Asuka Kumon Internship Report

Name: Asuka Kumon

Current status: just finished part III; PhD in number theory at King's College London from October.

Where I worked: Cambridge Institute of Medical Research, Haematology lab.

Supervisor: Dr. Anagha Joshi

Summary of work: Haematology is the study of blood and diseases of the blood. At the CIMR, researchers are looking to find the causes and possible forms of treatment for patients with blood disorders, including cancers such as leukaemia. Samples collected from patients at Addenbrooke's hospital are analysed in lab and the data studied by bioinformaticians.

My project was to model the behaviour of haematopoietic stem cells (HSCs) in a 10-day *in vitro* differentiation assay. Haematopoietic cells are arranged in a hierarchy (figure 1), with HSCs at the very top and cells such as red blood cells, platelets and white blood cells at the very lowest level. A cell can either divide to give two of its own kind (self-renewal) or divide to give two daughter cells that are one level lower in the haematopoietic cell hierarchy. A higher rate of self-renewal and the ability to differentiate into many different types of cell is what characterises ‘stemness'. In this project, we looked at two genes, JAK2 and TET2, where mutations in those genes are thought to influence the rates of self-renewal and cell division. It has already been shown in mouse that this is the case but the data from human patients have not been analysed in detail. Our aim was to create a model to investigate the roles of JAK2 and TET2 mutations in cell division rates and/or differentiation bias.

Each cell was cultured in the lab for 10 days, and at the end of the 10 days a cell count was obtained. The cells were then sorted into ‘Mix', GM, E or other (figure 2). We were also given the JAK2 and TET2 genotypes for each cell, which were normal (1), one gene mutant (2) or both mutant (3).

We used MATLAB to compute the mean and standard deviation of the day 10 counts according to genotype, and obtained the following table (see also figure 3):

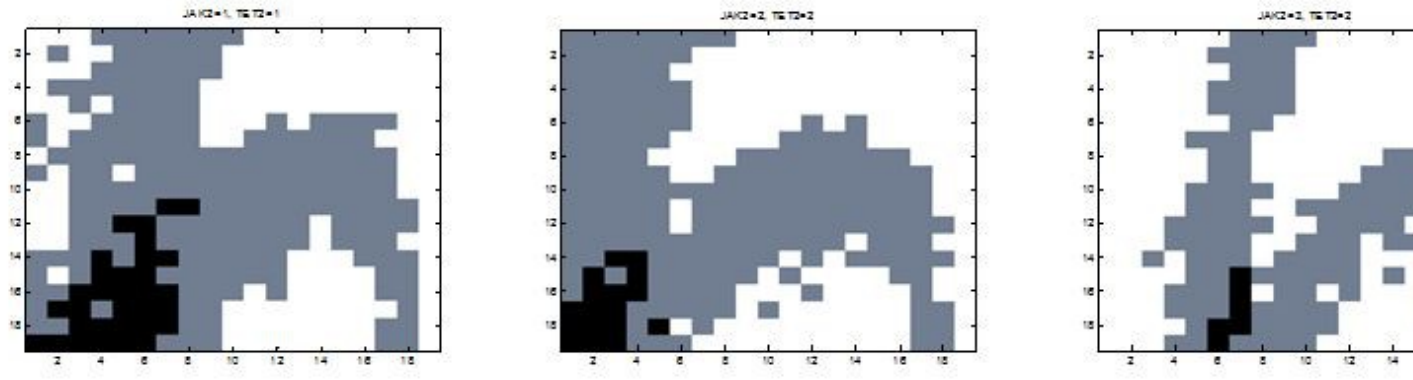
	JAK2=1	JAK2=2	JAK2=3
TET2=1	7.3	8.3	No data
TET2=2	5.1	5.9	7.0

We can infer from this that the rate of cell division is affected by the genotype of the starting cell, and that the rate of increase is proportional to the extent of the mutation of the gene.

Next we compared the number of ‘mix' cells according to genotype. This will measure the extent of the self-renewal potential of the cell, especially in the HSCs. 3% of cells without a TET2 mutation

gave mix cells at the end of 10 days, whereas those with one TET2 gene mutant gave double that at 7%.

In our model (figure 2), the cells in the HSC and CMP compartments were counted as ‘mix' cells. Our next task was to determine the range of ε and δ that fit the original data, for each genotype. So we ran our code several times, varying ε and δ, and produced the following diagrams:



ε increases in intervals of 5% across the x-axis; δ increases in intervals of 5% down the y-axis.

This clearly shows that when both JAK2 genes are mutant, ε (the rate of self-renewal of HSC) is a lot higher. In our sample, all cells with both JAK2 mutant also had a TET2 mutation. This suggests that when a cell acquires a second JAK2 mutation when a TET2 mutation is already present, HSCs have the tendency to self-renew more frequently.

In the coming months, I hope to refine the model and determine the other probabilities involved (α and ε'). We are hoping to obtain more data in a few weeks' time, which will allow us to test other ideas such as whether mutations interact with each other.

I am extremely grateful that I was given this opportunity, since it gave me the chance to learn coding and study areas of science that are very remote for pure mathematicians. I hope to continue working with my supervisor throughout my PhD, and we are planning to submit the final results to conferences and journals in due course.

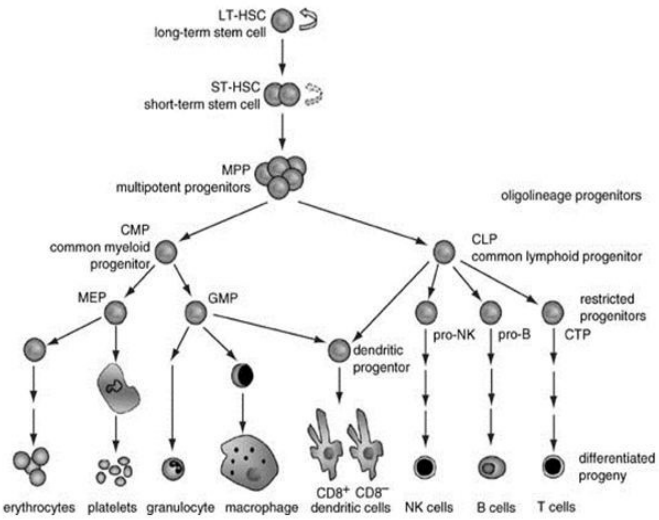


Figure 1:

Stem cells: an overview; Denham et al, 2005

Figure 2:

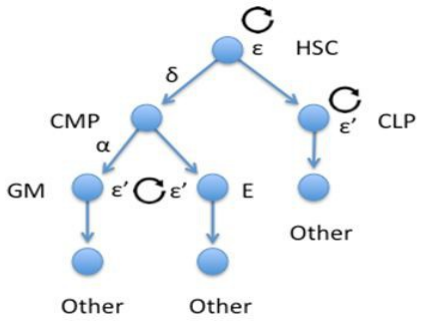


Figure 3: