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Physiologically realistic study of subcellular calcium dynamics with nanometer resolution

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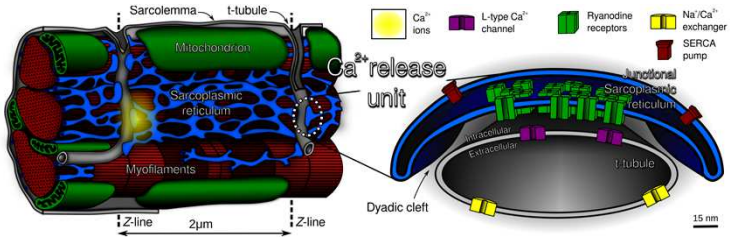
Background

To initiate a heartbeat, calcium is released from numerous tiny storage units inside each cardiac cell. Synchronous and stable calcium handling is vital for normal heart contraction. In failing cells, calcium release becomes dyssynchronous, slower and less reliable, leading to arrhythmogenic and potentially lethal conditions. However, there lacks a physiologically accurate description of both healthy and pathological calcium releases.

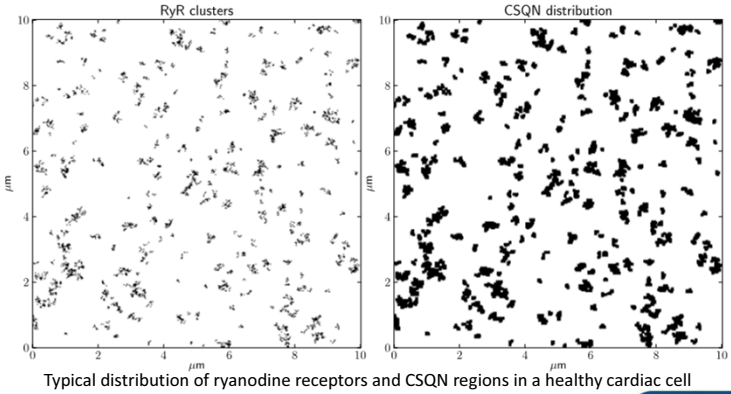


A schematic overview of a sarcomere (1/50 of a cardiac cell) and a calcium release unit

Challenges & objectives

There are about 10,000 calcium release units in each heart cell. Some of the structural details are down to the nanometer scale. Computer simulations of subcellular calcium dynamics, by solving elaborately coupled differential equations, require very high resolutions and thereby huge computations that are only possible on supercomputers.

We want to enable subcellular calcium dynamics simulations with physiological realism, for studying the impacts of cardiac pathological changes, including structural changes in the shape and spread of calcium release units, altered number of calcium release channels, and altered gating kinetics of the channels. Also, we want to enrich the general knowledge about performance optimization of multiple inter-tangled stencil computations, and investigate the possibility of analyzing huge volumes of simulation results in-situ with help of high-speed file cache systems.



Typical distribution of ryanodine receptors and CSQN regions in a healthy cardiac cell

Research plan

Starting from an existing small-scale subcellular calcium dynamics simulator, using Oakforest-PACS as well as Reedbush-U, we envision a project period of two years, involving the following main activities:

- *Single-core optimization on Knights Landing processor (M1-M6)*
- *Single-node of Knights Landing optimization (M7-M8)*
- *Multi-node of Knights Landing optimization (M9-M10)*
- *Small and medium-scale simulations (M10-M14)*
- *Large and extreme-scale simulations (M15-M18)*
- *Experiments with high-speed file cache systems (M19-M22)*
- *Project conclusion and review (M23-M24)*

The project team consists of researchers from the University of Tokyo and Simula Research Lab, spanning the expertise areas of mathematical modeling, numerical methods, parallel programming and high-performance computing.

Significance of research

Current simulations of subcellular calcium dynamics have insufficient physiological realism due to (1) The true 3D geometries of the calcium release units are not properly resolved; (2) The computational domain only covers a tiny piece of the cell involving a very small number of calcium release units.

This project will help to consolidate a multi-scale mathematical model that gives a physiologically accurate description of healthy and pathological calcium releases, advancing the current scientific understanding of subcellular calcium dynamics. The work on optimizing the subcellular simulator for Oakforest-PACS will produce new knowledge about coding multiple inter-tangled stencil computations for the Knights Landing architecture. Important experience will also be obtained on using high-speed file cache systems with respect to in-situ huge-scale data analysis.

References

- J. Chai, J. Hake, N. Wu, M. Wen, X. Cai, G. T. Lines, J. Yang, H. Su, C. Zhang, and X. Liao. ***Towards simulation of subcellular calcium dynamics at nanometre resolution***. International Journal of High Performance Computing Applications, 29(1):51–63, 2015.
- J. Hake, A.G. Edwards, Z. Yu, P.M. Kekenes-Huskey, A.P. Michailova, J.A. McCammon, M.J. Holst, M. Hoshijima, A.D. McCulloch. ***Modelling cardiac calcium sparks in a three-dimensional reconstruction of a calcium release unit.*** Journal of Physiology, vol. 590:18, pp. 4403-4422, 2012.
- K. Nakajima et al. ***ppOpen-HPC: Open Source Infrastructure for Development and Execution of Large-Scale Scientific Applications on Post-Peta-Scale Supercomputers with Automatic Tuning (AT).*** Optimization in the Real World –Towards Solving Real-Worlds Optimization Problems, Mathematics for Industry 13, pp. 15-35, Springer, 2016.
- K. Nakajima, T. Hanawa. **Communication-Computation Overlapping with Dynamic Loop Scheduling for Preconditioned Parallel Iterative Solvers on Multicore/Manycore Clusters.** IEEE Proceedings of P2S2 2017.
- J. Langguth, C. Jarvis, X. Cai. ***Porting tissue-scale cardiac simulations to the Knights Landing Platform.*** Proceedings of ICS 2017, Springer LNCS vol. 10524, pp. 376-388, 2017.