

# Using Stochastic Control Methods and Pharmacokinetics to Individualise Drug Therapy:



## A Case Study with the Enzyme Inhibitor Imatinib.

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### Introduction

The list of drugs which exist in healthcare to treat various conditions and diseases is vast with new drugs added every year. Many drugs cause adverse events which are dose dependent, consequently there is a need to identify the correct dose for the patient which minimises the chances of these adverse events developing, while at the same time maximising the efficacy of the drug. However, finding the correct dose is complicated by the inter-individual variability in the pharmacokinetics of each individual patient. A drug dose algorithm is required to account for all the sources of variability in drug dose response.

### Aim

To develop an algorithm that will enable greater individualisation of drug therapy for patients, providing informed doses which aim to induce therapeutic plasma concentration levels as quickly as possible

### Model Developed

The model is based upon a recent new parameterisation of a system of stochastic differential equations proposed by Delattre et al. at PAGE 2011. For imatinib we used a one compartment bolus PK model:

$$\frac{dCA_t}{dt} = -k_a CA_t \quad \frac{dC_t}{dt} = -k_e C_t + \frac{k_a}{V_d} CA_t \quad \frac{dk_a}{dt} = (k_a^* - k_a) + d\rho_t \quad \frac{dk_e}{dt} = (k_e^* - k_e) + d\rho_t$$

where  $CA_t$  is the oral bolus compartment,  $C_t$  is the central plasma concentration compartment,  $k_a$  is the constant of absorption,  $k_e$  is the constant of elimination with their respective estimates  $k_a^*$ ,  $k_e^*$ ,  $V_d$  is the volume of distribution and  $d\rho_t$  is the Wiener process.

### Methods

The dose algorithm is developed using stochastic control methods, which utilising post population pharmacokinetic data to make response estimates, which can then be compared against noisy measurements of the response from each specific patient. Using noisy measurements to update the analysis allows the system to become interactive; ultimately seeking to reduce the overall uncertainty of prediction and providing dose estimates which are tailored to the patient's requirements.

### Control

The control is set to judge 'performance' of a dosage regimen by squaring the distances from the Therapeutic Trough Level (TTL) of 1000ng/ml (Picard et al., 2007 and Larson et al., 2008) over the seven days of the dosage regimen. The dosage regimen which causes, in simulation, the smallest sum of squared deviation from TTL is deemed the recommended dosage regimen for the patient.

### Results

Patient ID	Current		Revised	Average Deviance from TTL (ng/ml)	Mean Dosage Difference (mg)
	Daily Dose (mg)	Average Deviance from TTL (ng/ml)	Seven Day Dosage Regimen (daily mg)		
28	400	-400	800, 700, 700, 700, 700, 700, 700.	30	314
54	400	-328	700, 600, 600, 600, 600, 600, 600.	13	214
56	400	-442	800, 700, 700, 700, 700, 700, 700.	-43	314
78	400	-489	800, 800, 800, 800, 800, 800, 800.	0	400
91	400	453	200, 200, 300, 300, 300, 300, 200.	47	129
101	400	-512	800, 800, 800, 800, 800, 800, 800.	-54	400
118	400	-504	800, 800, 800, 800, 800, 800, 800.	-29	400
119	800	-13	No revision needed		
122	800	432	400, 500, 600, 600, 500, 600, 600.	9	143
124	400	-244	600, 500, 500, 500, 500, 500, 500.	-50	114
244	400	-13	No revision needed		
328	400	21	No revision needed		

Table 1: Dosage Regimens for Each Patient

From the set of twelve patients included in the study, Table 1 demonstrates how the drug dosing algorithm has determined that all but three patients require dosage adjustment. None of the revised dosage regimens return the patient to their original standard dosing. This suggests that the standard 400mg dose of imatinib does not bring the majority of patients to the TTL of 1000ng/ml.

If the patient's who were shown to require a revised dosage regimen were to stay on their standard daily doses then we see that they will be up to 48.9% away from the TTL, further seven of the ten patients will be between 24.4-48.9% below the TTL which would lead to doubts as to whether the drug is indeed providing sufficient effectiveness.

Of the revised dosage regimens the largest average deviation is 5.4% below TTL which demonstrates that the drug dose algorithm is trying to bring the patient into TTL.

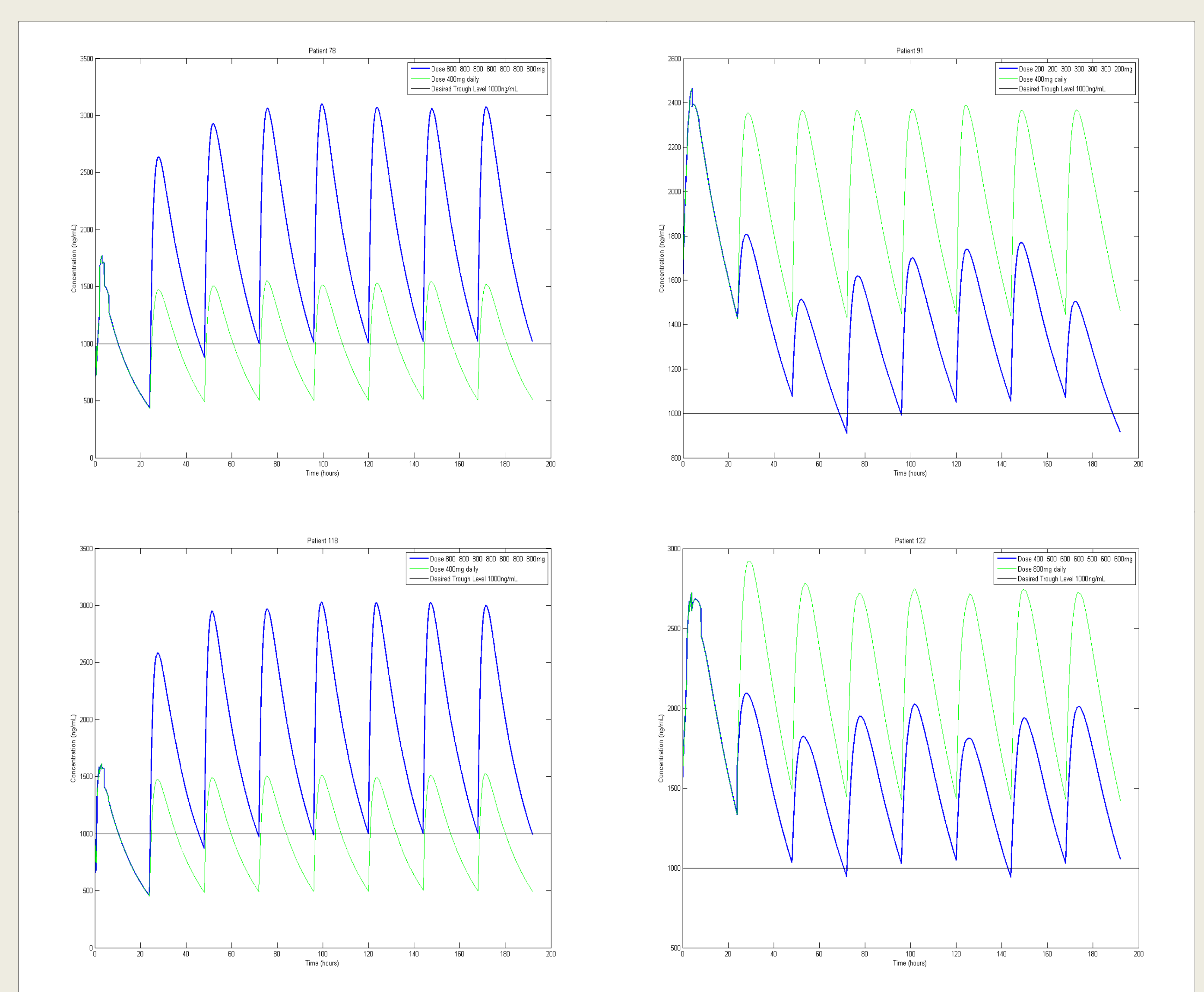


Figure 1: Concentration time curves for patients 78, 91, 118 and 122 on the Seven Day Dosage Regimens given in Table 1.

### Conclusions

From the results we see that prospective dosage adjustments are informed if ran through this drug dose algorithm which incorporates simulation and stochastic control. Another advantage of the algorithm is that it is able to be updated at any time when a plasma concentration sample from a patient becomes available and a new dosage regimen of any length can be derived to meet a TTL.

There is a need for individualised dosing regimens that maximise efficacy of the drug, whilst at the same time minimising the risk of adverse drug reactions; results from this case study show that revised regimens derived using stochastic control methods actively seek to bring a patient taking Imatinib to a therapeutic trough level. The algorithm can be applied to dose any patient on a drug which has a developed pharmacokinetic model with an appropriate therapeutic target.