A Grid Computing-based Approach for the Acceleration of Simulations in Cardiology

José M. Alonso, José M. Ferrero (Jr.), Vicente Hernández, Germán Moltó, Javier Saiz, *Member, IEEE*, and Beatriz Trénor

***Abstract*—This paper combines High Performance Computing and Grid Computing technologies to accelerate multiple executions of a biomedical application that simulates the action potential propagation on cardiac tissues. First, a parallelization strategy was employed to accelerate the execution of simulations on a cluster of PCs. Then, Grid Computing was employed to concurrently perform the multiple simulations that compose the cardiac case studies on the resources of a Grid deployment, by means of a service-oriented approach. This way, biomedical experts are provided with a gateway to easily access a Grid infrastructure for the execution of these research studies. Emphasis is stressed on the methodology employed. In order to assess the benefits of the Grid, a cardiac case study, that analyses the effects of premature stimulation on reentry generation during myocardial ischemia, has been carried out. The collaborative usage of a distributed computing infrastructure has reduced the time required for the execution of cardiac case studies, what allows, for example, to take more accurate decisions when evaluating the effects of new antiarrhythmic drugs on the electrical activity of the heart.**

***Index Terms*—Grid computing, action potential propagation, service-oriented architecture, high performance computing, myocardial ischemia.**

I. Introduction

MATHEMATICAL models of propagation of cardiac electrical potentials are considered a powerful and helpful tool to better understand the mechanisms involved in the development of ventricular fibrillation, a lethal arrhythmia. By means of modelling and simulation in computers, the origin and evolution of fibrillation can be first studied *in silico*, where hypotheses can be formulated and studied prior to their validation *in vivo*, thus reducing the requirements of many complex intrusive techniques.

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J.M. Alonso, V. Hernández and G. Moltó are with the Departamento de Sistemas Informáticos y Computación, Universidad Politécnica de Valencia, Camino de Vera s/n, 46022 Valencia, Spain (e-mail: {jmalonso,vhernand,gmolto}@dsic.upv.es)

J.M. Ferrero (Jr.), J. Saiz and B. Trenor are with the Departamento de Ingeniería Electrónica, Universidad Politécnica de Valencia, Camino de Vera s/n, 46022 Valencia, Spain (e-mail: {cferrero, btrenor, jsaiz}@eln.upv.es).

It is known that the action potential is propagated along a specialized conduction system in the heart, until it reaches all the cardiac muscle cells. The arrival of this signal to a cell provokes several phenomena that results in its contraction. This way, action potential and the electric conduction system guarantee the synchronized contraction of cardiac muscle and the effective blood pump [1].

The electrophysiological data obtained with the help of experimental techniques has led to the formulation of mathematical models of the electrical behavior of excitable cells. Specifically, the electrical activity of cardiac cells has been quantitatively described, since the early 1960s, by models that have become more and more detailed as new ion channels and channel properties have been discovered and studied in depth. One of the most detailed models of ventricular action potential is the Luo-Rudy Phase II [2].

If the mathematical formulation of the membrane ion kinetics (the cellular model) is combined with a representation of the electrical characteristics of the tissue, the resulting mathematical model (a system of differential equations) can be used to simulate the electrical activity, that is the action potential propagation, of cardiac preparations, or even of the whole heart.

However, as the size of the simulated cardiac tissue increases, the very large numerical burden resulting from calculating currents and voltages on many cells, and then simulating electrical interactions among the coupled cells, require the usage of very large-scale computational resources. For instance, taking into account that a cardiac tissue consists of irregular, densely packed cells of 30-100 μm long and 10-20 μm width, a 1cm x 1cm tissue is composed of approximately 100.000 coupled cells. A simulation of action potential propagation during 2 seconds requires the execution of 250.000 timesteps of typically 8 μs, what implies a total simulation time that can last almost 4 days on a Pentium IV with 1 GByte of RAM. Moreover, ischemic behavior may require the simulation of a cardiac tissue electrical state during several minutes. As an example, a simulation of 5 minutes would require 18 months of computation in such platform.

In addition, studies of vulnerable windows in ischemia require to vary the time interval between two consecutive stimuli in order to detect the range of values which provokes a reentry, a phenomenon that can derive into heart fibrillation. Besides, to study the effects of late ischemia it is necessary to vary the coupling resistances in all the dimensions of the tissue and investigate the evolution of the electrical activity for different anisotropy ratios.

Moreover, to evaluate the influence of certain drugs it is crucial to alter the concentration of these drugs, over a determined range, to study how it affects the propagation of action potential in the tissue. All of them are parametric studies composed of independent cardiac simulations.

With the advent of recent increases in the bandwidth of communication networks, the idea of linking machines across the world to create a distributed computing infrastructure, known as the Grid [3], has been leveraged. The Grid can be defined as a service for sharing the computational power and the data storage capacity of resources, as much as the web is a service for sharing information. This provides an ideal infrastructure to concurrently execute the different simulations of a case study.

Currently, there is not much related work concerning the application of Grid Computing to the simulation of the cardiac electrical activity. The Integrative Biology project [4] aims at developing the Grid infrastructure for the execution of simulations related to cancer and heart. Recently, the Johns Hopkins University is leading the Cardiovascular Research Grid project [5], which aims at creating a digital network to exchange data and computational tools regarding heart-related diseases.

Indeed, using Grid Computing for the execution of scientific applications is still difficult due to the inherent complexity of the underlying Grid middleware. Therefore, we have developed a service-oriented architecture that enables the biomedical experts to interact with a Grid infrastructure, via graphical applications, to execute cardiac simulations. This approach combines High Performance Computing and Grid Computing, via the GMarte framework [6], to accelerate the execution of these simulations.

The remainder of the paper is structured as follows: First, section II briefly describes the simulator of the electrical activity of the heart. Next, section III details the development of service-oriented architecture that simplifies the usage of the Grid for biomedical experts. Later, section IV introduces the cardiac case study executed in order to assess the effectiveness of Grid Computing. Finally, section V summarizes the paper.

II. Simulation of Action Potential Propagation

A. Mathematical Formulation of the Problem

The action potential propagation on a monodomain modelization of a cardiac tissue can be described by the following equation, using the notation in [7]:

$$\nabla \cdot \sigma \nabla V_m = C_m \cdot \frac{\partial V_m}{\partial t} + I_{ion} + I_{st}, \qquad (1)$$

where σ represents the conductivity tensor, V_m is the membrane potential of the cells, C_m stands for the membrane capacitance, I_{st} represents a stimulus current to provoke an action potential and I_{ion} is the sum of ionic currents traversing the membrane of each cell, computed by the comprehensive Luo-Rudy Phase II ionic model [2].

In our modelization, the cardiac cells are linked with resistances within a two-dimensional geometry [8]. Cardiac muscle fibers are assumed to have faster longitudinal conductivity than transversal or transmural one, considering the anisotropy condition of a ventricular cardiac tissue.

Equation (1) is spatially discretized using finite differences and employing the Crank-Nicolson's semi-implicit method [9], what leads to the following algebraic equation:

$$G_L \cdot V_m^{t+1} = G_R \cdot V_m^t + I_{ion}^t + I_{st}, \forall t = 1, 2, ..., n. \qquad (2)$$

The matrices G_L and G_R account for the conductivity along the cells of the tissue. The I_{ion} term encapsulates the cellular ionic model, requiring the resolution of several time-dependent ordinary differential equations. Thus, the simulation turns into an iterative process where the membrane potential of the cells is reconstructed through the resolution of a large sparse system of linear equations for each simulation time step.

In a previous work [10], we performed the parallelization of the simulation code for bidimensional tissues via the PETSc software package [11] and over the standard MPI (Message Passing Interface) library [12]. Efficiencies of 94.2% were obtained with 32 processors when simulating an action potential propagation on a 1000x1000 cells cardiac tissue on a cluster of PCs (Pentium Xeon 2 GHz, 1 GByte of RAM, SCI network). We employed a strategy based on allocating a different group of consecutive cardiac cells to each processor. All the data involved in each simulation were distributed among the processors following a rowwise block-striped distribution. Applying such a High Performance Computing approach we achieved a two-fold benefit. On the one hand, the usage of multiple processors in a cluster of PCs dramatically reduced the simulation time. On the other hand, as the global memory available is the sum of the local memories of each computing node in the cluster, larger tissues were able to be simulated by only means of adding more processors.

To be able to execute the application on a Grid infrastructure, we produced a statically-linked self-contained executable file, without architecture-dependent optimizations, as described in [13].

III. Architecture of the System

In order to ease the process of using a Grid infrastructure by the biomedical experts, we have developed a service-oriented approach by using the Grid Services technology provided by the Globus Toolkit 4 [14]. The metascheduling functionality of GMarte [6] has been integrated as part of the implemented Grid service [15]. This system enables the users to create sessions for the execution of cardiac simulations on a Grid infrastructure. The interaction with this service is typically performed by means of a graphical component (GMarte Client GUI) which hides all the complexity. In addition, the service can also be accessed programmatically via a Java API to include the metascheduling functionality as a part of user applications. The Grid service has been developed using the standard WSRF (Web Services Resource Framework)

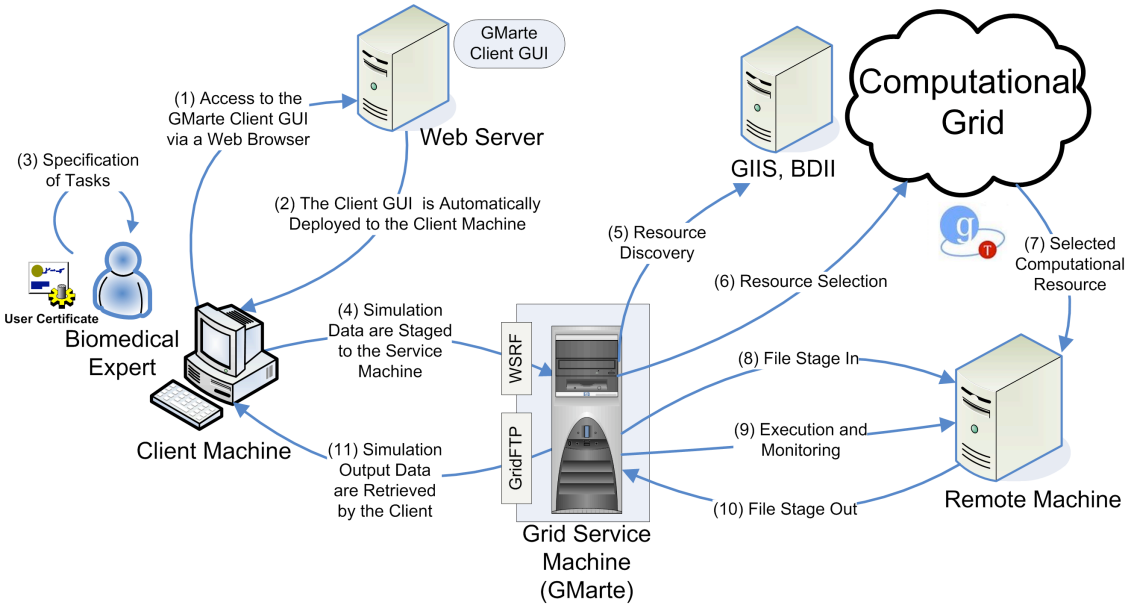

Fig. 1. The service-oriented architecture, and the interaction diagram, developed to accelerate cardiac simulations.

[16] specifications, thus enabling an easy interoperability with other Grid services and applications. Figure 1 exposes the architecture and the interaction diagram.

First of all, the biomedical expert accesses a web server that hosts the GMarte Client GUI application employed to interact with the Grid service. The Java Web Start technology has been employed to deploy this graphical application, which ensures that the client uses the latest version. The client only requires a Java-enabled web browser, thus being able to use this application in virtually any operating system. Access to the Grid service is controlled via X.509 certificates [17] so that only authorized users can submit simulation requests. Also, a configuration of the client firewall is required to allow the GridFTP-based data transfers from/to the Grid service machine.

Once the graphical application has automatically started, it is time for the biomedical expert to define the computational tasks of the case study to be executed on the Grid. For that, the user specifies the simulator executable file to be used, the dependent input files archives, the output data files that should be retrieved when the execution finishes, the computational requirements of the task, etc. This information is currently specified in XML (eXtensible Markup Language) language, which is both easily understood by humans and machines. In addition, we are developing specific graphical components to supply this information via an even easier interface.

Once this information has been specified, all the simulation data are automatically transferred to the Grid service machine, via the GridFTP protocol, and the metascheduling process starts, enabling the biomedical experts to track the current state of their simulations as well as to know the resources they are running on via the tables shown in the graphical application.

The task allocation is performed by GMarte. First of all, the *resource discovery* phase obtains a list of potential execution machines from a Grid infrastructure. In GMarte, the resource discovery is implemented by accessing the GIIS (Grid Index Information Service) or the BDII (Berkeley Database Information Index) components of a Grid, which provide aggregate information about the resources of a site. Additionally, the Grid service can be configured to use a pre-defined list of machines. Afterwards, for each task, the *resource selection* phase is in charge of choosing the most appropriate resource on which to schedule the job. Finally, the remote task execution takes place by staging in the application and the dependent input files to the remote machine, performing the execution and staging out all the simulation results generated.

When each task finishes, its results can be retrieved, via GridFTP, by the client machine in order to start data post-processing. The Grid service machine can also be employed as a temporary storage space, as data are only erased after 15 days of session inactivity. Fault-tolerant mechanisms have been included to allow the disconnection of clients without losing their sessions.

It should be clear that the user is completely unaware of the Grid complexity, but instead is provided with a software tool that enables to execute more simulations per time unit by concurrently performing the executions on the different resources of a Grid deployment. The service-oriented approach implemented allows the biomedical experts to focus on the problem itself, while the Grid service manages all the computational details. This architecture is currently being employed in production by the scientists at the Center for Research and Innovation in Bioengineering, at the Polytechnic University of Valencia.

In the following section we both assess the benefits of using the Grid Computing technology and the Grid service implemented by executing a real cardiac case study.

IV. Case Study: Studying the effects of Premature Stimulation on Reentry Generation During Ischemia

Arrhythmic episodes in heart ventricles can derive into ventricular fibrillation, which is known to be a major cause of death. This lethal arrhythmia is usually provoked by the generation of reentry, i.e. self-perpetuating circulating wavefronts of electrical activity around an anatomic or functional obstacle within the heart [18].

Two factors are to be considered when analyzing reentries. On the one hand, the instant of time of premature stimulation determines the possibility of reentry generation. In fact, a stimulus must be delivered prematurely in order to encounter a refractory zone. However, a wavefront can only be elicited provided that the stimulus is not too early delivered. In this way, the instant of time of the premature stimulus is an important factor in the initiation of reentry. On the other hand, the electrophysiologic conditions of the tissue , such as cellular oxygen depletion, extracellular potassium accumulation and acidosis, predispose the heart to the occurrence of reentrant arrhythmias [19], and are responsible for its maintenance.

The novel aspect of this theoretical biomedical study is the analysis of the intricate mechanisms leading to figure-of-eight reentry during the acute phase of myocardial ischemia. In this computational study, not only the effects of different factors are analyzed but also a realistic process of ischemia is simulated, in order to provide realistic and detailed findings about the initiation of reentry.

A. Methods

1) Action potential model: The Luo and Rudy phase II model [2], [20] of the action potential (AP) has been used to simulate electrical activity in ventricular cells. It has also been considered the Ferrero formulation [21] of the ischemic effects exterted by ATP sensitive potassium current activation.

2) Model description of the ischemic tissue: In our simulations, a 2D tissue model has been considered [8], [22]. A square 55x55 mm sheet is divided into elements of 100x100 μm as depicted in Figure 2. It represents an anisotropic ventricular tissue affected by regional acute ischemia. Three zones are distinguished with different electrophysiological conditions: normal zone (NZ), border zone (BZ) and central ischemic zone (CZ). To simulate myocardial ischemia, several physiological parameters have been altered in the central ischemic zone. The extracellular potassium concentration ($[K^+]_o$) is elevated [23], the depletion of oxygen in the cell is represented as a decrease in intracellular ATP concentration ($[ATP]_i$) and an increase in intracellular ADP concentration ($[ADP]_i$), which are responsible for ATP sensitive potassium channels activation [21]. Finally, a partial block of sodium and calcium channels provoked by acidosis has also been taken into account in the CZ. The values of these parameters are shown in Figure 2. As regards the border zone, we have considered a spatial gradient of variation for each

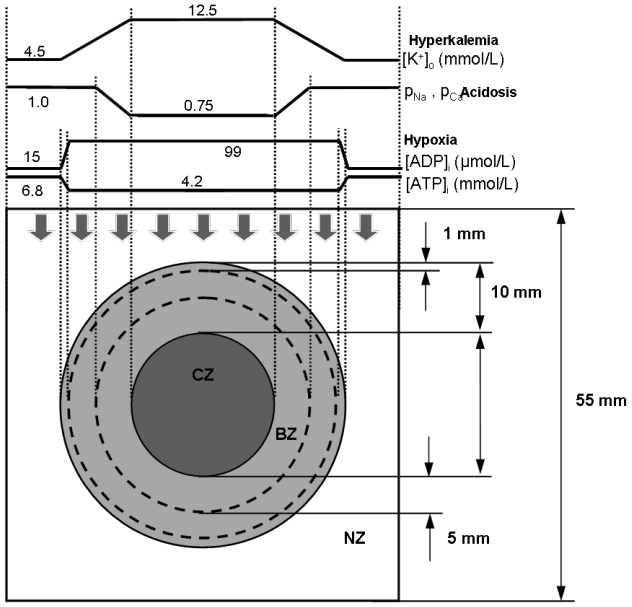

Fig. 2. Ischemic tissue of 55x55 mm with a normal zone (NZ), a border zone (BZ) and a central ischemic zone (CZ).

parameter from its normal value to the ischemic value, according to experimental studies. An anisotropic ratio of 3:1 is considered in the tissue through the values of longitudinal and transversal resistance (see [8], [22] for details).

3) Stimulation Protocol: In order to analyze vulnerability to reentries of the ischemic tissue, a vulnerable window (VW) was defined. This interval of time includes the instants of premature stimulation generating a reentry. The wider the vulnerable window is the more vulnerable the tissue is to reentry generation provoked by premature stimulation.

In first instance, we have monitored a basic simulation in which the upper edge of the tissue was stimulated with a current pulse of 90 nA in amplitude (corresponding to 1.5 times the threshold current) and 2 ms in duration, with 50 ms delay, in order to allow initial variables stabilization.

In second instance, we have applied a second and premature stimulus at instant t_2 at the same place in our tissue, and with the same amplitude. Next, we carried out 20 simulations varying the instant of premature stimulation ($t_2 = t_i$). This way, the tissue was stimulated with different coupling intervals. $t_i s$ were taken every 5 ms in order to stimulate between the instant 200 ms and 300 ms. We will refer to this method as the S_1-S_2 protocol, where S_1 is the basic stimulus and S_2 is the premature one.

B. Grid Infrastructure Employed

To support the execution of the cardiac case study, we have used a Grid infrastructure composed of three clusters of PCs within one of our research groups, whose main features are exposed in Table I. All the clusters of PCs are dual-processor machines and have the Globus Toolkit 2.4.3 installed, as this is a production Grid. However, GMarte

TABLE I
Detailed machine characteristics

Machine	Processors	Memory
Kefren	20 dual Intel Xeon 2.0 Ghz	1 GByte
Ramses	12 dual Intel Pentium III 866 Mhz	512 MBytes
Odin	55 dual Intel Xeon 2.8 Ghz	2 GBytes
Seker	1 quad Intel Xeon 2.0 Ghz	4 GBytes

TABLE II
Summary of the task allocation in the Grid deployment

Machine	Simulations
Kefren	1 (8 p.), 1 (4 p.), 1 (5 p.)
Ramses	1 (4 p.)
Odin	15 (8 p.), 1 (4 p.)

can also interact with GT4-based resources. In addition, a workstation server (Seker) hosts the GT4 deployment with the GMarte Grid service.

The machines are not exclusively dedicated to Grid purposes. In fact, the number of available computing nodes of each cluster before the Grid execution started was 17 (Kefren), 2 (Ramses) and 55 (Odin).

C. Computational Description of the Case Study

In order to perform an efficient execution of the case study, we decided to first execute a single simulation to obtain an application checkpoint at 200 ms, which represented a complete snapshot of the current state of the simulation (compressed to 72 MBytes), from which other simulations could resume execution. This information includes a copy of the value of each feature (membrane potential, ionic currents, etc.) for all the cells of the tissue. Therefore, the 20 simulations started from the previously generated checkpoint, as this information is transferred by GMarte to the remote machine before execution is started. Simulations were performed from 200 to 600 ms which was long enough to detect a reentry in the cardiac tissue. The simulation time step was 0.024, which was previously assessed to be small enough to capture the dynamics of ion currents. The membrane potential of all the cells of the tissue, in each simulation, was stored every 4 ms, what led to a total amount of data of 229 MBytes per simulation. This data enabled to generate a video animation, as part of the post-processing phase, which allowed the biomedical expert to visually detect reentries. It is important to point out that these executions enabled to obtain the vulnerable window with a resolution up to 5 ms. Additional simulations were required to provide a detailed window with a 1 ms resolution.

The varying parameter is the delay before the application of the second stimulus. We also limited up to 8 the number of processors to be employed in each parallel execution. This represents a simple and smart policy that enabled to allocate multiple executions to a resource instead of filling its capacity with just one simulation.

D. Execution Results

Table II summarizes the task allocation procedure. First of all a total of 16 simulations were dynamically assigned to Odin, with 8 or 4 processors each. On Kefren, three simulations were allocated with a different number of processors. On Ramses, only one execution was scheduled, with 4 processors. It should be pointed out that the metascheduler dynamically distributed the workload among the clusters of PCs according to their computational capacity, based on the number of available processors.

The case study execution required 336 minutes, since the scheduling started until the output data of the last task were retrieved by the local machine. Using a traditional sequential approach, executing one simulation after another on just 1 node of Odin cluster, required 17468 minutes (more than 12 days). Using only a High Performance Computing (HPC) approach, performing two simultaneous executions of 8-processors, in Odin cluster, required 2812 minutes. Thus, the Grid Computing approach was almost 52 times faster than sequential execution and achieved an speedup of 8.3 when compared to the HPC alternative. Regarding this HPC approach, we have considered a 16-processor cluster to be an average commodity machine, typically available in medium-sized research centres.

As a general rule, as the number of computational resources is increased, more simulations will be concurrently executed, thus reducing the total execution time. As a side effect, this increases the time invested in the resource selection phase, as this typically requires a time linear with the number of machines. In addition, moving to a geographically distributed Grid increases the time spent in the data transfers, what can be alleviated by resource selection policies that consider resource proximity. However, these costs can be clearly outweighed by the increased concurrency ratio, specially for long-running simulations. When all executions can proceed simultaneously, the only benefit of a larger infrastructure resides in the possibility of selecting better resources.

E. Case Study Results

Our results suggest that ischemic conditions predispose the heart to reentry occurrence and its generation strongly depends on the instant of premature stimulation. Vulnerability to reentries and intrinsic causes of reentrant arrhythmias were analyzed. The mechanistic insight gained from the monitored simulations is discussed below.

1) Reentrant patterns of activation and vulnerable window: We analyzed the patterns of excitation of the simulated tissue according to the S_1-S_2 protocol described in section IV-A3. As a consequence of the delivery of the basic stimulus S_1, APs wave propagated through the whole tissue. However, after the delivery of S_2, the patterns of excitation depended on the coupling interval used.

On the one hand, if S_2 was delivered before the instant 243 ms, where the stimulated cells have not recovered from refractoriness, no wavefront was elicited. On the

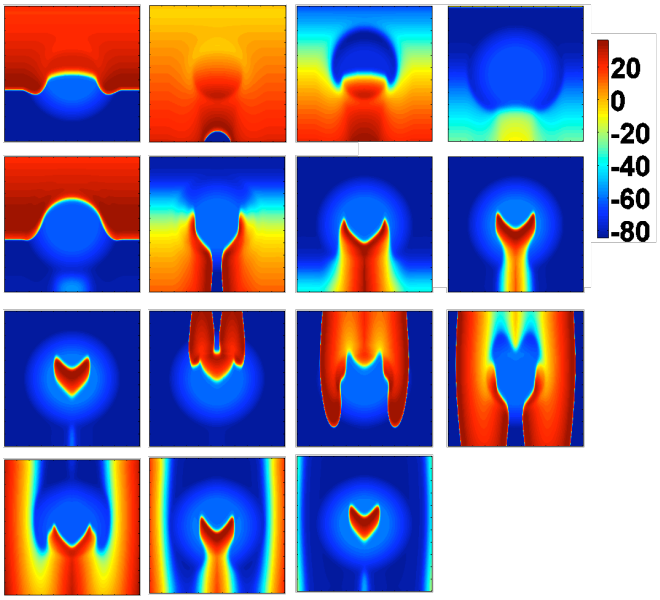

Fig. 3. Transmembrane voltage snapshots of the virtual tissue. Snapshots are separated by 50 milliseconds intervals, starting from instant 100 milliseconds up to 800 ms. The red (light) color indicates depolarized voltage and blue (dark) color repolarized voltage. The sequence starts in the upper-left corner, from left to right. The upper row shows the effect of the S_1 stimulus. S_2 was applied at the instant 250ms to the upper edge of the regional ischemic tissue. Electrical propagation goes up-down.

other hand, after instant 267 ms, the upper edge cells had recovered their excitability and so had also ischemic cells when the elicited wavefront reached them. Thus, the wavefront propagated through the whole tissue. Nevertheless, when S_2 was delivered between these two instants of time, reentrant patterns of excitation aroused in the simulated tissue. Therefore, the vulnerable window for reentry yielded [243,267] ms.

Figure 3 shows different stages of the electrical activity applying S_2 at instant 250 ms, thus within the vulnerable window. Each snapshot represents the spatial voltage distribution in the tissue, codified in a colored scale, at a given instant of time. As depicted in the first panels, in the initial stages of tissue activation following the delivery of stimulus S_2, the upper edge had already recovered its excitability and a downwards propagating wavefront was elicited. The excitation wave was planar in the proximal NZ but it curved when it reached the BZ and the CZ. This curvature is explained by the differences in longitudinal conduction velocity within each zone. Indeed, there is experimental evidence that action potential propagation is delayed within ischemic zones, whereas the border zone is characterized by supernormal conduction [19].

The reentry pattern consisted of two parallel reentry circuits closely resembling a figure-of-eight reentry obtained by Janse et al. in an ischemic pig heart [24]. In their experiments, they ligated the left anterior descending coronary artery of pig hearts. A few minutes after the ligation, similarly to our simulations, patterns of excitation consisting of figure-of-eight reentry were found, immediately before the onset of ventricular fibrillation.

V. Conclusions

This paper has addressed the combination of High Performance Computing and Grid Computing technologies to simulate the electrical activity on cardiac tissues. To efficiently execute the computationally intensive cardiac case studies, we have developed a service-oriented architecture, based on GMarte, that simplifies the usage of Grid Computing infrastructures running on the standard Globus Toolkit. This way, users need only focus on the definition of the tasks to be executed, whereas all the underlying complexity is handled by the developed system. This approach has proved to reduce the global execution time of cardiac case studies, compared with a traditional, sequential execution alternative. Therefore, more simulations per time unit can now be carried out, thus enabling to speed up the research procedure.

Concerning the case study, it is well known that under pathophysiological conditions abnormal automaticity can prematurely stimulate the tissue giving rise to reentrant circuits, as confirm our results. However, it is hard to analyze experimentally the intricate mechanisms standing for these patterns of activation. Our results suggest that different degrees of ischemia would change the vulnerability to reentries. In addition, the analysis of ionic mechanisms is a very helpful tool to approach therapies against reentrant arrhythmias which can degenerate into ventricular fibrillation. Not only should antiarrhythmic drugs be addressed, but also vasodilator drugs, such as potassium channel openers, could suppose a novel pharmacological approach in the treatment of reentrant arrhythmias.

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José M. Alonso obtained the MSc degree in Computer Science from the Universidad Politécnica de Valencia (UPV), Spain, in 1997. He is member of the High Performance Networking and Computing group of UPV since 1996. Since 2000 is an assistant lecturer in the same university. He is currently working towards the Ph.D. degree in the field of parallel and grid computing in simulation of building structures. He has also participated in different research projects concerning the application of parallel and grid computing techniques to several engineering areas.

José M. Ferrero (Jr.) was born in Madrid, Spain, in 1966. He became an Electronic Engineer in 1990 (Universidad Politécnica de Valencia, UPV, Spain) and received his Ph D. Degree from the same university in 1995. Part of his Ph. D. thesis was developed in the Department of Biomedical Engineering of the Johns Hopkins University (Baltimore, USA), where he was a research trainee in 1995. He is currently Full Professor in the Electronic Engineering Department and co-leader of the Cardiac Modelling Group in the Institute for Research and Innovation in Bioengineering of the UPV. His research interests include cardiac electrophysiology, computer modeling of the cardiac electrical activity, biomedical signal processing and bioelectronic instrumentation.

Vicente Hernández obtained the PhD degree in Mathematics from the Universidad de Valencia, Spain, in 1979. From 1991 he is full Professor in the Department of Information Systems and Computation, Universidad Politécnica de Valencia, Spain. Leader of the High Performance Networking and Computing Group, he has written over 220 journal and conference papers on Numerical Methods, Parallel Computing, Grid Computing and their Applications on different fields. He has supervised over 20 PhD thesis on Computational Science and Applied Mathematics. He has acted as coordinator or main researcher in more than 30 projects funded by national and international programmes.

Germán Moltó received the MSc degree in computer science from the Universidad Politécnica de Valencia (UPV) in 2002. Since then, he has been a researcher at the High Performance Networking and Computing Group, at UPV. In 2005 he obtained an Assistant Lecturer position. He is currently working towards the Ph.D. degree in the field of Grid Computing applied to biomedical applications such as the cardiac electrical activity simulation and the design of proteins.

Javier Saiz became an Electronic Engineer (1986) and received his Ph D. Degree (1992) from the Universidad Politécnica de Valencia (UPV), Spain. He is currently Full Professor in the Electronic Department and co-leader of the Cardiac Modelling Group in the Institute for Research and Innovation in Bioengineering of the UPV. In 1995 he was a Postdoctoral Research Fellow at Department of Biomedical Engineering at Johns Hopkins University, Baltimore, where he was involved in developing mathematical models of action potential propagation in heart tissue. His research interests include cardiac electrophysiology, computer modeling of cardiac electrical activity, biomedical signal processing and bioelectronic instrumentation.

Beatriz Trénor became an Electronic Engineer in 1997 (Universidad Politécnica de Valencia, Spain) and received her Ph D. Degree from the same university in 2001. She is Assistant Professor in the Electronic Department and researcher of the Cardiac Modelling Group in the Institute for Research and Innovation in Bioengineering of the UPV. Her research interests include cardiac electrophysiology and computer modeling of cardiac electrical activity.