# **Stochasticity** may save leukemia patients during **antibody** based **immunotherapy**.

## Modeling dynamics of undetectable disease and therapy in leukemia


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## Introduction

- A 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.
- The primary treatment for ALL is chemotherapy, which combines anti-leukemic drugs targeting cell proliferation.

- 40%-50% of 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; from whereon, the system is driven by stochastic fluctuations.

## Aim

1. Formulate a model capturing the stochasticity of the system.
2. Simulate chemotherapy and immunotherapy.
3. Study effect of stochasticity 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 activation rate constants | $5 \cdot 10^{-5},\ 10^{-4}\ day^{-1}$ |
| $\alpha$ | 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

- Tumor populations faced extinction that was subject to chance during treatment.
- Significant variation was observed at the end of the treatment.
- Tumor cell numbers and fraction of slow cells are important initial conditions that shape the relapse, and differences in them can lead to diverse relapse profiles, generating within cohort variability.

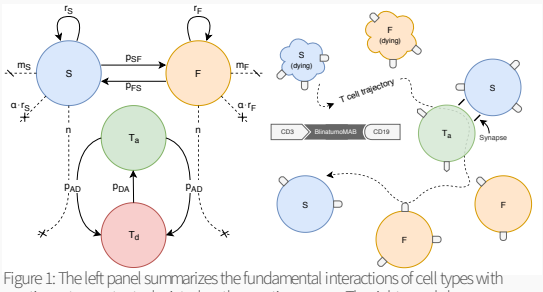


Figure 1: The left panel summarizes the fundamental interactions of cell types with reaction rate constants depicted on the reaction arrows. The right panel shows a BlinatumoMAB activated T cell performing serial killing of tumor cells.

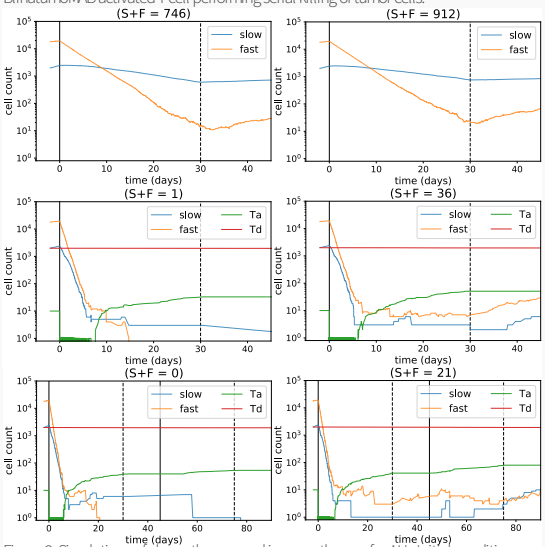


Figure 2: Simulations of chemotherapy and immunotherapy for ALL. Initial conditions are (S, F, $T_a$, $T_d$) = (2000, 18000, 10, 1990). Panel titles report total tumor cells remaining at the end of the therapy. Panels (a) - (d) are single-cycle treatment simulations. Panels (a), (b) are chemotherapy,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

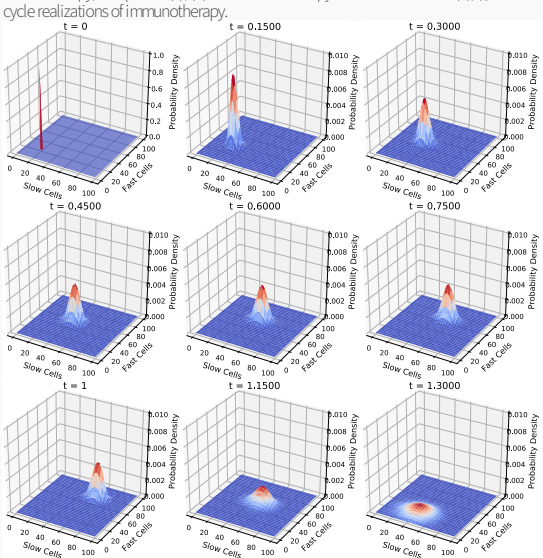


Figure 3: Numerical solutions of the Fokker-Planck equation. Panel titles report different time points. Initial conditions are Pr(S, F, 0) = δ(S − 20) δ(F − 20). Panels (a) - (f) correspond to the pre-therapy period. Panels (g) - (i) correspond to the chemotherapy period.


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