Integrated Simulation of Implantable Cardiac Pacemaker Software and Heart Models

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Abstract: This paper presents an approach for integrated simulation of pacemaker models and heart models, each developed with the appropriate formalism. Heart models are developed in MathWorks, a powerful tool for the simulation of complex systems, whereas pacemakers are developed in PVS, a theorem-proving environment enabling both simulation and formal verification of safety requirements. The two tools communicate over a Web-based interface, which makes it possible to integrate the simulation of the MathWorks model of the heart and the PVS model of the pacemaker. In this paper, we illustrate the architecture developed for integrated simulation of the pacemaker-heart system and present an example application for realistic models.

1 INTRODUCTION

Software incorporated in pacemakers must be demonstrably safe and effective. To this aim, software engineers need to resolve two different challenges:

1. Make sure that the software is exempt from design errors, such as deadlocks.
2. Make sure that software behaviour correctly incorporates medical-domain specific knowledge, such as how the pacing technique should adapt to the patient's conditions.

To address the first concern, software engineers can create mathematical models of the software, use verification tools such as model-checkers and theorem provers to analyse all software behaviours described in the models, and then generate pacemaker code from the verified models using automatic code-transformation techniques. Techniques for addressing this concern are overviewed in (Jiang et al., 2012b).

To address the second concern, on the other hand, software engineers need to engage with medical-domain experts. This is usually done by creating realistic simulations that demonstrate the software behaviour and the hypotheses under which the software has been verified. This concern is key to deliver a better quality of life to patients. In this work, we focus on this second concern.

1.1 Problem Statement

Pacemaker software is usually analysed using tools that enable the analysis of safety requirements, such as UPPAAL (Behrmann et al., 2006) or PVS (Owre et al., 1996). Sophisticated heart models, on the other hand, are usually developed in MathWorks, which offers a modelling language more appropriate for physiological systems. Software engineers would benefit from using all above tools in combination – each part of the system could be modelled using the most appropriate tool. In reality, however, the above tools are *not interoperable*. To simulate the whole system, models need to be translated, as each model can be executed only in its native simulation environment. This is, however, not always feasible, e.g., because environments like MathWorks use proprietary languages (Hamon and Rushby, 2004), or convenient, e.g., because a single modelling environment does not fit all analysis needs.

1.2 Contribution

An approach is presented for integrated simulation of pacemaker models developed in PVS and heart models developed in MathWorks without the need of model translation. The approach uses two web-services, ICP-web and heart-web, to intercept relevant simulation events, and forward them from one simulation environment to the other (Figure 1).

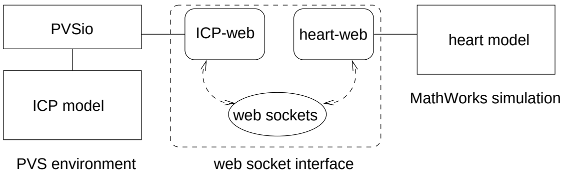


Figure 1: Integrated simulation approach.

Using this approach, the pacemaker and heart models can be executed in their native simulation environments. A demonstration of the approach is given for a software model of a modern dual chamber implantable cardiac pacemaker (ICP) and a detailed model of the heart. A snapshot of an integrated simulation example is in Figure 4.

2 METHODS

Two web-services, *ICP-web* and *heart-web*, are used to integrate PVS simulations of pacemaker software and MathWorks simulations of the heart (Figure 1):

- ICP-web is linked to the PVSio simulation environment of PVS. It uses a socket connection to receive events (atrial and ventricular signals) from the heart model. The events are transmitted to the ICP simulation. The same socket connection is used to send pacing events generated by the ICP simulation to the heart simulation.
- Heart-web is linked to MathWorks. It receives pacing events over a socket connection with ICP-web. The events are injected in the heart simulation. Atrial and ventricular events from the heart simulation are sent to the ICP simulation using the same socket connection.

The above approach builds on and extends the framework presented in (Masci et al., 2014) for integrated simulation of PVS models and Stateflow models. In that work, we used web-services to generate infusion pump simulations, where the user interface component is developed in PVS, and the pump controller is developed in Stateflow.

2.1 Pacemaker Model in PVS

Pacemaker software is usually modelled with *timed automata* (TA) (Alur and Dill, 1994). TAs operate in a number of distinct *modes*, switching between them when certain *events* occur. While the system remains in a given mode, its state is given by the values of *state variables*, representing the program variables used by the pacemaker software. Each TA has a unique initial state, modelling the initial value of program variables.

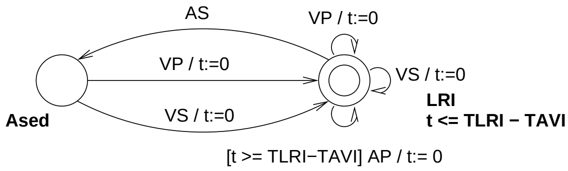


Figure 2: A timed automaton modelling the behaviour of a pacemaker software routine.

Figure 2 (adapted from (Jiang et al., 2012b)) shows an example of TA model. It defines the behaviour of the *Lower Rate Interval* routine of an ICP software, responsible for keeping the heart rate above a minimum value. The TA remains in the initial mode LRI at most TLRI − TAVI milliseconds, where TLRI and TAVI are the periods of the Lower Rate Interval and Atrio-Ventricular Interval of the cardiac cycle.

Transitions are labelled by *actions* (AS, AP, VS, VP), *guards* (in square brackets), and clock *assignments* (denoted by '`:=`'). The actions represent occurrences of the events *Atrial Sense*, *Atrial Pulse*, *Ventricular Sense*, and *Ventricular Pulse*, respectively. Three transitions, labelled with actions VS, VP, and AP, leave the automaton in mode LRI and reset clock t. Transition AS, on the other hand, brings the automaton from mode LRI to mode Ased. From the latter, transitions labelled with VS and VP bring the automaton back to LRI, resetting the clock. The transition guards specify the conditions under which a transition may occur. For example, transition AP may occur only if the guard $t \geq$ TLRI − TAVI is satisfied.

Within the PVS verification system, TAs are specified using higher-order logic:

- The state of the automaton is defined by a record type representing the mode, plus one real-valued variable for each clock. One record field, *time*, represents the global time.
- For each transition τ, (i) a transition function returns the next state as a function of the current state, and (ii) a permission predicate specifies the states where τ is allowed, and its guard.
- A time advancement function updates *time*.

The following PVS fragment shows part of the PVS model for the TA of Figure 2:

```
Mode: TYPE = { LRI, Ased }
state: TYPE = [# time: real, mode: Mode #]
per_APout(st: state): boolean =
    mode(st) = LRI AND time(st) >= TLRI-TAVI
APout(st: (per_APout)): state =
    (# time := 0, mode := LRI #)
```

The first two lines define the set of modes and the structure of the state record, containing the *mode* and *time* variables. Functions *per_APout* and *APout* are the permission predicate and the transition function, respectively, of the transition labelled with AP. The complete PVS model of the ICP is in a technical report (Masci P. et al., 2014).

The PVS is an interactive environment, wherein a user proves a logical statement by manipulating it with commands provided by the environment. For example, the following statement can be proved with a single command:

```
lri_ap: LEMMA
  FORALL (s0, s1: State):
    per_APout(lri(s0)) AND s1 = APout(s0)
    IMPLIES
    mode(lri(s1)) = LRI AND time(lri(s1)) = 0
```

The above lemma means: "*It is always the case that module lri is in mode* LRI *and its clock is reset when transition AP is executed*." Lemmas like this allow us to perform essential sanity checks for the model, and verify that the model definition correctly incorporates hypotheses about the behaviour of the system. In our case, an attempt to prove this lemma on an early version of the model failed, leading us to the discovery of an error in another part of the specification.

2.2 MathWorks Model of the Heart

Heart models are generally built using *hybrid automata* (HA) (Henzinger, 1996). Also HAs are characterised by different modes of operation. However, differently from TAs, in each mode their state varies continuously with time according to some mathematical law, e.g., a differential equation. In different modes, the state may follow different laws.

In this paper, we use the Simulink model developed by Chen *et al.* in (Chen et al., 2014). In their model, the heart's electrical conduction system is specified as a network of HAs implemented in MathWorks/Simulink. The HAs representing ventricular cells have four modes: *resting and final repolarization*, *stimulation*, *upstroke*, and *plateau and early repolarization*. In each mode, the membrane voltage follows a specific differential equation. The complete MathWorks/Simulink model consists of over 200 functional blocks. A detailed illustration of the model is in (Chen et al., 2014). Here, we illustrate the overall architecture and the input and output parameters of the model, as this is sufficient for the scope of this work.

The heart model has two main functional modules, `Atrium` and `Ventricle`, representing the electrical behaviour of the atrium and ventricle (see Figure 3). The two modules communicate through an `AV` module, which represents the AV node of the heart. Two input parameters allow designers to inject pacemaker signals in the heart: *AP* (Atrial Pacing), is used to inject the pacing stimulus generated by the pacemaker in the atrium; *VP* (Ventricle Pacing), is used to inject the pacing stimulus generated by the pacemaker in the ventricle. Another input, *sasignal* (Sinoatrial node signal), represents the firing frequency of the impulse-generating tissue of the heart. This input can be used to change the heart behaviour and explore different scenarios (e.g., normal sinus rhythm, bradycardia, tachycardia). Two output parameters, *Abeat* and *Vbeat*, are used to check whether the electric signal from the atrium and the ventricle has reached given thresholds.

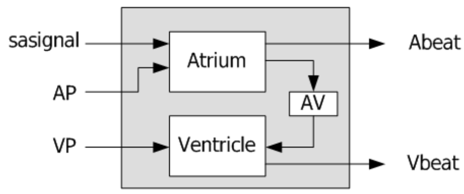


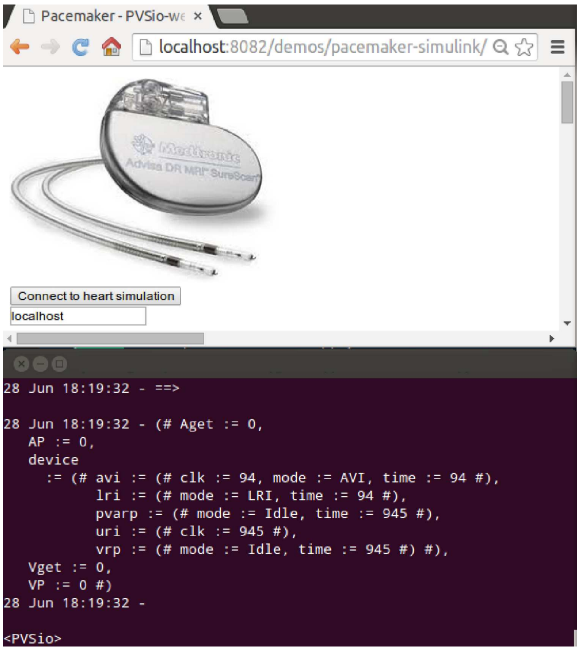
Figure 3: Architecture of the heart model.

3 RESULTS

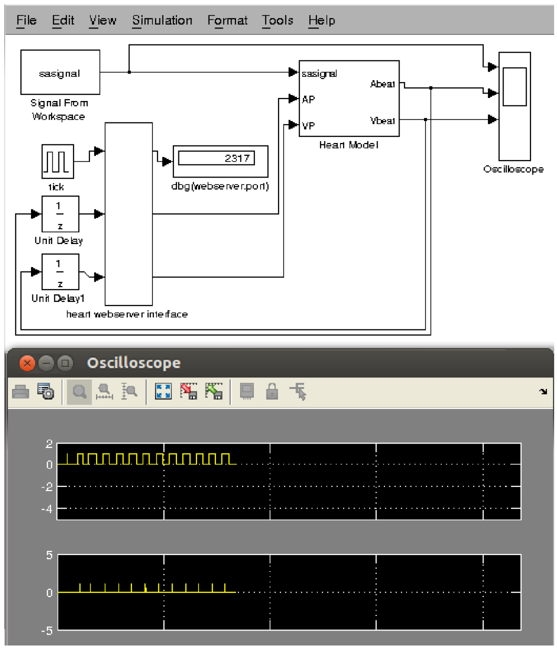
To demonstrate the integrated simulation approach, we consider a pacemaker model and a heart model independently developed by two research groups.

The pacemaker model describes the behaviour of software used in modern dual-chamber ICPs (Jiang et al., 2012b). It is a network of five automata, each managing a specific aspect of the cardiac cycle: the Lower Rate Interval, the Upper Rate Interval, the Atrio-Ventricular Interval, the Post Ventricular Atrial Refractory Period, and the Ventricular Refractory Period. The state of the system is given by the union of the component states. This model has been translated into the PVS language as outlined in Section 2.1. The translated model was then interfaced to the ICP-web service using our PVSio-web tool (Oladimeji et al., 2013), which creates the communication infrastructure to support the exchange of simulation events between PVS and MathWorks/Simulink.

The heart model is a realistic model developed in MathWorks/Simulink. The model was presented by others in (Chen et al., 2014). We interfaced this model to the heart-web service by adding a communication interface module (block `heart_webservice_interface` in the Simulink model in Figure 4). This communication module enables seamless exchange of simulation events with the pacemaker: (i) pacemaker signals AP and VP received from the pacemaker simulation are injected in the heart model; (ii) heart signals Abeat and Vbeat are intercepted and forwarded them to the



(a) PVSio simulation of the ICP model.



(b) MathWorks simulation of the heart model.

Figure 4: Example of integrated simulation.

```
(# Aget := 0,
   AP := 0,
   device
     := (# avi := (# clk := 94, mode := AVI, time := 94 #),
           lri := (# mode := LRI, time := 94 #),
           pvarp := (# mode := Idle, time := 945 #),
           uri := (# clk := 945 #),
           vrp := (# mode := Idle, time := 945 #),
   Vget := 0,
   VP := 0 #)
```

Figure 5: PVS state of the ICP model of Figure 4(a).

pacemaker simulation.

Screenshots from an integrated simulation example are in Figure 4 (the specific parameters used in the simulation are not relevant for sake of this example):

- The PVS simulation of ICP model is in Figure 4(a). The screenshot at the top is the browser interface we use for setting up and start the ICP-web service. The one at the bottom is the current state of the PVS model during the simulation (reproduced for convenience in Figure 5). In the state, field `device` holds the state of the pacemaker software modules, while the other fields (`Aget`, `Vget`, `AP`, `VP`) are auxiliary variables for storing input and output signals of the pacemaker.
- The MathWorks/Simulink simulation of the heart model is in Figure 4(b). The screenshot at the top is the heart model interfaced with the heart-web service and with an oscilloscope for rendering the input stimulus `sasignal` and information about atrial and ventricular signals. An example of oscilloscope output during a simulation is at the bottom of the figure.

4 RELATED WORK

Formal verification and validation of the whole pacemaker-heart system has been explored in several papers using multiple analysis tools and modelling formalisms.

For example, in (Jiang et al., 2010) and (Jiang et al., 2012a), a pacemaker-heart system is verified and validated using MathWorks/Simulink and UPPAAL (Behrmann et al., 2006). The former is used for realistic simulations, the latter is used to verify safety requirements of the pacemaker-heart system using formal methods technologies. Ad hoc models are developed in UPPAAL to translate core parts of the Simulink models needed for the verification.

Similarly, in (Chen et al., 2014), MathWorks/Simulink is used in conjunction with Prism (Kwiatkowska et al., 2011). Ad hoc Prism models are developed that represent the behaviour of the pacemaker-heart system and verify pacemaker properties related to energy consumption.

Differently from the above works, our approach alleviates the problem of developing and maintaining multiple models by enabling integrated simulation. We demonstrated the approach for MathWorks/Simulink and PVS, but the approach is general and can be used to enable integrated execution of simulations for other analysis environments.

5 CONCLUSIONS

The construction of a formal model of the device and the application of formal verification techniques can help to prove that the device performs the required functions under all the stated conditions, thus enhancing patient safety.

We developed a framework that makes possible both the simulation of the device in conjunction with Simulink heart models built on medical domain-specific knowledge, and the verification of invariants of the device through the theorem proving approach. In this way, system designers may use simulation results to validate the system behaviour with the guidance of domain experts, and formal verification to ensure the correctness of its design.

Integrated simulation allows software engineers to demonstrate the functionalities of the pacemaker software, and discuss hypotheses about its behaviour for different physiological parameters of the patient. On the other hand, the correctness of the pacemaker design can be formally checked by assume-guarantee reasoning (Henzinger et al., 2001), i.e., by proving that the ICP *guarantees* the desired behaviour of the ICP-heart system under suitable *assumptions* on the heart model. Formalising these assumptions will be the object of further work.

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