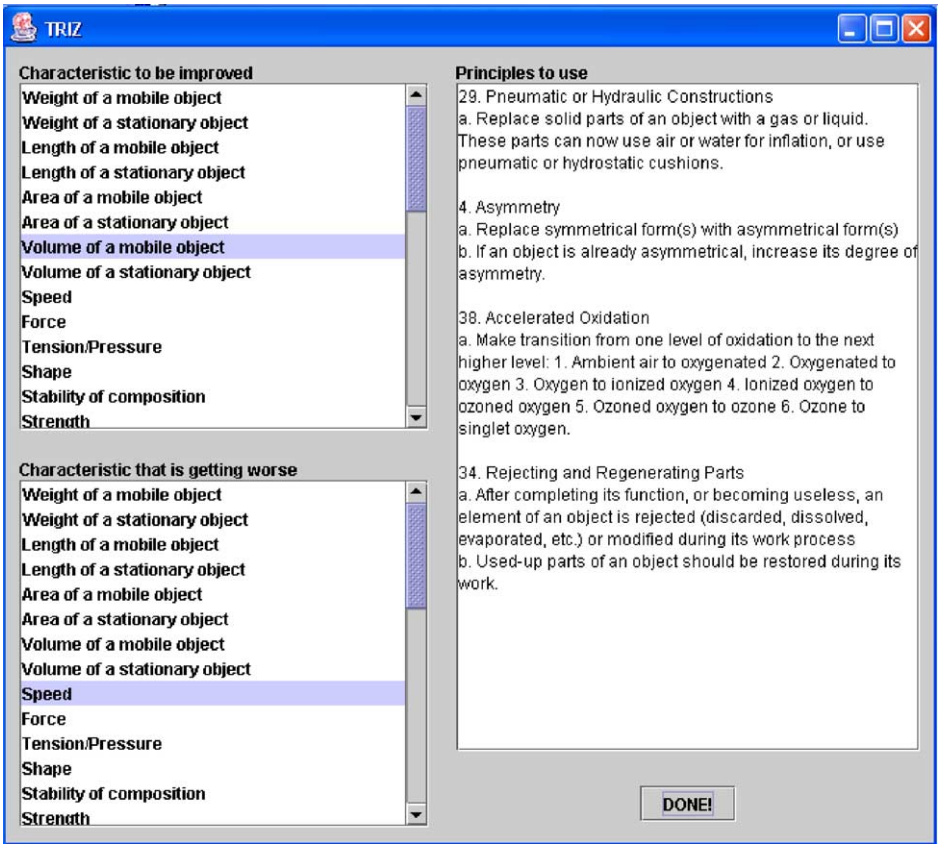

Fig. 9. Contradiction matrix for assisting problem solving using TRIZ [26].

these reactions to BioSim in more detail with a larger number of children of varying ages is a major future goal.

3.3. Supporting innovative problem solving

Encouraged by the results on stimulating active thinking in the users, we are now in the process of integrating BioSim with the TRIZ model (the acronym for "inventive problem solving" in Russian) to prepare for the next step, the use of BioSim for innovative problem solving (Fig. 9). TRIZ was originally developed by Altshuller [26] based on the hypothesis that innovation in a particular field can benefit from the general innovation experience from other areas through problem-solution analogy, and there are ways to extract these innovation principles. Over 2 million patents were examined, classified by level of inventiveness, and analyzed to look for principles of physical problem solving. We have implemented Altshuller's Contradiction Matrix in an external utility in Java. The matrix catalogues the parameters on the *X*- and *Y*-axes:

- *X*[1–39] = [weight of a mobile object | energy spent by a moving object. . .].
- *Y*[1–39] = [speed | force | temperature | shape | pressure. . .].

The matrix's cells (1521 except diagonal) contain principles which should be considered for simultaneous optimization of parameters. For example, to improve the intersection volume (the 7th parameter) versus energy spent (the 19th parameter) of a moving object refer to the principal number 12 (Equipotential), 18 (Vibration), and 31 (Porous Materials) as appropriate concepts to build up solutions. Currently, these principles are limited to the physics domain, and we are planning to expand the knowledge base to the biomedical domain.

4. Summary

Future biomedical problem solving is beyond traditional means because of the existing challenges in cross-disciplinary communication and interpretation and utilization of vast quantities of available biomedical data. We want to build a virtual PSE that combines advanced computer graphics, computer vision, artificial intelligence technologies and creative instruction technologies. In this PSE, cross-disciplinary education will be on-demand, entertaining and interactive. This will allow focus on discovery and creativity rather than one-way tutoring. Towards this long-term goal, here, we have presented a game-based PSE, where users can explore complex biological interactions with navigation, role-play, and networked collaboration. The study investigates the system architecture of the biological game, bio-morphing characters, and bio-interactions with bio-sensing and bio-dynamics. The game is based on realistic biological models, such as logistic growth models of simple organism reproduction and immigration models of cell movements. The prototype has been implemented on PC and tested in a preschool environment where users have little knowledge in biology. The experiment shows that the game greatly inspires users both in concept learning and entertainment. It supports strategic and creative thinking, as well as innovative problem solving.

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