Computational modelling of immune cell behaviour in inflammatory events

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Background

My name is Kate Doyle, I am in fourth year studying Mechanical Engineering with Biomechanics. I have wanted to get more involved in the INSIGNEO Institute as it is one of the reasons I was attracted to the University of Sheffield in the first place. It has always been my aim to use my mechanical engineering in the medical world hence why I chose mechanical engineering with biomechanics. This project interested me as I have learnt about a number of computational models and the suitability of different models for different conditions e.g. turbulence and near wall models. Analysing experimental data to look for trends in biological processes interests me greatly as this is one of the key ways we as engineers contribute to solving medical problems.

Neutrophils are immune cells which rapidly migrate to an area where there is an infectious threat. The speed of the neutrophils response to the threat determine the success of the inflammatory process. The neutrophils navigate throughout the body by sensing an underlying chemical gradient. The understanding of this process and the neutrophils perceptions of the underlying chemical gradient is essential to developing new treatment strategies. Currently, the best way of studying these cells in with in vivo experiments. This allows researchers to observe the neutrophils reaction to inflammatory events in their natural environment. However in vivo microscopy obscures the gradients driving cell migration therefore in silico modelling of the gradient sensed by the neutrophils would shed light on this process. The project aims to create a computational framework for data-driven modelling of cell-environment interaction during an inflammatory response. The experimental data used in this project is from the response of neutrophils to a gradient in zebra fish larvae. A simple parametric model of the gradient field is needed so it can be estimated from the observed cell behaviour.

The aims of this project were:

- To create an image and data processing tool to provide a unified input for the estimation framework.
- Create a computational framework for the analysis of the interaction between immune cells and the chemical gradients driving their migration in inflammatory response
- Process experimental data to analyse interactions between neutrophils and their environment at different stages of the inflammatory response

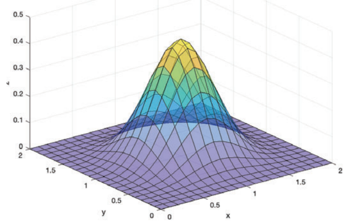

Figure 1

Methods

B-splines

In order to create a computational model of the underlying chemical gradient in the Zebra fish tensor product b-splines were manipulated in MATLAB to represent the environment. The underlying chemoattractant field in zebrafish is modelled using a 4x4 grid of overlapping tensor product b-splines. This grid of b-splines is placed on a map of 1000x1000 arbitrary units. The magnitude of the b-splines corresponds to the gradient of the field. A b-spline surface function was created in MATLAB and integrated into existing code. Figure 1 shows the tensor product b-spline plotted using the function created.

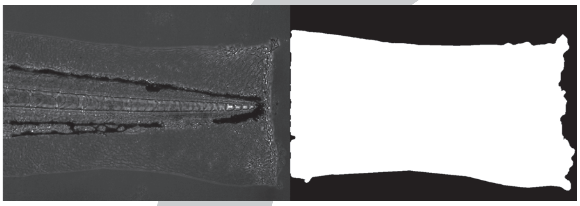

Figure 2

Fish Mask

A mask needed to be created for each zebrafish image to isolate the fish body from the background. To automate this process for every image many different functions were used in MATLAB. Functions used include edge detection, blurring, removing background noise and filling functions. Figure 2 shows the original fish image compared to the generated mask.

Interface

To make this data more accessible for a user who is unfamiliar with MATLAB an interface was created to display the data options clearly. To do this the GUIDE Layout Editor was used in MATLAB. GUIDE is used to create graphical user interfaces to provide simple was of accessing and displaying the data.

Differentiating B-splines

The analytical solution to spline differentiation was explored through a literature review. The derivative of the b-splines was compared to the output of the gradient function. To do this a function was written in MATLAB to differentiate that evaluate the partial derivative of a tensor product b-spline. Figure 3 shows the partial derivative with respect to x of a cubic tensor product b-spline. Figure 4 shows the first to fourth derivative of a cubic spline.

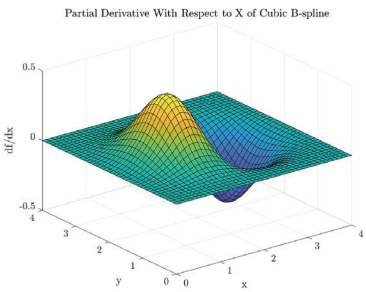

Figure 3

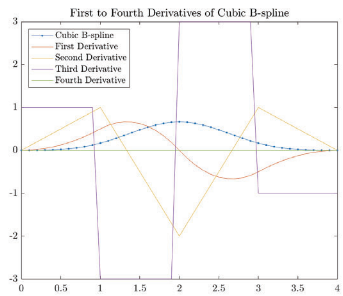

Figure 4

Results

B-splines

A multi-grid of b-splines was created to represent the slow and rapid spacial changes in the neutrophil behaviour. Two grids of B-splines, one coarse and one fine are plotted using the grid example function. The fine grid of splines is used to plot the details of the surface and the rapid spacial changes. The coarse grid is used to pick up slower spacial changes in the overall surface. The figure shows a plot of a grid of 6 splines on top of a grid of 4 splines. A Hierarchical grid of b-splines was also created to pick up of detailed changes in the area with most neutrophil tracks.

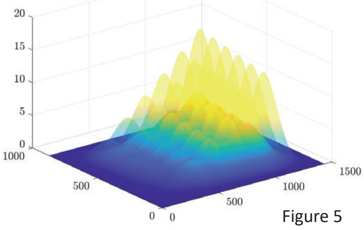

Figure 5

Fish Mask

Many existing MATLAB functions were used to a function that generated a fish mask for each zebra fish image.

Interface

The interface created in easy to use, it can display multiple sets of data from all zebra fish images with just a few clicks.

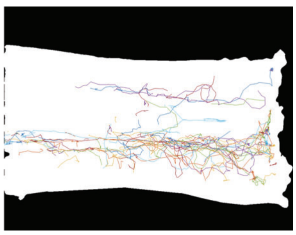

Figure 6

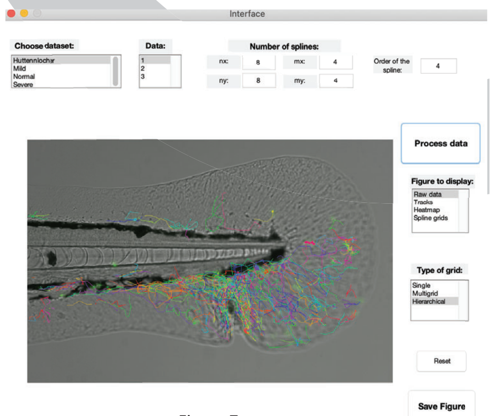

Figure 7

Conclusions

Several automated tools were developed and integrated into existing code to reduce computing time and simplify the process. Functions for processing microscopy images, creating basis function models of the underlying field and computing its gradient were written. These functions are used within the framework to estimate the field. Figure 8 shows the result of the field gradient using the functions written throughout the project. In conclusion, by the end of this 10-week project I have gained invaluable skills and learnt a lot about the research process. I have:

- Improved literature research and MatLab skills
- Learnt how to use GitHub, GitKraken and LaTex
- Worked with regular meetings in order to meet deadlines
- Collaborating to write code
- Gained an understanding of tensor product b-splines and how they are used to model the underlying chemical gradient

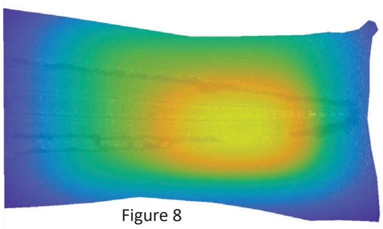

Figure 8

Acknowledgements

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