Stanford Living Heart Project Focusing on Drug Induced Arrhythmia with Abaqus in the Cloud

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The UberCloud and Stanford University

***Abstract**: This project has been performed by researchers from the Living Matter Laboratory at Stanford University, supported by Living Heart Project members from SIMULIA (Abaqus 2017), Advania (cloud resources), and UberCloud (software containers), and sponsored by Hewlett Packard Enterprise and Intel. It is based on the development of a Living Heart Model (LHM) for Abaqus that encompasses advanced fluid-structure-electro-physiological modeling. The goal of this project was to create a biventricular finite element model to be used to study drug-induced arrhythmias of a human heart. The team was able to perform 1600 hours on 160 CPU cores, and simulation results compared with physical measurements show excellent consistency.*

***Keywords**: Abaqus, Biomechanics, Cloud Computing, Digital Twins, Electro-Physiological Modeling, Finite Element Analysis, Living Heart Project, Software Containers, Stanford University, and UberCloud Containers.*

1. Introduction

Before a new drug reaches the market, pharmaceutical companies need to check for the risk of inducing arrhythmias. This process takes years and involves costly animal and human studies. In this project, the Living Matter Laboratory of Stanford University developed a software tool enabling drug developers to quickly assess the viability of a new compound. This means better and safer drugs reaching the market to improve patients' lives.

Cardiac arrhythmia can be an undesirable and potentially lethal side effect of drugs. During this condition, the electrical activity of the heart turns chaotic, decimating its pumping function, thus diminishing the circulation of blood through the body. Some kind of cardiac arrhythmia, if not treated with a defibrillator, will cause death within minutes.

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2. The project team

This was a one-year project with the following team members: End User Francisco Sahli Costabal, PhD Candidate, and Prof. Ellen Kuhl, Living Matter Laboratory at Stanford University; Software Provider Dassault/SIMULIA with Tom Battisti and Matt Dunbar, providing Abaqus 2017 software and support; Resource Provider Advania Cloud in Iceland, represented by Aegir Magnusson and Jon Tor Kristinsson, providing access and support for the HPC server from HPE; and the HPC Cloud Expert Fethican Coskuner from UberCloud, with providing novel HPC container technology for ease of Abaqus cloud access and use. The authors also thank the Sponsor Hewlett Packard Enterprise, represented by Bill Mannel and Jean-Luc Assor.

3. The living heart project use case

This cloud experiment for the Living Heart Project (LHP) is a follow-on work of Team 196 first dealing with the implementation, testing, and Proof of Concept in the Cloud. It has been collaboratively performed by Stanford University, SIMULIA, Advania, UberCloud, and sponsored by Hewlett Packard Enterprise. It is based on the development of a Living Heart Model that encompasses advanced electro-physiological modelling. The goal is to create a biventricular finite element model to study drug-induced arrhythmias of a human heart.

The **Living Heart Project** is uniting leading cardiovascular researchers, educators, medical device developers, regulatory agencies, and practicing cardiologists around the world on a shared mission to develop and validate highly accurate personalized digital human heart models. These models will establish a unified foundation for cardiovascular in silico medicine and serve as a common technology base for education and training, medical device design, testing, clinical diagnosis and regulatory science —creating an effective path for rapidly translating current and future cutting-edge innovations directly into improved patient care.

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Before a new drug reaches the market, pharmaceutical companies need to check for the risk of inducing arrhythmias. Currently, this process takes years and involves costly animal and human studies. With this new software tool, drug developers would be able to quickly assess the viability of a new compound. This means better and safer drugs reaching the market to improve patients' lives.

The Stanford team in conjunction with SIMULIA have developed a multi-scale 3-dimensional model of the heart that can predict the risk of this lethal arrhythmias caused by drugs. The project team added several capabilities to the Living Heart Model such as highly detailed cellular models, the ability to differentiate cell types within the tissue and to compute electrocardiograms (ECGs). A key addition to the model is the so-called Purkinje network. It presents a tree-like structure and is responsible of distributing the electrical signal quickly through the ventricular wall. It plays a major role in the development of arrhythmias, as it is composed of pacemaker cells that can self-

excite. The inclusion of the Purkinje network was fundamental to simulate arrhythmias. This model is now able to bridge the gap between the effect of drugs at the cellular level to the chaotic electrical propagation that a patient would experience at the organ level.

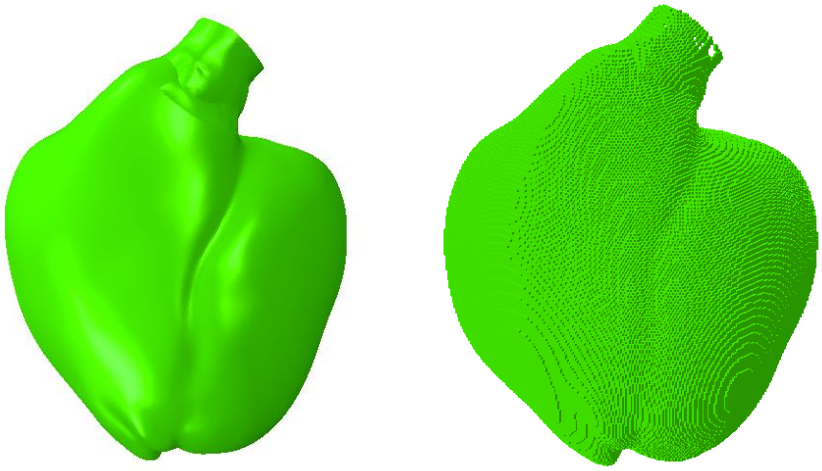

Figure 1: Tetrahedral mesh (left) and cube mesh (right).

4. Computational modeling

A computational model that is able to assess the response of new drug compounds rapidly and inexpensively is of great interest for pharmaceutical companies, doctors, and patients. Such a tool will increase the number of successful drugs that reach the market, while decreasing cost and time to develop them, and thus help hundreds of thousands of patients in the future. However, the creation of a suitable model requires taking a multiscale approach that is computationally expensive: the electrical activity of cells is modelled in high detail and resolved simultaneously in the entire heart. Due to the fast dynamics that occur in this problem, the spatial and temporal resolutions are highly demanding.

During the preparation and Proof of Concept phase (UberCloud Experiment 196) of this LHP project, we set out to build and calibrate the healthy baseline case, which we then used to perturb with different drugs. After creating the UberCloud software container for SIMULIA's Abaqus 2017 and deploying it on HPE's server in the Advania cloud, we started refining the computational mesh which consisted of roughly 5 million tetrahedral elements and 1 million nodes. Due to the intricate geometry of the heart, the mesh quality limited the time step, which in this case was 0.0012 ms for a total simulation time of 5000 ms. After realizing that it would be very difficult to calibrate our model with such a big runtime, we decided to work on our mesh, which was the current bottleneck to speed up our model. We created a mesh that was made out of cube elements (Figure 1). With this approach, we lost the smoothness of the outer surface, but

reduced the number of elements by a factor of ten and increased the time step by a factor of four, for the same element size (0.7 mm).

Figure 2: The final production model with an element size of 0.3 mm. The Purkinje network is shown in white. Endocardial, mid layer and epicardial cells are shown in red, white and blue respectively.

After adapting all features of the model to this new mesh with now 7.5 million nodes and **250,000,000 internal variables that are updated and stored within each step of the simulation** (Figure 2), we were able to calibrate the healthy, baseline case, which was assessed by electro-cardiogram (ECG) tracing (Figure 3) that recapitulates the essential features.

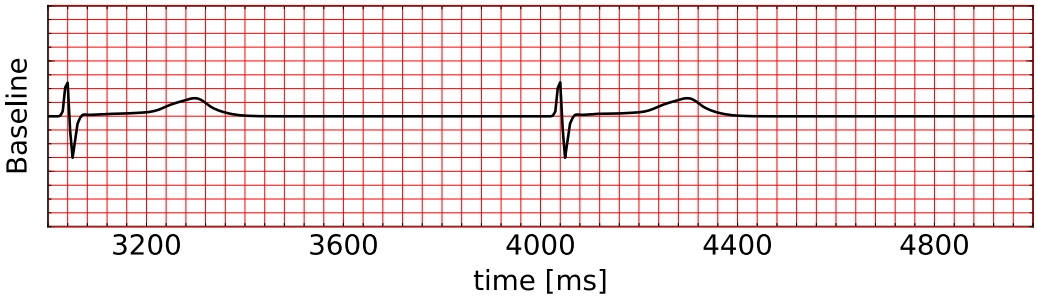

Figure 3: ECG tracing for the healthy, baseline case.

5. Simulations and results

During the final production phase, we have run 42 simulations to study whether a drug causes arrhythmias or not. With all these changes we were able to **speed up one simulation by a factor of 27** which then (still) took 40 hours using 160 CPU cores on Advania's HPC as a Service (HPCaaS) hardware configuration built upon HPE ProLiant servers XL230 Gen9 with 2x Intel Broadwell E5-2683 v4 with Intel OmniPath interconnect. We observed that the model scaled

without a significant loss of performance up to 240 compute cores, making the 5-node sub-cluster of the Advania system an ideal candidate to run these compute jobs. In these simulations, we applied the drugs by blocking different ionic currents in our cellular model, exactly replicating what has been observed before in cellular experiments. For each case, we let the heart beat naturally and see if the arrhythmia is developing.

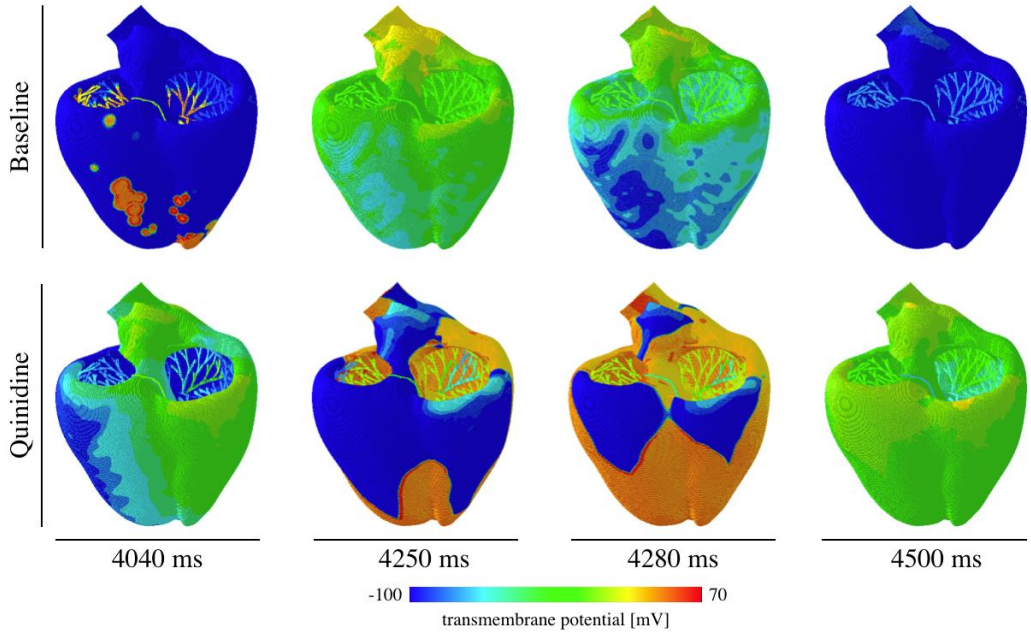

Figure 4: Evolution of electrical activity for the baseline case (no drug) and after the application of the drug Quinidine. The electrical propagation turns chaotic after the drug is applied, showing the high risk of Quinidine to produce arrhythmias.

Figure 4 shows the application of the drug Quinidine, which is an anti-arrhythmic agent, but it has a high risk of producing Torsades de Pointes, which is a particular type of arrhythmia. It shows the electrical transmembrane potentials of a healthy versus a pathological heart that has been widely used in studies of normal and pathological heart rhythms and defibrillation. The propagation of the electrical potential turns chaotic (Figure 4, bottom) when compared to the baseline case (Figure 4, top), showing that our model is able to correctly and reliably predict the anti-arrhythmic risk of commonly used drugs. We envision that our model will help researchers, regulatory agencies, and pharmaceutical companies rationalize safe drug development and reduce the time-to-market of new drugs.

Some of the challenges that we faced during the project were:

- Although the remote desktop setup enabled us to visualize the results of our model, it was not possible to do more advanced operations. The bandwidth between the end user and the servers was acceptable for file transfer, but not enough to have a fluid remote desktop. We suggested to speed-up remote visualization which has now been implemented including NICE Software's DCV into the UberCloud software container "(Gentzsch, 2016)", making used of GPU accelerated data transfers.
- Running the final complex simulations first on the previous-generation HPC system at Advania took far too long and we would have not been able to finish the project in time. Therefore, we moved our Abaqus 2017 container seamlessly to the new HPC system (which was set up in July 2017) and got an immediate speedup of 2.5 between the two HPE systems.

Some of the benefits that we experienced:

- Gaining easy and intuitive access to sufficient HPC resources enabled us to study drug-induced arrhythmias of a human heart in a reasonable amount of time. With our local machines, with just 32 CPU cores, these simulations would have been impossible.
- As we had a dedicated 5-node HPC cluster in the cloud, it was easy to run post-processing scripts, without the need of submitting a second job in the queue, which would be the typical procedure of a shared HPC resource.
- Since all project partners had access to the same Abaqus 2017 container on the HPC server, it was easy to jointly debug and solve problems as a team. Also, sharing models and results between among the end user and the software provider was straight-forward.
- The partnership with UberCloud has allowed us to perform virtual drug testing using realistic human heart models. For us, UberCloud's high-performance cloud computing environment and the close collaboration with HPE, Dassault, and Advania, were critical to speed-up our simulations, which help us to identify the arrhythmic risk of existing and new drugs in the benefit of human health."

6. References

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