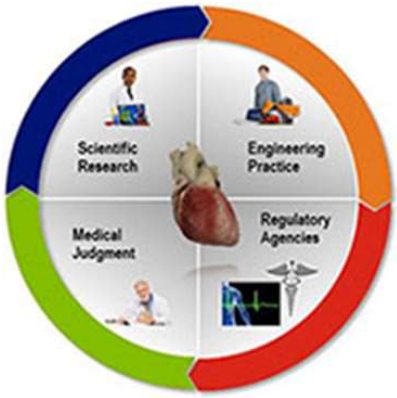
Studying Drug-induced Arrhythmias of a Human Heart with Abaqus 2017 in the Cloud

An UberCloud Experiment for the Living Heart Project



Stanford University

SIMULIA

advania data centres

With Support From:

UberCloud

Hewlett Packard Enterprise

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This UberCloud Experiment received two prestigious awards during the Supercomputing Conference 2017 in Denver:

1. **The 2017 HPCwire Editors Choice award for Best use of HPC in the Cloud**
2. **The 2017 Hyperion/IDC Innovation Award**

UberCloud Case Study 197

http://www.TheUberCloud.com

September 21, 2017

Welcome!

The UberCloud* Experiment started in July 2012, with a discussion about cloud adoption in technical computing and a list of technical and cloud computing challenges and potential solutions. We decided to explore these challenges further, hands-on, and the idea of the UberCloud Experiment was born, then also due to the excellent support from INTEL generously sponsoring these experiments since the early days!

We found that especially small and medium enterprises in digital manufacturing would strongly benefit from technical computing in HPC centers and in the cloud. By gaining access on demand from their desktop workstations to additional and more powerful compute resources in the cloud, their major benefits became clear: the **agility** gained by shortening product design cycles through shorter simulation times; the superior **quality** achieved by simulating more sophisticated geometries and physics and by running many more iterations to look for the best product design; and the **cost** benefit by only paying for what is really used. These are benefits that obviously increase a company's innovation and competitiveness.

Tangible benefits like these make computing - and more specifically technical computing as a service in the cloud - very attractive. But how far are we from an ideal cloud model for engineers and scientists? At first we didn't know. We were facing challenges like security, privacy, and trust; traditional software licensing models; slow data transfer; uncertain cost & ROI; lack of standardization, transparency, cloud expertise. However, in the course of this experiment, as we followed each of the 197 teams closely and monitored their challenges and progress, we've got an excellent insight into these roadblocks, how our teams have tackled them, and how we are now able to reduce or even fully resolve them.

This cloud experiment is a follow-on work of Team 196 and was 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 modeling. The goal is to create a biventricular finite element model to study drug-induced arrhythmias of a human heart.

We want to thank all team members for their continuous commitment and contribution to this project. And we want to thank our main Compendium sponsors **Hewlett Packard Enterprise** and **INTEL** for generously supporting these 197 UberCloud experiments. A big Thank You also to the **HPCwire Team** which published it as a Special Feature, and to the readers of HPCwire who nominated this project for the 2017 **HPCwire Readers' Choice Award**!

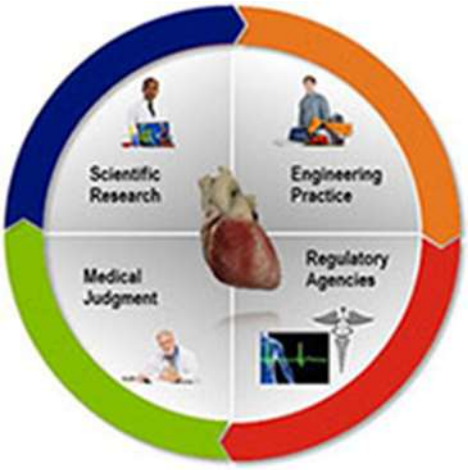
Now, enjoy reading!

Wolfgang Gentzsch and Burak Yenier

**) UberCloud is the online community & marketplace where engineers and scientists discover, try, and buy Computing Power as a Service, on demand. Engineers and scientists can explore and discuss how to use this computing power to solve their demanding problems, and to identify the roadblocks and solutions, with a crowd-sourcing approach, jointly with our engineering and scientific community. Learn more about the UberCloud at: http://www.TheUberCloud.com.*

Team 197

Studying Drug-induced Arrhythmias of a Human Heart with Abaqus 2017 in the Cloud



"We were able to easily access sufficient HPC resources to study drug-induced arrhythmias in a reasonable amount of time. With our local machines, with just 32 CPU cores, these simulations would have been impossible."

MEET THE TEAM

End User – Francisco Sahli Costabal, PhD Candidate, and Prof. Ellen Kuhl, Living Matter Laboratory at Stanford University.

Software Provider – Dassault/SIMULIA (Tom Battisti, Matt Dunbar) providing Abaqus 2017 software and support.

Resource Provider – Advania Cloud in Iceland (represented by Aegir Magnusson and Jon Tor Kristinsson), with access and support for the HPC server from HPE.

HPC Cloud Experts – Fethican Coskuner and Wolfgang Gentzsch, UberCloud, with providing novel HPC container technology for ease of Abaqus cloud access and use.

Sponsor – Hewlett Packard Enterprise, represented by Stephen Wheat, Bill Mannel, and Jean-Luc Assor

"Our successful 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."

Prof. Ellen Kuhl, Head of Living Matter Laboratory at Stanford University

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.

Cardiac arrhythmias 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 arrhythmias, if not treated with a defibrillator, will cause death within minutes.

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.

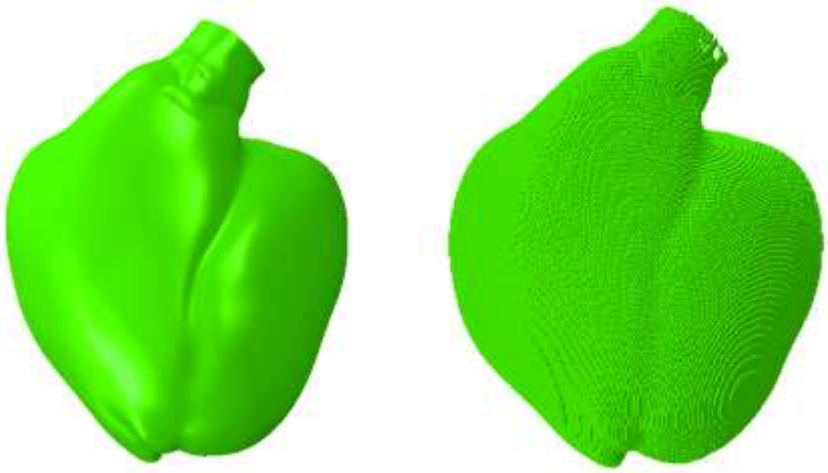


Figure 1: Tetrahedral mesh (left) and cube mesh (right)

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.

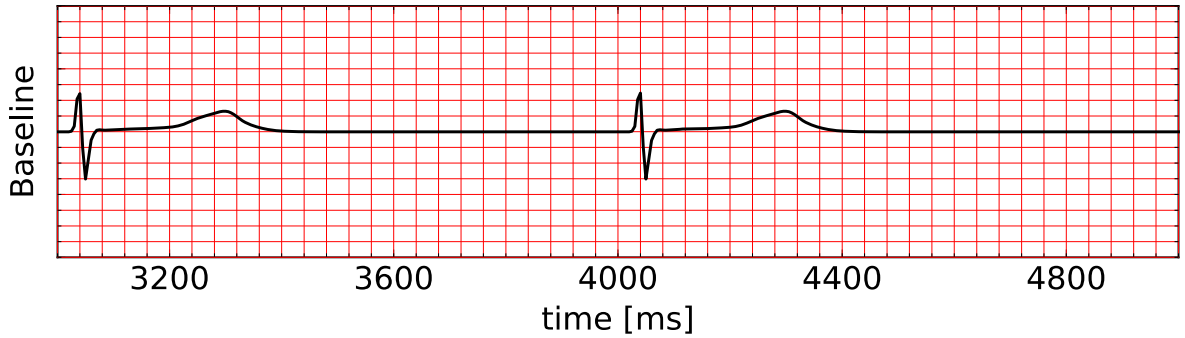


Figure 3: ECG tracing for the healthy, baseline case.

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.

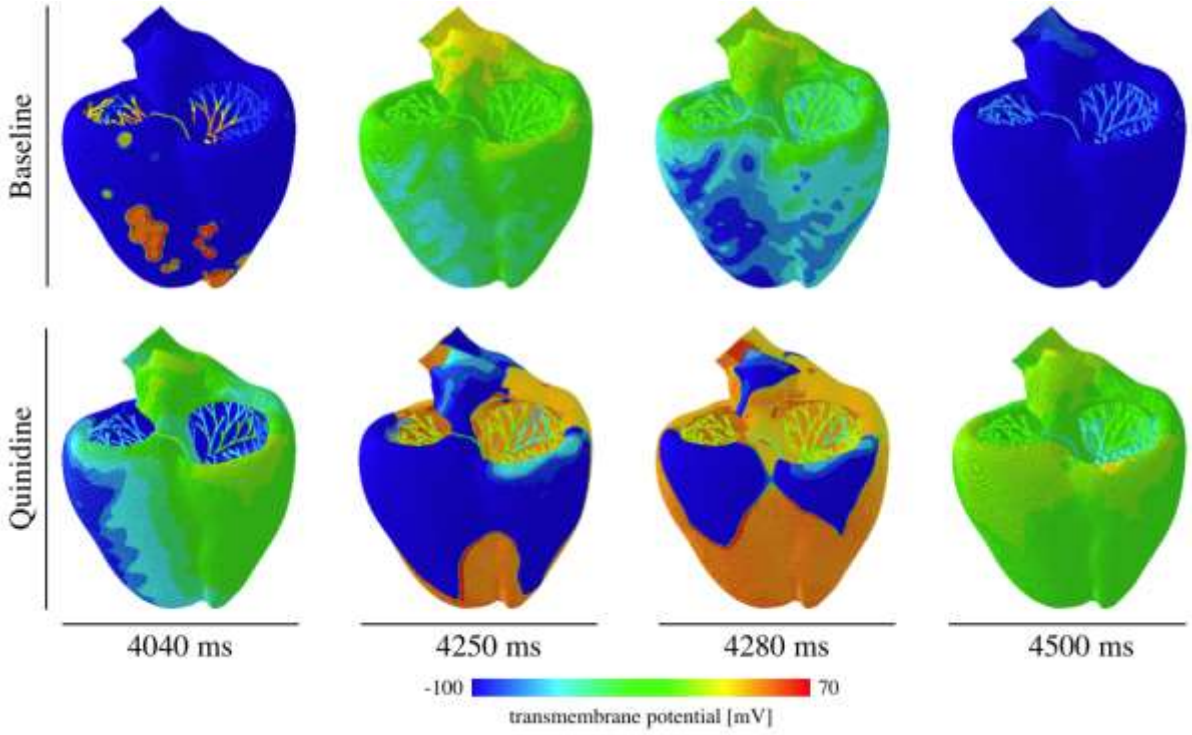


Figure 4: Evolution of the electrical activity for the baseline case (no drug) and after the application of the drug Quinidine. The electrical propagation turns chaotic after the drug is applied, showing the high risk of Quinidine to produce arrhythmias.

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, 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.

Case Study Author – Francisco Sahli Costabal together with Team 197.

Appendix

This research has been presented at the Cardiac Physiome Society Conference in Toronto November 6 – 9, 2017, https://www.physiome.org/cardiac2017/index.html.

Title: Predicting drug-induced arrhythmias by multiscale modeling

Presented by: Francisco Sahli Costabal, Jiang Yao, Ellen Kuhl

Abstract:

Drugs often have undesired side effects. In the heart, they can induce lethal arrhythmias such as Torsades de Points. The risk evaluation of a new compound is costly and can take a long time, which often hinders the development of new drugs. Here we establish an ultra high resolution, multiscale computational model to quickly and reliably assess the cardiac toxicity of new and existing drugs. The input of the model is the drug-specific current block from single cell electrophysiology; the output is the spatio-temporal activation profile and the associated electrocardiogram. We demonstrate the potential of our model for a low risk drug, Ranolazine, and a high risk drug, Quinidine: For Ranolazine, our model predicts a prolonged

QT interval of 19.4% compared to baseline and a regular sinus rhythm at 60.15 beats per minute. For Quinidine, our model predicts a prolonged QT interval of 78.4% and a spontaneous development of Torsades de Points both in the activation profile and in the electrocardiogram. We also study the dose-response relation of a class III antiarrhythmic drug, Dofetilide: At low concentrations, our model predicts a prolonged QT interval and a regular sinus rhythm; at high concentrations, our model predicts the spontaneous development of arrhythmias. Our multiscale computational model reveals the mechanisms by which electrophysiological abnormalities propagate across the spatio-temporal scales, from specific channel blockage, via altered single cell action potentials and prolonged QT intervals, to the spontaneous emergence of ventricular tachycardia in the form of Torsades de Points. We envision that our model will help researchers, regulatory agencies, and pharmaceutical companies to rationalize safe drug development and reduce the time-to-market of new drugs.

Thank you for your interest in the free and voluntary UberCloud Experiment.

If you, as an end-user, would like to participate in an UberCloud Experiment to explore hands-on the end-to-end process of on-demand Technical Computing as a Service, in the Cloud, for your business then please register at: http://www.theubercloud.com/hpc-experiment/.

If you, as a service provider, are interested in building a SaaS solution and promoting your services on the UberCloud Marketplace then please send us a message at https://www.theubercloud.com/help/.

2013 Compendium of case studies: https://www.theubercloud.com/ubercloud-compendium-2013/
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HPCwire Readers Choice Award 2013: http://www.hpcwire.com/off-the-wire/ubercloud-receives-top-honors-2013-hpcwire-readers-choice-awards/
HPCwire Readers Choice Award 2014: https://www.theubercloud.com/ubercloud-receives-top-honors-2014-hpcwire-readers-choice-award/
Gartner Cool Vendor Award 2015: http://www.digitaleng.news/de/ubercloud-names-cool-vendor-for-oil-gas-industries/

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