Fourth semester report

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1 Research work

1.1 Complication with the WBC in the bone marrow

From our previous experience with the model appreciate the important role that the interaction function between the bone marrow and blood plays in the shape of the blood percentage and bone marrow percentage. The intensity of the transit between the bone marrow and blood compartments is also important for control the growth of cells in the bone marrow.

From previous work, we have results for the linear, and logarithmic interactions. In the case of the linear interaction, we explored this type of interaction briefly, because it produced a sequential removal of the levels in the top of the hierarchy. This behaviour will lead to a limit when only the mutant stem cells will remain in the bone marrow. This behaviour is not only incorrect for the description of CML progression, but it is also unreal. The results achieved in previous semesters had some quantities which were out of the range reported in clinical estimations. The number of total WBC in the blood at the beginning of the blast crisis it was above realistic values.

In our simulations, the WBC at the onset of the blast crisis was around 10^14 cells. This amount of cells was higher than any estimated amount of cells reported in clinical data. It is higher by several orders of magnitude. The highest amount reported in clinical estimates is around 8×10^{11}. This highlighted the necessity of a hard restriction in the number of cells, the interaction between the number of cells and the available space in the bone marrow should lead to a constant final number of cells at the end of the disease. In the case that the carrying capacity of the bone marrow is not achieved the number of cells present at the end of the simulation should not be bigger than 1×10^12 cells.

1.2 Finite space versus flexible bone marrow

Our first attempt was the introduction of an exponential increasing interaction function concerning the total number of cells in the bone marrow. This type of function will provide us with a sudden increase in the movement of cells from the bone marrow. The exponential increase in the migration will increase just before the carrying capacity of the This will lead to a sigmoid type function for the number of WBC in the bone marrow and after some time it will also lead to the same type of curve in the blood compartment.

From the first analysis, it became noticeable that the exponential increase has some characteristics who are not entirely compatible with the abstract model of the leukemia phases. The initial transit of cells from the bone marrow to the blood is very small. This is in contrast with the fact that the blood production process being tightly regulated. A slight variation in the total number of cells or an

increase in the number of one type of haematopoietic cells will produce an immediate response from the body.

The second feature of the exponentially shaped migration from bone marrow to blood is the fast movement of cells from mature levels when approaching the carrying capacity of the bone marrow. This is problematic for *high* values of the exponential constant of the migration distribution because it will lead to the complete extinction of the mature of cells in the bone marrow. The mature cells in the chronic and advanced phases are expected to drop steadily but still be present in low percentages, it is only at the end of the blast phase when the mature cells are expected to be absent.

This feature contrast with the previous attempts for curves of transport intensity. The logarithmic function used in previous simulations allowed for a flexible bone marrow in which the number of cells will grow exponentially without reaching carrying capacity. This leads us to the problem of hypercellular bone marrow with an excess of cells. The *hard wall* potential for a finite space bone marrow solved the problem of overpopulated bone marrow, but introduced new undesired behaviours which will be explained in the following sections.

1.3 Are critical cells driven by the stem cells or progenitor levels?

At this point in the project, we decided to change the strategy and use the *hard wall* exponential function with a smaller difference of migration by level in the hierarchy. In other words a value for the parameter α bigger than 1.75 in the equation $\frac{1}{\alpha^{n-k}}$. Using this approach we control the growth of cells in the bone marrow and also avoid leaking levels in the hierarchy sequentially. By reducing the possible growth of mature and progenitor levels in the bone marrow, the appearance of new critical cells with extra mutations aside the BCR-ABL should be driven by lower levels.

In the case of a flexible bone marrow which allows for a bigger WBC in bone marrow, the blast level can host approximately 10^11 cells. This number of cells is sufficient to produce blast cells with the critical number of mutations, capable to trigger the neoplastic uncontrolled growth. On the other hand, with a fixed size for the bone marrow and fast increase of cell transit close to the carrying capacity, the number of BCR-ABL mutant cells reaches a steady state. The production of supercritical cells is shifted to lower levels, the stem cell level is responsible then for the creation of mutant cells.

The timescale of the simulation depends on the amplification factor of the hierarchy and fitness of mutant cells. The mutation rate can also affect the simulation pace, but the dynamics described previously influence also the speed of cell production. This is an indirect effect, it cannot be obtained by controlling only one of the parameters but it's a combination of parameters responsible for the transition between fast and slow regimes for progression to blast crisis. The production of supercritical cells within the blast level is, in general, faster than the production of cells driven by stem cells. Because stem cells have a low division rate and the fitness of the BCR-ABL mutant is bigger than the rest of generic mutations.

The difference in the time scale is in the order of years, the stem cell-driven criticality can increase the duration of the chronic phase by a factor of two, approximately 10 years.

1.4 Bimodal histogram for blast cell percentage

In the previous section, we describe two different mechanisms for mutant cell production. Can both behaviours be present for the same set of parameter values? From a manual inspection of a sample of simulations, we concluded that both regimes are present for a realistic set of parameters. This leads to the question: Is it possible to detect the two regimes from the chronic phase duration histogram? Is the histogram for the blast percentage reflecting these two mechanisms? We have analysed the shape of the previously mentioned histograms, but the answer to the last questions remains still inconclusive. The blast histogram shows *clear* bimodal features, but the other histograms (time to criticality and

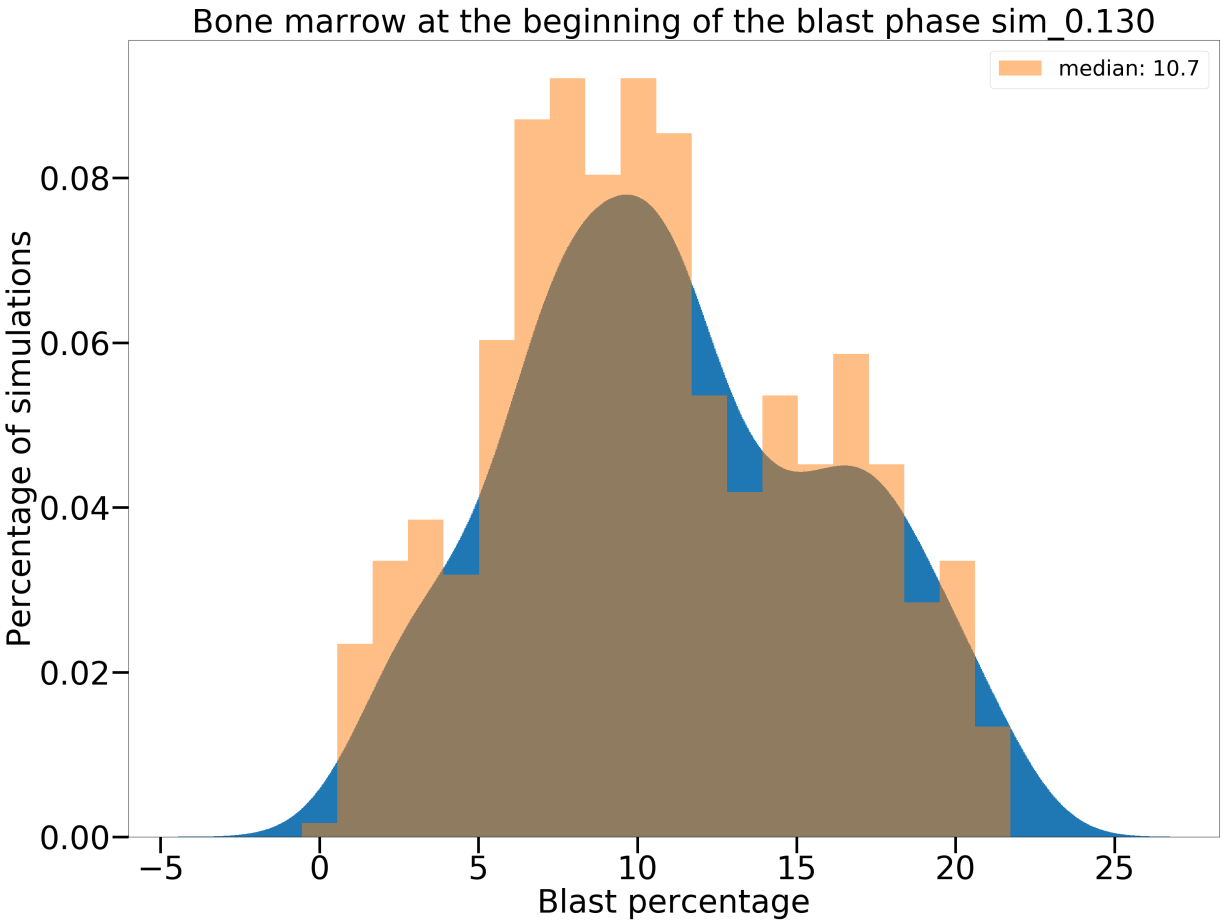

Figure 1: Histogram and kernel density estimate for the blast percentage in bone marrow.

WBC) don't look like bimodal distributions. The bimodal distribution can also have been introduced by the introduction of the transit of cells from bone marrow to blood.

The bimodal distribution may be produced by a window of opportunity which can be closed for critical blast cells. This window of opportunity is the chance that blast cells have to escape the stochastic extinction events and proliferate to produce a stable population. This window is closed, for example, in the case of *hard wall* dynamics when the blast levels are transferred to the blood. In this case, the window opens and closes very fast because of the fast pace. The simulations which achieve criticality before the transfer of cells begins will represent the blast level mechanism. When the transport of cells increases the window closes, and the slow stem cells driven simulations need to wait until the opening of a new window of opportunity. This question still needs a clear answer from a set of simulations that allows the inference of the mechanisms responsible for this apparent bimodal distribution of the blast cells percentage in the bone marrow.

We include a graph that shows the suspected bimodal histogram in Figure 1.

1.5 Timescale dependence on the α parameter

The timescale dependence on the leaking function was introduced in previous sections, but the α parameter of the transit distribution by level is present independent of the intensity of the migration. The intensity of the migration changes the dynamics with respect of time, but α defines the maximum possible number of cells, and also the possibility of leaking all of the mature cells.

There is also a critical difference that can be controlled with the value of α. For $1 < \alpha \lesssim 1.75$ all the levels in the hierarchy participates in the *competence* for bone marrow space. This can lead to the

extinction of all of the wild type cells in the bone marrow. This will be in clear contradiction with the recovery of patients after treatment with TKI drugs. It is not trivial to set a lower bound for the *alpha* parameter, due to the extinction of wild type cells happening after approximately 20 years. This will add a further dependence on the mutation rate.

For $1.75 \gtrsim \alpha$ only the mature levels will be interaction, the levels at the bottom of the hierarchy will not be affected by the presence of other cells in the bone marrow, this will have the effect of not expel the wild type cells but instead the death of mature cells. This type of interaction is typical of fast evolution in the simulation.

1.6 Phylogeography side project

In this semester I also started a side project in phylogeography. This project aims to investigate the difference in a phylogenetic and phylogeography tree. For this project we are using the Covid-19 gene databank available in GISAID webpage. In this project, we use Bayesian inference to reconstruct the phylogenetic relations among different virus strains. This project is under development in the initial phase. This project has helped me to get involved with bioinformatics software relevant to the analysis of genetic data. This software includes BEAST and Iqtree, the phylogeography analysis is an interesting and relevant topic not only for viruses, but it can also be applicable for track and evolution of migrating species.

2 Attended courses

- Networks in bioinformatics teach by Gergely Palla.

3 Conferences

I didn't attend any conferences this semester