

# A Framework For Considering Costs and Benefits of Additional Complexities in Personalized Medicine

Working Title Need a New One

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## 1 Introduction

Personalized medicine has four goals: 1) to identify drugs for which between-subject variability in effectiveness or toxicity is a key issue for effective treatment, 2) to identify predictors which may explain this variability, 3) to decide on the right dose of the right drug by considering aforementioned factors, 4) and to aid in the prevention of adverse reactions of said drugs [1]. Progress in all four goals has accelerated within the last decade. As an example, recent studies on DPYD genotype testing prior to starting fluoropyrimidine-based chemotherapy showed promise in preventing adverse events, making good arguments for integration of DPYD genotype testing into standard of care practices [2]. Despite this progress, personalized medicine still faces barriers to widespread adoption.

The cost of instruments, technicians, and leadership required to operate a personalized medicine clinic are non-negligible, and it is not yet clear if personalized medicine is sufficiently cost effective to offset operating costs [3]. Additionally, some perspectives on personalized medicine focus on the use of demographic and clinical/biological information (including biomarkers, genotyping, and diagnostic tests) as a means of optimizing treatments, but largely ignore needs, constraints, and utilities of the patient [4] (for example their availability or willingness to be subject to multiple blood draws to measure blood serum concentrations). Ignoring these constraints may result in a method of personalization which, although effective, may not be realistic to implement at scale because the cost to the clinic, or the burden to the patient, is just too large.

An additional expertise cost is added as machine learning (used interchangeably with the term “artificial intelligence”) is adopted into personalized medicine initiatives. Cutting edge machine learning models for prediction or decision making can be prohibitively complex to implement correctly and at scale, requiring the partnership of experts in data science, computer science, statistics, engineering, etc. Collaboration between experts in these disciplines and physicians (among other stakeholders) is crucial to make effective use of data, rigorously internally validate models, and temper expectations which may be skewed from hype surrounding these algorithms [5]. Thus, new approaches to personalization may be out of reach without financial means to hire experts should they not be available for collaborative work (vis à vis large research grants, etc).

These costs may be payable for some, but the question then turns to if the result is worth the expense. Answering that question is difficult without an idea how the additional cost of collecting data, or implementing new algorithms, will benefit the clinic or the patient subject to inherent constraints. In this study, we present a new framework for helping practitioners interested in implementing personalized medicine to answer these

questions while considering practical limitations, and we present a case study using the framework applied to apixaban dosing.

For our case study, we fit a Bayesian model to existing data on the pharmacokinetics of apixaban. The resulting Bayesian model is used to generate synthetic pharmacokinetic data for use in experiments to compare different forms of personalization. Treating personalization as a dynamic treatment regime, we propose six policies, each increasing in complexity and clinic/patient burden, for personalizing doses of apixaban with the goal of keeping blood serum concentrations within a desired range for as long as possible. Under the assumption that the fitted Bayesian model can produce similar data to what might be observed in the future from new patients, we can make inferences as to how different policies for personalizing doses may improve upon one another, and compare if the additional burden of implementing a more complex or costly form of personalization can generate a more desirable outcome for the patient or healthcare provider.

We begin with an overview of dynamic treatment regimes and how personalizing doses can be framed as such. Afterwards, we describe how estimating an optimal policy for a dynamic treatment regime can be done using Q learning (the most complex method we entertain here). We discuss the details of the Bayesian model we use to fit the real pharmacokinetic data, and present model fit diagnostics to argue that our model is satisfactory for generating synthetic data for use in our simulations. We then present and discuss the results of our simulation in light of the costs presented to a clinic to implement personalized medicine, and how this framework can be integrated to make decisions about what form of personalization to implement.

## 2 Dynamic Treatment Regimes

In this section, we discuss the theory of dynamic treatment regimes and how personalization can be thought of as a dynamic treatment regime. We describe our experiments in the context of dynamic treatment regimes and introduce our reward function.

### 2.1 Trajectories

Our goal is to find the dose or sequences of doses for a subject to keep their blood serum concentration within a desired range for as long as possible given the constraints: a) subject's blood serum concentrations cannot be measured very frequently, and b) we are limited to pre-dose clinical measurements to make our initial dosing decision. The theory of dynamic treatment regimes and statistical reinforcement learning offers a framework through which to understand our problem and construct one possible solution.

A dynamic treatment regime (DTR) is a sequence of decision rules for adapting a treatment plan to the time-varying state of an individual subject [6]. In DTRs, and their cousin topic in computer science *reinforcement learning*, an agent (often thought of as a robot in reinforcement learning, but within medicine sometimes thought of as a physician's computerized decision support system) interacts with a system for a number of stages. At each stage, the agent receives an *observation* of the system and then decides which *action* to take. This action will result in an observed *reward* which is followed by a new observation of the system after it has been impacted by the action. This cycle of observation, action, reward then repeats, with the agent aiming to take actions which yield the largest total reward.

Key to our DTR is the concept of a *trajectory*. Define a stage to be a triple containing an observation,

chosen action, and resulting reward. Let  $O_i$  denote an observation at the  $i$ th stage,  $A_i$  be the action at the  $i^{th}$  stage, and  $Y_i$  denote the reward at the  $i^{th}$  stage, denoted in capital letters when considering the observation, action, and reward as random variables. A trajectory is then the tuple  $(O_1, A_1, O_2, A_2, \dots, O_K, A_K, O_{K+1})$ . Following notation by Chakraborty and Moodie [6], we will denote a system’s history at stage  $j$  as  $H_j = (O_1, A_1, O_2, A_2, \dots, O_{j-1}, A_{j-1}, O_j)$ . The reward at stage  $j$  is then a function of the system’s history, the action taken, and the next observation  $Y_j = Y_j(H_j, A_j, O_{j+1})$ .

## 2.2 Policies, Value Functions, and Q-Learning

A deterministic policy  $d = (d_1, \dots, d_k)$  is a vector of decision rules each which take as input the system’s history and output an action to take. The stage  $j$  value function for a policy  $d$  is the expected reward the agent would receive starting from history  $h_j$  (here in lower case since it is an observed quantity) and then choose actions according to  $d$  for every action thereafter. The value function is written as

$$V_j^d(h_j) = E_d \left[ \sum_{k=j}^K Y_k(H_k, A_k, O_{k+1}) \middle| H_j = h_j \right]. \quad (1)$$

Here, the expectation is computed over the distribution of trajectories. Importantly, the stage  $j$  value function can be decomposed into the expectation of reward at stage  $j$  plus the stage  $j + 1$  value function [6]

$$V_j^d(h_j) = E_d [Y_j(H_j, A_j, O_{j+1}) + V_{j+1}^d(H_{j+1}) | H_j = h_j]. \quad (2)$$

The optimal stage  $j$  value function is the value function under a policy which yields maximal value. Mathematically,

$$V_j^{opt}(h_j) = \max_{d \in \mathcal{D}} V_j^d(h_j) \quad (3)$$

A natural question is “what policy maximizes the value?”. Estimating such a policy can be achieved by estimating the optimal Q function [6]. The optimal Q function at stage  $j$  is a function of the system’s history  $h_j$  and a proposed action  $a_j$ ,

$$Q_j^{opt} = E [Y_j(H_j, A_j, O_{j+1}) + V_{j+1}^{opt}(H_{j+1}) | H_j = h_j, A_j = a_j] \quad (4)$$

Note that the optimal Q function has similar form and interpretation to the optimal value function (namely, it is the expected reward starting at stage  $j$  but with the added condition that we take action  $a_j$  and then follow the optimal policy thereafter). Due to the decomposition of the reward function at stage  $j$ , estimation of the optimal Q function can be performed by choosing the action which yields the largest reward at each stage assuming we act optimally in the future. Below, we describe how we choose optimal actions using a posterior distribution of a subject’s pharmacokinetics.

## 2.3 Experimental Design In Terms of Stages of a DTR

In our experiments, we develop a DTR for selecting the best dose for keeping a patient’s blood plasma concentration within a desired range. Here, we present details of the experimental design in the DTR framework, leaving simulation details (including how the data were simulated) for our methods section.

Our experiment consists of 1000 simulated subjects taking a dose of apixaban once every 12 hours with perfect adherence for a total of 10 days. Sometime in the second 12 hour period on the fourth day (between 108 and 120 hours after the initial dose), we have the opportunity to measure the simulated subject’s blood concentration, should our policy allow for it. At the start of the fifth day, the dose is adjusted based on all the pre-dose clinical measurements plus the observed concentration. The dose will be adjusted so as to attempt to maximize the time spent between 0.1 mg/L and 0.3 mg/L. Thus, our DTR consists of two stages (the first five days, and the latter five days), however the size of the range may be adapted for different scenarios. We choose this range as it is not so narrow that even optimal doses perform poorly, but not so wide that any dose can achieve high reward.

In terms of the DTR, the system is the patient for whom a dose is selected, the actions correspond to selection of dose sizes, and the reward is the proportion of time spent within the desired concentration range. The trajectories we will use to estimate the optimal Q functions are of the form

$$O_1, A_1, Y_1, O_2, A_2, Y_2, O_3 \quad (5)$$

The interpretation of a given trajectory is:

- $O_1$  is any pre-dose clinical measurements of the subject. In our experiments, we consider age in years, renal function (as measured by serum creatinine in mMol/L), weight in kilograms, and dichotomous biological sex (dummy coded so that male=1 and female=0). We choose these variables as they are known to affect the pharmacokinetics of apixaban [7].
- $A_1$  is dual action of initial dose to provide the subject plus a time in the future at which to measure the subject’s blood serum concentration.
- $Y_1$  is the proportion of time spent within the concentration range in the first five days.
- $O_2$  is the pre clinical measurements of the subject plus the observed concentration made on the fourth day.
- $A_2$  is the dose adjustment
- $Y_2$  is the proportion of time spent within the concentration range in the last five days after the dose adjustment.
- $O_3$  would be pre-dose clinical measurements, the observed concentration made on the fourth day, and the next concentration measurement, were it to be made. As we examine just the two actions  $A_1$  and  $A_2$ , we do not make use of  $O_3$  but include it here to adhere with our definition of trajectories above.

The reward function we use depends on the subject’s true latent concentration. Let  $c_j, j = 1 \dots K$  be the  $j^{th}$  latent concentration value at time  $t_j$ . The reward function is

$$Y(c_1, c_2, \dots, c_k) = \frac{1}{k} \sum_{j=1}^K \mathbb{I}(0.1 < c_j < 0.3) \quad (6)$$

Here,  $\mathbb{I}$  is an indicator function returning 1 if the argument is true, and 0 else. To leverage off-the-shelf optimization tools, we approximate this reward function with a continuously differentiable function, namely

$$Y(c_1, c_2, \dots, c_k) = \frac{1}{k} \sum_{j=1}^K \exp \left( - \left[ \frac{c_j - 0.15}{0.05} \right]^{2\beta} \right) \quad (7)$$

Here,  $\beta$  is a positive integer. For sufficiently large  $\beta$ , our approximation becomes arbitrarily close to our intended reward function. In practice we set  $\beta=5$  to balance between good approximation of our intended reward and vanishing gradients impeding our optimization. We suppress the dependence on the history in the definition of the reward as the reliance on the history is implicit. The reward depends on the latent concentrations which depend on previous doses (actions) and potentially on the previous dose measurements (observations of the system).

Our stage 2 optimal Q function is then

$$Q_2^{opt}(H_2, A_2) = E \left[ Y(c_{j+1}, c_{j+2}, \dots, c_{j+n}) \middle| H_2, A_2 \right], \quad (8)$$

and our stage 1 optimal Q function is

$$Q_1^{opt}(H_1, A_1) = E \left[ Y(c_1, c_2, \dots, c_j) + \max_{a_2 \in \mathcal{A}} Q_2^{opt}(H_2, a_2) \middle| H_1, A_1 \right] \quad (9)$$

We seek to maximize the stage 1 optimal Q function to learn the optimal policy for dosing subjects under the constraint we can measure them at most once and are limited to the aforementioned pre-dose clinical variables. The interpretation of stage 1 optimal Q function is as follows: *Given the pre-dose clinical variables of the subject and a proposed initial dose and measurement time, the stage 1 optimal Q function gives the proportion of time the subject's blood serum concentration is between 0.1mg/L and 0.3mg/L assuming that we provide the subject with the best dose possible at the start of the 5<sup>th</sup> day.* The actions  $A_1$  and  $A_2$  which maximize these functions constitute the optimal policy.

The concentration values  $c_j$  in the optimal Q functions are latent, meaning we have no direct access to them in practice. Furthermore, obtaining measurements with high enough frequency so that the reward is faithfully estimated would be too burdensome on the patient. What is left to explain is how these concentrations are computed. In the next section, we describe how we use a Bayesian model to obtain latent concentration predictions and compute the required expectations.

### 3 Bayesian Models of Pharmacokinetics

In order to estimate the optimal Q functions, we need to be able to predict how a subject's concentrations respond to any given dose. These predictions can be passed to the reward function to compute the values of  $Q_1$  and  $Q_2$ . Bayesian models of pharmacokinetics are capable of providing distributions of concentrations and can account for pre-dose clinical variables, as we will describe. The model we construct takes as inputs pre-dose clinical variables (age, sex, weight, and creatinine) and provides a distribution of plausible concentrations prior to seeing data. We can pass these prior predictions to our Q function and determine what dose keeps the subject in range for the longest time prior to seeing any data. Once we observe a concentration measurement from the subject, we can condition our model on that observation, and perform the optimization again to adjust the subject's dose in light of new information. For our experiments, we first fit a Bayesian pharmacokinetic model to real pharmacokinetic data collected by our colleagues in clinical pharmacology [8] and then use the fitted model to simulate patients and make predictions for our experiments.

We extend a previously proposed one compartment Bayesian pharmacokinetic model [9] to include fixed effects of covariates on pharmacokinetic parameters. The model presented in [9] is a hierarchical Bayesian

model of apixaban pharmacokinetics, in which the clearance rate (L/hour), time to max concentration (hours), absorption time delay (hours), and ratio between the elimination and absorption rate constants (called alpha, a unitless parameter) are hierarchically modelled. We extend that model by regressing the latent pharmacokinetic parameters on the aforementioned pre-dose clinical variables.

The model fit to real data, which we refer to as  $\mathcal{M}_1$ , is

$$y_{i,j} \sim \text{Lognormal}(C_i(t_j), \sigma_y^2) \quad (10)$$

$$\sigma^2 \sim \text{Lognormal}(0.1, 0.2) \quad (11)$$

$$C_i(t_j) = \begin{cases} \frac{D_i \cdot F}{Cl_i} \cdot \frac{k_{e,i} \cdot k_{a,i}}{k_{e,i} - k_{a,i}} \left( e^{-k_{a,i}(t_j - \delta_i)} - e^{-k_{e,i}(t_j - \delta_i)} \right) & t_j > \delta_i \\ 0 & \text{else} \end{cases} \quad (12)$$

$$k_{e,i} = \alpha_i \cdot k_{a,i} \quad (13)$$

$$k_{a,i} = \frac{\log(\alpha_i)}{t_{max,i} \cdot (\alpha_i - 1)} \quad (14)$$

$$\delta_i \sim \text{Beta}(\phi, \kappa) \quad (15)$$

$$\text{logit}(\alpha_i) | \beta_\alpha, \sigma_\alpha^2 \sim \text{Normal}(\mu_\alpha + \mathbf{x}_i^T \beta_\alpha, \sigma_\alpha^2) \quad (16)$$

$$\log(t_{max,i}) | \beta_{t_{max}}, \sigma_{t_{max}}^2 \sim \text{Normal}(\mu_{t_{max}} + \mathbf{x}_i^T \beta_{t_{max}}, \sigma_{t_{max}}^2) \quad (17)$$

$$\log(Cl_i) | \beta_{Cl}, \sigma_{Cl}^2 \sim \text{Normal}(\mu_{Cl} + \mathbf{x}_i^T \beta_{Cl}, \sigma_{Cl}^2) \quad (18)$$

$$p(\phi) \sim \text{Beta}(20, 20) \quad (19)$$

$$p(\kappa) \sim \text{Beta}(20, 20) \quad (20)$$

$$p(\mu_{Cl}) \sim \text{Normal}(\log(3.3), 0.15^2) \quad (21)$$

$$p(\mu_{t_{max}}) \sim \text{Normal}(\log(3.3), 0.1^2) \quad (22)$$

$$p(\mu_\alpha) \sim \text{Normal}(-0.25, 0.5^2) \quad (23)$$

$$p(\sigma_y) \sim \text{Lognormal}(\log(0.1), 0.2^2) \quad (24)$$

$$p(\sigma_{CL}) \sim \text{Gamma}(15, 100) \quad (25)$$

$$p(\sigma_{t_{max}}) \sim \text{Gamma}(5, 100) \quad (26)$$

$$p(\sigma_\alpha) \sim \text{Gamma}(10, 100) \quad (27)$$

$$p(\beta_{Cl,k}) \sim \text{Normal}(0, 0.25^2) \quad k = 1 \dots 4 \quad (28)$$

$$p(\beta_{t_{max},k}) \sim \text{Normal}(0, 0.25^2) \quad k = 1 \dots 4 \quad (29)$$

$$p(\beta_{\alpha,k}) \sim \text{Normal}(0, 0.25^2) \quad k = 1 \dots 4 \quad (30)$$

Here, normal distributions are parameterized by their mean and variance, lognormal distributions are parameterized by the mean and variance of the random variable on the log scale, and gamma distributions are parameterized by their shape and rate. The  $\mu$  in the model above represent population means on either the log or logit scale, the  $\beta$  are regression coefficients for the indicated pharmacokinetic parameter, the sigmas are the population level standard deviations on the log or logit scale,  $\delta$  is a parameter which relaxes the assumption that the dose is absorbed into the blood immediately upon ingestion,  $F$  is the bioavailability of apixaban (which

we fix to 0.5 [7]) and  $D$  is the size of the dose in milligrams. All continuous variables were standardized using the sample mean and standard deviation prior to being passed to the model.

Once fit,  $\mathcal{M}_1$  can be used to predict the pharmacokinetics of new patients, using the patient's covariates as predictors. To do so, the marginal posterior distributions for  $\mu_{Cl}$ ,  $\mu_{t_{max}}$ ,  $\mu_\alpha$ ,  $\beta_{Cl}$ ,  $\beta_{t_{max}}$ ,  $\beta_\alpha$ ,  $\sigma_{Cl}$ ,  $\sigma_{t_{max}}$ ,  $\sigma_\alpha$ , and  $\sigma_y$  must be summarized. We use maximum likelihood on the posterior samples to summarize the marginal posterior distributions. We model the population means and regression coefficients as normal, and the standard deviations as gamma. The maximum likelihood estimates are used to construct priors for a new model, which we call  $\mathcal{M}_2$ . We construct  $\mathcal{M}_2$  so as to be able to predict plasma concentration after multiple doses (of potentially different sizes) administered over time, and remove the time delay ( $\delta$ ) to simplify our simulations. Model priors for  $\mathcal{M}_2$  are then

$$p(\mu_{Cl}) \sim \text{Normal}(0.5, 0.04) \quad (31)$$

$$p(\mu_{t_{max}}) \sim \text{Normal}(0.93, 0.05) \quad (32)$$

$$p(\mu_\alpha) \sim \text{Normal}(-1.35, 0.13) \quad (33)$$

$$p(\sigma_{Cl}) \sim \text{Gamma}(69.15, 338.31) \quad (34)$$

$$p(\sigma_{t_{max}}) \sim \text{Gamma}(74.96, 349.56) \quad (35)$$

$$p(\sigma_\alpha) \sim \text{Gamma}(10.1, 102.07) \quad (36)$$

$$p(\beta_{Cl,1}) \sim \text{Normal}(0.39, 0.08^2) \quad (37)$$

$$p(\beta_{Cl,2}) \sim \text{Normal}(0.19, 0.04^2) \quad (38)$$

$$p(\beta_{Cl,3}) \sim \text{Normal}(0.02, 0.04^2) \quad (39)$$

$$p(\beta_{Cl,4}) \sim \text{Normal}(0.01, 0.04^2) \quad (40)$$

$$p(\beta_{t_{max},1}) \sim \text{Normal}(-0.01, 0.08^2) \quad (41)$$

$$p(\beta_{t_{max},2}) \sim \text{Normal}(0.09, 0.05^2) \quad (42)$$

$$p(\beta_{t_{max},3}) \sim \text{Normal}(-0.05, 0.04^2) \quad (43)$$

$$p(\beta_{t_{max},4}) \sim \text{Normal}(-0.01, 0.04^2) \quad (44)$$

$$p(\beta_{\alpha,1}) \sim \text{Normal}(-0.19, 0.17^2) \quad (45)$$

$$p(\beta_{\alpha,2}) \sim \text{Normal}(0.33, 0.11^2) \quad (46)$$

$$p(\beta_{\alpha,3}) \sim \text{Normal}(-0.06, 0.1^2) \quad (47)$$

$$p(\beta_{\alpha,4}) \sim \text{Normal}(-0.09, 0.1^2) \quad (48)$$

$$(49)$$

For our experiments, we generate the pharmacokinetic parameters of 1000 subjects from the prior predictive model of  $\mathcal{M}_2$ . Bayesian models are generative models, meaning they can generate pseudodata by drawing ran-

dom variables according to the model specification going from top (model priors) to bottom (model likelihood). To do so, we begin by resampling 1000 tuples of age, sex, weight, and creatinine from the dataset used to fit  $\mathcal{M}_\infty$ . We sample one draw of  $\mu_{Cl}$ ,  $\mu_{t_{max}}$ ,  $\mu_\alpha$ ,  $\beta_{Cl}$ ,  $\beta_{t_{max}}$ , and  $\beta_\alpha$  from their respective prior distributions in  $\mathcal{M}_2$ . The values of these parameters remained fixed for all 1000 subjects. Conditioned on the values of these mus and betas, we compute the expectation of the population distribution for each pharmacokinetic parameter by computing  $\mu_{Cl} + \mathbf{x}^T \beta_{Cl}$ ,  $\mu_{t_{max}} + \mathbf{x}^T \beta_{t_{max}}$ ,  $\mu_\alpha + \mathbf{x}^T \beta_\alpha$ , where  $\mathbf{x}^T$  is the resampled tuple. From the prior distribution of M2, we sample one draw of  $\sigma_{Cl}$ ,  $\sigma_{t_{max}}$ ,  $\sigma_\alpha$ , and  $\sigma_y$ . These remained fixed for all 1000 subjects. Using the previously computed expectations and  $\sigma$ , we sample 1000 tuples of pharmacokinetic parameters, one for each of the simulated subjects. The clearance rate and time to max concentration were sampled assuming a lognormal distribution. Alpha was sampled using a logitnormal distribution. The pharmacokinetics can then be determined conditional on the pharmacokinetic parameters. Each of simulated subjects' pharmacokinetic parameters remained fixed through the experiments. We simulate the latent concentration using  $C(t)$  as written in  $\mathcal{M}_2$ , and can simulate observed concentrations by drawing a sample from a lognormal distribution with mean  $\ln(C(t))$  and standard deviation  $\sigma_y$ .

We use Stan, an open source probabilistic programming language, for fitting our Bayesian models via Hamiltonian Monte Carlo (a Markov Chain Monte Carlo technique) and computing markov chain diagnostics. Twelve chains are initialized and run for 2000 iterations each (1000 for warmup allowing the Markov chain the opportunity to find the correct target distribution and 1000 to use as samples from the posterior).



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