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Mathematical Modeling of Muscle Cramps

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Abstract

Muscle cramps are an unexpected and sudden tightening of a muscle that are a common occurrence among adults. The components of muscle including the motor unit and sensory organs of muscle spindle and golgi tendon organ have been studied but their role in creating, sustaining ,and relaxing a cramp are unknown. The goal of this present work is to develop a closed loop feedback system to model the force generation in a motor unit and the behavior of each sensory afferent. A muscle fiber, muscle spindle, and golgi tendon organ were represented using viscoelastic elements and modeled in Python. Closed loop models were developed by applying external stimuli of either efferent input or muscle stretch. Gains between the sensory organ firing and the subsequent central nervous system output were varied to see the effect on force generation at 5 seconds. Conditions representing increased muscle spindle sensitivity and decreased number of active golgi tendon organs produced cramp-like behavior.

Keywords: Muscle cramps, Golgi tendon organ, muscle spindle

Introduction

Cramps are an unexpected, sudden tightening of a whole or part of a muscle. They are a common occurrence among adults and develop in a variety of situations such as during rest, during exercise, and in different health conditions. Many treatments that are suggested to individuals are based on potential causes such as muscle fatigue, dehydration, electrolyte imbalance, stress, sitting for too long or overusing muscles, and lack of stretching[1]. Although it widely affects individuals, the mechanism of cramp formation and alleviation has not been studied. This paper outlines a computational model created to represent the behavior of muscle components to investigate different etiologies of cramping.

Muscles consist of extrafusal fibers that stretch and contract, muscle spindles, and Golgi tendon organs. When a muscle is stretched, a muscle spindle (MS) senses the change in length and sends information to the central nervous system (CNS) about the length of the muscle and the speed of stretching. This feedback is excitatory and leads to muscle contraction[2]. Golgi tendon organs (GTOs) are muscle tension receptors and produce inhibitory feedback when the tendon is stretched by the contraction of the muscle. This provides the central nervous system with information regarding the tension applied to the tendon, or the force of muscle contraction[3].

The GTO's response to single motor unit contractions has been studied and is most relevant to our current work[4]. Single motor units, composed of multiple muscle fibers, create tension on their connected tendons when contracting, which the GTO detects. Additionally, the response of the GTO has both a dynamic and static component that is proportional to the amount of tension applied, suggesting that the rate of tension applied and the absolute tension both affect signaling to the CNS[6].

The muscle spindle also has both a dynamic and static response, but to lengthening of the muscle[7]. The spindle is a unique structure that gives information to the central nervous system, receives information from the muscle, and receives information from the central nervous system via gamma efferent fibers. Literature suggests that these fusimotor drives can affect the muscle spindle's sensitivity to task requirements[9]. Knowledge on these components have been used to model prostheses and voluntary control of muscle, but have not been combined in a model for muscle cramps[10-12].

There are two main hypotheses in literature on cramping[13]. One hypothesis is the central origin of cramp formation which results from the hyperexcitability of motor neurons. The focus of this hypothesis is the motor neuron and its excitation, and specifically states that the hyperactivation of sensory afferents after either the contraction of muscle fibers or the stimulation of these afferents produces consistent inward action potentials to the spinal cord. This synaptic input to the central nervous system will affect the efferent signals given to the muscle fibers and produce the cramp. The second hypothesis

surrounding cramp formation is the peripheral origin hypothesis which results from an electrolyte imbalance or mechanical disturbance at the terminal branches of motor neuron axons[14]. These two factors theoretically will cause spontaneous discharges from motor neurons and spread to neighboring excitable axons through direct contact, eventually producing the cramp.

In support of the first hypothesis, the involvement of the spinal pathways in cramp origin and sustenance is directly shown in nerve block experiments. In such experiments, cramps are induced through electrical stimulation at the nerve terminal branches and subsequent EMG data are recorded. By blocking peripheral nerves leading to the muscle, cramp induction results in discharges that are smaller in duration and intensity, more variable, and have a greater threshold of cramp elicitation when compared to trials with the peripheral nerves intact[15]. Nerve block experiments suggest a larger importance of efferent and afferent activity in the origin, sustenance, and extinction of cramps[15]. Therefore, we focused on the central origin hypothesis when researching and creating this model. Additionally, while the MS and GTO are known to alter firing to the muscle, it is not known to what extent their firing alters the CNS response. The gain between the sensory organ's firing and the CNS response is unknown because most studies have been conducted in cat muscle and focused on the baseline firing and change in firing when the muscle is stretched[16]. This paper shows that the gains and alteration of sensory afferent sensitivity can recreate cramp-like force generation.

Results

Figure 1 displays the function of the force generation model. Figure 1a shows the force of a single muscle twitch. This twitch was produced in response to one action potential from the central nervous system, and it shows the ramp up, peak, and decay of the force over time. Figure 1b shows the force generation over a time period of five seconds in response to different firing rates. Each firing rate was provided as neural input consistently throughout the duration of the modeled time. This graph allows us to see the varying maximum forces at different stimulus rates as well as the force ramp up and tetanus when high enough stimulus is applied. Figure 1c shows the maximum force generated by all possible firing rates in this model, ranging from 0 to 1000 pulses per second. The force was recorded in each condition after five seconds of modeled time. The purpose of this graph is to display the behavior of the model in response to every firing rate that may be applied by the

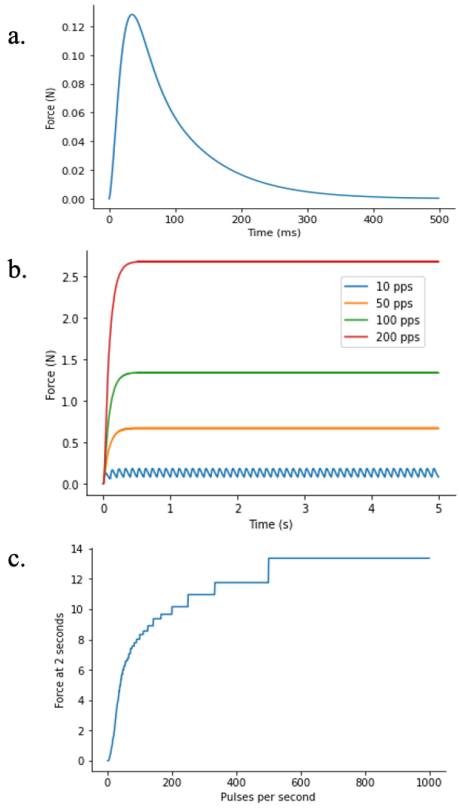

Fig. 1. Response of the force generation model to (a) a single action potential, (b) different rates of stimulus over five seconds, and (c) stimulus rates varying from 0 to 1000 pulses per second.

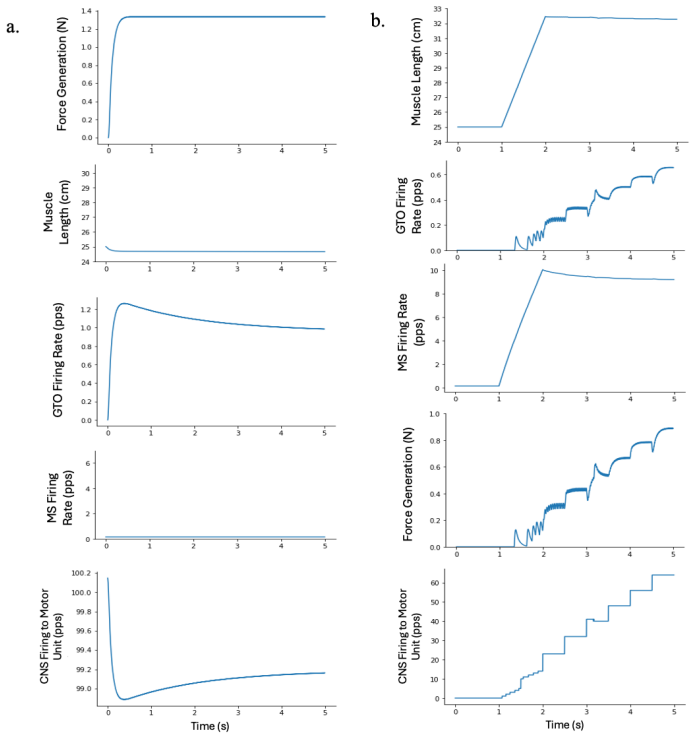

Fig. 2. Closed loop model response for (a) an initial force generation given by 100 pulses per second (pps) firing by the CNS to the muscle and (b) an initial stretch of 75 mm of the muscle.

central nervous system, thus showing the bounds of force generated by this model.

For simplicity, the model was created as one motor unit connected to both a muscle spindle and golgi tendon organ. Model responses to different external stimuli are shown in Figure 2 and were used to see the behavior of each component throughout the 5 second simulation. Figure 2a shows the model's response to a small force stimulation of one motor unit. Contraction leads to a small shortening in muscle length and the GTO responds. Conversely, the MS does not respond to this contraction. Feedback from the GTO leads to inhibitory signals to the CNS and resultant decrease in firing to the motor unit. In Figure 2b, an external stretch of 75 mm is applied to the whole muscle, and causes the muscle spindle to respond, leading to contraction in the motor unit. Subsequent force generated in the motor unit causes a comparatively insignificant GTO response. CNS receives feedback from both sensory organs and compositely efferent firing.

Figure 3 allows us to compare the effects of each sensory organ on the force generated by the model. The gain between the sensory organ's firing and the central nervous system's response is unknown, thus the purpose of this surface plot is to investigate the model's behavior at varying combinations of gain values. From the graph we can see that the muscle spindle gain has a greater effect on the overall force, with more variation shown along the muscle spindle axis compared to the golgi tendon organ axis. It also displays maximum force generation at high levels of muscle spindle gain and low levels of golgi tendon organ gain. Finally, when there is no muscle spindle gain, the model is inactive.

Figure 4 shows the behavior of the muscle with varying golgi tendon organ gains and muscle spindle sensitivity when no stimulus is provided. Each surface plot represents a different muscle spindle gain applied to show

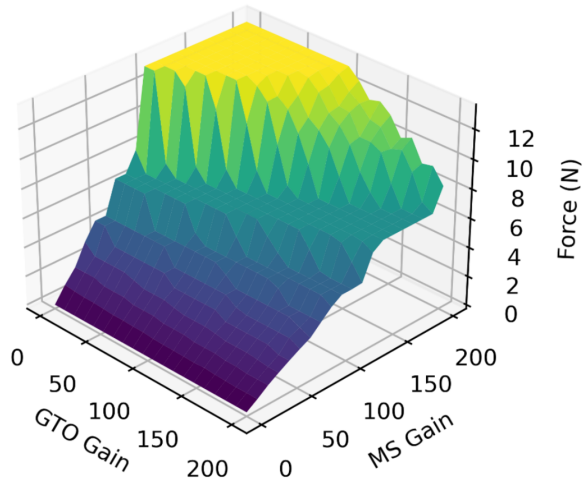

Fig. 3. Force generated by model in response to a 75 mm stretch of the total muscle plotted over varying golgi tendon organ and muscle spindle gain values. Force recorded after 5 seconds of modeling.

the difference in behavior between no gain (spindle response of approximately 1 pps), a gain of 10, and a gain of 100. The force shown is the force generated five seconds into the simulation. At a muscle spindle gain of 100, almost every condition produces the maximum contraction force, with the lowest force occurring at a golgi tendon organ gain of 200 and no added muscle spindle sensitivity. Similar behavior is seen with a muscle spindle gain of 10, but with more variety among the golgi tendon gain and added muscle spindle sensitivity values. At high muscle spindle sensitivity and low GTO gain, the maximum contractile force is reached. Finally, with no muscle spindle gain, the behavior of the model is similar, but in a lower range of forces. The higher sensitivity numbers still produce sustained contraction, but do not reach the maximum force value. In all three conditions, the model outputs some form of sustained force even though no initial external stimulus is applied.

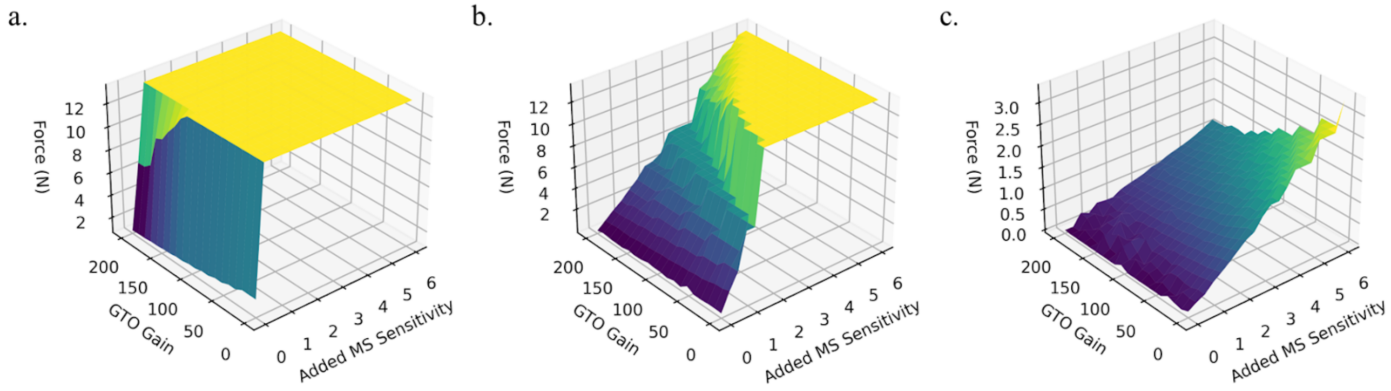

Fig. 4. Force generated by model with no initial stimulus over varying golgi tendon organ gain values and varying muscle spindle sensitivity values. Force plotted after 5 seconds of modeling with a constant muscle spindle gain of (a) 100, (b) 10, and (c) 1 (no added gain).

Discussion

Our model has shown to be a functional closed loop feedback system of a motor unit and its sensory components. An action potential pulse train to the motor unit contracts the muscle fiber and the subsequent tension created elicits a response from the GTO and therefore sends inhibitory signals to the CNS to decrease firing to the motor unit (Figure 2). Similarly, a large stretch of the muscle elicits activity from the muscle spindle and subsequent contraction of the muscle.

The force generation model shows an upper bound of force generation in response to rising frequencies of action potentials (Figure 1), as in normal muscle physiology. However, a limitation exists within the model that is also displayed by this graph by the discrete jumps in force at certain frequencies. This is not an accurate representation of physiology, but the model is limited by the discrete representation of time. To understand this, we need to first observe how the code works.

The program is constructed such that it iterates through a loop that runs once every "millisecond" of modeled time. The neural input is represented as an array of ones and zeroes, with each index acting as one millisecond. During every iteration of the loop, the neural input array is read at the index corresponding to the current time point in the model. If the value at that index is one, an "action potential" occurs and a twitch is initiated. The overall force is calculated by summing the forces of all active twitches at the current time step. This neural input array is constructed at the beginning of the model and altered when the firing rate from the central nervous system changes. The program divides the number of array indexes per second, 1000, by the firing rate to find the interval between pulses. The array is then filled with a one at each interval, and a zero everywhere else. In order to fit the discrete nature of the array, the intervals between pulses can only be whole numbers, since the computer cannot place a value at any fraction of an index. As such, the code truncates any decimal when the interval is computed, causing many firing rates to produce the same neural input array, and thus the same force output. The groups of firing rates that yield the same force increase in size as the rate increases, and all rates from 501 to 1000 pulses per second produce a neural input array with an action potential occurring at every index.

Based on the model behaviors displayed in Figure 4, we can conclude that the conditions represented in these trials produce cramp-like behavior, as a sustained contraction occurred in the absence of voluntary muscle activation. Altering the baseline sensitivity of the muscle spindle agrees with prior literature in which muscle spindles in fatigued muscle have altered discharge patterns[17]. Our results imply that there is a possibility that the sensitivity of the muscle spindle can be modulated to independently cause a force generation in the motor unit.

Thus, the set of conditions that produced these responses is a potential explanation for the mechanism of cramp formation. In this version of the model, the muscle spindle sensitivity is adjusted by raising the overall response of the spindle to stimulus. This also raises the baseline firing rate, which in its original state was very small. The model also includes a representation of motor adaptation occurring in the central nervous system. When feedback from the sensory organs is sustained for a period of time, the central nervous system activity is adjusted, creating a functional memory and adaptation of the nervous system to the feedback it receives. These two conditions together produce a feedback loop that causes a ramp up of contraction If the motor unit is well connected to many golgi tendon organs, the force is reduced by negative feedback, stabilizing the muscle at normal, non-cramping conditions. However, if the motor unit is not well connected and less golgi tendon organs are responding to the contraction, the negative feedback cannot overcome the force generated by the increasing sensitivity of the muscle spindle. In our model, the degree of connectivity is represented by the gain values. If the muscle spindle gain is increased, the ability of the GTO to balance the force becomes increasingly inadequate.

The modeling conditions in Figure 4 represent varying degrees of connectivity between the motor unit and sensory organs. The added muscle spindle sensitivity, varied on the right most axis of the figure, represents the adjustment in muscle spindle sensitivity caused by gamma efferent firing[18]. The gamma efferent nerves connect to the muscle spindle, sending signals that can raise or lower its sensitivity and change the baseline rate of firing. Our model represents this by adding to the response of the spindle, which increases both the baseline and stimulus responses.

At lower muscle spindle gain values and medium to low muscle spindle sensitivity, cramp-like behavior still occurs when the golgi tendon organ gain is low. The variation of gain values represents either a variation in level of impact of the GTO firing on the central nervous system output, a range of numbers of golgi tendon organs connected to the area of active muscle, or a combination of both. The first case serves a similar purpose to the muscle spindle gain, allowing us to test a range of possible interactions between the sensory organ and the central nervous system, which is usually left as a black box. The second case, focusing on the geometry of the muscle and sensory organs, represents a hypothesis for cramp formation. Lower gain values correspond to fewer golgi

tendon organs connected and responding to the contraction of one part of the muscle. A higher GTO gain models a motor unit in which more golgi tendon organs are connected and send feedback to the central nervous system. This variance of how many golgi tendon organs are connected to a motor unit comes from the conclusions drawn in literature about the organization of muscle fibers within motor units and the innervation of golgi tendon organs. Not every muscle fiber innervates a tendon organ, thus, not every motor unit is associated with the same number of tendon organs[19,20]. A motor unit comprised of several fibers may only have one or two fibers innervating a GTO. Furthermore, many or all of the fibers that do innervate a tendon organ might be connected to the same one, reducing the number of tendon organs sensing contraction of the motor unit. In the same way, there could be greater negative feedback associated with a motor unit if it happens to have a larger number of fibers that all innervate different tendon organs. The gain within our model simply represents a combination of these anatomical variations.

These conditions and the results they produced suggest that in a cramping muscle, muscle spindle sensitivity is increased, fewer golgi tendon organs are connected to or accurately sensing force from the system of motor units that is contracting, and the central nervous system adapts with some type of memory to sensory organ firing. Based on our model, we conclude that this is a physiologically and mathematically realistic explanation of muscle cramps.

The model contains several simplifications that allow us to represent the muscle more easily and still observe relatively accurate system behaviors. One main simplification is the discrete representation of time. The model operates on a time step basis, with each step equaling one millisecond. This helps speed up the calculation of force by quickly indexing into the twitch array and summing the force of all action potentials. It does, however, prevent us from modeling continuous conditions. This has an effect on the force generation model, as explained in the discussion section of this paper. It creates discrete groups of forces produced by various firing rates, which is shown by the "jumps" in some of the graphs. While we are still able to observe the overall behaviors of the model, we lose some information about the intermediate results. Additionally, a limitation could be the source of the data to which our model was fitted. These data come from cat muscle and not human, leading to inaccurate numerical results for the development of a cramp in humans.

Thus far, our model has shown responses to external stimuli and also exhibited cramp-like behavior when some components are modulated at rest. Future work should focus on setting up the model to test different hypotheses on the etiology of cramps and influences for its formation, sustenance, and relaxation. In studies eliciting a cramp via electrical stimulation, there was recruitment of additional motor units implying that a cramp not only forms, but spreads in a way that is connected to the central nervous system[21,22]. This model should be replicated to represent multiple motor units and connected to investigate the spread of force generation between motor units. Additionally, the specific arrangement and exact densities of tendon organs, muscle spindles, and connected units were shown to vary throughout one muscle and across different muscles[23], suggesting a variance in connections between the muscle spindles and golgi tendon organs. Therefore another step to use this model can be to represent multiple motor units, with some being connected only to muscle spindles or golgi tendon organs. Lastly, in electrically elicited cramp formation, there has been evidence to show that reduced inhibitory feedback from golgi tendon organ afferents play an important role in cramp generation[24]. This, along with the change in sensitivity of muscle spindles, is a step future researchers should take to further research the role of sensory afferent firing in cramps. Ultimately, this project's innovation in creating a comprehensive model to explain muscle cramps is significant because it will provide a framework to test different ways a cramp is formed, sustained, and relaxed. We hope that this model will be used to further investigate different types of cramps that may affect various populations, such as pregnant individuals or those undergoing kidney dialysis, and aid in the development of treatments and preventative measures for such individuals.

Materials and Methods

Development of the model started by representing the muscle spindle and golgi tendon organ using viscoelastic elements. The muscle spindle was previously modeled by McMahon[25] and Milneusic et al.[26], which is what was implemented in the model, shown in Figure 5. The muscle spindle response equation parameters were found by fitting the equations to MS responses of cat muscle[27]. The golgi tendon organ was modeled as a standard linear solid, and equation parameters were found by fitting the equation to cat GTO response data[28] shown in Figure 6. The combined feedback model with all components is shown in Figure 7. The force generation model was represented by the behavior of one muscle twitch in one motor unit. Based on equations from a mechanical muscle modeling paper[29], a single muscle twitch was defined as an array of force over time. When a twitch is initiated, the starting time point is saved. The

overall force at any given time point is calculated by summing the current force of every active twitch based on their start times.

The model was developed in the Python programming language and exists as a set of multiple files. The muscle spindle, golgi tendon organ, and force generation components were first created individually, and exist in separate python files. The sensory organs exist as defined functions that take in their respective parameters and output firing rate. To represent the whole system, these components are included at the beginning of every file, allowing the functions to be called within the code. Force generation is built iteratively throughout the duration of the simulation, so it is defined within the model's main loop. Each type of simulation is contained in one Python file, all with similar structures. First, the component models are included, and the twitch and force arrays are defined. If there is any external stimuli to initiate the model, such as stretch or a neural firing rate, it is defined here. After this setup, a for loop is initiated, which iterates the time array in one millisecond intervals. During each iteration of the loop, the program carries out many functions. First, it checks for an action potential in the central nervous system stimulus array, initiating a twitch if appropriate. Next, the current generated force is calculated, followed by the calculation of the muscle length. These values of force and stretch are then given as inputs to the golgi tendon organ and muscle spindle functions, respectively, which return the firing rates of each sensory organ. Finally, the central nervous system firing rate is modulated based on the sensory organ feedback, with the golgi tendon organ subtracting from the firing rate and the muscle spindle adding to it. This modulation is where the gains are implemented to run the tests discussed in the paper. At certain time intervals, the central nervous system baseline firing rate is updated based on prolonged sensory organ feedback. This represents motor adaptation, which has been shown to occur in a variety of sensorimotor conditions[30]. It is unknown for sure if this is how the central nervous system adapts during cramp formation, but the results produced by this adjustment in our model suggest that this is a key aspect of cramp formation. After the iteration is complete, time is adjusted incremented, and the loop is run again.

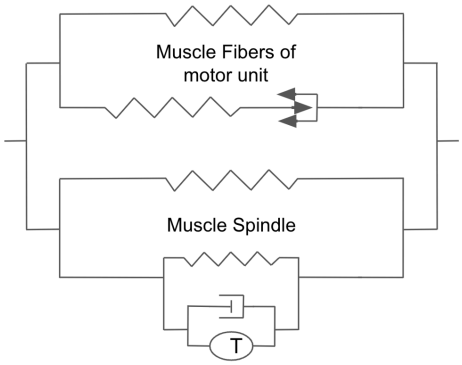

Fig. 5. Viscoelastic Representation of muscle spindle in parallel with muscle fibers from one motor unit. T represents an efferent drive to the muscle spindle that alters the organ's sensitivity to stretch. Arrow component in muscle fiber represents the active component of contracting muscle.

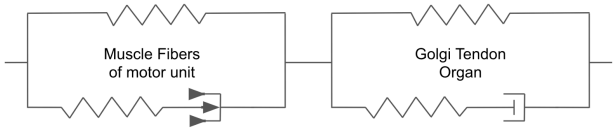

Fig. 6. Viscoelastic representation of Golgi tendon organ in series with muscle fibers from one motor unit. Arrow component in muscle fiber represents the active component of contracting muscle.

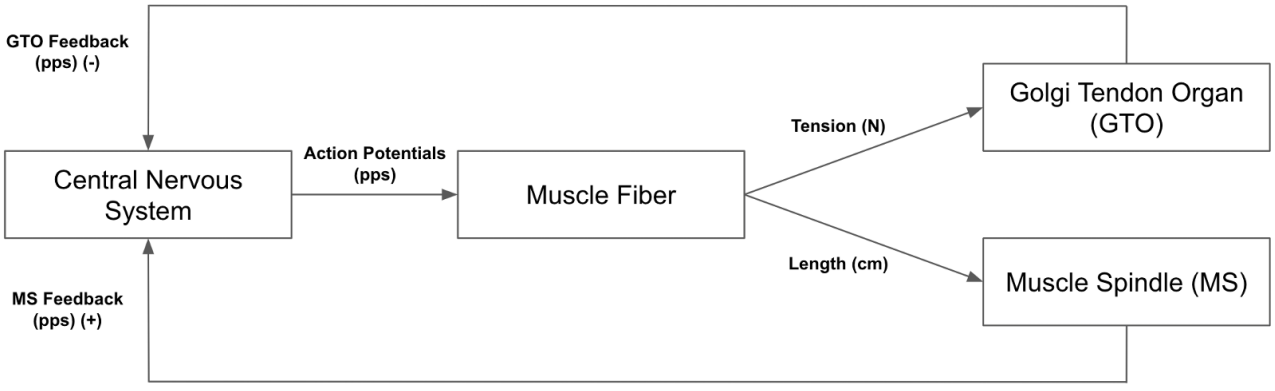

Fig. 7. Visualization of component organization in the muscle. The central nervous system sends action potentials to motor units, eliciting muscular contraction of each fiber. Figure also shows inputs and outputs of each component. Units are given in parentheses.

References

1. *Muscle Spasms and Cramps: What Causes Them?*. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/muscle-spasms-muscle-cramps (accessed 2023-11-09).
2. Kröger, S.; Watkins, B. Muscle Spindle Function in Healthy and Diseased Muscle. *Skeletal Muscle* 2021, *11* (1), 3. https://doi.org/10.1186/s13395-020-00258-x.
3. *Golgi Tendon Organ*. Physiopedia. https://www.physiopedia.com/Golgi_Tendon_Organ (accessed 2023-11-09).
4. Binder, M. D.; Kroin, J. S.; Moore, G. P.; Stuart, D. G. The Response of Golgi Tendon Organs to Single Motor Unit Contractions. *The Journal of Physiology* 1977, *271* (2), 337–349. https://doi.org/10.1113/jphysiol.1977.sp012003.
5. Stephens, J. A.; Reinking, R. M.; Stuart, D. G. The Motor Units of Cat Medial Gastrocnemius: Electrical and Mechanical Properties as a Function of Muscle Length. *Journal of Morphology* 1975, *146* (4), 495–512. https://doi.org/10.1002/jmor.1051460406.
6. Gregory, J. E.; Proske, U. The Responses of Golgi Tendon Organs to Stimulation of Different Combinations of Motor Units. *The Journal of Physiology* 1979, *295* (1), 251–262. https://doi.org/10.1113/jphysiol.1979.sp012966.
7. Edin, B. B.; Vallbo, A. B. Dynamic Response of Human Muscle Spindle Afferents to Stretch. *J Neurophysiol* 1990, *63* (6), 1297–1306. https://doi.org/10.1152/jn.1990.63.6.1297.
8. Matthews, P. B. C. Muscle Spindles and Their Motor Control. *Physiological Reviews* 1964, *44* (2), 219–288. https://doi.org/10.1152/physrev.1964.44.2.219.
9. Ribot-Ciscar, E.; Hospod, V.; Roll, J.-P.; Aimonetti, J.-M. Fusimotor Drive May Adjust Muscle Spindle Feedback to Task Requirements in Humans. *Journal of Neurophysiology* 2009, *101* (2), 633–640. https://doi.org/10.1152/jn.91041.2008.
10. Zhang, H.; Mo, F.; Wang, L.; Behr, M.; Arnoux, P.-J. A Framework of a Lower Limb Musculoskeletal Model With Implemented Natural Proprioceptive Feedback and Its Progressive Evaluation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering* 2020, *28* (8), 1866–1875. https://doi.org/10.1109/TNSRE.2020.3003497.
11. Williams, I.; Constandinou, T. G. Computationally Efficient Modeling of Proprioceptive Signals in the Upper Limb for Prostheses: A Simulation Study. *Frontiers in Neuroscience* 2014, *8*.
12. *Modeling and Identification of a Realistic Spiking Neural Network and Musculoskeletal Model of the Human Arm, and an Application to the Stretch Reflex | IEEE Journals & Magazine | IEEE Xplore*. https://ieeexplore.ieee.org/document/7271085 (accessed 2023-11-09).
13. Minetto, M. A.; Holobar, A.; Botter, A.; Farina, D. Origin and Development of Muscle Cramps. *Exercise and Sport Sciences Reviews* 2013, *41* (1), 3. https://doi.org/10.1097/JES.0b013e3182724817.
14. Layzer, R. B. The Origin of Muscle Fasciculations and Cramps. *Muscle & Nerve* 1994, *17* (11), 1243–1249. https://doi.org/10.1002/mus.880171102.
15. Minetto, M. A.; Holobar, A.; Botter, A.; Ravenni, R.; Farina, D. Mechanisms of Cramp Contractions: Peripheral or Central Generation? *J Physiol* 2011, *589* (Pt 23), 5759–5773. https://doi.org/10.1113/jphysiol.2011.212332.
16. Macefield, V. G.; Knellwolf, T. P. Functional Properties of Human Muscle Spindles. *Journal of Neurophysiology* 2018, *120* (2), 452–467. DOI:10.1152/jn.00071.2018.
17. Windhorst, U.; Kokkoroyiannis, T. Interactions of Recurrent Inhibitory and Muscle Spindle Afferent Feedback during Muscle Fatigue. *Neuroscience* 1991, *43* (1), 249–259. https://doi.org/10.1016/0306-4522(91)90432-n.
18. Dimitriou, M. Human Muscle Spindles Are Wired to Function as Controllable Signal-Processing Devices. *eLife* 2022, 11. https://doi.org/10.7554/elife.78091.
19. Reinking, R. M.; Stephens, J. A.; Stuart, D. G. The Tendon Organs of Cat Medial Gastrocnemius: Significance of Motor Unit Type and Size for the Activation of Ib Afferents. *The Journal of Physiology* 1975, *250* (3), 491–512. https://doi.org/10.1113/jphysiol.1975.sp011067.
20. Stuart, D. G.; Mosher, C. G.; Gerlach, R. L.; Reinking, R. M. Mechanical Arrangement and Transducing Properties of Golgi Tendon Organs. *Experimental Brain Research* 1972, *14* (3), 274–292. https://doi.org/10.1007/bf00816163.

21. Layzer, R. B. The Origin of Muscle Fasciculations and Cramps. *Muscle & Nerve* 1994, *17* (11), 1243–1249. https://doi.org/10.1002/mus.880171102.
22. Baldissera, F.; Cavallari, P.; Dworzak, F. Motor Neuron 'Bistability': A Pathogenetic Mechanism for Cramps and Myokymia. *Brain* 1994, *117* (5), 929–939. https://doi.org/10.1093/brain/117.5.929.
23. Ribot-Ciscar, E.; Hospod, V.; Roll, J.-P.; Aimonetti, J.-M. Fusimotor Drive May Adjust Muscle Spindle Feedback to Task Requirements in Humans. *Journal of Neurophysiology* 2009, *101* (2), 633–640. https://doi.org/10.1152/jn.91041.2008.
24. Khan, S. I.; Burne, J. A. Reflex Inhibition of Normal Cramp Following Electrical Stimulation of the Muscle Tendon. *Journal of Neurophysiology* 2007, *98* (3), 1102–1107. https://doi.org/10.1152/jn.00371.2007.
25. McMahon, T. A. *Muscles, Reflexes, and Locomotion*; Princeton University Press, 2020.
26. Mileusnic, M. P.; Loeb, G. E. Mathematical Models of Proprioceptors. II. Structure and Function of the Golgi Tendon Organ. *Journal of Neurophysiology* 2006, 96 (4), 1789–1802. https://doi.org/10.1152/jn.00869.2005.
27. Bessou, P.; Emonet-Dénand, F.; Laporte, Y. Motor Fibres Innervating Extrafusal and Intrafusal Muscle Fibres in the Cat. *The Journal of Physiology* 1965, 180 (3), 649–672. https://doi.org/10.1113/jphysiol.1965.sp007722.
28. Gregory, J. E.; Proske, U. Motor Unit Contractions Initiating Impulses in a Tendon Organ in the Cat. *The Journal of Physiology* 1981, 313 (1), 251–262. https://doi.org/10.1113/jphysiol.1981.sp013662.
29. Carriou, V.; Sofiane Boudaoud; Laforet, J.; Mendes, A.; Canon, F.; Guiraud, D. Multiscale Hill-Type Modeling of the Mechanical Muscle Behavior Driven by the Neural Drive in Isometric Conditions. *Computers in biology and medicine* 2019, *115*, 103480–103480. https://doi.org/10.1016/j.compbiomed.2019.103480.
30. Mathew, J.; Crevecoeur, F. Adaptive Feedback Control in Human Reaching Adaptation to Force Fields. *Frontiers in Human Neuroscience* 2021, *15*. https://doi.org/10.3389/fnhum.2021.742608.