Treatmen t of Blood Cancers and the Importance of Quiescence
Modelling of Quiescent Stem Cells
in Relation to Myeloproliferative Neoplasms

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Background
Myeloproliferative Neoplasms (MPNs) is a family of diseases in the bone marrow, which lead to an excessive production of hematopoietic cells. Through a mechanism-based modelling approach, the behaviour of the hematopoietic system has been modelled with satisfactory results [1]. Preliminary results comparing the results of the model to clinical data show great promise for future prediction of the development of the disease. This work aims to extend the model, based on mechanisms suggested by clinical intuition, particularly, the addition of quiescent (or dormant) stem cells.

Assessment of clinical data
While the mathematical model considers different types of cells, clinical decisions often have to rely on certain indicators of the disease level. On such indicator is the JAK2 allele burden, shown to be well associated with the MPN diagnosis [2]. The JAK2 allele burden measures the ratio of mutated mature cells in the total number of mature cells. In the mathematical model, this would correspond to \( \frac{r_{J2}}{r_{J2} + r_{J}} \).

In figure 1, previously unpublished time-series measurements of the JAK2 allele burden are shown for patient undergoing treatment with Interferon-α.

![Figure 1: Simple decay rate of JAK2 allele-burden for patients treated with Interferon-α](image)

The development is shown to follow that of an exponential decay with a half-life of 2.85 years, and thus, the development of the disease can easily be estimated, regardless of the specific level.

However, for a small group of patients, the behaviour of the JAK2 allele burden during treatment with Interferon-α displays a delayed reaction, with a short period of growth before the decay starts. These patients are shown in figure 2, with the simple treatment response curve added for comparison.

![Figure 2: JAK2 allele-burden for the delayed reaction group of patients treated with Interferon-α](image)

Mathematical model
The Cancitis model [1] comprises a system of six coupled ordinary differential equations (ODEs). The model consists of the healthy stem cells \( (x_0) \) and differentiated healthy blood cells \( (x_1) \), while MPN-mutated counterparts are represented by \( y_0 \) and \( y_1 \). The debris of dead cells is denoted \( a \), while the dimensionless number \( s \) represent the load on the immune system. The proposed extension adds two additional ODE’s representing quiescent healthy stem cells and MPN-mutated stem cells, denoted \( z_q \) and \( y_q \) respectively. The model is shown schematically in figure 3.

![Figure 3: Compartment diagram](image)

The model has been described to show the time-development of MPN’s well, while demonstrating the effects of inflammation (determined by parameter \( I \)). This type of ODE model is prevalent in the literature, and comparison with state-of-the-art models are being done.

Results
Through analysis of literature and communications with clinical professionals, it was determined that the parameters mostly influenced during treatment with Interferon-α, were the self-renewal rates \( r_q \) and \( r_s \), as well as the activation rates of the quiescent stem cells. Modifying these rates yields in silico treatments fitting well with data, as shown in figure 4.

![Figure 4: Model simulations fitted with the five patients after untreated growth](image)

Conclusions and future perspectives
The addition of the quiescent stem-cell compartments allows for an in silico treatment more closely resembling the clinical intuition about the effects of Interferon-α. Preliminary fitting of the parameters of the extended model shows great promise, enabling the model to successfully describe the development of the JAK2 allele-burden for a minor group of patients which previously could not be modelled. While the parameters are currently individually estimated by hand, future work formalising an algorithm for the determination of the parameters based on medical knowledge could prove useful for clinical assessments of the response to treatment for individual patients. As such, this could ultimately lead to personalised treatment schemes, based on the initial response to treatment.

References