Towards Modeling and Analysis of Cyber-Physical Medical Systems

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ABSTRACT

Contemporary health care systems are increasingly incorporating medical sensors and automatically controlled actuation devices to deliver smart and proactive health services. The embedded devices used in this regard continuously interact with the human body or patient either through sensing of physiological signals or through the execution of critical medical actuation such as drug delivery. Given the high risks in their deployment, patient safety during operation of these Cyber-Physical Medical Systems (CPMSes) has to be guaranteed even before use. This paper proposes *CPS-MAS*, a cyber-physical medical system modeling and analysis framework for safety verification. However, given the complex nature of interaction of the medical devices with the human body, characterized by non-linearity, transport delay, spatio-temporal effects, and nontrivial aggregation of interaction during networked operation of devices, such modeling and analysis is a challenging problem. The paper describes an approach to formal modeling and analysis of CPMSes with the help of two examples related to analgesic drug delivery and chemotherapy.

1. INTRODUCTION

Rapid development of embedded computing and sensing technology has resulted in emergence of smart bio-medical devices such as the automatic infusion pump, non-invasive electrocardiogram sensors and implantable imaging systems. These systems are often embedded in the human body and interact with them through sensing and actuation. These Cyber-Physical Medical Systems (CPMSes), are being increasingly used in mission critical scenarios such as post operative health care [9], drug delivery [10], and chemotherapy [5]. Being mission critical in nature, CPMSes should be verified to meet desired properties of safe and hazard less operation even before their deployment. This paper takes a model based engineering approach towards safety analysis of CPMSes. However, the close interaction of CPMSes with the human body are characterized by non linearity, transport delays, spatio-temporal effects, and nontrivial aggregation of interactions, which aggravates modeling and analysis complexity.

In the proposed approach, abstract models of CPMSes are developed that consider the operation of the CPMS as definite steps in an algorithm and simulate them as a state machine. These abstractions are then analyzed under given operating conditions to obtain the variation of system properties represented as *model parameters*. The model parameters are then compared with the safety requirements, represented as constraints, to analyze CPMS safety.

In CPMSes, changes in the physical environment directly affect execution sequences in the computing units. Hence models of CPMSes, are composed of a *discrete* model of the computing system and a *continuous dynamical* model of the physical environment interlinked by information transfer between the two. Thus, modeling of CPMSes require a hybrid modeling approach having both discrete and continuous elements. Further, the operation of the physical environment introduces several complexities in the CPMS model. Typically, the variation of the properties of a physical system are governed by *non-linear time delayed* physical processes. For example, the variation of the concentration of a drug administered by an infusion pump is governed by the nonlinear diffusion process of fluids. Moreover, physical processes cause system properties to vary over *space and time*. For example, the drug concentration at different points in the blood stream vary drastically driven by the complex blood flow and drug diffusion dynamics. Further, in case of networked operation of multiple computing units there can be aggregate effects of interactions with the physical environment. These cause variation in the system properties in a non-trivial manner. For example, in case of simultaneous infusion of multiple drugs in chemotherapy [5] has shown increased cell death rates as opposed to their sequential infusion. These characteristics of the physical environment and their interaction with the computing unit introduce high order multi-dimensional nonlinear partial differential equations in the models of CPMSes, whose parameters and inputs are governed by the discrete operation of the device.

Traditionally, several assumptions are made to simplify these complex models of the physical environment. For example, the system of partial differential equations governing the spatio-temporal variation of the drug concentration for an infusion pump is approximated as a linear equation [1]. These simplifications reduce CPMS models to modeling abstractions which are well studied in the literature such as finite state automata or timed automata. However, such approximations do not capture the dynamic cyber-physical interactions in a CPMS and hence, have errors in estimation of the system properties, which may falsify the safety analysis. In this regard, this paper proposes, *CPS-MAS*, a modeling and analysis framework for safe CPMSes, that captures the dynamic, non-linear, time-delayed, and spatio-temporal cyber-physical interactions and considers aggregate effects of networked CPMSes.

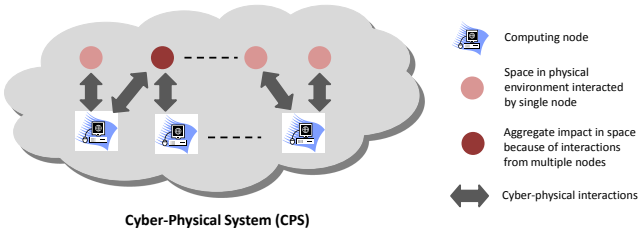

Figure 1: Cyber-physical system architecture

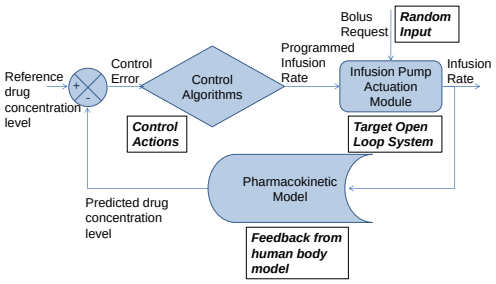

Figure 2: Infusion pump control system

In *CPS-MAS*, we propose generic constructs for formal specification of CPMSes. The safety requirements of the CPMS are specified as constraints on the model properties. Finally, the models are analyzed using domain specific analysis algorithms to check compliance of the model properties with the constraints. We show the usage of the modeling and analysis framework using two representative CPMS example problems - analgesic infusion pump drug overdose safety analysis and aggregate effect modeling for multi-channel chemotherapeutic infusion.

The rest of the paper is organized as follows - Section 2 describes the characteristics of a CPMS and the two representative examples, Section 3 discusses the proposed modeling and analysis framework, Section 4 discusses the usage of the modeling framework for the two examples, and Section 5 concludes the paper.

2. CYBER-PHYSICAL SYSTEMS

A CPMS consists of one or more computing nodes distributed in a physical environment. The computing nodes can be networked as in a medical device network. The computing nodes also interact with the physical environment (Figure 1). Such interactions, referred as the cyber-physical interactions in Figure 1, can occur between computing entities and spatial regions or particular locations in the environment. Such generic model can have different manifestations depending on the specific applications. In Figure 2, we show two examples of cyber-physical systems - analgesic infusion pump and a multi-channel chemotherapeutic infusion system.

EXAMPLE 1. *Analgesic Infusion Pump Control System: The infusion pump control system is shown in Figure 2. The target open loop system is the infusion pump actuation module, which infuses drug into the human body (cyber-physical interaction). The target open loop system has two types of inputs: 1)* `programmed infusion rate`*, the pump administers a constant infusion rate until changed; and 2)* `bolus request`*, a random request for drug infusion from the patient, which causes a step rise in infusion rate for a given amount of time.*

The control algorithm for the infusion pump varies the programmed infusion rate of the pump to maintain a given concentration of the drug in the blood. The drug concentration to maintain is given as the `reference input` *to the control system. The control algorithm receives feedback from the human physiology. The feedback is obtained from a mathematical model representing the drug diffusion process in human body, also called a pharmacokinetic model. This model predicts the future drug concentration due to the current infusion rate administered by the pump. The predicted drug concentration depends on the previous history of infusion, current infusion rate and the diffusion coefficients of the blood. The control algorithm takes the reference and the predicted drug concentration as input and computes the future infusion rate of the pump that is required to maintain the reference drug concentration.* ◇

EXAMPLE 2. *Aggregate Effects in Multi-channel Chemotherapeutic Infusion: In this example, a multi-channel infusion pump is considered [5], which simultaneously infuses different types of drugs in the human tissue for chemotherapy. Infusion of a chemotherapeutic drug in the human body causes reduction in the radius of tumor tissue and finally causes cell death. The amount of radius reduction of the tumor tissue depends on the type of the drug, the time for infusion and the spatial location of the tumor tissue with respect to the infusion site. Apart from destroying tumor cells a major side effect of chemotherapy is that it also kills normal cells. In case of multi-channel simultaneous infusion of chemotherapeutic drugs it has been observed that the death rates of both the tumor and normal cells increase. This is attributed to the aggregate effects of simultaneous infusion of multiple drugs. It is thus required to ensure that the amount of normal cells destroyed due to aggregate effects in multi-channel infusion is not hazardous.* ◇

Given these two representative example CPMSes, we next observe the salient features of CPMSes which makes its modeling complex.

2.1 Spatio-temporal variations

Cyber-physical interactions manifest spatio temporal variation of system parameters. In Example 1, the drug concentration, controlled by the control algorithm is maximum at the point of infusion and gradually decreases as we move further away from the site of infusion. Further, as more and more drug is infused over time the drug concentration at a particular point in the blood stream varies. In chemotherapy, the aim of the infusion is to kill the cancer cells at a particular region in the human body without killing healthy cells. The dosage of the drug is determined so that its effects pervade over the given region of cancer cells for an appropriate duration of time.

2.2 Non-linear Time-delayed dynamics

In Example 1, the pharmacokinetic model for the diffusion process relates the drug concentration in the blood and tissue in terms of the infusion rate through a set of complex **non-linear** differential equations. The drug concentration is affected by the transport delays caused due to blood circulation. Hence, at a given time it is dependent on the past history of drug infusion [10]. This **time-delayed** behavior of the physiological process incorporates complexity in the modeling and analysis of the CPMS.

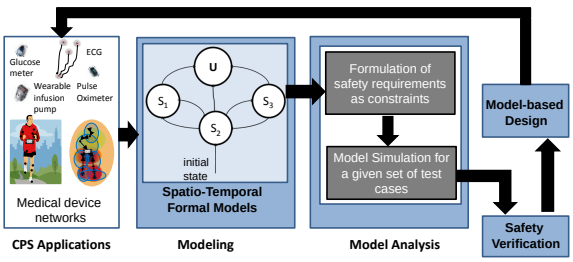

Figure 3: CPMS modeling and analysis framework

2.3 Aggregate Effects

In case of networked operation of multiple medical devices, the effects of cyber-physical interactions on the human body are non-trivial combination of the effects of individual systems. In case of the multi-channel infusion for chemotherapy in rheumatoid arthritis [5] ((Example 2)) separate sequential infusion of MTX and cA2 drugs has far less therapeutic efficiency than their simultaneous administration. Experimental results [5] suggest that the death rate of the tumor cells increase considerably when the two drugs are infused simultaneously. However, the death rates of the normal cells also increase, which is harmful for the human body.

2.4 Safety in CPMS

ISO 60601, a standard for medical devices, defines safety as the avoidance of unacceptable risks of hazards to the physical environment (i.e. to the patient) due to the operation of a medical device under normal or single fault condition. Following similar arguments in this paper we define safety of a CPMS as avoidance of risks of the computing unit or the physical environment from harmful effects of cyber-physical interactions. The ISO standard lists seven aspects of safety, including operational aspect, error-free operation of the medical devices software, radiation aspect, e.g. safety from X-ray radiation, thermal aspect, safety from heat dissipated because of medical device operation, and bio-compatibility. Note that the basic objective of all the safety aspects is to avoid harm caused by medical devices to the patients. Although the manifestation of this objective (and potential harm to the patient) may be different for different safety aspects, it is important to understand that safety of CPMS essentially means safety of the patient on whom the CPMS is deployed. The principal question therefore is given all the different aspects how do we ensure patient safety. In Example 1, if the pump infuses analgesic then excessive infusion of analgesic may cause respiratory distress [10] and in Example 2, drug overdose may cause excessive death of healthy cells in the human body. Hence, the notion of safety in Examples 1 and 2 is to keep the drug concentration level below a certain maximum.

3. CPS-MAS FRAMEWORK

CPS-MAS is a framework for model-based design and analysis of CPMSes to ensure safety. The cyber-physical interactions and the aggregate effects of these interactions have direct consequences on the safety of the CPMS design. In this research, we concentrate on both formal modeling and behavioral modeling of CPMSes to capture these interactions and develop their tractable analysis. Figure 3 shows the proposed modeling and analysis framework. The following subsections describe the different components of the modeling and analysis framework.

3.1 CPMS Formal Modeling

A formal model generally represents the operation of a CPMS using a finite set of states, where each state represents certain condition on the system variables or on their rate of variation. System variables can be properties such as drug concentration in case of Example 1 or cell death rate in Example 2. The model can transit from one state to another either on occurrence of any random event or when any system variable satisfies a condition. Certain states in the formal model can be marked *undesirable* to indicate that system variables with such conditions are undesirable. The notion of unsafe states can be used to effectively analyze safety of a CPMS. In case of Example 1, states with drug concentration greater than the maximum allowable value can be considered as undesirable while in Example 2 states with cell death rates of healthy or normal cells more than desirable limits can be marked undesirable.

However, any formal model for CPMS should be able to characterize cyber-physical interactions. This imposes the following requirement on any formal model of a CPMS -

R1: The states in a formal model should represent both continuous and discrete domain operation.

R2: The state variables can have continuous dynamics, specified in terms of differential equations, with respect to both time and space.

R3: State transitions can take place through event occurring in both time and space continuum.

R4: Formal models of multi-device systems should capture the aggregate behavior.

Given the aforementioned requirements, it is intuitive that a hybrid modeling approach is necessary. A hybrid automaton [3] provides unified specification of continuous dynamics and discrete operation of systems. Most of them are limited to the time domain analysis and do not consider aggregate effects due to cyber-physical interactions in networked CPMSes [2].

The formal model can establish scientific foundation for CPMSes and perform theoretical model-checking for safety verification. The behavior model, on the other hand, can allow model-based engineering of the CPMSes and allow safety verification based on the component behavior without requiring any mathematical insight from the CPMS designer.

3.2 Model-based Analysis

The models are used to perform analysis (Figure 3), which extracts specific details of the cyber-physical interactions from the models and computes the effect of those interactions on the entire CPMS. *CPS-MAS* performs simulation based analysis of the formal models of CPMSes. The formal analysis simulates the formal model for a given set of inputs and tests the reachability of undesirable states. Depending on the analysis results, the design of the CPMS applications can be updated and refined at an early design phase.

4. CASE STUDIES

In this section we show the usage of *CPS-MAS* for safety analysis of single and multi-channel infusion pumps.

4.1 Analgesic Infusion Pump

The analgesic infusion pump control algorithm obtains feedback from the human body and attempts to keep the drug concentration in the blood at a desired value C_d. The drug diffusion model takes the infusion rate as input and estimates the drug concentration in

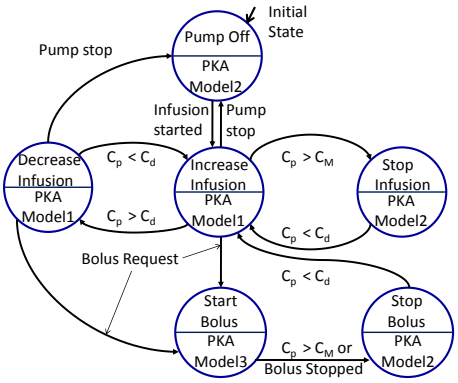

Figure 4: Figure shows spatio-temporal formal model of the infusion pump control system. The states are indicated by circles while the transitions are indicated by arrows.

blood (C_p) using a spatio-temporal partial differential Equation 1.

$$\frac{\partial d}{\partial t} + \nabla(ud) = \nabla(D(r) \nabla d) + \Gamma(r)(d_B(t) - d) - \lambda d \qquad (1)$$

where $d(r,t)$ is the tissue drug concentration at time t and distance r from the infusion site, $u(t)$ is the infusion rate, $D(r)$ is the spatially varying diffusion coefficient of the blood, $\Gamma(r)$ is the spatially varying blood to tissue drug transfer coefficient, and $d_B(t)$ is the desired drug concentration level after time t. However, in case of analgesic infusion only the drug concentration at the infusion site is considered important [10]. Hence, the spatial region in the human body is discretized into two compartments: 1) the tissue and 2) the capillary blood. The Equation 1 is then simplified to the pharmacokinetic Equation 2 (PKA model) proposed in [10], also called the two compartment model.

$$\begin{aligned} \dot{y_1} &= A_1 y_1 + B_1 z_2 + E_1 u(t - T_i) \qquad (2) \\ z_1 &= C_1 y_1 (t - T_p) \\ \dot{y_2} &= A_2 y_2 + B_2 z_1 \\ z_2 &= C_2 y_2 (t - T_r) \end{aligned}$$

Here y_1 and y_2 are intermediate variables of the equation. A_1, A_2, B_1, B_2, C_1, C_2 and E_1 are constants. z_1 is the drug concentration in the blood while z_2 is the drug concentration of the tissue. In Equation 2, the first two lines represent the diffusion process in the tissue, while the next two lines represent the diffusion process in the blood. Also the equations governing diffusion in these to spatial locations are interrelated and cannot be solved separately. This shows the strong spatial nature of variation of the drug concentration. u(t) is the infusion rate of the infusion pump. The differential equations in the model are time-delayed. This is because they consider time delays related to the infusion input (T_i), cardio-pulmonary transport delay T_p and the arterial, capillary and venous transport delays T_r. The controller first considers an initial infusion rate, which is the default infusion rate provided by the care giver, and estimates the drug concentration C_p using Equation 2. If $C_p > C_d$ then the controller increases the infusion rate by an increment δx, else it decreases by the same amount. The controller queries the PKA Model every δt time interval.

4.1.1 Infusion Pump Formal Model

The formal model for the infusion pump control system is shown in Figure 4. It has six states, each state is represented jointly by a discrete state in the infusion pump and a variant of the PKA model which governs the state variables - infusion rate and drug concentration. Initially the pump is in *Pump Off* state with zero infusion rate and waits for `Infusion Start` event from the care giver. In this state, the variation of the drug concentration follows *P*KA Model 2, which is Equation 2 with $u(t-T_i) = 0$. On the `Infusion Start` the infusion pump model goes to the *Start Infusion* state, where the infusion rate is set to a default value x_0. In this state, the *P*KA Model 1 is used to estimate the drug concentration C_p, where $u(t-T_i)$ is a non zero constant. If $C_p < C_d$ then the pump transits to the *Increase Infusion* state where the infusion rate is increased by an amount δx, else if $C_p < C_d$, then the pump transits to the *Decrease Infusion* state, where the infusion rate is decreased by δx amount. These two states also use the *P*KA Model 1 to evaluate drug concentration in the blood. In the *Increased Infusion* state if the drug concentration exceeds allowable maximum C_M then the model goes to *Stop Infusion* state where the infusion rate is zero and drug concentration follows *P*KA Model 2. However, if $C_d < C_p < C_M$ then the model transits to the *Decrease Infusion* state and stays there until $C_p < C_d$ again when it comes back to the *Increase Infusion* state. When in *Increase Infusion* or *Decrease Infusion* states, if a `bolus request` event occurs, then the model transits to the *Start Bolus* state. In this state, the drug concentration is governed by PKA Model 3, where the infusion rate in Equation 2 is a step input for a short duration T_b. When the bolus duration elapses or when $C_p > C_M$ in the *Start Bolus* state the model transits to the *Stop Bolus* state where the infusion rate is again set to zero. From *Stop Bolus* state the model comes back to the *Increase Infusion* state whenever $C_p < C_d$.

4.2 Multi-Channel Chemotherapeutic Infusion

In [4], the authors give a spatio-temporal model of drug concentration in the human tissue for single channel infusion in case of chemotherapy. It considers the continuous decay of tumor and normal cells due to drug effects, the resulting change in volume of the cells, the spatial variation of the diffusion coefficient, the spatial variation of blood to tissue drug transfer and the rate of drug decay due to metabolism. Consideration of these phenomenon results in a spatio-temporal non-linear partial differential Equation 1.

The formal model for this infusion system is similar to the one in Figure 4 having the same discrete states as the analgesic pump, however the PKA model is replaced by the spatio-temporal second order partial differential Equation 1. Given this model of an individual drug, the model for the drug concentration variation and the cell decay rate for multiple drugs has to consider the aggregate effects. These aggregate effects again follow a complex non-linear spatio-temporal time-delayed dynamic equation, which is often a non-intuitive combination of the dynamics of the individual models. The aggregate effects of multiple drugs cause the death rates of tumor cells p to increase. However, it also increases the death rate of the normal cells q, which can be harmful to the human body. The death rates for simultaneous infusion of two drugs can be modeled using Equation 3. It is a set of four non linear partial differential equations governing the cell death rates and the drug concentrations in tissue for both the drugs given their infusion rates u_1 and u_2.

$$\frac{\partial d_1}{\partial t} + \nabla(u_1 d_1) = \nabla(D_1(r) \nabla d_1) + \Gamma_1(r)(d_{1B}(t) - d_1) - \lambda_1 d_1 \qquad (3)$$

$$\frac{\partial d_2}{\partial t} + \nabla(u_2 d_2) = \nabla(D_2(r) \nabla d_2) + \Gamma_2(r)(d_{2B}(t) - d_2) - \lambda_2 d_2 \qquad (4)$$

$$\frac{\partial p}{\partial t} + \nabla((u_1 + u_2)p) = M_p \delta p + F_p(p) - C_p(d_1, p) - C_p(d_2, p) \qquad (5)$$

$$\frac{\partial q}{\partial t} + \nabla((u_1 + u_2)q) = M_q \delta q + F_q(q) - C_q(d_1, q) - C_q(d_2, q) \qquad (6)$$

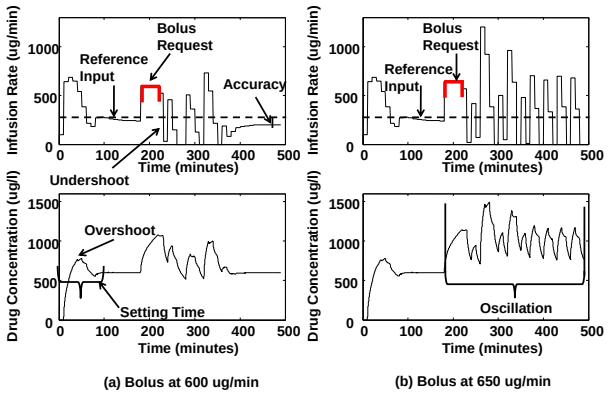

Figure 5: Anesthesia pump simulation with no bolus and at different levels of bolus (marked by bold lines) showing overshoot, settling time, stable, and oscillatory behavior.

The first two equations in this set are the same as Equation 1 for two different drugs. The third and fourth equations in the series represent the death rate of the tumor cells (p) and the normal cells (q) in space and time. These death rates depend on the mobility of the cells M_p or M_q and the proliferation rate F_p and F_q for the tumor and normal cells respectively. C_p and C_q describe the effects of chemotherapy on a given type of cell for a given drug. They satisfy Michaelis and Menten kinetics [6] and can be written in the general form of Equation 7.

$$C_p(d, p) = \beta_p dp/(\gamma_p + p) \tag{7}$$

Further, it is assumed that there are no voids in the space occupied by the tumor and normal cells. Hence, from conservation of mass principle it is assumed that $p + q = k = constant$. Thus, in case of multi-channel drug infusion the cell death rates can be obtained by simultaneously solving these non-linear spatio-temporal time-delayed set of partial differential equations. The aggregate effects are manifested by the terms C_p and C_q in the third and fourth equations of the series in Equation 3. These terms depend on the concentration of both the drugs and will lead to a different solution for p and q than for the single channel infusion case.

4.3 Model Analysis

According to the infusion pump safety criteria as listed in the generic infusion pump project [7], the infusion rate should not exceed $x\%$ of a preset value. However, when the medical device operates in a control loop with the human body as a feedback the drug concentration in the blood can oscillate and reach unacceptably high values even if the infusion rate remains within $x\%$ of the preset value, hence hampering patient safety. In this paper, we implement the PKA model in Simulink and simulate the state transition of the formal model in Matlab. The parameters for the pump and the PKA model were obtained from a case study on anesthesia infusion [10]. Figure 5(a) shows the infusion rate and the drug concentration in the blood over time for anesthesia infusion. From Figure 5(a) it can be seen that the infusion rate over time has significant *overshoot and undershoot* before it reaches a stable point. Further, significant amount of time, *settling time*, is required for the drug concentration in blood to reach the reference level set by the operator. A large settling time may lead to delay in the therapeutic effect of the drug. In case of mission critical operations such as drug infusion to prevent cardiac arrest [8], a short settling time is essential to provide therapeutic effects within a window of opportunity. Figures 5(a) and (b) also show the case when bolus is requested by a patient. From figure 5(a) it can be seen that after bolus administration the pump dynamics becomes oscillatory. However, after some time the control actions brings the infusion rate and the drug concentration to a stable value. Figure 5(b) shows the same pump but now with a higher bolus rate (50 ul/min higher) causes oscillation in the system. Due to this oscillations the infusion rate can go above the limits and the safety criteria can be violated. Further, in case of an oscillatory behavior the reference level of drug concentration is never reached.

5. CONCLUSION

In this paper, we presented CPS-MAS, a framework for formal modeling and analysis of CPMSes. We showed two examples related to drug delivery for pain relief and chemotherapy and developed formal models for them. The concept of spatio-temporal formal modeling developed in this paper will open up new research directions in model based safety verification and will enable development of safety guaranteed smart medical devices.

Acknowledgments

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