Fitting Personalized Mechanistic Mathematical Models of Acute Myeloid Leukaemia to Clinical Patient Data

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Abstract: In this position paper, we discussed the potential to fit mechanistic mathematical models of acute myeloid leukaemia to patient data. The overarching aim was to estimate personalized models. We briefly introduced one selected mechanistic ODE model to illustrate the approach. The usually available outcome measures, e.g. in clinical datasets, were aligned with the model's prediction capabilities. Among the most relevant outcomes (blast load, complete remission, and survival), only blast load turned out to be well suited to be used in the model fitting process. We formulated an optimization problem that, finally, resulted in personalized model parameters. The degree of personalization could be chosen by selecting only a subset of parameters within the optimization problem. To illustrate the fitness landscape for individual patients we performed a grid search and calculated the fitness values for each grid point. The grid search revealed that an optimum exists, but that the fitness landscape can be very noisy. In these cases, gradient-based solvers will perform poorly and other algorithms needs to be chosen. Finally, we belief that personalized model fitting will be a promising approach to integrate mechanistic mathematical models into clinical research.

1 INTRODUCTION

Acute myeloid leukaemia (AML) is a haematological cancer caused by genetic mutations and cytogenetic aberrations in haematological stem cells (O'Donnell et al., 2017). AML emerges in the myeloid line, i.e. it affects the differentiation cascade that produces the specific blood cells (erythrocytes, platelets, basophils, neutrophils, eosinophils, monocytes, macrophages). Most AML patients show too many immature white blood cells, mainly myeloblasts, in their bone marrow. These blasts also migrate to the peripheral blood. Overall, patients suffer from frequent and severe infections (often lethal), tiredness, fever, and other symptoms.

AML is a heterogenous disease and for an overview on AML subtypes, outcomes and treatment approaches see (Döhner, 2015; Döhner 2017; Estey, 2020). A number of combination chemotherapy protocols are used in clinical practice to treat AML patients. Major protocols (like the "7+3"–Schema) consists of a combination of cytarabine and an anthracycline. Beside the cytotoxic combination chemotherapy, newer approaches e.g. based on chimeric antigen receptor T cells (CAR-T) (Gill, 2019) exist and might be widely introduced into AML treatment in near future.

Therapy protocols for AML treatment still are less personalized. Nevertheless, personalization promises e.g. reduce treatment doses to a patient specific optimal level, or reliably prediction of individual disease courses for medical decision-making.

From the theoretical side, a number of mathematical models for AML have been published and should be evaluated for their usefulness in personalization (Rubinow and Lebowitz, 1975; Röder and Glauche, 2006; Stiehl and Marciniak-Czochra, 2012; Fimmel, 2013; Stiehl et al. 2014; Friedman et al. 2016, Banck and Görlich, 2019).

We belief that mathematical models can qualify to be used for personalized predictions in a clinical setting. Fitting mathematical models to patient data is a prerequisite on the path to personalization.

The aim of this position paper is to discuss relevant aspects of AML models and clinical patient data. Especially, we will discuss available outcome measures and the model's capacity to produce realistic estimates on these clinical outcomes. Finally,

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an optimization problem will be set up which can be applied to fit personalized mechanistic models to patient data. First results from a grid search will be presented.

2 THE AML MODEL

We here briefly introduce the mathematical AML model as published in (Görlich and Banck, 2019). The model was based on the Stiehl model (Stiehl et al., 2014) and extended by a treatment mechanism. Many aspects discussed here and later in the paper can be applied to other published AML models.

The AML model is a system of four ordinary differential equations (ODE). Two equations (dC1/dt; dC2/dt) describe the healthy haematopoiesis while the other two equations (dL1/dt; dL2/dt) describe the leukaemic compartments. Please see Görlich and Banck (2019) for the exact mathematical model.

In the following, the focus lies mainly on the model parametrization. In particular, the model catches the stem cell's proliferation rate (p) and a self-renewal rate (a). While the proliferation rate describes the kinetics of cell growth and division, the self-renewal rate describes the production of stem cells, capable of replacing itself. Additionally, a density term parameterizes the bone marrow's capability to hold stem cells. Finally, two parameters (k_{cyt}, k_{anthra}) control the treatment efficacy/resistance of two main cytotoxic chemotherapy components (cytarabine, anthracycline). The "differentiated" compartments C2 and L2 do not proliferate anymore and, additionally, contain an apoptosis term (d).

Healthy haematopoiesis was calibrated to a typical human body (Stiehl et al., 2014). The leukaemic compartments have a different set of parameter values to respect the major changes in cellular behaviour due to the carcinogenic mutations within the stem cells. Model analysis (Görlich and Banck, 2019) showed that for the leukaemic system larger self-renewal and/or larger proliferation rates lead to the emergence of a persisting leukaemia in the human body. It is unclear which combinations of the parameter values are present in actual patients.

3 ASPECTS OF PERSONALIZATION

Mathematical and statistical models are generated to explain real world phenomena for a whole (sub-) group of patients. Thus, these models usually represent an "averaged" view onto these phenomena. Personalized predictions calculated from "average" models can work, but also may perform poorly for e.g. rare patient characteristics that might have been under-represented during model fitting.

For the AML model, an important assumption is that the basic mechanisms are also valid for a single patient. The model then can be directly used in a personalized setting. This assumption is reasonable, since the mathematical form of the kinetics was developed from the *in-vivo* mechanisms.

The "average" model's interpretation is caused by the calibration of the model parameters. The crucial point, to introduce personalized model fitting and prediction, thus, is the individual calibration of the model to a single patient. Each patient should contain his or her own set of parameter values.

Personalization via the model parametrization can be done on different levels of detail. Full personalization uses all model parameters. Healthy haematopoiesis parameters, bone marrow capacity, apoptosis, and treatment susceptibility parameters can be considered as functions of general patient characteristics. Although, the biological relationship between age, gender, height, weight, sex, general health status, chronic diseases, genetic mutations, and biological variation on the parameters of the healthy haematopoiesis is unclear.

Furthermore, the parameters for the leukaemia system are likely influenced by the leukaemic stem cell's genetic setup. The occurrence of mutations leading to leukaemic behaviour may act in two fashions: (H1) a gradual modification of the healthy parameter set is introduced, comparable to a more or less homogenous proportionality parameter here. (H2) A discrete, complete change of parameters might occur. While the first mechanism (H1) suggests that, the leukaemia shifts the stem cell's behaviour to an unfavourable region of the parameter space, but stays in the neighbourhood of the healthy system, the second hypothesis (H2) allows for jumps in the parameter space, i.e. also, large steps might be possible leading very clinically severe parameter combinations. In addition, the healthy haematopoiesis is less relevant for the leukaemia's behaviour in H2 compared to H1. Current hypotheses about clonal haematopoiesis in leukaemia (Hartmann and Metzeler, 2019) are consistent with both hypotheses. Under H1, each relevant mutation shifts the system to a more severe leukaemic state, while under H2 each hit jumps through the parameter space.

Finally, personalization can now be introduce by estimating patient-specific model parameters. Depending on the selected subset of parameters, the level of personalization is determined. Different levels occur if (i) healthy haematopoiesis and

leukaemic compartment parameters are personalized; or (ii) only leukaemic compartment parameters are personalized. A third aspect (iii) here is the estimation of personalized treatment parameters. Considering the three subgroups of parameters (healthy, leukaemic, treatment) eight scenarios with different interpretations emerge. A full personalization can only be reached when parameters from all three subgroups are estimated in a personalized way. Leaving one or two parameter subgroups at the population parameter values changes the interpretation of the resulting predictions.

4 ALIGNING MODEL OUTCOMES WITH CLINICAL DATA

To be able to fit the AML model to patient data an analysis of, on the one hand, the availability of relevant clinical patient (outcome) data is necessary. On the other hand, the mechanistic model, due to the introduced abstraction, needs to be capable to predict these selected aspects of AML in a sufficiently detailed manner.

4.1 Typical Variables Collected in Clinical AML Datasets

Data, which is e.g. regularly collected within clinical research about AML can be structured into four domains: (i) patient characteristics at diagnosis/baseline; (ii) leukaemia characteristics (molecular genetics, cytogenetics) and blood laboratory; (iii) treatment related information (schemata, dose); and (iv) outcomes (blast load, complete remission, blood laboratory, survival). With respect to identify a suitable set of clinical variable to estimate model parameters, we will focus onto outcome data here.

In the following, the clinical definitions of major patient outcomes are briefly summarized.

Blast load

Patients typically undergo blood laboratory analysis and bone marrow (BM) aspirations. Peripheral blood (pB) can be analysed more often than BM samples, since the latter need an invasive biopsy of the bones, to be collected. Nevertheless, the BM samples are the more reliable source to judge a patient's leukaemic load more accurately (Percival et al. 2017). Blast load is defined as percentage of blast cells in the collected sample, either pB or BM.

Survival

Patient survival is one of the main outcomes in oncological clinical research. It can be observed directly and plays a major role within therapy optimization trials.

Complete remission

Complete remission (CR) is the favourable situation that leukaemic cells are sufficiently eradiated from the patient's body. CR is the primary aim of any curative AML treatment approach. To identify a CR a number of clinical requirements needs to be met (Döhner et al., 2017)) : (i) Bone marrow blasts <5%; (ii) absence of circulating blasts and blasts with Auer rods; (iii) absence of extramedullary disease; (iv) ANC $\geq 1.0 \times 10^9$/L (1000/μL); (v) platelet count $\geq 100 \times 10^9$/L (100 000/μL). More response categories, like CR(MRD-), CRi, or partial remission (PR), can be reached, representing other system states.

4.2 Predictability of Clinical Outcomes within the Mechanistic Model

The mechanistic model, as described in section 2, aggregates a rather complex biological system into a system of only four ODEs. To be able to explain a real world system, the mathematical model needs to be able to assign model outcomes to entities observable in the real world.

The system's four state variables can be directly interpreted as coarse-grained compartments in the differentiation cascades. Thus, there should be a direct relation between model predictions (i.e. the ODE model's solution over time) and the observed cell number in a patient. In the following, four main outcome measures, regularly documented in clinical trials (cp 4.1.4), will be discussed.

4.2.1 Predicting Blast Load

Blast load is a direct measurement of a cellular quantity. It thus can be directly related to the respective modelled compartments.

Both leukaemic compartments (L1, L2) can be interpreted to represent blasts cells. Blast load (in percent) can then be computed as relative proportion of leukaemic cells in all bone marrow cells, i.e. the sum of the leukaemic compartments plus the BM compartment of the healthy haematopoiesis (L1,L2,C1).

4.2.2 Predicting Complete Remission

The definition of CR (4.1) shows a clear problem, here. Some criteria, necessary to determine a CR, are not represented nor predictable by the model, e.g. extramedullary disease, ANC, or platelet count. Thus, for a clinically comparable prediction of CR, our model is not well suited. Reasons for this, are for example that for these criteria a concise mechanistic understanding how to include these terms is lacking.

To produce clinical valid predictions model's, models should allow for an as perfect alignment to clinical reality as possible and CR should not be used here.

4.2.3 Predicting Survival

Similarly, survival is hard to predict from dynamic models. The only possibility to predict survival is to define a set of system states to be interpreted as "patient death". E.g. a situation where the healthy haematopoiesis is completed eradicated by the leukaemic cells. Of course, this might be still a severe, but manageable situation, if the patient is hospitalized. Thus, this surrogate definition only partly covers clinical reality. Calibrating mechanistic models to accurately predict patient death would be a strong advantage, since it opens the possibility to access clinical survival data.

4.2.4 Predicting Relapse

Prediction of relapse can be realized by identifying a system state where blast load rises again, after a CR was reached. Relapse occurs when leukaemic cells remain in the patient after chemotherapy. These cells can still reproduced and overtake the bone marrow, again, after some time. To simulate relapse a mechanistic model, thus, needs to be able to reach a CR state with a residual disease. A prerequisite for relapse is a CR and since CR cannot be predicted in a sufficient level of detail compared to the clinically defined criteria, relapse prediction will be not completely reliable.

5 FORMULATION OF THE OPTIMIZATION PROBLEM

Summarizing the considerations from 4.2.1 to 4.2.4 the only remaining, reliable variable is blast load (or percentage). It is a variable that is frequently observed in patients and blast load can be directly calculated from the system state at each point of time. Although, the model is abstract and course-grained, the level of detail should be sufficient to produce a valid blast load estimation. All other outcomes would be more interesting from a clinical point of view, but cannot be reproduced from the model with sufficient detail and validity. Thus, blast load will be used as main observable to link model prediction with patient data.

In the following section, an optimization problem for fitting the AML model to clinical data is proposed.

At first, a dataset $\mathbb{D}$ of individual patient data is defined as

$$\mathbb{D} = \{d_i \mid i = 1, \dots, N\}, \tag{1}$$

with

$$d_i = \{(t_{i,1}, b_{i,1}), \dots, (t_{i,\tau_i}, b_{i,\tau_i})\} \tag{2}$$

as a set of ordered tuples $(\mathrm{t_{i,j}},\mathrm{b_{i,j}})$. Each tuple $(\mathrm{t_{i,j}},\mathrm{b_{i,j}})$ represents the blast load $b_{i,j}$ of patient i at time $t_{i,j}$. Each patient can have 1 to τ_i assessments. This formulation allows that different patients had their blast assessment at different time points $\mathrm{t_{i,j}}$ and that the number of assessments τ_i may be different between patients.

Predicted blast load at time $\mathrm{t_{i,j}}$ is denoted as

$$\begin{aligned} &B_i\left(\mathcal{M}(\beta_i; t_{i,j})\right) \ with \\ &\beta_i = (p_i^c, a_i^c, p_i^l, a_i^l, k_i^{cyt}, k_i^{anthra}). \end{aligned} \tag{3}$$

β_i is the personalized vector of model parameters.

Given a data set $\mathbb{D}$ and the model $\mathcal{M}$ the goodness-of-fit measure $\mathcal{F}_i(d_i, \mathcal{M}, \beta_i)$ assesses the model with respect to the patient's observations d_i with parametrization β_i. Goodness-of-fit $\mathcal{F}_i$ is defined as

$$\mathcal{F}_i(d_i, \mathcal{M}, \beta_i) = c \cdot \sum_j \left(b_{i,j} - B_i\left(\mathcal{M}(\beta_i; t_{i,j})\right)\right)^2 \tag{4}$$

over all $j \in \{1, \dots, \tau_i\}$ time points of patient i.

The factor c is introduced to shift the fitness measure to a range of values that are beneficial for the optimization procedure. The solution of the optimization problem is a vector of optimal model parameters β_i^*, which minimize

$$\beta_i^* = argmin_{\beta_i}\left(\mathcal{F}_i(d_i, \mathcal{M}, \beta_i)\right) \tag{5}$$

One optimization problem per patient needs to be solved.

Due to the structure of the ODE system a closed solution to this optimization problem cannot be given.

The model was explicitly solved for each parameter vector in a grid search approach. The grid was defined by a selection of four relevant model parameters, i.e. $p_i^l, a_i^l, k_i^{cyt}, k_i^{anthra}$. Table 1 shows the applied grid step sizes.

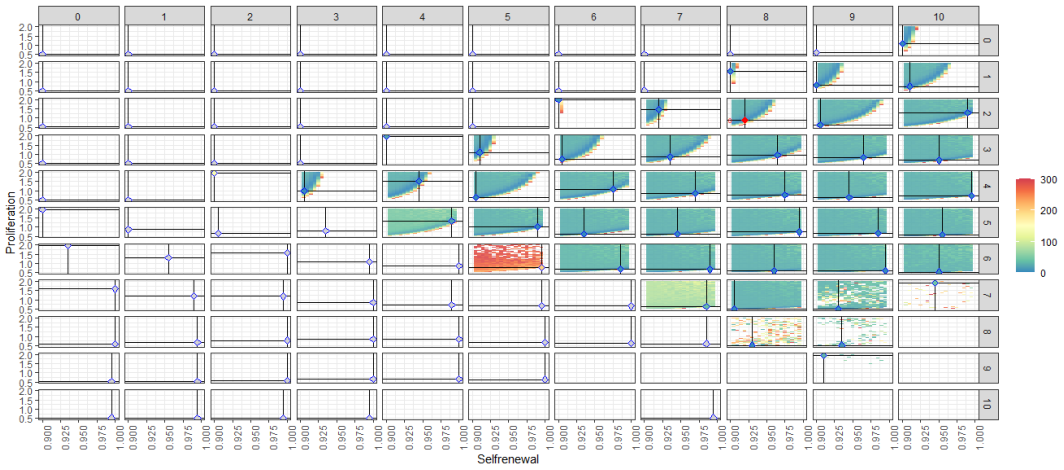

Figure 1: Heatmap panel-plot of all fitness values F_i computed for the whole parameter grid for one patient. A single panel represent (k_{cyt}, k_{anthra}) combinations. Within each panel the (a^l, p^l)-plane (selfrenewal, proliferation) is plotted. Colour was assigned to fitness values between 0 and 300. Within each panel, the local minimum is marked by a filled circle. Black coordinate lines indicate the position of the minimum for better orientation. The global minimum is marked by a filled red circle. Here, the global minimum is located in panel (2,8).

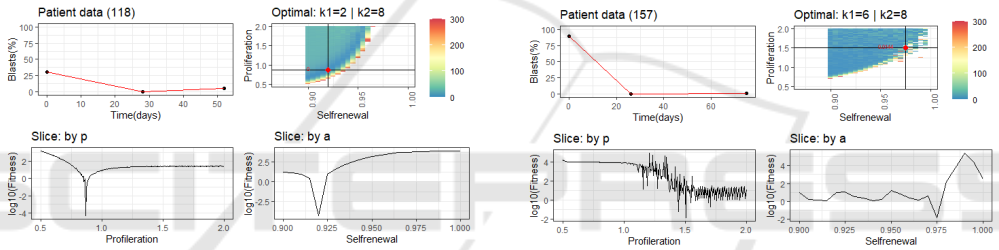

Figure 2: Exemplary results of the fitness landscape for two individual patient datasets (left side vs right side). For each patient the upper left shows d_i and the fitted B_i over time; the upper right shows a subplot of the fitness landscape of the combination of k_{cyt} and k_{anthra} where the global optimum for this patient is located. Color represents F_i. Only values between 0 and 300 have been plotted. The two lower panels on each side show slice plots along the proliferation (p) and self-renewal (a) axes. While the patient shown on the left side has a rather smooth fitness landscape along the relevant axes, the other patient shows a noisy fitness landscape. This is a frequent observation.

Table 1: Definition of the grid search step sizes.

Parameter	Minimum	Maximum	Step size
p_i^l	0.5	2	0.005
a_i^l	0.9	1	0.005
k_i^{cyt}	0	10	1
k_i^{anthra}	0	10	1

For the healthy haematopoiesis, an averaged (and not individualized) behaviour was assumed, thus, the respective parameters were not included in the grid search.

For each combination in the grid a fitness value was computed by solving the ODE system numerically (using the `deSolve` package (Karline et al. 2010) in R (R Core Team, 2020)). Figure 1 shows the fitness values $\mathcal{F}_i$ in the expanded parameter grid for one exemplary AML patient. The plot shows nicely that for the treatment related parameters (k_{cyt}, k_{anthra}) a compact region with (near) optimal values exist. Within each therapy combination, the (a,p)-fitness landscape has a specific form showing a band of very good solutions ranging from low self-renewal proliferations to combinations with increased self-renewal and proliferation. The finally identified global optimum can be found uniquely as Figure 2 illustrates. If the step size is decreased the optimum can be identified with more accuracy.

Figure 2 also shows that the fitness landscape can be very noisy. This should be considered when a numerical optimization algorithm is chosen. While smooth fitness landscapes can be easily handled with usual gradient-descent techniques, the noisy situations needs special consideration. We propose e.g. to apply the differential evolution (DE) algorithm (Kenneth et al., 2006) which can overcome the local minimal in the fitness landscape. A first attempt to apply the DE algorithm for this task showed promising results (data not shown).

6 SUMMARY AND CONCLUSION

With this position paper, we aimed to explain the challenges to align mechanistic mathematical models of AML and patient datasets.

A point to consider is the selection of personalization parameters. A full personalization, i.e. including all model parameters in the personalized optimization problem, might be hard to solve. Nevertheless, the full personalization is the most stringent approach.

We, here, demonstrated that the numerical solution identified by grid search for a reduced set of personalization parameters lead already to usable results. Furthermore, we implicitly introduced an assumption about the parameters, namely that healthy haematopoiesis equates to the population average. This may be reasonable in certain situations. E.g. within clinical trials, or standardized treatment regimens, the dose of chemotherapy is fixed. Assuming non-personalized treatment parameters for an analysis of a trial cohort might be justifiable. Overall, the degree of personalization should be selected according to the intended analysis.

Future research in the field of AML models should focus on a qualitative and quantitative validation strategy. A more stringent validation will lead to greater acceptance of modelling results in the clinical practice. Furthermore, the sensitivity analysis of personalized parameters will give valuable insights for the quality and interpretability of model predictions.

The integration of mechanistic modelling into the clinical practice can have a great impact, e.g. to provide personalized prediction of treatment success, and thus should be a major aim.

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