

The University of York

Department of Computer Science

**Submitted in part fulfilment for the degree of MEng.**

# **Parallel Programming Tools for Exploring Immune System Development**

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## **Abstract**

More powerful computers are paving the way for sophisticated simulations of previously underexplored complex biological systems. Agent-based modelling has been previously used to implement this type of simulation, showing how the behaviour of a number of individual agents can contribute to the system as a whole.

As advancements in computing tend towards parallelism and distributed systems, these increasingly elaborate simulations must take full advantage of this change in order to be computed in a reasonable time period. Creating programs and simulations that make efficient use of this parallelism can be technically challenging. In particular it requires implementing an optimal distribution of tasks over the system and ensuring the integrity of any memory that is shared across multiple threads. Some significant problems, including a substantial computer science skills shortage, are slowing down the rate of progress in this area.

In this project the FLAME GPU framework is used to help mitigate some of the difficulties with implementing parallel programs, in order to build on an existing sequential Java MASON simulation. I also propose model-driven engineering (MDE) as a potential short-term solution to the skills shortage, exploring some of the current MDE technologies for creating simulations and proposing further advancements to these tools for the future.



## **Acknowledgements**

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## **List of Listings**

# 1 Introduction

## 1.1 Project Overview

TALK ABOUT MODELING AND THE DESIRE FOR  
Faster AND More Accessible Simulation

## 1.2 Motivation

The motivation behind this project is the new knowledge that could be gained from the ability to create efficient parallel biological simulations more easily. While many biological systems can not be fully studied in-vitro, simulations can provide a valid alternative. Indeed previous work has been used to prove some hypotheses wrong.

This type of in-silico experimentation could significantly improve the process by which drugs are developed. Extensive in-silico testing can be performed much more quickly than the current in-vitro testing, reducing the time it takes to research new drugs and cures. Drugs and cures would be available for patients earlier, saving many lives. Additionally, the significant financial burden of drug development, which is estimated to be around \$2.9bn[1], could be reduced, freeing up heavily contested funds for additional research. Finally, the use of animal testing could be reduced and, in the long term, eliminated completely.

## 1.3 Project Aims

In summary, the aims of this project are to

1. Establish a firm grounding for the future development of new tools to allow fast, parallel simulations of biological systems to be easily created by non-technical users.
  - a) Explore the findings of the new implementation and discuss how these can be generalised to new simulations.

- b) Discuss techniques for allowing non-technical users to easily create formal models that can be transformed into new simulation implementations.
- 2. Develop a **parallel** implementation of an existing **sequential** simulation of Peyer's Patch development and explore any speed increases that can be produced using General Purpose GPU programming.
- 3. Review of the use of simulations, with a particular focus on computational biology. This review should explore the advantages that in-silico testing provides over in-vitro experimentation and the problems that must be overcome for the mass adoption of biological simulations.

## 1.4 Statement of Ethics

This project was conducted in accordance with the University of York's code of practice on ethics. This project does not involve human participants, so guidelines on informed consent and confidentiality will be met. No confidential medical data or personal information has been used during the course of the project development. This project has involved no direct animal participation.

The simulation of the biological model is for the purpose of developing understanding of applying GPGPU methods to an agent based model of a biological system. It will not be used in its current form to publish novel biological findings and does not fully simulate a biological process.

## 1.5 Report Structure

This report details the work done throughout the project and

- 1. Chapter 2 gives an overview of simulations and the benefits and limitations of their use particularly with regard to computational biology.
- 2. Chapter 3 details the development of an improved, inherently parallel, implementation of PPSim (PPSim v2).
- 3. Chapter 4 evaluates the progress that this project has made towards making fast, parallel simulations more accessible.

## 2 Literature Review

### 2.1 Simulation

Simulations are model-based imitations of a system which feature its key characteristics and behaviours. Computer simulations are used in a wide range of disciplines on applications such as video games, medicine, product development and even nuclear weapons.

The models of systems used in simulations may have a varying amounts of abstraction. Simulations used for teaching will likely have models which remove significant amounts of complexity from the system. Removing complexity from the original system can also help to reduce the time it takes to run the simulation, a key focus of this project. Simulations used for video games tend to be as realistic as possible as realism has been shown to produce a higher level of immersion[2], a highly desirable attribute of games.

In particular this project will focus on simulations created using Agent-Based Modelling (ABM). ABM is a technique that explores the autonomous behaviour and interaction between a number of individuals, known as agents. The aim of this is to show how the individuals' behaviours interact to produce the system as a whole. This is in contrast to more traditional mathematical top-down models which consist of a set of equations which establish relationships between a set of variables.

This chapter begins by outlining the benefits and current limitations of using simulations generally. It then discusses some potential solutions to some of these limitations before applying this to some of the existing simulations that have been developed.

#### 2.1.1 Benefits

##### Feasibility

Exploring computer simulations is can be far more feasible than exploring a real world environment. Video games are simulations which may allow players to experience scenarios that they may not otherwise get the

opportunity to encounter. For example, car racing games are significantly cheaper and safer than real life racing.

Real-world scientific testing may not be feasible for a number of reasons. Simulating the aerodynamics of new car designs virtually is far quicker and cheaper than creating multiple different prototypes for physical tests. Morality may be a factor, animal testing for cosmetic products or medicine is a good example of this. With nuclear weapons, legality is a key issue, as some weapon testing is banned under a number of global treaties[3], [4]. Finally, some real-world tests may be too dangerous to perform, such as in the case of invasive medical examinations. In all of these examples, computer simulation is routinely used to reduce or replace real-world testing.

### **Reducing Complexity**

Reducing complexity through abstraction allows better understanding of the system to be gained as the complexity may initially be overwhelming.

### **Environmental Control**

Computer simulations allow for the environment to be more easily controlled. The ability to adjust external factors and independent variables that may affect the system on demand can be particularly useful. This ability can be used for illustrating why different variables in system processes are important.

Time can be manipulated to show system processes at more reasonable time scales. A chemical process that takes a fraction of a second can be slowed down to ensure that it can be seen.

Simulations allow for additional tests to be easily added at a later date. If the researcher wants to discover how an additional variable is related to system behaviour, it can be added and the simulation can be easily re-run.

### **Visualisation**

One of the biggest benefits of simulation is the ability to graphically visualise a system or its constituent parts. Using simulation for visualisation has number of benefits over attempting to demonstrate real world systems. Several of these benefits translate from the previous two

sections- they can be more feasible to explore than a real world environment and featuring a reduced complexity can allow the key concepts to be understood without overwhelming the user.

Simulation can be particularly useful for visualising concepts for education.

Particularly immersive visualisations can also be produced using virtual and augmented reality. The Virtuali-Tee is an educational tool that uses simulation and augmented reality to provide a view at the body's internal organs[5]. Little Journey aims to reduce kids' anxiety about surgery by providing a realistic tour of their hospital ward given by animated cartoon characters[6].

### 2.1.2 Limitations and Constraints

While simulations seem very useful across a wide number of fields, there are some significant limitations as to where and how they can be used.

#### Insufficient Domain Knowledge

A simulation is based on a model of a system. A model is an abstraction from reality representing only the necessary key characteristics and behaviours of the system. A lack of knowledge regarding the domain of the simulation is one of the most significant constraints regarding its implementation. If this is the case, the model produced may be incorrect or abstractions may remove necessary detail required for the system to function as expected.

For complex systems, having too many abstractions from the original domain may invalidate the model and produce incorrect results[CITATION NEEDED].

#### Compute Power

Complex models with too few abstractions from their domain may require significant computing power to simulate. Additional abstractions may not be possible as they may invalidate the model. In these cases, cutting edge hardware may be needed for the simulation to be run in an acceptable time.

Powerful hardware is expensive to access, so this may be a significant constraint on the ability to simulate.



### **Skills Shortage**

The previous section discussed reliance that complex simulations have on advanced hardware. However, advanced hardware alone will not necessarily allow a simulation to compute in a reasonable amount of time. With modern architectures which are becoming increasingly parallel, the simulation code must be tailored to take advantage of the computing power available. Efficient parallel programs that do this rely on the availability of experienced programmers. Many recent studies have highlighted the existence of significant computer science skills shortages, across the world[7], [8]. These skills shortages may be significantly limiting the possibility for cross-disciplinary work to utilise fast, advanced simulations.

### **Bugs**

As with any form of computer program, mistakes can be made causing bugs to be present in the simulation code. Bugs may cause the simulation to be incorrect meaning any hypotheses and results are based on incorrect data.

This is linked to, but not the same as, having insufficient domain knowledge. Both of these limitations will cause the simulations fail silently, produce incorrect results with no immediately obvious failure[CITE]. However, while these problems are specific to simulation, they are not dissimilar from the issues that can occur from poorly designed real-world testing.

If the simulation needs to be safety-critical, developing it using formal methods and refinement may be a good way to ensure that no bugs are present in the code.

## **2.2 Improving Simulations**

Significant constraints on when simulations can be used were discussed in the previous chapter. In order for simulations to become more widely adopted, some of these constraints must be overcome. In particular, this project focuses on two particular sections of which I believe will have the biggest immediate impact.

Firstly, attempting to overcome the problems provided by the current computing skills shortage. Initial work to help overcome the skills shortage will likely come by providing tools that can automate work done by

technical users in order to increase their productivity. Eventually, if this technical work can be fully automated, non-technical users will be able to easily create advanced simulations.

Secondly, simulations need to be able to generate results in a realistic amount of time. As many biological simulations include significant elements of randomness, they must be run a large number of times in order to produce reliable results.

This chapter discusses the potential solutions to each of these problems.

### 2.2.1 Ease of Creation

Ease of creation (and maintenance) is an important feature for future simulation particularly due to the aforementioned computer science skills shortage (Section 2.1.2).

#### Flexible Modelling

Flexible Modelling tools could be a good method for allowing new simulations to be created more easily. Using flexible modelling, non-technical users would be able to create sketches which can be automatically processed by tools into formal models and prototype metamodels[9]. Flex-iSketch is a good example of this and provides a good tool for creating models and metamodels for software development[10].

### 2.2.2 Speed Up

#### Machine Learning

A solution to the speed problem that has been proposed recently is to use machine learning on a small set of results to produce[11] This has problems in that... likely affected by Standard Machine Learning issues? Bias? Overfitting?

Already an ongoing area of research..

#### Parallelism

Parallelism fundamentally changes the game and allows computers to keep following Moore's law even as engineers are struggling to make transistors ever smaller and smaller[12]. As modern computers tend further towards parallelism to keep providing the speed-ups that have been inherent in the industry over recent years, new parallel algorithms

need developing in order to take full advantage of the computing power available.

**Distributed Systems** MapReduce is a programming model that is generally used for processing big data in parallel using distributed systems.

**CPU vs GPU** Modern computers provide two main methods for parallelising code. We are building on a previous project[13] which laid the groundwork for this. This previous project outlined the choice between CPU and GPU parallelism and makes the case for exploring GPUs- simplistically put, this is due to the significantly greater speed ups that can be achieved. Indeed it has been shown that GPU simulation on a standard desktop computer can easily produce performance rates that are better than those of a high-performance computing cluster[14].

Multiple CPU cores are now commonplace in modern computers, including smartphones. GPU normally only found in gaming PCs and consoles This is changing, Apple now includes a custom GPU in many of its mobile devices- metal

**OpenGL vs CUDA** A previous project compared OpenGL and CUDA in detail.

## 2.3 Existing Simulations

### 2.3.1 Agent-Based Modelling

While, agent-based modelling is more computationally expensive than top-down mathematical modelling, it is also more natural to model and intuitive to parallelise[14]. Communication between individual agents can be difficult to implement in parallel but parallel communication is by no means limited to ABM.

Mention Flame (traditional) is an attempt to make simulations more accessible via ABM.

### MASON

MASON is a multi-agent simulation library for Java. Evaluated as the one of the fastest sequential ABM libraries available[15].

## FLAME GPU

FLAME (Flexible Large-Scale Agent Modelling Environment) GPU is an extension of the original version of FLAME, where the simulations that are created are compiled down to parallelised CUDA code. This means the simulation can take full advantage of the significant power of modern NVIDIA GPUs. As its name suggests, FLAME GPU uses agent-based modelling to implement simulations.

While relying on a framework such as FLAME GPU can cause problems if support is stopped, FLAME GPU is an open source project, so this should slightly be less of a concern.

The FLAME GPU framework brings its own advantages. As it maps a model to simulation code, it brings with it many of the advantages of model-driven engineering. In particular, it gives domain experts with limited programming knowledge the ability to understand and help design models. Additionally, the auto-generation of artifacts, such as simulation code templates, significantly lowers the boundary to entry to less advanced programmers. Finally, As FLAME is continuously updated to support new hardware advances, such as multicore GPU architectures[14], the implementations can always be certain of taking advantage of the latest hardware optimisations and portability features that FLAME provides. Existing simulation models that are implemented on top of FLAME GPU may receive these performance improvements without major code changes.

FLAME GPU takes input in the form of an XMML model which defines the types of agents that feature in the simulation and their interactions

FLAME also provides a message passing interface which abstracts away from the underlying agent communication. This means that programmers need not be concerned with communication between threads which is one of the most difficult tasks in parallel programming.

### 2.3.2 Biological Simulations

Computational Biology is a relatively new field of study that has been growing significantly over the last decade[CITATION NEEDED].

Within Biology, simulation is often required as an alternative to invasive medical testing/animal testing

Simulations have even been proposed as a method for exploring a potential set of first principles and mathematics that are specific to biology which could even constitute a new subject- theoretical biology[16].

**Genome**

**Cell Dynamics**

**2.3.3 PPSim**

This project focuses on simulation as a tool for exploring biological systems at cell level. It uses the existing simulation of Peyer's Patch[17] and attempts to use parallel computer architectures in order to speed this simulation up.

Finally, I propose a new tool, which builds on existing work in order to make this power available to non-technical users.

## 3 Methods

### 3.1 The Domain Model

The domain model is taken from the existing sequential simulation of Peyer's patch development described in Section 2.3.3. Peyer's patches are clusters of cells that form on the lining of the small intestine.

In this simulation there are three types of agent which are all types of cells; LTo, LTin and LTi. Stationary LTo cells

### 3.2 The Platform Model

In the platform model there is a single *active* LTo cell in the centre of the environment. There are no LTi and LTin cells in the environment when the simulation is initialised. A host function manages cell migration into the environment by creating these cells in random positions at a constant rate.

### 3.3 FLAME GPU

Building FLAME simulations requires the creation of two artifacts (Fig. 3.1), a structural 'XML Model File' which defines the agents in the system and their allowed channels for communication and a C source code file of 'Scripted Behaviour' which defines the actual behaviour of agents.

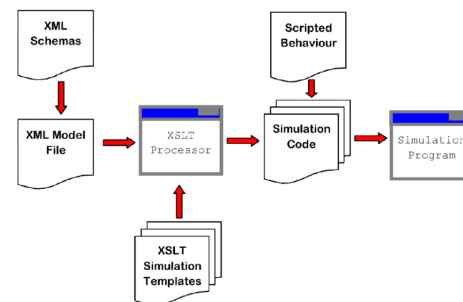


Figure 3.1: FLAME Development Process (Taken from [14])

Custom Code?[13] not well tested less easy to update to sup-

port new tools and hardware, new

CUDA GPUs Each custom code simulation must be updated separately  
model based -> FlameGPU[18] restricted to the framework limitations  
Host cell creation into the system is a work in progress for next FlameGPU  
release? helper LTi/LTin agent factory is be required to facilitate this  
functionality?

A state-based platform model design is already available from the original MASON implementation of this simulation. As FLAME GPU uses state machines for each agent type in its implementation, these have been directly implemented into it.

Due to time constraints, I have not been able to implement environmental growth.

#### 3.3.1 Epsilon

In the creation of the FLAME XML model, I decided to implement a new tool, built using the Epsilon Modelling Framework. This new tool contains a graphical editor which allows the FLAME model to be created diagrammatically. This should significantly improve the model design experience and allow for domain experts to be kept more involved with the simulation creation. Figure 5.1a shows the Peyer's Patch simulation created within this graphical editor. The XML model used for the final simulation was automatically generated from this diagram.

The Epsilon Validation Language has allowed well-formedness constraints to be implemented for the FLAME input model. This should provide intuitive feedback (Fig. 5.1b) in cases where the model may be incorrect, in order to prevent an invalid XML model from being produced. Quick fixes (Fig. 5.1c) have also been implemented to guide the user through easily correcting their invalid model.

One final benefit of this new approach to model generation, is that it makes it far simpler to .

#### 3.3.2 Testing

As the new simulation is a re-engineering of the existing PPSim, it can inherit the validation of the existing simulation. This requires the new simulation to be demonstrably similar with similar components, behaviours and results.

Talk about how the model was tested to ensure correctness  
Mention missing link in (incorrect) model from Kieran's paper

### **3.4 Tools**

Version Control for both the simulation code and this report has been managed through Git and is available on GitHub. In order to produce a working simulation of Peyer's Patch formation, I have used an unreleased version (1.5) of FLAME GPU. As FLAME GPU is developed openly, this version is freely available online[19]. FLAME has been added to the project repository as a submodule, to ensure version compatibility between FLAME and PPSim v2.



## **4 Results and Evaluation**

### **4.1 Findings**

#### **4.1.1 Ease of Use**

"Further work is now being developed with Paul Richmond's FLAME GPU group, to enhance the accessibility of FLAME for simulation developers." "This should allow the simulation developer to focus on getting their domain details correct, rather than battling the agent platform.o"

#### **4.1.2 Speed Up**

[20] could be important for evaluating the performance of FlameGPU against original PPSim

### **4.2 Conclusion**

### **4.3 Further Work**

#### **4.3.1 Hardware Availability**

#### **4.3.2 Software Generalisability**

While the use of Epsilon has allowed for domain experts to be kept involved with the model implementation, there is still a final, most technically challenging, stage of the simulation creation where the agent behaviour is programmed. Further work will need to study agent behaviour in these forms of simulation generally...

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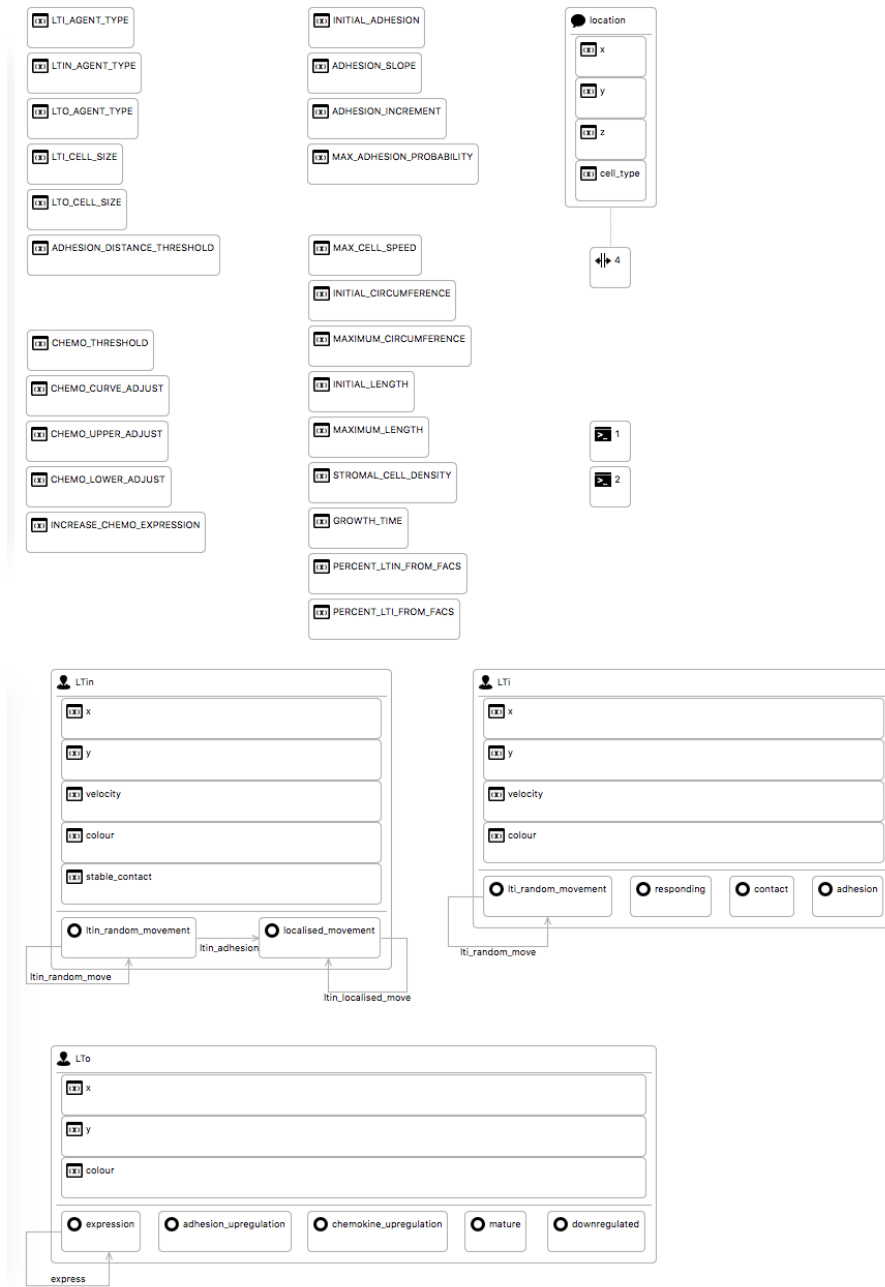
## **5 Appendix**

### **5.1 Simulation Parameters**

### **5.2 Cell Data Structures**

### **5.3 Other**

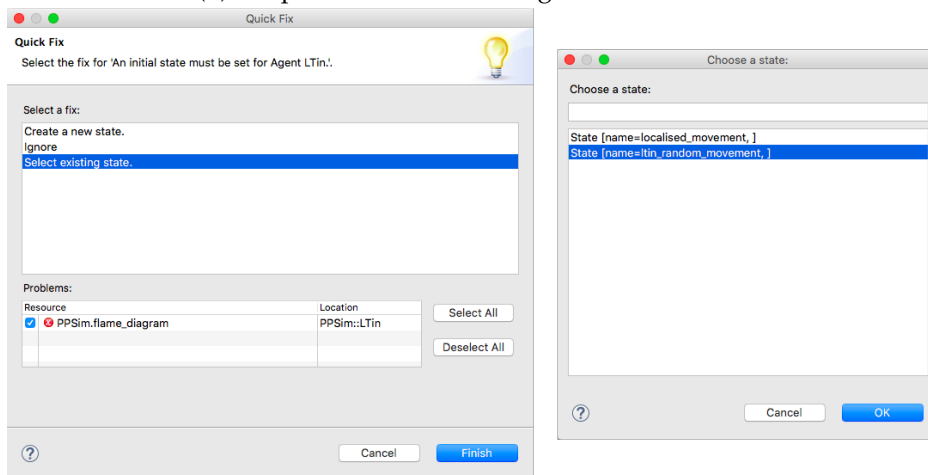
## 5 Appendix



(a) Graphically produced FLAME Simulation model for Peyer's Patch

Description	Resource	Path	Location
▼ ✖ Errors (4 items)			
✖ Agent LTin must have a unique name.	PPSim.flame_diagram	/Models	PPSim::LTin
✖ Agent LTin must have a unique name.	PPSim.flame_diagram	/Models	PPSim::LTin
✖ An initial state must be set for Agent LTin	PPSim.flame_diagram	/Models	PPSim::LTin

(b) Graphical validation using EVL constraints



(c) Quick fix of invalid model

Figure 5.1: Graphical Tool for creating FLAME GPU models