Stochasticity saves leukemia patients during **antibody** based **immunotherapy**.

Modelling dynamics of undetectable disease in leukemias concerning therapy.

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Introduction

- Series of specific lesions in white blood cell precursors leads to acute lymphoblastic leukemia (ALL).
- ALL is a malignant disease and leads to differentiation arrest and abnormal proliferation of white blood cells.
- Primary treatment for ALL is chemotherapy, which combines anti-leukemic drugs targeting cell proliferation.

- Most adults with ALL experience a relapse in the course of the treatment and disease doesn't respond favorably to chemotherapy.
- Relapsed ALL patients are then advised for immunotherapy.
- Bi-specific T cell engager (BiTE) monoclonal antibody drives CD3+ T cells to eliminate CD19+ B cells.
- Within 3 days of immunotherapy CD19+ cell counts drop below 1 cell/µl; thus, the system is driven by random fluctuations.

Aim

1. Formulate a stochastic model capturing randomness of the system.
2. Simulate chemotherapy and immunotherapy.
3. Study effect of randomness on the treatment outcome.

Model

Symbol	Description	Values
S	slowly proliferating cells	
F	rapidly proliferating cells	
T_a	activated cytotoxic T cells	
T_d	de-activated cytotoxic T cells	
$r_S,\ r_F$	birth rate constants	$5 \cdot 10^{-2},\ 10^{-1}\ day^{-1}$
$p_{SF},\ p_{FS}$	conversion rate constants	$10^{-3},\ 10^{-2}\ day^{-1}$
$m_S,\ m_F$	death rate constants	$10^{-2},\ 5 \cdot 10^{-1}\ day^{-1}$
$p_{ad},\ p_{da}$	de-activation and de-activation rate constants, respectively	$5 \cdot 10^{-5},\ 10^{-4}\ day^{-1}$
α	efficacy of chemotherapy drug	3
n	serial killing efficacy of T cells	6 *cells*

Table 1: Symbols used in the model.

Reaction	Rate	Stoiochiometric vector	
$S \longrightarrow S + S$	$r_S\ S$	$\boldsymbol{r}^1 = (1,0,0,0)$	(1)
$F \longrightarrow F + F$	$r_F\ F$	$\boldsymbol{r}^2 = (0,1,0,0)$	(2)
$S \longrightarrow F$	$p_{SF}\ S$	$\boldsymbol{r}^3 = (-1,1,0,0)$	(3)
$F \longrightarrow S$	$p_{FS}\ F$	$\boldsymbol{r}^4 = (1,-1,0,0)$	(4)
$S \longrightarrow \phi$	$m_S\ S$	$\boldsymbol{r}^5 = (-1,0,0,0)$	(5)
$F \longrightarrow \phi$	$m_F\ F$	$\boldsymbol{r}^6 = (0,-1,0,0)$	(6)
$S \longrightarrow \phi$	$\alpha\ r_S\ S$	$\boldsymbol{r}^7 = (-1,0,0,0)$	(7)
$F \longrightarrow \phi$	$\alpha\ r_F\ F$	$\boldsymbol{r}^8 = (0,-1,0,0)$	(8)
$T_d + S \longrightarrow T_a + S$	$p_{da}\ T_d\ S$	$\boldsymbol{r}^9 = (0,0,1,-1)$	(9)
$T_d + F \longrightarrow T_a + F$	$p_{da}\ T_d\ F$	$\boldsymbol{r}^{10} = (0,0,1,-1)$	(10)
$T_a + nS \longrightarrow T_d$	$p_{ad}\ T_a \binom{S}{n}$	$\boldsymbol{r}^{11} = (-n,0,-1,1)$	(11)
$T_a + nF \longrightarrow T_d$	$p_{ad}\ T_a \binom{F}{n}$	$\boldsymbol{r}^{12} = (0,-n,-1,1)$	(12)

Table 2: Reactions used in the model.

State of the system $\boldsymbol{x} = (S, F, T_a, T_d)$

Master equation

$$
\begin{aligned}
\partial_t \Pr(\boldsymbol{x},t) = {} & r_S\ (S-1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^1,t) + r_F\ (F-1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^2,t) \\
& + m_S\ (S+1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^3,t) + m_F\ (F+1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^4,t) \\
& + p_{SF}\ (S+1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^5,t) + p_{FS}\ (F+1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^6,t) \\
& + \alpha\ r_S\ (S+1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^7,t) + \alpha\ r_F\ (F+1)\ \Pr(\boldsymbol{x}-\boldsymbol{r}^8,t) \\
& + p_{da}\ (T_d+1)\ S\ \Pr(\boldsymbol{x}-\boldsymbol{r}^9,t) + p_{da}\ (T_d+1)\ F\ \Pr(\boldsymbol{x}-\boldsymbol{r}^{10},t) \\
& + p_{ad}\ (T_a+1) \binom{S}{n} \Pr(\boldsymbol{x}-\boldsymbol{r}^{11},t) + p_{ad}\ (T_a+1) \binom{F}{n} \Pr(\boldsymbol{x}-\boldsymbol{r}^{12},t) \\
& - [(r_S + m_S + p_{SF} + \alpha\ r_S)S + (r_F + m_F + p_{FS} + \alpha\ r_F)F]\ \Pr(\boldsymbol{x},t) \\
& - [(p_{da}\ S\ + p_{da}\ F)T_d + (p_{ad} \binom{S}{n} + p_{ad} \binom{F}{n})T_a]\ \Pr(\boldsymbol{x},t)
\end{aligned}
$$

Fokker-Planck equation

$$
\begin{aligned}
\partial_t \Pr(\boldsymbol{x},t) = {} & [(\alpha-1)\ r_S + (\alpha-1)\ r_F + m_S + m_F + p_{SF} + p_{FS})\ \Pr(\boldsymbol{x},t) \\
& + \{[1+\alpha]\ r_S + m_S + p_{SF} - p_{FS} + [(\alpha-1)\ r_S + m_S + p_{SF}]\ S - p_{FS}\ F\}\ \partial_S\ \Pr(\boldsymbol{x},t) \\
& + \{[1+\alpha]\ r_F + m_F + p_{FS} - p_{SF} + [(\alpha-1)\ r_F + m_F + p_{FS}]\ F - p_{SF}\ S\}\ \partial_F\ \Pr(\boldsymbol{x},t) \\
& + \frac{1}{2}\{[(1+\alpha)\ r_S + m_S + p_{SF}]\ S + p_{FS}\ F\}\ \partial_{SS}\ \Pr(\boldsymbol{x},t) \\
& + \frac{1}{2}\{[(1+\alpha)\ r_F + m_F + p_{FS}]\ F + p_{SF}\ S\}\ \partial_{FF}\ \Pr(\boldsymbol{x},t) \\
& - (p_{SF}S + p_{FS}F)\ \partial_{FS}\ \Pr(\boldsymbol{x},t)
\end{aligned}
$$

Conclusion

- Significant variation is observed in tumor cell numbers at the end of treatment
- Tumor population faced extinction during treatment that were subject to chance
- Differences in treatment outcome can lead to a broad diversity of post-treatment responses as tumor cell numbers, and the fraction of slow cells serve as an initial condition for a potential relapse.

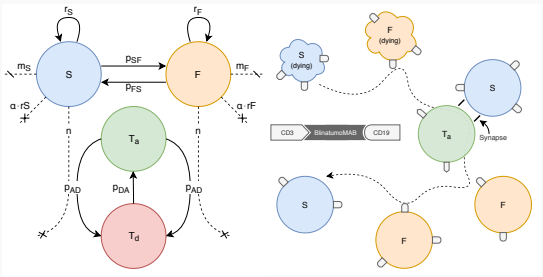

Figure 1: The left panel summarizes the fundamental interactions of cell types with reaction rate constants depicted on the reaction arrows. The right panel shows a BlinatumoMAB activated T cell performing serial killing of tumor cells.

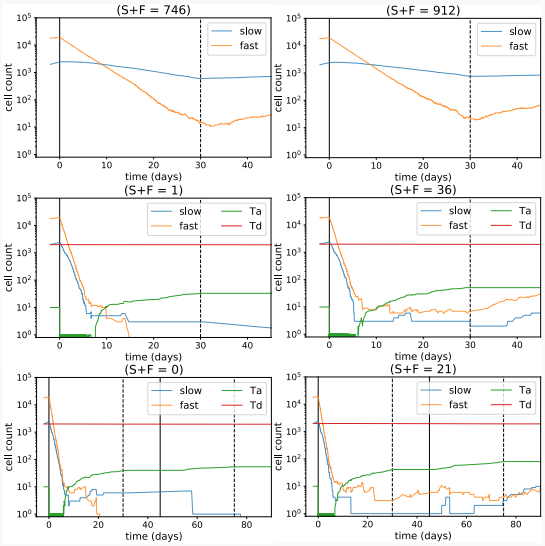

Figure 2: Simulations of chemotherapy and immunotherapy for ALL. Initial conditions are (S, F, Ta, Td) = (2000, 18000, 10, 1990). Panel titles report total tumor cells remaining at the end of the therapy. Panels (a) - (d) are single-cycle treatment simulations. Panels (a), (b) are chemotherapy, and panels (c), (d) are immunotherapy realizations. Panels (e), (f) are two-cycle realizations of immunotherapy.

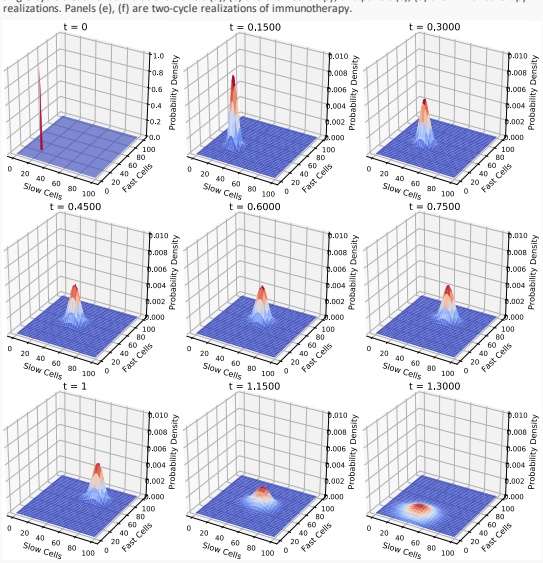

Figure 3: Numerical solutions of the Fokker-Planck equation. Panel titles report different time points. Initial conditions are Pr(S, F, 0) = δ(S − 20) δ(F − 20). Panels (a) - (f) correspond to the pre-therapy period. Panels (g) - (i) correspond to the chemotherapy period.

References: 1. Gardiner, C. W. (2009). Stochastic methods: a handbook for the natural and social sciences.
2. Zugmaier, G., N. Gokbuget, M. Klinger, et al. (2015). Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment.

Detailed report

Figure 3 animation