

# Developing and Evaluating Pharmacokinetics-Driven Dynamic Personalized Medicine: A Framework and Case Study

Acknowledgements: The authors wish to thank A.J.B for their comments on health economic impacts of this work, as well as R.K and their lab for providing pharmacological expertise.

## Abstract

**Background:** One goal of personalized medicine is to select the right dose for a drug by considering factors which may explain variability in effectiveness or toxicity. Most efforts to personalize dose size seek to inform dose selection at a single time, with the goal of eliminating the need for dose adjustments (titration). We refer to this as static personalization. Despite progress, the need for titration has not been eliminated and thus there is an opportunity to personalize the titration process as well. We refer to this as dynamic personalization. Despite its potential to improve care, dynamic personalization imposes additional burden on the patient and provider, because it requires ongoing monitoring, for example by gathering lab results and requiring additional clinic visits. It is natural to ask: is the additional control over dose worth the additional burden? **Objective:** To develop a framework for the simulation based evaluation of static and dynamic personalization based on pharmacokinetic modelling. **Methods:** We frame dynamic personalization as a dynamic treatment regime and describe how Bayesian pharmacokinetic models can be used to estimate the optimal policy with Q learning, and we propose a simulation-based strategy for internal evaluation. **Results:** We demonstrate the use of our framework to investigate the potential benefits of static and dynamic personalization for apixaban dosing. **Conclusions:** The proposed framework can help compare potential burden and benefits of different modes of personalized dosing and it can be integrated with other system level decision making frameworks in order to evaluate whether such a personalized medicine program should be implemented into a particular health care system.

**Highlights:** Bayesian pharmacokinetic models can enable personalized dosing strategies by making tailored predictions of drug concentration as a function of dose and patient characteristics. These models can also be updated with new measurements to adjust dose over time. We frame this process as a dynamic treatment regime, describe how Bayesian pharmacokinetic models can be used to estimate the optimal policy with Q learning, and propose a simulation-based strategy for internal evaluation. The proposed framework can help assess potential benefits of personalization to help decide whether it should be considered for further evaluation and deployment.

## 1 Introduction

Personalized medicine has been characterized by 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 these factors, and 4) to prevent adverse reactions to drugs [1]. Progress in all four goals has accelerated within the last decade: For 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].

With regard to the third goal—personalized dosing—the intent of most efforts has been what we call *static* personalization. Such approaches inform dose at one point in time (usually induction) with the goal

of eliminating the need for “trial-and-error” adjustments (titration) where the dose is adapted to the patient over time in response to its effects, both therapeutic and adverse [1]. Although significant progress has been made, for example in warfarin dosing [3], the need for titration has been reduced but not eliminated. Thus, there is an opportunity to personalize not only the initial doses but also the titration process to achieve the best result—we call this *dynamic* personalization. This approach has been used in other contexts by applying techniques from disciplines such as control theory, operations research, machine learning, and biostatistics to define and apply models for optimal sequential decision-making for patient care [4, 5].

Despite its potential to improve care, dynamic personalization imposes additional burden on the patient and provider, because it requires ongoing monitoring, for example by gathering lab results and returning for additional clinic visits. It is therefore natural to ask whether dynamic personalization is “worth it.” Is the additional control over dose worth the additional burden? To help answer this question, we present a unified framework for the development and simulation-based evaluation of static and dynamic personalization based on pharmacokinetic (PK) modelling. The knowledge created by our framework can be integrated into a system-level decision-making framework like Know4Go, for example, which can be used to evaluate whether such a personalized medicine program should be implemented into a particular health care system [6]. Having established our framework, we investigate the static and dynamic personalization of apixaban dosing as a case study.

We begin in Section 2 with an overview of dynamic treatment regimes, which underpin our models for dynamic personalization, and we review Bayesian PK modelling, which allow us to predict drug concentrations and to generate simulated patient data. In Section 3, we present our framework, which describes how to estimate optimal dynamic treatment regimes for personalization by combining Bayesian PK modelling with Q-learning, and describes a simulation-based approach for assessing the potential benefits of different modes of static and dynamic personalization. We then present our case study of personalized apixaban dosing in Section 4. Finally in Section 6 we discuss the results of the case study, and we identify broader issues relevant to the further development and implementation of PK-driven static and dynamic personalization.

## 2 Methods

We briefly review dynamic treatment regimes, which are used to develop optimal decision-making models, and Bayesian PK models, which are used to capture relationships among patient characteristics, measurements, pharmacokinetics, and dose so that optimal dosing decisions can be derived using the dynamic treatment regime framework.

### 2.1 Dynamic Treatment Regimes

A *dynamic treatment regime* (DTR) is a mathematical formalism intended to model the practise of evaluating a patient, choosing a treatment, and observing a response. A DTR is defined as a sequence of decision

rules  $d = (d_1, \dots, d_K)$ , each of which is a function that takes information about a patient produces an *action*, like a dose initiation or change, that is intended to affect the status of the patient, like their plasma concentration [7, 8, 9]. The application of each decision rule is called a *stage* in the DTR, and applying a DTR generates a *trajectory* of data  $O_1, A_1, O_2, A_2, \dots, O_K, A_K, O_{K+1}$ ; these are represented in upper case to emphasize that they are random variables which represent potentially noisy observations of a patient and actions which depend on the observations. We define the *history* of the patient at stage  $j$  to be  $H_j = (O_1, A_1, O_2, A_2, \dots, O_{j-1}, A_{j-1}, O_j)$ ; this encompasses all information available for decision-making at stage  $j$ .

### 2.1.1 Defining and Estimating Optimal DTRs

To define the performance of a decision rule (and of a DTR) we also define a *reward*  $Y_j = Y_j(H_j, A_j, O_{j+1})$  which is a quantitative measure of success of the outcome that follows the stage  $j$  action, coded so that higher values are preferable. The sum of the rewards achieved over a single trajectory is called the *return*. Given this definition, the *value* of a DTR is given by

$$V^d = \mathbb{E} \left[ \sum_{k=1}^K Y_k \right], \quad (1)$$

which is the expectation of the return if we follow DTR  $d$ . Typically, a DTR is defined to be optimal if it achieves the highest possible value among those under consideration; this corresponds to the concept of maximizing utility or minimizing expected loss in statistical decision theory [10].

There are different ways of estimating an optimal DTR [9]. One way, called “Q-learning” relies on estimating the optimal Q function. We give an overview of Q-learning for DTRs here, and refer the reader to other sources for more detail [7]. The optimal Q function at stage  $j < K$  is a function of the observed history  $h_j$  and a proposed action  $a_j$  given by

$$Q_j^{\text{opt}}(h_j, a_j) = \mathbb{E} \left[ Y_j(h_j, a_j, O_{j+1}) + \max_a Q_{j+1}^{\text{opt}}(H_{j+1}, a) | H_j = h_j, A_j = a_j \right]. \quad (2)$$

and  $Q_K^{\text{opt}}(h_K, a_K) = \mathbb{E}[Y_j(h_K, a_K, O_{K+1}) | H_K = h_K, A_K = a_K]$ . The function  $Q_j^{\text{opt}}$  represents the expected return if we choose action  $a_j$  when history is  $h_j$  and subsequently always choose actions that are optimal, that is, give highest expected return. Given the optimal Q function, an optimal DTR is given by choosing the action that maximizes it:

$$d_j^{\text{opt}}(h_j) = \arg \max_{a \in \mathcal{A}} \{ Q_j^{\text{opt}}(h_j, a) \}. \quad (3)$$

The Q-learning algorithm proceeds by first estimating  $Q_K^{\text{opt}}$ , often by acquiring a dataset of tuples of the form  $(h_K, a_K, y_K)$  and regressing the  $y_K$  on the  $h_K$  and  $a_K$ . The resulting  $\hat{Q}_K^{\text{opt}}$  can estimate the expected reward for any choice of  $h_K$  and  $a_K$ . It is then used to estimate  $Q_{K-1}$ , which is in turn used to estimate  $Q_{K-2}$ , and so on. This “backward induction” approach emphasizes that the optimal decision rule at earlier stages depends on the decision rules at later stages, and that they cannot in general be optimized independently.

## 2.2 Bayesian Models of Pharmacokinetics

In order to estimate the optimal Q functions, we need to be able to predict how a patient’s concentration is likely to evolve over time in response to a hypothetical dose (action). Our approach is to build a Bayesian model of patient pharmacokinetics that can use baseline clinical information, as well as any available concentration measurements, to make tailored predictions of future concentrations that are as accurate as possible given the model structure and available data. The model is flexible in that it can condition on whatever information is available—for example, if previous dose and measurement information is not available for a specific patient, the model will rely on baseline information alone. If it is available, the model will use it to (hopefully) make improved predictions. This allows us to optimize both initial doses and later dose adjustments after additional information about concentration is acquired.

Bayesian models have another key property that we use in our framework. Once they are fit to data, and assuming the model is fit well, they are able to simulate the trajectories of patients drawn from a distribution that is similar to the distribution of the data that the models were trained on, but in the simulated data, *all* variables—including normally-hidden PK parameters—are fully observed. This allows us to conduct a form of internal validation where we use the simulated patients to assess the relative benefits of different modes of static and dynamic personalization, because we can know for each simulated patient exactly what the effect of any dose would be. This process is described in detail in the next section, where we present our framework, and the details of the Bayesian model itself are provided in Appendix A.

## 3 Framework

In this section, we present the components of our framework for assessing static and dynamic personalization, including details for fitting a hierarchical Bayesian PK model to concentration data from a cohort of patients, assessing the behaviour of Markov chains via diagnostics, and using the Bayesian model to generate simulated data for evaluation. We then outline several modes of static and dynamic personalization ranging from no personalization (every patient gets the same dose) to a complex dynamic mode of personalization (estimation of the optimal Dynamic Treatment Regime for dosing). Finally, we outline steps for assessing the benefits of each mode of personalization.

### 3.1 Bayesian Modelling

The first step in our framework is to fit a Bayesian model that relates patient covariates and dose to drug concentration as a function of time. For example, previous work [11] describes a hierarchical Bayesian model of apixaban pharmacokinetics, in which the clearance  $Cl$  (L/hour), time to maximum concentration  $t_{max}$  (hours), absorption time delay  $\delta$  (hours), and ratio between the elimination and absorption rate constants ( $\alpha = k_e/k_a$ , a unitless parameter) are hierarchically modelled. In our case study, we extend that model by regressing the latent pharmacokinetic parameters on baseline clinical variables (age, sex, weight, and

creatinine) to permit personalization. The model could equally well be extended with pharmacokinetic or biomarker information if the relevant theory and data were available for a particular use case. We details for our Bayesian hierarchical pharmacokinetic model and information on interpretation of sampler diagnostics in appendix A.

### 3.2 Modes of Personalization & Assessment of Personalization

The second step in our framework is to identify modes of personalization that we wish to evaluate. We classify these modes of personalization into two types: static and dynamic personalization.

Static modes of personalization seek to inform the dose at one point in time (usually treatment initiation) with the goal of eliminating the need for “trial-and-error” adjustments. We consider two modes of static personalization in our case study:

1. **One size fits all.** This mode of personalization is not very personal at all. All patients receive the same dose size at the onset of treatment ( $\approx 8.5mg$  taken twice daily). This dose was selected so that the average value across patients was maximized.
2. **Dose based on clinical variables.** In this mode of personalization, the patient’s covariates, for example age, sex, weight, creatinine (a measure of kidney function )measurements, and possibly genetic or biomarker information, are provided to the pharmacokinetic model. A dose size is then selected using the model to maximize the value function conditional on these measurements.

Dynamic modes of personalization seek to personalize the initial doses but also the titration process. We consider four modes of dynamic personalization for our case study:

1. **One size fits all initial dose *and* one dose adjustment.** This mode of personalization provides patients the same dose to start, but requires a concentration measurement to be made sometime in the future, which is then used to adjust the dose. For example, in our case study, patients take their initial dose once every 12 hours with perfect adherence for five days, and, a sample is taken randomly in the second 12 hour period of the fourth day. Our pharmacokinetic model conditions on this measurement, and the dose is adjusted in order to maximize the reward for another five days by updating our Bayesian model with the measurement.
2. **Initial dose based on clinical variables *and* one dose adjustment.** Here, the initial dose provided to the patient is determined by the patient’s clinical measurements. For example, in our case study, in the second half of the fifth day, a concentration measurement is made at a random time. The model is conditioned on this concentration and the dose is adjusted to optimize the reward.
3. **Initial dose based on clinical variables *and* optimally-timed observation.** Similar to the previous mode of personalization, but the time at which the measurement is made is under our control

and tuned to maximize reward. The time at which the sample is taken can yield more or less information about particular parameters in the model, but increases the burden by necessitating an additional constraint on when the observation should be obtained. For example, measuring much later after the dose is taken yields more information about the elimination rate constant  $k_e$  than it does about the absorption rate constant  $k_a$  because later in time, the majority of the dose has been absorbed and is now being eliminated by the body. In this mode of personalization, the initial dose and the timing of the adjustment are optimized independently.

4. **Optimal sequential dosing.** The approach of this mode is the same as the previous mode, except that the initial dose and the timing of the adjustment are *jointly optimized* using Q-learning to maximize the expected reward.

We stress that these are just examples of some modes of personalization, and that we do not mean that these modes should always be candidate modes for personalization, nor that they are the only modes of interest. These modes may not be appropriate for all drugs across all indications, and were selected in order to illustrate natural extensions and combinations of static personalization with additional information collection. A strength of our approach is that many possible modes of personalization may be considered depending on what is appropriate for the use-case at hand.

Each simulated patient has their dose(s) selected under each mode of personalization. Since the patients are simulated, we can compute what the return under the proposed dose(s) obtained from each mode of personalization and compare the return achieved to the largest return theoretically possible (i.e. the return achieved were we to know the pharmacokinetic parameters exactly when providing the initial dose, which is not possible in practice). The difference between this optimal return and the actual return is called the *regret*. Comparing the regrets achieved by different modes allows us to assess their relative performance, and helps us decide which are most appropriate for a given personalized medicine problem.

## 4 Case Study

We present a case study of applying our framework to investigate the potential benefits of static and dynamic personalization of apixaban dosing. Apixaban is a direct acting anticoagulant medication used to treat active blood clots occurring with deep venous thrombosis or pulmonary embolism, or to prevent stroke in patients with atrial fibrillation. Prescribing an apixaban dose that achieves blood concentrations within an optimal range is expected to provide optimal treatment benefits while minimizing harms (e.g., serious bleeding). Clinical variables measuring age, weight, and kidney function are routinely used for dosing, and female sex, co-medications and genetic factors are known to contribute to higher circulating apixaban concentrations [12]. However, these variables only explain 35% of the pharmacokinetic variability in apixaban, which serves as rationale for considering dynamic dose optimization supported by post-initiation blood concentration monitoring.

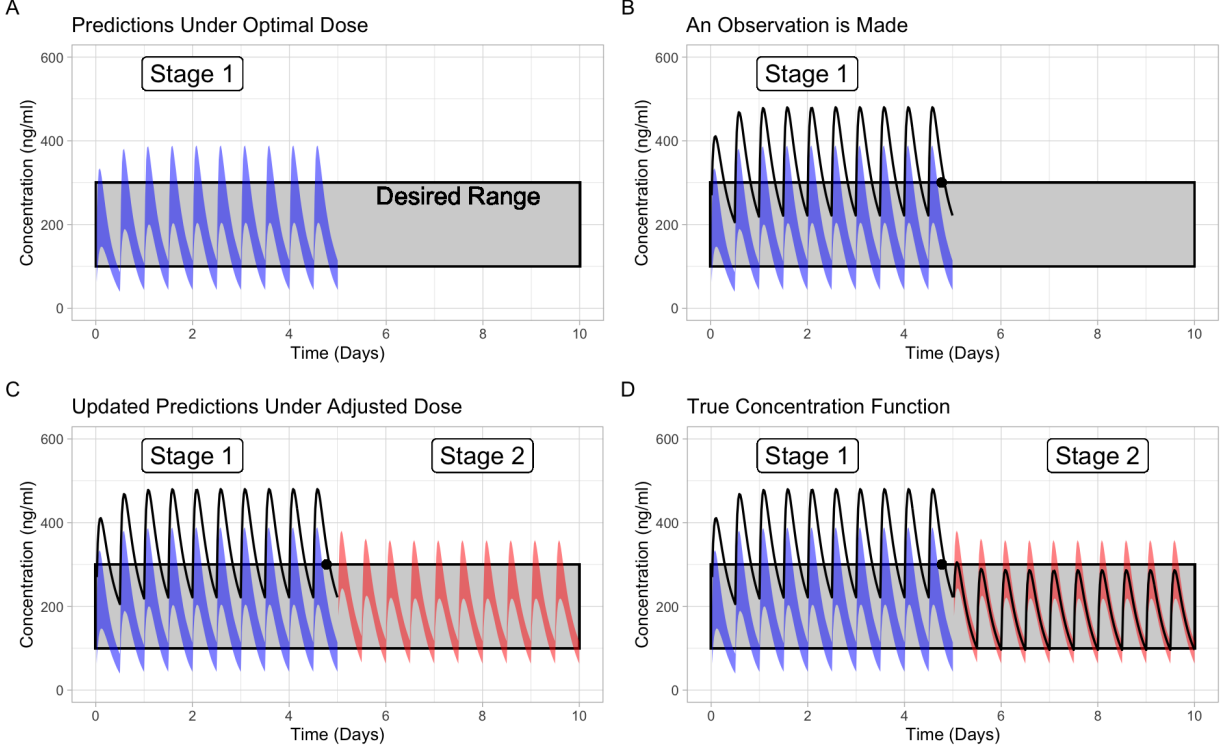


Figure 1: Visual representation of the steps in our framework. **A** Using only clinical information, the model is used to select a dose that is expected to keep the patient in the desired range for as long as possible. The blue ribbon indicates 90% credible interval for the latent concentration. **B** Some time later, the patient's blood serum concentration is measured (black dot). **C** The observation is incorporated into the model and a new dose is selected to keep the patient in range for as long as possible. The red ribbon indicates 90% credible interval for the latent concentration after adjusting the dose. **D** The black line indicates the true latent concentration under each dose. Note the observation (black dot) is not on the black line (true concentration) because there is measurement error, which the model accounts for.



## 4.1 Bayesian Modelling

To create the necessary model for apixaban personalization, we extend a previously proposed one-compartment Bayesian pharmacokinetic model [11] to include fixed effects of covariates on pharmacokinetic parameters in order to incorporate baseline clinical information (age, sex, weight, and creatinine.) Full details of the model structure, fitting, and diagnostic checks are provided in Appendix A. We fit the model to previously-collected data on apixaban concentration [13] and then use the fitted model to simulate patients with known "ground truth" pharmacokinetic parameters as described previously. We then use this population of simulated patients in our experiments to explore different modes of dose personalization and their relative benefits.

## 4.2 Modes of Personalization

We consider the 6 modes of personalization as outlined in section 3. To evaluate these modes of personalization, we generate 1000 simulated patients taking a dose of apixaban once every 12 hours with perfect adherence for a total of 10 days. The goal is to maximize the time spent with blood concentration level between between 100 ng/ml and 300 ng/ml. 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. For static modes of personalization, the selected initial dose is fixed over the 10 day period. For dynamic modes of personalization, some time in the second 12 hour period on the fourth day (between 108 and 120 hours after the initial dose), the simulated patient's blood concentration is measured, and then at the start of the fifth day, the dose is adjusted based on all the pre-dose clinical measurements plus the observed concentration by incorporating the new information into the Bayesian model.

### 4.2.1 Defining the Dynamic Treatment Regimes

To implement the two dynamic modes of personalization, we estimate DTRs with two stages (the first five days, and the latter five days). For the dynamic personalization policies our experiments, we develop a DTR for selecting the best dose for keeping a patient's blood plasma concentration within a desired range. 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 a time in the future to sample the patient, should the DTR require that), 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

$$O_1, A_1, Y_1, O_2, A_2, Y_2 \tag{4}$$

The interpretation of a given trajectory is:

- $O_1$  is any pre-dose clinical measurements of the patient. 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 [14].

- $A_1$  is the initial dose to provide the patient. If the DTR allows us to specify a time in the future at which to measure the patient's blood serum concentration, then  $A_1$  is the dual action of initial dose plus a time in the future at which to measure.
- $Y_1$  is the proportion of time spent within the concentration range in the first five days.
- $O_2$  is the pre clinical measurements of the patient 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 final five days after the dose adjustment.

The actions  $A_j$  affect the reward  $Y_j$  mediated by their effects on concentration. For example, a larger dose will elicit larger concentrations which may put the patient in range for longer (more reward) or take them out of range for some time (less reward). Thus, our reward function can be thought of as a composition of the reward function and the concentration function. In our experiments, we create a mesh of  $2K$  times at which we can evaluate the latent concentration and compute the reward function. Each stage in our DTR consists of  $K = 240$  times (equivalent to evaluating the latent concentration function every 30 minutes after ingestion). Let  $c_i, i = 1 \dots 2K$ , be the  $i^{th}$  latent concentration value at time  $t_i$ . The reward function in the first stage is

$$Y_1(H_1, A_1) = Y_1(c_1(A_1), \dots, c_K(A_1)) = \frac{1}{K} \sum_{i=1}^K \mathbb{I}(0.1 < c_i(A_1) < 0.3) \quad (5)$$

Here,  $\mathbb{I}$  is an indicator function returning 1 if  $c_i$  is between 100 ng/ml and 300 ng/ml and 0 else. The reward function in the second stage is

$$Y_2(H_2, A_2) = Y_1(c_{K+1}(A_2), \dots, c_{2K}(A_2)) = \frac{1}{K} \sum_{i=1}^K \mathbb{I}(0.1 < c_{K+i}(A_2) < 0.3) \quad (6)$$

Our stage 2 optimal Q function is then

$$Q_2^{\text{opt}}(H_2, A_2) = E \left[ Y_2(c_{K+1}(A_2), \dots, c_{2K}(A_2)) \middle| H_2, A_2 \right], \quad (7)$$

and our stage 1 optimal Q function is

$$Q_1^{\text{opt}}(H_1, A_1) = E \left[ Y_1(c_1(A_1), \dots, c_K(A_1)) + \max_{a_2} Q_2^{\text{opt}}(H_2, a_2) \middle| H_1, A_1 \right] \quad (8)$$

We seek to maximize the stage 1 optimal Q function to learn the optimal DTR for dosing patients 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 patient and a proposed initial dose and measurement time, the stage 1 optimal Q function gives the expected proportion of time the patient’s blood serum concentration is between 100 ng/ml and 300 ng/ml assuming that we provide the patient with the best dose possible at the start of the 5<sup>th</sup> day.* The decision rules which choose  $A_1$  and  $A_2$  to maximize these functions constitutes the estimated optimal DTR.

### 4.3 Evaluating Modes of Personalization

We measure the performance of different modes in terms of *regret*, the difference between theoretically largest possible return if the individual’s PK parameters were precisely known and the achieved return by each mode of personalization. The results are shown in figure 2, ordered from least amount of information and burden (top) to most amount of information and burden (bottom) and colored by their personalization strategy (static or dynamic).

Modes of personalization which use less information have larger regret. The One Size Fits All approach (which uses no information about the patient) performs worst with a median regret of 0.145. The distribution of regrets for this mode is right skewed with some exceeding 0.95, meaning the patient could have been in range for nearly the entire time if the correct PK parameters were known, but the mode selected a dose which failed to put the patient in range.

The Clinical Variables mode nearly cuts the regret in half, achieving a median regret of 0.086 with smaller right skew. Modes which use observed concentration information (Clinical Variables + One Sample, Optimal Sampling Time, and Optimal Sequential Dosing) lead to slightly lower median regrets (0.075, 0.076, 0.079 respectively) as compared to the Clinical Variables mode.

## 5 Limitations

Our framework relies on the quality of the Bayesian model used to predict plasma concentrations. The data required to construct a high quality Bayesian model of pharmacokinetics require multiple observations of a single patient over an extended time, preferably over multiple well timed doses with near perfect adherence. Obtaining such data requires well organized efforts and is high burden for both investigators and participating subjects. This makes acquiring a robust Bayesian model for use in dose personalization difficult. For this reason, our framework is not intended to replace prospective evaluation of personalized medicine programs; rather it is intended to estimate relative performance given existing evidence so that the most promising modes of personalization can be identified for potential implementation and further study.

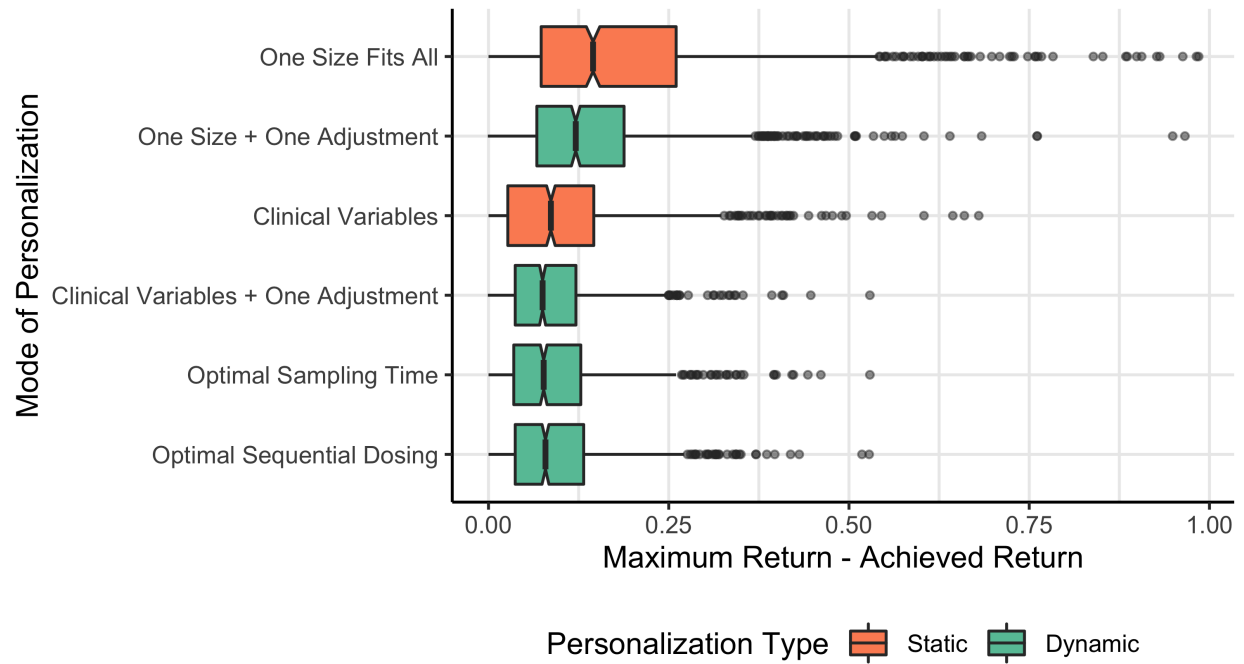


Figure 2: Boxplots of the *regret* – the difference between the largest possible return and the achieved return for each of the 1000 simulated patients. patients who achieve a return close to their maximum possible return have a regret near 0, while patients who achieve a return less than their maximum possible have larger regrets, with the largest possible regret being 1.

## 6 Conclusions

As expected, modes of personalization that use more information result in lower regret (larger achieved rewards.) The static Clinical Variables mode balances relatively low implementation burden with high reward. However, there is right skew in the distribution of regret, with some ‘outliers’ who are at risk of obtaining less than half of their best possible return. If avoiding this risk is important, the Clinical Variables + One Adjustment mode may be preferable, even though it imposes additional burden.

The Optimal Sampling Time and Optimal Sequential Dosing modes use the same information as Clinical Variables + One Adjustment, but impose more burden on the patient and clinic. Both require samples be taken at specified times, and the second uses a more complex optimization procedure. Neither of these improved performance beyond the simpler modes in our study. There are two characteristics of our study that may explain this result. First, the clinical variables used are known to affect the pharmacokinetics of apixiban and are useful for predicting concentrations for static personalization, hence their use alone makes it possible to choose good doses. In other settings where clinical variables are not as predictive, we would expect dynamic personalization to have a bigger advantage. Second, the elimination rates  $k_e$  in our study were relatively high. This means that the effect of an initial dose on levels at the time subsequent doses are taken (i.e., a day later) is relatively small, so that doses can be optimized largely independently. If this were not the case, optimization using Q-learning would be expected to be more important to ensure that initial doses were not too large to successfully adapt later.

## 7 Implications

Any decision to implement personalized medicine must assess the costs and benefits of doing so. Despite the potential for personalized medicine to reduce health care costs [15, 16], the cost of patient testing and monitoring, personnel, and training required to operate a personalized medicine clinic carry a burden, and it is not yet clear in what circumstances personalized medicine is cost effective. In their 2019 scoping review of personalized medicine cost effectiveness, Kasztura et al [17] found that willingness-to-pay thresholds vary wildly from country to country (citing that cost per quality adjusted life year (QALY) for some modes of personalized medicine range from \$20,000 USD per QALY in Europe and the United Kingdom to \$200,000 USD per QALY in the United States). This high variability means the burden required for start up may result in a positive return on investment in some areas but not others. This variability should prompt would be adopters to more closely examine whether taking on the initial burden is worth the result.

Others have noted that much work on personalized medicine has not centred the needs, constraints, and utilities of the patient [18, 19]. Patients can be burdened by frequent followup for clinical measurement (as in the case with warfarin), be burdened by costly expenses related to obtaining care, or may be more risk adverse/tolerant than the “typical” patient. As an example, transportation has been found to be a large financial burden for patients receiving cancer treatment [20], and continues to burden patients, with a 2020

study finding that the cost of parking alone can climb as high as \$1600 over the course of treatment in the United States [21]. Additional visits to a clinic have the potential to further burden patients by requiring them to miss a day of work, and find means of childcare during their absence (if necessary). Incorporating patient preferences and reducing the burden of personalization on the patient can result in sustained adherence [22], thereby increasing effectiveness and further preventing adverse events.

The complexity of balancing these burdens means that Implementation decisions made at the organizational level need to attend to a broad array of evidence and contextual factors. Know4Go [23] is one framework for explicitly considering factors from expanded domains of influence surrounding adoption of new technologies/interventions in a healthcare setting (like a clinic or hospital). These expanded domains of influence include: social, legal, ethical, environmental/institutional, political, entrepreneurial/innovative, research opportunity, and reversibility factors in conjunction with objective evidence of benefits versus risks, systematic review, and costs. Broadly, once evidence has been synthesized through systematic review and/or meta-analysis, the evidence is contextualized to local healthcare system perspective. Evidence is converted onto a benefit scale, derived from the number of patients likely to benefit from adoption of the technology/intervention. Budget impact of the adoption is estimated using costing data from the hospital/clinic, and new technologies can be triaged according to their impact and cost.

Policy decisions around personalization are complex. They carry burden for health systems and patients that vary widely by context. While there are frameworks like Know4Go for navigating these decisions, applying them requires quality evidence for the potential benefits of different kinds of personalization, even for deciding on potential pilot studies. Our framework can produce evidence for the potential effectiveness of a range of modes of personalization to inform organization-level decisions surrounding the investigation and implementation of personalized medicine programs that reduce cost, respect burden, and improve outcomes.

## References

- [1] Bridget L Morse and Richard B Kim. Is personalized medicine a dream or a reality? *Critical reviews in clinical laboratory sciences*, 52(1):1–11, 2015.
- [2] Theodore John Wigle, Brandi Povitz, Wendy Teft, Robin Legan, John Gordon Lenehan, Markus Gulilat, Stephanie Nevison, Justin Kritzing, Veera Punaganty, Denise Keller, et al. Prospective cohort study of the impact of hospital-wide dihydropyrimidine dehydrogenase (dpyd) genotype testing for fluoropyrimidine-based chemotherapy on adverse events and hospital costs. *American Society of Clinical Oncology*, 2019.
- [3] Inna Y Gong, Rommel G Tirona, Ute I Schwarz, Natalie Crown, George K Dresser, Samantha LaRue, Nicole Langlois, Alejandro Lazo-Langner, Guangyong Zou, Dan M Roden, et al. Prospective evaluation of a pharmacogenetics-guided warfarin loading and maintenance dose regimen for initiation of therapy. *Blood, The Journal of the American Society of Hematology*, 118(11):3163–3171, 2011.
- [4] Kristine Zhang, Yuanheng Wang, Jianzhun Du, Brian Chu, Leo Anthony Celi, Ryan Kindle, and Finale Doshi-Velez. Identifying decision points for safe and interpretable reinforcement learning in hypotension treatment, 2021.
- [5] Barbara E Engelhardt, Niranjani Prasad, Li-Fang Cheng, Corey Chivers, Michael Draugelis, Kai Li, and Finale Doshi-Velez. The importance of modeling patient state in reinforcement learning for precision medicine. 2021.
- [6] Janet Martin, Avtar Lal, Jessica Moodie, Fang Zhu, and Davy Cheng. *Hospital-Based HTA and Know4Go at MEDICI in London, Ontario, Canada*, pages 127–152. Springer International Publishing, Cham, 2016. ISBN 978-3-319-39205-9.
- [7] Bibhas Chakraborty. *Statistical methods for dynamic treatment regimes*. Springer, 2013.
- [8] Marie Davidian, Brian Everitt, Ron S. Kenett, Geert Molenberghs, Walter Piegorsch, and Fabrizio Ruggeri, editors. *Wiley StatsRef*, chapter Reinforcement Learning. Wiley, 2017. 3000 words.
- [9] A.A. Tsiatis, M. Davidian, S.T. Holloway, and E.B. Laber. *Dynamic Treatment Regimes: Statistical Methods for Precision Medicine*. Chapman & Hall/CRC Monographs on Statistics & Applied Probability. CRC Press, 2019. ISBN 9781498769785. URL <https://books.google.ca/books?id=FD0PEAAAQBAJ>.
- [10] James O Berger. *Statistical decision theory and Bayesian analysis*. Springer Science & Business Media, 2013.

- [11] A Demetri Pananos and Daniel J Lizotte. Comparisons between hamiltonian monte carlo and maximum a posteriori for a bayesian model for apixaban induction dose & dose personalization. In *Machine Learning for Healthcare Conference*, pages 397–417. PMLR, 2020.
- [12] Markus Gulilat, Denise Keller, Bradley Linton, A Demetri Pananos, Daniel Lizotte, George K Dresser, Jeffrey Alfonsi, Rommel G Tirona, Richard B Kim, and Ute I Schwarz. Drug interactions and pharmacogenetic factors contribute to variation in apixaban concentration in atrial fibrillation patients in routine care. *Journal of thrombosis and thrombolysis*, 49(2):294–303, 2020.
- [13] Rommel G Tirona, Zahra Kassam, Ruth Strapp, Mala Ramu, Catherine Zhu, Melissa Liu, Ute I Schwarz, Richard B Kim, Bandar Al-Judaibi, and Melanie D Beaton. Apixaban and rosuvastatin pharmacokinetics in nonalcoholic fatty liver disease. *Drug Metabolism and Disposition*, 46(5):485–492, 2018.
- [14] Wonkyung Byon, Samira Garonzik, Rebecca A Boyd, and Charles E Frost. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. *Clinical pharmacokinetics*, 58(10):1265–1279, 2019.
- [15] Margot de Looft, Bob Wilffert, Cornelis Boersma, Lieven Annemans, Stefan Vegter, Job FM van Boven, and Maarten J Postma. Economic evaluations of pharmacogenetic and pharmacogenomic screening tests: a systematic review. second update of the literature. *PloS one*, 11(1):e0146262, 2016.
- [16] Fatiha H Shabaruddin, Nigel D Fleeman, and Katherine Payne. Economic evaluations of personalized medicine: existing challenges and current developments. *Pharmacogenomics and personalized medicine*, 8:115, 2015.
- [17] Miriam Kasztura, Aude Richard, Nefti-Eboni Bempong, Dejan Loncar, and Antoine Flahault. Cost-effectiveness of precision medicine: a scoping review. *International journal of public health*, 64(9):1261–1271, 2019.
- [18] Wolf Rogowski, Katherine Payne, Petra Schnell-Inderst, Andrea Manca, Ursula Rochau, Beate Jahn, Oguzhan Alagoz, Reiner Leidl, and Uwe Siebert. Concepts of ‘personalization’ in personalized medicine: implications for economic evaluation. *Pharmacoeconomics*, 33(1):49–59, 2015.
- [19] Antonello Di Paolo, François Sarkozy, Bettina Ryll, and Uwe Siebert. Personalized medicine in europe: not yet personal enough? *BMC health services research*, 17(1):1–9, 2017.
- [20] Peter S Houts, Allan Lipton, Harold A Harvey, Barbara Martin, Mary A Simmonds, Richard H Dixon, Santo Longo, Thomas Andrews, Robert A Gordon, John Meloy, et al. Nonmedical costs to patients and their families associated with outpatient chemotherapy. *Cancer*, 53(11):2388–2392, 1984.
- [21] Anna Lee, Kanan Shah, and Fumiko Chino. Assessment of parking fees at national cancer institute–designated cancer treatment centers. *JAMA oncology*, 6(8):1295–1297, 2020.



- [22] Rachel A Elliott, Judith A Shinogle, Pamela Peele, Monali Bhosle, and Dyfrig A Hughes. Understanding medication compliance and persistence from an economics perspective. *Value in health*, 11(4):600–610, 2008.
- [23] Janet Martin, Avtar Lal, Jessica Moodie, Fang Zhu, and Davy Cheng. Hospital-based hta and know4go at medici in london, ontario, canada. In *Hospital-Based Health Technology Assessment*, pages 127–152. Springer, 2016.
- [24] Michael Betancourt. A conceptual introduction to hamiltonian monte carlo, 2018.
- [25] Steve Brooks, Andrew Gelman, Galin Jones, and Xiao-Li Meng. *Handbook of markov chain monte carlo*. CRC press, 2011.
- [26] Aki Vehtari, Andrew Gelman, Daniel Simpson, Bob Carpenter, and Paul-Christian Burkner. Rank-normalization, folding, and localization: An improved r-hat for assessing convergence of mcmc. *arXiv preprint arXiv:1903.08008*, 2019.
- [27] Andrew Gelman, Daniel Lee, and Jiqiang Guo. Stan: A probabilistic programming language for bayesian inference and optimization. *Journal of Educational and Behavioral Statistics*, 40(5):530–543, 2015.