Neural-Driven Activation of 3D Muscle in a Finite Element Framework: Exploring Healthy and Neurodegenerative Simulations

Colton D. Babcock[1], Victoria L. Volk[1], Wei Zeng[2], Landon D. Hamilton[2], Kevin B. Shelburne[2], Clare K. Fitzpatrick[1]
[1]Boise State University, Boise, ID, [2]University of Denver, Denver, CO
coltonbabcock@boisestate.edu

Disclosures: Colton Babcock (N), Victoria Volk (N), Wei Zeng (N), Landon Hamilton (N), Kevin Shelburne (N), Clare Fitzpatrick (N)

INTRODUCTION: Neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), present significant challenges to global healthcare systems, impacting millions of lives and imposing substantial economic burdens [1]. Despite extensive research and clinical efforts, effective treatments for these diseases remain elusive [2]. The complexity of clinical trials and limited insights into disease mechanisms necessitate innovative approaches to study these conditions. Computational modeling, particularly multiscale neuromusculoskeletal (NMS) models, offers a non-invasive platform to enhance our understanding of neurodegenerative diseases and facilitate the development of patient-specific treatment strategies [3]. Current approaches, such as the application OpenSim, offer valuable tools for analyzing muscle dynamics and motion, yet they often rely on simplified representations of muscles and lack the neural input required to fully capture neuromuscular interactions. Finite element (FE) models can potentially address these limitations, offering the capacity to simulate complex biomechanical and structural behaviors in biomedical systems [4]. In the context of neuromusculoskeletal modeling, the integration of neural elements becomes crucial for a comprehensive understanding of physiological and pathological conditions. Our novel approach combines neural and musculoskeletal components in a predictive neuromusculoskeletal model, focusing on the tibialis anterior (TA) muscle. We demonstrate the model's predictive capabilities under both healthy and early-stage ALS conditions to simulate disease-specific alterations in muscle force and tendon elongation, considering the effects of progressive motor neuron loss, characteristic of ALS.

METHODS: We developed a NMS model that accurately represents the 3D geometry and physiological function of the TA muscle (Fig. 1). This model integrates muscle fiber orientations and muscle fiber types (Type I, IIA, IIB), incorporating a motor unit pool generated through the NEURON simulation environment [5]. The motor unit pool, comprised of 320 motor neurons, couples with an FE framework using Abaqus/Explicit [3,6]. The individual motor neuron cell, incorporating Hodgkin-Huxley ion channels, generates action potentials. Action potential discharge times were simulated to reflect the Henneman size principle with orderly motor unit recruitment based on physiologically-scaled axonal cell diameters with additional modulation performed by motor unit rate coding. These potentials are then fed to a modeled neuromuscular junction which, through calcium dynamics and activation dynamics, calculates muscle activation levels. The resulting activation levels from the modeled motor neuron pool were used as input to the muscle material model demonstrating neural drive to the TA muscle. The material model, represented through a user-defined Fortran-based subroutine (VUMAT), was built upon a previously published Hill-type muscle model [7] and modified to assign fiber types and fiber orientations within the FE model. This integration enables the simulation of neural-driven activation of the TA muscle, allowing for dynamic predictions of force generation and tendon elongation. Our NMS model was used to represent 80% of maximal effort dorsiflexion force production for two conditions: 1) a "healthy" condition at time zero (no neuron death); and 2) an ALS model with progressive loss of neurons: 14%, 26%, and 30% neuron loss at 60, 90, and 120 days, respectively.

RESULTS: During dorsiflexion, the simulated TA in the healthy model produced a peak of 13.02 mm of tendon elongation and a peak force of 203 N before plateauing at 187 N of force (Figs. 2, 3). During 80% MVC contraction, Stotz et al. [8] reported that the TA produces approximately 200 N of force and Tilp et al. [9] reported tendon stretch of 12.26 mm, verifying the behavior of the 3D TA muscle in the NMS model under healthy conditions. Tendon elongation had a maximum stretch of 12.34 mm, 12.26 mm, and 11.39 mm at 60, 90, and 120 days, respectively (Fig. 2). Peak forces generated in ALS simulations at 60, 90, and 120 days were measured at 187 N, 178 N, and 155 N, and plateaued at 158 N, 166 N, and 137 N, respectively (Fig. 3). The simulated force values correlated with experimental findings [10].

DISCUSSION: By enabling the integration of complex neural and musculoskeletal components, our model offers an initial step towards a non-invasive and patient-specific platform for investigating disease mechanisms, predicting disease progression, and evaluating potential therapeutic interventions. The model's ability to simulate healthy and pathological conditions positions it as a potential tool for advancing research in neurodegenerative diseases. However, several limitations and avenues for further development should be acknowledged; the current model focuses on a single muscle and incorporates simplifications in joint mechanics and tissue interactions. By bridging the gap between neural and musculoskeletal elements, our NMS model demonstrates the potential for the development of a tool that will improve the understanding of neuromuscular pathologies and their impact on musculoskeletal function.

SIGNIFICANCE/CLINICAL RELEVANCE: Developing a predictive neuromuscular model with accurate neural-musculoskeletal interaction is essential to better understand complex neurodegenerative conditions. Most importantly, these models need to accurately model the interaction between the nervous system and musculoskeletal system to be effective in informing the treatment of complex neurodegenerative diseases and predicating post-treatment function. This NMS model uses patient-specific muscle geometry, FE material models, and advanced neurological modeling through NEURON software in order to model this interaction. This model closes the distance between current NMS models and the end goal of a fully integrated 3D muscle and neuron model which can be used to guide rehabilitation or surgical treatment of patients with neurodegenerative and neurodevelopmental conditions.

REFERENCES: [1] Thorpe et al., US Burden of Neurodegenerative Disease (web), 2021. [2] Chou et al., Fac Rev, 2021. [3] Volk et al., Sci Rep, 2021. [4] Schmidt et al., J Biomech, 2013. [5] Hines and Carnevale, Neuroscientist, 2001. [6] Feinstein et al., Acta Anat, 1955. [7] Lu et al., CMBBE, 2011. [8] Stotz et al., BMC Sports Sci Med Rehabil, 2022. [9] Tilp et al., Eur J Appl Physiol, 2012. [10] Rushton et al., Neurology, 2017.

ACKNOWLEDGEMENTS: This work was supported in part by NIH grant U01 AR072989.

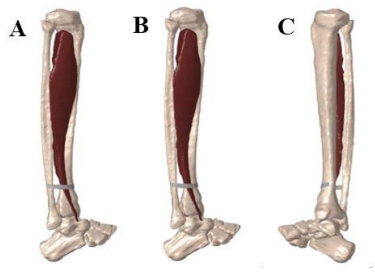

Fig. 1: FE model with TA and surrounding bone geometry. Lateral (A), anterior (B), and medial (C) view of right shank.

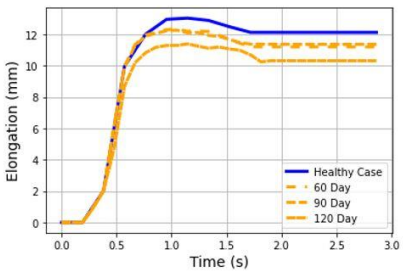

Fig. 2: Comparison of all four elongation computational situations.

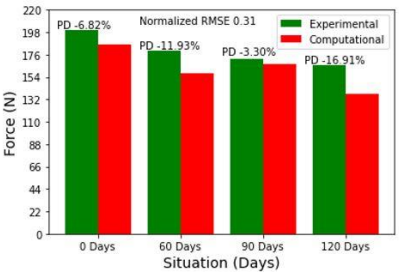

Fig. 3: Comparison of four computational situations compared to experimental force results including percent difference and RMSE.