**Proceedings of the 7th GACM Colloquium on Computational Mechanics
for Young Scientists from Academia and Industry
October 11-13, 2017 in Stuttgart, Germany**

Modelling the neuromuscular system using HPC systems

Thomas Klotz[1]*, Nehzat Emamy[2], Thomas Ertl[3], Dominik Göddeke[4], Aaron Krämer[4], Michael Krone[3], Benjamin Maier[2], Miriam Mehl[2], Tobias Rau[3] and Oliver Röhrle[1]

Micro Abstract
Modelling the neuromusclular system is challenging due to its high compexlity and variability. Formulating models that account for a realistic biophysical motivated activation process leads to computational expensive multi-scale simulations, in which the availible computing environment limits model detail and model size. We aim to push these boundaries by using massively parallel HPC clusters and efficient algorithms.

[1]Institute of Applied Mechanics (CE) - Group on Continuum Biomechanics and Mechanobiolgy, University of Stuttgart, Stuttgart, Germany

[2]Institute for Parallel and Distributed Systems, University of Stuttgart, Stuttgart, Germany

[3]Visualisation Research Center of the University of Stuttgart (VISUS), University of Stuttgart, Stuttgart, Germany

[4]Institute of Applied Analysis and Numerical Simulation, University of Stuttgart, Stuttgart, Germany

***Corresponding author**: thomas.klotz@mechbau.uni-stuttgart.de

Introduction

Skeletal muscle contraction and force production is caused by a complex interplay of a large set of muscle fibres. Therefor muscle fibres are activated (frequency coded signals) by motor neurons, that integrate signals from the central nervous system and sensory receptors. Due to the huge number of possible stimulation patterns, the neuromuscular system is able to perform various, partly contradictory tasks (e.g., lifting heavy weights and peforming brain surgery). Even though the main functional principles of individual muscle components are well understood, it is challenging to experimentally analyse skeletal muscles control principles and function in-vivo, due to the complex interplay of multiple functional units. Detailed biophysical models of skeletal muscle tissue can overcome these limitations, because it is possible to perform numerical experiments in a controlled environment. However, from a modelling perspective, the high variability of the neuromuscular system is challenging, since the complex, adaptable behaviour of skeletal muscles can not be reproduced by a simple lumped model. Formulating models that account for a realistic biophysical motivated activation process leads to computational expensive multi-scale simulations, what limits the applicability of such models. In order to overcome these limitations, we want to optimise our multi-scale skeletal muscle model [2–4] for the use on HPC clusters by using the open source software library OpenCMISS [1] for modelling and simulating different biomedical engineering applications. Further, specialised visualisation tools need to be developed, that are able to handle the generated data efficiently. Within that contribution we want to demonstrate our multidisciplinary approach how we optimise our multi-scale skeletal model [2–4] for the use on HPC clusters.

The multi-scale skeletal muscle model

Anatomically, skeletal muscles are constructed in a hierarchical structure. Starting at the micro-scale, the sarcomere is the smallest functional unit of the muscle, consisting of a periodical structure of thin actin and thick myosin filaments. Multiple sarcomeres (in series and in parallel)

form a muscle fibre and multiple fibres connected by extracellular matrix form fasciles, that determine the properties of the muscle. Muscle fibres are innervated from lower motor neurons, leading to the propagation of action potentials along the muscle fibres. When activated through an action potential, actin filaments and myosin filaments can form cross-bridges stimulated by calcium as an second messenger. The repeated process of cross-bridge binding, power-stroke and detachment leading to active contraction and force generation is known as cross-bridge cycle.

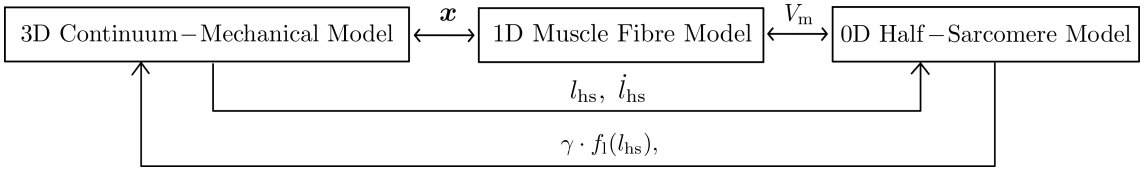

Figure 1. Schematic overview of the multi-scale skeletal muscle modelling framework [2–4].

Due to skeletal muscles hierarchical structure, the macroscopic tissue properties can be derived from the muscles' cellular behaviour. Therefore, we use a multi-scale modelling approach, linking the macroscopic tissue properties to a biophysical description of the muscle cell. We use a continuum-mechanical modelling approach based on the theory of finite elasticity to simulate the macroscopic deformations and stresses of skeletal muscle tissue. The electrophysiological properties of muscle fibres can be simulated using the monodomain model. In the multi-scale model, the monodomain model, which is a reaction-diffusion equation [5], is solved on a set of representative computational muscle fibres that are embedded into the three-dimensional muscle geometry.

The monodomain model can be derived from Maxwell-equations and is based on the homogeneity assumption, that intracellular and extracellular space occupy the same physical space and are seperated by the muscle fibre membrane (sarcolemma). The monodomain model assumes that intracellular and extracellular space are electrically coupled through ion channels and capacitive properties of the membrane. We use a detailed biophysical sub-cellular model of the muscle fibre membrane, intracellular calcium dynamics and cross-bridge cycling [6] (system of ordinary differential equations). The mondomain model can be summarised by the following set of equations:

$$\frac{\partial V_\mathrm{m}}{\partial t} = \frac{1}{A_\mathrm{m} C_\mathrm{m}} \left(\frac{\partial}{\partial s} \left(\sigma_\mathrm{eff} \frac{\partial V_\mathrm{m}}{\partial s} \right) - A_\mathrm{m} I_\mathrm{ion}(V_\mathrm{m}) \right) , \tag{1a}$$

$$\frac{\partial \boldsymbol{y}}{\partial t} = G_{\boldsymbol{y}} \left(\boldsymbol{y}, V_\mathrm{m} \right) , \tag{1b}$$

therein V_m is the trans-membrane potential, A_m is the fibre surface-to-volume ration, C_m is the capacity of the sarcolemma, I_ion the ionic current flowing through the ion channels, $\boldsymbol{y}$ is a vector containing the state variables of the cell model, $G_{\boldsymbol{y}}$ summarizes the right-hand-side of the ODE system, t is the time and s denotes the spatial coordinate.

The governing equation for the continuum-mechanical problem is the balance of linear momentum. When neglecting inertia forces and body forces, the balance of linear momentum reduces to the quasi-static problem

$$\operatorname{div} \boldsymbol{P} = \boldsymbol{0} , \tag{2}$$

where $\boldsymbol{P}$ denotes the first Piola-Kirchhoff stress tensor. It is assumed, that the overall mechanical behaviour of skeletal muscle tissue can be obtained by superposition, leading to an additive split of the stress-tensor into a passive contribution $\boldsymbol{P}_\mathrm{passive}$ and an active contribution $\boldsymbol{P}_\mathrm{active}$. Further is is assumed that skeletal muscle tissue is incompressible, i.e. $\det \boldsymbol{F} = 1$. The resulting first Piola-Kirchhoff stress tensor reads

$$\boldsymbol{P}(\boldsymbol{F}, \boldsymbol{\mathcal{M}}, \gamma) = \boldsymbol{P}_\mathrm{passive}(\boldsymbol{F}, \boldsymbol{\mathcal{M}}) + \boldsymbol{P}_\mathrm{active}(\boldsymbol{F}, \boldsymbol{\mathcal{M}}, \gamma) - p \boldsymbol{F}^{-T} , \tag{3}$$

where $\boldsymbol{F}$ is the deformation gradient tensor, $\boldsymbol{\mathcal{M}} = \boldsymbol{a}_0 \otimes \boldsymbol{a}_0$ is a structure tensor, $\boldsymbol{a}_0$ is the muscle fibre direction, γ is a lumped activation parameter, which is calculated by the sub-cellular model [6] and p is a Lagrangean multiplier, entering the equation to satisfy the incompressibility constraint.

State of the art and challenges

Since the different sub-models show significant differences in the characteristic time and length scales, the sub-models are solved by using different discretisation techniques.

The continuum-mechanical skeletal muscle model is solved by applying the finite element method. and the muscle geometry is represented using triquadratic/trilinear Lagrange basis functions, i.e., Taylor-Hood elements. Within this model, we assume that the computational muscle fibres are represented by much finer one-dimensional finite-element meshes, that are embedded into the three-dimensional finite-element mesh. Further a first-order operator splitting method (Godunov splitting) is applied to solve the monodomain-equation, separating the diffusion term from the non-linear reaction term. An explicit Euler-method is used to integrate the ODE system describing the reaction term and the one-dimensional diffusion problem is solved by a GMRES solver. In order to exchange variables between the different sub-models, the macroscopic deformations are interpolated and evaluated at the node points of the one-dimensional fibre mesh. Further the activation parameter γ is homogenised ($T_{\mathrm{H}}: \ \gamma \rightarrow \bar{\gamma}$) and projected on the Gauss-points of the three-dimensional finite-element mesh.

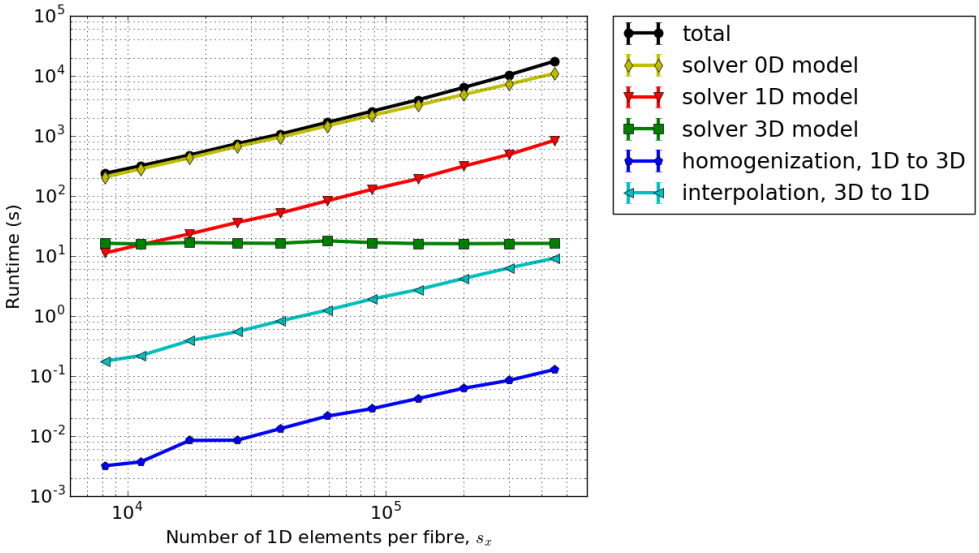

Figure 2. Evaluation of the runtime for the different sub-models. The setting contains a constant number of 2 x 2 x 2 elements in the 3D model and variable number of elements in the 1D model.

Before a computational framework can be run on a supercomputer, it's efficiency needs to be analysed as only efficient code should be ported. The analysis is done by investigating computational bottlenecks. Therefore the runtimes for the different submodels are first investigated. The evaluation of the runtime show (see Figure 2) some of the characteristics of the computational model:

1. The overall simulation time is dominated by the solver of the sub-cellular ODE model (0D model). This is due to the characteristics of the temporal action potential evolution, showing a steep rise when the membrane depolarise, i.e., solving a stiff ODE with a

first-order forward Euler method. Consequently small timesteps are needed to simulate the sub-cellular behaviour.

2. The runtime of the muscle fibre-model increase nearly linear with the problem size.

3. The computational costs for solving the three-dimensional, continuum-mechanical model and for the exchange of variables between the sub-models are negligible compared to the computational costs to solve the one-dimensional muscle fibre model. This is due to the relative coarse finite elment mesh for the continuum-mechanical skeletal muscle model.

Scaleability and numerical improvements

In a weak-scaling study (see Figure 3), i.e. the problem size was linearly increased with the number of processes, we checked the parallel performance of the computational model. By exploiting the model assumption that individual muscle fibres can be considered to behave electrical independent from each other, the multi-scale skeletal muscle model shows promising results for a weak-scaling test. The runtime for the ODE solvers, which dominate the overall runtime, is almost constant when increasing the problem size. However the solver for the one-dimensional diffusion problem shows potential for optimisation with respect to parallel simulation execution.

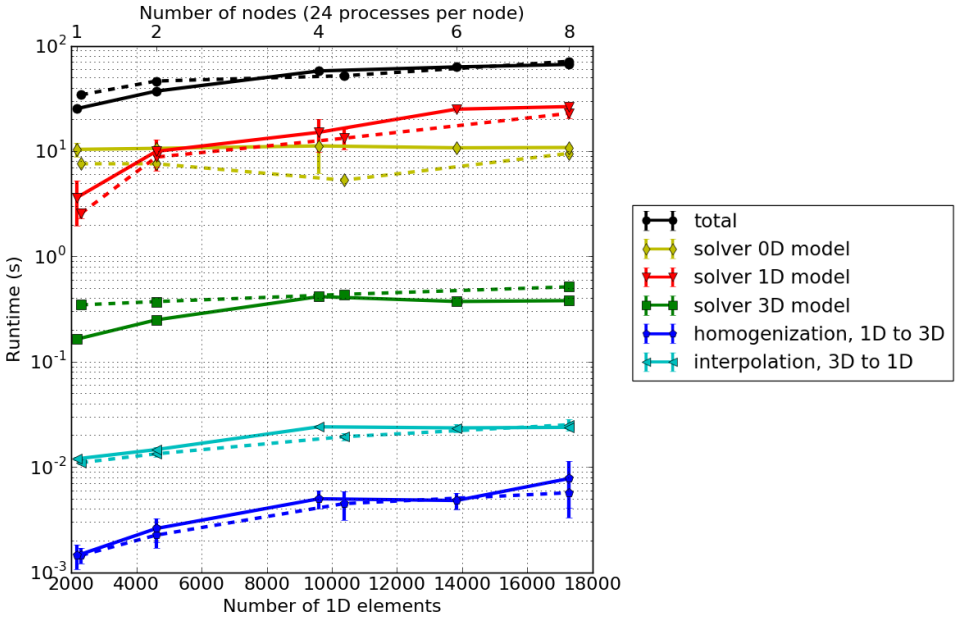

Figure 3. Weak scaling study on multiple nodes. The problem size is scaled equally to the number of processes while preserving the approximate shape of the physical domain. The solid lines are for a domain decomposition strategy with preferably cube shaped subdomains, the dashed lines correspond to a domain decomposition with elongated subdomains.

Further, as a result of the runtime evaluation (see Figure 2), we optimised the numerical solution strategy of the muscle fibre model, by replacing the first-order Godunov splitting method with a second order Strang splitting method and replace the GMRES solver for the diffusion problem with more efficient solution method, e.g., a Conjugate Gradient (CG) method.

Conclusion and Outlook

Large-scale simulations accounting for realistic muscle geometries, the electrophysiological properties of skeletal muscle tissue and a realistic activation process, can contribute to a better

understanding the neuromuscular system and generate benchmark results for simplified modelling approaches. Using the open-source software library OpenCMISS, we demonstrate the general suitability of our multi-scale skeletal muscle model for parallel simulations on HPC clusters, i.e., making large-scale simulations of the neuromuscular system feasible.

Acknowledgements

The research leading to these results has received funding from the Baden-Württemberg Stiftung (High Performance Computing II).

References

[1] C. P. Bradley, A. Bowery, R. Britten, V. Budelmann, O. Camara, R. Christie, A. Cookson, A. F. Frangi, T. Gamage, T. Heidlauf, S. Krittian, D. Ladd, C. Little, K. Mithraratne, M. Nash, D. Nickerson, P. Nielsen, O. Nordbø, S. Omholt, A. Pashaei, D. Paterson, V. Rajagopal, A. Reeve, O. Röhrle, S. Safaei, R. Sebastián, M. Steghöfer, T. Wu, T. Yu, H. Zhang, and P. J. Hunter. OpenCMISS: A multi-physics & multi-scale computational infrastructure for the VPH/Physiome project. *Progress in Biophysics and Molecular Biology*, 107:32–47, 2011.

[2] T. Heidlauf, T. Klotz, C. Rode, E. Altan, C. Bleiler, T. Siebert, and O. Röhrle. A multi-scale continuum model of skeletal muscle mechanics predicting force enhancement based on actin–titin interaction. *Biomechanics and Modeling in Mechanobiology*, 15(6):1423–1437, 2016.

[3] T. Heidlauf and O. Röhrle. Modeling the Chemoelectromechanical Behavior of Skeletal Muscle Using the Parallel Open-Source Software Library OpenCMISS. *Computational and Mathematical Methods in Medicine*, 2013:1–14, 2013.

[4] T. Heidlauf and O. Röhrle. A multiscale chemo-electro-mechanical skeletal muscle model to analyze muscle contraction and force generation for different muscle fiber arrangements. *Frontiers in Physiology*, 5(498):1–14, 2014.

[5] A. J. Pullan, L. K. Cheng, and M. L. Buist. *Mathematically modelling the electrical activity of the heart: from cell to body surface and back again.* World Scientific, 2005.

[6] P. R. Shorten, P. O'Callaghan, J. B. Davidson, and T. K. Soboleva. A mathematical model of fatigue in skeletal muscle force contraction. *Journal of Muscle Research and Cell Motility*, 28(6):293–313, 2007.