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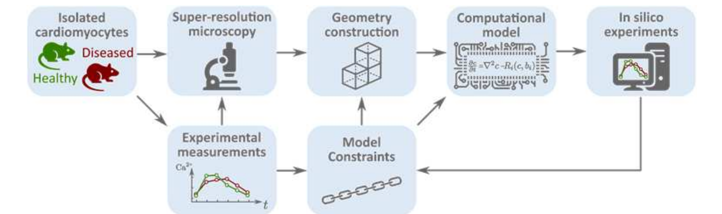
Kengo Nakajima (The University of Tokyo, Japan)

Physiologically realistic study of subcellular calcium dynamics with nanometer resolution

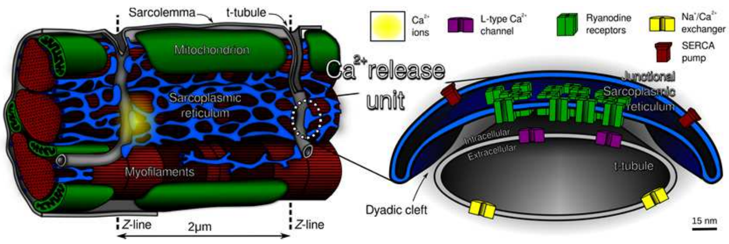
X. Cai, G. T. Lines, C. Jarvis, J. van den Brink, J. Langguth (Simula Research Laboratory, Norway)
A. Ida, T. Hanawa, T. Hoshino, M. Matsumoto (The University of Tokyo, Japan), M. Kawai (RIKEN R-CCS, Japan)

Motivation

Cardiac diseases can degrade the micro-anatomical structures in cardiac muscle cells responsible for the excitation-contraction (EC) coupling, which is vital for the functioning of the heart. *In silico* experiments (computer simulations) are important for studying the structure-functional relationships of EC coupling and the functional impacts of disease-driven structural remodeling, *e.g.*, disintegration of calcium release units, as well as changes in the number and distribution of calcium release channels.



The pipeline for studying the structure-functional relationships of EC coupling in the heart and the effects of disease-driven remodeling



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

Challenges & goals

In each heart cell, there are about 10,000 calcium release units, with structural details down to the nanometer scale. Extremely high spatial and temporal resolutions are thus needed to solve the involved differential equations, leading to huge computations that require efficient use of supercomputers.

In this project, we aim to enable subcellular calcium dynamics simulations with physiological realism. This requires (1) using data provided by 3D super-resolution microscopy and (2) simulating a large number of calcium release units together. The challenges include hardware-compatible optimizations of an old 3D simulator of subcellular calcium dynamics, plus calibration and validation of the mathematical model and the parameters.

This project will help to consolidate a multi-scale mathematical model that gives a physiologically accurate description of healthy and pathological calcium releases, thus advancing the current scientific understanding of subcellular calcium dynamics. The work on optimizing the subcellular simulator for Oakforest-PACS will also produce new knowledge about coding multiple inter-tangled stencil computations for the Knights Landing architecture.

Results obtained in FY2018

1. OpenMP parallelization added to the old MPI-only simulator.

	OpenMP	Average per MPI process	Max per MPI process	Min per MPI process
MPI communication	N/A	25.69	27.78	3.56
Diffusion comp.	31.17	27.18	29.57	25.58
Reaction comp.	16.86	14.50	15.46	14.34
Increment comp.	12.21	3.94	4.68	3.45
Whole simulation	64.05	79.70	79.76	79.60

2. Reduction of memory footprint by adopting a lookup table for the diffusion computation involved, instead of using 3D arrays of coefficients. The saving of memory usage is more than 50%.

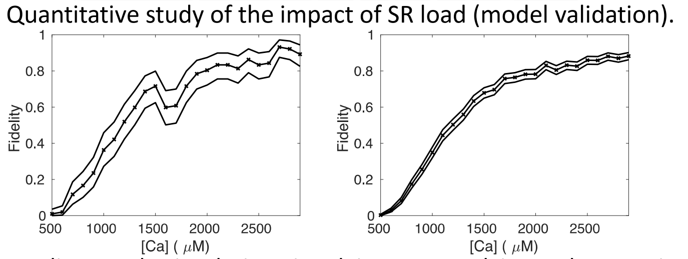
```
int di = domain_ids[xi][yi][zi];
int di_xm = domain_ids[xi-1][yi][zi], di_xp = domain_ids[xi+1][yi][zi];
int di_ym = domain_ids[xi][yi-1][zi], di_yp = domain_ids[xi][yi+1][zi];
int di_zm = domain_ids[xi][yi][zi-1], di_zp = domain_ids[x][yi][zi+1];
du[xi][yi][zi] = (lookup[di][di_xm]*(u[xi-1][yi][zi]-u[xi][yi][zi])
            + lookup[di][di_xp]*(u[xi+1][yi][zi]-u[xi][yi][zi])
            + lookup[di][di_ym]*(u[xi][yi-1][zi]-u[xi][yi][zi])
            + lookup[di][di_yp]*(u[xi][yi+1][zi]-u[xi][yi][zi])
            + lookup[di][di_zm]*(u[xi][yi][zi-1]-u[xi][yi][zi])
            + lookup[di][di_zp]*(u[xi][yi][zi+1]-u[xi][yi][zi]))/h/h*dt;
```

3. Explicit code vectorization using AVX-512 intrinsics, applied to the diffusion and reaction computations. (Experiments show that compiler-enabled auto vectorization is not sufficiently effective.)

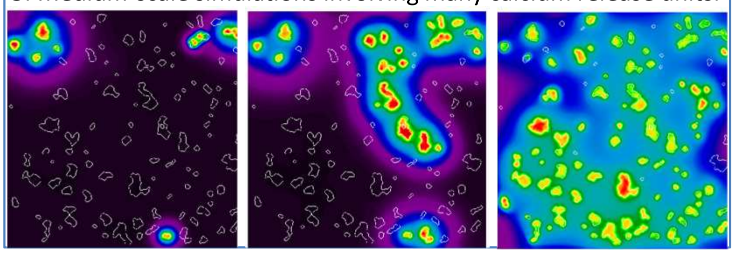
Global computational mesh: $672 \times 672 \times 168$, time steps: 1000

Version	CA_auto		LUT_auto		CA_man		LUT_man1		LUT_man2	
MPI procs	T_R	T_D	T_R	T_D	T_R	T_D	T_R	T_D	T_R	T_D
$4 \times 2 \times 2 = 16$	73.7	127.7	73.7	184.7	24.8	102.5	24.6	84.6	24.5	60.1
$4 \times 4 \times 2 = 32$	36.9	65.4	36.9	92.0	12.4	50.7	12.4	42.7	12.4	30.5
$4 \times 4 \times 4 = 64$	18.0	48.8	18.0	59.7	6.7	36.1	6.7	27.7	6.7	21.5
$8 \times 4 \times 4 = 128$	11.9	45.9	12.0	51.1	4.6	37.2	4.5	24.0	4.7	20.7
$8 \times 8 \times 4 = 256$	10.7	41.2	10.6	43.2	4.8	36.9	4.5	24.3	4.4	21.7

4. Quantitative study of the impact of SR load (model validation).



5. Medium-scale simulations involving many calcium release units.



Plan for FY2019

We will continue with the following activities in FY2019:

- *Verification of the single-processor-core* SIMD *performance*
- *Profiling and optimization of the* MPI *communication*
- *Performance tuning of the hybrid* MPI+OpenMP *code*
- *Further validation of the mathematical model*
- *Large and extreme-scale simulations on* Oakforest-PACS
- *Experiments with high-speed file cache systems*