A Framework for the Personalized Treatment of Acute Myeloid Leukaemia

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1. Aim of Research

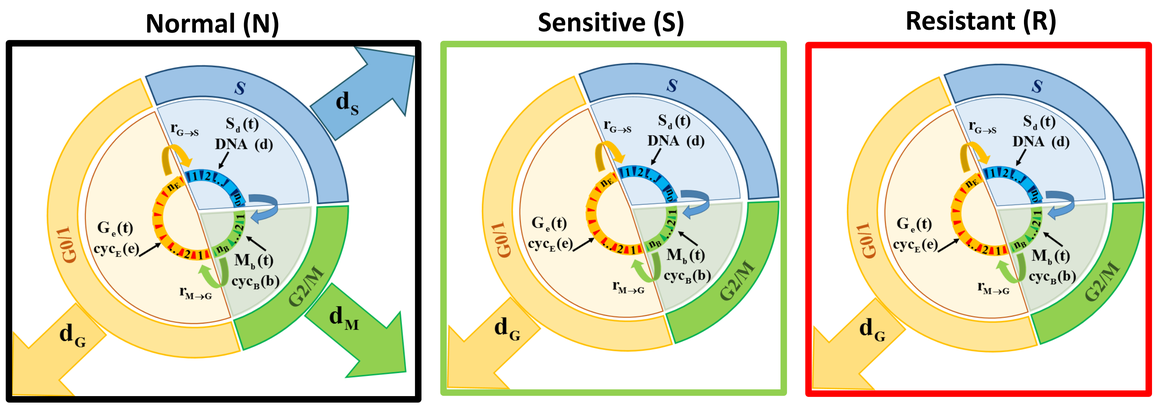
Acute Myeloid Leukaemia (AML) is a cancer of the bone marrow (BM) and blood (PB) which results from mutations causing uncontrolled proliferation, maturation arrest and reduced death rates of myeloid blood progenitors. This work presents:

- A novel gPROMS-based modeling framework describing AML progression in the BM with neutrophil dynamics under standard treatment protocol including cytarabine (Ara-C) and daunorubicin (DNR)
- Validation and assessment of the predictive power of the framework using real clinical data for heterogeneous patient characteristics
- Development of new optimal chemotherapy schedules based on personalised treatment

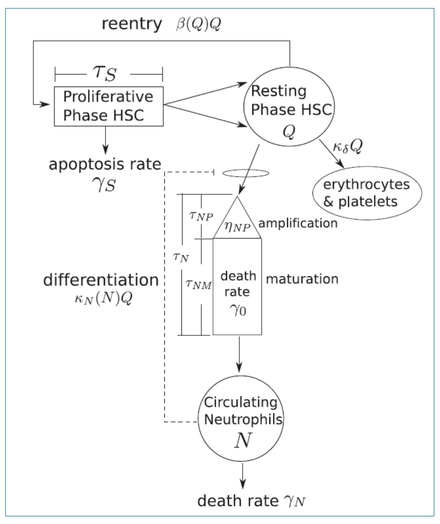
2. Mathematical Modelling

- Clonal growth under treatment is captured using novel population balance models (PBM)
- Cell cycle phases are discretized in cyclin E, DNA and cyclin B content which control the movement of cells in G0/1, S and G2/M phases respectively

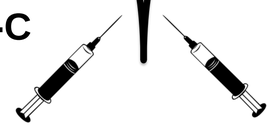
Clonal Populations



Neutrophil Dynamics



Low / High dose of Ara-C **DNR**



Model for Leukaemic Clones

$$\frac{\partial G(\mathrm{cyc}_E,t)}{\partial t}+\frac{\partial\left(G(\mathrm{cyc}_E,t)\cdot \mathrm{dcyc}_E/dt\right)}{\partial cyc_E}=-r_{G\to S}(\mathrm{cyc}_E)\cdot G(\mathrm{cyc}_E,t)-death_G-drug\ cytotoxicity$$

$$\frac{\partial S(\mathrm{DNA},t)}{\partial t}+\frac{\partial\left(\mathrm{S}(DNA,t)\cdot \mathrm{dDNA}/dt\right)}{\partial DNA}=-death_S-drug\ cytotoxicity$$

$$\frac{\partial M(\mathrm{cyc}_B,t)}{\partial t}+\frac{\partial\left(\mathrm{M}(\mathrm{cyc}_B,t)\cdot \mathrm{dcyc}_B/dt\right)}{\partial cyc_B}=-r_{M\to G}(\mathrm{cyc}_B)\cdot \mathrm{M}(\mathrm{cyc}_B,t)-death_M$$

Model for Neutrophil Dynamics

$$\frac{dQ}{dt}=-\left(\beta(Q)+\kappa_N(N)+\kappa_\delta\right)\cdot Q\cdot u+2\cdot e^{-\gamma_S\cdot\tau_S}\cdot\beta(Q_{\tau_S})\cdot Q_{\tau_S}\cdot u-drug\ cytotoxicity$$

$$\frac{dN}{dt}=-\gamma_N\cdot N+e^{n_{NP}\cdot\tau_{NP}-\gamma_0\cdot\tau_{NM}}\cdot\kappa_N(\mathrm{N}_{\tau_N})\cdot u-drug\ cytotoxicity$$

3. Model Input Data

NHS provided retrospective anonymized and ethical approved datasets from 10 patients with AML who underwent treatment with DNR + Ara-C or low dose Ara-C (LDAC):

- Percentage of blasts in BM before and after chemotherapy treatment cycle
- Treatment regimen (DNR + Ara-C or LDAC)
- Bone marrow cellularity
- Disease status: Complete remission or relapse
- Neutrophil counts before, during and after each cycle of chemotherapy

4. Model Analysis and Validation

Assumptions

- Calculations of the number of cells from patient data:

$$Cancer_t=\%blasts_t\cdot Cellularity_t\cdot Disease\ Burden$$

$$Normal_t=(1-\%Blasts_t)\cdot Cellularity_t\cdot Disease\ Burden$$

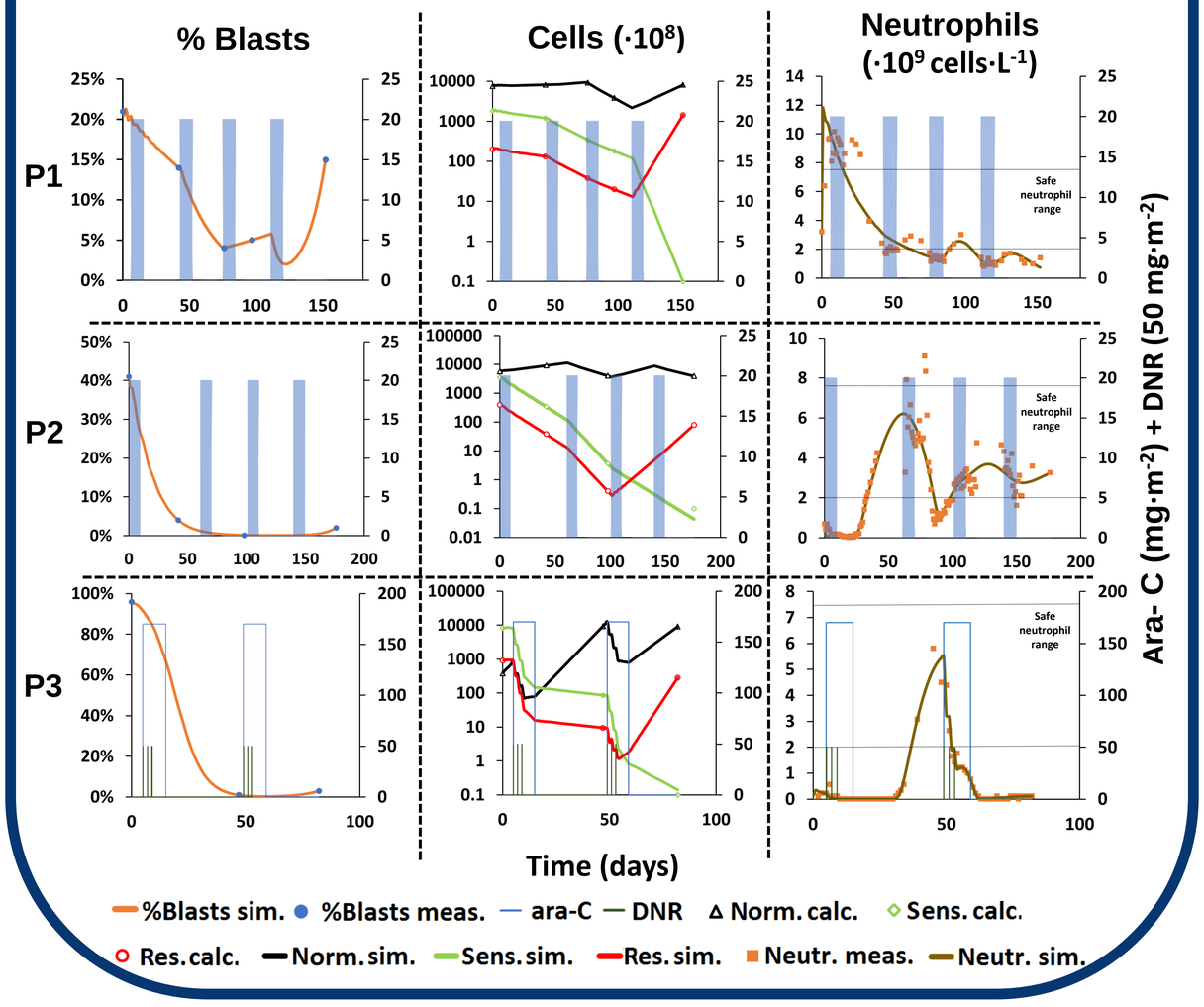
- 90% of cancerous cells are sensitive and 10 % resistant when complete remission occurs whereas 100% of cancerous cells are resistant in relapse
- Chemotherapy treatment affects cell cycle periods, especially in T_G, due to changes in BM microenvironment

Sensitivity Analysis

- Sensitivity analysis showed that 16 out of 58 parameters are important:
  * G0/1 and S phases in all clones (T_G, T_S), G2/M (T_M) phase in normal cells, death rates in G0/1 of all clones (d_G), cytotoxic rates ($E_{max,ara\text{-}C}$, $E_{50,ara\text{-}C}$, d_{DNR}), blood flow, doses and administration times

Model Results in 3 Clinical Cases (P1-P3)

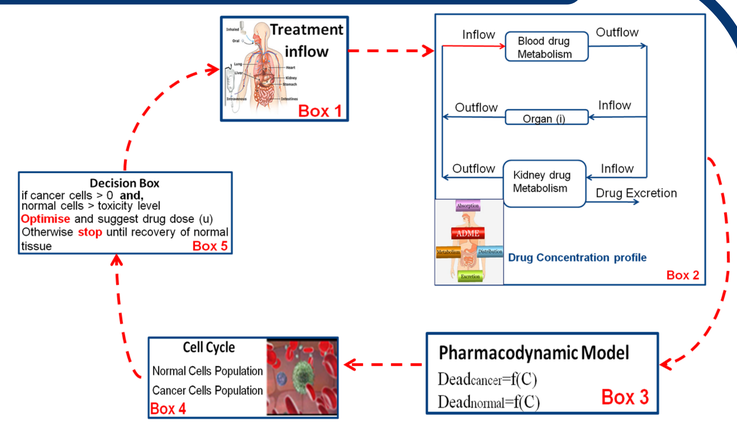
- Model predictions are in very good agreement with clinical data



5. Current Work

Degrees of Freedom = 6 :

1. Subcutaneous Ara-C
2. Intravenous Ara-C
3. Dose Ara-C
4. Administration time Ara-C
5. Dose DNR
6. Administration time DNR



Optimization of treatment :

Objective:
Minimize the number of leukaemia cells

Constraints:
- Minimum amount of normal cells required
- Maximum amount of chemotherapy allowed
- Maintain neutrophils within safe range in blood (2-7.5 $\cdot 10^9$ cells $\cdot L^{-1}$)

New Optimal Chemotherapy Schedules

6. Acknowledgements

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