Application of Simcyp's R Library Package in Simulation and Prediction of Metoprolol Compliance Using a Single Plasma Concentration Sample

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Introduction

It has been previously demonstrated that Simcyp can be used for the simulation and prediction of compliance scenarios.[1] This involved the creation of several data sets using results output from Simcyp simulations, which were then analysed in R using methods proposed by Barriere *et al* to predict the compliance scenario of a patient given their last sampled concentration.[2]

It would be more convenient, when analysing such data, to be able to run Simcyp directly from the software package (e.g. R or Matlab) being used for the analysis.

Objectives

- To develop a Simcyp R library package allowing the simulation of virtual clinical trials using the Simulator via R.
- To demonstrate the use of Simcyp's R package by generating plasma concentration-time profiles of Metoprolol in two populations: CYP2D6 Extensive Metabolisers (EM) and CYP2D6 Poor Metabolisers (PM).
- To predict the compliance of Metoprolol from a patient's single PK sampling point, and to determine the optimal time point for correctly identifying the compliance scenario in each population

Methods

We developed an R package to enable running Simcyp and generating output data within R. Prior *in vitro* and physicochemical parameters for Metoprolol and the Healthy Volunteer population were used to generate plasma concentration profiles of 500 CYP2D6 EM and PM patients over 6 days using a 100mg Metoprolol BID dose. Figure 1 shows the R code used to generate these profiles.

The dose in the original Simcyp workspace was changed in R to accommodate different compliance scenarios and the workspace was then re-run to generate new plasma concentration profiles. In all simulations the first 10 doses were always taken and the final two doses were one of the following scenarios: full compliance, missing the first dose, missing the second dose, taking both doses together and missing both doses. Figure 2 shows the R code used to change the dose in the workspace to accommodate different compliance scenarios.

```
#1. Specifies location of the Simcyp Workspace
SetWorkspace("")

#2. Runs Simcyp from R
Simulate()

#3. Outputs plasma concentration profiles for individual 1
Time <- GetProfile(0, -1, 0)
Conc <- GetProfile(6, 0, 0)
```

Figure 1: R code to generate Concentration-time Profile from Simcyp

```
#4.Changing dose 11 and 12 to zero
SetDose("idDose", 0, 10, 0)
SetDose("idDose", 0, 11, 0)
Simulate()
```

Figure 2: Changing doses in workspace and re-running Simcyp

We applied the Barriere *et al.* method[2] to predict a patient's compliance using plasma concentrations taken at 0, 12, 24, 36, 48, 60 and 72 hours after the scheduled final dose.

The probability of a compliance scenario, s_j, given a plasma concentration, C_t, measured at time t was calculated using Bayes theorem:

$$P(s_j|C_t) = \frac{P(s_j)P(C_t|s_j)}{P(C_t)} \qquad (1)$$

where $P(s_j)$ is the prior probability of compliance scenario s_j, $P(C_t|s_j)$ is the probability of concentration C_t given compliance scenario s_j and $P(C_t) = \sum_j P(C_t|s_j)\,P(s_j)$ is the probability of concentration C_t.

Given the simulated plasma concentrations and the known compliance scenarios, the probability of each compliance scenario given the plasma concentration was calculated for all time points in both CYP2D6 populations.

For a given concentration, C_t, the predicted compliance scenario was determined using Bayes decision theory, where compliance scenario s_i is predicted if:

$$P(s_i|C_t) > P(s_j|C_t)\ for\ all\ j \neq i$$

The reliability of the predictions was assessed by calculating, for each compliance scenario and sampling time, the probability of correctly predicting the compliance scenario (true positive) and the probability of correctly rejecting the compliance scenario (true negative). A Receiver operating characteristic (ROC) curve was then plotted comparing true positives and false positives to determine the optimal sampling time for predicting a patient's compliance scenario in each population.

Results

Plasma concentration profiles of 100 patients were simulated for each compliance scenario by running Simcyp from R. As equal numbers of simulations were generated for each compliance scenario the posterior probability $P(s_j|C_t)$ was calculated for each compliance scenario and sampling time assuming a prior probability of $P(s_j) = 0.2$.

Figure 3 and Figure 4 present the probability of correctly predicting a compliance scenario (true positive) over time after the final scheduled dose for the CYP2D6 EM and PM populations respectively. In general, the probability of a true positive in the EM population was greatest at the time of the final dose for all scenarios and decreased over time. In the PM population the probability of a true positive is lowest at the time of the final dose, increases rapidly by 12 hours and then remains fairly constant over the remainder of the sampling times. In both populations, the probability of a true negative is high for all sampling times.

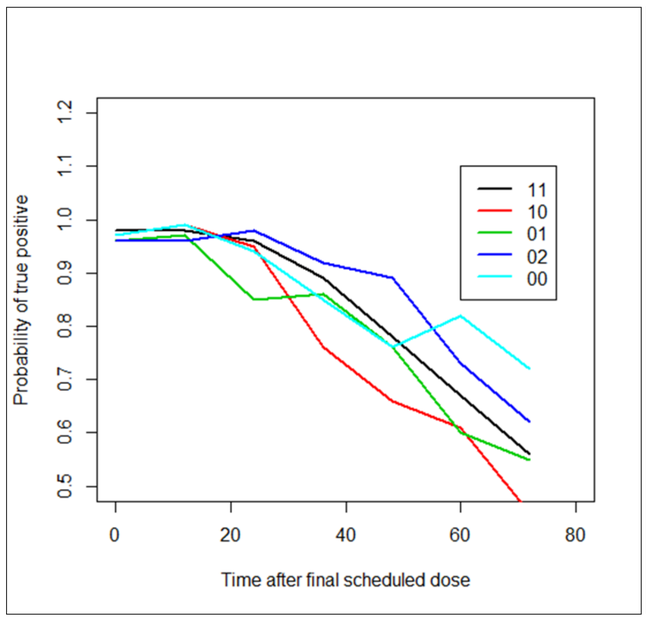

Figure 3: Probability of true positive over time (hours) by compliance scenario in CYP2D6 EM population

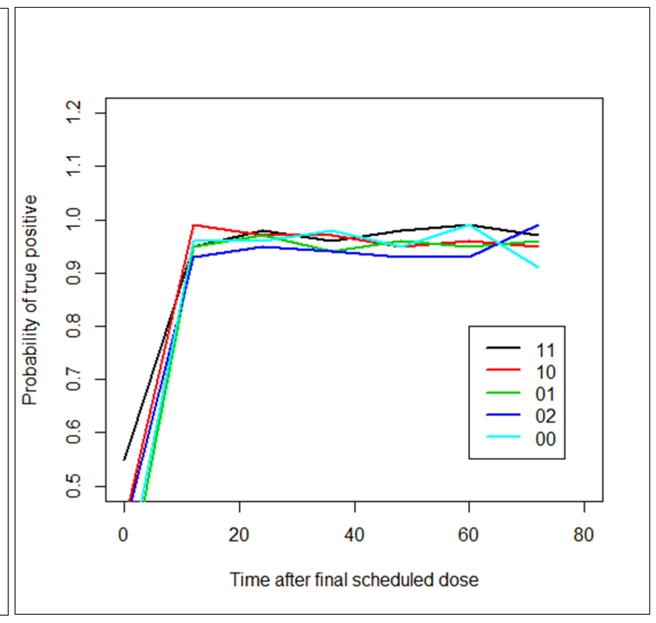

Figure 4: Probability of true positive over time (hours) by compliance scenario in CYP2D6 PM population

Figures 5 and 6 present the ROC curves for the CYP2D6 EM and PM populations respectively, where each point represents a sampling time for a compliance scenario. The diagonal line represents the points where the sum of the true positive probability and the true negative probability is equal and therefore all sampling times on this line are equivalent. For each compliance scenario the optimal sampling time is determined to be the point nearest the top left corner of the graph. The ROC curve shows that for the EM population, the concentration taken at 12 hours after the final dose is the best at predicting all compliance scenarios apart from where two doses are taken together when the 0, 12 and 24 hour samples (after the final dose) are all equally good predictors. For the PM population the optimal times varied by compliance scenario.

Tables 1 and 2 show the optimal sampling times for each compliance scenario for the CYP2D6 EM and PM population respectively, along with the probabilities of a true positive and a true negative. The probabilities in Tables 1 and 2 show that in the EM population the compliance scenario where both doses are missed (0,0) is the easiest to predict and in the PM population the compliance scenarios where either both does (1,1) are taken or the last one is missed (1,0) are the easiest to predict.

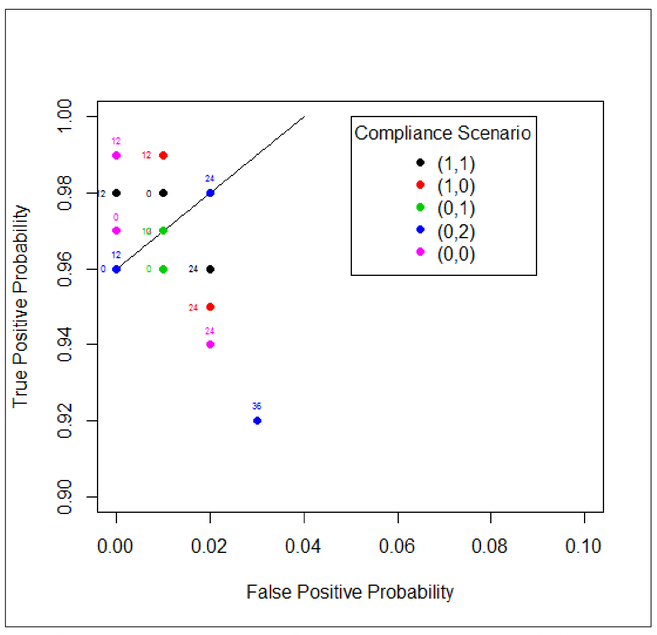

Figure 5: ROC curve for CYP2D6 EM population

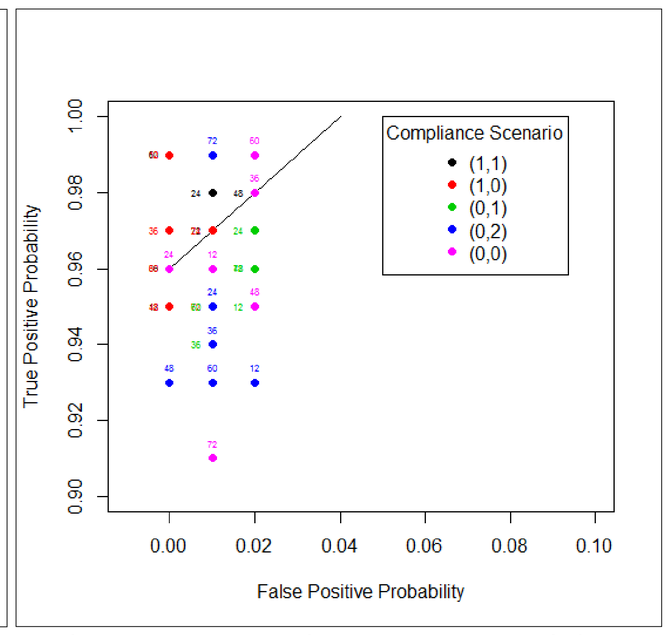

Figure 6: ROC curve for CYP2D6 PM population

Compliance Scenario	Sampling Time	P(+|+)	P(-|-)
11	12	0.98	1
10	12	0.99	0.99
01	12	0.97	0.99
02	0	0.96	1
	12	0.96	1
	24	0.98	0.98
00	12	0.99	1

Table 1: Probability of true positive and true negative for the optimal sampling times (after the final dose) of each compliance scenario in an EM population

Compliance Scenario	Sampling Time	P(+|+)	P(-|-)
11	60	0.99	1
10	12	0.99	1
01	24	0.97	0.98
02	72	0.99	0.99
00	60	0.99	0.98

Table 2: Probability of true positive and true negative for the optimal sampling times (after the final dose) of each compliance scenario in a PM population

Conclusion

An R library package for Simcyp has been developed that enables running virtual clinical trials from within R (which is also possible from within Matlab). This R package was used to show that the optimal time for predicting compliance after taking Metoprolol in the EM population is greatest for samples taken at 12 hours after the final dose for all scenarios. However, the optimal sampling time in the PM population depends on the compliance scenario.

References

1. Cain et al. Prediction of Rosiglitazone compliance from last sampling information using Population based PBPK modelling and Bayes theorem. *22nd PAGE meeting, Glasgow,* 11-14th June 2013 (poster presentation).

2. Barriere O et al., J Pharmacokinet Pharmacodyn. 2011 Jun 1;38:333-351.