Accurate Modeling and Simulation of Heart Tissue with GDEVS/Cell-DEVS

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ABSTRACT - *We present a model describing the electrical behavior of the heart tissue. Previous research in this field have studied this problem using PDEs (Partial Differential Equations) and CA (Cellular Automata). A radically different approach considers using discrete-event techniques to solve this kind of problems, which has showed to be challenging, but provided excellent results in terms of simulation execution times. In this context, a fundamental issue is related to how to bridge the gap between a continuous variable formalism like PDEs, and a discrete event description like DEVS. We show that the GDEVS formalism is perfectly suited to attack this problem. We will also show that the GDEVS/Cell-DEVS model proposed is easily extensible to provide different kind of cell-behaviors, while not affecting performance.*

Keywords: DEVS models, Cell-DEVS models, G-DEVS, Cellular Automata, Discrete-event simulation.

1. INTRODUCTION

The Cell-DEVS formalism [1] allows defining asynchronous cell spaces with explicit timing delays. This approach permits describing cell spaces as discrete events models, based on the formal specifications of the DEVS formalism [2]. In Cell-DEVS, each cell is seen as a DEVS atomic model, and a procedure to couple cells is defined based on the neighborhood relationship. Explicit timing delay constructions can be used to define precise timing in each cell, which is defined by a local computing function combined with a delay construction.

Cell-DEVS enabled us to successfully solve a variety of complex problems in different areas [3, 4, 5]: biology (watersheds, fire spread, ant colonies), physics (crystal growth, lattice gases, heat diffusion), chemistry (flow injection analysis), and several artificial systems (autonomous robots, heat seekers, urban traffic, etc.). Our current research has been focused in providing better mechanisms for model definition, concentrating in physical systems that can be described as cellular models. We want to achieve higher precision and improved resolution in the results obtained when executing cellular models. We also want to take advantage of current expertise of scientists in different domains, letting them to describe individual components of cellular models using PDEs approximations. This approach could result in enhanced model definition and smoothing the transition between traditional models and cell spaces.

The idea is to analyze systems using Cell-DEVS models, in which each component can be defined using a PDE. An important issue is related to how to bridge the gap between a continuous variable formalism like PDEs, and a discrete event description like DEVS. Our thesis is that the use of the GDEVS formalism [6] is perfectly suited to attack both of these problems simultaneously. GDEVS is a formalism for the specification of discrete event abstractions and discrete event simulation of dynamic systems. The originality of GDEVS stems from the use of polynomials of arbitrary degree, as opposed to constant values, to represent the piecewise input-output trajectories.

Classical discrete event abstraction of a dynamic system is based on the mapping of piecewise constant input-output segments of (obtained perhaps through threshold sensors) into discrete

events. GDEVS adopted a radically new approach based on a new definition of the concept of event [7, 8]. In GDEVS, the target real-world system is modeled through piecewise polynomial segments. A coefficient event is considered as an instantaneous change of, at least, one of the value of the coefficients defining the piecewise polynomial trajectory of the considered variable. An event is a list of coefficient values defining the polynomial, which describes the trajectory of the ariable. Using GDEVS to define the behavior for each cell will also enable us to highly improve the model precision while incurring in fewer timesteps when compared with traditional numerical methods. The use of GDEVS will also improve the precision obtained if we compare the results obtained by traditional CA (GDEVS of order 0), due to the improved precision of model states.

Using this approach, we are able to get the advantage of traditional CA, v.g., a model that is very simple in terms of representation. We have successfully tested our approach in different complex models, but here we focus on a model describing the electrical behavior of the heart tissue. Previous research in this field has studied this problem using PDEs and CA, and we will show that we can provide adequate levels of precision at a fraction of the computing cost of PDEs. We will also show that the model is easily extensible to provide different behavior in different cells, while not affecting performance.

2. MODELING BEHAVIOR OF HEART TISSUE

The heart is a muscle responsible for the pumping blood into the circulatory system. Behavior of the phenomena occurring in the heart muscle and tissue has been extensively studied and it has been reported in almost every existing medical treaty (see, for instance [9, 10]). In these documents, heart behavior is usually analyzed according to three kinds of activities: mechanical, electrical and cellular.

In terms of **mechanical** activities, the blood returns to the heart through the vena cava superior and inferior, and flows to the right atria. The blood flows to the right ventricle, where it is pumped to the lungs to return oxygenated to the left atria. Then, it flows to the left ventricle, which returns the oxygenated blood to the body through the aorta. The heart muscle is excitable, and it responds to external stimuli by contracting itself. If the stimulus is too weak, the muscle does not respond; instead, if the voltage received is adequate, it contracts at maximum capacity.

Therefore, mechanical activity is triggered by **electrical** activity in the cells. The electrical conduction system of the heart is responsible for the control of its regular pumping. This activity is originated in the SinoAtrial (SA) node, also known as the pacemaker. This is an electrically active region of the heart that exhibits automaticity. Cells in the heart tissue are excitable, and when an adjacent cell is charged positively, it excites the nearby cells, provoking an upstroke of its Action Potential (AP). All excitable tissue, once activated, exhibits a refractory period before returning to rest.

This electrical activity is triggered by the **cellular** activities, which consists on the interchange of ions of Potassium and Sodium in the walls of the cells. This chemical reaction produces potential differences measurable in millivolts. This activity was characterized by Hodgkin and Huxley in [11], who defined the inter-membrane AP function. They recognized different phases in this function: a) heart tissue relaxed, interior of the membrane electrically negative with relation to the surface; difference of potential: 50 mV; b) surface membrane repolarized, two zones with a potential difference; c) electrical activity starts; external surface became negative, with a potential difference of 30 mV (depolarization); d) negative voltage in the surface trespasses the membrane; original status is recovered (repolarization).

The guiding formalism of virtually all membrane current models is that the total membrane current can be written as a sum of individual currents, each carried by a different ion, through a specific channel. The calculation is based on Sodium ion flow, Potassium ion flow, and leakage ion flow. Hodgkin and Huxley computed empirical formulas for the Sodium gate activation, Sodium particle activation probability, and Potassium gate activation probability. They also found the values of the remaining parameters, which where shown to be fixed variables. By solving the Hodgkin-Huxley equations, we can obtain the AP function for different cells in different tissue in the heart, according to the varia-

tion in the conductivity, length of the fibers, etc. For instance, the following figure 1 shows the results obtained when solving the equations to find the voltage in the atria cells. It has been shown that this function is equivalent to the ones found in experimental data. We will use this example in following sections to build a GDEVS/Cell-DEVS model of the hear tissue.

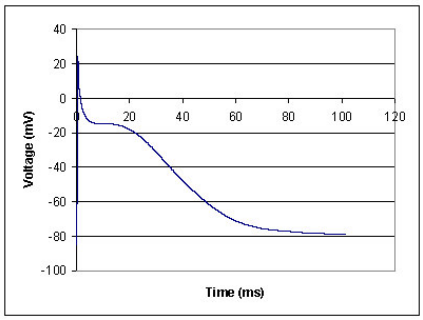


Figure 1. AP in the atria cells.

The Hodgkin-Huxley model has been extensively used in different studies, as it has been shown that this model reproduces adequately the behavior of the electrical properties in the myocardium cells. Nevertheless, solving this equation using numerical methods can be computationally expensive. As a result, different authors tried to simplify the complexity.

As mentioned earlier, we intend to use GDEVS of order 1 to describe the behavior of each cell in a Cell-DEVS model. Cell-DEVS state variables can be continous, but in general, representing continous functions in a Cell-DEVS model results in defining discrete time versions of the PDEs running in this cells. This desvirtuates two of the main advantages of using Cell-DEVS: the advance of models using discrete events, and the specification of cellular models as a composite of cells described with very simple rules. We will show how to build Cell-DEVS models whose components are defined using GDEVS. The idea is that a continous local computing function τ will be approximated by piecewise polynomial signals of the desired precision.

In the best possible case, linear approximations will be able to provide high precision at a low cost of execution and easier definition than PDEs. Higher precision can be achieved at a cost of the complexity of the rules defined. We will show these ideas using a well-known problem of heart tissue behavior, which has been solved using multiple approaches. This will permit us to show the power of our approach.

In a GDEVS model ***an event is an instantaneous change in at least one of the values of the coefficients of the polynomial describing the signal***. For the heart tissue modeling we consider piecewise linear trajectories, i.e. GDEVS of order 1. Then, an event is a pair of coefficient values with a time stamp. More formally, a piecewise linear trajectory, expressed by the symbol w, is a collection of individual segments over a continuous time base. For an individual linear segment w<ti, tj>, its coefficient value, EL(t), is defined by the pair (ai, bi), where bi is the value of the segment at time ti, termed intercept or level, and ai is its first gradient. Formally, the **"Coef"** function associates the coefficient pair of a linear function, w(t)<ti, tj>, with all continuous linear segments over a time interval <ti, tj>.

Thus, Coef: L → AxA, where L represents the set of the linear functions, and A represents a subset of the real number line. Thus, for a given continuous linear segment w<ti, tj>, over the time interval <ti, tj>, the components of the coefficient, EL<ti,tj> are constants. To determine the linear input-output trajectory, given the coefficient value as a function of time, an inverse function, Coef-1 is defined:

Coef-1: AxA→ L, Coef-1(ai, bi) = ait + bi

As a generalization, under GDEVS, events are defined for the coefficients obtained from a piecewise polynomial trajectory.

Definition: A coefficient-event for a piecewise polynomial trajectory is an instantaneous change of at least one of the elements of the tuple that defines the coefficient values.

For a piecewise linear segment w<t0, tn>, there exists a coefficient event at time ti if either b0≠ bi and/or a0 ≠ ai, where the coefficient value is given by (a0, b0). That is, an event exists in the coefficient space at time ti, if Coef(w<tk, ti[≠ Coef(w[ti,tj>).

Definition: As a part of the generalization, GDEVS introduces the notion of order of events that is equal to the number of coefficients of the underlying polynomial minus one.

For piecewise linear trajectories, the order of the events is 1 while for piecewise constant trajectories (classical discrete event models), the order of the events is 0.

An atomic G-DEVS model is a structure:

A = < Coef., X, Y, S, δ ext, δ int, λ, D >

Coef. as defined before,

X : the set of input events, X = AxA

Y: the set of output events, Y = AxA

S: the set of discrete states,

δ_{ext} is the external transition function that specifies the state changes due to external events (as in DEVS),

δ_{int} is the internal transition function (as in DEVS). It permits to capture the autonomous evolution of the model. When a model is in state *si* at time *ti*, it will transition to state $sj=\delta_{int}(s)$ at time *ti*+D(*si*), provided no external event occurs.

λ is the output function, and the function

D: S $\rightarrow R^{+} \cup \infty$ represents the lifetime of a state. Thus, for a given state, *si*, D(*si*) represents the interval during which the model will remain in the state si if no external event occurs.

3. G-DEVS FIRST ORDER MODEL OF HEART TISSUE

Having defined the heart tissue model using two traditional approaches (i.e., cellular automata and PDE equations), we then attacked the problem using Cell-DEVS/G-DEVS. The first step in this study was to find a linear approximation to the original PDE defining the cell's behavior, showed in figure 2.

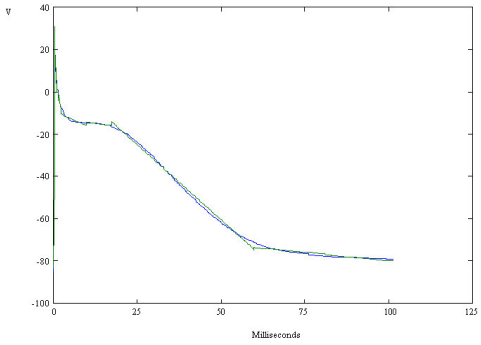


Figure 2. AP Linear approximation.

We approximated the initial equation experimental data using 8 polynomials of degree 1. The identification of the parameters in each of the polynomials was obtained minimizing a quadratic criterion using minimum squares. The polynomials we used in Figure 2 are defined by:

$$P_i(t) = a_i t + b_i \qquad \forall i \in [1, 8]$$

using the following coefficients:

i	*ai*	*bi*	*Time (ms)*
1	1.0250	-83.1478	[0, 0.35)
2	6.4555	-275.5886	[0.35, 0.43)
3	-0.2765	37.4703	[0.48, 1.48)
4	-0.0661	8.7840	[1.48, 2.48)
5	-0.0073	-8.6492	[2.48, 9.98)
6	-0.0022	-12.1344	[9.98, 17.48)
7	-0.0143	10.6898	[17.48, 60)
8	-0.0016	-64.0617	[60, +∝)

Table 1. Polynomial coefficients for AP model

Even the original function has an appearance to be simple, we needed to use eight polynomials. This was because, when analyzing the Hodgkin-Huxley model, the signal obtained when it is triggered, it is highly non-linear. Thus, between 0 and 2 ms we needed to approximate the AP using four different polynomials (as shown in Table 1). We also need a polynomial ending in the first positive value, which will trigger activity in the neighboring cells (polynomial P2 is in charge of this).

When using GDEVS for this model, we need to transform the coefficients in the polynomials into discrete event signals, as explained in section 2. Each cell will use polynomial coefficients to compute the current state, and to inform the cell's state to the neighbors. The specification of the local computing function included in each of the cells will now receive the coefficient-events from the neighboring cells. The cell's outputs will now be the current cell states specified as polynomial coefficients. Timing of activation for each polynomial can be easily defined using the model delay functions.

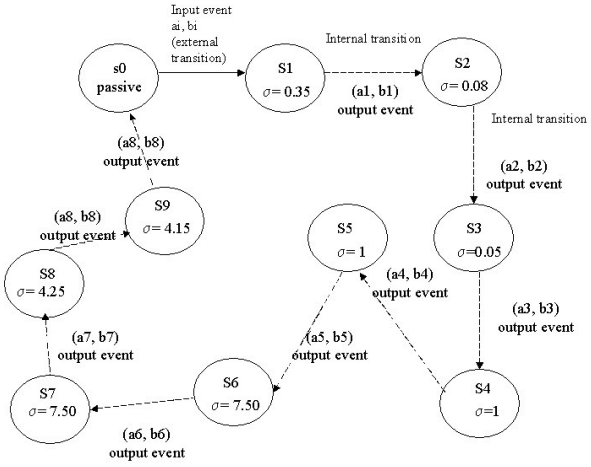


Figure 3. GDEVS specification of a cell.

Using the polynomial definitions in Table 1, we can now define the behavior of each of the cell's local computing functions, which is described by the GDEVS state graph in the figure

3. Internal transitions are in dotted lines, and external transitions in full lines. As we see, the cell is inactive until it receives an external stimuli from a neighboring cell. In that case, the cell is activated, and it produces internal state changes generating the current state (represented by the coefficient in the polynomials). This is repeated in every step. This specification will generate an output trajectory as the one described by the linear approximation. As we can see, this highly improves model precision at a low cost, in terms of both execution time and ease of modeling. We used the cell's specification in Figure 3 to define this model using the CD++ toolkit [12].

```
[heart-GDEVS]
type : cell         dim : (6,6)    delay : transport  border : nowrapped
neighbors : (0,-1) (0,0) (-1,0) (-1,-1) (0,1)  (1,0) (-1,1) (1,1) (1,-1)
localtransition : heart-rule-GDEVS

[heart-rule-GDEVS]
rule : { S0 }  0 { (0,0)=-83 and volts(0,-1)>0 or volts(-1,-1)>0 or volts(-1,0)>0 }
rule : { S1, send(1.0250,-83.1478)      }  0.35      { (0,0) = S0 }
rule : { S2, send(6.4555,275.5886)      }  0.08      { (0,0) = S1 }
rule : { S3, send(-0.2765,37.47)        }  0.05      { (0,0) = S2 }
rule : { S4, send(-0.0661,8.784)        }  1         { (0,0) = S3 }
rule : { S5, send(-0.0073,-8.6492)      }  1         { (0,0) = S4 }
rule : { S6, send(-0.0022,-12.1344)     }  7.50      { (0,0) = S5 }
rule : { S7, send(-0.0143,10.6898)      }  7.50      { (0,0) = S6 }
rule : { S8, send(-0.0016,-64.0617)     }  4.25      { (0,0) = S7 }
rule : { S0, send(-0.0016,-64.0617)     }  4.15      { (0,0) = S8 }
rule : { (0,0) }                           0         { t }

[voltage-function]
volt(cellpos) = cell.ai * time + cell.bi
```

Figure 4. Cell-DEVS/GDEVS implementation of the heart tissue model.

This specification starts by defining the size of the cell space (6 x 6), and the remaining parameter needed by GDEVS/Cell-DEVS specifications. In this case, transport delays, a non-wrapped model (cells in the border will use a different neighborhood), and the neighborhood shape, which includes all the adjacent cells. Then, we define the local computing function, *heart-rule-GDEVS*. This local computing function follows the specification in Figure 3 for a cell. If a stimulus is received when the cell is inactive (*(0,0)=-83*), it will check the voltage received from the cells in the neighborhood (which is received through ports *ai* and *bi*, and it is computed by the *voltage* function) and will react to positive voltage in any of them. It will change to the corresponding state (*Si*, to the left of the specification), and will send the current *ai, bi* coefficients to the neighboring cells after the consumption of the delay. Each of the rules represents a cell's state change, and the spread of the coefficient to the neighbors.

The GDEVS simulation gives output trajectories more precise than the one obtained with classical discrete event Cellular Automata. This gain of precision involved only a low extra cost in terms of computing time. Likewise, the complexity added to the cellular model developed in Cell-DEVS is reduced, moreover when compared with the solution using PDE (which required implementation the Hodgkin -Huxley functions).

The results of our experience are summarized in the following. In Figure 5, we show the number of messages involved in simulating the heart tissue model using different approaches. We computed the number of messages issued in a Cell-DEVS model using a simple set of rules and a second Cell-DEVS model with a larger number of intermediate states. We also compared the result with the ones obtained with a traditional CA, and with two numerical approximations for the Hodgkin-Huxley PDEs. The logarithmic scale shows exponential growth with the number of cells, but we can see that GDEVS, which provides a much more precise signal, only reduces performance in less than 5% when compared with traditional Cell-DEVS models. Cellular Automata take longer, as we have to execute every cell in every time step. Therefore, for a small number of cells, the execution time keeps controlled. How-

ever, when large cell spaces are considered, the performance approaches the one of cell spaces running partial differential equations in each of the cells.

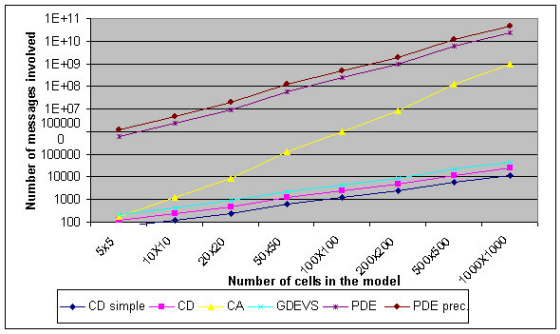
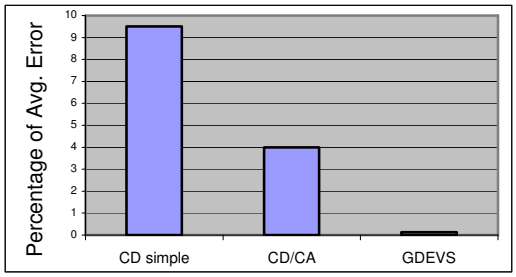
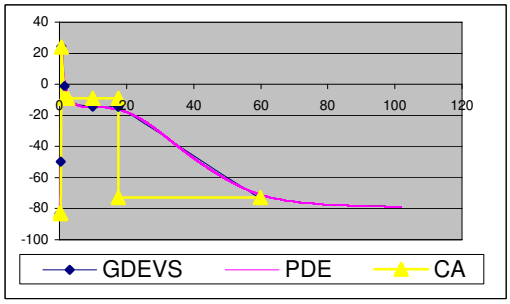


Figure 5. Comparing simulation models (logarithmic scale)

Furthermore, GDEVS approximation highly improves performance when compared with traditional numerical methods, while improving precision. This can be seen in Figure 6, where we include a comparison of the average error in the heart tissue model when we compare CA, Cell-DEVS models with different number of intermediate states, and GDEVS.



(a) Average error



(b) comparing output trajectories

Figure 6. Analyzing model error

We see that the cost of running Cell-DEVS/GDEVS models is minimum when compared with Cell-DEVS or CA models. As we can see, GDEVS approximates adequately the original signal, whereas discrete variable models (like CA) introduce a larger amount of error. These discrete values simplify the basic definition of the model, but can make it difficult to detect state values with significance for other phenomena, avoiding the provision of good modeling results.

Furthermore, our approach has several other advantages. First, we can approximate the function by a higher degree polynomial to achieve higher precision, if needed. Second, we can easily modify the model to identify different phenomena. For instance, a bad behavior in certain cells can obtain by changing parameter values and defining a Cell-DEVS zone with that behavior. Likewise, we can define a more general model by making the slope and gradient (ai, bj) of each state to be define as external parameters. Finally, in this particular definition of the model, we are reacting to external voltages, but we could easily modify the model specification to analyze more complex circumstances, for instance, arrhythmia problems (which are related with inadequate excitation of a cell due to deformation to the AP), detailed analysis of the Na/K channels, etc. This new behavior can be achieved by simply modifying the rules described in figure 4 accordingly.

4. CONCLUSION

We showed how to combine Cell-DEVS and GDEVS to build very complex systems. The Cell-DEVS formalism allows (based on the DEVS formalism) defining asynchronous cell spaces with timing delays. Here, we combined Cell-DEVS with GDEVS models, permitting defining complex continuous systems easily.

We focused on the Hodgkin-Huxley model of electrical behavior of the heart tissue, and compared the results obtained against those originally built with PDEs and cellular automata. We showed that we can provide adequate levels of precision at a fraction of the computing cost of differential equations.We proved that the GDEVS formalism is perfectly suited to attack problems like this one, improving complex systems analysis. Cell-DEVS permits enhancing the modeling activities, as the automatic definition of cell spaces is allowed, simplifying the construction of new models, and easing the automatic verification of the structural models. In this way, efficient development of complex models can be achieved. The hierarchical nature of the DEVS formalism permits attack different levels of ab-

straction permitting, for instance, build more detailed models about the behavior of ion interchange within each of the cells in the system. Likewise, the definition of different phenomena in groups of cells is straightforward, in terms of both Cell-DEVS and GDEVS specifications.

At present, we are working on the definition of other complex models using this approach (mainly, a fire spread model, and a watershed formation system). This will provide us with a variety of different models enabling us to start detailed studies on characterization of the error of this approach. We are also starting some work in related areas, namely Quantized DEVS models [13] and derived research, as we obtained good results in modeling continuous systems using quantized Cell-DEVS [14]. Nevertheless, at this stage there is still much research to do in terms of simplify the definition of rule definition for quantized models (for instance, we are working in finding quantized versions of the Hodgkin-Huxley equations, which proved not to be as simple as finding GDEVS approximations). This particular area requires a great deal of effort in order to facilitate any future developments in building complex continuous systems using DEVS-based approaches.

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