

Immune Attack Game Building Biological Simulations for Education

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Immune Attack – an instructional tool to teach immunology

■ *Goals:*

- ❑ Teach immunology concepts, using biologically correct simulations and “characters”
- ❑ Demonstrate players of the game are more engaged in the subject; more positive attitude towards science

■ *Target audience:* senior high school students

■ *Collaborators:*

- ❑ Federation of American Scientists: learning content, including oversight of Ed Adv Panel; game design and development; implementation and evaluation of the game
- ❑ Brown University: Andries van Dam (PI) graphics R&D related to how to handle deformable objects; visualize cell signaling
- ❑ Adv. Panel: immunologists, learning scientists, biology teachers, students

■ *Funding:* National Science Foundation Information Technology Research Grant --\$1.3M, over 3 years

Immune Attack Overview

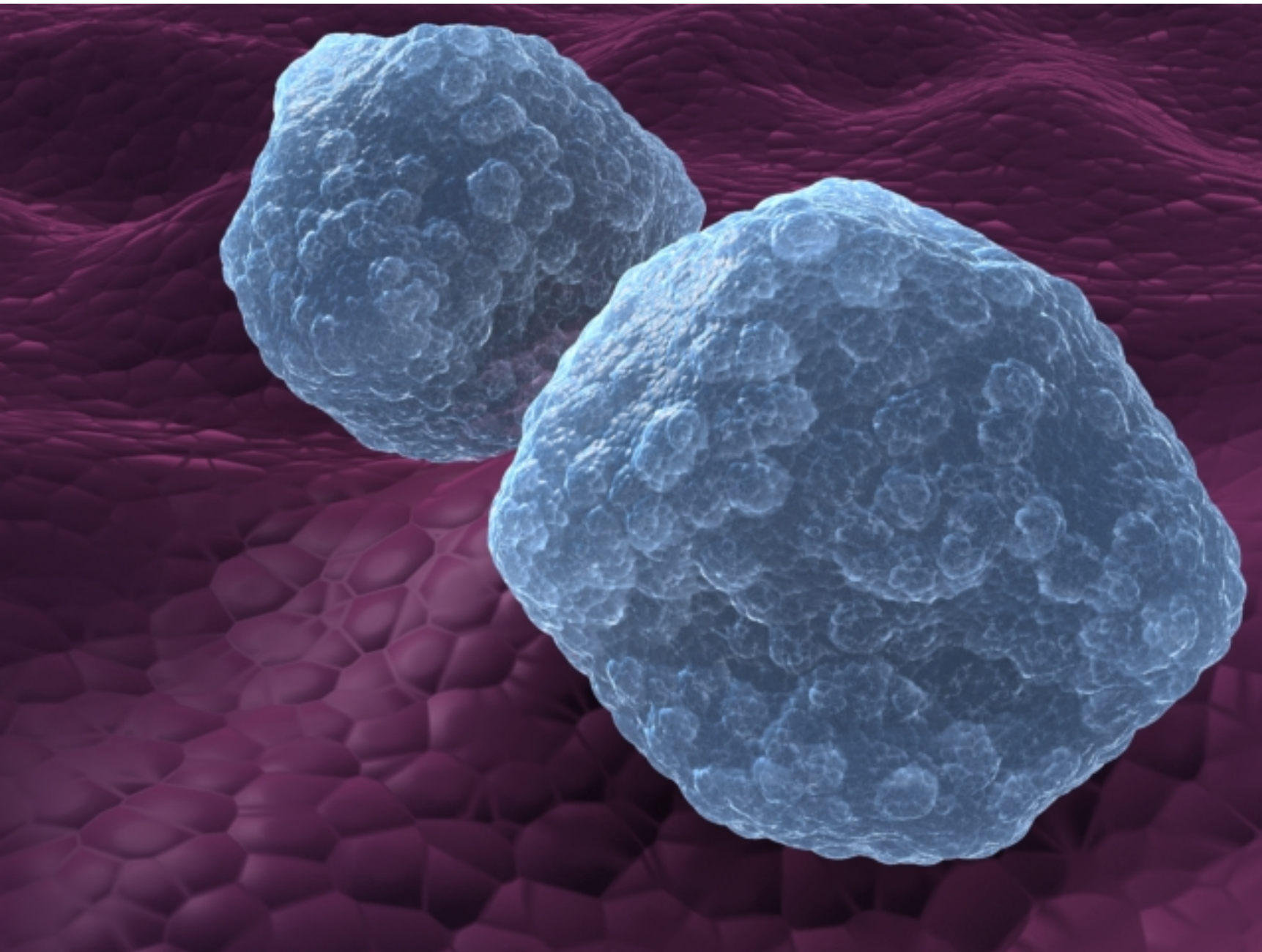


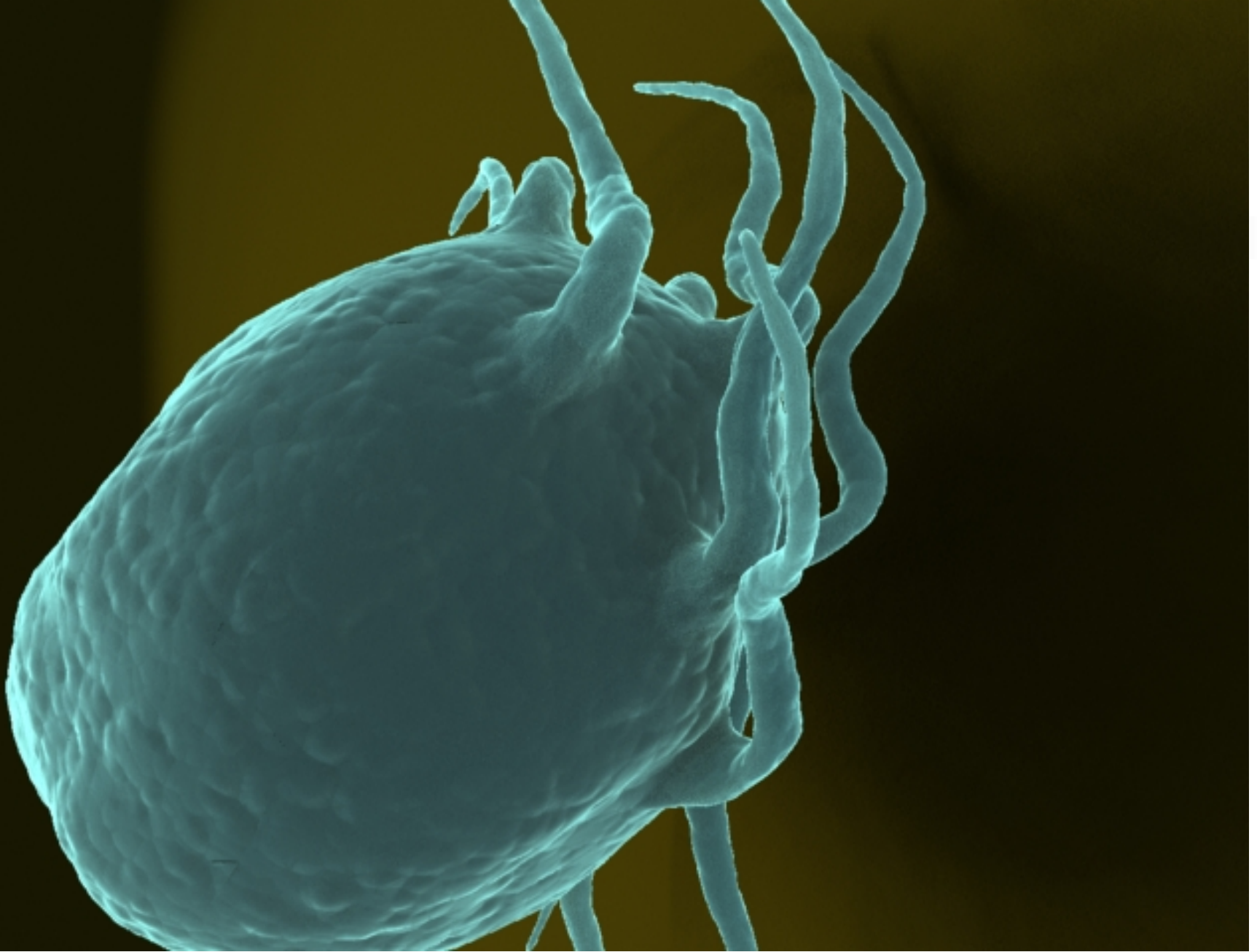
- 18 months to build and test game
- Evaluation begins March 2006, at 2 high schools and 2 computer technology centers
- Game development by team of commercial game developers, under contract to FAS
- Game engine: Ogre
- PC and X-box versions

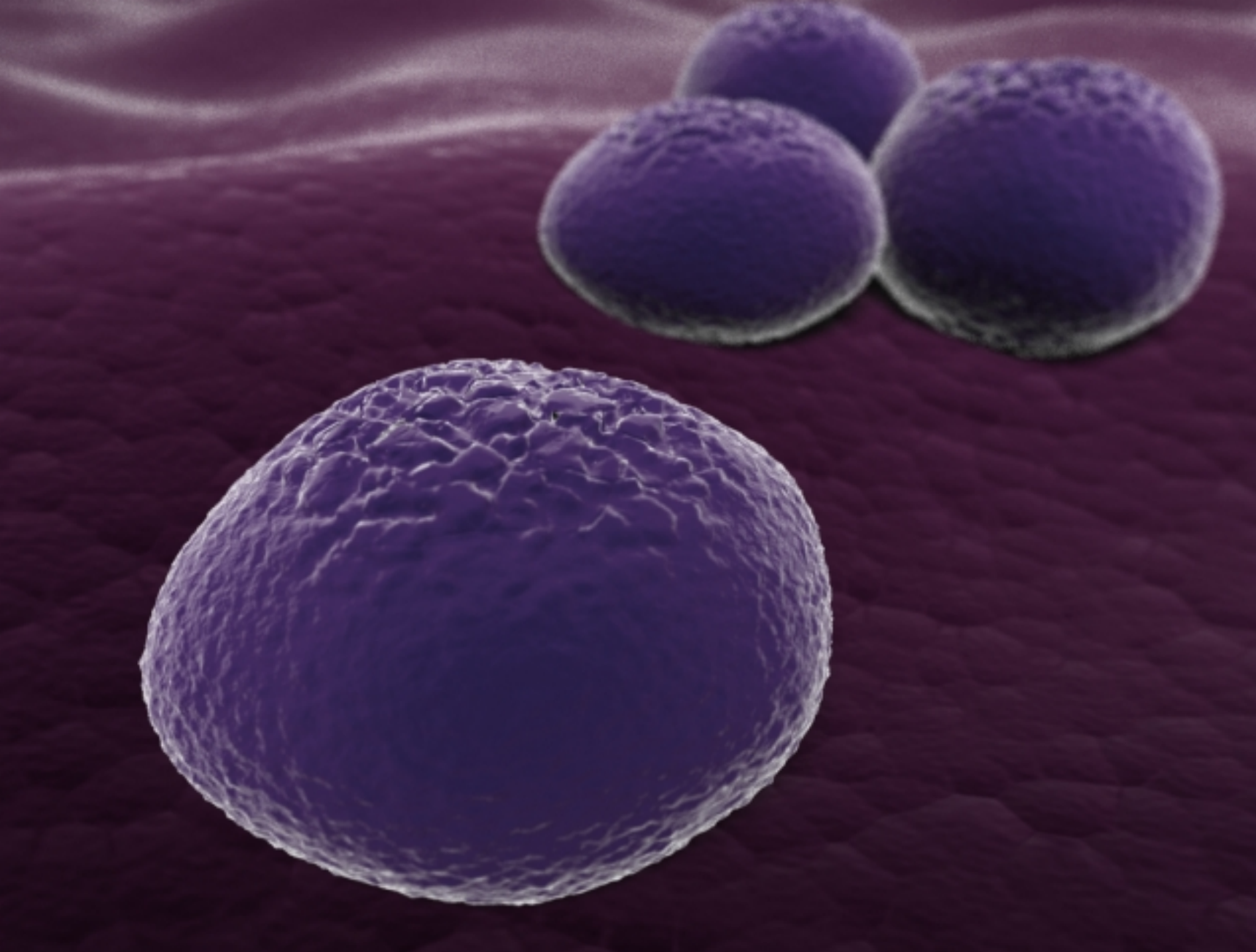
Game Features



- Immersive physical environments, representing different landscapes, including skin wounds, lymph infections and GI infections
- Interoperable cells & environments, allowing students to piece together individual cells, cell groups, cell surface constituents & organ systems
- Cellular detail and simulations, including photorealistic 3D textures and accurate polygonal models of different cell types, both friend (e.g., lymphocytes) and foe (e.g., bacteria, viruses)
- AI, based on actual cell behaviors, enhanced for real-time game play and interaction
- Real-time help, Question & Answering, Coaching & Debriefing







Immune Attack - *an instructional tool to teach immunology*

Learning Objectives

- Describe how immune cells recognize 'self' peptides versus 'non-self' peptides
- Comprehend the different stages of cell development such as maturation and activation.
- Identify and apply the chemical compounds that are used to defeat certain pathogens.

Game Play Strategy

- The challenge is to train macrophages by selecting receptors that will identify pathogens and then choose functions that will help to destroy the pathogens
- As monocytes enter tissues they will develop into dendritic cells and macrophages, and as T cells encounter antigens they become activated to proliferate. As phagocytic cells encounter stimuli they become activated.

Immune Attack - learning objectives & play strategy

Learning Objectives

- Identify and understand the different areas of the lymph node and where and how the lymphocytes interact with the antigen presenting cells
- Comprehend and apply the mechanism of processing and presenting pathogens to generate a secondary immune response
- Understand and synthesize how cells of the immune system, microbes, and other relevant cells in the body interact

Game Play Strategy

- The player can navigate a selected cell type through the lymph node to locate the relevant helper cells
- The player will take control of a macrophage or dendritic cell, and guide interaction with T and B cells to generate clonal expansion by locating, then matching the receptor to the ligand
- At this level the player will manipulate the cells to work together to defeat the pathogen. The pathogen will be at an advanced stage and therefore can manipulate or take over a cell and rapidly multiply in the host cells

Immune Attack Game Play

The screenshot displays the 'Immune Attack' game interface. The central 3D environment shows a large, spiky, yellowish-green macrophage engulfing numerous small, green, rod-shaped bacteria. The background is a reddish-brown, textured surface representing tissue.

Dialogue Box (Top Left):

player: Why are the macrophages getting sick after they eat the bacteria?

expert: We need some additional information before that question can be answered. What species of bacteria are you dealing with?

player: Well, I think it's yersinia pestis. Is that a very dangerous one?

DATA BANK (Top Right):

- Hints
- Library
- Maps
- Memory
- Save Game
- Evaluation

Left Panel (Navigation):

- Hand icon with a crosshair (navigator)
- Hand icon with a red mark (bacteria)
- Five small images in a vertical stack: a spiky cell, a cluster of red cells, a single red cell, a green rod-shaped bacterium, and a blue cell.

Bottom Panel (Player Status):

- Temp:** 36
- Vit:** 20
- ATP:** 31
- WBC:** 36
- RBC:** 20
- Antibod:** 31
- ECG:** A line graph showing heart rate.
- Resources:** A bar chart showing resource levels.
- WARNING:** A red text box indicating a low resource level.
- Time:** 18:30 hours
- Location:** Arizona desert
- Event:** Bacteria encounter
- Genus:** Yersinia
- Player:** Joshua
- Level:** 2.4
- Investigation:** current
- Contact:** Epidemiologist
- connection to Xbox:** off

Immune Attack Game Play

- You succeed if you're able to tell the dangerous cells from your own cells and are able to train your agents to mount an effective attack before the invading forces multiply and overwhelm you
- You'll need to figure out how to operate each major part of your arsenal including macrophages, neutrophils, dendritic cells, T and B cells, each following biologically correct behavior
- When you've taken over a particular piece of your arsenal, such as a neutrophil, you have to program the rules to build your immune system
- Nearly all the winning strategies require cooperative operation of different units. For example, if you train your macrophages to send a coded call for help when they're being overwhelmed, you also need to program neutrophils to listen for the code and act appropriately when they get it

Levels of Play (7 are planned)

	Disease	Symptoms	What's going wrong	Winning Strategy
1	Salmonellosis (can be benign or very serious depending on point of entry/bacterial load)	<i>Salmonella enteritis</i> bacteria cause abdominal pain, vomiting, diarrhea leading to death by dehydration and intestinal bleeding if untreated	The bad guys are multiplying faster than bunnies	Macrophage recognizes and follows the trace of the bacteria, identifies the code on its surface, and envelops it in a vacuole.
2	Staph infection (can be benign or very serious depending on point of entry/bacterial load)	<i>Staphylococcus Aureus</i> bacteria if introduced into a skin can cause pain at infection site that can lead to massive tissue damage and deadly toxin production	Macrophages overwhelmed by rapid multiplication of the bacteria	Macrophage exercise strategy in step 1 but also release a signal that attracts neutrophils to the scene. Neutrophils must be trained to find the infection site, escape the blood vessel, follow the trail to the infection site, and kill.
3	Chicken Pox Shingles	<i>Varicella zoster</i> virus enters and destroys cells in the lung and eventually all parts of the body including skin (pox).	Bad guys are hiding inside friendly cells and many are therefore invisible to the macrophages and neutrophils	Dendritic cells attack external virus and present body fragments on their surface. Go active, set sail for lymph nodes. Navigate lymph nodes to find and activate a CD8. Inactive CD8 cells go active after reading code on the dendritic cells. Multiply like crazy and shoot out. Must recognize the two independent indicators of a friendly cell that's been invaded (MHC and coded target) and proceed to attack.

Game Strategy

- Recognize good guys from bad guys
- Give the good guys the assets they need (receptors)
- Program rules that tell the good guys what to do
- Each rule is created by selecting a detector (receptor) and connecting it to an action

IF {receptor A is activated} THEN {take an action}

- Rules are programmed via a PDA-like interface
- Whenever the rule is programmed, the receptors appear as icons all over the surface of the macrophage

Level 1 Programming Rules

Rules needed to win at Level 1

If {the monocyte's LFA-1 receptor is activated} then
 {the monocyte squeezes between the cells of the
 blood vessel}

If {receptor for histamine/complement is activated =
 C3a} then {move to where the cloud gets denser =
 follow gradient}

If {receptor + C3b is activated} then {eat/phagocytize
 the cell with the C3b decoration}

You can tell that you're winning when the macrophages start
 converging on the infection site and start chomping up the
 bacteria

kh4

Level 1 will be repeated with several different kinds of infectious agents requiring using LPS receptors, Mannose Receptors and Glucan receptors as appropriate. The player should discover that using the C3b receptor alone will not lead to an energetic response and therefore may not act fast enough to kill off infecting bacteria faster than they multiply. Specialized receptors such as LPS will greatly accelerate the process by making the macrophages more active.

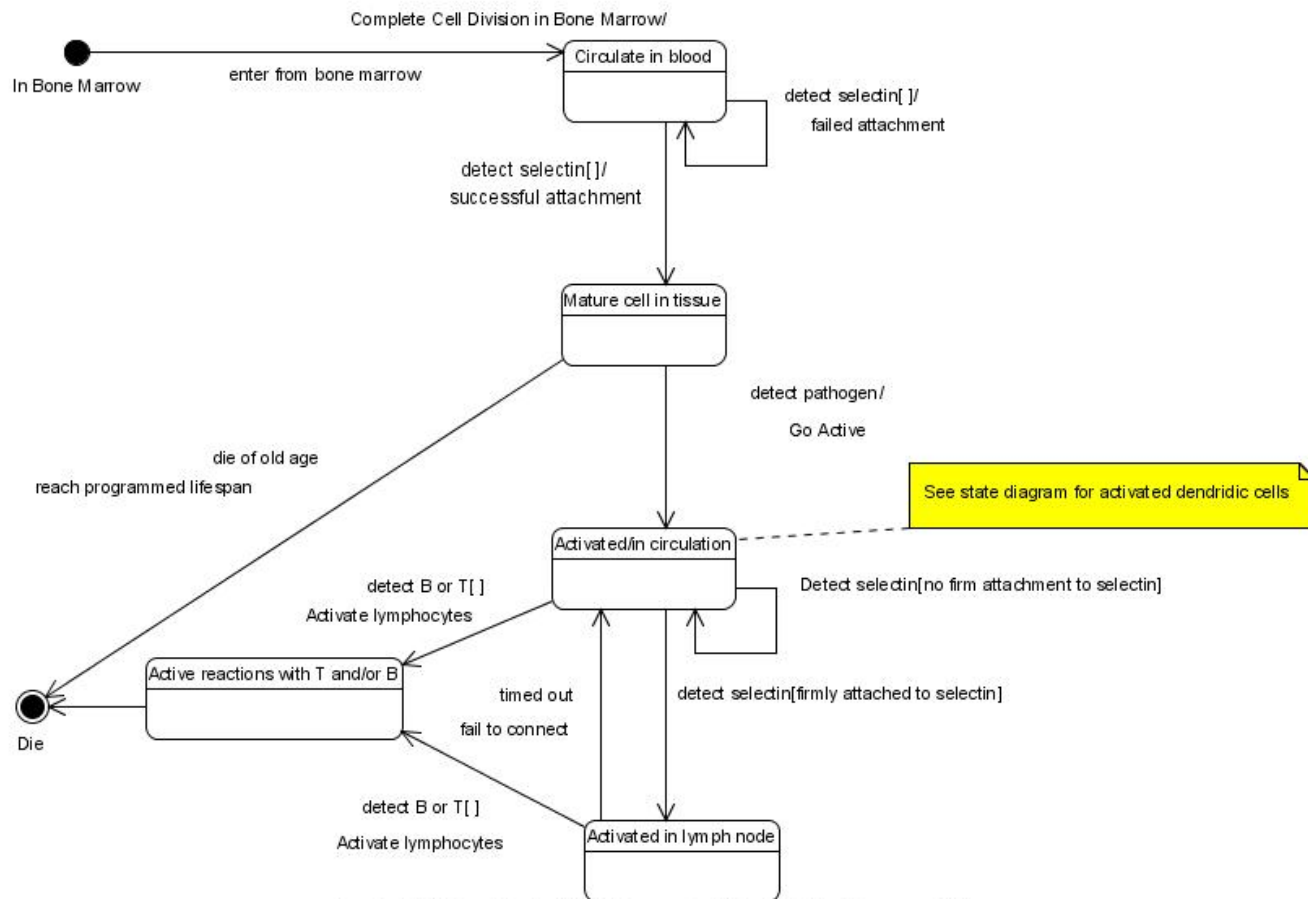
Kay Howell, 6/8/2005

Building an Educational Game is *HARD*

Just a partial list of *Immune Attack* challenges:

- Getting immunologists to define the "rules" of the game
- Getting game developers to understand the importance of "technically accurate"
- Translating language between gamer developers and immunologists
- Speed at which field of immunology adds knowledge
- Convincing teachers to make time to use the game as part of their course; spend time to provide advice to the project; take time out of classroom time for evaluations
- Convincing teachers that students can master complex information
- Complexities of scale and time for the simulations
- Visualization challenges

A Common Language: Unified Modeling Language



Created with Poseidon for UML Community Edition. Not for Commercial Use.

Visualization Challenges

- Need to represent the dimension of time as well as 3D space
- The biological processes are often enormously complex - the simplest signaling process may involve a dozen steps in which proteins and other structures react and diffuse
- The number of elements involved can be huge and many important phenomena depend on the combined effect of large numbers of processes:
 - A single T-cell in the immune system can have 5-10,000 similar receptors that look for chemical signals in the environment
 - These receptors detect chemical signals in the environment - very subtle gradients in the chemicals in their environment and direct movement to or away from the direction of the gradient
- The scale of important elements varies over many orders of magnitude from simple ions, amino acids that could be 0.2 to 1nm to immune cells that could be several orders of magnitude larger in size
- The reaction rates of different active antibodies can vary broadly

Hard Problem #5: Matching

- When an alarm is spread from a site of infection, specialized messenger cells carry pieces of the invader to the lymph nodes and try to find a specialized immune cell which matches the pattern
- The lymph nodes have a series of elaborate chambers stuffed with tens of thousands of specialist cells. The messenger cell needs to grope all of them to try to find a match and, on failing, move on
- In more complicated cases two different kinds of cells must be activated and must find each other (a two key system)

Challenge: *How to represent the “groping”? There are 10^5 to 10^6 different kinds of specialists; or there may not be any at all - how to reduce the problem scale to one that’s suitable for an interactive game?*

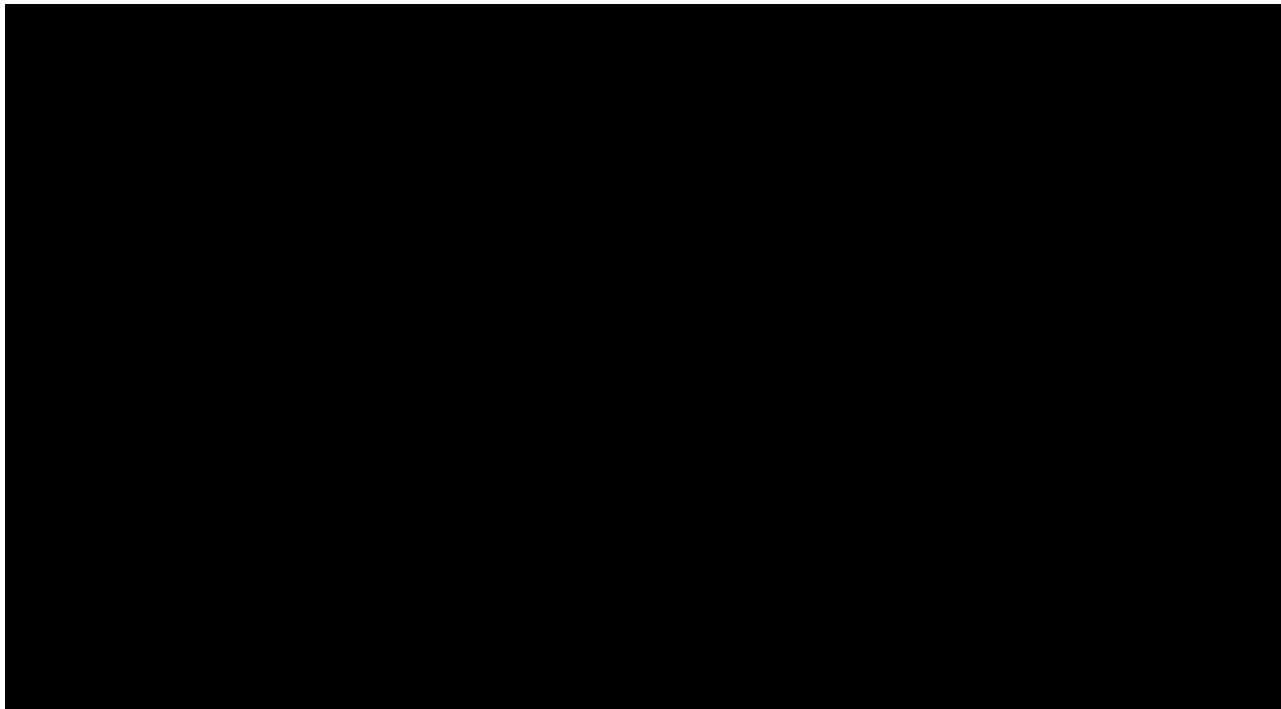
Game Play

- Tension mounts as attacks become increasingly life threatening - as soon as you feel confident that you've got a team that can resist any assault you get hit by something really nasty
- You may have to recruit an entirely new set of allies to manage the attack and develop new strategies for familiar players. You may find that the enemy has taken the battle to places you've never visited - let alone fought in: the tissue in the inner eye; the stomach wall; the strange and wonderful caverns of the lymph nodes; the electrically charged synapses of the brain
- You'll get hit by botulism, toxoplasmosis, TB and other infections. By the end of the game you will have built the most exotic and powerful defense system ever discovered - one prepared to take on any and all attacks -

well almost all

The human body awaits...

Early Animation



Contact Information



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