# Project Preparation Report
# Bayesian Inference Using Sequential Monte-Carlo Algorithm for Dynamic System Models

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# Contents

# 1 Introduction

This report focuses on the work in the preparation phase of MSc High-performance Computing with Data Analysis Dissertation Project. The project is built around a biological dynamical systems model with parameter estimation and model comparison being the primary tasks. The complex interactions between several cells and molecules in zebrafish spinal cord regeneration is the modelling target.

Previous dissertation review section gives comments on the content and presentation of a dissertation report. The background of this project is introduced in detail regarding several aspects of the project with the motivation and related literature discussed. The preliminary work includes background research, literature review, tools and techniques research and their results are illustrated. The final project proposal and workplan breakdown are given with regards to the conclusion from background research and discussion with supervisors, together with a estimated project timeline. Risk analysis and possible outline of dissertation report are also addressed.

The project aims at the parameter estimation and model comparison. As a kind of computational Bayesian inference methods, Approximate Bayesian computation (ABC) approaches will be used to estimate parameters of mathematical models and compare our model with alternative ones. A parallel implementation is of our interests and performance data and inference outputs from ABC will be analysed then to evaluate the result.

# 2 Previous Dissertation Review

The reviewed previous dissertation is *Modelling Room Acoustics with a GPU* by Jacob Josiah Webber, finished in August 2017.

## Summary

Finite-difference time-domain (FDTD) techniques are introduced to numerically solve an acoustics model. The sound will be affected by the room it is in. The solution of wave equations of the sound can be computationally approximated using FDTD. It is a traditional simulation job for GPU. To improve the performance, the author proposed a 'bounding box' method, whose accompanied data structure significantly reduced memory usage and resultant simulation computation time is saved.

## Does the dissertation adequately explain the context in which the problem is set?

The motivation is addressed in Chapter 1 (Introductions) and the first part of Chapter 2. It briefly introduced together with its performance concerns. More details could be added to describe the meaning of this modelling mission and performance optimisation mission with relevant application or implementation examples given to clarify it.

The background and literature review is represented adequately in details. Section 2.1 derived formulas about acoustics wave, applied finite-difference on them and obtained an iterative propagation computation equation (Equation 2.15) which is the operation o the numerical modelling. Related boundary conditions and stencilling operations are also properly described. Later sections (2.3 and 2.4) addressed the GPU-based parallelisation and FDTD performance issues in the acoustics modelling context.

The background and literature review section is well structured and addressed and explains the problem background in a way that readers without much-related background knowledge (e.g. acoustics, GPU structures) could understand it.

### Has the student adequately explained the scope of the problem, the approach that they would take, how success would be measured and reflected on the outcomes?

The aim of the project is to propose a new method and improve the modelling performance. To address the benefits of the proposed method, the author gave both theoretical (section 3.3)and experimental (section 5.2) analysis to prove its effectiveness. The software development process (section 4.2) and theoretical derivation and implementation of the 'bounding box' method (2.4.1 and 3.2) are reasonable and adequate.

The reproducibility is achieved by giving the specific hardware platforms (NVIDIA K20 GPU server) and its environment (Appendix B), as well as source code and building instructions. As the author addressed in section 5.3, the replication of the program should output a consistent timing results to ones in Table 5.1 and 5.2.

In regard of the limitations, as stated in the conclusion section, 'particular effort was made to avoid choosing rooms that were overly suited to the new method'; however more test case should be given to make the results more convincing. Another limitation has been stated in the introductory paragraphs of Chapter 4, where experimentation and results analysis are not fully explored due to lack of time.

The overall outcome is satisfying as it matches the theoretical prediction and the improvement is significant compared to previous method, regardless of the above limitations.

### Quality of presentation

The language is accurate and descriptions of the theories, designs and implementations are clear to follow.

The listed figures are informative. E.g., Figure 2.1 gives clear representation of the stencilling operations, and Figure 3.1 is a suitable example to illustrate the theories.

The dissertation is well structured such that the process of the project and the works in each stage of the project are included. The tables and algorithm blocks are all represented in clear academical forms, so do their placement and alignment. The formulas and equations, algorithm blocks and figures are all consistently numbered and referred properly.

The references are managed in a consistent manner and are correctly referred when needed. The appendices include original unsummarised data, code and GPU device information which provide meaning supplement when readers want to check some details not mentioned in the main body. However some other content should also be presented here, e.g. implementation environment, experiment input (boundary settings) and benchmarking tools/methods.

## 3 Background and Literature Review

Mathematical models are helpful in resolving complex interactions in real-life dynamical systems. The project will use a mathematical model to represent zebrafish spinal cord regeneration process, then determine its parameter estimation and compare it with alternative models.

Zebrafish is one kind of freshwater fish that is widely used in scientific research for its regenerative abilities. Zebrafish can regenerate their spinal cord after injury. Tsarouchas et al.[1] revealed how the

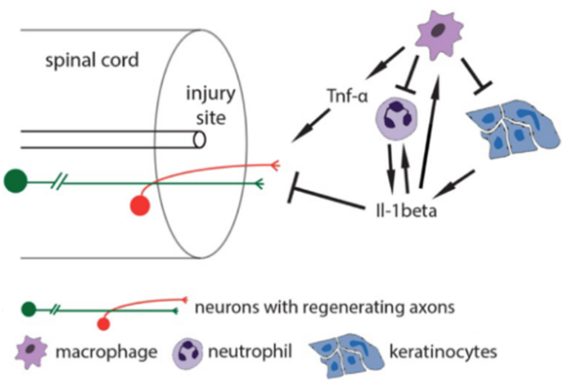


Figure 1: Interactions in zebrafish spinal cord regeneration, proposed by Tsarouchas et al[1]. Lines ended with an arrow indicate promotion and lines ended with a short segment indicate inhibition

immune system responds to allow axons of nerve cells growth across the lesion site. The experiments showed evidence that several kinds of immune cells and cytokines play determinative roles in regulating inflammation and repair. Cytokines are small proteins secreted by certain cells to pass signals across cells. The regeneration process is controlled by two cytokines, Il-1$\beta$ and Tnf-$\alpha$. Generally, Il-1$\beta$ inhibits the regeneration while Tnf-$\alpha$ promotes it, both of which are dynamically controlled by mainly two kinds of immune cells (i.e. macrophage, neutrophil). Based on these experimental results the initial hypothesis is proposed that the repair process are dynamically controlled by interactions between these cells and cytokines. Figure 1 illustrates the basic interactions.

Mathematical models used to describe complex interactions of dynamical systems are usually in the form of differential equations. Analytically solving differential equations is not always feasible and the solution can be extremely complicated especially for complex systems, so often dynamical system models are solved numerically to generate data, which can be compared with real data and determine model error. According to our hypothesis an initial ordinary differential equation system can be built by describing the dynamics of number or concentration of immune cells and cytokines. The initial equations shown in (1) are preliminary equations that represent the dynamical model, which might be adjusted or calibrated according to modelling results and real-world data.

In (1), $N$ and $\Phi$ represent the number of neutrophil and macrophage respectively, $\alpha$ and $\beta$ denotes the relative concentration of cytokines Tnf-$\alpha$ and Il-1$\beta$. $\lambda$, $\kappa$, $\mu$, $s$, $i$ and $\nu$ with different subscripts are all model parameters i.e. coefficient in the interactions.

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= \lambda_N + \kappa_{N\beta}\beta - \mu_N N - \nu_{N\Phi} N\Phi \\
\frac{\mathrm{d}\Phi}{\mathrm{d}t} &= \lambda_\Phi + \kappa_{\Phi\beta}\beta - \mu_\Phi \Phi \\
\frac{\mathrm{d}\beta}{\mathrm{d}t} &= \frac{s_{\beta N} N}{1+i_{\beta\Phi}\Phi} - \mu_\beta \beta \\
\frac{\mathrm{d}\alpha}{\mathrm{d}t} &= s_{\alpha\Phi}\Phi - \mu_\alpha \alpha
\end{aligned} \tag{1}$$

A mathematical model will introduce parameters (e.g. $\kappa$, $\mu$ ,etc in (1)), which are to be determined to give a specific model using observed data. A traditional method to find the best desired parameter sets is to apply an optimisation-based fitting, where the discrepancy of the model's predictions and experimental data is minimised. Alternatively, by adopting Bayesian inference, we can focus on the experimental data and try to infer the parameter sets. Many approaches have been proposed and used in the area of systems biology[2]. Compared to optimisation-based fitting methods, Bayesian inference approaches can relieve the concerns of over-fitting and local optima. It focuses on posterior distribution which represents parameters' 'uncertainty' given the observation data. As Bayes rule stated, the posterior distribution $p(\theta|D)$ is proportional to product of likelihood and prior

$$p(\theta|D) \propto l(\theta|D)p(\theta) \tag{2}$$

where $\theta$ denotes parameter vector, $l$ is the likelihood function and $D$ is the observed data.

The prior distribution $p(\theta)$ is given to specify the initial estimates on parameters before observing the data; the likelihood is given as conditional probability $l(\theta|D)$ which indicates how well the observed data is explained by the parameter $\theta$.

It can be hard to find an analytical expression for likelihood, especially in large complex models. Computational approaches such as Markov Chain Monte Carlo[3] techniques could be used to solve this, where sampling methods are provided to computationally evaluate the likelihood. Approximate Bayesian computation (ABC) methods are alternative solutions. They are likelihood-free methods that simulate data from model and approximate posterior distribution instead of evaluating the likelihood. There are several ABC approaches e.g. ABC-rejection, ABC-MCMC and ABC-SMC (sequential Monte Carlo)[4]. S.A. Sisson[5] suggested that sequential Monte Carlo sampler in ABC can be more powerful and efficient than ABC-MCMC and traditional ABC rejection methods.

ABC approaches have been widely used in biology applications due to their 'likelihood-free' feature. In many systems biology models, the likelihood is intractable, meaning that it cannot be defined as a function of the parameters $\theta$ analytically. Liepe et al.[6] showed a successful application of ABC-SMC in systems biology with a software package ABC-SysBio, where ABC-SMC is used both in parameter estimation and model selection.

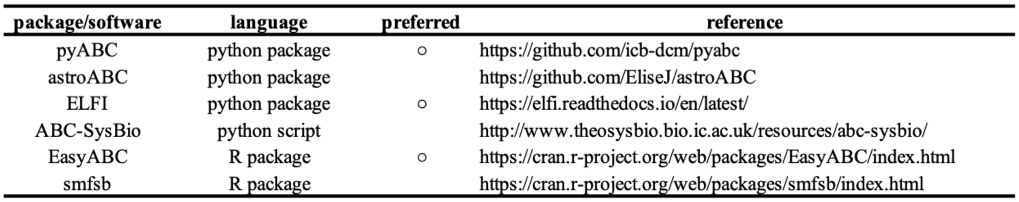
Parameters of the zebrafish spinal cord regeneration model can be estimated using ABC-SMC as it is hard to find exact likelihood here and an efficient approximation approaches might help us in exploring the uncertainty in parameter sets and comparing our model with alternative ones.

# 4 Preliminary Investigations

Preliminary works include background material study and tools research, which aims to build a concrete start of the project and explore the uncertainty and suitability of tools.

## 4.1 Background Research

The two key background papers[1, 6] were studied firstly. Tsarouchas et al.[1] illustrated the biology process (zebrafish spinal cord regeneration after injury) that we want to model and introduced the dynamic controls within the process in details. As shown in the paper the process requires related biology background knowledge, especially in immunology, thus related necessary background materials were studied to form a more comprehensive understanding and could help in future analyse of results. The other background paper focuses on the algorithms that are expected to be implemented in the project. More materials related to Bayesian inference were studied, including tutorials, books and articles. Basic theories of Bayesian inference and practical examples were studied with several ABC tutorial examples practised to improve understanding. Other background materials include papers on ABC-SMC algorithm, including the theory, implementation steps and comparison with other ABC algorithms.



| package/software | language | preferred | reference |
|---|---|---|---|
| pyABC | python package | ○ | https://github.com/icb-dcm/pyabc |
| astroABC | python package | | https://github.com/EliseJ/astroABC |
| ELFI | python package | ○ | https://elfi.readthedocs.io/en/latest/ |
| ABC-SysBio | python script | | http://www.theosysbio.bio.ic.ac.uk/resources/abc-sysbio/ |
| EasyABC | R package | ○ | https://cran.r-project.org/web/packages/EasyABC/index.html |
| smfsb | R package | | https://cran.r-project.org/web/packages/smfsb/index.html |

Figure 2: Studied packages

The mathematical models were also preliminarily studied, with concerns over model building, data processing and solving. Ordinary differential equation computational solution and its solver were reviewed in preparation for the future actual implementation.

The background research is the most important work in the preparation phase, as it converted the first impression and interests of the project into concrete knowledge in the biology and statistical inference basis such that the mission, risks and challenges of the project could be discussed and analysed; it also ensured an easier technically start of the project.

## 4.2 Tools Research

Besides the background research, tools that might be used in the project, mainly the packages and libraries, were studied, compared and evaluated.

There are currently varies of tools and softwares that implement ABC-SMC. A desirable tool should take many technical aspects into account, e.g. working environment, mathematical models solvers, parallelisation support and reliability.

ABC-SMC is expected to be applied in Python or R languages, as most of the published packages are implemented on these two languages; further studies may use other languages if a more suitable software package for that is found or we need to build our own code for optimising.

The studied packages are listed in Figure 2. Their user guidance, documentations (if exist) are viewed, from which their features are concluded in a note (taskPackages.md under tasks directory in project repository); their main features are listed below.

1. pyABC
   - It has built-in support for multiple types of parallelisation, e.g., multicore processing and distributed cluster
   - Stored runs can be resumed
   - Several built-in visualisation for the results are provided
2. astroABC
   - It supports parallel sampling using MPI or multiprocessing
   - Every run of the sampling can be paused and resumed later
3. ELFI
   - It allows user to connect to `ipyparallel` for more parallelisation options

- It uses directed acyclic graph as input model; a conversion is needed before implementation

4. ABC-SysBio
    - It has experimental CUDA accelerated parallelisation support
    - It is specially designed for systems biology applications
5. EasyABC
    - It supports multicore parallelisation
    - Several different sequential algorithms are offered
6. smfsb
    - It provides simple and basic output of parameter estimations

Some examples given in their documentations have been practised to explore the details and features of ABC-SMC algorithm in these packages and determine which of them meet our requirements. The three preferred packages are pyABC, EasyABC and ELFI. All of them are well documented and support different kinds of parallelisation; other features include support for built-in visualisation, pause-and-restart and easy to use. The choice is limited in the preliminary practise and may be changed accordingly in the future practical implementation as more packages will be studied.

Tools research provides grounded comprehension and conclusion on packages choosing in this project and finds the initial tools to start with. More tools will be studied and possibly used in the future.

# 5 Final Proposal

The project research consists of six parts. The first two parts are preparation work that would result in a mathematical model to implement our algorithms. Part 3, 4 and 5 are the practical session including several experiments and implementations to explore and analyse the model. The last part is to organise the works into report and dissertation.

## 5.1 Background Research and Project Preparation

This part focus on the preparation of the project, including background reading, tools research and regular discussion with supervisors. It will build a concrete ground to start the later tasks. Most of the work have already been done.

## 5.2 Dynamical System Modelling

Non-linear differential equations will be adapted to represent the dynamic system of zebrafish spinal cord regeneration process. Under the hypothesis1, there are complex interactions between two types of cytokines and three types of cells at the wounded site and the expected mathematical model representing by ODE systems will be built to describe these interactions.

## 5.3 Parameter Estimating

The parameters in the ODE system will be estimated using experimental data1. ABC-SMC will be applied to approximate the posterior distribution of parameters and produce reliable parameter estimates of the model. A distance function will be built to measure the discrepancy between the model and simulated data before applying the algorithm, together with coping with missing data in certain time points.

As the SMC sampling process is computation-intensive and thus time-consuming, a parallel sampling technique will be of our interest.

## 5.4 Results Interpretation and Analysing

This part focuses on the evaluation of the parameterised model and analysis of the SMC results. Inference results will be tested using synthetic data and used to evaluate how well the model fits the data and how much confidence we have on the parameter estimates.

## 5.5 Model Comparison

ABC-SMC can also be implemented to compare our model with alternative ones. Similar procedures will be applied to model candidates and result in an approximation of each model's marginal distribution, which could be the main criteria for our model selection.

## 5.6 Performance Analysis

The performance data of the sampling process will be analysed to reveal performance of the parallelisation implementation, including parallel speedup and efficiency. Trade-offs between cost, runtime and energy will also be discussed.

## 5.7 Dissertation and Report Writing

A project study report and final dissertation will be written to address all works and results in the project research process.

## 5.8 Estimated Computational Resources Usage

The computational resources usage estimation is a provisional rough estimation, which can be changed as the implementation and performance test proceeds.

**Cirrus**

Most of the computational work in this project is expected to be deployed on Cirrus.

- CPU hrs needed (standard compute nodes): 7200 CPUh (2 hrs per run × 36 cores× 100 runs)
- Disk storage needed: 10 GB, including data and softwares
- Access to GPU compute nodes is also needed for possible parallelisation using CUDA

# 6 Workplan

Each part of the project research is planned as followed. The first stage is to prepare for the project in Semester 2 and possibly in the Easter holidays; the second stage will start at 18 May when the last examination ends.

1. Background Research and Project Preparation, Dynamical System Modelling
   - Start time: 21/01/2020
   - Duration: 8 weeks
   - The later Easter holidays could be used to do more research
2. Parameterising
   - Start time: 18/05/2020
   - Estimated duration: 7 weeks
3. Results Interpretation and Analysing
   - Start date: 22/06/2020
   - Estimated duration: 5 weeks
4. Model comparison
   - Start date: 15/06/2020
   - Estimated duration: 5 weeks
5. Performance Analysis
   - Start date: 13/07/2020
   - Estimated duration: 2 weeks
6. Dissertation and report writing
   - Start date: 20/07/2020
   - Estimated duration: 5 weeks

The Gantt chart is shown in Figure 3. The two stages are separately listed.

# 7 Risk Analysis

Possible risks and challenges are addressed in this section. These risks are concluded from the preliminary researches. Though we tried to predict and evaluate all risks in the project, new risks may appear as the project proceeds.

## 7.1 Technical Problems

**Tools/software problems**

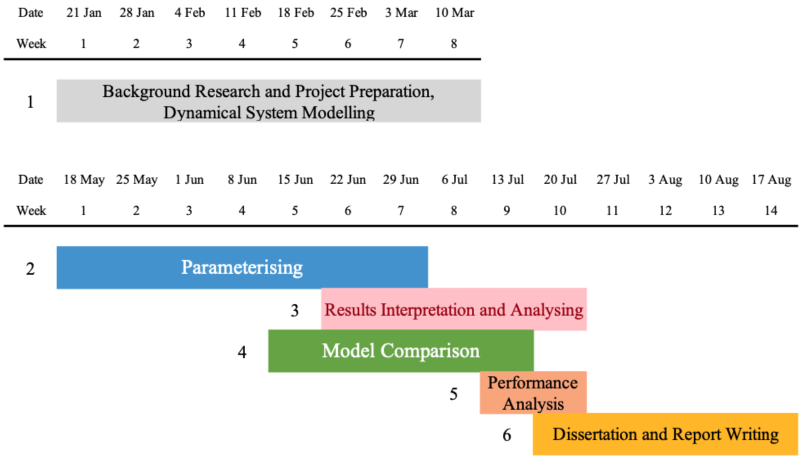


Figure 3: Workplan Gantt chart

- There could be unforeseen bugs in the code of the tools or software that are used in the project; softwares may crash, leading to possible data damaging. It is usually unpreventable.

  Probability: moderate

  Mitigation: in this case, we may need to find and fix the bug, switch tool/softwares and/or make a data protection plan to reduce the impact.

- There could be problems in the implementation environment where the compatibility is our main concern. The implementation may require certain environment conditions (e.g. operating system, compiler version, dependencies, etc) to be performed, or they could be incompatible with the hardware (e.g. CUDA acceleration and multithreading).

  Probability: high

  Mitigation: we have studied a variety of packages (section 4.2) to ensure that we have alternatives when it is necessary to switch tools, and will take more tools into the backup plan. Another solution is to change or built the required environment if applicable, i.e. switching OS, compile environment or hardware platform.

- The worst case could be that we may need to write our code to implement the ABC-SMC algorithm and complete the rest study, which would heavily increase the workload.

  Probability: low

  Mitigation: The workplan should be adjusted once it happens to ensure more time devoted to algorithm code and debug process. The rest work may be simplified.

**Hardware problems**

- Hardware failures and hardware unavailability could intrude considerable impact on the project process. Hardware failure may cause data damaging; hardware unavailability may break the estimated workplan.

  Probability: low

Mitigation: a regular data backup should be planned where experiments records, results and configurations should be well protected. In this case to proceed the project we may need to seek for hardware alternatives.

## 7.2 Parallelisation Concerns

- The project seeks to implement a parallel sampling. The first risk could be that different tools use different parallel techniques targeting different hardwares, where the parallel performance comparison across hardware is a problem.

  Probability: high

  Mitigation: more study on the cross-platform benchmark should be conducted to give a reasonable comparison of performance.

- Another risk can be the tricky parallel implementations, as there are different parallel systems with different configuration; it may cost time to find which kinds of implementation would work before we proceed to parallel performance analyse.

  Probability: moderate

  Mitigation: more investigation of the parallel implementations should be performed, which can reduce the effort in finding working schemes along with investigations in section 4.2.

- The execution time of parameterising using ABC-SMC is mainly determined by problem size and sampling parameters (number of generations, tolerance sequence and population size); it may cost time to obtain a reasonable parameter input that avoids long execution time and in the meantime give precise results. Another trade-off we may face could be the common scalability trade-offs where a suitable scale-up is to be discussed.

  Probability: high

  Mitigation: It is usually unavoidable. To minimise the cost and effort a plan on the implementation experiment should be made and discussed where only necessary experiment should be conducted and redundant parameter space enumeration should be avoided.

## 7.3 Modelling

- The main risk in the modelling process is model misspecification.

  Probability: moderate

  Mitigation: we may need to calibrate our model or adopt another model. These changes could consequently affect all later works in parameterising and analysis and the workplace should be adjusted accordingly.

- There is also risks in experiment data processing: variables are measured in different time steps and data on gene expression uses different scales from the differential equations. These problems will introduce some difficulties in the model fitting.

  Probability: high

  Mitigation: the processing methods should be studied and backup plan should be made to enable a successful fitting.

### 7.4 Other Risks

As far as this project concerns, certain cases of force majeure could affect the project progress which are low in probability. It should be noted that the current Coronavirus epidemic could affect some part of the project process, e.g. supervision meetings and access to certain physical resources.

The project may face failure, e.g. undesirables results, critical technical problems and running out of time. These failures should be noticed as early as possible through the risk analysis and management throughout the project time and be avoided as much as we can.

## 8 Outline of the Dissertation Report

A possible outline of the Dissertation Report is structured as below.

1. Introduction
2. Background and Literature Review
   - 2.1. Zebrafish spinal cord regeneration
   - 2.2. Mathematical modelling
   - 2.3. Bayesian Inference
3. Modelling
4. Design and Implementation
   - 4.1. Parameter estimation
   - 4.2. Model comparison
   - 4.3. High-performance implementations
5. Results and Analysing
   - 5.1. ABC-SMC results
   - 5.2. Performance analysis
   - 5.3. Discussions
6. Future Works
7. Conclusions

# References

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