Optimisation of Two-Drug Chemotherapy for Neuroblastoma Using a Genetic Algorithm

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INSIGNEO
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Background

About:

Neuroblastoma is a common paediatric tumour, with 90% of diagnoses being made before the patient turns 5 years old. It is the most common cancer found in infants and is not usually found in children over 10 years of age [1]. Neuroblastoma originates in the neural crest cells, which have the ability to migrate along the neuraxis and differentiate into a range of cell types [2]. The cancer is both heterogeneous and metastatic in the majority of cases (over 60%) and has a variety of possible outcomes [3].

Treatment:

Neuroblastoma is usually treated using a variety of chemotherapy drugs. These work by causing DNA damage and inhibiting its replication via various mechanisms, which leads to the activation of apoptosis. The treatments used will often depend on a number of factors, such as age, weight and risk category. The risk categories for neuroblastoma include very low, low, intermediate and high, where low risk has an 85% survival rate in comparison to high risk cases, which have a survival rate of less than 50% [4]. High risk cases often respond to treatment at first and then relapse after acquiring resistance to certain drugs. Resistance is generally most likely to occur when high doses of a particular drug are administered for long periods of time.

Therefore, resistance is an important issue which needs to be considered when developing the most promising drug regimen for a given patient. Further, the doses, length of time of administration and order in which a drug combination is administered plays a major role in the treatment outcome.

Focussing on a combination of two chemotherapy drugs, cisplatin and etoposide, known to have been used together in a regimen to treat neuroblastoma [5], it was investigated how to combine the two for the optimum treatment outcome.

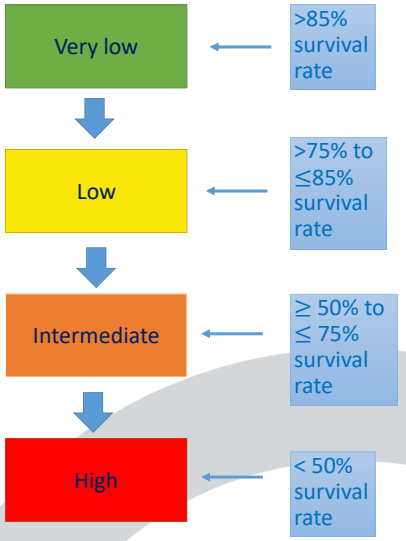


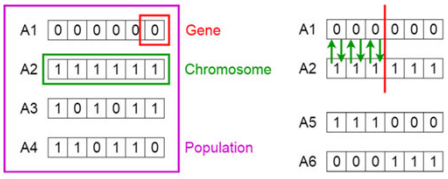
Figure 1: Illustrative diagram of risk categories, using statistics from [4].

Methods

Python code provided by Dr Kenneth Wertheim was adapted which models tumour growth in neuroblastoma. The model is

- agent based (neuroblast cells),
- able to simulate the effects certain drugs will have on a population of neuroblasts during a cell cycle in terms of population decrease (or growth).
- Includes the effects of specific resistance pathways associated with these drugs.

A genetic algorithm (GA) was incorporated into the model to select for the optimum drug schedule. GAs work by selecting for the fittest "chromosome".



Source: https://towardsdatascience.com/introduction-to-genetic-algorithms-including-example-code-e396e98d8bf3

Chromosomes represent a particular drug schedule and its "genes" represent whether a particular drug is present at a given time step.

At each step in a GA

- there is a new generation of chromosomes.
- So many of the fittest chromosomes are chosen to reproduce.
- They reproduce via a crossover process.
- Some offspring's genes become mutated.

This process continues until the average fitness of consecutive chromosome generations converge, meaning hopefully an optimal drug schedule has been reached.

Fitness is represented using a fitness function, such as

$$fitness = \frac{400}{end\ cell\ count+1} - \frac{\sum resistance\ strength}{600}.$$

Figure 2: Example plot of change in neuroblast population size overtime during a chemo cycle.

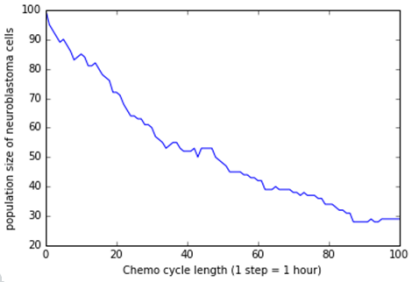


Figure 4: Schematic of chromosomes and their crossover process. A6 displays drug 1 is switched off over all 3 time steps and drug 2 is always on.

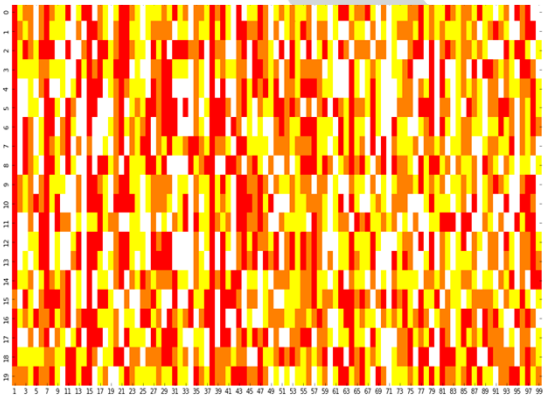


Figure 3: Heat map of case 1 produced from running a simulation consisting of 50 generations and 20 chromosomes. Each row represents a separate chromosome from the final generation and each column represents a separate time step. A given block is yellow if only cisplatin is administered on that particular time step, red if only etoposide is administered and orange if both are given. A white block represents no drug being administered on that particular time step.

Results

Four simple scenarios were focused on when obtaining results:

(1) Half the initial population of cells carry a resistance strength of 2, the other half are not resistant and the initial probability of proliferation and apoptosis is 0.02 and 0.005 respectively.

(2) The same resistance strength groupings as in case 1 however the initial probability of proliferation and apoptosis is 0.005 and 0.02 respectively.

(3) There are 2 initial groups of clones with resistance strengths 1 and 2 (equally sized) and a non-resistant group of cells. The initial probability of proliferation and apoptosis is 0.005 and 0.02 respectively.

(4) The same resistance strength groupings as in case 3 however the initial probabilities of proliferation and apoptosis are both 0.005.

These distinct cases may reveal drug schedules or elements of a schedule which might be used to optimise patient outcome under certain scenarios. Heat maps were produced of the final generations of chromosomes using my simulations, which aimed to optimise the chromosomes (drug schedules) with respect to my fitness function. Figure 3 displays the results from case 1 and unfortunately demonstrates no clear patterns in drug schedule.

Conclusions

Despite no clear patterns being found so far, a number of adjustments to the model could be beneficial:

(1) Run simulations with a greater number of generations.

(2) Harsher early stopping conditions.

(3) An alternative fitness function and additional tweaks to my GA.

(4) More complexity surrounding the effect of the drugs on the neuroblasts.

Note, the student also spent part of this project compiling a list of all drugs used to treat neuroblastoma alongside their mechanisms of action, side effects, how they are administered and their resistance mechanisms. This list consisted of 18 drugs and 117 references in total.

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Acknowledgements

Original code for my model was provided by Dr Kenneth Wertheim, which I then adapted for my needs.

References

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