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An Extended Personalised Chemotherapy Response Model Incorporating Inflammation and Individual Variability in Childhood Acute Lymphoblastic Leukemia

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Abstract: *This study aims to develop a personalised pharmacokinetic / pharmacodynamic model for 6-mercaptopurine (6-MP) used in the treatment of childhood acute lymphoblastic leukemia (ALL). The developed model considers both neutrophil count and white blood cells in the context of lifestyle-related inflammatory responses (affected by nutrition, diet, and the vitamin D), genetic variations (e.g., TPMT), and also age-related pharmacokinetic values. In detail, the model is structured by equations corresponding absorption of 6-MP in the body, its metabolites (6-TGN, 6-mMPN, 6-TU), and also suppressive effects of the metabolites over the hematopoietic system. One unique aspect of the study is that the inflammatory response is integrated into the system as an additional component evaluating the lifestyle impact on hematopoietic production. The study confirms the model by running simulations for the patient profiles with different ages, genetic factors, and inflammatory conditions. The findings reveal leukocyte responses and ensure a basis for personalised dose optimisation.*

Keywords: *childhood acute lymphoblastic leukemia; computational patient model; 6-mercaptopurine.*

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1. Introduction

Childhood acute lymphoblastic leukemia (ALL) is a cancer of blood and bone marrow, and it is known as the most common haematological malignancy seen in children. As with other cancer types, treatment of childhood ALL has been researched intensively, and current therapies have been shaped by the use of a variety of drugs. Although drugs are used within determined treatment protocols, it is also important that each patient may experience different responses to a drug, as for example genetic variations in the activity of specific liver enzymes can cause variability in drug metabolism. Even such genetic variations can affect effectiveness of the treatment and trigger side effects accordingly (Eichmeyer et al., 2020). Because of this, it is a critical approach to consider genetic factors at the time of setting treatment dosages.

Setting treatment dosages is related to creating personalised treatment plans. When it comes to personalised treatment, there are more factors than only genetic ones. In this context, blood test findings / values, some biochemical test results should also be used for ensuring better planning at the end. Notably, certain drug combinations can enhance the quality of treatment and even improve recovery rates in cancer, also covering childhood ALL. Today, 6-mercaptopurine (6-MP) is known as one of widely used drugs for childhood ALL, and it demonstrates a synergistic interaction with methotrexate (MTX). Both drugs are co-administered as an effective combination in different phases of childhood ALL treatment. Recently, Köse et al. (2025) introduced mathematical models, which are able to simulate the 6-MP-MTX combination. According to their study, it is possible to have precise predictions based on variables such as neutrophil count, mean corpuscular volume (MCV), and white blood cell count. This points that further research can be done by considering more individual parameters so that modelling of drugs can be further expanded. This is also a critical way to enhance the role of more advanced data-driven tools developed by using data science and most importantly AI models. Another perspective presented by Köse et al. (2025) is that there is always a need for evaluating the drugs individually in modelling complete frameworks of treatment protocols and even developing advanced AI-based decision support systems.

In oncology, treatment response is a complicated issue. Considering childhood ALL, the treatment response to chemotherapy is affected by different factors. The related factors include physical activity, vitamin D levels, and even dietary practices. For example, vitamin D has the role of increasing immunity and strengthening bones, but unfortunately, patients often neglect supplementation (Bhattacharya et al., 2019). It is therefore important to analyse a patient's vitamin D state at the beginning of the treatment flow and direct a personalised plan accordingly. The literature already pointed out that vitamin D supplements taken in compliance with chemotherapy regimens reduce metabolic problems and even bone density caused by chemotherapy (Orgel et al., 2017). Evidence also suggests that chemotherapy response is positively affected by regular exercise as well as a nutritious diet. A balanced and adequate nutrition can increase the patient's resistance, by preventing nutrient deficiencies appearing during the treatment and also strengthening the immune system generally. On the other hand, exercise is already known to lower the risk of issues such as muscle atrophy and fatigue, both of which can be caused by chemotherapy. Exercise is also clearly effective in increasing circulation, so this helps in a more rapid influence of chemotherapy drugs. Eventually, all these mentioned factors: vitamin D, exercise, and nutrition should be taken into consideration and managed accordingly during the treatment of childhood ALL.

When today's modelling studies are considered, it can be seen that extensive patient models mimicking metabolic processes and treatment plans are widely defined to introduce personalised patient scenarios (Barbiero & Liò, 2020). As such models can enable us to analyse patients' evolving physiological reactions for treatment, additional AI-based algorithms can also be effectively used for establishing personalised dose modifications for chemotherapy (Derclé et al., 2020; Su et al., 2022). The literature shows that such models and tools can contribute to improved treatment outcomes with personalised flows and fewer side effects (El Alaoui et al., 2022; Bernsen et al., 2025; Tan et al., 2022).

Moving from the explanations so far, this study aims to extend the modelling for childhood ALL treatment by focusing on the 6-MP drug and integrating lifestyle factors, genetic factors and biological parameters to create a personalised perspective. There are recent studies analysing potential drug candidates for the treatment of childhood ALL. These studies generally included AI techniques with validation steps to define some personalised treatment approaches (Köse, 2025; Uysal & Köse, 2023). The authors of this study were motivated to extend the drug treatment model and to evaluate it using synthetic patient scenarios through three-month dose simulations. In order to see if the model confirms correct treatment flows, the changes in 6-TGN, WBC, and ANC over time were analysed accordingly. It is remarkable that the study's strategy is consistent with a recent project (STING), which employs AI-based decision support approach and patient-related PK/PD modelling to optimise 6-MP treatments in childhood ALL (Köse, 2025). Figure 1 illustrates the general modelling flow in the study.

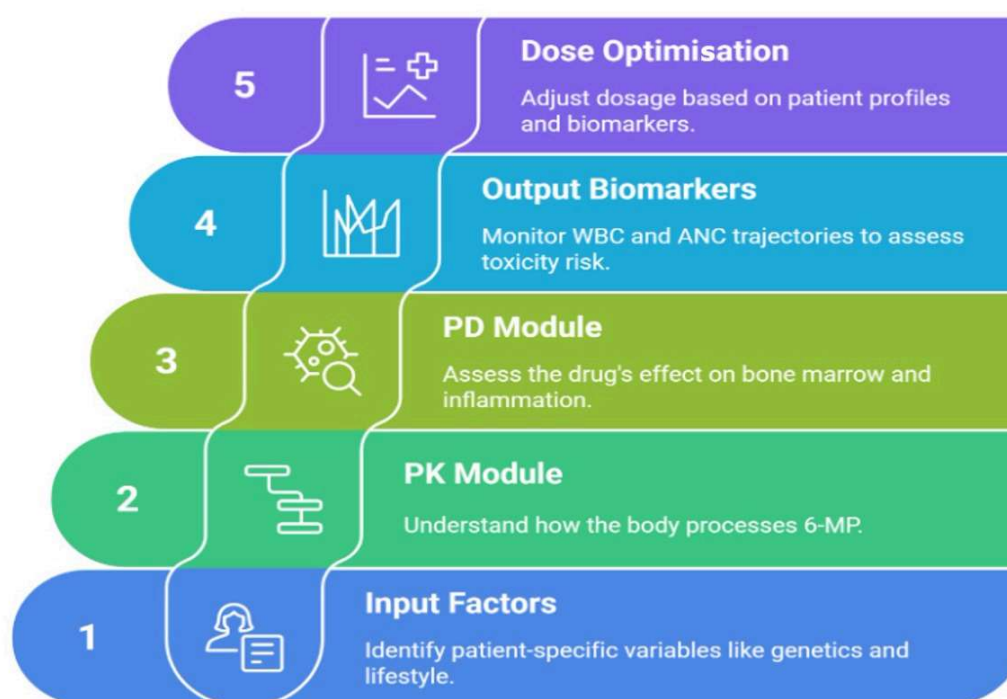


Figure 1. The 6-MP therapy optimisation model introduced in this study.

As illustrated in Figure 1, the 6-MP therapy optimisation model starts by considering lifestyle factors and patient-related traits (entry factors) as the input data for the model. In the second step, these data are integrated into a pharmacokinetics (PK) module, which can evaluate how the 6-MP is metabolised in the patient body. In the third step, the data are transferred to the pharmacodynamics (PD) module, which can evaluate the 6-MP's effects on bone marrow and inflammation. Subsequently, the model continues to evaluate toxicity risks (considering WBC and ANC) and finally determines the optimal dosage value as per the patient's profile and trends of the biomarkers.

2. Related Work

When analysing drug kinetics and their effects, PK / PD modelling plays an essential role in research studies. It enables the evaluation of drug absorption kinetics, duration of therapeutic effects and even their interactions with haematological parameters during the treatment. In terms of childhood ALL, one remarkable finding is that body surface area adjustments and TPMT genotyping to optimise 6-MP dosage have improved treatment outcomes (Hawwa et al., 2008;

Jayachandran et al., 2014; Le et al., 2019; Jost et al., 2020; Gebhard et al., 2023; Netterberg et al., 2017). In addition, the use of combined PK and PD models with machine learning techniques has been shown to be effective in improving patient-related predictions further (Gobburu & Chen, 1996; Nasim & Nasim, 2024).

Today, modelling efforts are associated with also a new technological perspective called digital twin. The digital twin enables the creation of personalised treatment simulations in near real time by integrating computational models with continuously updated electronic health records and laboratory data (Randles, 2025; Vallée, 2023). These synthetic (virtual) patient models are particularly valuable in ALL research, where high-quality, comprehensive real-world datasets are scarce. Considering AI models, Generative Adversarial Networks (GANs) and variational autoencoders (VAEs) can synthesise realistic patient features and medical images, which mitigates privacy concerns and data shortages (Shi et al., 2022; Tucker et al., 2020). However, the combination of synthetic data and AI models within a cohesive digital twin pipeline has yet to be used for longitudinal forecasting of key clinical markers such as ANC or WBC levels. Traditional approaches to classifying white blood cells have predominantly used convolutional neural networks (CNNs) to analyse static images, achieving reliable accuracy in differentiating cellular subtypes (Jawahar et al., 2024; Cheuque et al., 2022). While these static models are sufficient for diagnostic purposes, they fail to capture the temporal evolution of cellular characteristics, which limits their utility for monitoring treatment response. Only a limited number of studies have applied temporal modelling to predict how quickly neutrophils recover after therapy, and even fewer have incorporated these predictions into a temporal AI-based learning architecture (Choo et al., 2023). The latest digital twin developments consider integrating AI models to overcome these limitations by incorporating dynamic multi-view representations of vital signs that fluctuate during chemotherapy. Such change improves their applicability in clinical decision-making and better fits the clinician's workflow. One method, for instance, is to encode temporal snapshots as graph nodes with sequentially connected edges. This embeds temporal dependencies, the data structure's primary defining characteristic. The most recent developments in multi-scale temporal AI models are consistent with this (Zhou et al., 2025; Fan et al., 2025). Furthermore, the imaging-related clinical parameters—body size, frequency of physical activity, 6-MP dosage, and vitamin D intake—are combined to create a more complete picture of the patient that facilitates more focused clinical decision support.

Findings from alternative studies highlight the quick uptake of AI in healthcare modelling while also revealing significant gaps. Before moving on to AI modelling, more modelling work is still required to predict WBC and absolute neutrophil counts in children with leukaemia. Now, a scalable, interpretable path to customising treatment regimens and controlling the side effects of chemotherapy can be provided by fusing artificially generated patient data with time-aware architectures and AI models. Future efforts should focus on clinical implementation, testing them on long-term observational datasets, and boosting their clarity by applying AI support. First, advancing pharmacotherapy models of drugs and producing useful data are critically important for further data-driven applications. In this context, this study considered the extension of a drug for chemotherapy response analysis, which will then take place inside a general AI-based decision support system.

3. Age- and Genotype-Informed Computational Patient Modelling for 6-MP Pharmacokinetics

The journey of 6-MP in the body is a pharmacokinetic process consisting of absorption, distribution, metabolism and excretion steps. In order to simulate this process in a computer environment, each step must be modelled mathematically. Accordingly, the pharmacokinetic process of 6-MP is structured using differential equations, encompassing the steps of oral administration, gastrointestinal absorption, plasma transport, distribution to target tissues, enzymatic metabolism, and metabolite excretion, as detailed below.

6-MP absorption in the gastrointestinal tract is determined by the following first-order linear ordinary differential equation

$$\dot{x}_1(t) = -k_a x_1(t) + Fu(t), \quad (1)$$

where k_a , $x_1(t)$, F and $u(t)$ are the absorption rate constant, the amount of 6-MP in the gastrointestinal system, the bioavailability factor and the time-dependent drug dose, respectively (Jost et al. 2020). The change of 6-MP in plasma is given by the following first-order linear differential equation

$$\dot{x}_2(t) = k_a x_1(t) - k_{20} x_2(t), \quad (2)$$

where k_{20} , $x_2(t)$ are the elimination rate constant of 6-MP from plasma and the amount of 6-MP in plasma, respectively. Conversion of 6-MP drug to the active metabolite called 6-TGN by the HGPRT enzyme is described by the following a first-order linear ordinary differential equation

$$\dot{x}_3(t) = FM_3 k_{me} x_2(t) - CL_{6tgn}(BSA) x_3(t), \quad (3)$$

where FM_3 , $x_3(t)$, k_{me} and $CL_{6tgn}(BSA)$ are respectively the fraction of 6-MP converted to 6-TGN, the concentration of 6-TGN in plasma, metabolic rate constant and the clearance rate of 6-TGN from plasma which is obtained by $CL_{6tgn}(BSA) = 0.00914(BSA)^{1.16}$ (see, Hawwa et al., 2008; Jayachandran et al., 2014; Le et al. 2018; Jost et al. 2020). This differential equation describes the conversion and elimination of 6-MP to 6-TGN.

Conversion of 6-MP drug to the metabolite 6-methylmercaptopurine nucleotide (6-mMPN) by thiopurine methyltransferase (TPMT) enzyme is expressed by the following first-order linear ordinary differential equation:

$$\dot{x}_4(t) = FM_4 k_{me} x_2(t) - CL_{6mpn} x_4(t) \quad (4)$$

where FM_4 , $x_4(t)$, k_{me} and CL_{6mpn} are respectively the fraction of 6-MP that is converted to 6-mMPN, the concentration of 6-mMPN in plasma, the metabolic rate constant and the clearance rate of 6-mMPN from the plasma. The elimination rate of 6-mMPN CL_{6mpn} is a constant 0.0228.

Conversion of 6-MP drug to the inactive metabolite 6-thiouric acid (6-TU) by the enzyme xanthine oxidase (XO) is described by the following first-order linear ordinary differential equation

$$\dot{x}_5(t) = FM_5 k_{me} x_2(t) - CL_{6tu}(BSA) x_5(t), \quad (5)$$

where FM_5 , $x_5(t)$, $CL_{6tu}(BSA)$ are respectively the fraction of 6-MP converted to 6-TU, the concentration of 6-TU in plasma and the clearance rate of 6-TU from plasma. 6-TU is completely eliminated from the body close to 12 hours after drug administration (Hawwa et al., 2008). According to classical PK rules, the drug is mostly cleared from the body after 5–6 half-lives. Since 6 half-life is 12 hours, 1 half-life should be 2 hours. The relationship between half-life and clearance CL_{6tu} is given by

$$t_{1/2} = \frac{0.693V}{k_{me}} = \frac{0.693}{CL_{6tu}},$$

where $t_{1/2}$ is the drug's half-life, CL_{6tu} is the clearance and V is the theoretical volume in which the drug is distributed within the body. In order for 6-TU to be completely eliminated within 12 hours, 5 half-lives must pass (because 97–99% of the drug is eliminated after 5 half-lives). Since the total time is $5t_{1/2} = 12$, then $t_{1/2} = 2.4$. Thus, it is found that

$$CL_{6tu} = \frac{0.693}{2.4} \approx 0.289 \text{ sa}^{-1},$$

that is, Eq. (5) is written independently of BSA. From this stage onward, age and gender factors were considered together to develop a personalised model. However, a review of existing BSA formulas revealed that no tested formula provides gender-specific accuracy in paediatric patients. Therefore, gender was not considered in the modeling. Instead, age-based modelling will be performed using the Haycock Formula

$$BSA = 0.024265H^{0.3964}W^{0.5378},$$

where H is patient height, W is patient weight (Haycock et al., 1978), which is widely used in paediatric patients and is considered one of the most reliable and accurate BSA calculation methods in the literature. (In the study, a margin of error of approximately 10^{-6} and 10^{-6} percent was used in the coefficients.) By using Haycock Formula in (3), the PK model (1-5) of childhood ALL patients depending on age is the differential equations (1) and (2) together with the following equations

$$\dot{x}_3(t) = FM_3 k_{me} x_2(t) - 0.0012233H^{0.4598}W^{0.6180}x_3(t) \quad (6)$$

$$\dot{x}_4(t) = FM_4 k_{me} x_2(t) - 0.0228x_4(t) \quad (7)$$

$$\dot{x}_5(t) = FM_5 k_{me} x_2(t) - 0.289x_5(t). \quad (8)$$

Because TPMT has the greatest genetic influence on the pharmacokinetics and pharmacodynamics of 6-MP, modeling studies have generally relied on TPMT polymorphisms. Although other enzymes such as HGPRT, ITPA, or XO also participate in 6-MP metabolism, they have generally not been considered in pharmacokinetic modeling studies because the impact of genetic polymorphisms on drug response is less pronounced than that of TPMT. The TPMT genotype was included in the model via the FM_3 parameter, and the relationship between them is $FM_3 = 0.019(2.56)^{TMPT}$. On the other hand, assuming that 6-MP is metabolised in the body only via the FM_3 , FM_4 , and FM_5 pathways, the relationship $FM_4 = 1 - FM_3 - FM_5$ exists (see Brunton, et al., 2018). Substituting this formula into (7) and (8), it is obtained the following first order linear equations

$$\dot{x}_3(t) = 0.019(2.56)^{TMPT} k_{me} x_2(t) - CL_{6tgn}(BSA)x_3(t) \quad (9)$$

$$\dot{x}_4(t) = \left(1 - 0.019(2.56)^{TMPT} - FM_5\right) k_{me} x_2(t) - 0.0228x_4(t). \quad (10)$$

Therefore, the PK model in patients with the TPMT genotype is governed by the first order linear differential equation systems (1), (2), (8), (9) and (10).

4. Inflammation-Modulated Pharmacodynamic Modeling of WBC and Dynamic During 6-MP Chemotherapy

In this section, various PD models are developed to examine the biological effects of 6-MP and its metabolites. These models integrate drug effects with diverse biological processes, such as inhibition of WBC production, ANC (neutrophil) dynamics, the effects of nutrition and exercise on the haematopoietic system, and the role of vitamin D (VitD) levels in immune responses. These models aim to enable multidimensional modelling of drug-induced changes in immune responses.

Building on Friberg et al. (2002) work, Le et al. (2019) used a five-compartment system to model the effects of chemotherapeutic agents such as 6-MP and MTX on WBC production. Based on these models, the drug's effects on the active and inactive metabolites of 6-MP, 6-TGN, 6-mMPN, and 6-TU, are defined by

$$E_{drug} = \ln\left(slope\left(\frac{p_{6tgn}x_3 + p_{6mpn}x_4 + p_{6tu}x_5}{1000}\right) + 1\right), \quad (12)$$

and

$$E_{drug(anc)} = slope(x_3 + x_4 + x_5)$$

where p_{6tgn} , p_{6mpn} , p_{6tu} are respectively 6-suppression coefficient of TGN (positive, main factor), side toxicity coefficient of 6-mMPN (generally lower effect), effect of 6-TU (very small or close to zero because inactive), x_3 , x_4 , x_5 are respectively amounts of 6-TGN, 6-mMPN and 6-TU in plasma, slope is the general slope coefficient, E_{drug} is the drug effect (inhibition rate for WBC) and $E_{drug(anc)}$ is the drug effect (inhibition rate for ANC). It should be noted that, with appropriate slope parameter selection, both formulae are suitable for drug effect use. Both formulations are mentioned here for consistency with the literature. The expected hierarchy is $p_{6TGN} \geq p_{6mMPN} \geq p_{6TU}$. That is, 6-TGN is the main agent, 6-mMPN has mild side effects, and the effect of 6-TU is negligible. The reference range for *slope* is chosen as 0.0015–0.0035 (pmol/8x10⁸ RBC)⁻¹ (see, Le et al., 2019; Jost et al., 2020; Jayachandran et al., 2014). Inhibition of WBC production (proliferation) in the bone marrow is defined as:

$$\dot{x}_6(t) = k_{prol}x_6(t)\left(1 - E_{drug}\right)\left(\frac{Base_WBC}{x_{10}(t)}\right)^\gamma - k_{tr}x_6(t),$$

where x_6 is the amount of proliferative WBC precursors in the bone marrow, x_{10} is the amount of mature WBC in the blood, k_{prol} is the cell proliferation rate constant, k_{tr} is the transit rate constant, *Base_WBC* is the initial (homeostatic) WBC level, and γ is the homeostatic feedback strength coefficient. Transits are modeled as follows:

$$\begin{aligned}\dot{x}_7 &= k_{tr}(x_6 - x_7), \dot{x}_8 = k_{tr}(x_7 - x_8) \\ \dot{x}_9 &= k_{tr}(x_8 - x_9), \dot{x}_{10} = k_{tr}x_9 - k_{circ}x_{10},\end{aligned}$$

where x_7 , x_8 , x_9 are the mature WBC in the circulation in transit 1, transit 2, transit 3, respectively, and k_{circ} is the elimination rate of WBC in the circulation (see Le et al., 2019; Jost et al., 2020; Jayachandran et al., 2014; Friberg et al., 2002).

ANC represents the number of mature neutrophils circulating in peripheral blood and serves as a key biomarker for evaluating the immune system's capacity to respond to infections. During 6-MP therapy, accumulation of the active metabolite 6-TGN can suppress neutrophil production in the bone marrow, leading to a decrease in ANC levels. To model this effect, a five-compartment pharmacodynamic model adapted from Jost et al. (2020) will be used. The inhibition of ANC production (proliferation) in the bone marrow is modeled as follows:

$$\dot{x}_{11}(t) = k_{prol}x_{11}(t)\left(1 - E_{drug(anc)}\right)\left(\frac{Base_ANC}{x_{15}(t)}\right)^\gamma - k_{tr}x_{11}(t),$$

with

$$\begin{aligned}\dot{x}_{12} &= k_{tr}(x_{11} - x_{12}), \dot{x}_{13} = k_{tr}(x_{12} - x_{13}) \\ \dot{x}_{14} &= k_{tr}(x_{13} - x_{14}), \dot{x}_{15} = k_{tr}x_{14} - k_{ma}x_{15}\end{aligned}$$

where $x_{11}(t)$ is the amount of proliferative ANC precursors in bone marrow, $x_{12}(t)$, $x_{13}(t)$, $x_{14}(t)$ are transit maturation compartments, $x_{15}(t)$ are circulating mature neutrophils (ANC), k_{prol} is the cell proliferation rate constant, k_{tr} is the transit rate constant, k_{ma} is the apoptosis rate constant of mature neutrophils and *Base_ANC* is the initial (homeostatic) ANC level.

Recent studies have demonstrated the impact of environmental factors on immune system function. Especially in paediatric patients receiving ALL treatment, a balanced diet, regular physical activity, and optimal VitD levels play an important role in both improving the response to treatment and reducing treatment-related complications. Physical exercise helps reduce

treatment-related side effects such as muscle loss, decreased bone density, and reduced functional capacity in ALL patients, while also contributing to the regulation of the immune system and the modulation of the inflammatory response (Marchese et al., 2003; National Comprehensive Cancer Network [NCCN], 2024). Dietary habits, especially excessive glucose intake and obesity, can indirectly influence the haematological response by influencing inflammatory processes (Barbiero & Lió, 2020). Insufficient or excessive energy intake can exacerbate immune imbalance during treatment. VitD plays a regulatory role in both innate and adaptive immune responses. Adequate VitD levels support haematopoietic processes by reducing inflammatory cytokine production (Aranow, 2011).

In this section, inspired by the inflammation-based approach proposed by Barbiero & Lió (2020), the impact of exercise, nutrition, and VitD is integrated with haematological parameters such as WBC and ANC dynamics through the level of inflammation. The model will mathematically describe the effect of poor eating habits and drug therapy on inflammation, and the suppressive effect of regular physical activity and adequate VitD levels.

$$\frac{dI_R}{dt} = k_D x_2(t) + k_g \text{Diet}(t) - (k_{base} + \beta_D D(t) + \beta_E E(t)) I_R(t), \quad (15)$$

where $I_R(t)$ is the level of inflammation, k_D , k_g and k_{base} are respectively the inflammation-increasing effect of the drug and coefficient of nutrition and the body's natural rate of resolving inflammation, $\text{Diet}(t)$ is a nutrition function, $D(t)$ is the VitD level, β_D and β_E are respectively anti-inflammatory effect of VitD and exercise and $E(t)$ is exercise level. This model is integrated into the WBC production (proliferation) model as

$$\dot{x}_6(t) = k_{prol} x_6(t) \left(1 - E_{drug} - \theta I_R(t)\right) \left(\frac{Base_WBC}{x_{10}(t)}\right)^Y - k_{tr} x_6(t),$$

where θ is the weight of the suppressive effect of inflammation on WBC production.

Inflammation is the body's natural immune response to stress, infection, or cellular damage and has a regulatory effect on the haematopoietic system. Similar to the WBC model, the ANC production model of this effect obtained from equation (15) can be given as follows:

$$\dot{x}_{11}(t) = k_{tr} x_{11}(t) \left(1 - E_{drug(anc)} - \theta I_R(t)\right) \left(\frac{Base_ANC}{x_{15}(t)}\right)^Y - k_{tr} x_{11}(t).$$

5. Model Performance and Reliability Analysis

The analysis performed in this section is implemented to evaluate the impact of the model measuring the haematological toxicity of 6-MP drug on WBC and ANC in different synthetic patient profiles. The developed mathematical model simulates the accumulation of drug metabolites and the dynamics of the haematopoietic cell lineage based on the PK and PD properties of 6-MP.

The synthetic patients used in the simulation were differentiated by clinical parameters such as age, body weight, height, and TPMT genotype. Table 1 summarises the patient information used.

Table 1. Synthetic patient profiles.

Patient	Age	Weight (kg)	Height (cm)	TPMT	Starting Dose (mg)
1	10	33	132	1	60
2	12	40	145	0	65
3	3	13	95	1	35
4	5	28	110	0	45
5	8	27	124	0	50

The model consists of a pharmacokinetic structure that includes the absorption, biotransformation and effect of 6-MP via three main metabolites (6-TGN, 6-mMPN, 6-TU) and a pharmacodynamic structure that suppresses WBC and ANC production via a logarithmic drug effect for WBC and a standard drug effect for ANC. In this section, the effects of exercise, vitamin D, and nutrition are excluded in order to make comparisons with published literature data. In the simulation, the fixed

dose determined for each patient is administered without change for 3 months. The aim is to analyse whether WBC and ANC can be maintained within the target therapeutic range under fixed-dose regimen. The model outputs are evaluated within the ranges of WBC $2.0\text{--}4.5 \times 10^9$ cells/L and ANC $1.0\text{--}2.5 \times 10^9$ cells/L. These ranges are selected in accordance with the literature to ensure therapeutic efficacy while preventing excessive immunosuppression, and they are indicated by a grey background in the graphs (Figure 2).

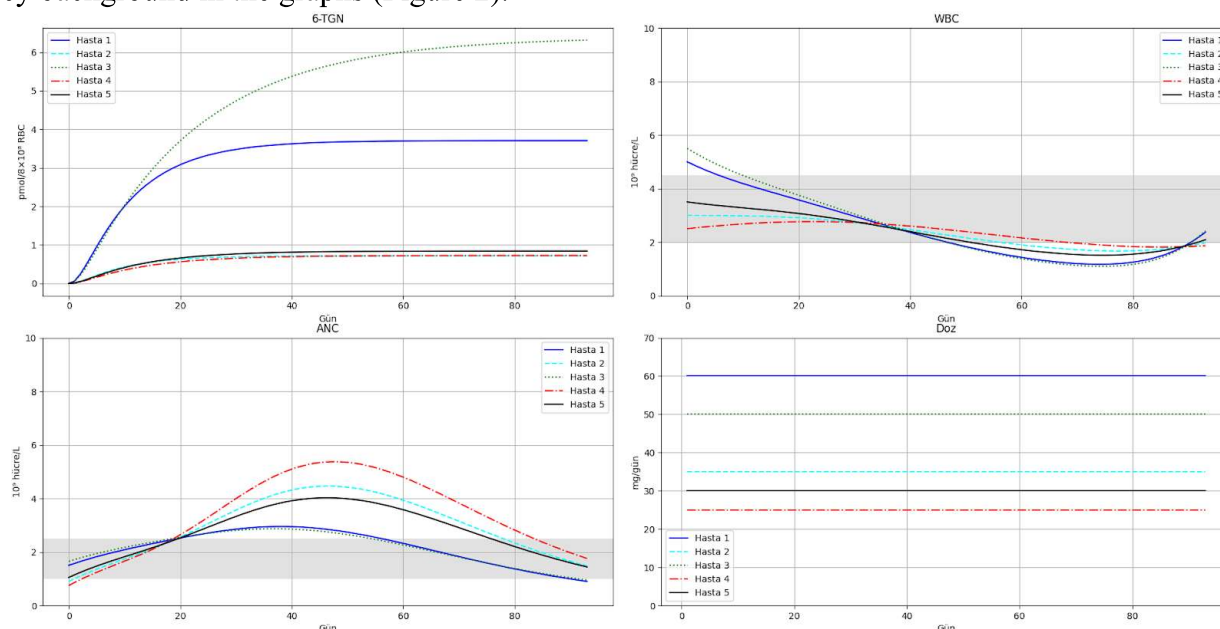


Figure 2. Simulation results of 3 months 6-MP use

Figure 2 shows that 6-TGN levels differ depending on TPMT genotype. Patients with low TPMT activity exhibit significantly higher 6-TGN accumulation, while those with high TPMT activity show lower levels. WBC counts declined rapidly during the first 4-6 weeks but stabilised in subsequent weeks. ANC values mostly remained within the target range. Additionally, paediatric patients with smaller body surface area demonstrated higher 6-TGN accumulation. Here, the obtained findings point that the TPMT genotype as well as body surface area both have a critical role in 6-MP effectiveness and the experienced side effects.

It is also important that the model outcomes are consistent with published literature. In this context, the CPIC guidelines indicate a significant dose reduction to minimise toxicity risk in patients with a low TPMT genotype (Relling et al., 2011). Lennard (2002) expressed that the activity of TPMT correlated directly with the 6-TGN levels, which are essential to predict haematological toxicity. At this point, it has been demonstrated that modelling can be effective in ensuring dose optimisation (Hawwa et al., 2008). Here, Hawwa et al. (2008) provided a population pharmacokinetic analysis, which showed that the 6-MP dose-response varied according to individual pharmacogenetic characteristics. In their study, Le et al. (2019) suggested genotype-related models for optimising the dose according to patients' characteristics and they also indicated that TPMT and NUDT15 genotypes influence the development of 6-MP tolerance as well as the toxicity. It is remarkable that a machine learning-based modeling was done by Jost et al. (2020) to show that effective predictions of haematological responses to the 6-MP can be done through advanced algorithmic steps. By moving from the expressed studies, the PK/PD model provided in this study is thought to be in a correct route in clinical adaptability with its coverage for actual biological processes leading to forecasting analyses on WBC and ANC values.

6. Effect of Environmental Factors on Haematological Responses

This section is devoted to further analyses of haematological responses, by considering different environmental conditions affecting the developed 6-MP PK / PD model. At this stage, the effects of dietary habits, physical activity state, and vitamin D levels on WBC production and ANC (with inflammation dynamics) are analysed. For this purpose, four different scenarios are defined, and in each scenario, plasma 6-MP concentration, RBC intracellular 6-TGN levels, inflammation level, WBC and ANC dynamics are simulated over time. To observe the impact of environmental factors on haematological responses, the scenarios to be used can be determined as follows:

Scenario 1. Normal diet, normal VitD, light exercise and standard 6-MP dose.

Scenario 2. Poor diet, low VitD, sedentary lifestyle and standard 6-MP dose.

Scenario 3. Good diet, high VitD, intensive exercise and standard 6-MP dose.

Scenario 4. Poor diet, low VitD, sedentary lifestyle and high 6-MP dose (to observe toxicity).

For each scenario, plasma 6-MP concentration RBC intracellular 6-TGN level inflammation level WBC production and ANC production are observed over a simulation period of 0–120 days. Basically, the workflow first examines the standard (BSA-based) PK model, the age-adjusted PK model and the genetic factor-adjusted PK model separately. Based on drug effects determined and according to the constructed PD models, WBC and ANC variations are observed separately under conditions with and without inflammation. The schematic explaining the structure described is presented in Figure 3.

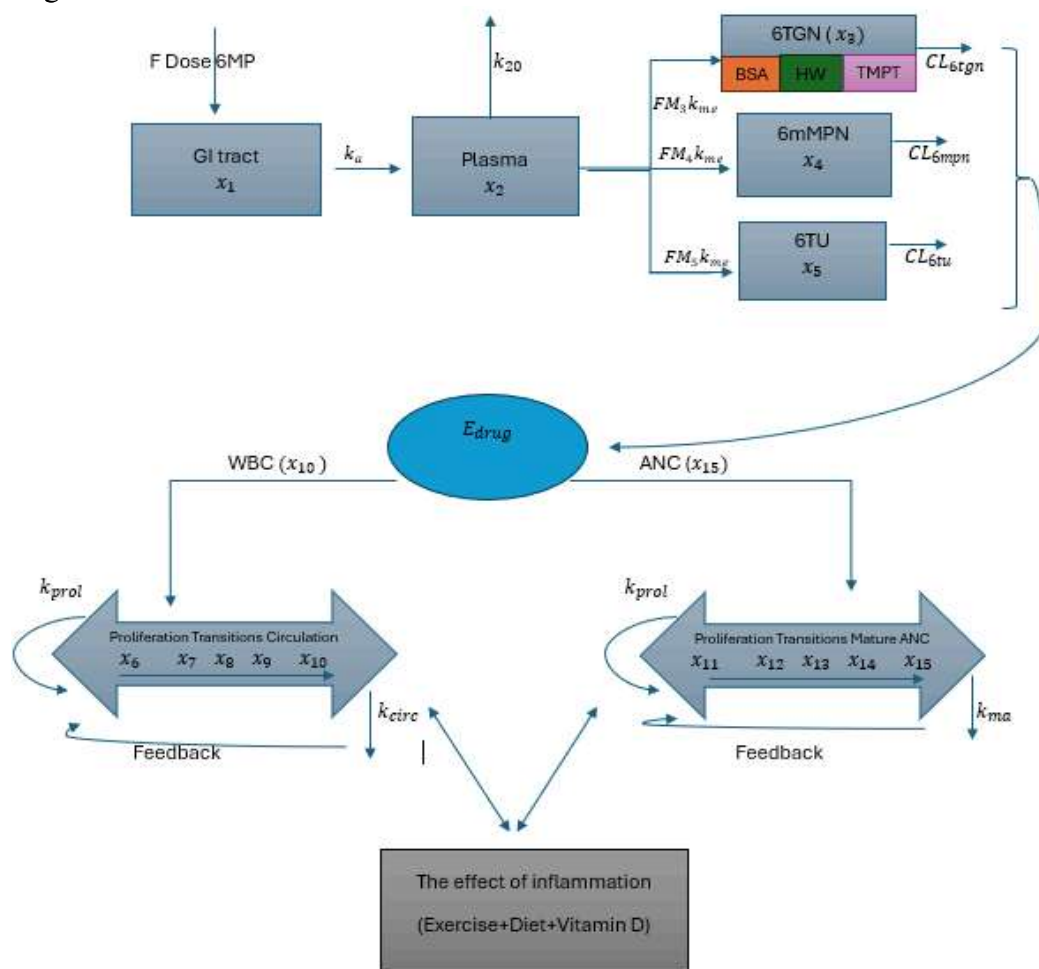


Figure 3. 6-MP, PK and PD models' operational scheme

The simulations were applied to a single patient profile. The initial values for this patient were set as follows: body weight of 33 kg, height of 132 cm, TPMT genotype 1, and an initial mature WBC value of 20×10^9 cells/L. Mature neutrophils (ANC), proliferative cells, and other

cellular components were initialised with fixed model starting values. The parameters used in the four different scenarios are summarised in Table 2.

Table 2. Scenario parameters used in the simulation

Scenario	VitD (ng/mL)	Diet Score (0–1.5)	Exercise Score (0–1.5)	6-MP Dose (mg/day)	Description
1	30	1.0	0.5	50	Normal environmental support
2	10	0.1	0.0	50	Weak environmental support
3	50	1.5	1.5	50	Strong environmental support
4	10	0.1	0.0	90	Toxic dose

The simulation findings clearly demonstrate the impact of environmental factors on the haematopoietic system. Specifically, under the conditions defined in Scenario 3 (high vitamin D levels, adequate nutrition, and regular exercise), both WBC and ANC production are observed to be activated earlier and reach higher levels. In contrast, in the suppressive environment created in Scenario 4 by solely increasing the 6-MP dose, haematopoietic production is both delayed and remains at a more limited level (Figure 4).

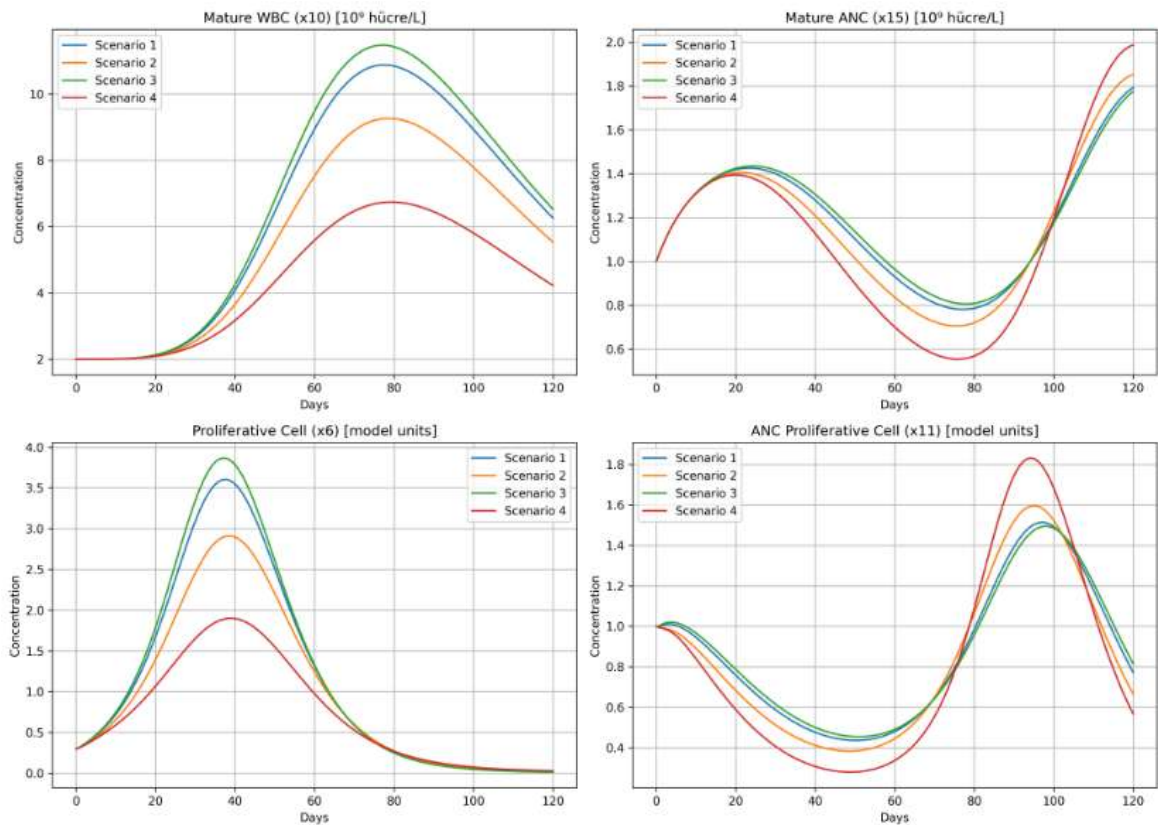


Figure 4. WBC, ANC and proliferative cell responses in different scenarios.

The results indicate that supportive environmental factors have a protective, pro-haematopoietic influence, whereas high-dose therapy exerts a restrictive and partially toxic effect on marrow dynamics. This contrast is visible across both lineages. In the ANC pathway, the early proliferative compartment x_{11} shows more stable expansion under favourable conditions (Scenario 3), while the high-dose case (Scenario 4) displays deeper suppression followed by a delayed rebound, consistent with strong homeostatic feedback after prolonged inhibition.

For the WBC, the proliferative pool x_6 —the entry point of mature WBC production—responds promptly to external inputs and drug pressure. In Figure 4, x_6 is highest in the environmentally supported setting (Scenario 3) and clearly suppressed when environmental stressors are present (Scenario 2). Keeping those stressors but doubling the dose (Scenario 4) further depresses x_6 , indicating that dose escalation under unfavourable conditions does not restore marrow output and may even delay recovery. The mature compartments reflect these upstream signals: WBC (x_{10}) exhibits a broad peak and then declines as negative feedback strengthens, whereas ANC (x_{15}) shows a deeper mid-course nadir and a later compensatory rise in Scenario 4 compared with Scenarios 1–3.

From a clinical point of view, these comparisons only show that the adjustments made in the drug dose are insufficient and that the general physiological status and lifestyle factors of the patient should also be taken into account during the treatment process. Optimising factors such as nutritional status, VitD levels, and physical activity, especially in patients at risk of neutropenia, may provide compensatory effects on bone marrow suppression. This model not only quantifies the biological effects of environmental factors, but also provides clinical decision-making support via holistic patient management and pharmacological interventions.

7. Personalised Daily Dose Simulation and Genetic Algorithm-Based Optimisation Process

In this section, an optimisation framework, which helps in evaluating the PK and PD models under clinical conditions is introduced. The framework briefly uses genetic algorithms to determine a customised chemotherapy approach by analysing the daily impact of the 6-MP drug on haematological parameters: WBC, and ANC. In detail, the aim was to optimise the 6-MP dosage according to the target patient's haematological state. Thus, the model allows for a maximisation of treatment effectiveness while reducing toxicity risks. In this step, the study employed a simulation perspective to ensure a personalised treatment flow by adjusting dose rates daily, after evaluating the patient's biological reactions. During the process, the model also keeps haematological parameters within safe ranges.

Methodologically, the developed model is structured over a multi-component design, with an environmentally interactive and dynamic simulation venue for dosage optimisation. Considering PK and PD details, the steps of the model can be explained as follows:

- ✓ *Data Generation (DummyDataGenerator)*: The simulation is conducted using artificially generated synthetic patient data. The DummyDataGenerator module produces individual parameters such as age, height, weight, body surface area (BSA), TPMT genotype, nutritional quality (diet), exercise level, and VitD levels. These parameters are essential for modelling the absorption, metabolism and effect of the drug on a patient-specific basis. The generated data has been structured to align with realistic clinical profiles.
- ✓ *PK Modeling (EquationSystem)*: At this stage, the PK behaviour of 6-MP is modelled parametrically for each individual patient. The model calculates the levels of the active metabolite 6-TGN and the inactive metabolites 6-mMPN and 6-TU. Genetic variants of TPMT, particularly by influencing 6-TGN accumulation, determine the toxicity risk. Additionally, variables such as age and BSA, which affect metabolism and drug distribution rates, are used to create personalised metabolite profiles within the model. This enables the simulation of pharmacokinetic variations at the patient level.
- ✓ *PD Modeling (EquationSystem)*: The PD model suppresses WBC and ANC production through drug effect (E_{drug} , $E_{drug}(anc)$), calculated based on plasma metabolite levels. Additionally, the model accounts for how environmental factors—such as nutrition, exercise, and VitD levels—modulate haematological response through inflammation. This approach

enables quantitative assessment of not only dosage but also the impact of the patient's lifestyle on haematological outcomes.

- ✓ **Dose Optimisation Using Genetic Algorithm (GA) (*optimise_dosage_6mp*):** The WBC value obtained at the end of each day is evaluated using a GA approach. This method aims to maintain the target WBC range of $1.5\text{--}3.0 \times 10^9/\text{L}$. GA is fine-tuned to identify the optimal dose multiplier (*param_6mp*) that produces WBC results closest to the target value. The fitness function employed in this process works to minimise the absolute difference between the calculated value (obtained by multiplying the given WBC value with *param_6mp*) and the desired target. As a result, outcomes closer to the target are rewarded with higher fitness values. The algorithm operates using a population-based approach. Individuals, initiated randomly, each represent a different dose multiplier. Through the application of crossover, mutation, and selection operations on these individuals, better dose candidates are evolutionarily generated. Among the operators used are Blend crossover (*cxBlend*) and Gaussian mutation. The dose multiplier is typically set within the range of 0.0 to 2.5. This multiplier allows for the adjustment—either an increase or decrease—of the dose administered to the patient based on current needs. For instance, applying a 1.2 multiplier to a base dose of 50 mg results in a new dose of 60 mg. This method enables flexible, patient-specific dose adjustments based on daily biological responses. The model aims to dynamically maintain the target WBC level, overcoming the inadequacies of fixed-dose regimens. After the simulation is completed, the daily 6-MP dose, WBC and ANC levels are presented graphically as time series.

8. Review and Interpretation of Results and Conclusion

The *runner_daily.py* module was developed to examine the daily effects of 6-MP on haematological parameters and to develop a personalised chemotherapy management strategy. Using the module, the daily dose of 6-MP is optimised through a genetic algorithm-based approach, and the resulting changes in WBC and ANC over time are modelled. The model determines the optimised 6-MP dose for each day and advances the simulation, recalculating the corresponding biological responses at every step.

Application of the model: The model performs a personalised treatment simulation by optimising the daily 6-MP dose for an individual patient. At the end of each day, the WBC count is evaluated, a new dose is determined using a genetic algorithm, and the outcomes are updated. The simulation automatically stops once WBC and ANC values reach the predefined target ranges. Sample outputs from the model are illustrated in the following figures: 6-MP dosage (Figure 5), WBC levels (Figure 6), and ANC values (Figure 7).

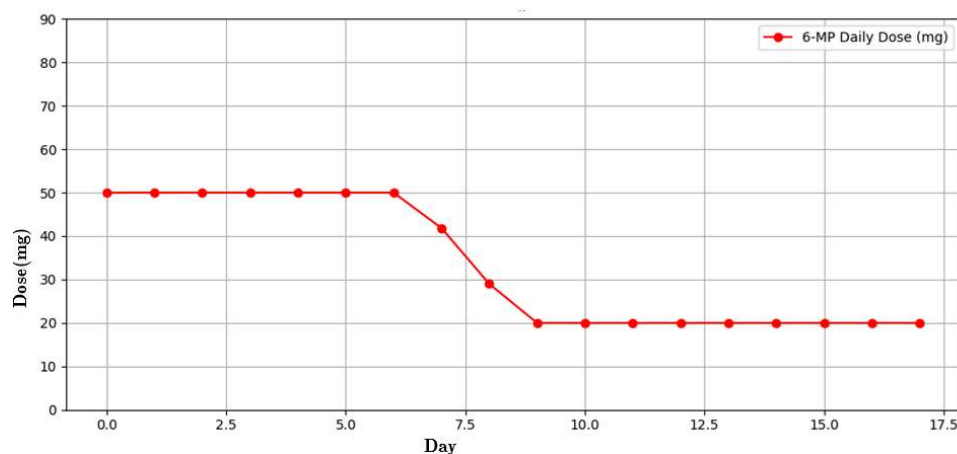


Figure 5. Optimised daily 6-MP dose level

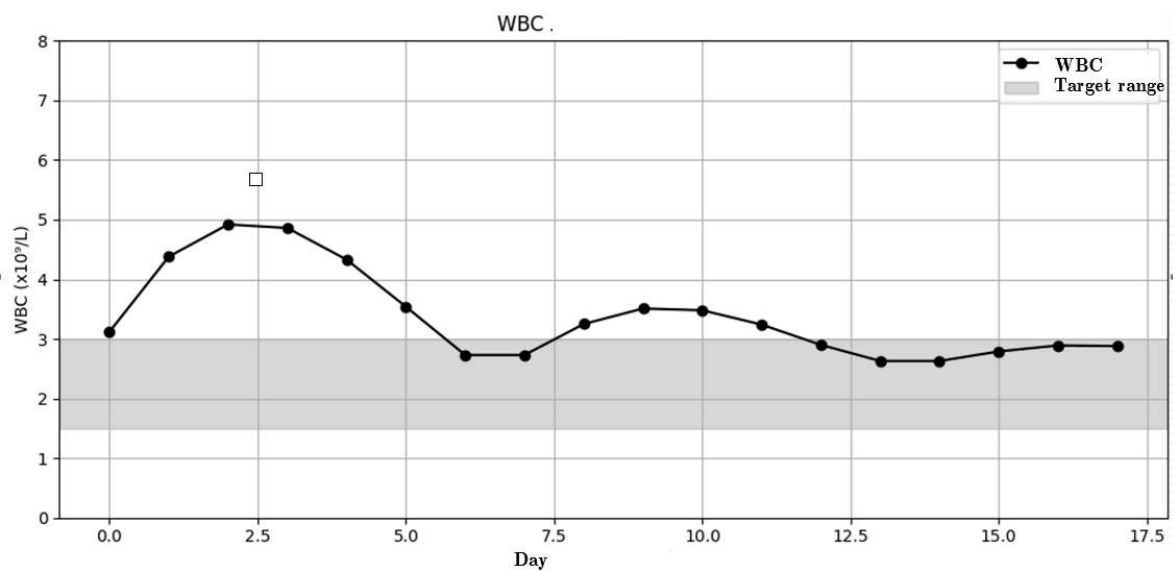


Figure 6. Change in WBC value over time

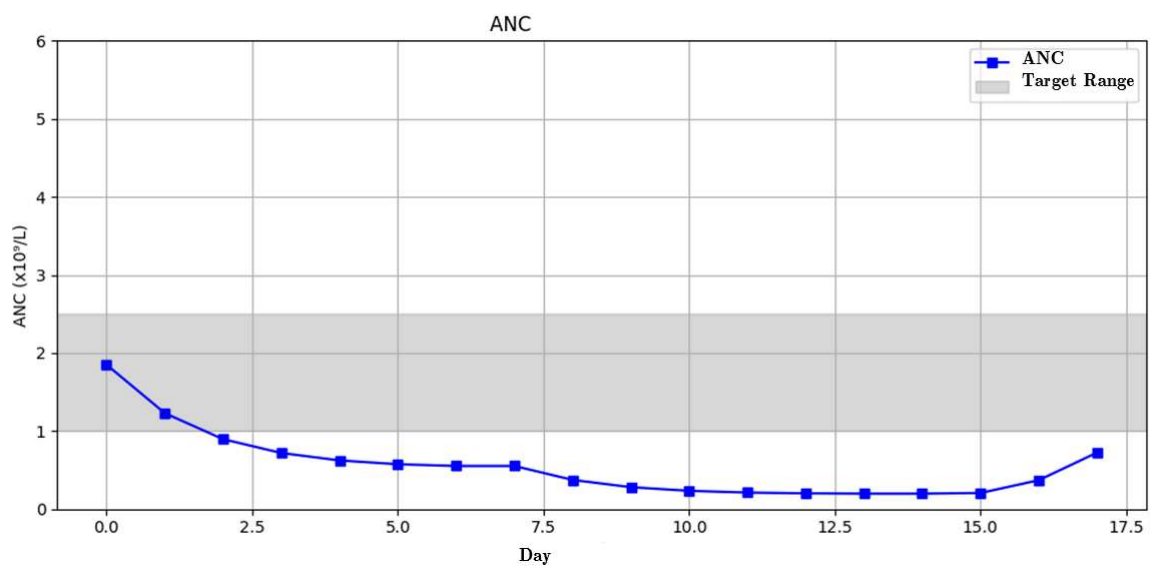


Figure 7. ANC time series

The different outputs produced by the model are observed as a result of a 60-day simulation, as shown in Figure 8:

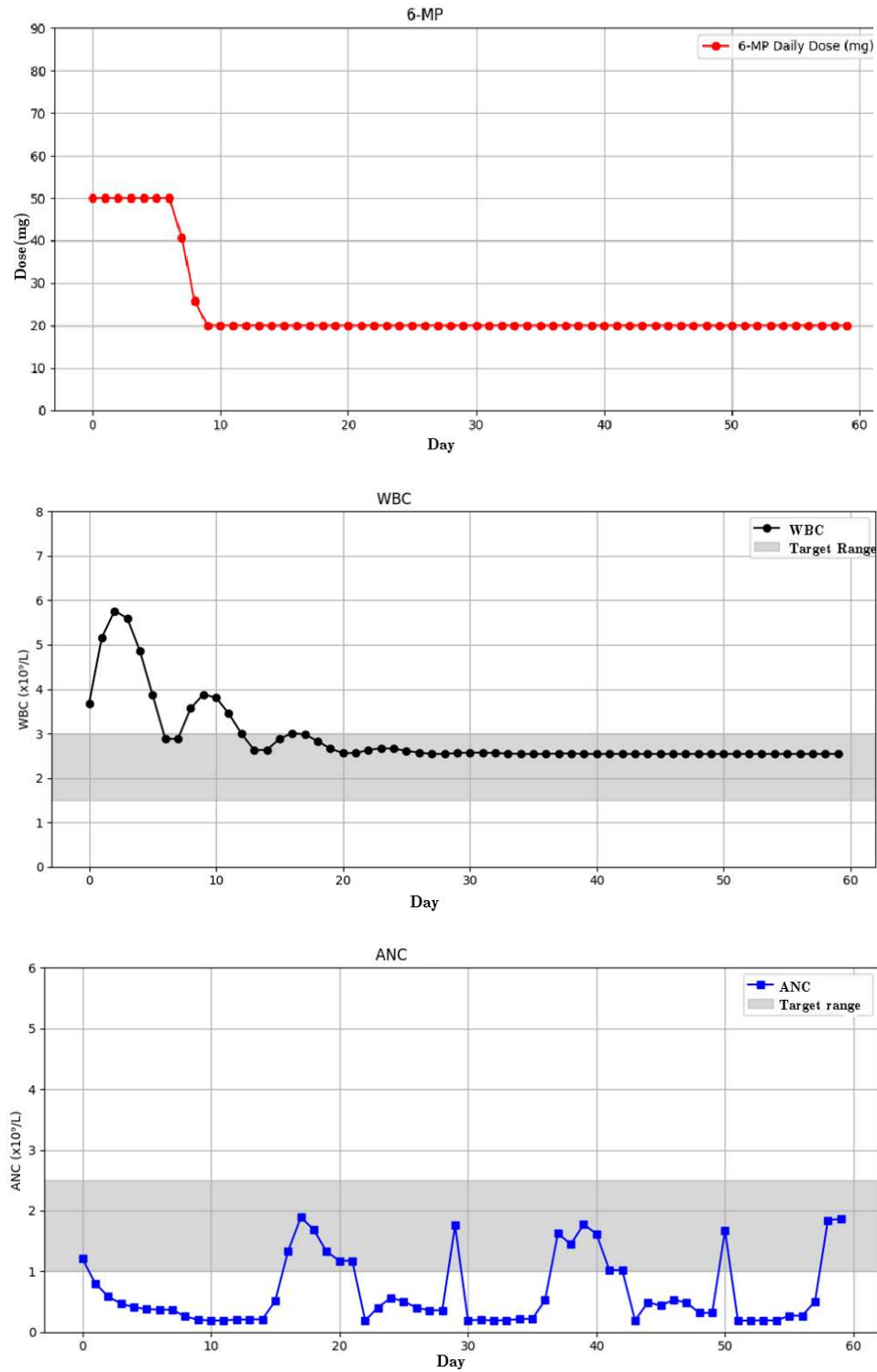


Figure 8. 60-day simulation results

In the following example, the drug was tested in cases where the body responded positively and showed stability. However, due to variations in individual characteristics, the dose simulations generated by the model also differ accordingly. For example, consider a patient with normal environmental factors as in Scenario 1. Under normal conditions, the k_{prol} and k_{tr} values are between 0 and 1. If both are set to 1, the system reaches a steady state and the patient's response to the drug remains stable (Le et al., 2019). In the simulations, both values for the PD model of WBC are set to 1 (Le et al., 2019). For the PD model of ANC, both values were set to 0.148 (Jost et al.,

2020). As a result, WBC stabilised after a certain period. However, if the patient experienced severe bone marrow suppression, the k_{tr} value was lower, making it more difficult to stabilise WBC. For clinical application, it is recommended that all these parameters are entered externally according to the patient's individual data. With the model we establish, a dose simulation can be generated accordingly. For example, for a patient with $k_{prol} = 0.5$ and $k_{tr} = 0.148$ for WBC, the 365-day simulation result is presented in Figure 9.

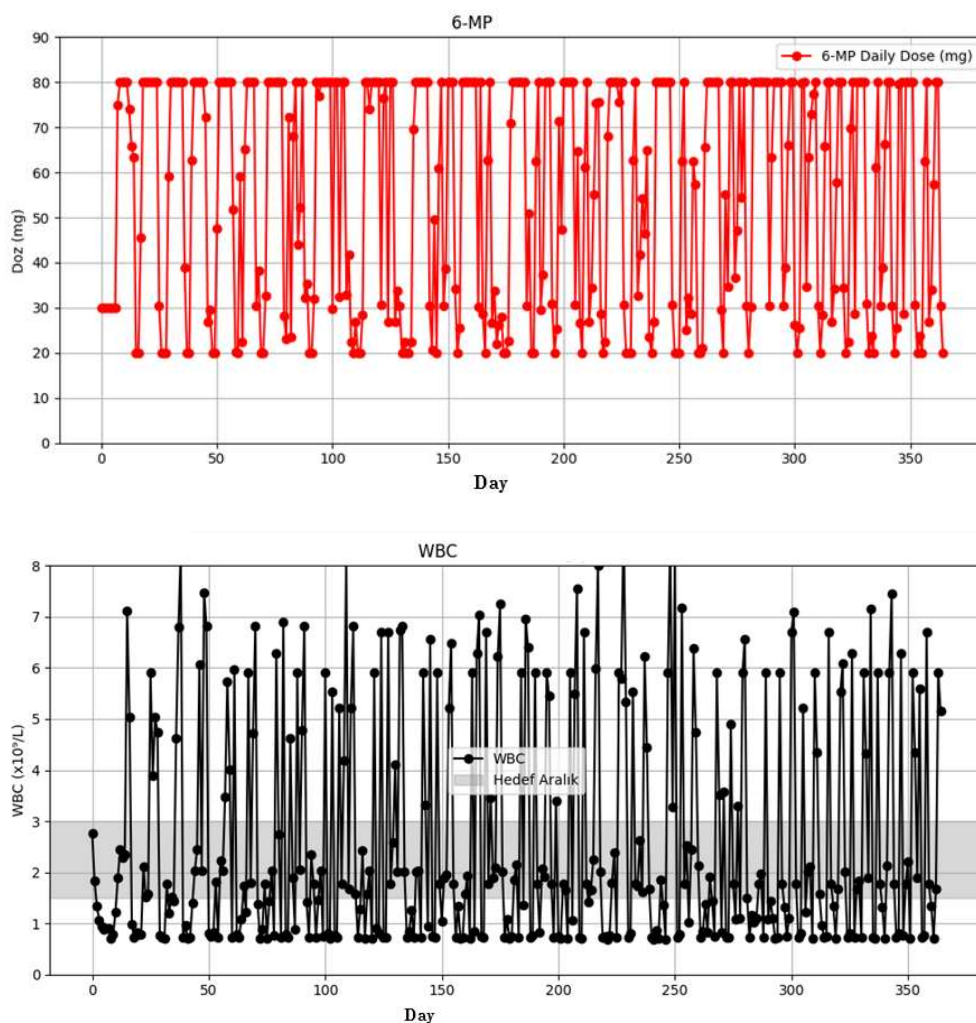


Figure 9. 365-day dose optimisation process

In the model, for another patient with similar characteristics, optimisation was performed so that ANC and WBC values first reached the target range after day 7. The results of this optimisation are presented in Figure 10.

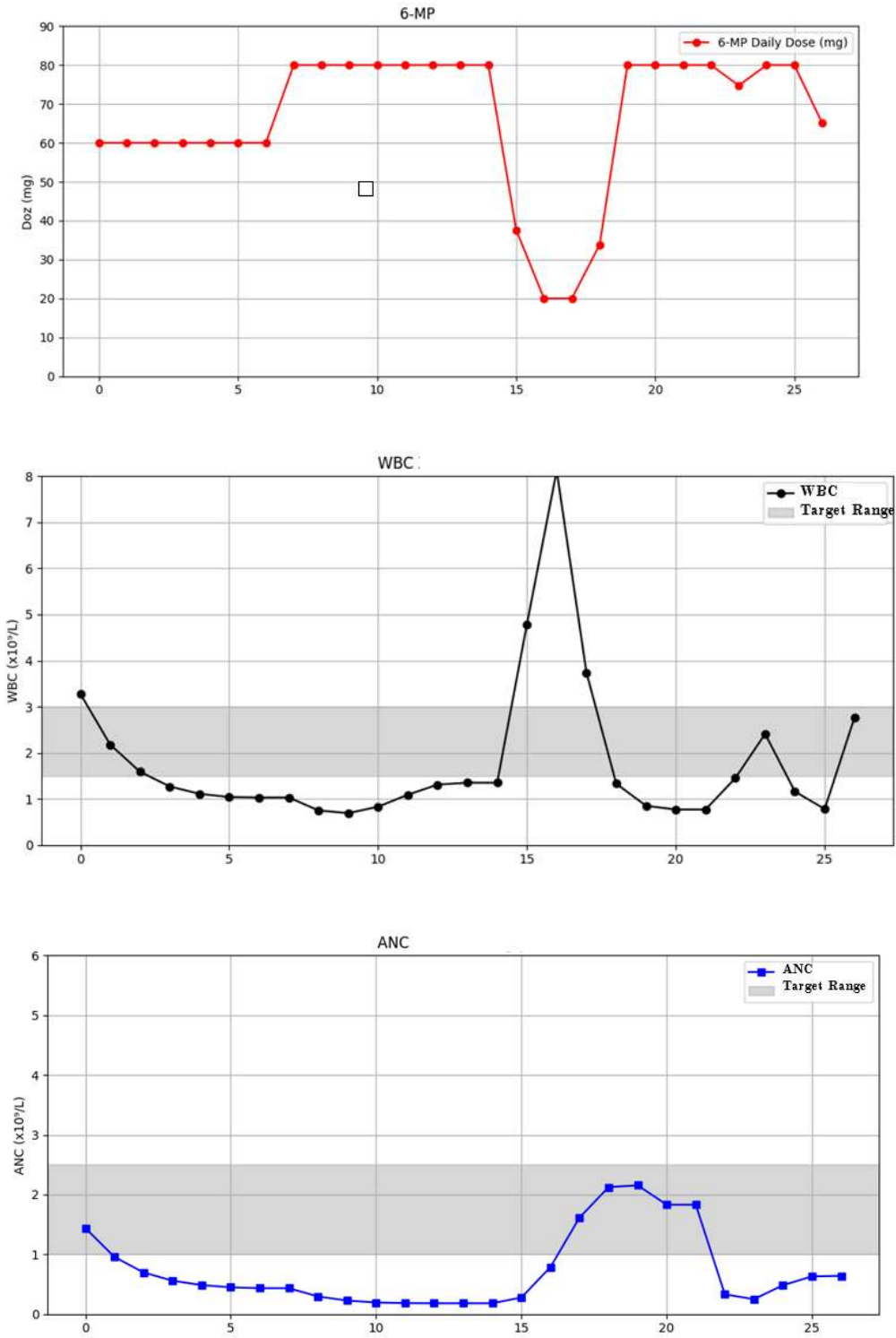


Figure 10. Dose optimisation simulation result of patient with high bone marrow pressure

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Appendix

Table 3. Parameters of the PK Model (see, Hawwa et al., 2008; Jayachandran et al., 2014; Le et al. 2018; Jost et al. 2020)

Parameters	Values	Units	Description
k_{α}	4.8	1/hour	6-MP absorption rate from GI tract
k_{20}	0.53	1/hour	6-MP absorption rate from plasma
k_{me}	0.4134	1/hour	Metabolic rate constant
F	0.45		Bioavailability

Table 4. Parameters of the PD Model (see, Friberg et al. 2002; Le et al. 2018; Jost et al. 2020)

Parameters	Values	Units	Description
k_{prol}	0.25	1/hour	Cell proliferation rate
k_{tr}	0.148	1/hour	Transition rate
k_{circ}	0.022	1/hour	Apoptosis rate mature WBC
k_{ma}	0.099	1/hour	Apoptosis rate constant of mature neutrophils
γ	0.769		Feedback factor
Base_WBC	2.0	$\dots \times 10^9 / 1$	Baseline value of WBC count
Base_ANC	1.2	$\dots \times 10^9 / 1$	Baseline value of ANC count
slope		1/pmol	Drug effect coefficient
P_{6TGN}	1		Constant for unit consistency
P_{6mMPN}	0.3		Constant for unit consistency
P_{6TU}	0.01		Constant for unit consistency

Table 5. Inflammation Dynamics (see, Barbiero & Lio, 2020)

Parameters	Values	Description
k_D	0.001	Inflammation-increasing effect of the drug
k_q	0.03	Inflammation-increasing coefficient of nutrition
k_{base}	0.04	Body's natural rate of resolving inflammation
β_D	0.05	Anti-inflammatory effect of VitD
β_E	0.05	Anti-inflammatory effect of exercise