ENISI Visual, an agent-based simulator for modeling gut immunity

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***Abstract*— This paper presents ENISI Visual, an agent-based simulator for modeling gut immunity to enteric pathogens. Gastrointestinal systems are important for intaking food and other nutritions and gut immunity is an important part of human immune system. ENISI Visual provides quality visualizations and users can control initial cell concentrations and the simulation speed, take snapshots, and record videos. The cells are represented with different icons and the icons change colors as their states change. Users can observe real-time immune responses, including cell recruitment, cytokine and chemokine secretion and dissipation, random or chemotactic movement, cell-cell interactions, and state changes. The case study clearly shows that users can use ENISI Visual to develop models and run novel and insightful *in silico* experiments.**

I. Introduction

The gastrointestinal system of vertebrates includes mouth, esophagus, stomach and intestines. The Gastrointestinal system digest food into nutrients and provide energy and the building blocks required for growth and maintenance of homeostasis. Gut immunity plays an important role in protecting the gastrointestinal system and the whole body from the invasion of gastroenteric pathogens such as *Helicobacter pylori*, *Escherichia coli*, and *Clostridium difficile*.The gut immune system accounts for about 70% of the human immune systems.

ENISI, developed by MIEP, is an agent-based simulator for modeling and simulating gastrointestinal (GI) infections caused by immune responses to invading microbe [10], including commensal bacteria and pathogens. To our best knowledge, ENISI is the first agent-based simulator dedicated for gut immunity. Generally, agent-based models are more complex than equation-based models, requiring highly on computational resources. The implementation of ENISI was based upon high-performance computing [2] and it scaled up to 10^8 cells.

This paper presents ENISI Visual, a single machine version of ENISI with quality visualizations. ENISI Visual, adapted from our HPC version of ENISI [2], is implemented based upon Repast Symphony [9], a popular platform for agent-based modeling.

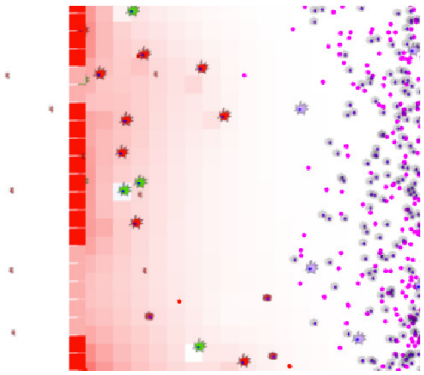

Fig. 1. ENISI Visual simulating gut immunity: compartments, bacteria, epithelial cells, immune cells, cytokine, chemokine, and immune cell recruitment.

ENISI Visual provides quality visualizations for simulating gut immunity to enteric pathogens and is capable of simulating gut immunity, including pathogen invasion, pro-inflammatory immune responses, pathogen elimination, regulatory immune responses, and restoring homeostasis. Users can build their own models using ENISI Visual. ENISI Visual provides rich graphic user interfaces. Users can control initial cell concentrations, simulation speed, data and graphic outputs. Users can take snapshots and record videos of the simulations. ENISI Visual also simulates the secreting and diffusing of cytokines and chemokines. Each grid has a value indicating the concentrations of cytokines or chemokine and the background colors of grids changes as the values change. The visualizations can help modelers to test,

978-1-4673-2560-8/12/$31.00 ©2012 IEEE

verify, and tune their models. The visualizations can also help immunologists to test novel hypotheses and design their biological experiments accordingly. Figure 1 provides a snapshot of ENISI Visual simulations.

The remaining of this paper is organized as follows. We first review the literature and then present the simulator. After that we show a case study with simulation results demonstrating its capabilities of novel insights and discoveries. At the end, we conclude the paper.

II. Related Work

Generally there are two categories of modeling technologies in computational biology. The first is equation-based modeling, EBM, such as ordinary-differential equation or ODE-based modeling. EBM has many nice properties, including smaller set of parameters, less computational complexity, and high capability of parameter estimations. The Systems Biology Markup Language, SBML, [6] has good support for ODE-based models and COmplex PAthway SImulator (COPASI) [5] is a popular and user friendly tool for ODE based modeling. However, EBM is not easy to represent individual behaviors and locations such as the mucosal immune system of the gut. The second category is agent-based modeling, ABM. ABM represents each individual of the simulated entities as an agent, or typically an object in software implementations. ABM can better model individual entities and their interactions. Based upon simple rules of individual interactions, ABM can simulate extremely complex system behaviors, which usually requires high performance computing and does not have effective ways for parameter estimations. This paper focuses on ABM based immune modeling and simulations.

Macal et al. [7] published a tutorial on ABM including model design and implementations. For ABM of immunity, Bauer et al. [1] surveyed several ABM systems for host-pathogen responses. Efroni et al. [3] discussed the importance of animation and user interfaces in simulating reactive and complex systems.

ENISI Visual is built upon Repast Symphony [9], an open source agent-based modeling and simulation platform. It is implemented in Java language and is highly portable. We have successfully run ENISI Visual simulations on Windows, MAC, and Linux machines. To our best knowledge, ENISI is the first Agent-based modeling simulator for gut immunity. ENISI HPC implementations [2] [10] have been published previously by our team. This paper focuses on ENISI Visual that provides high quality user interfaces and animations that are very helpful for developing models and performing *in silico* experiments of complex systems. BIS [4] is the simulator closest to ENISI Visual in implementations. However, it is not targeted for gut immunity. Mogilner et al. [8] classified models using two criteria: focused or broad, conceptual or mechanistic. In this paper, we use ENISI Visual to develop a model that is broad, in the sense that it can be used to model gut immune responses to different pathogens as well as immune responses to immune-mediated and allergic diseases, and conceptual, in the sense that it can give you qualitative insights. However, ENISI Visual can be used to develop models that are focused and mechanistic, and give quantitative predictions.

III. ENISI Visual, the Simulator

This section discusses the implementation details of ENISI Visual, including 1) compartments and environment such as cytokines and chemokines; 2) agents of different cell types, their states and movements; 3) the user interface and animations.

A. Compartments and simulation environment

ENISI Visula has the following five compartments: lumen, epithelium, lamina propia, draining lymph notes, and blood.

- Lumen is the inner open space of a tubular organ such as the stomach or intestine.
- Epithelium is the thin monolayer of epithelial cells separating the lumen and lamina propria.
- Lamina propria (LP) is the connective tissue underlying the epithelium where most of the immune cells associated with the stomach mucosa reside. Functionally the LP is an effector site.
- Gastric lymph nodes (GLNs) are secondary lymphoid organs draining the stomach and initial portions of the duodenum. They belong to the intra-abdominal lymph node cluster and are designated as gastric and pancreaticoduodenal. The GLNs are sites where immune responses are induced.
- Blood is the source for the monocytes such as Macrophages, dendritic cells, and neutrophils.

Currently, the simulator is implemented as 2-dimensional grid space. ENISI compartments are divided into grids and each grid represents a unit of a square area. We sometimes call the each grid cell as a sub-location. Inside each grid, the cells are considered as neighbors. Each grid shares the same environment, with same concentrations of cytokines and chemokines. Figure 1 shows the three compartments of ENISI: lumen is on its left side; Epithelium is the middle vertical layer; and Lamina Propia is on the right side. The gastric lymph node and blood are not shown in the visualization. Both compartments can provide immune cells during immune responses. The recruitment of immune cells is

represented by the influx of immune cells from the right side of Lamina Propia.

In immune responses to pathogen invasions, the immune cells release cytokines and chemokine that are important for cell-cell communications, cell signaling, and cell movement. ENISI uses a single value layer of REPAST Symphony to represent both cytokines and chemokines since they are usually secreted in parallel. We use background colors to represent the cytokine or chemokine gradient. For example in Figure 1, in contacting with pathogenic bacteria, the epithelial cells become pro-inflammatory and release cytokines and chemokines. The cytokines and chemokines diffuse inside the Lamina Propia and form the gradient. The diffusion of cytokines and chemokines follows equation (1), where V_n^{self} is the value of the grid cell itself at step n. The values of C_e and C_d are evaporation constant and diffusion constant.

$$V_n^{self} = C_e*(V_{n-1}^{self}+\Sigma_{neighbors}C_d*(V_{n-1}^{neighbor}-V_{n-1}^{self})) \quad (1)$$

B. Agents, cell Types, cell movement, and state transitions

The cell types modeled in ENISI Visual and their visualizations are represented in Table I.

TABLE I

AGENTS, STATES, AND LOGOS.

Cells	State 1	State 2	State 3
Epithelial Cells	Normal	Pro-inflammatory	
Macrophages	Immature	M1	M2
Dendritic Cells	Immature	Effector	Tolerogenic
Neutrophils	Naive		
B Cells	Naive	Plasma	
T Cells	Resting	T Helper	T Reg
Bacteria	Infectious	Tolerogenic	

1) State Transition: Each cell has different states or phenotypes as we discussed above. For example, an immature macrophage cell can become pro-inflammatory state, i.e., M1, when in contact with pro-inflammatory T helper cells. In each simulation cycle or step, each cell checks its neighbors and its environment and determine whether it keeps its state or changes to another state. Different cel types are represented by different logos and the logos change colors when the cells change cell types.

In general, with pro-inflammatory neighbor cells and pro-inflammatory cytokines, a cell has high probability to change its state to pro-inflammatory. State transitions in this agent-based simulator are stochastic processes, not deterministic.

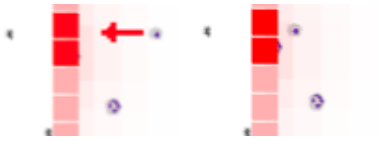

Fig. 2. Chemotactic movement: a macrophage moves following the chemokine gradient, the red arrow.

2) Cell Movement: Current ENISI has two types of movement models: random and chemotactic. Random movements are directionless and chemotactic movements follow the chemokine gradient. The movement speed is controllable and configurable.

C. User Interfaces, Snapshots and Animations

The interface allows users to control the initial cell concentrations, simulation outputs, and simulation speed etc. The users can also set batch simulation mode. Simulation outputs can be the animations, the figures, and output data files. The data can be further processed through other data processing tools like Excel or Matlab.

In addition to controlling the simulation speed, user can initiate, step, run, pause, and reset the simulation. Users can take snapshots and record videos. Figure 3 shows the ENISI interface. The top line of buttons is for controlling the simulations. The windows on the left side can change simulation settings. The right two windows are the upper one of figure and the lower one of animations. The windows can be dragged and relocated.

IV. A CASE STUDY

In this section, we develop a model using ENISI Visual. We target this model for gut immune responses to invasions of gastroenteric pathogens. This model can show how the inflammatory immune responses remove the pathogens, how the lesions are forming, and how regulatory immune responses restore the intestinal homeostasis.

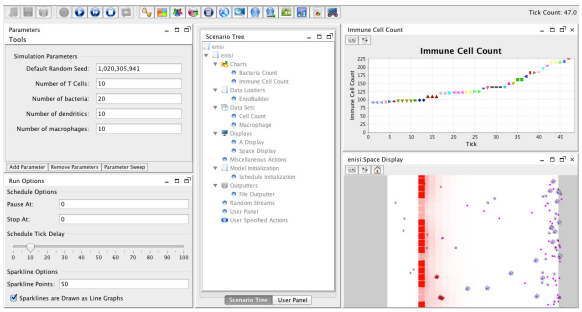

Fig. 3. ENISI Visual user interface.

A. Model: Rules and Settings

State Transition Rules: State transition rules comprise three types: contact dependent, environment dependent, and time dependent. 1) If a cell changes its state because of it is in contact with another cell, i.e., a neighbor cell, this is contact dependent state transition rule. 2) If a cell changes its state because of its environment such as a high concentration of a specific cytokine, this rule is environment dependent. 3) If a cell changes its state because of having stayed in a state for a certain amount of time, this is called time dependent rule. State transition rules can also be composite rules. For example, a cell changes its state after having stayed in a specific environment for longer than a certain amount of time.

- Epithelial Cells: 1) Normal state transits to infected state with probability $P_{EB} = 0.5$ when in contact with infectious bacteria; 2) Infected state transits to normal state after time $T_{E1} = 192$.
- Dendritic cells: 1) Immature state transits to Effector state with probability $P_{DB1} = 0.54$ when in contact with Infectious Bacteria; 2) Immature state transits to Tolerogenic state with probability $P_{DB2} = 0.36$ when in contact with Infectious Bacteria; 3) Immature state transits to Effector state with probability $P_{DC1} = 0.6$ when the concentration of pro-inflammatory cytokines is larger than $V_{DP} = 5$; 3) Immature state transits to Tolerogenic state when the concentration of regulatory cytokines is larger than $V_{DR} = 5$.
- Macrophages: 1) Undifferentiated state (M0) transits to M1 with probability $P_{MB1} = 0.9$ when in contact with Infectious Bacteria; 2) M0 transits to M2 with probability $P_{MB2} = 0.1$ when in contact with Infectious Bacteria; 3) M1 transits to M2 with probability $P_{MD1} = 0.4$ when in contact with Tolerogenic dendritic cells or TReg cells; 4) M2 transits to M1 with probability $P_{MD2} = 0.4$ when in contact with Effector dendritic cells or TH1 cells; 5) M0 to M1 when the concentration of pro-inflammatory cytokines is larger than $V_{MP} = 7$; 6) M0 to M2 when the concentration of regulatory cytokines is larger than $V_{MR} = 7$.
- T Cells: 1) Resting T to TH1 with probability $P_{TD1} = 0.9$ when in contact with Effector dendritic cells; 2) Resting T to TReg with probability $P_{TD2} = 0.9$ when in contact with Tolerogenic dendritic cells; 3) Resting T to TH1 when the concentration of pro-inflammatory cytokines is larger than $V_{TP} = 5$; 4) Resting T to TReg when regulatory cytokines is larger than $V_{TR} = 5$.

Cytokines and Chemokine Secretion Rules: 1) Pro-inflammatory epithelial cell releases $V_E = 10$ pro-inflammatory chemicals into the grid it locates each simulation cycle; 2) Effector dendritic cell releases $V_{D1} = 2$ pro-inflammatory chemicals into its grid each cycle; 3) Tolerogenic dendritic cell releases $V_{D2} = 2$ regulatory chemicals into its grid each cycle; 4) M1 Macrophage releases $V_{M1} = 2$ pro-inflammatory chemicals into its grid each cycle; 3) M2 Macrophage releases $V_{D2} = 2$ regulatory chemicals into its grid each cycle.

Cell Recruitment Rules: 1) When one epithelial cell changes state into pro-inflammatory, number $N_{ED} = 2$ of Dendritic Cells are recruited into Laminia Propia. 2) When one dendrtic cell changes state into Effector or Tolerogenic, number $N_{DT} = 5$ of resting T Cells and number $N_{DM} = 5$ of undifferentiated Macrophages will be recruited into the Laminia Propia from lymph nodes. The initial locations of the newly recruited cells are in the right side of Laminia Propia compartment.

Motion Rules: There are two types of motion rules, random move and chemokine movement. In this model, Epithelial cells do not move while Becteria move randomly. Dendrtic cells, Macrophages, and T Cells follows chemotactic movement when chemokine gradient is present; otherwise random movement.

Cross Compartment Rule: Bacteria in Lumen can get through the epithelial layer into the Laminia Propia with probability of $P_{BCR} = 0.5$ when the neighbor cell is pro-inflammatory Epithelial cell.

B. Simulation Results

Figures 4 and 5 show the numbers of bacteria and immune cells change along the simulation time. We have performed four *in silico* experiments as shown as the four scenarios in the figures. In the first experiment, noChemo_noCyto, the chemotactic movement and cytokine-induced state change are both disabled. In the second experiment, noChemo_Cyto, chemotactic movement is disabled. In the third experiment,

Chemo_noCyto, cytokine-induced state change is disabled. In the fourth experiment, Chemo_Cyto, both chemotactic movement and cytokine induced state change are enabled.

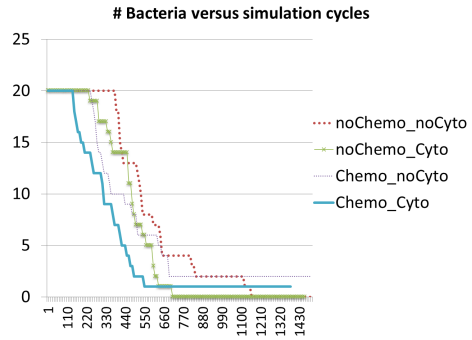

Fig. 4. Number of bacteria of four scenarios.

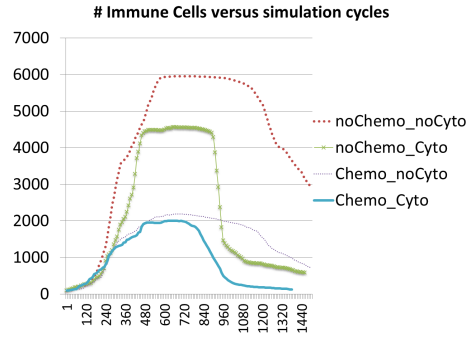

Fig. 5. Number of immune cells of four scenarios.

From the comparisons, we can see that the chemotactic movement and cytokine-induced cell state change play critical roles in host-pathogen immune responses. Chemotactic movement enables immune cells moving quickly to the inflammation sites and the cytokine-induced state change enables more efficient state changes. With both enabled, the bacteria are eliminated the fastest, the immune response is the shortest, and the maximum number of immune cells is the smallest. With both disabled, the bacteria are eliminated the slowest, the immune response is the longest, and the maximum number of immune cells is the largest. When either feature is disabled, the results are in between. Comparing the two in-between scenarios, Chemo_noCyto gives quicker initial immune response because the chemotactic movement but last longer due to slow phenotype change, while noChemo_cyto initiates immune response slower without chemotactic movement but more effective in phenotype change thus with shorter immune responses. Clearly these insights we gain from novel *in silico* experiments can potentially lead to novel biological experiments.

V. Conclusions

ENISI Visual is the first agent based simulator targeting for gut immunity and providing quality visualizations. In this paper, we have discussed its design and implementation. We have used a case study to show that ENISI can perform insightful *in silico* experiments that can lead to novel biological experiments and discoveries.

Acknowledgement

Supported in part by National Institutes of Health 5R01AT004308 to JB-R, NIAID Contract No. HHSN272201000056C to JB-R and funds from the Nutritional Immunology and Molecular Medicine Laboratory.

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