



Graph Neural Networks-Based Digital Twin Modeling of WBC and ANC Dynamics for Personalized Time-Series Prediction

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Abstract— This study introduces a digital twin model approach with Graph Neural Networks (GNNs) to forecast white blood cell (WBC) and absolute neutrophil count (ANC) levels during 6-mercaptopurine (6-MP) chemotherapy for treating childhood acute lymphoblastic leukemia (ALL). For incorporating clinical and lifestyle factors like daily medication dosage, anthropometric measurements (weight, height, and body surface area), diet, exercise, and vitamin D intake, the model is constructed using a synthetic patient dataset based on personalized computational Pharmacokinetics (PK) / Pharmacodynamics (PD) mathematical models. To capture temporal relationships, each data point is connected to earlier observations and is defined as a node within a time-dependent graph structure. The model, which was created with PyTorch Geometric, was evaluated by using MAE, MSE, and RMSE metrics after being trained with inputs, which are normalized by z-scores. The study results point that the developed GNN-based method works well as a digital twin tool for customized chemotherapy simulations and can predict changes in hematological parameters over time.

Keywords—graph neural networks; 6-mercaptopurine; acute lymphoblastic leukemia; hematological response

I. INTRODUCTION

Graph-based deep learning techniques have become more and more popular in biomedical research in recent years. In particular, accurate treatment process monitoring and the

development of customized treatment plans depend heavily on the modelling of intricate temporal dependencies in patient data. Hematologic parameters, which can have a complicated and fluctuating course over time, are essential biomarkers for assessing chemotherapy response and managing treatment. It might not be possible to fully capture all these dynamics with conventional statistics or machine learning. In this regard, Graph Neural Networks (GNN) is an effective tool for resolving these issues since it treats every observation as a node and models temporal relationships using earlier observations.

A unique contribution in terms of methodology and social impact can be made by using a GNN architecture to model temporal changes in WBC and ANC in pediatric patients undergoing 6-MP treatment. Treatment-sensitive hematological parameters can be predicted earlier and more accurately with GNN models, which represent clinical parameters as nodes throughout the time series. This is especially useful for integration into digital twin applications. Such approach is an innovation for both the management of drug toxicity and personalized dose adjustments [1, 2]. In this study, a GNN-based model was developed by focusing on 6-MP, one of the drugs used in the treatment of childhood acute lymphoblastic leukemia (ALL). The study predicts the change of hematological parameters over time and presents an innovative digital twin-based approach for personalized chemotherapy simulations.

Predicting hematologic responses in diseases such as childhood ALL directly impacts treatment management. During maintenance therapy periods using drugs such as 6-MP, parameters such as WBC and ANC show large individual variation due to pharmacological and genetic factors. The authors in [3] and [4] developed population PK models to explain these processes and demonstrated the critical role of TPMT genotyping in dose individualization. On the other hand, the studies [5] and [6] modeled the PK/PD processes of 6-MP, incorporating factors such as drug absorption, metabolite levels, genetic polymorphisms, and hematological responses, and adapting these models to individual patient characteristics to predict treatment outcomes and assess toxicity risk. In their pharmacodynamic models for the diseases they study, the authors in [7] considered environmental conditions, immune system responses, and changes in metabolic processes that may affect infection dynamics. As associated with PK/PD dynamics covered by drug repositioning purposes, Köse et al. proposed an extended solution methodology, which combines deep learning models with digital twin-based perspective to lead disease modeling as well as treatment optimization in a decision support environment [8, 9]. In [10], Köse et al. worked on PK/PD models by considering previous PK/PD computational patient models. Called as STING, the proposed solution by Köse et al. [9] was moved further by including environmental factors (vitamin D, nutrition and sports) in PK/PD models, as introduced in this study. In this context, the personalized PK model for pediatric ALL patients can be obtained as a first-order linear differential equation system as follows:

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

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

$$\dot{x}_3(t) = 0.019(2.56)^{TPMT} k_{me} x_2(t) - 0.0012233 H^{0.4598} W^{0.6180} x_3(t) \quad (1)$$

$$\dot{x}_4(t) = (1 - 0.019(2.56)^{TPMT} - FM_5) k_{me} x_2(t) - 0.0228 x_4(t)$$

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

where $x_1(t)$ and $x_2(t)$ are respectively the amount of 6-MP in plasma and the GI system, k_a is the absorption rate constant, k_{20} is the elimination rate constant of 6-MP from plasma, F is the bioavailability factor and $u(t)$ is the time-dependent drug dose, $x_3(t)$, $x_4(t)$ and $x_5(t)$ are respectively the concentration of 6-TGN, 6-mMPN and 6-TU in plasma, FM_3 , FM_4 and FM_5 are the fraction of 6-MP converted to 6-TGN, 6-mMPN and 6-TU, respectively. k_{me} is metabolic rate constant and $CL_{6tgn}(BSA)$, CL_{6mpn} and $CL_{6tu}(BSA)$ are the clearance rate of 6-TGN, 6-mMPN and 6-TU from plasma, H is patient height and W is patient weight. PD model for pediatric ALL patients for WBC and ANC production are respectively given by the following equations

$$\dot{x}_6(t) = k_{prol} x_6(t) \left(1 - E_{drug} - \theta I_R(t)\right) \left(\frac{Base}{x_{10}(t)}\right)^\gamma - k_{tr} x_6(t) \quad (2)$$

and

$$\dot{x}_{11}(t) = k_{prol} x_{11}(t) \left(1 - E_{drug} - \theta I_R(t)\right) \left(\frac{Base}{x_{15}(t)}\right)^\gamma - k_{tr} x_{11}(t), \quad (3)$$

where θ is the weight of the suppressive effect of inflammation on WBC (and ANC in Eq. (3)) production, $I_R(t)$ is the level of

inflammation that changes over time, 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, $Base$ is the initial (homeostatic) WBC level, and γ is the homeostatic feedback strength coefficient, $x_{11}(t)$ is the amount of proliferative ANC precursors in bone marrow, $x_{15}(t)$ are circulating mature neutrophils and E_{drug} is the drug effect (see [9] for details).

The model developed in this study simulates the temporal effects of the 6-MP drug used in the treatment of ALL hematological parameters through PK/PD mathematical models developed by Köse et al. (2025) and adapted to patient characteristics. These models generate synthetic patient data by individualizing processes such as drug absorption, distribution, metabolite conversion, and inflammatory response. With the time series data obtained, a time-dependent GNN model is trained, and the error metrics of the model are calculated for 30 randomly generated synthetic patient data. As a result of this evaluation, the average MAE for WBC estimates are 0.197, RMSE is 0.289; and the average MAE for ANC estimates is 0.0602, RMSE is 0.084.

This study demonstrates the significant potential offered by GNN models in creating more accurate and personalized treatment plans for ALL patients through the integrated use of deep learning and artificial intelligence methods with clinical data. Furthermore, the developed system makes a concrete contribution to digital twin technologies thanks to its ability to not only analyze historical data but also predict patients' future treatment responses.

II. METHODOLOGY

GNN-based approaches aim to predict changes in WBC and ANC in patients diagnosed with childhood ALL. The dataset related to this study was produced via PK and PD mathematical models developed by Köse et al. (2025) [10] and adapted to patient characteristics. The individualized PK model (1) and the PD models (2) and (3) obtained depending on environmental factors are called "real" for convenience. Python programming language is used for the estimation process. Python libraries such as PyTorch, Pandas, NumPy and Matplotlib are used in model development and data processing. The dataset used in the training of the model is loaded from the Runner.csv file containing GNN data and modeled in DataFrame format. The dataset includes both input features and target variables. The target variables are the WBC and ANC measurements. Introductory features of the model; Day (time in days), 6MP_Daily_Dose_mg (daily dose of 6-Mercaptopurine in mg), Weight, Height and BSA (physical characteristics of the patient: weight, height and body surface area), Diet, Exercise and Vitamin_D (nutritional quality, exercise level and vitamin D supplementation) and derived characteristics derived from the PK/PD model. These variables are converted to multidimensional array format using the NumPy library and made suitable for use in the GNN model.

GNN models consist of a graph structure that represents data points as nodes and the relationships between them as edges. In this study, each patient measurement corresponds to each data

point and is represented as a node. To model temporal relationships, each node is connected to nodes in the three preceding time steps. Bidirectional edges are created to create an undirected graph structure. The edge list is converted to the edge_index input format from the PyTorch library and combined with the Data object. If the edge list is empty, the process is terminated with an error message. The GNNRegressor class takes the values in_channels, hidden_channels, and out_channels as constructor parameters.

The trained model weights and trained GNN models are loaded from the pth file. The model is switched to evaluation mode (eval()) to make predictions. The model generates predictions using normalized features and a graph structure. torch.no_grad() is used to disable gradient calculations, which increases computational efficiency. Then, the model's outputs are converted back to the original scale by inverse normalization.

This study focuses on the usefulness of a GNN-based model for forecasting on time-series data from pediatric ALL patients. The model makes it possible to predict dynamic processes like the course of a disease and the response to treatment by using a graph representation to model the relationships between time-dependent multidimensional data. In this context, essentials steps were organized through preprocessing the data, establishing node and edge relationships, training the model, generating predictions, and visualizing the findings.

For analyzing the model's sustainability and consistency, each GNN model was run 30 times, and the error metrics (MAE, MSE, RMSE) of the WBC and ANC predictions were computed for each run. Based on synthetic patient data, the GNN model consistently performed well in predicting WBC and ANC, according to the error metrics. The model appears to better capture the spatial dynamics of this parameter, as indicated by the lower error rates for ANC. The model might need more features or a more intricate graph structure for this variable, though, given the comparatively higher error rates for WBC predictions. These findings support the potential of the digital twin approach in the assessment of drug effects.

III. APPLICATION AND FINDINGS

Considering the GNN-based model, further applications were done to forecast WBC and ANC values, thanks to the synthetic patient dataset support. At this point, the related model generated a digital twin flow for analyzing the drug effects during a childhood ALL treatment. It was done by detecting relationships among the time-dependent clinical variables. Fig. 1 presents the real and predicted WBC values in days. In this graph, the real WBC values are represented by the black line, and the model-predicted values are represented by the blue line. Similarly, Fig. 2 shows a comparison of the actual and predicted ANC values. Both plots demonstrate that the model successfully learned the structural and temporal features in the time series data, and the resulting predictions exhibit a trend that is highly consistent with the actual values.

Mean Absolute Error (MAE), Mean Square Error (MSE) and Root Mean Square Error (RMSE) metrics were calculated to evaluate the prediction performance of the model in this example. The findings obtained are summarized in Table 1.

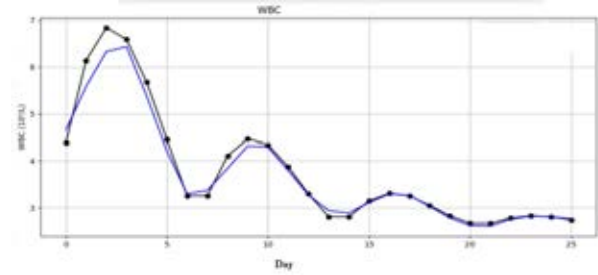


Fig. 1. WBC estimation with 6 MP GNN.

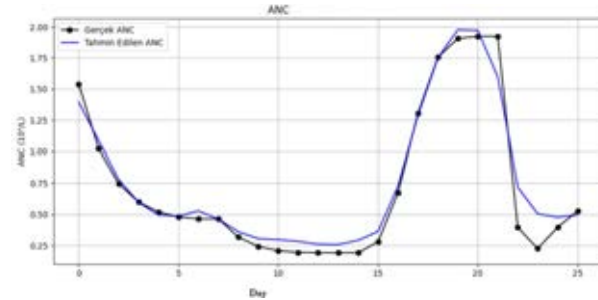


Fig. 2. ANC prediction with 6MP GNN.

TABLE I. TABLE 1. ERROR FINDINGS OF GNN ESTIMATIONS.

Parameter	MAE	MSE	RMSE
WBC	0.1251	0.0373	0.1932
ANC	0.0837	0.0148	0.1217

WBC Estimates: The MAE value is calculated as 0.1251, the MSE value was 0.0373, and the RMSE value is 0.1932. These metrics show that the model predicts WBC values with relatively low error rates. **ANC Estimates:** MAE value was 0.0837, MSE value was 0.0148 and RMSE value was 0.1217. Lower error values for ANC suggest that the model predicts this parameter with greater accuracy. The model is controlled by running it on different days according to different patient characteristics and visualizes some results as follows (Fig. 3).

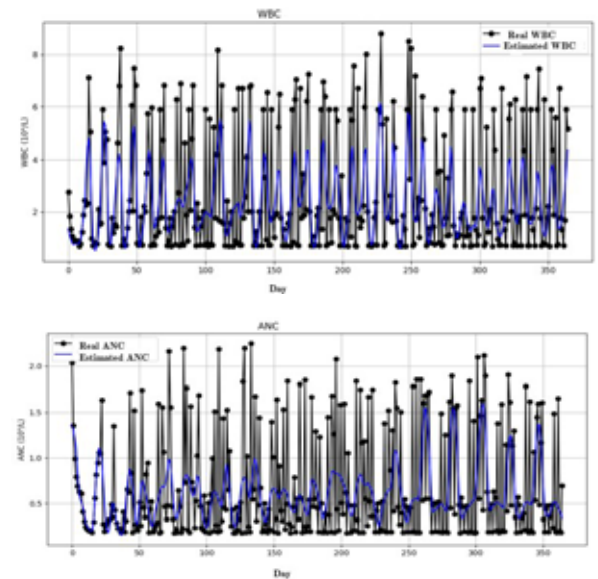


Fig. 3. GNN estimations for different patients.

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To assess the sustainability and consistency of the GNN model, each model is run 30 times. For each run, error metrics (MAE, MSE, RMSE) are calculated for the WBC and ANC predictions. The mean and standard deviation of these metrics are then computed. Finally, the overall mean and standard deviation are obtained for the 30 simulated patients (Fig. 4).

	MAE	MSE	RMSE		MAE	MSE	RMSE
WBC	0.188	0.0787	0.28	ANC	0.056	0.00498	0.071
WBC	0.114	0.0224	0.15	ANC	0.062	0.00526	0.073
WBC	0.084	0.0119	0.109	ANC	0.053	0.00552	0.074
WBC	0.117	0.0303	0.174	ANC	0.051	0.00365	0.060
WBC	0.176	0.0465	0.216	ANC	0.050	0.00470	0.069
WBC	0.085	0.0199	0.141	ANC	0.052	0.00463	0.068
WBC	0.173	0.0476	0.218	ANC	0.061	0.00602	0.078
WBC	0.143	0.0456	0.214	ANC	0.061	0.0046	0.068
WBC	0.118	0.0255	0.16	ANC	0.063	0.00513	0.072
WBC	0.169	0.0698	0.264	ANC	0.055	0.0118	0.109
WBC	0.127	0.0271	0.165	ANC	0.051	0.00568	0.075
WBC	0.193	0.0874	0.296	ANC	0.059	0.00723	0.085
WBC	0.075	0.0105	0.103	ANC	0.052	0.00498	0.07
WBC	0.157	0.0446	0.211	ANC	0.05	0.00403	0.064
WBC	0.155	0.0494	0.222	ANC	0.051	0.00429	0.065
WBC	0.138	0.029	0.17	ANC	0.05	0.00432	0.066
WBC	0.2	0.0788	0.281	ANC	0.0444	0.00389	0.062
WBC	0.163	0.0377	0.194	ANC	0.047	0.00522	0.072
WBC	0.164	0.0613	0.248	ANC	0.072	0.0184	0.136
WBC	0.266	0.0834	0.289	ANC	0.058	0.00578	0.076
WBC	0.09	0.0202	0.142	ANC	0.059	0.00519	0.072
WBC	0.48	0.606	0.778	ANC	0.086	0.00947	0.097
WBC	0.491	0.511	0.715	ANC	0.136	0.0679	0.261
WBC	0.39	0.306	0.553	ANC	0.063	0.00725	0.085
WBC	0.448	0.733	0.856	ANC	0.081	0.0083	0.091
WBC	0.479	0.6	0.781	ANC	0.059	0.00619	0.079
WBC	0.138	0.0315	0.178	ANC	0.040	0.00396	0.063
WBC	0.104	0.0211	0.145	ANC	0.077	0.00830	0.091
WBC	0.118	0.0312	0.177	ANC	0.050	0.00412	0.064
WBC	0.168	0.0620	0.249	ANC	0.102	0.013	0.114

Fig. 4. Error findings regarding GNN estimations for 30 different patients. The mean MAE value for the WBC estimates of the model is 0.197, the RMSE value is 0.289, and the standard deviations of these metrics are 0.124 and 0.210, respectively. These values reveal that the model may occasionally deviate from the WBC estimation but generally offers acceptable accuracy. In the ANC estimates, the mean MAE value is 0.0602 and the RMSE value is 0.084, with standard deviations of 0.019 and 0.0369, respectively. These findings suggest that the model provides lower errors and higher consistency in ANC predictions. The error metrics show that the GNN model performs consistently in predicting WBC and ANC on synthetic patient data. Lower error rates for ANC suggest that the model better captures the spatial dynamics in this parameter. However, relatively high error rates in WBC estimates indicate that the model may require additional features or a more complex graph structure for this variable.

The model developed in this study is structurally designed to be compatible with all drug models and integrated into every stage of pediatric ALL treatment process. The results of the individualized model, specifically for 6-MP, demonstrated that it produced highly accurate predictions based on the statistical tests performed. However, some limitations should be considered when interpreting the findings. The synthetic dataset used in training and testing the model may not fully reflect the full clinical and genetic diversity of the real patient population. Therefore, validation studies with real patient data are necessary to increase clinical applicability and generalizability of the developed model.