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Chemotherapy Optimization in Leukemia: Selecting the Right Mathematical Models for the Right Biological Processes ⋆

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Abstract: Clinical chemotherapy dosage strategies for leukemia rely on weight/height calculations theoretically correlated to patient drug tolerance. However, over- and under- dosage still exist in clinical practice, which could be overcome by quantifying the actual fraction of cancer cells susceptible to be eradicated. In this work, we show how choosing models that are accurate enough in simulating the biological processes ultimately affecting drug efficacy is critical in order to disentangle patient to patient heterogeneity. Incorporating heterogeneity from measurable sources in such a manner brings us a step closer in our path towards the development of personalized rational therapies.

Keywords: Biomedical systems, cell cycle, mathematical models, pharmacodynamics, leukemia

1. INTRODUCTION

Acute Myeloid Leukemia (AML) is a type of blood cancer that affecting 2,600 new people in the UK every year; it is characterized by a rapid increase in immature blood cells with highly proliferative features (Lane et al. (2009)). It is a severe condition requiring immediate chemotherapy treatment. Traditional chemotherapy dosage strategies rely on empirical calculations theoretically correlated to patient drug tolerance and pharmacokinetics/drug distribution. However, patient-to-patient variability in drug metabolism can result in over- or under- dosing, ultimately causing extreme toxicities or decreased treatment performance respectively. Since most standard chemotherapy agents target proliferative cells only, we postulated dosage should be calculated according to cancer debulking needs (within tolerance limits, Pefani et al. (2013)).

Proliferation occurs during the cell cycle, which is a four step process highly controlled by the timed expression of proteins (Fig. 1). Cells start at G1: they grow in size and produce an intracellular protein (cyclin E) which peaks at the end of G1, triggering the transition to S phase. During S phase, cells duplicate their DNA. They then move to G2, where their cyclin B content increases and peaks, marking the transition to M phase, where the cell gives birth to two new cells which can in turn enter the cell cycle or remain in quiescent state (G0). Typically, chemotherapeutics attack cells during one of the four cell cycle phases, making it crucial to assess the cellular fraction in that specific phase for treatment optimisation. Importantly, this should be done on a patient-by-patient basis since AML is inherently heterogeneous. For patients undergoing chemotherapy, it is unethical to do frequent bone marrow tests to monitor cell cycle kinetics; therefore, simulating patient response *in silico* is a promising alternative. In this way, possible treatment outcomes can be anticipated and a better treatment

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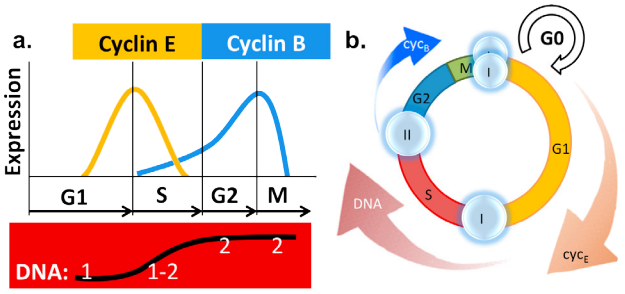

Fig. 1. Overview of biological events occurring during the cell cycle: **a.** Sequence of phases and cell statuses; **b.** Content of key cyclins and DNA throughout cell cycle phases

for that particular patient can be designed. Clinicians may then be able to make more informed decisions based on quantitative, patient-specific information (Fuentes-Garí et al. (2015b)).

Up to now, mathematical models of pharmacokinetics / pharmacodynamics (PK/PD) have been developed to capture all drug transport and reaction processes occurring inside the patient during chemotherapy. The PK and PD sections of these models have progressively been upgraded and validated with clinical data; however, most of the cell cycle models used there remain simplistic and inherently lack the structure to capture heterogeneity and sensitivity to drugs. The cell cycle is typically an oscillating system; its equilibrium lies at the steady-state cell cycle fractions and exponential growth. However, when taken out of the equilibrium, cell fractions undergo a transient state that is characterized by the oscillatory properties of the specific model chosen (Ferrell et al. (2011)). Especially under chemotherapy treatment, oscillations play a key role as they determine how much room there is for chemotherapy action (favourable times being target phase highs and unfavourable times, target phase lows). The ability to capture oscillatory behavior and the availability of measurable parameters are two essential model features for accurate clinical predictions (Di Ventura et al. (2006); Csete and Doyle (2002)). Mathematical models of the cell cycle have been widely developed both at the mechanistic and descriptive levels (Anderson and Quaranta (2008)). Mechanistic models typically represent protein networks or other biological signals in an effort to explain the underlying causes for cell growth (Weis et al. (2014); Singhania et al. (2011); Alarcon et al. (2004)). In contrast, descriptive models represent observable cause-effect phenomena (Sherer et al. (2006); Daukste et al. (2012)).

In this manuscript, we review the parameters needed by three types of cell cycle phase models and compare their performance in capturing processes occurring during chemotherapy treatment. More specifically, examples of ordinary differential equation (ODE), delay differential equation (DDE) and population balance models (PBM) are selected for the comparison and embedded into a previously developed PK/PD model (Pefani et al. (2013)). A hypothetical patient case is run for one chemotherapy cycle, revealing how phase progression mechanisms impact cell kill and cell cycle distribution over time in all three models. Next, an overview of PBM model flexibility in capturing heterogeneous oscillatory behaviors is given; the PBM has been validated with chemotherapy-free experimental cell cycle data for several cell lines, including in mixtures (Fuentes-Garí et al. (2015a); Munzer et al. (2014)). Overall, cell cycle models should be selected according to the specific application, an example of which is given in this paper in the form of chemotherapy simulation with PK/PD.

2. MODEL DEFINITIONS

An initial approach is to model cell cycle phases with ODEs, with the parameters needed being the transition rates and the initial cell populations for each phase. Pefani et al. (2013) give an example with three compartments (G0/G1: lumped quiescent and G1 phases, S and G2/M: lumped G2 and M phases), which we will call cell cycle phase ODEs (CCP-ODE):

$$\begin{aligned}\frac{dG(t)}{dt} &= 2\cdot 1/\tau_M \cdot M(t) - 1/\tau_G \cdot G(t) \quad - k_{D,G}(t)\cdot G(t)\\ \frac{dS(t)}{dt} &= 1/\tau_G \cdot G(t) - 1/\tau_S \cdot S(t) \quad - k_{D,S}(t)\cdot S(t)\\ \frac{dM(t)}{dt} &= 1/\tau_S \cdot S(t) - 1/\tau_M \cdot M(t)\end{aligned} \tag{1}$$

where G, S and M are the cell numbers and τ_G, τ_S and τ_M are the phase durations of the G0/G1, S and G2/M phases and $k_{D,S}$, $k_{D,G}$ are the chemotherapy drug effect parameters for S and G1 phases respectively. The death rates $k_{D,S}(t)$, $k_{D,G}(t)$ are calculated by the PD model of Pefani et al. (2013), which is based on E_{max} dose-response curves, and have a time dependence due to the scheduling of the drug and the delay in the transport and absorption of the drug through body compartments, as calculated by the PK model; their definition and time dependence remain for all other equations in the manuscript.

An alternative model accounts for the temporal discrepancy between cells entering and exiting phases. For this, we developed a new DDE model by introducing a time delay equal to phase duration, which we call cell cycle phase DDEs (CCP-DDE):

$$\begin{aligned}\frac{dG(t)}{dt} &= 2\cdot 1/\tau_M \cdot M(t-\tau_M) - (1/\tau_G + k_{D,G}(t))\cdot G(t)\\ \frac{dS(t)}{dt} &= 1/\tau_G \cdot G^*(\tau_G) - (1/\tau_S + k_{D,S}(t))\cdot S(t)\\ \frac{dM(t)}{dt} &= 1/\tau_S \cdot S^*(\tau_S) - 1/\tau_M \cdot M(t), \text{ where}\\ \frac{dG^*(t^*)}{dt*} &= -k_{d,G}\cdot G^*(t^*) \quad \text{with} \quad G^*(0) = G(t-\tau_G)\\ \frac{dS^*(t^*)}{dt^*} &= -k_{d,S}\cdot S^*(t^*) \quad \text{with} \quad S^*(0) = S(t-\tau_S)\end{aligned} \tag{2}$$

where all variables and parameters are defined as in CCP-ODE and $(t-\tau_X)$ represents the value of the cell cycle phase X at time $t-\tau_X$. Of note, the proposed model is not completely balanced (terms $-1/\tau_G \cdot G(t)$ and $+1/\tau_G \cdot G(t-\tau_G)$ not cancelling out) however the effect of this is only visible in the beginning of the transient state and doesn't impact the steady state. An important advantage of CCP-DDE is that it adds a phase coordinate dimension to the system (i.e., cell populations are not eligible to exit a phase as soon as they enter), so any disturbances in