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Interactive Media in Training and Therapeutic Intervention

Editors:
Brenda K. Wiederhold, PhD, MBA, BCIA
Giuseppe Riva, PhD, MS, MA
Alex H. Bullinger, MD, MBA

Interactive Media Institute

Immune Attack: Building Biologically Based Immune System Simulations for Education and Training

K. Howell, B.A., MBA

Federation of American Scientists, Washington, DC

Abstract: *A growing literature suggests that simulation, visualization and gaming can play an important role in deepening understanding of difficult concepts in mathematics, engineering, and science. Learning sciences research suggests that learning by doing with understanding produces better transfer than mere doing alone.[1,2] Challenge-based simulations can provide students opportunities to receive feedback and revise their thinking, a critical part of the learning process.[3,4] Immune Attack is a simulation game to teach biological concepts related to immunology and wound infection, allowing the student to explore the internal compartments and cells of the human body and visualize immunological processes. Simulations of biological functions at a variety of levels, from subcellular to organ systems, that are easily navigable by instructors and students with a range of backgrounds will provide a rich exploratory environment for learning immunology.*

BACKGROUND

Immune Attack is a simulation game to teach biological concepts related to immunology and wound infection, allowing the student to explore the internal compartments and cells of the human body and visualize immunological processes, including pathology. The game combines three-dimensional visualizations of biological structure and function with advanced educational technologies to provide an introduction to basic concepts in immunology for high school students. *Immune Attack* is intended to be as fun and compelling as the computer games currently played by many adolescents and young adults. Students are motivated with a series of progressively more difficult challenges in a gaming environment in which success depends on increasingly sophisticated grasp of concepts in immunology. The learning experiences are individualized by use of context-sensitive help and dialogues and continuous assessment techniques to determine when the learner is ready to move to a new level. The project is funded by a National Science Foundation Information Technology Research grant.

The goal of this research is to test the hypothesis that visualization of, and immersion in realistic depictions of human biology will be highly engaging to high school students and hold their interest long enough for learning to occur. Advances in cognitive science point to new strategies for increasing the productivity and depth of learning if the learner is continuously given challenges whose solution depends on mastering the material.[2] The game-based simulations that are integral to the gameplay will let learners apply their knowledge immediately in an attempt to defeat a variety of diseases, from simple infections to more challenging infections. The student's success in designing an immune strategy capable of overcoming an array of infectious agents will provide a much richer measure of understanding than standardized tests. Learning is further enhanced if the students are so motivated to meet the challenges that they are eager to ask questions that can help them – and if they are able to get timely, accurate answers tailored to the student and the context of the question.[5]

METHOD/TOOLS

The biological models for the game were developed working closely with prominent immunology researchers and educators. Experienced video game developers are developing the game and assisting in integrating the learning tools. The learning objectives and instructional strategies are being developed in consultation with biology teachers, at both the high school

LEARNING OBJECTIVES	GAME DESIGN/PLAY
General	
The student will comprehend the basic strategies of major pathogens	Simple rules govern the stylized but accurate behaviors of a variety of bacteria, viruses, and toxins.
The student will be able to identify and understand role of key components of the immune system including innate responses, inflammatory responses, and secondary response systems	The player must master the rules that govern the behavior of macrophages, neutrophils, mast cells, NK cells, T and B cells and will be able to guide these cells by following key signals, such as proteins.
The student will have knowledge of how the immune systems and its component results clinical symptoms	Pop up tutorials, a health status bar, and visualizations of the patient provide clinical information to alert the player as to the patient's physiologic condition and introduce medical terminology.
The student will be knowledge about defects in the immune system	Allergies, autoimmune disease, AIDS are included to show the how the disease progression changes in individuals with compromised immune systems.

Table 1. Example Learning Objectives

and college freshmen levels, and with learning research scientists.

Development of valid educational content coupled with simulations of biological components and their processes and interactions is a key component of the project. We have worked closely with leading immunologists and the teachers participating in the evaluation of the game to develop an instructional plan for the game based on introductory curricula, including immunology content, determination of educational objectives, strategy for integration of learning tools into the game, and evaluation of the game. Particular emphasis was placed on determination of appropriate levels of content for the target audience. A sample of the learning objectives is shown in Table 1.

A major challenge of the project was to define the learning content so that it would be easily accessible and understandable both by the biologists who need to ensure that it is correct and the software engineers who will need to instantiate it in code. One of the great challenges in developing reusable software objects is that they are often so difficult to understand that it is easier to build from scratch rather than risk misinterpreting often sparse instructions about how to use legacy objects. We have developed formalisms that minimize the difference between the question "how does this object operate?" and the question "how does the biological system work?" While the details of the implementation may be captured in complex equations, the vocabulary, rules represented, and terms used to describe inputs and outputs are all easily understandable in biological terms.

Our formalism is based on the Universal Modeling Language (UML).[6] UML tools were used to build a formal map of knowledge about the immune system that includes named variables and formal relationships (that should be covered by the ontology), information about rules and equations describing behavior, clear English descriptions of what is being represented available through some kind of introspection, the referenced source of the information encapsulated, and mechanisms for maintaining version control. The structures extend the structures of the ontology to ensure consistent inheritance of both fields and functions. For example, a component representing the essential elements of a cell can be extended to represent a generic leukocyte that can in turn be extended to represent a generic lymphocyte and then a specific B cell. Such structures provide a seamless connection between ontologies and the framework of software objects. It provides a way to ensure that functionality and updated data at the root of an object tree are accurately propagated.

The central challenge of the game is to teach rules to a set of players that represent all the

important elements of the immune system (e.g., macrophages, neutrophils, dendritic cells, T, B, and NK, etc.) These rules will operate the software objects representing the cell types. As rules are turned on, more complex phenomena will be exposed. A key part of the educational game is understanding the way the characters (cell types) pass messages to each other interact.

The levels of the game involve an ability to address different attack strategies. The gameplay starts with a simple infection that can be mastered with the innate immune system. Progressively more sophisticated viruses and bacteria require mastery of more sophisticated strategies and understanding how to use an increasing number of immune cells. See Table 2 for a sample of the levels. The core challenge and excitement of the game will is being presented with a novel class of infection or a known infection agent at a new site. Each will simulate the progression of an actual disease – which can be as simple as a simple skin infection or as complex as AIDS or TB. At an early stage, for example, a player may be confronted by a simple skin infection that can be addressed by using macrophages and the innate immune response. The key issue is telling friend from foe. As a player becomes increasingly comfortable with play at this level, a new pathogen is introduced that multiplies so fast that the macrophages are overwhelmed. A new strategy must be developed to send signals recruiting help – say from neutrophils. This means understanding the signaling and the combined behaviors of the senders and receivers of the signal. As the player becomes comfortable managing an array of diseases at this level, she is confronted with infectious agents that operate from within friendly cells such as viral attacks. This requires determining a strategy for detecting the invasion and recruiting specialized help from specialized T cells. The player must find ways to send messengers (e.g., dendritic cells) to lymph nodes that may be distant from the infection. Simulations capable of supporting this kind of game play must be able to operate at many different levels and at many scales.

At each level the student can elect to get a briefing on the material or elect to discover the material by experimentation. Help is available at all times through the game's artificial intelligence and from teachers and peers.

EVALUATION

The game will be used to supplement immunology taught as a part of biology courses given to high school students and will be evaluated in high school biology classes. The project will be evaluated based on the degree to which it successfully addresses the research challenges identified above. These challenges center on three main questions:

Game Play Levels (partial list)	
LEVEL 1:	**Innate Immunity-1**
The student will be able to analyze the concept of how immune cells recognize 'self' peptides versus 'non-self' peptides	The challenge is to train macrophages by selecting receptors that identify pathogens and then choose functions that help to destroy the pathogens
LEVEL 2:	**Innate Immunity-2**
The student will understand how cytokines and other proteins that can recruit neutrophils to the infection site	The challenge is to train macrophages to release the appropriate signaling proteins and train neutrophils in the blood stream to recognize the signal and behave appropriately
LEVEL 3:	**Adaptive-1**
The student will understand how dendritic cells become active and carry signals to recruit T8 cells in lymph nodes	To succeed, the player must train a dendritic cell and guide interaction with T to generate clonal expansion by locating, then matching the receptor to the ligand
LEVEL 4:	**Additional levels of sophistication**

Table 2. Game Play Levels

- Has the project developed biologically correct, visually compelling simulations of the immune system that can be easily navigated by people without specialized technical proficiency?
- Do the simulations effectively incorporate state-of-the-art open architectures and interoperability frameworks that will both facilitate revisions and augmentations for a variety of purposes and encourage use of simulation components in the work of others?
- Can the simulations be used in conjunction with existing instructional tools to develop a prototype instructional system that incorporates a variety of assessment, feedback, and augmentation tools?

For the first two research challenges, assessments will be conducted through workshops that are planned annually for each year of the project. A panel of experts will be convened as part of the workshops to assess the biological accuracy of the simulations at various stages of design and development and the interoperability frameworks. The panel will consist of biologists, immunologists, computational biologists, and medical professionals. The evaluation plan for the instructional game will be developed with advice by the Education Advisory Panel. The evaluation will focus on four key questions:

1. Does use of the instructional game improve the performance of students on tests now given by instructors in applicable courses?
2. Does the system improve understanding in areas of immunology that are particularly difficult to master?
3. Does the system increase student interest in science and their interest in a career in science?
4. Does the effect of 1-3 depend significantly on sex, ethnicity, or other characteristics of the learners?

NOVELTY/DISCUSSION

Computer games hold special interest to a generation who has grown up with them, and as such, they show promise as educational tools. Whether this is due to the inherent challenge built into game play, the richness of graphics presented to the user, the opportunity to interact with other users (in web-based games), the story or context in which the game is couched, or some other feature is an important part of this research project. Exploiting the inherent motivational aspects of games and simulations for education and training must be based on a sound understanding of which features of these systems are important for learning and why.

The instructional game will be used to supplement immunology taught as a part of introductory biology courses given to high school students. The research will provide the basis for building engaging simulations that teachers can use to convey subtle concepts in the immune system and infection control. It should improve biology education by presenting educational materials in a way that is engaging and useful to people with a variety of interests and backgrounds. A student motivated to learn the complexities of the immune system can also have the basis for understanding a wide range of biological concepts. The interest generated by the game could encourage students from many different backgrounds to enter a scientific or medical profession. While the initial target audience will be senior high school and first-year college students, we expect that the system will facilitate learning for a broad class of learners, including the many professionals that need to master elementary concepts in infection and infection control – such as people who now must be trained to deal with potential biological attacks. The research will result in tools that can assist people to improve their own health care by presenting difficult concepts in ways that a typical patient can understand. It is also likely to help research specialists get a clear, visual understanding of the way their research specialties fit into the extravagantly complex network of operations that combine to make the immune system.

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Contact

H. Kay Howell, B.A., MBA
Federation of American Scientists
1717 K. St., NW
Suite 209
Washington, DC 20036
Ph: 202.454.4685 Fax: 202.6751010
khowell@fas.org