Specification and Verification of Pharmacokinetic Models

YoungMin Kwon and Eunhee Kim

Abstract A model checking technique to specify and verify temporal properties of drug disposition changes is proposed. In pharmacokinetics and pharmaceutics, drug kinetics is often modeled as single or multiple compartment models. In this paper, a probabilistic temporal logic, called *iLTL*, is introduced to specify many interesting properties of drug kinetics. Given a specification, a computerized technique, called *model checking* [1], is used to check whether all drug disposition changes of a compartment model comply with the specification.

Key words: Computer-based medical systems, Computational systems biology

1. Introduction

Compartment models [5] have long been used as a mathematical model to describe the drug concentration level changes in our bodies. These models help our understanding of the relationship between drugs and their clinical effects. Thus, many compartment models exist for many types of drugs. However, compared to their importance, systematic evaluation methods on them are not well developed: most notably, they are manually examined by drawing graphs.

To address this problem, we propose to use a computerized systematic evaluation method based on iLTL model checking [2]. Specifically, the model checker searches for a trajectory of drug disposition changes that would violate the specification. Since the search completely explores every possible combination of doses, one can determine the existence of a satisfiable dose. Also, by checking the negated specification, a desirable dose can be found as a counterexample.

In the compartment model, the amount of drug leaving from one compartment to another is proportional to the amount of drug present in the first compartment. This relation makes the *memoryless* property: future drug dispositions will depend only on its current disposition. Because of this memoryless property, we can transform the compartment models to *Continuous Time Markov Chains* (CTMCs), and convert them again to *Discrete Time Markov Chains* (DTMCs) [3,7], which are

YoungMin Kwon: Microsoft Corp. Redmond, WA, USA. email: ykwon4@cs.uiuc.edu

Eunhee Kim: 2e consulting Corp. Seoul, Korea. email: keh@2e.co.kr

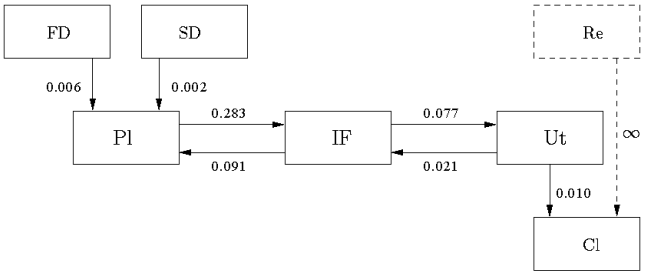

Fig. 1 CTMC model of an insulin compartment model. The boxes are the states and the numbers are the transition probability rates. The states represent: *FD*: unabsorbed fast acting drug, *SD*: unabsorbed slow acting drug, *Cl*: cleared drug, *Pl*: plasma, *IF*: interstitial fluid, *Ut*: site of utilization and degradation. *Re* is an additional state to make the specification in physical units

the formal model of iLTL. After a slight modification, the DTMCs can describe the changes of physical quantities instead of probabilities.

Throughout this paper, we explain our techniques with a three compartment model of insulin [6]. However, application to other compartment models should be straightforward.

2. Model

Compartment models are composed of one or more compartments that represent a group of tissues with similar blood flow and drug affinity, and drug transition rates between the compartments [5]. As the compartment models have the *memoryless property*, they can be naturally converted to Markov processes. The conversion steps to CTMCs are:

- The states of the CTMC are the compartments and a fresh sink state for the cleared drug.
- The transition probability rates between states are (1) the fractional turnover rates between the corresponding compartments and (2) the fractional drug elimination rates from the corresponding compartment to the fresh sink state.

With this representation, the probability that a CTMC is in a certain state is equal to the fraction of the drug in the corresponding compartment. Figure 1 shows a CTMC model for a compartment model of insulin−^{131}I. This compartment model is obtained by extending the three compartment model of Silvers *et al* [6]. This CTMC has a set of states {*Pl, IF, Ut, Cl, FD, SD, Re*}. Among the seven states, *Pl*, *IF*, and *Ut* states and the transition rates between them are from the original compartment model. *Cl* state is the fresh sink state. In order to compute the dose later in the example section, we extended the model with two more compartments: *FD* for unabsorbed fast acting drug and *SD* for unabsorbed slow acting

drug. We choose the rates from *FD* and *SD* to *Pl* such that the drug concentration at *Ut* reaches its maximum at about 2.5 *hours* and 4.5 *hours* respectively. *Re* state is introduced to make the specification in physical units instead of probability.

Given a CTMC *C*, one can compute a DTMC *D* whose *probability mass function* (pmf) changes are equal to the sampled pmfs of *C*. Let $\mathbf{R} \in \Re^{n \times n}$ be an infinitesimal generator matrix with $\mathbf{R}_{i,j}$ being the rate from state s_j to state s_i. Using a probability vector function $\mathbf{x}$: $\Re \rightarrow \Re^n$ with $\mathbf{x}(t)_i = \mathrm{P}[C(t)=s_i]$, we can simply write $\mathbf{x}(t)=e^{\mathbf{R} \cdot t} \cdot \mathbf{x}(0)$. Periodically sampling *C* with a period *T* results in a DTMC whose probability transition matrix is $\mathbf{M}=e^{\mathbf{R} \cdot T}$. Let a probability vector function $\mathbf{y}$: $\aleph \rightarrow \Re^n$ be $\mathbf{y}(k)_i = \mathrm{P}[D(k)=s_i]$, and let $t=k \cdot T$, then $\mathbf{x}(t)=e^{\mathbf{R} \cdot t} \cdot \mathbf{x}(0)=\mathbf{M}^k \cdot \mathbf{y}(0)=\mathbf{y}(k)$. Observe that $\mathbf{M}_{i,j}=\mathrm{P}[D(k+1)=s_i \mid D(k)=s_j]$, and *D* satisfies the Chapman-Kolmogrov equation: $\mathbf{y}(k+1)=\mathbf{M} \cdot \mathbf{y}(k)$.

Now, let us consider using physical units in the specification. The linearity of *C* and *D* plays a crucial role here. If we disregard the fact that $\mathbf{x}(t)$ and $\mathbf{y}(t)$ are pmfs, whose elements add up to one, and scale their initial pmfs, then their trailing pmfs would scale by the same amount because of the linearity. For example, if *d* (*mg*) of slow acting drug is administrated, then its initial state is $\mathbf{x}(0) = d \cdot [0, 0, 0, 0, 0, 1]^{\mathrm{T}}$ and $\mathbf{x}(t)_i$ is the fraction of the *d* (*mg*) of the drug in s_i at time *t*.

However, if we consider the fact that $\mathbf{x}(0)$ and $\mathbf{y}(0)$ are pmfs, then we cannot scale them arbitrarily: their sum must add up to one. In order to address this problem, we introduced the *Re* state of Figure 1. *Re* state is instantly sinked to *Cl* state without interacting with other states. To introduce physical units in the specification, one can simply choose large units so that the physical amounts can be fit in the probability range [0, 1], and put the remaining probability in *Re* state. As an example, let us consider a combined dosage of 10 *mg* of intravenous injection, 20 *mg* of fast acting drug, and 30 *mg* of slow acting drug. This dosage is equivalent to 0.01 *g*, 0.02 *g*, and 0.03 *g* of the drugs respectively and the corresponding pmf is $\mathbf{x}(0) = [0.01, 0, 0, 0, 0.02, 0.03, 0.94]^{\mathrm{T}}$. Handling the infinite rate from *Re* state to *Cl* state could be problematic in the CTMC; however, it simply becomes one in the corresponding DTMC. The extended probability transition matrix of *D* that has *Re* state is $\mathbf{M}'_{i,j} = \mathbf{M}_{i,j}$ for $1 \le i,j \le 6$, $\mathbf{M}'_{4,7}=1$, and $\mathbf{M}'_{i,j}=0$ in other cases.

3. Logic

In this section, we briefly describe the syntax and an informal semantics of iLTL. For detailed description about the logic, please refer to [2].

The *syntax of iLTL* formula Ψ is as follows:

$$\begin{aligned} \Psi ::= {} & \mathrm{T} \mid \mathrm{F} \mid ap \mid (\Psi) \mid \\ & \sim \Psi \mid \Psi \wedge \Psi \mid \Psi \vee \Psi \mid \Psi \rightarrow \Psi \mid \Psi \leftrightarrow \Psi \mid \\ & \mathrm{X}\, \Psi \mid \mathrm{G}\, \Psi \mid \mathrm{F}\, \Psi \mid \Psi\, \mathrm{U}\, \Psi \mid \Psi\, \mathrm{R}\, \Psi \end{aligned}$$

An *atomic proposition* (ap) is an equality or an inequality about an *expected reward* [4] of a DTMC. Let $\{s_1,\ldots,s_n\}$ be the set of states of a DTMC *D,* then the atomic propositions are defined as follows:

$$ap ::= r_1 \cdot \mathrm{P}[D(t_1)=s_1] + \cdots + r_n \cdot \mathrm{P}[D(t_n)=s_n] \lozenge r,$$

where $t_i \in \aleph$ is a time offset, $r_i \in \Re$ is a reward associated with the state s_i, and $\lozenge$ is one of $<, \leq, =, \geq,$ or $>$.

The meaning of *atomic propositions* is $r_1 \cdot \mathrm{P}[D(t_1)=s_1] + \cdots + r_n \cdot \mathrm{P}[D(t_n)=s_n] \lozenge r$ at time t is true *if and only if* (iff) $r_1 \cdot \mathrm{P}[D(t+t_1)=s_1] + \cdots + r_n \cdot \mathrm{P}[D(t+t_n)=s_n] \lozenge r$. The meanings of *logical operators* are as usual and the meanings of *temporal operators* are: X Ψ is true at t iff Ψ is true at t+1, G Ψ is true at t iff Ψ is always true from t, and F Ψ is true at t iff eventually Ψ becomes true at some time $t_1 \geq t$. Ψ U Φ is true at t iff there is a time $t_1 \geq t$ when Φ is true and Ψ is true at t_2 for $t \leq t_2 < t_1$. Ψ R Φ is true at t iff Φ is true while Ψ is false from t and up to the moment when Ψ becomes true.

4. Examples

Finally, in this section, we demonstrate the usefulness of our specification and verification techniques through three drug administration examples. We use the three compartment model of Figure 1 sampled at a 10 *min* interval. Throughout this section, we assumed that the body weight is 60 *Kg*, the volume of display of the *Ut* compartment is 15.8 % of the body weight.

As a first example, we compute a dose for an oral drug administration that could satisfy: *(1)* the onset time is no later than 1.5 *hours*, *(2)* the active duration is at least 6 *hours*, *(3)* the *Minimum Effective Concentration* (MEC) is 1.4 $\mu g/ml$, and *(4)* the *Minimum Toxic Concentration* (MTC) is 2.1 $\mu g/ml$. Based on these parameters, the mass of the drug in the *Ut* compartment at the MEC and at the MTC are *mem* = 0.019908 *g* and *mtm* = 0.013272 *g* respectively.

Let us specify the desired onset time of 1.5 *hours*. Because the sampling period is 10 *min*, the drug concentration level at *Ut* should be larger than the MEC at the ninth step. Using the time offset, this condition can be simply expressed as:

$$\Psi_{\text{onset}} : \mathrm{P}[D(9)=Ut] > mem.$$

The condition about the active duration can be specified similarly using the time offset. However, the 6 *hour* duration and the 10 *min* sampling period require 37 different inequalities. We reduced the number of atomic propositions to 10 using the *next* operator X (we can reduce the number to the square root of the consecutive steps). The 10 atomic propositions are $e_i : \mathrm{P}[D(i)=Ut] > mem$ for i=0, 4, 8,…, 36. Let Ψ_{quarter} be $e_0 \wedge e_4 \wedge e_8 \wedge e_{12} \wedge e_{16} \wedge e_{20} \wedge e_{24} \wedge e_{28} \wedge e_{32}$ then the 6 *hour* duration can be written as:

$$\Psi_{\text{dur}} : \Psi_{\text{quarter}} \wedge \mathrm{X}\, \Psi_{\text{quarter}} \wedge \mathrm{XX}\, \Psi_{\text{quarter}} \wedge \mathrm{XXX}\, \Psi_{\text{quarter}} \wedge e_{36}.$$

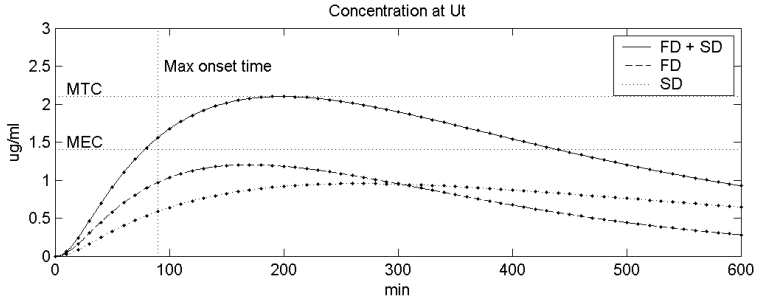

Fig. 2 Drug disposition changes for fast acting drug (dashed line), slow acting drug (dotted line), and their combined effect (solid line).

Since this active duration will not start immediately after the drug is administrated, we wrote the specification as F Ψ_{dur}, meaning that the active duration should eventually occur.

The third condition is about the MTC: the concentration level at the *Ut* compartment should never exceed the MTC. This condition can be easily specified using the *always* operator G as follows:

$$\Psi_{mtc} : \mathrm{G}\ (\ \mathrm{P}[D{=}Ut] > mtm\ ).$$

The drug administration options can be specified as a precondition about the initial condition. The oral drug administration option makes the precondition as Ψ_{ia} : P[*D*=*SD*] + P[*D*=*FD*] + P[*D*=*Re*] = 1. That is, all drugs are at these three states initially.

To sum up, a desirable dose can be found by model checking the combined specification:

$$\Psi_a : \Psi_{ia} \rightarrow \sim (\ \Psi_{onset} \wedge \mathrm{F}\ \Psi_{dur} \wedge \Psi_{mtc}\ ).$$

Observe that we negated the required conditions in the specification. Thus, any counterexample would satisfy $\Psi_{ia} \wedge \Psi_{onset} \wedge \mathrm{F}\ \Psi_{dur} \wedge \Psi_{mtc}$.

Model checking Ψ_a showed that a combined dose of 47.845 *mg* of fast acting drug and 74.432 *mg* of slow acting drug could achieve the goal. Figure 2 shows the drug concentration level change for this dosage. The dashed line and the dotted line in this graph are the drug concentration due to the fast acting drug and the slow acting drug respectively. The solid line is their combined effect. From the graph we can check that the three requirements are all satisfied. We further discovered that the requirements cannot be satisfied by the fast acting drug alone or the slow acting drug alone.

As a second example, we compute a dose for the multi-dosage regimen. Specifically, we look for a repeatable state with 6 *hour* period that could satisfy the MTC and the MEC conditions during the transition. Once such a state is reached, the drug concentration level can be maintained in the band between the MTC and the MEC by simply taking the same amount of the drug at 6 *hour* intervals.

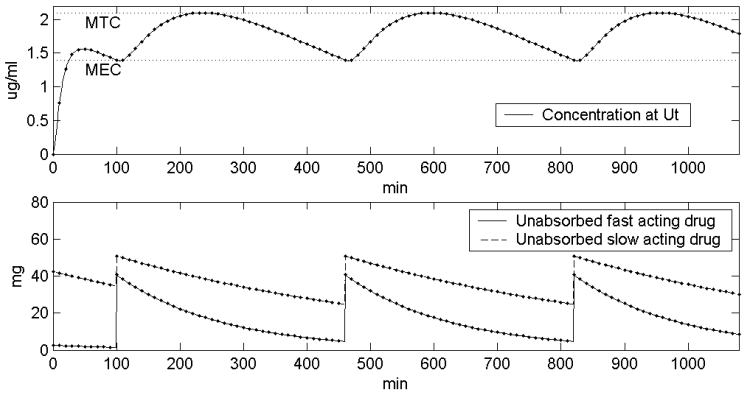

Fig. 3 The drug concentration level changes at the *Ut* compartment from a multi-dosage regimen (top), and the amount unabsorbed fast acting drug (solid line) and slow acting drug (dotted line) (bottom). The jumps are the required dose.

Among the 7 states of the DTMC *D*, the *FD* and the *SD* states are our control variables, and the *Cl* and the *Re* states are for the non-interacting drugs. Thus, we want to have the *Pl*, the *IF*, and the *Ut* states repeated. One concern here is that $\lim_{t\to\infty}$P[$D(t)$=s] = P[$D(t$+36)=s] for $s \in \{Pl, IF, Ut\}$, which violates one of the *completeness condition* of iLTL model checking that the RHS of an atomic proposition is not equal to its LHS (to prevent the transient modes keep changing the truth value of atomic propositions). To avoid this problem, we replaced the equality with a small interval. Let a parameterized formula Ψ^{s}_{rep} be (P[D=s] < P[D(36)=s] + 10^{-9}) ∧ (P[D=s] > P[D(36)=s] - 10^{-9}), then the specification can be written as:

$$\Psi_{\text{b}} : \sim (\text{G}\, \Psi_{\text{mtc}} \wedge \Psi_{\text{dur}} \wedge \Psi^{\text{Pl}}_{\text{rep}} \wedge \Psi^{\text{IF}}_{\text{rep}} \wedge \Psi^{\text{Ut}}_{\text{rep}}).$$

Model checking the negated specification, Ψ_{b}, reported a pmf vector [1.862, 4.877, 12.272, 888.540, 40.600, 50.850, 0] · 10^{-3} as a counterexample. Interpreting the pmf vector, if 1.862 *mg*, 4.877 *mg*, and 13.272 *mg* of the drug were in the *Pl*, the *IF*, and the *Ut* compartments respectively, then the same amount of drug will be found in these compartments 6 hours later if 40.6 *mg* of fast acting drug and 50.85 *mg* of slow acting drug were in their unabsorbed states.

Figure 3 shows the concentration level change for this multi-dosage regimen. From 100 *min*, the 6 *hour* cycle begins. The first graph shows the concentration level change of the *Ut* compartment, and the second graph shows the amount of unabsorbed fast acting drug (solid line) and slow acting drug (dashed line). The last two jumps in this graph are the required amount of drug to maintain the cycles. They are 35.918 *mg* of the fast acting drug and 26.099 *mg* of the slow acting drug. The first jump is different than the other two. We will explain the difference along with the first 100 *min* of the graph in the next example.

As a final example, let us find how to get to this repeatable state. In this example, we assume that the available drug administration options are the IV bolus, fast

acting drug, and slow acting drug. These available options make the initial condition Ψ_{ic} : P[*D*=*Pl*] + P[*D*=*SD*] + P[*D*=*FD*] + P[*D*=*Re*] = 1. The condition that the repeatable state is arrived at is:

$$\Psi_{arr} : P[D=Pl] = 1.862e^{-3} \wedge P[D=IF] = 4.877e^{-3} \wedge P[D=Ut] = 13.272e^{-3}.$$

The numbers in Ψ_{arr} are from the counterexample of the previous example. Because we want to have this condition occur eventually, we write the requirement as F Ψ_{arr}. Combining the conditions, the whole specification to check is as follows:

$$\Psi_c : \Psi_{ic} \rightarrow \sim (G\ \Psi_{mtc} \wedge F\ \Psi_{arr}).$$

Model checking Ψ_c showed that if 23.78 *mg* of the drug is intravenously injected and 2.624 *mg* of fast acting drug and 42.343 *mg* of slow acting drug are orally administered, then the repeatable state of the previous example will be reached. The initial part of the graphs in Figure 3 confirms it. The formula Ψ_{arr} does not include any conditions about the *FD* or the *SD* states. Thus, when the repeating state is reached, the amount of drug in these states might be different than the other cycles. Hence, the first jump in the second graph is different than the others. The required dose at 100 *min* is 39.160 *mg* of fast acting drug and 16.182 *mg* of slow acting drug.

5. Conclusions

In this paper, we demonstrated the usefulness of *iLTL* in specifying and verifying many interesting properties about drug kinetics. This computerized model checking technique not only proves certain drug disposition properties, but also computes a dose that could satisfy complicated requirements. The DTMC model of the logic can also be directly obtained from the compartment models after a simple conversion. We demonstrated all the steps from end to end using a three compartment model of insulin.

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