

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**

Oliver Binns

28th April 2018

Supervisor: Dr. Fiona Polack, Dr. Kieran Alden

Number of words = 6578, as counted by texcount.  
This includes the body of the report only.



## **Abstract**

More powerful computers are paving the way for sophisticated simulations of complex biological systems which are inaccessible to live in-vitro study. 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.

The desire to create larger and more elaborate simulations, while still ensuring results can be obtained in a reasonable amount of time, makes it necessary to use parallel and distributed systems. 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 computer science skills shortage, are slowing down the rate of progress in this area.

This project investigates the challenges and advantages of using a parallel agent-based modelling platform, FLAME GPU, by re-implementing an existing sequential simulation of the immune-system, developed using MASON. During the building of the simulation, I have discovered that it is not trivial to compare between the old and new implementations, due to differences in the frameworks used. For this reason, the final comparison will be done directly to the domain model itself.

Finally, in order to improve the mapping from the biological domain model to FLAME GPU simulation code, I propose a Model-Driven Engineering (MDE) approach to development. This approach reduces the parallel computing skill required to develop FLAME GPU implementations and improves traceability from the biological domain to the implementation.



## **Acknowledgements**

I would like to thank my supervisors, Fiona Polack and Kieran Alden, for their support and guidance throughout this project.

I also express my thanks to Richard Paige for his pastoral support throughout this academic year, as well as his help in obtaining access to a suitable GPU machine.

Finally, I would also like to thank the FLAME GPU development team at the University of Sheffield for their help in utilising the latest and pre-released features of this framework.



# Contents

<b>List of Figures</b>	<b>ix</b>
<b>List of Tables</b>	<b>x</b>
<b>1 Introduction</b>	<b>1</b>
1.1 Motivation . . . . .	2
1.2 Project Aims . . . . .	3
1.3 Statement of Ethics . . . . .	3
1.4 Report Structure . . . . .	4
<b>2 Literature Review</b>	<b>5</b>
2.1 Simulation Background . . . . .	5
2.1.1 Benefits . . . . .	5
2.1.2 Limitations and Constraints . . . . .	7
2.2 Existing Simulations . . . . .	9
2.2.1 Biological Simulations . . . . .	9
2.2.2 Agent-Based Modelling . . . . .	9
2.3 Improving Simulations . . . . .	12
2.3.1 Ease of Creation . . . . .	12
2.3.2 Speed Up . . . . .	13
<b>3 Tools and Platform</b>	<b>17</b>
3.1 Tools . . . . .	17
3.2 Peyer's Patch Case Study . . . . .	17
3.2.1 The Domain Model . . . . .	18
3.3 The Platform Model . . . . .	19
<b>4 Methods</b>	<b>20</b>
4.1 FLAME GPU Simulation . . . . .	20
4.1.1 Structural Model . . . . .	20
4.1.2 Behavioural Model . . . . .	22
4.1.3 Testing . . . . .	22
4.2 Graphical Modelling Tool . . . . .	22
4.2.1 Metamodel . . . . .	24

## *Contents*

4.2.2	EuGENia . . . . .	24
4.2.3	Epsilon Generation Language . . . . .	24
4.2.4	Epsilon Validation Language . . . . .	25
<b>5</b>	<b>Results and Evaluation</b>	<b>26</b>
5.1	Findings . . . . .	26
5.1.1	Ease of Creation . . . . .	26
5.1.2	Speed Up . . . . .	26
5.2	Conclusion . . . . .	28
5.3	Further Work . . . . .	28
5.3.1	Peyer's Patch Case Study . . . . .	28
5.3.2	Software Generalisibility . . . . .	28
5.3.3	Hardware Availability . . . . .	29
<b>6</b>	<b>Appendix</b>	<b>35</b>



## List of Figures

1.1	Complex Systems Modelling and Simulation Infrastructure (CoSMoS) Process (Taken from [3]) . . . . .	2
2.1	FLAME GPU Development Process (Taken from [20]) . . .	11
2.2	Silicon Space Allocation (Taken from [32, p.2]) . . . . .	15
3.1	Images of In-Vitro Peyer’s Patch (Provided by Mark Coles, University of York) . . . . .	18
4.1	Autogeneration of FLAME GPU Model File . . . . .	21
4.2	Visualisation of <i>PPSim v2</i> produced using FLAME GPU .	23
4.3	Autogeneration of FLAME GPU Artifact as part of the CoSMoS Development Process . . . . .	24
4.4	Graphical validation using Epsilon Validation Language (EVL) constraints . . . . .	25
4.5	Quick fix of invalid model . . . . .	25
5.1	Traceability from Domain Model to FLAME GPU Implementation . . . . .	27
6.1	Domain Model State Diagrams . . . . .	36
6.2	Platform Model State Diagrams[1] . . . . .	38
6.3	Graphically produced FLAME GPU Simulation model for Peyer’s Patch . . . . .	39

## List of Tables

# Acronyms

**ABM** Agent-Based Modelling. 3, 13, 18, 19

**CoSMoS** Complex Systems Modelling and Simulation Infrastructure. 21

**CPU** Central Processsing Unit. 18

**CUDA** Compute Unified Device Architecture. 18

**EVL** Epsilon Validation Language. 23, 31

**FLAME** Flexible Large Scale Agent Modelling Environment. 19

**FLAME GPU** FLAME for the GPU. 3, 5, 19–24, 30, 31

**GPGPU** General Purpose GPU programming. 11

**GPU** Graphics Processing Unit. 11, 18, 19, 21

**LTi** Lymphoid Tissue inducer cell. 22

**LTin** Lymphoid Tissue initiator cell. 22

**LTo** Lymphoid Tissue organiser cell. 22

**MASON** Multi-Agent Simulator Of Neighborhoods. 3, 19, 22, 24

**MDE** Model-Driven Engineering. 3, 17, 19

# Glossary

- FLAME GPU** An extension of the FLAME framework which uses GPUs for parallelism. 3, 5, 19–24, 30, 31
- LTin** A moving cell that can bind to any static cell. Responds to chemokine expression. 22
- LTi** A moving cell that can bind to any static cell. Believed to be responsible for initiating Peyer’s Patch development. 22
- LTo** A static cell. Divides on stable bind with an LTin and LTi cell. 22
- MASON** A Java framework for producing simulations using ABM. 3, 19, 22, 24
- Host** In GPGPU programming, the computer containing the GPU is referred to as the host. 22
- in-silico** Scientific tests conducted using computer simulation. 10
- in-vitro** Scientific tests conducted using real biological systems under laboratory conditions. 10, 11
- Peyer’s Patch** Clusters of cells that form in the small intestine. 11, 21

# 1 Introduction

Agent-Based Modelling (ABM) has been successfully used to simulate biological systems and develop new scientific knowledge[1], [2]. While traditional mathematical-based models are generally much more efficient to compute and produce good results when exploring how biological factors effect populations as a whole, ABM is particularly useful when considering how individuals and their interactions produce emergent system behaviour. Mathematical-based models are limited in this aspect as they assume that each individual within the population is identical. ABM explicitly represents each individual, meaning these can have state and attributes and are independent and fully autonomous. Unfortunately, these agent-based simulations require significantly more compute resources, thus taking a long time to run, particularly as simulations become more and more complex.

Here, and throughout this report, the term complexity does not necessarily refer to simulations that contains several components that are difficult to engineer. Rather, we discuss simulations that are made up of lots of simple components that interact with each other and the environment in such a way that the system behaviour is so elaborate that it can only be predicted by running the simulation.

As these simulations often contain non-deterministic behaviour, numerous runs are required to ensure that results are statistically significant. Consequently, it is important to ensure that the simulations make efficient use of the available compute resources, in order to gather these results in a reasonable amount of time. The inability to obtain simulation results in a reasonable time is one of the most significant constraints upon the current use of agent-based simulations within biological research.

Another constraint affecting the adoption of ABM simulations is the ease with which they can be created. At present, domain experts with knowledge of a particular biological system produce domain models of the system. With the aid of software developers, these domain models are then converted into platform models. The domain experts verify that the platform models are reasonable abstraction of the system, and they are implemented in code by the software developers. This is the CoSMoS

process (Fig. 1.1).

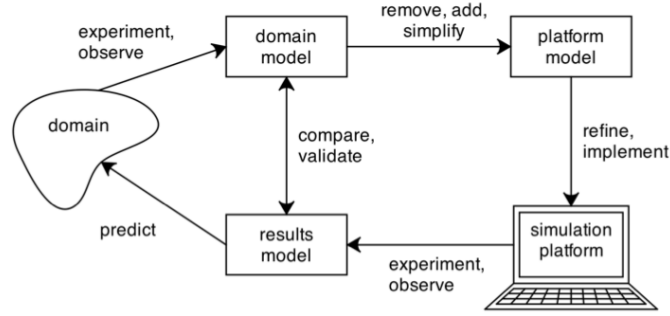


Figure 1.1: CoSMoS Process (Taken from [3])

A shortage of software developers who are proficient at creating efficient, parallel simulations is the current bottleneck in the adoption of the ABM simulations of processes. If this development process can be automated by creating general solutions for common biological processes, such as cell division, it will allow simulations to be created by domain experts.

## 1.1 Motivation

The motivation behind this project stems from the new knowledge that could be gained from the ability to easily create efficient, parallel biological simulations. As many biological systems cannot be fully studied in-vitro, simulations can provide a valid alternative. Indeed previous work has been used to produce novel biological hypotheses which have been shown to be statistically similar to those observed in the laboratory[1, p.174].

However, these previous simulations of biological systems have had to make significant trade-offs in their implementation. For example, 3D environments have had to be mapped into 2-dimensional simulations, cell migration into the system has been modelled as random rather than systematic[1], and environmental growth has been ignored[4]. The impact that these compromises have on the validity of the platform model as a representation of the domain is currently unknown. A core motivation of this project is that, by addressing the difficulties of creating efficient, parallel, agent-based simulations, we can support simulations with fewer trade-offs in their realisation.

There are several compelling reasons for the interest in simulation of immune-related biology. Firstly, extensive in-silico testing could 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[5], 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.

## 1.2 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 by using General Purpose GPU programming (GPGPU).
3. Review the use of simulations, with a particular focus on computational biology. This review explores 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.

## 1.3 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 ability to reduce, and ultimately replace, experimentation on animals is a positive ethical advantage of work on efficient immune-related simulation.

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.

## 1.4 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 4 details the development of an improved, inherently parallel, implementation of PPSim (*PPSim v2*) and the MDE tools that were developed to aid this work.
3. Chapter 5 evaluates the progress that this project has made towards making **fast**, parallel simulations more **accessible**.



## 2 Literature Review

### 2.1 Simulation Background

Simulations are model-based imitations of a system which feature its key characteristics and behaviours. The system being modelled is referred to as the domain, while this simulation is known as the platform. 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. Using abstraction to remove some of the complexity present in the domain 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[6], 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 using ABM.

#### 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, a good example of this is animal testing for cosmetic products or medicine. With nuclear weapons, legality too is a key issue, as some weapon testing is banned under a number of global treaties[7], [8]. 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. Abstractions need to be made to an appropriate layer, models should represent the layer being investigated, but remove any unnecessary further detail. For example, attempting to model simulations exploring cell development down to the atomic or quantum level or up to an entire organism would be completely unnecessary. Attempting to do so with current technology would also be completely intractable. This is an important balancing act as, if too much detail is abstracted away, simulations will likely fail to produce the expected emergent behaviour[9].

### **Environmental Control**

Computer simulations allow for the environment to be more easily controlled. While the initial setup of a realistic environment may be difficult, once this has been achieved the simulations can be run in a known, constant environmental context. It can be more easily ensured that the environment remains unaffected by any external factors. The ability to adjust external factors and independent variables that may affect the system on demand can also be particularly useful. This ability can be used for illustrating how different variables affect system processes.

Furthermore, simulations allow for additional tests to be easily added at a later date. For example, if measurements are not made for a particular variable, it can be easily added to the implementation and the simulation

can be easily re-run. This is not the case with in-vivo experimentation, which would require the laboratory to be fully set-up again, with new test-subjects for repeat experiments.

### 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 educational 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[10]. Little Journey aims to reduce kids' anxiety about surgery by providing a realistic tour of their hospital ward given by animated cartoon characters[11].

### 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. In order for the model to be faithful to its original domain it must be able to produce demonstrably similar behaviour from similar system components.

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. With biological simulations in particular, it is often hard to make assumptions about how particular processes occur[9]. Unfaithful models can also be a result of *incorrect* knowledge of the domain. For complex systems, having

## 2 Literature Review

too many abstractions from the original domain may also invalidate the model and produce incorrect results[12, p.8], [9].

While knowledge of a system needs to be sufficient to produce reasonable assumptions, it need not be perfect. This is particularly the case with the type of simulation discussed later in this report. In this case, assumptions about the domain are made

### **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[9]. 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 the latest advanced hardware capabilities. 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. May recent studies have highlighted the existence of significant computer science skills shortages, across the world[13], [14]. These skills shortages may be significantly limiting the possibility for cross-disciplinary work to utilise fast, advanced simulations.

Many initiatives are being rolled out to address this issue. Computing was added to the National Curriculum in 2013[15], [16] and numerous technology companies are also creating their own campaigns[17], [18]. It is likely that these will take a number of years to yield results, but should eventually mean that even domain-experts have a basic grasp of code.

### **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 simula-

tion 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 introduced in the code.

## 2.2 Existing Simulations

### 2.2.1 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. Simulation has 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[19].

### 2.2.2 Agent-Based Modelling

As previously mentioned, ABM models the autonomous behaviour of individual agents and the interaction between them. Agents are often confused with objects, a commonly-used programming concept. However, it's important to emphasize the differences between them. In particular, while both agents and objects recognise the importance of interactions, objects are totally obedient to their method calls whereas agents have autonomy. This means that agents can interact and react to communications according to their own agenda.

While, Agent-Based Modelling is more computationally expensive than top-down mathematical modelling, it is also more natural to model and intuitive to parallelise[20]. Communication between individual agents can be difficult to implement in parallel but parallel communication is by no means limited to ABM.

### Custom Code

A custom code ABM simulation was used to investigate the processes of auxin transport in plants.[9] The simulation focussed on how the transport canals in the stems of plants develop. Unfortunately this simulation did not produce the auxin transportation canals that would be expected from the biological model.

This report builds on an existing custom code example of ABM simulation which utilised Graphics Processing Unit (GPU) parallelism.[4] This simulation was built on a tried and tested domain model of Peyer's Patch development[1]. The simulation was successful in demonstrating the development of Peyer's Patches described in its domain model.

While it is clearly possible for agent-based simulations to be created from scratch there are several distinct disadvantages to doing so. Firstly, using existing frameworks avoid programmers having to reinvent the wheel, massively reducing the amount of code that they need to produce. As well as saving a significant amount of time, commonly used frameworks are often well tested making software bugs less likely. Furthermore, unlike simulations that are created using ABM libraries, they do not inherit any support for new tools and hardware that come from updates to the library. Custom code simulations must each be updated separately with any enhancements required for.

### Proprietary Solutions

Some proprietary solutions are available to aid the creation of efficient ABM simulations. One example of this, with a reasonable level of industry support, is Biocellion[21]. While it is freely-available for non-profit use, it does not help with our aim of creating a simulation platform that is simple-to-use. While it makes the task of creating efficient parallel simulations which are portable far simpler, it requires a level of proficiency with the Linux OS, C++ programming and familiarity with mathematical modelling concepts. In particular, we cannot expect domain experts to be proficient at C++ programming. Software engineers will still be required in the simulation development process. In the future productivity layers which allow simulations to be created by less technical users will be added to Biocellion, but these are not yet available.[21] Biocellion's closed source approach rules out the ability for us to build on this work, while a license agreement has hindered adoption[22]

### MASON

MASON is a multi-agent simulation library for Java. MASON has been previously evaluated as the one of the fastest ABM libraries available[23], however this evaluation took place over a decade ago and does not factor in any of the recent work into GPU parallelism[20]–[22]. Meanwhile, MASON only supports Central Processing Unit (CPU) parallelism, this will be discussed in more detail in Section 2.3.2.

### FLAME GPU

The Flexible Large Scale Agent Modelling Environment (FLAME) project is an attempt to make GPU-based ABM simulations more accessible. FLAME simulations consist of two artefacts, an ‘XML Model File’ containing the structure of agents and their channels of communication and C source code file of ‘Scripted Behaviour’ which defines the actual behaviour of agents. FLAME for the GPU (FLAME 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 power of modern NVIDIA GPUs.

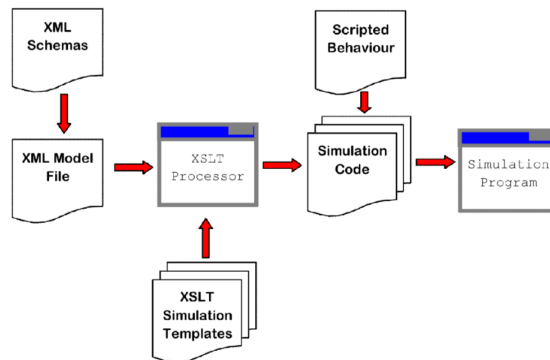


Figure 2.1: FLAME GPU Development Process (Taken from [20])

FLAME’s use of MDE could give domain experts with limited programming knowledge the ability to understand and help design the simulation models, however a software engineer is still needed for the final implementation.

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

relying on any framework is that implementations are restricted by any of the framework's limitations. For example, the current stable release of FLAME GPU does not allow new agents to be created by the Host between simulation steps.

However, the FLAME GPU framework does bring a number of advantages. Firstly, it provides a Message Passing Interface (MPI) which abstracts away from the underlying agent communication. This MPI supports spatial partitioning allowing messages to be passed only to nearby agents. Communication between threads which is one of the most difficult tasks in parallel programming. FLAME GPU manages this communication in its entirety, meaning programmers can instead focus on ensuring the agent behaviour is correct.

FLAME GPU also provides visualisations for simulations straight out of the box. The benefits of visualisation are discussed in Section 2.1.1. Visualisations in FLAME GPU run in real-time and can be useful for quickly verifying whether a simulation is behaving as expected.

Many other advantages come directly from FLAME GPU's use of MDE. FLAME GPU is continuously updated to support new hardware advances, such as multicore GPU architectures[20]. FLAME GPU simulations can always be certain of taking advantage of the latest hardware optimisations and portability features that the framework provides. Existing simulation models that are implemented on top of FLAME GPU may receive these performance improvements without any major code changes.

Some notable benefits of MDE are not exploited in the current implementation of FLAME GPU.

## 2.3 Improving Simulations

Significant constraints on when simulations can be used were discussed in Section 2.1. 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. This section discusses the potential solutions to each of these problems.

### 2.3.1 Ease of Creation

A major constraint on the adoption of simulations is how difficult and time-consuming they are to create. This constraint is exacerbated by



a current shortage of experienced programmers. Initial work to help overcome this skills shortage will likely come by providing tools that can automate work done undertaken 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.

### **Model-Driven Engineering**

This project has already discussed abstractions with regards to modelling for simulations. Abstractions are also particularly useful in software engineering. As software gets more complex, addition abstraction is generally needed in order to extract the important details of the implementation[24, p.24].

MDE is a software abstraction for creating and exploiting domain models, such as those that have been previously discussed with regards to simulations. MDE has shown a promising increase in understanding between stakeholders and can produce productivity gains when models are reused across projects[25].

**Epsilon** Epsilon is a set of tools and languages for supporting MDE. It provides tools for creating metamodels, model validation, model-to-model transformation, code generation and more.[26]

**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[27]. FlexiSketch is a good example of this and provides a good tool for creating models and metamodels for software development[28].

### **2.3.2 Speed Up**

Simulations need to be able to generate results in a realistic amount of time. Many biological simulations include significant elements of randomness meaning must be run a large number of times in order to produce statistically significant results[29]. With novel applications attempting to simulate increasingly complex models, it is becoming more

and more difficult to ensure that they have reasonable runtimes. This section evaluates recent work into achieving faster simulations.

### **Machine Learning**

An upcoming paper explores the possible use of machine learning to emulate and predict the output of an existing simulator[30]. This emulation method produced some very accurate results within seconds, however it still requires an initial training set, and so does not fully remove the desire for fast simulations. As the number of parameters increase, the training set size must also increase in order to produce accurate results. This technique also requires expertise in machine learning which conflicts with our other aim- to make simulations more accessible.

### **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[31]. 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.

Managing parallel implementations of algorithms has significant overheads due to the need to ensure memory integrity when transferring data between parallel tasks. The different approaches to parallelism make different trade-offs, meaning some may be more suited to a particular task than others. In order to ensure that the gains made by parallelising the task are not overshadowed by the overheads of managing a parallel implementation, the simulation programmer must have sufficient knowledge of the approach being used.

**Distributed Systems** A distributed system is a method for running a computer program across multiple computers on a network. Unlike parallelism that is local to a particular computer, with a distributed system there is generally no global clock to ensure that processors are kept in sync. In order for any distributed system model to provide speed improvements, the gains provided by parallelising the data processing step must be substantial enough to overcome the time taken for data transfer between computers.

DMASON is an enhanced version of MASON library which aims to harness unused PCs as a makeshift distributed system. DMASON can also be set up to run on a compute cluster.

**CPU vs GPU** Modern computers provide two main means for parallelising code. We are building on a previous project[4] 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[20]. One case study even reduced the time taken for a simulation to be computed from hours on a CPU to just seconds on a GPU[2].

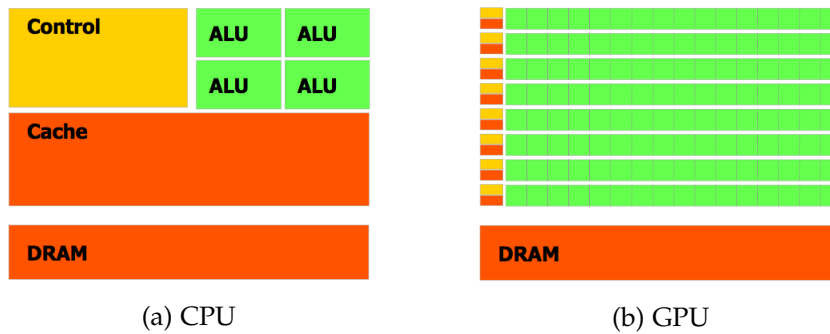


Figure 2.2: Silicon Space Allocation (Taken from [32, p.2])

The key difference between CPU and GPU parallelism lies in the Flynn's taxonomy classification[33] of architecture used by each. CPUs use a Multiple Instruction, Multiple Data (MIMD) paradigm- this is parallelism of instruction as different CPU cores can each be running different instructions concurrently. Meanwhile, GPUs use a Single Instruction, Multiple Data (SIMD) paradigm- this is parallelism of data as the same program is executed on a large quantity of data. These differences can be most starkly visualised by observing the difference in the allocation of transistors between the two components (Fig. 2.2). While the CPU devotes a large amount of space to data caching and flow control, the GPU allocates the vast majority of its capacity to data processing.[32, p.2]

Multiple CPU cores are now commonplace in modern computers, including smartphones. In contrast to this, dedicated GPUs are normally

only found in gaming PCs and consoles.

**CUDA vs OpenCL** A previous project compared CUDA and OpenCL in detail. The key advantage that OpenCL has over CUDA is its portability. Where CUDA is proprietary and runs only on NVIDIA hardware, OpenCL implementations are available for the majority of GPU hardware including AMD, Apple[34], Imagination and NVIDIA.[35] Nevertheless, this portability comes with a cost, code for different hardware must be tailored specifically to each hardware platform and performance has been shown to be consistently poorer[36]. The previous report also concluded that Compute Unified Device Architecture (CUDA) has better library support and is simpler to use[4].

## 3 Tools and Platform

### 3.1 Tools

This project was developed on a machine running Ubuntu 16.04 with Intel i5 (650 @ 3.20 GHz) and 8GB of RAM. The GPU utilised was an NVIDIA GeForce GTX 1050. GPU programming utilised the latest version of CUDA (9.1). CUDA was selected over OpenCL due to it being a requirement of FLAME GPU. Minimal knowledge of CUDA was needed for the development of the project as FLAME GPU handles the majority of the GPU hardware management.

In order to produce a working simulation of Peyer's Patch formation, I have used an unreleased version (v1.5) of FLAME GPU. Amongst other features, FLAME GPU v1.5 adds the ability to create agents from a host function between simulation steps. As FLAME GPU is developed openly, this version is freely available online[37]. FLAME GPU has been added to the project repository as a submodule, to ensure version compatibility between FLAME GPU and *PPSim* v2.

Eclipse Neon v4.6 and Epsilon v1.4 have been used with Java Runtime Environment 1.8.0 for developing the input XML model for FLAME GPU.

Version-control for both the simulation code and this report has been managed through Git and is available on GitHub. As this is an individual project, Git has been an acceptable solution. If the scope of the project is to expand, it may become necessary to move the modelling section of the development into a more suitable version-control system, such as EMFStore[38] which is specifically designed for models.

### 3.2 Peyer's Patch Case Study

This project focuses on simulation as a tool for exploring biological systems at cell level. It uses an existing sequential MASON simulation of Peyer's Patch development[1], [29], [30], [39], [40] (*PPSim*) and attempts to use parallel computer architectures in order to speed this simulation up. The sequential *PPSim* had a runtime of 94.265 seconds and 585,000

executions were required for the statistical sampling technique being used. Even with a significant amount of CPU parallelism (138 processors) available, the combined runtime of these executions is inconvenient and would be intractable for larger scale simulations.[30] As previously stated, FLAME GPU can easily produce results to better a high-performance cluster, such as the one used to compute *PPSim*, even on a standard desktop PC.

### 3.2.1 The Domain Model

This domain model for *PPSim* was developed according to the CoSMoS process[12], which was introduced in Section 1. The model describes the cell behaviour over a 72 hour period in which Peyer's Patches develop. Peyer's Patches are clusters of cells that form on the lining of the small intestine (Fig 4.2).

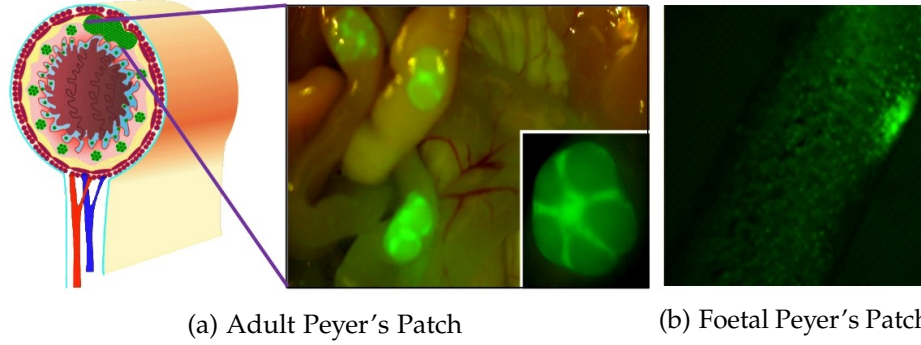


Figure 3.1: Images of In-Vitro Peyer's Patch (Provided by Mark Coles, University of York)

The environment of the model is a 3-dimensional tube modelled in 2-dimensions. Agents leaving the environment in the x-direction are removed from the population and no longer considered. Agents leaving the environment in the y-direction wrap around to the origin.

In this model there are three types of agent which are all types of cells; Lymphoid Tissue organiser cell (LTo), Lymphoid Tissue initiator cell (LTin) and Lymphoid Tissue inducer cell (LTi). State diagrams that describe the behaviour of each of these cells were presented as part of the original domain (Fig. 6.1) and platform models (Fig. 6.2)[1].

Stationary LTo cells

The model starts when L<sub>Ti</sub>/L<sub>Tin</sub> cells begin migrating into the environment. As such, at the beginning of the simulation, neither of these cells are present. L<sub>Ti</sub> and L<sub>Tin</sub> cells migrate into the environment at a constant rate, such that the correct number of cells is reached at the 12 hour time-step.

Initially the L<sub>Ti</sub> and L<sub>Tin</sub> cells move randomly around the environment.

### 3.3 The Platform Model

In this platform model there is a single *active* L<sub>To</sub> cell in the centre of the environment.

These L<sub>To</sub> cells divide every 12 hours. A previous project on this topic stated that L<sub>To</sub> cell division must be performed sequentially on a host function in order to prevent new cells occupying the same space[4]. However, by adding a force resolution step, as used in previous FLAME GPU simulations[2], this has been implemented in parallel, on the device. As well as the speed up from parallelising the division step, implementing the feature in this way has also removed the cost of data transfer between the Device and Host.

There are no L<sub>To</sub> and L<sub>Tin</sub> cells in the environment when the simulation is initialised. A Host function manages the migration of L<sub>To</sub> and L<sub>Tin</sub> cells into the environment by creating these cells in random positions at a constant rate.

## 4 Methods

The chapter details the simulation experiment that has been performed and the development of new tools to aid the implementation of this, and future simulations. The experiment involved the development of a new GPU-based *PPSim v2* platform implementation as well as a new tool for mapping and transforming biological models into FLAME GPU simulations. Having previously established the current difficulties with biological simulation, this chapter also details how these are overcome in the implementation of this project.

### 4.1 FLAME GPU Simulation

As previously mentioned the FLAME GPU implementation requires the creation of two artifacts. A structural ‘XML Model File’ which defines the agents in the system and their allowed channels for communication. A C source code file of ‘Scripted Behaviour’ defines the actual behaviour of agents.

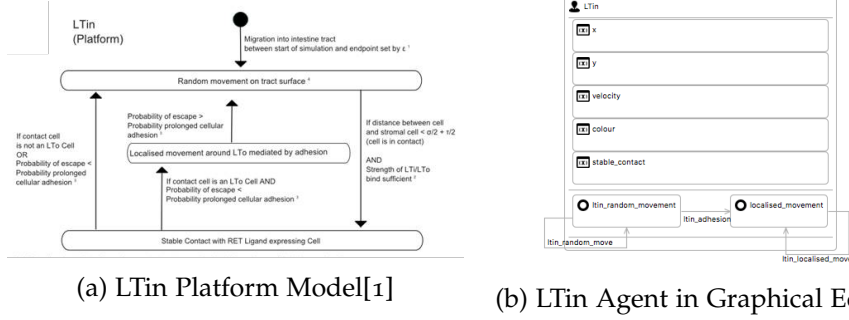
#### 4.1.1 Structural Model

FLAME GPU defines agents as X-machines in its XML model. X-machines are structurally identical to finite state machines, other than that they have memory, which means it was possible to directly implement most of the platform model state diagrams directly into the FLAME GPU model (Fig. 4.1).

During the development of the model implementation, there were many occasions where the XML of the model became invalid because of mistakes. These mistakes either caused ill-formed XML or an XML model which did not conform to the FLAME GPU model schema. In order to mitigate the issues caused by these mistakes, a new tool was created using the Epsilon Modelling Framework. The new tool ensures that any XML files that are created are valid XML and conform to the FLAME GPU model schema.



In the tool FLAME GPU models are designed using a graphical interface (Figs. 4.1b, 6.3) and then exported to the required XML file format. Adding this GUI front end to FLAME GPU is a major step towards ensuring these parallel ABM simulations are more easily accessible by non-technical users.



```

<gpu:xagent>
  <name>LTin</name>
  <description>Lymphoid Tissue initiator cell</description>
  <memory>
    <gpu:variable>
      <type>float</type>
      <name>x</name>
    ...
  </memory>
  <functions>
    <gpu:function>
      <name>ltin_random_move</name>
      <currentState>ltin_random_movement</currentState>
      <nextState>ltin_random_movement</nextState>
    ...
  </functions>
  <states>
    <gpu:state>
      <name>ltin_random_movement</name>
    </gpu:state>
    ...
    <initialState>ltin_random_movement</initialState>
  </states>
  <gpu:type>continuous</gpu:type>
  <gpu:bufferSize>5530</gpu:bufferSize>
</gpu:xagent>

```

(c) Autogenerated FLAME GPU XML Model for LTin Agent

Figure 4.1: Autogeneration of FLAME GPU Model File

In addition to ensuring that only valid models can be produced the graphical tool has a number of other benefits. The original platform model (Fig. 4.1a) and the FLAME GPU implementation (Fig. 4.1b) can now be compared at a glance. For example, it is immediately obvious that the platform model has been refined to include only two states in the final implementation. The removal of the ‘Stable Contact’ state is logical- this state is instantaneous and immediately transitions into either

## 4 Methods

localised movement or random movement, meaning its transitions can be merged into those which already exist between the other two states.

A number of other differences were made to the platform model, mainly because of the time limitations of the project. The decision to only include a single central LTo cell in the simulation meant that the 'No Expression of RET-Ligand' state could be removed, as it cannot be reached.

The platform model diagram for LTi cells has a missing transition. As LTo cells do not constantly release chemokines, it is possible for the cell to make contact with an LTo cell without first transitioning through the response to chemokine state. This transition was present into the original MASON implementation of *PPSim*, but was never corrected in the state diagram. It has also been added into the new FLAME GPU implementation.

### 4.1.2 Behavioural Model

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

### 4.1.3 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

## 4.2 Graphical Modelling Tool

In order to implement a tool to support my FLAME GPU development, the Epsilon Modelling Framework was selected. The decision to use this framework was simple, as it provides all the tools required and I was already familiar with it. The aim was for the tool to *directly* map the platform model structures into the required FLAME GPU XML model. This should significantly improve the model design experience and allow for domain experts to be kept more involved with the simulation creation. This new process is shown as part of the CoSMoS process in Fig. 4.3.

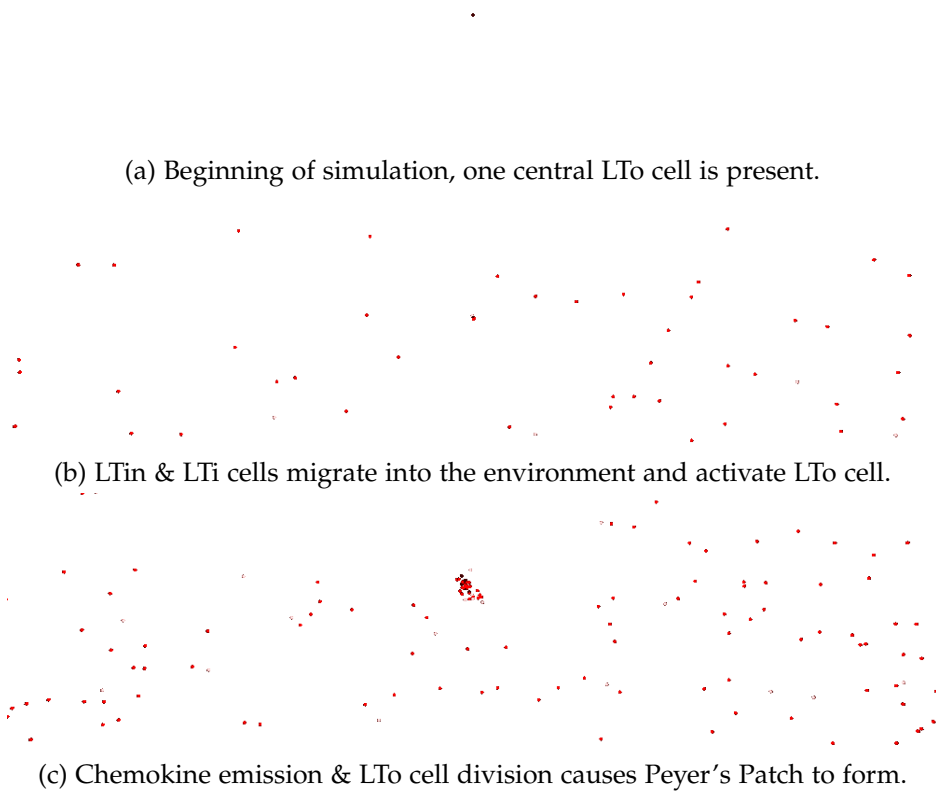


Figure 4.2: Visualisation of *PPSim v2* produced using FLAME GPU

Figure 6.3 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.

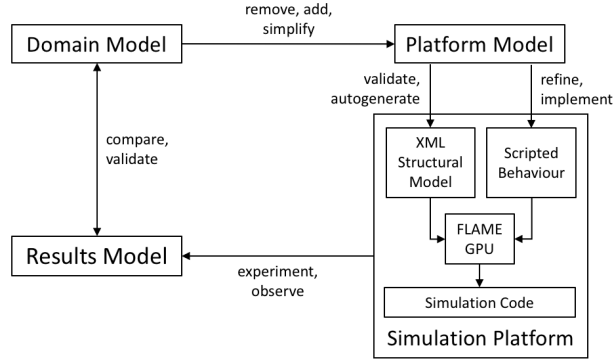


Figure 4.3: Autogeneration of FLAME GPU Artifact as part of the CoS-MoS Development Process

#### 4.2.1 Metamodel

The development of a metamodel was guided by the existing FLAME GPU XML model schema. This model schema is itself a metamodel for the FLAME GPU model file.

Much of the new metamodel matches the FLAME GPU schema. There is a top level simulation object which contains a list of agents, a list of messages that agents can send, a list of global variables, etc. The main difference in the new metamodel is its ability to utilise references to objects.

Using references to objects ensures that the objects being referenced exist, which must be the case for model to be valid.

#### 4.2.2 EuGENia

#### 4.2.3 Epsilon Generation Language

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

### 4.2.4 Epsilon Validation Language

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

Figure 4.4: Graphical validation using EVL constraints

The EVL has allowed well-formedness constraints to be implemented for the FLAME GPU input model. This should provide intuitive feedback (Fig. 4.4) in cases where the model may be incorrect, in order to prevent an invalid XML model from being produced.

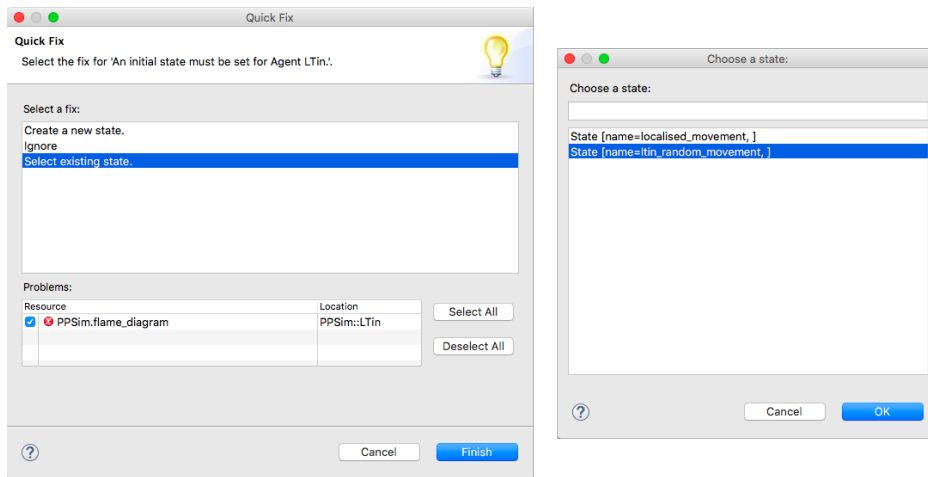


Figure 4.5: Quick fix of invalid model

Quick fixes (Fig. 4.5) have also been implemented to guide the user through easily correcting their invalid model. The error feedback provided by these quick fixes is much more intuitive than that provided by FLAME GPU.

## 5 Results and Evaluation

### 5.1 Findings

#### 5.1.1 Ease of Creation

This proof of concept has shown that direct mappings from a biological domain model to a platform implementation are possible. Based on this, further work is now being developed with Paul Richmond's FLAME GPU group, to enhance the accessibility of FLAME GPU for simulation developers. This should allow the simulation developer to focus on getting their domain details correct, rather than battling the agent platform. An improved mapping, which abstracts away all implementation details, could bring additional benefits in this area, including ensuring that the simulation code always supports the latest hardware features.

An additional benefit of this mapping, provides traceability from the domain model through to the simulation code. We can have greater certainty that the simulation is faithful to the domain and no bugs have been produced during the implementation.

*This work is ongoing.*

#### 5.1.2 Speed Up

An initial aim of this project was '*to explore the speed increases that can be produced by using GPGPU programming*'. Unfortunately the differences between the MASON and FLAME GPU platforms have meant that it is not trivial to compare them. This initial hypothesis of the platform models being comparable is untenable.

Instead, a new hypothesis is that the platform model for the FLAME GPU implementation is comparable to the original biological model. If our new platform model can be shown to be similar to the original PPSim domain model, we can say that this simulation also shows Peyer's Patch development..?

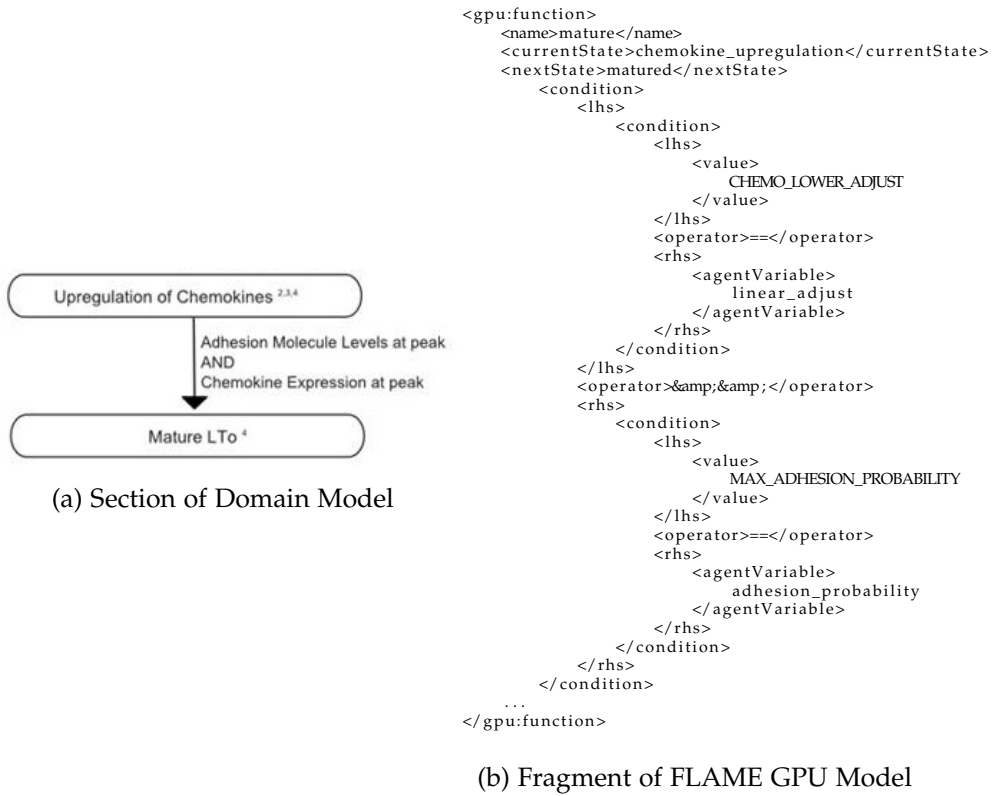


Figure 5.1: Traceability from Domain Model to FLAME GPU Implementation

## 5.2 Conclusion

## 5.3 Further Work

### 5.3.1 Peyer's Patch Case Study

While the simulations are not entirely comparable, I have shown that fast, parallel implementations can be created using FLAME GPU. Further work on this topic is needed to show that these implementations can also produce results quickly when scaled up. With this simulation in particular some options for increasing the scale include modelling in 3-dimensions, adding further cell types and biological factors and cell types into the model, and simulating the whole length of the gut rather than a small section.

While the two Peyer's Patch simulations are both derived from the same domain model, there are clearly significant implementation differences between these, as is discussed earlier in this report. Future work will need to explore the meaning of the differences between simulations and whether that have any effect on their validity against the domain model.

Spartan is a tool for understanding relationships and providing novel biological insight into simulation behaviour. Spartan was use for analysing the results of the original PPSim implementation[29] and may provide an insight into validity of the parallel *PPSim v2* implementation.

### 5.3.2 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 general agent behaviour in these forms of biological simulation. The reuse of a previous simulation's implementation of cell division behaviour, has shown that at least some behaviour is common across different simulations. The power of MDE is such that this repeated behaviour should be generalised to reduce the time needed and prevent the mistakes that occur during reimplementing of the similar software features.

On top of this, with the current implementation, technical implementation details (layer functions and agent partitioning) have become part of the model. Ideally these should be extracted from the model implementation and automated.



### **5.3.3 Hardware Availability**

One of the greatest challenges of this project has been gaining access to NVIDIA GPU hardware. While these are available off the shelf in most high-street computer retailers, they are not commonly found as part of standard desktop PCs, which generally containing integrated graphics hardware. Indeed, none of the software lab PCs at the University of York contain the dedicated graphics chips required to run this software. Future work could reevaluate whether the benefit of a cross-platform API, such as OpenCL, could outweigh the performance benefit provided by CUDA.

## Bibliography

- [1] K. J. Alden, “Simulation and Statistical Techniques to Explore Lymphoid Tissue Organogenesis”, PhD thesis, University of York, Heslington, York, 2012.
- [2] P. Richmond, D. Walker, S. Coakley and D. Romano, “High performance cellular level agent-based simulation with FLAME for the GPU”, *Briefings in Bioinformatics*, vol. 11, no. 3, pp. 334–347, 2010. DOI: 10.1093/bib/bbp073.
- [3] M. N. Read, “Statistical and Modelling Techniques to Build Confidence in the Investigation of Immunology through Agent-Based Simulation”, PhD thesis, University of York, Heslington, York, 2011.
- [4] P. Drew, “Parallel Programming Tools for Exploring Immune System Development”, Master’s thesis, University of York, Heslington, York, 2017.
- [5] J. A. DiMasi, H. G. Grabowski and R. W. Hansen, “Innovation in the pharmaceutical industry: New estimates of R&D costs”, 2016, pp. 20–33. DOI: 10.1016/j.jhealeco.2016.01.012.
- [6] K. Cheng and P. A. Cairns, “Behaviour, Realism and Immersion in Games”, in *CHI ’05 Extended Abstracts on Human Factors in Computing Systems*, ser. CHI EA ’05, Portland, OR, USA: ACM, 2005, pp. 1272–1275, ISBN: 1-59593-002-7. DOI: 10.1145/1056808.1056894. [Online]. Available: <http://doi.acm.org/10.1145/1056808.1056894>.
- [7] United Nations Office for Disarmament Affairs. (Oct. 1963). Partial Nuclear Test Ban Treaty, [Online]. Available: [http://disarmament.un.org/treaties/t/test\\_ban](http://disarmament.un.org/treaties/t/test_ban) (visited on 08/02/2018).
- [8] U.S. Department of State. (Dec. 1990). Threshold Test Ban Treaty, [Online]. Available: <https://www.state.gov/t/isn/5204.htm> (visited on 08/02/2018).

- [9] P. Garnett, S. Stepney and O. Leyser, “Towards an Executable Model of Auxin Transport Canalisation”, in *Proceedings of the 2008 Workshop on Complex Systems Modelling and Simulation, York, UK, September 2008*, 2008, pp. 63–91. [Online]. Available: <http://www.cs.kent.ac.uk/pubs/2008/2920>.
- [10] Curiscope Ltd. (). Curiscope, [Online]. Available: <https://www.curiscope.co.uk> (visited on 05/02/2018).
- [11] Little Sparks Hospital Ltd. (). Little Sparks Hospital, [Online]. Available: <https://littlesparkshospital.com> (visited on 05/02/2018).
- [12] P. S. Andrews, F. A. C. Polack *et al.*, “The CoSMoS Process, Version 0.1: A Process for the Modelling and Simulation of Complex Systems”, 2010. [Online]. Available: <http://www.cs.york.ac.uk/ftpdireports/2010/YCS/453/YCS-2010-453.pdf> (visited on 19/04/2018).
- [13] Ecorys UK, “DIGITAL SKILLS for the UK ECONOMY”, Jan. 2016. [Online]. Available: <https://www.gov.uk/government/publications/digital-skills-for-the-uk-economy> (visited on 15/01/2016).
- [14] Microsoft. (Dec. 2012). Investing in American Innovation and the Next Generation, [Online]. Available: <https://blogs.microsoft.com/on-the-issues/2012/12/12/investing-in-american-innovation-and-the-next-generation/> (visited on 16/01/2018).
- [15] Department for Education, UK. (11th Sep. 2013). National curriculum in England: computing programmes of study, [Online]. Available: <https://www.gov.uk/government/publications/national-curriculum-in-england-computing-programmes-of-study> (visited on 19/04/2018).
- [16] —, (3rd Jun. 2014). Microsoft, Google and IBM to help train computing teachers, [Online]. Available: <https://www.gov.uk/government/news/microsoft-google-and-ibm-to-help-train-computing-teachers> (visited on 23/04/2018).
- [17] Apple. (24th May 2017). Apple launches app development curriculum for high school and community college students, [Online]. Available: <https://www.apple.com/uk/education/teaching-code/> (visited on 19/04/2018).

## Bibliography

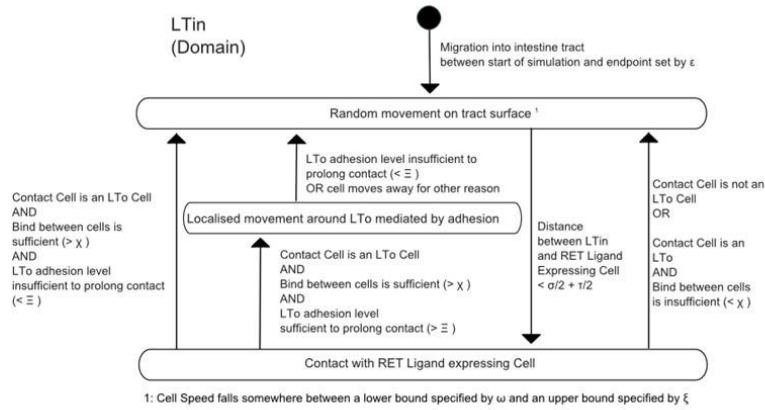
- [18] Microsoft News Center. (16th Sep. 2015). Microsoft expands global YouthSpark initiative to focus on computer science, [Online]. Available: <https://news.microsoft.com/2015/09/16/microsoft-expands-global-youthspark-initiative-to-focus-on-computer-science/> (visited on 23/04/2018).
- [19] D. Noble, “The rise of computational biology”, *Nature Reviews Molecular Cell Biology*, vol. 3, pp. 459–463, 2002. DOI: 10.1038/nrm810.
- [20] P. Richmond and D. Romano, “Template-Driven Agent-Based Modeling and Simulation with {CUDA}”, in *{GPU} Computing Gems Emerald Edition*, ser. Applications of GPU Computing Series, W.-m. W. Hwu, Ed., Emerald Edition, Boston: Morgan Kaufmann, 2011, pp. 313–324, ISBN: 978-0-12-384988-5. DOI: <https://doi.org/10.1016/B978-0-12-384988-5.00021-8>.
- [21] S. Kang, S. Kahan, J. McDermott, N. Flann and I. Shmulevich, “Biocellion : accelerating computer simulation of multicellular biological system models”, *Bioinformatics*, vol. 30, no. 21, pp. 3101–3108, 2014. DOI: 10.1093/bioinformatics/btu498. [Online]. Available: <http://dx.doi.org/10.1093/bioinformatics/btu498>.
- [22] A. Ghaffarizadeh, R. Heiland, S. H. Friedman, S. M. Mumenthaler and P. Macklin, “PhysiCell: An open source physics-based cell simulator for 3-D multicellular systems”, *PLOS Computational Biology*, vol. 14, no. 2, pp. 1–31, Feb. 2018. DOI: 10.1371/journal.pcbi.1005991. [Online]. Available: <https://doi.org/10.1371/journal.pcbi.1005991>.
- [23] S. F. Railsback, S. L. Lytinen and S. K. Jackson, “Agent-based Simulation Platforms: Review and Development Recommendations”, *SIMULATION*, vol. 82, no. 9, pp. 609–623, 2006. DOI: 10.1177/0037549706073695.
- [24] R. E. Bryant and D. R. O’Hallaron, *Computer Systems: A Programmer’s Perspective*, 2nd ed. Prentice Hall, 2011.
- [25] J. Hutchinson, J. Whittle and M. Rouncefield, “Model-driven engineering practices in industry: Social, organizational and managerial factors that lead to success or failure”, *Science of Computer Programming*, vol. 89, no. Part B, pp. 144–161, 2014, Special issue on Success Stories in Model Driven Engineering, ISSN: 0167-6423. DOI: <https://doi.org/10.1016/j.scico.2013.03.017>. [Online]. Available: <http://www.sciencedirect.com/science/article/pii/S0167642313000786>.

- [26] D. Kolovos, L. Rose, A. García-Domínguez and R. Paige, *The Epsilon Book*. 30th Nov. 2017. [Online]. Available: <https://www.eclipse.org/epsilon/doc/book/> (visited on 17/12/2017).
- [27] R. F. Paige, A. Zolotas and D. Kolovos, ““The Changing Face of Model-Driven Engineering””, in *Present and Ulterior Software Engineering*, M. Mazzara and B. Meyer, Eds. Cham: Springer International Publishing, 2017, pp. 103–118. DOI: 10.1007/978-3-319-67425-4\_7. [Online]. Available: [https://doi.org/10.1007/978-3-319-67425-4\\_7](https://doi.org/10.1007/978-3-319-67425-4_7).
- [28] D. Wüest, N. Seyff and M. Glinz, ““FlexiSketch: a lightweight sketching and metamodeling approach for end-users””, *Software & Systems Modeling*, Sep. 2017, ISSN: 1619-1374. DOI: 10.1007/s10270-017-0623-8. [Online]. Available: <https://doi.org/10.1007/s10270-017-0623-8>.
- [29] K. Alden, M. Read, J. Timmis, P. S. Andrews, H. Veiga-Fernandes and M. Coles, ““Spartan: A Comprehensive Tool for Understanding Uncertainty in Simulations of Biological Systems””, *PLOS Computational Biology*, vol. 9, no. 2, pp. 1–9, Feb. 2013. DOI: 10.1371/journal.pcbi.1002916. [Online]. Available: <https://doi.org/10.1371/journal.pcbi.1002916>.
- [30] K. Alden, J. Cosgrove, M. Coles and J. Timmis, ““Using Emulation to Engineer and Understand Simulations of Biological Systems””, unpublished.
- [31] H. Sutter. (Dec. 2004). The Free Lunch is Over: A Fundamental Turn Toward Concurrency in Software, [Online]. Available: <http://www.gotw.ca/publications/concurrency-ddj.htm> (visited on 08/02/2018).
- [32] NVIDIA. (Feb. 2018). CUDA C Programming Guide, [Online]. Available: [https://docs.nvidia.com/cuda/pdf/CUDA\\_C\\_Programming\\_Guide.pdf](https://docs.nvidia.com/cuda/pdf/CUDA_C_Programming_Guide.pdf) (visited on 25/04/2018).
- [33] M. J. Flynn, ““Some computer organizations and their effectiveness””, *IEEE transactions on computers*, vol. 100, no. 9, pp. 948–960, 1972.
- [34] Apple Inc. (8th Aug. 2013). About OpenCL for OS X, [Online]. Available: [https://developer.apple.com/library/content/documentation/Performance/Conceptual/OpenCL\\_MacProgGuide/Introduction/Introduction.html](https://developer.apple.com/library/content/documentation/Performance/Conceptual/OpenCL_MacProgGuide/Introduction/Introduction.html) (visited on 28/04/2018).

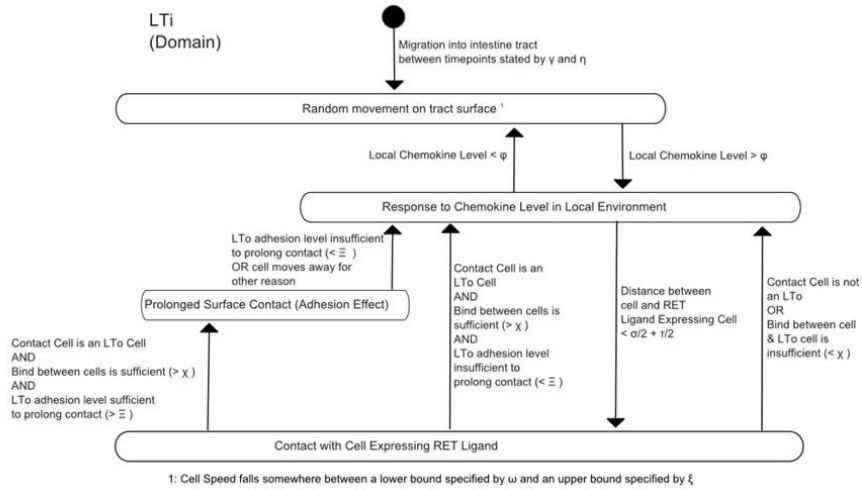
## Bibliography

- [35] The Khronos Group. (). Conformant Companies - The Khronos Group, [Online]. Available: <https://www.khronos.org/conformance/adopters/conformant-companies#opencl> (visited on 28/04/2018).
- [36] K. Karimi, N. G. Dickson and F. Hamze, "A Performance Comparison of CUDA and OpenCL", *CoRR*, vol. abs/1005.2581, 2010. arXiv: 1005.2581. [Online]. Available: <http://arxiv.org/abs/1005.2581>.
- [37] FLAMEGPU. (). FLAMEGPU, [Online]. Available: <https://github.com/FLAMEGPU/FLAMEGPU/branches> (visited on 18/03/2018).
- [38] M. Koegel and J. Helming, "EMFStore: a model repository for EMF models.", in *Proceedings - International Conference on Software Engineering*, vol. 2, Cape Town, South Africa, Jan. 2010, pp. 307–308. doi: 10.1145/1810295.1810364.
- [39] K. Alden, J. Timmis, P. S. Andrews, H. Veiga-Fernandes and M. C. Coles, "Pairing experimentation and computational modeling to understand the role of tissue inducer cells in the development of lymphoid organs", *Frontiers in immunology*, vol. 3, p. 172, 2012.
- [40] A. Patel, N. Harker, L. Moreira-Santos, M. Ferreira, K. Alden, J. Timmis, K. Foster, A. Garefalaki, P. Pachnis, P. Andrews *et al.*, "Differential RET signaling pathways drive development of the enteric lymphoid and nervous systems", *Sci. Signal.*, vol. 5, no. 235, ra55–ra55, 2012.

## 6 Appendix

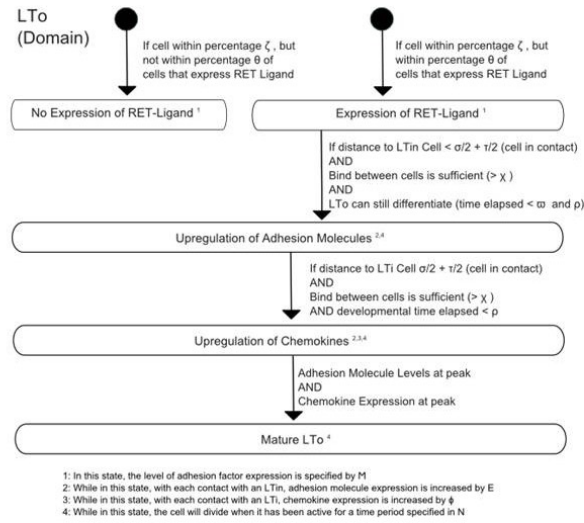


(a) LTI<sub>n</sub>



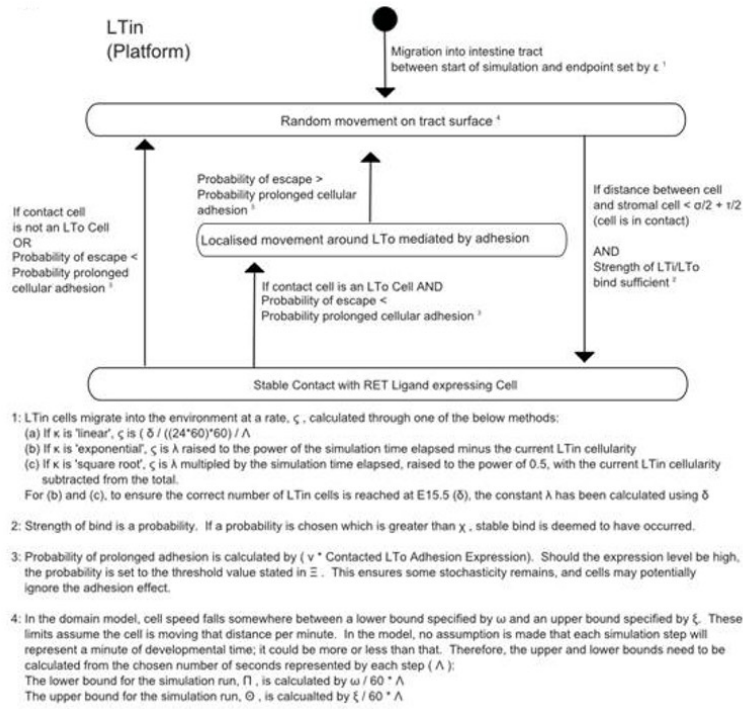
(b) LTI

## 6 Appendix



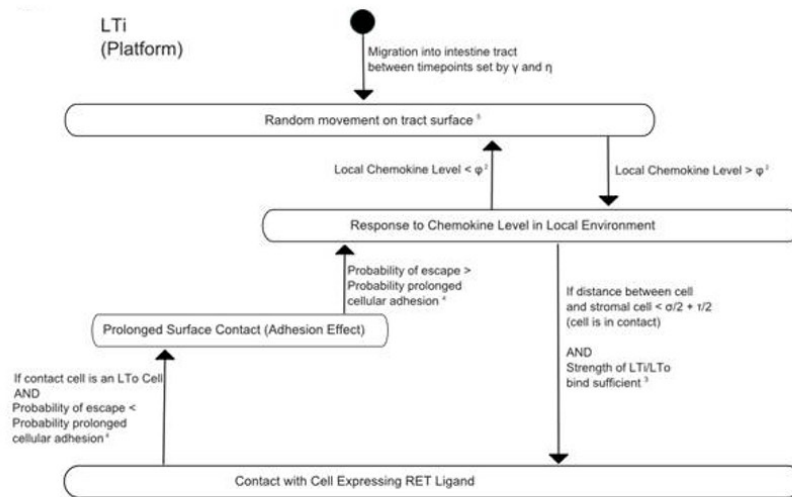
(c) LTo

Figure 6.1: Domain Model State Diagrams



(a) LTin



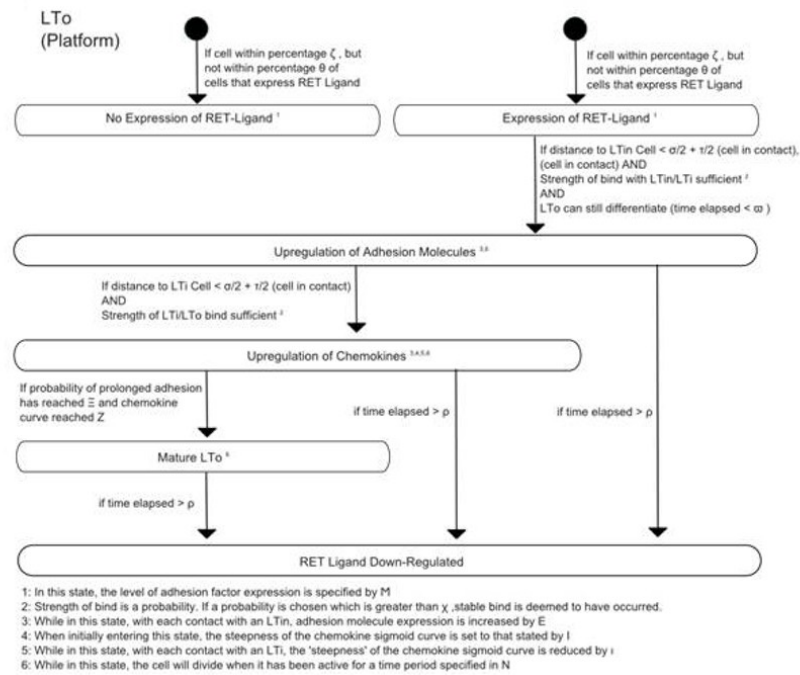


- 1: LTI cells migrate into the environment at a rate,  $\Psi$ , calculated through one of the below methods:
  - (a) If  $\gamma$  is 'linear',  $\Psi$  is  $(\delta / ((24 \times 60) \times 60)) / \Lambda$
  - (b) If  $\gamma$  is 'exponential',  $\Psi$  is  $A$  raised to the power of the simulation time elapsed minus the current LTI cellularity
  - (c) If  $\gamma$  is 'square root',  $\Psi$  is  $A$  multiplied by the simulation time elapsed, raised to the power of 0.5, with the current LTI cellularity subtracted from the total.
 For (b) and (c), to ensure the correct number of LTI cells is reached at E15.5 ( $\phi$ ), the constant  $A$  has been calculated using  $\phi$
- 2: To ascertain chemokine level, the model will calculate the level in each 'gridsquare' around the cell. More detail in the environment description on how this is done. If the strongest level is greater than  $\phi$ , the cell will move in that direction
- 3: Strength of bind is a probability. If a probability is chosen which is greater than  $\chi$ , stable bind is deemed to have occurred.
- 4: Probability of prolonged adhesion is calculated by  $(v \times \text{Contacted LTo Adhesion Expression})$ . Should the expression level be high, the probability is set to the threshold value stated in  $\Xi$ . This ensures some stochasticity remains, and cells may potentially ignore the adhesion effect.
- 5: In the domain model, cell speed falls somewhere between a lower bound specified by  $\omega$  and an upper bound specified by  $\xi$ . These limits assume the cell is moving that distance per minute. In the model, no assumption is made that each simulation step will represent a minute of developmental time; it could be more or less than that. Therefore, the upper and lower bounds need to be calculated from the chosen number of seconds represented by each step ( $\Lambda$ ):
 

The lower bound for the simulation run,  $\Pi$ , is calculated by  $\omega / 60 \times \Lambda$

The upper bound for the simulation run,  $\Theta$ , is calculated by  $\xi / 60 \times \Lambda$

(b) LTI



(c) LTo

Figure 6.2: Platform Model State Diagrams[1]

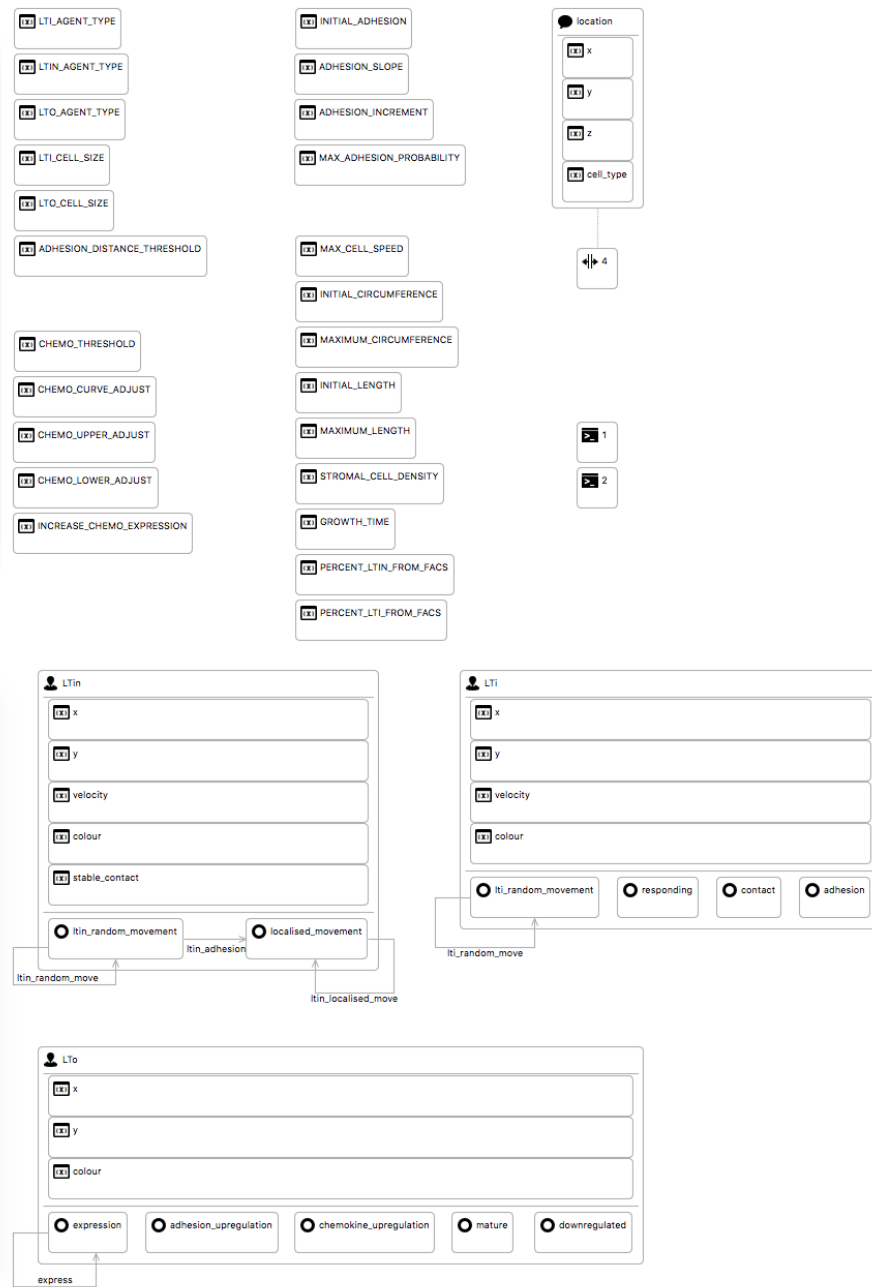


Figure 6.3: Graphically produced FLAME GPU Simulation model for Peyer's Patch