Visualization of Complex Biological Systems: An Immune Response Model Using OpenGL

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Abstract. In this paper we present an update on our novel visualization technologies based on cellular immune interaction from both large-scale spatial and temporal perspectives. We do so with a primary motive: to present a visually and behaviourally realistic environment to the community of experimental biologists and physicians such that their knowledge and expertise may be more readily integrated into the model creation and calibration process. Visualization aids understanding as we rely on visual perception to make crucial decisions. For example, with our initial model, we can visualize the dynamics of an idealized lymphatic compartment, with antigen presenting cells (APC) and cytotoxic T lymphocyte (CTL) cells. The visualization technology presented here offers the researcher the ability to start, pause, zoom-in, zoom-out and navigate in 3-dimensions through an *idealised* lymphatic compartment.

Keywords: Visualization, Emergent Behavior, Immune Response.

1 Introduction

Emergent behaviour is the process whereby global features or structures emerge naturally from a local system in which such features are not merely aggregates of microscopic interactions. However, emergent behaviour can be a difficult property to unambiguously identify, and therefore emergent behaviour is often characterised by the process of systemic *self-organisation* where the higher-level components of the model take on non-random spatial structures. Thus, self-organisation becomes apparent through visual representation of system components and patterns of change which occur over time.

Visualization is a burgeoning field of scientific computing which seeks to provide multi-dimensional graphical representation of underlying models or data. Such representations can typically be subject to manipulation such as rotation, transformation, animation and so on. Complex data sets are transformed into visually meaningful 2-D or 3-D realizations in order to improve understanding of the underlying data, and to aid in its interpretation. (See, eg, [1],[2] and [3])

One of the key pathways to successful and speedy drug design and development is creation of accurate and realistic computational models and simulations of all levels of human biological response. Such models would then enable researchers to both test their hypotheses as well as to form the basis of an advanced biological knowledge repository. We therefore need to address the question of how to effectively create a software application that will draw the experimental biology community in to the process of model design and development. In the past, this has proved to be extremely difficult, primarily, we feel, because such models rarely, if ever, provided the researcher with mechanisms to visualise the model dynamics. Therefore, it follows that this problem can be most effectively addressed by the development of a feature rich 3D Bio-Visualisation platform.

2 Research Objectives

The two key objectives of this research effort are two-fold:

1. To develop better in-silico disease models of human disease progression, in particular, the pathways and dynamics of inflammatory diseases (such as arthritis and asthma). This type of modelling should be based on a mechanistic understanding of the disease process as a function of time, and not merely on individual potential target molecules, in other words, systems simulation versus target simulation.
2. The development of a 3-D software visualisation platform that will enable us to integrate the domain expertise of experimental biologists. In addition, this platform would enhance learning in the laboratory or classroom, in that students of cellular biology might more quickly comprehend the complex dynamical nature of typical immune system functions.

At first, these two objectives are not necessarily related. However, in order to achieve the first of these objectives, we have concluded that the second objective will be a crucial step.

2.1 Contribution to Knowledge

We are strongly encouraged and motivated in this research by the findings of a recent EU report ("The Innovative Medicines Initiative (IMI) Strategic Research Agenda Creating Biomedical R&D Leadership for Europe to Benefit Patients and Society") (`http://www.efpia.org/4_pos/SRA.pdf`) which indicates that in-silico modeling and simulation of biological processes is a key requirement in the development of cost-effective and timely new disease therapies. We see this platform as a key enabler for this strategy, in that integration of the computing and bio/medical communities continues to be problematic and inconsistent.

3 Model-View-Controller

The architecture of the application is based on the common design pattern known as the *model-view-controller* (or MVC) pattern, popularised by [4]. In MVC, the model represents the information (the data) of the application and the business rules used to manipulate the data; the view corresponds to elements of the user interface such as text, checkbox items, and so forth; and the controller manages details involving the communication to the model of user actions such as keystrokes and mouse movements. This approach is presented in Fig 1.

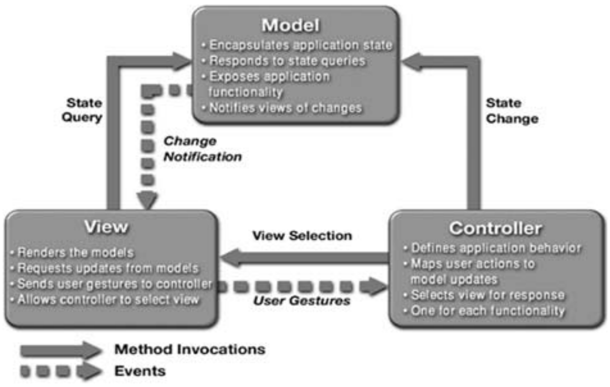
Model
• Encapsulates application state
• Responds to state queries
• Exposes application functionality
• Notifies views of changes
State Query
State Change
Change Notification
View
• Renders the models
• Requests updates from models
• Sends user gestures to controller
• Allows controller to select view
View Selection
User Gestures
Controller
• Defines application behavior
• Maps user actions to model updates
• Selects view for response
• One for each functionality
Method Invocations
Events

Fig. 1. Model View Controller architecture, (image courtesy of Sun Microsystems)

Thus, in our model, we have the simulation (model) component executing in a thread, with a shared data structure for the view thread to read and render every 10 seconds. A set of keyboard controls allow the user to navigate through the model space in 3 dimensions, moving to sites within the lymphatic compartment that may be of interest, and pausing the simulation to study individual cells, or clusters of cells, that may be of specific interest.

3.1 Model

The model has two classes of nodes, the immune cells (*ctl*) the antigen-presenting cells (*apc*). Although restricting the model to just *apc* and *ctl* cells is a simplification of actual biological systems, it is justified by noting that virus-specific CTL are generally considered to be the principal effectors in mediating recovery in the acute immune response to respiratory viral infection (see references contained in [5]). The model has some key parameters, such as initial cell levels, rates of change in the lifecycle, frequency of infection events and many others. Some viral pathogens are capable of persistent re-infection, in that, although population levels of infected antigen presentation cells may decline in response to clearance pressure by a specific CTL response, over time, the number of infected cells rises to chronic and sometimes acute levels. Examples of such viruses are HIV, HTLV, hepatitis C (HCV), hepatitis B virus, CMV EBV and rubella Such persistent re-infection pathogens have been associated with normal immune function suppression. This means that the model simulates persistent re-infection by randomly scattering a repeat 'dose' of the pathogen, introduced some 300 time-steps in the simulation. This re-infection pattern is a represents a resurgence of infected cells every 6.25 days, in discrete bursts. This model is discussed in more detail in [6], [7] and [8].

3.2 View

As mentioned, the visualization of biological processes offers the researcher the ability to speed-up, slow-down and hypothesize various parameters. Visualization aids understanding as we rely on visual perception to make crucial decisions. For example, with our initial model, we can visualize the dynamics of an idealized lymphatic compartment, with APC and CTL cells. However, the early models, although well received in the research community, still lack important characteristics such as 3D rendering, zoom-in, rotation, projection and instant reply. These initial deficiencies have now been rectified in the results presented in this paper.

OpenGL Texture Mapping. One of the strengths of this platform is that the user is always presented with visual cues which they can directly relate to images of cells that might be encountered in the actual lab setting. With very slight modifications we can convert typical 2D raster images into 3D spherical-based objects.

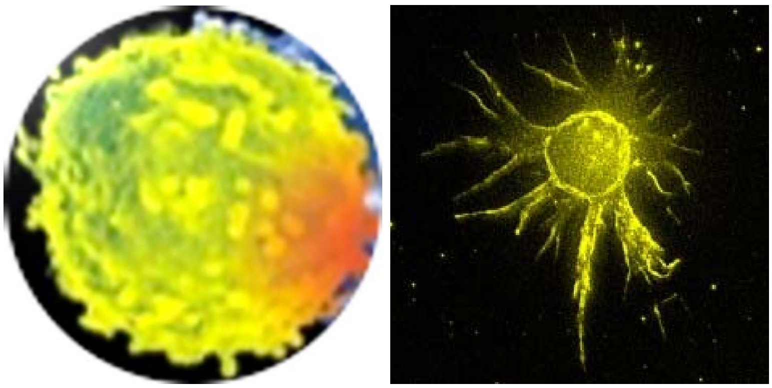

Fig. 2. Left, an actual laboratory photo of a CTL cell and right, an image of an antigen presenting cell. Images courtesy of the La Jolla Institute for Allergy and Immunology.

For this, we take freely available CTL images (see Fig. 2), convert them to .tga format, and then load and bind them into our visualisation engine:

```
//load the naive CTL:
pImage = gltLoadTGA("./images/ctl.tga",
          &iWidth, &iHeight, &iComponents, &eFormat);
glBindTexture(GL_TEXTURE_2D, CTL_IMAGE);
glTexImage2D (GL_TEXTURE_2D, 0, GL_RGBA, iWidth,
          iHeight, 0, GL_RGBA, GL_BYTE, pImage);
gluBuild2DMipmaps(GL_TEXTURE_2D, GL_RGBA, iWidth,
          iHeight, GL_RGBA, GL_UNSIGNED_BYTE, pImage);
//...
```

Then we use the following OpenGL calls we map these images to `GluSphere` objects:

```
glPushMatrix();
glColor3f(0.0, 0.0, 1.0);
//...
glBindTexture(GL_TEXTURE_2D, CTL_IMAGE);
gluSphere(qobj, 0.01, 20.0, 20.0);
glPopMatrix();
```

in this way, each of our biological entities (or agents) within the model, are visualised in turn, at each update step.

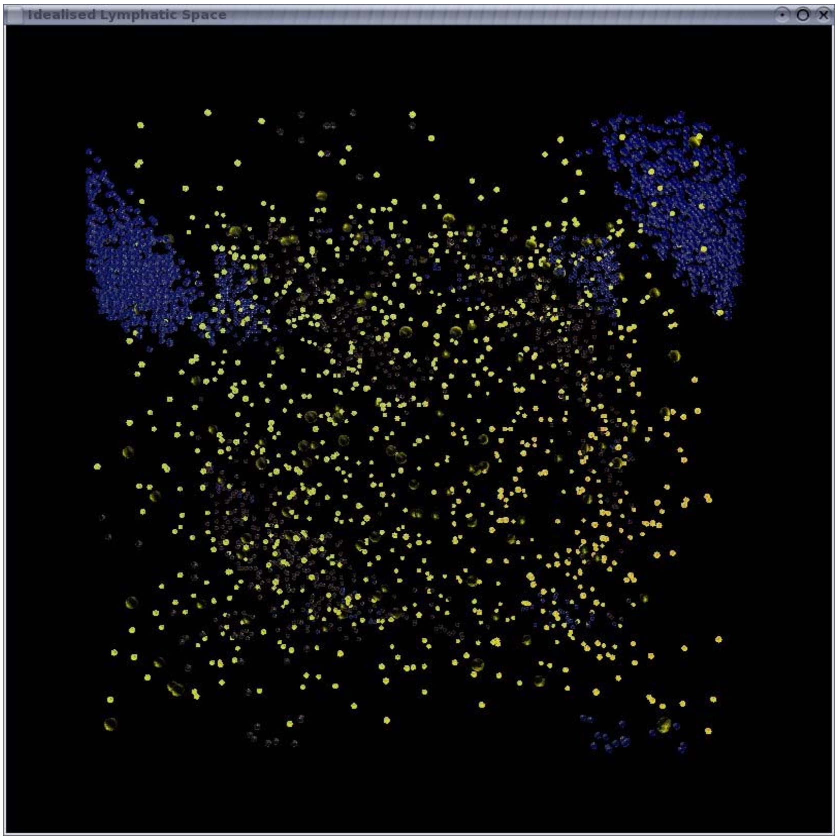

Fig. 3. The initial view of the model lymphatic compartment, with the viewer camera position placed far away along the z axis

4 Visualisation Results

Our results are presented here, in the form of four renderings of the lymphatic compartment outlined in the previous section. Although we model a space of some $x = y = z = 100$ in size, we normalise this space to the OpenGL co-ordinate space, which has each co-ordinate axis run from $[-1, 1]$. When the simulation begins, the viewers perspective always starts out placed $x = y = 0$ with $z = 20$. This has the effect of placing the viewer far outside the space, but looking towards the centre of the space, along the z-axis. This position is shown in the imgage in Fig. 3.

The user can now begin to navigate the space, by using the following key commands:

1. F2 key: move the camera postion along the z-axis towards the origin.
2. F3 key: move the camera postion along the z-axis away from the origin.

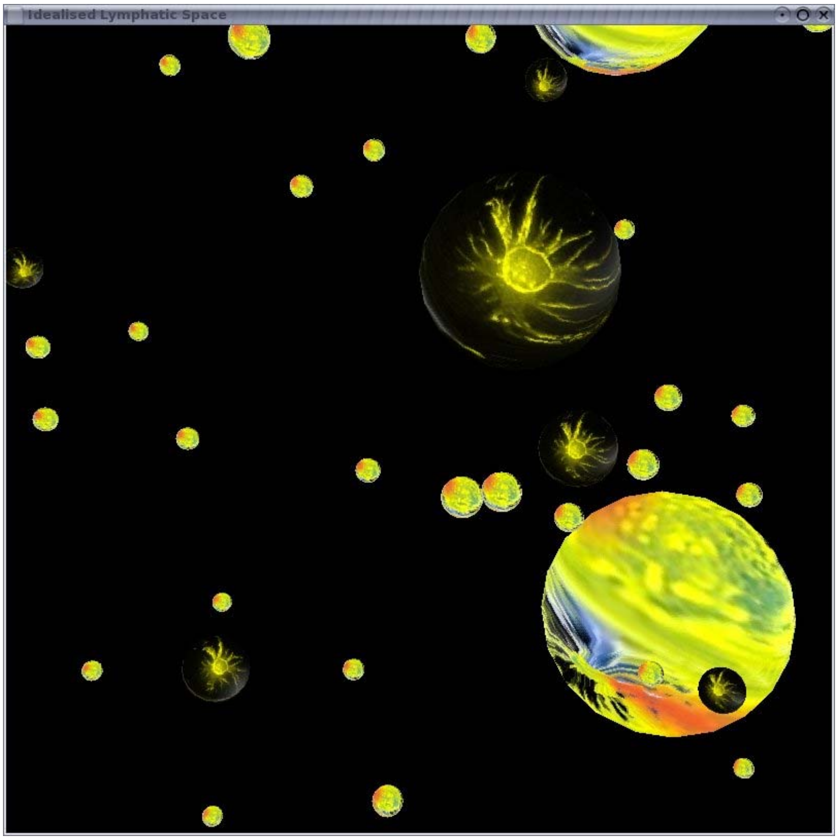

Fig. 4. Centre-right - above and behind is the APC, with the CTL visible to the front lower right

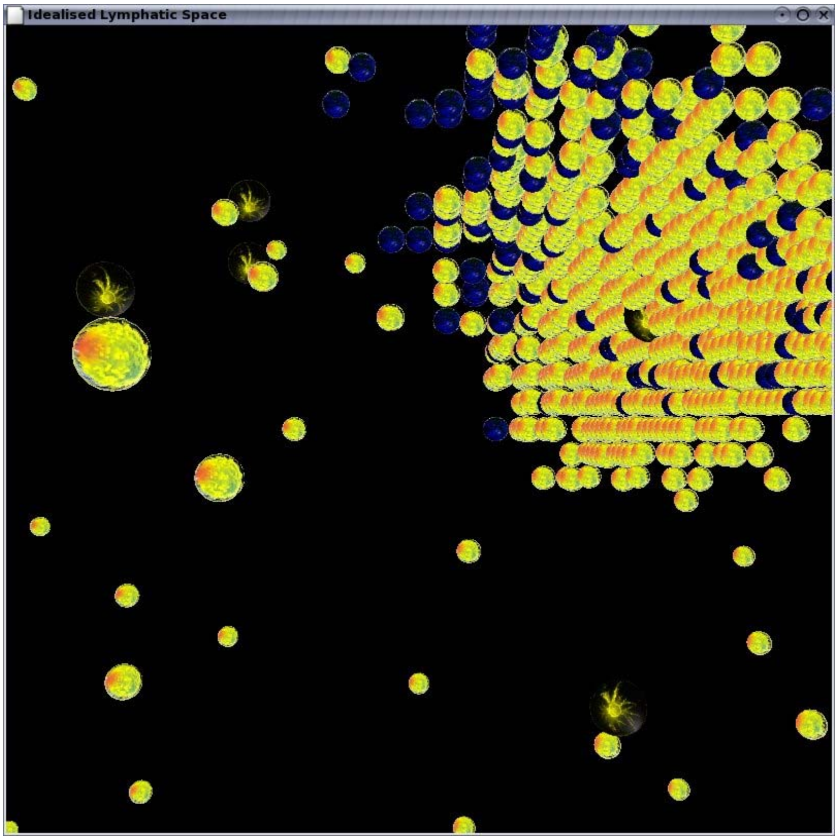

Fig. 5. An APC has been recognised, and the CTL cells begin their clonal expansion phase (the cluster of yellow cells), prior to departing the lymphatic compartment

3. Up arrow: move the camera up the y-plane.
4. Down arrow: move the camera down the y-plane.
5. Left arrow: move left along the x-axis.
6. Right arrow: move right along the x-axis.

In this position, the viewer has moved the camera into the lymphatic space and paused the simulation to examine two cells. Clearly visible in Fig. 4, the results of texture mapping the 2D images from Fig. 2, we can see the antigen presenting cell (with its characteristic centre and extended arms) above and behind a naive CTL. Also visible are more distant APC and CTL cells.

One of the strengths of OpenGL for this kind of visualisation is that completely automates and hides the details for scaling and managing object depth and distance. Using the `gluBuild2DMipmaps()` function call (as shown above), we request the OpenGL engine to build a series of scaled images of our object, which are then called directly by the rendering engine depending on the image postion in the space.

Fig. 5 we can see the camera has been moved to the proximity of a clonal expansion process, triggered by the recognition of an APC by a CTL [1]. This expansion is marked by a steep increase in the number of CTL cells dividing and arming in the search for more APC bearing the genetic material that triggered the recognition. This population increase is carefully controlled in order to prevent the lymphatic compartment becoming congested with cells.

4.1 Simulation Platform

DCU School of Computing has recently upgraded its cluster technology with the purchase of a Linux-based 448-core compute cluster. This advanced platform is crucial for the implementation of our research. We are also in the process of equipping a dedicated research space with large-screen digital display facilities for the projection of 3D graphical applications. In conjunction with ITT Dublin we are jointly developing and funding Bio-visualisation projects in order to promote the important work of our group.

5 Summary and Conclusions

We have developed a *front end* visualization platform, based on the MVC design pattern, to allow student and lecturers in the classroom and lab to experiment with a variety of parameters in order to study a range of possible outcomes from normal to abnormal disease clearance.

In an exciting collaboration between Dublin City University School of Computing, and ITT Dublin, we are developing novel visualization techniques to study cellular interaction from both the large-scale spatial and temporal perspectives. Visualization of processes offers the researcher the ability to speed-up, slow-down and hypothesize various parameters. Visualization aids understanding as we rely on visual perception to make crucial decisions. For example, with our initial model, we can visualize the dynamics of an idealized lymphatic compartment, with APC and CTL cells.

One of the strengths of this platform is that the user is always presented with visual cues which they can directly relate to images of cells that might be encountered in the actual lab setting. With very slight modifications we can convert typical 2D raster images into 3D spherical-based objects. We are strongly motivated in this research by the findings of a recent EU which indicates that in-silico modeling and simulation of biological processes is a key requirement in the development of cost-effective and timely new disease therapies.

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[1] See [9] for a good general treatment of basic immunology.

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