Project Network 2 “In Silico Models of Coupled Biological Systems”

PN 2-4a: “Machine learning-based decomposition of the activity of individual motor units from synthetic and experimental data”

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1 Summary

Within this project, we aim to use synthetic data obtained from simulations to develop novel machine learning-based decomposition algorithms for identifying the activity of individual motor units in skeletal muscles. Compared to existing methods, we expect significant computational speed-ups and decomposition algorithms that identify with much better accuracy more motor units. The results of applying our newly developed algorithms to experimentally measured electromyographic (EMG) recordings will improve the overall understanding of the control of the neuromuscular system. These novel machine learning-based decomposition algorithms will be achieved by developing a 3D multi-domain model to simulate the activity of selected motor units during iso- and non-isometric contractions in muscles of arbitrary shape. The use of a conditional generative adversarial network (cGAN) will provide a flexible and powerful framework for EMG to motor unit activity translation, even in a nonlinear environment. As in silico experiments firing times of individual neurons are no longer unknown, computing the resulting EMG signal provides a basis for designing, training and validating novel machine learning-based decomposition methods. Since the exact motor unit distribution is not known, new measures for comparing synthetic and actual EMG data will need to be developed. A further aim of this proposal is to use these findings to extend the algorithms in such a way that it also can decompose motor units during non-isometric contractions – something that cannot properly be decomposed with existing methods yet. One path to achieve this is to utilise (continuum-mechanical) models to predict motion, and, hence, deformation and the shift of the motor units during contraction. As such, this project directly links to the vision of a “Digital Human Model” as outlined within the SimTech proposal.

2 State of the Art and Preliminary Work

2.1 State of the Art and Current Challenges

One of the few non-invasive and clinically available diagnostic tools to obtain insights into the functioning (or disfunctioning) of the neuromuscular system are based on analysing electromyographic (EMG) recordings, i. e., measuring the activation-induced, resulting potentials on the skin surface. However, gaining from the neuronal drive insights to the neuromuscular system is a challenging and still an open research question. One of the crucial step hereby is the decomposition of the EMG signal to individual contributors, i.e., the fibers associated with a single motor unit. For this purpose, several decomposition algorithms have been proposed, e.g., [L1, L2, L3]. Despite the use of high-density multi-electrode arrays, there are still several challenges with respect to accuracy and reliability, e.g., [L4, L5], which have to be met. Furthermore, existing decomposition methods are black-box methodologies aiming to provide data for motor unit recruitment and thereby often ignoring any sensory inputs to the motor

neuron pool. As the inputs to the motor neuron pool cannot be experimentally measured, developing novel algorithms and validating them is challenging. The validation challenge is also true for existing algorithms. Note, non-isometric contributions pose hereby a particular and largely unresolved challenge. The challenge hereby is tracking the movement of individual motor units during contraction.

Mathematical models have a great potential to improve signal interpretation, in particular since there exist phenomenological or biophysical based motor unit recruitment models that can be used to generate synthetic yet realistic EMG data that can be used for algorithm development and benchmarking. From a simulation perspective, EMG signals are usually simulated by means of volume conductor models (see [L6] for a detailed review). Thereby, skeletal muscle tissue is assumed to be an (anisotropic) ohmic conductor and the bio-electrical activity arising from the depolarisation of the muscle fibre membranes is represented by spatially distributed current sources / sinks. A biophysically more detailed description of the propagation of action potentials along muscle fibres can be obtained by solving the monodomain model (cf. [P3]), which can be considered to be an one-dimensional extension of Hodgkin-Huxley type models. The biophysical models can hereby account for changes in the amplitude and propagation velocity of the AP that result, for example, from membrane fatigue. While most of the existing (single-physics) EMG models do not take into account tissue deformation, and hence are restricted to isometric conditions [L7], multi-physics models coupling EMG models to continuum-mechanical models [P3], can also simulate EMG generation during non-isometric conditions. The state of the are and the challenges from an machine learning point of view are explained in detail in Section 2.1 of project PN2-4b.

2.2 Previous Work of the Applicants

The applicant has been the first, who developed a three-dimensional, continuum-mechanically and biophysically based, multi-scale skeletal muscle modelling framework that is capable of integrating neuromuscular recruitment principles in a natural way [P1]. This chemo-electro-mechanical skeletal muscle modelling framework was extended in [P2] to also integrate a biophysical motor neuron pool model. Based on the input from the motor neuron pool model and the resulting electro-physiological state of skeletal muscle, i. e., the output of the chemo-electro-mechanical model, one can compute EMG signals for arbitrary muscle geometries [P3]. As computing the electro-physiological state of the skeletal muscle models, i. e., computing the propagation of the electrical signals (action potentials) along the respective muscle fibres is computational expensive, the applicant has teamed up with computer scientists and mathematicians to solve for the electrical signals using large scale HPC systems [P5]. Further, to speed up the computation of the electrical signals and the EMG, the applicant has developed model-order-reduction techniques to solve for the respective EMG signal [P4] close to real time.

2.3 Project-Related Publications of the Applicants (max. 5)

[P1] **O. Röhrle**, J. B. Davidson, and A. J. Pullan. A physiologically based, multi-scale model of skeletal muscle structure and function. *Frontiers in Physiology*, 3:1–14, 2012.

[P2] T. Heidlauf, F. Negro, D. Farina, and O. Röhrle. An integrated model of the neuromuscular system. In *Neural Engineering (NER),2013 6th International IEEE/EMBS Conference on*, pages 227–230. IEEE, 2013.

[P3] M. Mordhorst, T. Heidlauf, and **O. Röhrle**. Predicting electromyographic signals under realistic conditions using a multiscale chemo-electro-mechanical finite element model. *Interface Focus*, 5(2), February 2015.

[P4] M. Mordhorst, T. Strecker, D. Wirtz, T. Heidlauf, and **O. Röhrle**. Pod-deim reduction of computational emg models. *Journal of Computational Science*, 19:86–96, 2017.

[P5] Bradley, C., Emamy, N., Ertl, T., Göddeke, D., Hessenthaler, A., Klotz, T., Krämer, A., Krone, M., Maier, B., Mehl, M., Rau T., and **Röhrle, O.** Enabling Detailed, Biophysics-based Skeletal Muscle Models on HPC Systems. *Frontiers in Physiology*, 9 (816), 2018.

3 Project Description

3.1 Project Goals

Within this project, we aim to use synthetic data obtained from simulations to develop novel machine learning-based decomposition algorithms for determining the activity of individual motor units in skeletal muscles. To do so we aim to

- develop strategies for motor unit recruitment (particularly including feedback),
- create a rich, artificial dataset comprising hundreds of neurons firing in different conditions and different geometries,
- develop novel machine-learning based decomposition methods,
- test the validity of decomposition in ideal conditions (prescribed vs detected spikes), and
- test the robustness of decomposition against common real-life variable conditions.

3.2 Approach and Work Programme (3.5 years for doctoral researcher)

To achieve the above-mentioned project goals, we consider a part of the neuromuscular system consisting of motor neurons, their recruitment properties, and a skeletal muscle that is surrounded by a skin-fat layer. Motor neuron recruitment will be modelled by either a phenomenological or a biophysically based motor neuron recruitment model. Muscular activity is modeled with the chemo-electro-mechanical skeletal muscle model, which has been proposed by the lead applicant of this proposal. As muscle gemoetry, we choose either a rectangular idealisation of a muscle, the biceps brachii, or the tibialis anterior. From an experimental point of view, the biceps brachii and the tibialis anterior are ideal muscles, as they are well studied and close to the skin surface, i. e. one typically obtains high quality surface EMG signals. The computational framework builds on existing work [P1, P3, P5].

WP 1 Create a rich, synthetic dataset comprising hundreds of neurons firing in different conditions and different geometries (Lead: O. Röhrle)

Task A1.1 – EMG Model Improvements: If, like in the case of skeletal muscle, one uses the bidomain equations to model tissues with multiple intracellular spaces, then the solution of the discretised bidomain equations is strongly mesh dependent. This is mainly due to the discontinuities of the action potentials across the muscle fibres. To overcome this problem, we develop, based on the bidomain modelling assumptions, a more general multi-domain framework by assuming that each muscle fibre has its own individual intracellular space. Further, by introducing volume fractions for each individual fibre type, we will derive a generalised form of the bidomain equations. Solving the resulting system will require fast and efficient solvers for block-structured linear systems, which arise from the discretisation of the governing equations of the multi-domain model.

Task A1.2 – Creation of Synthetic Dataset: Data capable of investigating the robustness of the decomposition, needs to consider realistic conditions like electrode type, skin/fat tissue thickness, signal-to-noise ratio, or the spatial distribution of motor units. The generalised multi-domain approach will be utilised to create datasets that first only contain isolated firings of individual motor units. Then, subsequently more complex dataset wills be generated, e. g., datasets resulting from utilising a phenomenological motor unit recruitment model of Fuglevand (first an inter-spike variation of zero, before choosing more realistic inter-spike variabilities). In addition to the Fuglevand model, we also will generate datasets derived by integrating the biophysical motor neuron pool model of Negro and Farina (2011). In addition, geometrical considerations will be taken into account. e. g., for tissues with varying skin thickness, for the biceps brachii and for the tibialis anterior. Depending on the process of developing the multi-domain method and generating the data, we will also consider non-isometric conditions.

Task A1.3 – Improvement of the motor neuron model by integrating feedback mechanism: This task provides a direct link to PN2-3. Most motor neuron pool models ignore feedback mechanisms. While

the impact of feedback for isometric contractions will most likely be minimal, it is believed that it has a significant impact on the resulting EMG for non-isometric contractions. As appropriate, the feedback mechanism identified in PN2-3 will be integrated into a new biophysical motor neuron recruitment model and the new motor neuron model will be used to determine our synthetic datasets.

WP 2 Developing novel Machine-Learning-Based Algorithms for the Decomposition of the Activity of Individual Motor Units (Lead: B. Yang)

Task A2.1 – Interaction with PN2-4b: Based on preliminary work, we will provide PN2-4b with simulated EMG data right at the beginning. Further, PN2-4a acts as a link to PN2-3. It defines the experimental set-up and collects experimental data using the high-density EMG recording equipment available at SimTech's Neuromechanics Lab, e. g. for the biceps brachii and the tibialis anterior subject to various isometric conditions. Moreover, as synthetic data from WP1 will become available, the synthetic data will be exchanged via SimTech's open-access data management environment OpenDash.

Note, these are only tasks associated with this sub-project. For further details of this task see PN2-4b.

WP 3 Test the accuracy and robustness of decomposition against common real-life variable conditions (Lead: O. Röhrle/B. Yang)

Task A3.1 – Benchmarking and validation of the novel decomposition algorithm: The validity of the decomposition algorithm will be assessed by testing the algorithm first under ideal conditions. To do so, we investigate the difference between the prescribed versus detected spikes for different test scenarios. Given the complexity of the decomposition, it is likely that more suitable measures will need to be investigated, e. g., taking into account false positives. The goal are new Synthesis-Decomposition-Compare benchmark tests.

Task A3.2 – Robustness of the decomposition algorithms with respect to noisy data: In terms of the robustness of the decomposition, real-life conditions, such as the choice of electrode, skin and fat tissue thickness, signal-to-noise ratio and the motor unit distribution, need to be investigated. Noise, for example, can be investigated by contaminating spike trains, e. g., by adding or removing 5% - 50% of the spikes, and evaluating the outcome of the decomposition algorithm. Furthermore, new measures and analysis techniques need to be developed for testing the decomposition algorithm with experimentally measured data. This requires a systematic approach to analyse the various different error types.

Task A3.3 – Publishing benchmark problems for testing motor unit decomposition algorithms: The test will be published in a peer-reviewed journal. The data will be made available via the OpenDash platform.

4 Relevance for the Project Network and the Cluster

4.1 Relation to the Focus Challenges and Goals of the Project Network

The proposed project aims to address two focus challenges in data-integrated simulation science: (i) bridging data-poor and data-rich scales and (ii) merging physics- and data-based modelling. Both focus challenges will be simultaneously addressed within PN2-4 by developing novel multi-scale simulations predicting the electro-physiological state during (non-)isometric contractions. This is essential to train, analyse, and validate the proposed novel motor unit decomposition method. The challenge is to bridge data-poor scales, i. e., the input to or the output from the motor neuron pool (recruitment), with the data-rich scale, i. e., detailed spatial and temporal information about the electro-physiological and mechanical state of (parts of) the musculoskeletal system, to gain more information about the behaviour of the neuromuscular system. One key challenge will be to validate the proposed machine-learning based decomposition algorithms. While simulated cases provide excellent test and training data, the challenge will be to apply these methods to real data and overcome the inter-subject variability of biological systems. This challenge also addresses the "Individualisation" research question posed within this project

network. Furthermore, by extending the newly developed methods to non-isometric cases will require efficient and resource-limited simulations – a further research question of this project network.

4.2 Cooperation in ExC 2075

PN2 links and collaborates with the following projects (ordered by its intensity of collaboration):

PN2-3 One of the research focus of PN2-3 is to use EMG data to link sensory feedback and motor command strategies with EMG. While PN2-3 benefits from our novel decomposition algorithms, PN2-4 utilises the experimental setup to obtain EMG measurements.

PN7-1 The idea of PN7-1 is to enable complex musculoskeletal models in a pervasive computing environment. PN7-1 aims to use a hierarchy of recruitment models to drive the system. One of the recruitment models can be EMG measurements. For that reliable and fast decomposition methods are needed.

PN5-7 Profs Haasdonk and Pflüger focus in PN5-7 on physics- and data-based surrogate models for mechanical systems for UQ and beyond. Based on previous collaborations with both PN5-7 PIs, collaborations between PN2-4 and PN5-7 will benefit from surrogate models developed in PN5-7 to eventually realise model-based approches to decompose motor unit activity under non-isometric conditions.

PN4-4 Closely following project PN4-4 on “Theoretical Guarantees for Predictive Control in Multi-Agent Robotics Applications” (Profs Eberhard und Allgöwer) will potentially lead to new collaborations. The distributed control approach could potentially be translated to models of muscular recruitment, i. e., developing novel motor unit pool models for muscular recruitment.

4.3 Approval by the Project Network Board

The key focus of PN2-4 is on utilising multi-X models and machine-learning tools for developing novel motor unit decomposition methods in order to investigate aspects of the system response, i. e., the neuromuscular system. Project PN2-4 contributes to two focus challenges identified by the Cluster (FC2, FC3) and two research questions identified by the project network (RQ2, RQ5). Moreover, PN2-4 links to PN2-3 and significantly contributes to the SimTech’s vision of a “Digital Human Model”.

Therefore, the Project Network Board **approves** this project proposal.

5 Literature

[L1] Luca, C. J. D.; Adam, A.; Wotiz, R.; Gilmore, L. D.; Nawab, S. H.; Luca, D.; Carlo, J.; Adam, A.; Wotiz, R. and Donald, L.: Decomposition of Surface EMG Signals. Journal of Neurophysology 96, 2006.

[L2] Holobar, A. and Zazula, D.: Multichannel blind source separation using convolution Kernel compensation. IEEE Transactions on Signal Processing 55, 4487–4496, 2007.

[L3] Merletti, R.; Holobar, A. and Farina, D.: Analysis of motor units with high-density surface electromyography. Journal of Electromyography and Kinesiology 18, 2008.

[L4] Holobar, A.; Minetto, M. A.; Botter, A. and Negro, F.: Experimental Analysis of Accuracy in the Identification of Motor Unit Spike Trains. Transactions on Neural Systems and Rehabilitation Engineering 18, 2010.

[L5] Holobar, A.; Minetto, M. A. and Farina, D.: Accurate identification of motor unit discharge patterns from high-density surface EMG and validation with a novel signal-based performance metric. Journal of Neural Engineering 11, 2014.

[L6] Mesin, L.: Volume conductor models in surface electromyography: Computational techniques. Computers in Biology and Medicine, 43(7), p. 942–952, 2013.

[L7] Mesin, L., Joubert, M., Hanekom, T., Merletti, R., and Farina, D.: A Finite Element Model for Describing the Effect of Muscle Shortening on Surface EMG. IEEE Transactions on Biomedical Engineering, 53, p. 693–600, 2006.

6 Funds Requested and justification of additional funds

6.1 Standard funding

This project applies for the following standard package of funding:

	1st year	2nd year	3rd year	4th year	Total
Doctoral Position (TV-L 13)	0.5	0.5	0.5	0.25	1.75 years
PostDoc Position (TV-L 13)	-	-	-	-	0 years
HiWi hours (10h/week)	0.5	0.5	0.5	0.5	1.75 years
Consumables	1.000 €	1.000 €	1.000 €	500 €	3.500 €
Travel	500 €	1.500 €	1.500 €	1.500 €	5.000 €
Investments	750 €	750 €	750 €	0 €	2.250 €
Total	**2.250 €**	**3.250 €**	**3.250 €**	**2.000 €**	**10.750 €**

This project is ideal for a PhD student with knowledge about the musculoskeletal anatomy and physiology, advanced knowledge in computational techniques and signal processing, e.g. a person with a master in biomedical engineering who focused during his/her studies on Computational Biomechanics and Signal Processing. It provides the student with unique aspects to become an expert in the field of neuromechanics. Note, while only funding for a 0.5 position is requested, the research outline herein is for a full-time PhD student. The sudent will also be paid a 100% position. The missing half of the funding will be supplemented by Prof. Oliver Röhrle, PhD. The PhD student will closely engage with the PhD student of PN2-4B and the PhD student of PN2-3A.

The travel costs above deviate a bit from the standard rates. They have been budgeted such that the PhD student can attend one international conference within Year 2-4. The main equipment (EMG recording devices) exists already and the need for electrodes, etc. are already budgeted within the standard rates for consumables.

6.2 Extra funding for specific instrumentation and consumables (if applicable)

Beyond the standard package, we apply for the following extra funds for the following reasons: NONE.

Experimental measurements are conducted within the Neuromechanics Lab and are a “by-product” of PN2-3A.

6.3 Total funding requested

Standard funding (without personnel)	2.250 €	3.250 €	3.250 €	2.000 €	10.750 €
Extra funding	0 €	0 €	0 €	0 €	1.000 €
Total	**2.250 €**	**3.250 €**	**3.250 €**	**2.000 €**	**10.750 €**