Development of an application for individualized Warfarin treatment

Independent Project in Engineering Physics

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Abstract

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A problem with the widely used anticoagulant medicine Warfarin has always been that the therapeutic dose varies from person to person and that there has not been any methods to estimate individually-based dosing regimens. By using a new population model describing the relationship between Warfarin dose and INR (international normalized ratio) response for different individuals based on their age, weight and genotypes, a user friendly, dose estimating program has been developed in Java. The application estimates the INR given the individual parameters and dosing, but it's also possible to estimate the predicted dose given the desired INR. The application makes it possible for others to take part of the model, and to give a more individualized Warfarin treatment in clinical practice.
1 Introduction

1.1 Background

The anticoagulant ("blood thinning") medicine Warfarin inhibits the activation of several coagulation factors and thereby reduce the blood’s ability to coagulate. The intention is to prevent blood clots in veins and in the heart where they can travel to the brain and cause a stroke. Patients with atrial fibrillation and patients who have artificial heart valves implanted are typical candidates for the drug. The full effect of Warfarin is not reached until several days or even weeks into the therapy and it is not unusual to give a higher dose in the beginning until the desired effect is obtained and a maintenance dose can be administrated. The drug is widely used but it has to be monitored closely since the effect varies between individuals. Blood tests have to be performed regularly in order to set the correct maintenance dose. \(^1\)

INR (International Normalized Ratio) is used to measure the effect of Warfarin. It is derived from a laboratory test by taking the quota between the patients coagulation time over the normal coagulation time. In a healthy person the INR is approximately 1.0 and a higher INR means that it takes longer time for the blood to clot. An INR of 2.0 means that it takes twice the time for the blood to coagulate than it normally does. When a patient takes Warfarin a typical desired INR value is between 2.0 and 4.0, depending on the patient’s condition. A too high INR can lead to spontaneous bleeding and it is therefore important to monitor a patient’s INR by taking blood tests regularly. \(^2\)

Besides used as a medicine Warfarin is also used as a rat poison. This emphasizes the importance of monitoring a patient’s INR. In Swedish clinical practise the medicine Warfarin is most commonly known as Waran and is distributed in 2.5 mg tablets. They can be divided into four pieces which means that the dose can only be given in whole and quarter tablets.

Warfarin has been used for many decades within the health care system. A problem has always been that the therapeutic dose varies from person to person and that there have not been any methods to estimate individually-based dosing regimens. Instead, the patient gets a standard dose and then returns within a few days to measure the anticoagulant effect (INR), and based on the current INR value the dosage is modified to reach the desired INR. In recent years there has been some development, scientists have found variation in two genes named \(CYP2C9\) and \(VKORC1\) which can help determine the required dose. Anna-Karin Hamberg at the Department of Medical Science in Uppsala has developed a population model in NONMEM (software package for population pharmacokinetic modelling) that describes the relationship between Warfarin dose and a patients INR. The model includes the parameters clearance \((CL)\), the efficiency to clear the drug from the body) and \(EC_{50}\) (concentration producing 50% of the maximum effect). The clearance is dependant on age, weight and the \(CYP2C9\) genotype whilst \(EC_{50}\) is influenced by the \(VKORC1\) genotype. Hamberg derived the model using data from adult patients treated with Warfarin.

1.2 Problem

Hamberg’s model, which is derived and described in NONMEN, works but is limited. The program requires a certain knowledge and it is very time-consuming to do new calculations. But more importantly it is a licensed software that costs money. If the model is to be spread and tested it has to be transferred to a more user-friendly and free software.

1.3 Goal

The goal is a new graphical user interface (GUI) built with Java Swing components, that has an implemented ODE-solver which can solve the differential equations explaining the model. Any clinicians should be able to use the program with only basic computer knowledge and without assistance. The inputs parameters should easily be identified and the results displayed within seconds. If the model is proved accurate it may eventually be implemented into the health care system.

\(^1\)Medical products agency, Warfarin, 2012.
\(^2\)Heart Rhythm Society, INR, 2012.
The program should be able to estimate INR on a specific patient based on a certain dose, and also be able to estimate a therapeutic dose based on a given INR-interval. The estimated INR should be displayed as the mean value over the latest dose interval and the estimated dose as numbers in terms of mg/day, mg/week and the approximate number of whole and quarter 2.5 mg tablets/week. Both will have a graphical view of how the INR changes from the start to the end of the treatment.

1.4 Purpose

The program is primarily intended as a tool to show the model describing the relationship between Warfarin dose and INR response and how it can be used in the health care system. It will be uploaded to a server so that clinicians can download and possibly use it as a dose estimating tool.

2 Theory

The model developed by Hamberg et al. which is to be implemented in the GUI is a KPD (kinetic/pharmacodynamics) model and which describes the relationship between Warfarin dose and INR response.

2.1 KPD model

The KPD model is represented in figure 1 where compartment A represents the amount of drug in the body at any time after one or more administrated doses. The first-order rate constant $k_e$, governs the elimination of the drug from A but also the distribution of the drug to the site of action. The constant $k_e$ can be derived from the ratio of the parameters clearance and volume of distribution ($k_e = \frac{Cl}{V}$). The dose rate $DR$ together with parameters $E_{max}$ and $EDK_{50}$ (dose rate that leads to 50% inhibition) leads to inhibition of coagulation. The remaining fraction of activated coagulation factors is labelled $E$.

![Diagram of the KPD model](image)

Figure 1: A schematic picture of what the body does to the drug (pharmacokinetics) and what the drug does to the body (pharmacodynamics). CL, clearance; EDK50, dose rate that leads to 50% inhibition; INR, international normalized ratio; MTT, mean transit time for E.

The general form of the model is given by the following set of equations.

\[
\frac{dA}{dt} = -KDE \cdot A \\
DR = KDE \cdot A \\
EFF = \frac{E_{MAX} \cdot DR}{EDK_{50} + DR} \\
\frac{dE}{dt} = (1 - EFF) \cdot \frac{A}{MTT} - E \cdot \frac{A}{MTT}
\]

(1)

The initial conditions of $\frac{dA}{dt}$ and $\frac{dE}{dt}$ are 0 respectively 1. $EFF$ represents the inhibitory effect on VKORC1, the target enzyme for Warfarin. $E_{MAX}$ represents the maximum degree of inhibition of the coagulation factors that is caused by Warfarin. It can’t be estimated and is explicitly set to 1 (100%)

Hamberg et. al., 'A Pharmacometric Model Describing the Relationship Between Warfarin Dose and INR Response With Respect to Variations in CYP2C9, VKORC1, and Age', 2010.
inhibition). $EDK_{50}$ is the product between $CL$ and $EC_{50}$. Both $CL$ and $EC_{50}$ are functions depending on their associated genotype. A prediction for the observed INR is given by

$$INR_{PRED} = INR_{BASE} + INR_{MAX} \cdot (1 - (C1_3 + C2_3)/2)$$ (2)

where $INR_{BASE}$ is the INR at baseline (before treatment initiation), and $INR_{MAX}$, the theoretical maximum INR, was set to 20. $C1_3$ and $C2_3$ represent the values in the last compartments in the coagulation chains (See figure 1). Each chain is defined in terms of three differential equations. The three compartments of C1 is for example defined as:

$$\frac{dC1_1}{dt} = (1 - EFF) \cdot \frac{3}{MTT_{C1}} - C1_1 \cdot \frac{3}{MTT_{C1}}$$

$$\frac{dC1_2}{dt} = C1_1 \cdot \frac{3}{MTT_{C1}} - C1_2 \cdot \frac{3}{MTT_{C1}}$$ (3)

$$\frac{dC1_3}{dt} = C1_2 \cdot \frac{3}{MTT_{C1}} - C1_3 \cdot \frac{3}{MTT_{C1}}$$

3 Methods

The first step is to implement Hamberg’s model in MATLAB. It offers a lot of tools for solving the differential equations, plotting and vector matrix multiplications which makes it good to start with. The differential equations will be solved by using Heun’s method and the results will then be compared with the results given by NONMEN. Then the code is to be transferred from Matlab into a Java Swing application using NetBeans, that provides a graphical user interface independent of platform.

3.1 MATLAB

MATLAB is a numerical computing environment developed by MathWorks that allows matrix and vector operations, plotting of functions and data and implementation of algorithms. MATLAB also has a lot of numerical tools for solving all sort of mathematical problems like differentials equations, integrals, derivatives etc. MATLAB is intended primarily for numerical computing and mostly used by academics. To execute a Matlab program file (.m-file), MATLAB need to be installed and therefore the file cannot be executed on a computer without MATLAB. It is a proprietary product of MathWorks and requires a license.

3.2 Java

Java is a programming language originally developed by Sun Microsystems (which has merged into Oracle Corporation). Java is known to be a general-purpose, class-based, object-oriented language that is designed to have as few implementation dependencies as possible. The intention is to let application developers ”write once, run anywhere”, meaning that making a program that runs on one platform does not need to be recompiled to run on another. Java is currently one of the most popular programming languages in use.4

3.3 NetBeans

NetBeans refers to both a platform framework for Java desktop applications, and an integrated development environment (IDE) for developing with Java. The NetBeans Platform is a reusable framework for Java Swing applications. It provides the ”plumbing” that, before every developer had to write themselves - connecting actions to menu items, toolbar items and keyboard shortcuts, window management and so on. All of this is provided by NetBeans Platform and the user does not need to manually code all these or other basic feathers, which saves a lot of time and work. The IDE is an open source integrated development environment supporting development of all Java Application types.

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3.4 Heun’s method

Heun’s method is a numerical procedure for solving ordinary differential equations (ODEs) with a given initial value on the given form:

\[ y'(t) = f(t, y(t)), \quad y(t_0) \]  

Heun’s method is fast, easy to implement using vectors and stable for the given equations (see equations 1 and 3). The procedure for calculating the numerical solution to an ODE via Heun’s method is:

\[ \tilde{y}_{i+1} = y_i + hf(t_i, y_i) \]
\[ y_{i+1} = y_i + \frac{h}{2}(f(t_i, y_i) + f(t_{i+1}, \tilde{y}_{i+1})) \]

4 Results

The end result was a Java Application that can estimate INR or dose based on given covariates. The calculated values are illustrated in both a plot and in a text field. The GUI was built using Java Swing components in the Netbeans IDE. But before the application could be made, a first trial version was programmed and evaluated in Matlab.

4.1 The Matlab version

The first result was a lite version written in Matlab that only had hard coded individual parameters. Since the purpose only was to demonstrate that it was possible to calculate the differential equations using a self-made ODE-solver there was no need to integrate more advanced options than simply "run".

As can be seen in figure 2 the Matlab version displayed both the calculated INR and the drug amount in the body. The latter was eventually removed from the plot since it provided no useful information to the user. Once the Matlab version gave the same results as the NONMEN calculations the programming towards a Java Application were commenced.
4.2 Java Application

The final application has two settings, either estimate INR or estimate a dose. Besides the main window which is initially displayed the program also has several other options such as Advanced Settings, Set Dose, Help Section and About.

4.2.1 Estimate INR

When estimating INR the program will calculate a patient’s steady state INR when being treated with a specific dose of Warfarin and during a specific time period. We decided that when INR have reached steady state the application will display the mean value over the latest dose interval. If the patient have not yet reached steady state, it will instead display the INR value 16 hours after latest treatment.

Figure 3: Given a patient that is 60 years old, weighs 70 kg and has the genotypes *1/*3 and A/G, a 3.7 mg dose of Warfarin would give an estimated INR of 2.65.

The program can be seen in figure 3 estimating an INR for a 3.7 mg Warfarin dose. When the user have specified a method the first thing to do is to input individual parameters such as age, weight and genotype. If CYP2C9 or VKORC1 genotype is unknown the option missing should be chosen and the program will use the most common genotypes (*1/*1 and A/G). These first parameters have to be specified every time. Depending on which method is chosen different input boxes are enabled. When estimating INR the user have to specify a dose, here is also the option to use starting doses which essentially is used to reach the desired INR faster.

In order to use dose intervals the Starting doses box must be checked and then the Set doses button is enabled and can be clicked on. Now there is the option to individually choose the first seven doses in the new window that can be seen in figure 4. There is the choice not to insert a number in any of the boxes and the program will interpret that as to use the standard dose that is specified at the Dose option. It is possible to specify a target INR interval when estimating INR but it is not required for the program to work. The interval in this case will function as a way to better read the plot and help the user to adjust the dose in order to reach the desired INR. The Dose interval field is initially set to 24 hours (1 dose per day) and the last input specifies the number of doses a patient is to be treated with.

Figure 4: Starting dose options.
4.2.2 Estimate dose

When estimating a dose to reach a target INR the usual approach is to specify an interval for the INR to be inside. Since the INR value is changing during the time between treatments there’s no point in trying to reach a specific value, that is also a reason why the target INR is specified as an interval.

![Warfarin Dose Calculator](image)

**Figure 5:** Estimating a Warfarin dose of 3.88 mg/day in order to reach the specified target INR in the interval 2.5 - 3.0. The patient is 60 years old, weighs 70 kg and has the genotypes *1/*3 and A/G.

As can be seen in figure 5 the result that is displayed in the lower left corner in red is given in three formats. First the dose per chosen interval and the corresponding dose per week. The third line displays the number of 2.5 mg tablets per week that is closest to the estimated dose. Since the tablets only can be divided into quarters it is only relevant to give the answer in whole and quarter tablets.

To calculate what dose it will take to reach a specific INR (mean of an interval) the option *Estimate dose* should be chosen. When changing to that method the options *Dose* and *Number of doses* are disabled as can be seen in figure 5. The program will start by guessing a dose and calculate the INR after a 100 doses (to be certain we reach steady state). To make the next step faster the program will calculate how many doses it takes to reach steady state and then it will only have to use so many doses in future calculations. It will either reduce or increase the dose depending on if the reached INR is lower or higher than the mean value of the specified interval. When the mean value of the calculated INR is equal to the mean of the target INR interval the program stops and displays the dose corresponding to that INR in the lower left corner. The result is shown as drug amount per dose interval, as drug amount per week and the related number of 2.5 mg tablets per week.

5 Discussion

The results obtained from the Java Application differs slightly from those given by NONMEN. The error occurs at most in the third decimal and is in this case negligible compared to other approximations made in the model. NONMEN uses the fourth order ODE solver Runge-Kutta to solve the differential equations, which is of higher accuracy than Heun’s method (second order). The error is due to the different methods that are being used.
The small loss in precision is offset by the simplicity and increased calculation speed. The most important result however is that it is now possible for anyone to download the application, test and evaluate Hamberg’s model.

6 Conclusion

A new graphical user interface has been built that describes the relationship between Warfarin dose and INR response according to Hamberg’s model. The transfer from NONMEN to a Java Application was successful and the proprietary software NONMEN is no longer needed. The new application is free, user-friendly and independent of platform. It is now possible for others to take part of Hamberg’s model and to give a more individualized Warfarin treatment in clinical practice.

7 Bibliography


