Modeling dynamics of undetectable disease in leukemias concerning therapy

Saumil Shah
Mid-year report
Fall 2019
saumil.shah@students.iiserpune.ac.in

Introduction

The accumulation of a series of lesions in hematopoietic progenitors leads to cells with differentiation arrest and abnormal proliferation. Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid precursors due to specific genetic modifications (Pui et al. 2008). ALL is generally discovered either when the disease becomes symptomatic, or when the tumor burden is high enough to be detectable by a blood test. By the time one of these events occurs, the neoplasm becomes challenging to treat as leukemic cells can multiply not only faster (Cooperman 2004) but also invade the central nervous system, testis, and other vital organs.

ALL is the most common form of cancer among children between the age of 2 and 5. ALL is also the most diagnosed leukemia in adults after the age of 50. Due to the discovery of targeted and risk-adapted therapies, the 5-year survival rate has increased from under 10% to over 90% (Della Starza et al. 2019; Siegel et al. 2015). Leukemia treatment aims to induce a lasting remission, defined as the absence of detectable tumor cells. Currently, the main treatment type for ALL is chemotherapy, which combines anti-leukemic medications that primarily affect cell proliferation. It is apparent that compared to rapidly proliferating cells, slowly proliferating leukemic cells are more robust against chemotherapy. Slowly proliferating tumor cells can remain clinically asymptomatic and undetected post-therapy due to their quiescent nature. The conversion from and to the slowly proliferating phenotype may have an essential role in the development of a relapse (Almog 2010). In adults with B cell precursor ALL, a relapse often occurs after the remission induction phase. These patients are then staged for allogeneic bone marrow transplantation or immunotherapy, as a modern alternative, as relapsed leukemias are likely to respond unfavorably to chemotherapy.

BlinatumoMAB, a bispecific T cell engager (BiTE) antibody, was shown to increase remission rates and overall survival rates, without significant toxic effects (Kantarjian et al. 2017). BlinatumoMAB facilitates the formation of an immune synapse between cytotoxic T cells and B cells as it is a fusion of two monoclonal antibodies targetting CD19, a B cell marker, and CD3, a T cell marker. This synapse drives the patient's CD3+ T cells to eliminate CD19+ lymphoblasts without needing T-cell receptor or major histocompatibility complex specificities (Wolf et al. 2005). Lymphocyte count in a healthy individual typically does not exceed 10^4 $cells/\mu l$; counts larger than this are considered unhealthy and serve as a diagnostic parameter for ALL. Within a 30-day treatment cycle of BlinatumoMAB, a median depletion of CD19+ counts below 1 $cell/\mu l$ by day-3, and a complete depletion by day-8 can be achieved (Zugmaier et al. 2015).

Many models have been published considering the compartmental structure of the hematopoietic lineage, most of these use differential equations or agent-based models, later reduced to deterministic equations (Clapp and Levy 2015). Due to the low cell numbers encountered during the treatments, and the ability of the quiescent cells to remain unexpanded, random fluctuations are more likely to drive this system.

To address the possibly profound effect of randomness on disease dynamics and the outcome of treatment, we propose a stochastic model. The effects of present-day therapies and the two phenotypes, namely, slowly and rapidly proliferating, are taken into account. The modeling results will be compared

to a large scale dataset of long-term follow-up adults with refractory/relapsed ALL. This dataset will be provided by the Hematology Laboratory of the University Medical Center Schleswig-Holstein, a part of the German Multicenter Study Group for Adult ALL (GMALL).

Objectives

1. Formulate a two-compartment stochastic model for acute lymphoblastic leukemia.
2. Simulate chemotherapy and immunotherapy.
3. Analyze the model and compare it with the dataset.

Model

We consider a system size of $2\mu l$ volume of blood. The slowly proliferating tumor cell is denoted as S, the rapidly proliferating tumor cell as F, activated T cell as T_a, and de-activated T cell as T_d (Table 1).

It is assumed that the system is Markovian; that is, the future state of the system depends only on its most recent state. It is also assumed that the system is well-mixed, such that the cells are evenly distributed in the volume. For simplicity, we assume that the total T cell number is conserved; i.e., they do not die or give birth to other T cells. It follows from this assumption that T cells are not affected by chemotherapy; thus, we will omit to track them.

Symbol	Description	Range / Value
S	slowly proliferating cells	
F	rapidly proliferating cells	
T_a	activated cytotoxic T cells	
T_d	de-activated cytotoxic T cells	
r_i	birth rate constant of cell type i	10^{-2} *to* 10^{-1} day^{-1}
p_{ij}	conversion rate constant from cell type i to j	10^{-4} *to* 10^{-2} day^{-1}
m_i	death rate constant of cell type i	10^{-3} *to* 10^{-2} 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 Kinetics

The actions performed by different cells can be symbolized using the language of chemical reactions. Reactions corresponding to fundamental actions performed by cells are summarized in Table 2. The proliferation of tumor cells is depicted by reaction (2.1) and (2.2). The conversion between the tumor cell types is captured by reaction (2.3) and (2.4). The death of tumor cells is symbolized by reaction (2.5) and (2.6).

However, reactions are not sufficient to trace the dynamics of the system. Thus, we also require information about the rates at which the reactions occur. According to the first-order rate law, reaction rates are proportional to the concentrations of the reactants. Thus, cell type i is generated with a birth rate of r_i i and destroyed with m_i i, respectively, where r_i and m_i are birth and death rate constants, respectively. Cell type i switches to type j with a rate of p_{ij} i, where p_{ij} is conversion rate constant (Table 1).

The chemotherapeutic drug causes the death of leukemic cells proportional to their birth rates scaled by drug efficacy α, symbolized in reaction (2.7) and (2.8). We assume a non-limiting constant concentration of BlinatumoMAB during immunotherapy that is included in the reaction rate constants.

The de-activated T cells get activated in the presence of leukemic cells as expressed in reactions (2.9) and (2.10). Activated T cells kill n tumor cells in a process called serial killing (Wolf 2005) and get de-activated, shown in reactions (2.11) and (2.12).

Reaction	Rate	Stoiochiometric vector	
$S \longrightarrow S + S$	$r_S\ S$	$(1, 0)$	(2.1)
$F \longrightarrow F + F$	$r_F\ F$	$(0, 1)$	(2.2)
$S \longrightarrow F$	$p_{SF}\ S$	$(-1, 1)$	(2.3)
$F \longrightarrow S$	$p_{FS}\ F$	$(1, -1)$	(2.4)
$S \longrightarrow \phi$	$m_S\ S$	$(-1, 0)$	(2.5)
$F \longrightarrow \phi$	$m_F\ F$	$(0, -1)$	(2.6)
$S \longrightarrow \phi$	$\alpha\ r_S\ S$	$(-1, 0)$	(2.7)
$F \longrightarrow \phi$	$\alpha\ r_F\ F$	$(0, -1)$	(2.8)
$T_d + S \longrightarrow T_a + S$	$p_{da}\ T_d\ S$	$(0, 0, 1, -1)$	(2.9)
$T_d + F \longrightarrow T_a + F$	$p_{da}\ T_d\ F$	$(0, 0, 1, -1)$	(2.10)
$T_a + nS \longrightarrow T_d$	$p_{ad}\ T_a\ \binom{S}{n}$	$(-n, 0, -1, 1)$	(2.11)
$T_a + nF \longrightarrow T_d$	$p_{ad}\ T_a\ \binom{F}{n}$	$(0, -n, -1, 1)$	(2.12)

Table 2: Reactions used in the model.

Master equation

In order to make this description stochastic, we shall replace deterministic rate laws by probabilistic laws (Gardiner 2009). To make this process simpler, we omit T cell dynamics for now. Thus, the state of the system is expressed by only the tumor cell numbers (S, F). The stoichiometric vector gives the change in the state due to each reaction (Table 2). A probability distribution $\Pr(S, F, t)$ is defined for the state of the system (S, F) at a given time t. Suppose that for an infinitesimal time Δt, the following transition probabilities hold.

$$\begin{aligned}
\Pr(S \to S + 1; F \to F) &= r_S\ S\ \Delta t \\
\Pr(S \to S; F \to F + 1) &= r_F\ F\ \Delta t \\
&\vdots \\
\Pr(S \to S; F \to F - 1) &= \alpha\ r_F\ F\ \Delta t
\end{aligned}$$

Then we write the probability of state (S, F) at time $t+\Delta t$ as a sum of terms, each of which represents the probability of a previous state multiplied by the probability of transition to the state (S, F). This relation is known as the Chapman-Kolmogorov equation. After rearranging and letting $\Delta t \to 0$, we find the differential form of the equation commonly known as the master equation. This equation describes the probability flow responsible for creating and destroying any given state of the system.

$$\begin{aligned}
\partial_t \Pr(S, F, t) = {} & r_S\ (S - 1)\ \Pr(S - 1, F, t) + r_F\ (F - 1)\ \Pr(S, F - 1, t) \\
& + m_S\ (S + 1)\ \Pr(S + 1, F, t) + m_F\ (F + 1)\ \Pr(S, F + 1, t) \\
& + p_{SF}\ (S + 1)\ \Pr(S + 1, F - 1, t) + p_{FS}\ (F + 1)\ \Pr(S - 1, F + 1, t) \\
& + \alpha\ r_S\ (S + 1)\ \Pr(S + 1, F, t) + \alpha\ r_F\ (F + 1)\ \Pr(S, F + 1, t) \\
& - [(r_S + m_S + p_{SF} + \alpha\ r_S)S + (r_F + m_F + p_{FS} + \alpha\ r_F)F]\ \Pr(S, F, t)
\end{aligned} \tag{2.13}$$

It is also useful to look at the Taylor expansion of the master equation. Keeping the terms up to the second-order we find a quasi-linear convection-diffusion partial differential equation known as the Fokker-Planck equation. To make this description complete, we also include an initial condition $\Pr(S, F, 0) = \delta(S - S_0)\ \delta(F - F_0)$.

$$\begin{aligned}
\partial_t \Pr(S,F,t) = {} & [(\alpha-1)\ r_S + (\alpha-1)\ r_F + m_S + m_F + p_{SF} + p_{FS})\ \Pr(S,F,t) \\
& + \{[1+\alpha]\ r_S + m_S + p_{SF} - p_{FS} + [(\alpha-1)\ r_S + m_S + p_{SF}]\ S - p_{FS}\ F\}\ \partial_S\ \Pr(S,F,t) \\
& + \{[1+\alpha]\ r_F + m_F + p_{FS} - p_{SF} + [(\alpha-1)\ r_F + m_F + p_{FS}]\ F - p_{SF}\ S\}\ \partial_F\ \Pr(S,F,t) \\
& + \frac{1}{2}\{[(1+\alpha)\ r_S + m_S + p_{SF}]\ S + p_{FS}\ F\}\ \partial_{SS}\ \Pr(S,F,t) \\
& + \frac{1}{2}\{[(1+\alpha)\ r_F + m_F + p_{FS}]\ F + p_{SF}\ S\}\ \partial_{FF}\ \Pr(S,F,t) \\
& - (p_{SF}S + p_{FS}F)\ \partial_{FS}\ \Pr(S,F,t)
\end{aligned} \tag{2.14}$$

Results

We use Gillespie's stochastic simulation algorithm (Gillespie 1977) to simulate the reaction system using python (Hunter 2007; Oliphant 2007; Walt et al. 2011) and StochKit (Sanft et al. 2011). One realization of the simulation consists of three periods, i.e., pre-therapy, therapy, and post-therapy, where therapy period represents the remission induction stage of leukemia treatment (Figure 1a-d). Multiple cycles of remission induction can be produced by repeating therapy and post-therapy periods (Figure 1e-f). The reaction rate constants were chosen to qualitatively match a published pilot study by Zugmaier et al. (2015). We observe a significant variation in tumor cell numbers at the end of treatment, including extinctions of the tumor population subject to chance. These differences 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.

We also show the temporal evolution of the probability density of different states of the system for the pre-therapy (Figure 2a-f) and therapy(Figure 2g-i) periods.

Future direction

In the latter half of the project, we will calibrate the parameters quantitatively as soon as the latest large scale data is available from our collaborators. Then we will analyze the model for stability, cohort heterogeneity, and distribution of minimal residual disease response, defined as post-treatment tumor cell density below 10^{-4} per healthy cells (Zugmaier et al. 2015). We are particularly interested in treatment outcomes where the probability of extinction of the tumor is maximized in the context of immunotherapy. Hence, we will also determine the sensitivity of the outcome to all parameters tunable in real life. If time permits, we shall also look for the analytical solutions of the master equation and the Fokker-Planck equation.

References

Almog, N. (2010). "Molecular mechanisms underlying tumor dormancy". en. In: *Cancer Letters* 294.2, pp. 139–146.

Clapp, G. and D. Levy (2015). "A review of mathematical models for leukemia and lymphoma". In: *Drug Discovery Today: Disease Models* 16, pp. 1–6.

Cooperman, J. (2004). "Cell Division Rates of Primary Human Precursor B Cells in Culture Reflect In Vivo Rates". In: *Stem Cells* 22.6, pp. 1111–1120.

Della Starza, I., S. Chiaretti, M. S. De Propris, et al. (2019). "Minimal Residual Disease in Acute Lymphoblastic Leukemia: Technical and Clinical Advances". In: *Frontiers in Oncology* 9, p. 726.

Gardiner, C. W. (2009). *Stochastic methods: a handbook for the natural and social sciences*. 4th ed. Springer series in synergetics 13. Berlin: Springer.

Gillespie, D. T. (1977). "Exact stochastic simulation of coupled chemical reactions". In: *The Journal of Physical Chemistry* 81.25, pp. 2340–2361.

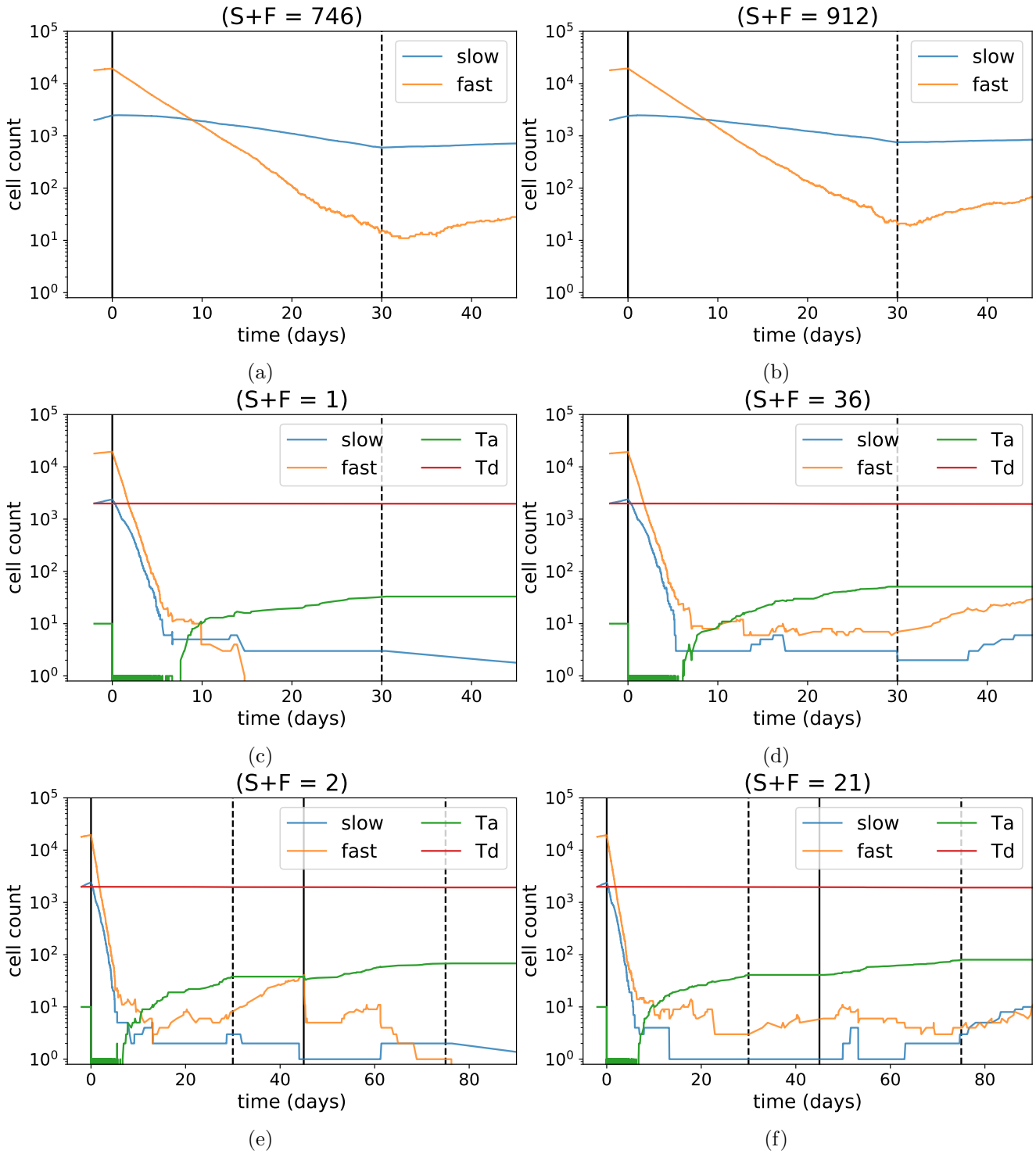

Figure 1: Simulations of chemotherapy and immunotherapy for ALL. Initial conditions are $(S, F, T_a, T_d) = (2000, 18000, 10, 1990)$. Panel titles report total tumor cells remaining at the end of the therapy. Panels (a) - (d) are single-cycle treatment simulations. Panels (a), (b) are chemotherapy, and panels (c), (d) are immunotherapy realizations. Panels (e), (f) are two-cycle realizations of immunotherapy.

Hunter, J. D. (2007). "Matplotlib: A 2D Graphics Environment". In: *Computing in Science & Engineering* 9.3, pp. 90–95.

Kantarjian, H., A. Stein, N. Gökbuget, et al. (2017). "Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia". In: *New England Journal of Medicine* 376.9, pp. 836–847.

Meurer, A., C. P. Smith, M. Paprocki, et al. (2017). "SymPy: symbolic computing in Python". In: *PeerJ Computer Science* 3, e103.

Oliphant, T. E. (2007). "Python for Scientific Computing". In: *Computing in Science & Engineering* 9.3, pp. 10–20.

Pui, C.-H., L. L. Robison, and A. T. Look (2008). "Acute lymphoblastic leukaemia". In: *The Lancet* 371.9617, pp. 1030–1043.

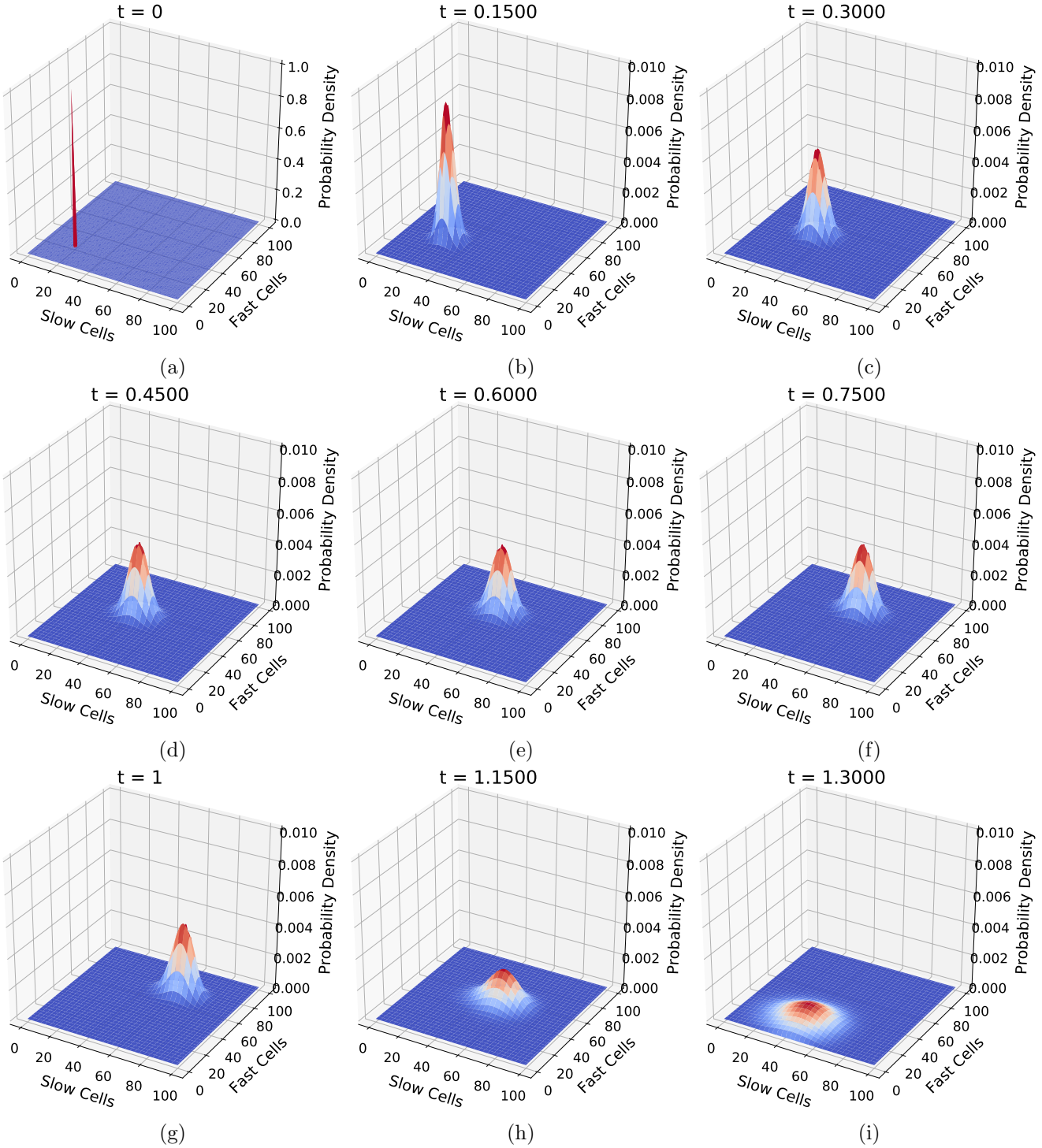

Figure 2: Numerical solutions of the Fokker-Planck equation. Panel titles report different time points. Initial conditions are $\Pr(S, F, 0) = \delta(S - 20)\ \delta(F - 20)$. Panels (a) - (f) correspond to the pre-therapy period. Panels (g) - (i) correspond to the chemotherapy period.

Sanft, K. R., S. Wu, M. Roh, et al. (2011). "StochKit2: software for discrete stochastic simulation of biochemical systems with events". en. In: *Bioinformatics* 27.17, pp. 2457–2458.

Siegel, R. L., K. D. Miller, and A. Jemal (2015). "Cancer statistics, 2015: Cancer Statistics, 2015". In: *CA: A Cancer Journal for Clinicians* 65.1, pp. 5–29.

Walt, S. van der, C. S. Colbert, and G. Varoquaux (2011). "The NumPy Array: A Structure for Efficient Numerical Computation". In: *Computing in Science & Engineering* 13.2, pp. 22–30.

Wolf, E., R. Hofmeister, P. Kufer, B. Schlereth, and P. A. Baeuerle (2005). "BiTEs: bispecific antibody constructs with unique anti-tumor activity". In: *Drug Discovery Today* 10.18, pp. 1237–1244.

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". In: *Blood* 126.24, pp. 2578–2584.