Automatic rule-based generation of spinal cord connectome model for a neuro-musculoskeletal limb *in-silico*

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Keywords: spinal neurons, muscles, connection-rules, connectome, proprioception, *in silico* stimulation

Supplementary material for this article is available online

Abstract

Studying spinal interactions with muscles has been of great importance for over a century. However, with surging spinal-related movement pathologies, the need for computational models to study spinal pathways is increasing. Although spinal cord connectome models have been developed, anatomically relevant spinal neuromotor models are rare. However, building and maintaining such models is time-consuming. In this study, the concept of the rule-based generation of a spinal connectome was introduced and lumbosacral connectome generation was demonstrated as an example. Furthermore, the rule-based autogenerated connectome models were synchronized with lower-limb musculoskeletal models to create an *in-silico* testbed. Using this setup, the role of the autogenic Ia-excitatory pathway in controlling the ankle angle was tested.

1. Introduction

The crux of spinal locomotor behaviour lies in the complex organization of its neuronal circuits [1, 2]. Beginning with the pioneering contributions of Sherrington in delineating the reflex arc, the last century has made tremendous contributions to spinal neurophysiological data. Notably, the proprioceptive connection postulates (figure 1) (table 1) and the identification of key functional neuronal types (table 2) helped decipher the spinal sensory-motor architecture in coordinating limb functions [3, 4]. Most spinal cord data are based on investigations involving single neuronal studies or isolated reflex pathways often studied in critically constrained animal or human *in vivo* setups. However, studying the complex interactions of spinal pathways is difficult and often requires simultaneous tracking of the systemic spatiotemporal activity of neuronal and muscular components. Hence, computational modelling of spinal neuronal circuits is gaining prominence [5]. Moreover, emerging platforms capable of modeling single ion channels and networks have greatly expanded the possibilities of testing various hypotheses, often offsetting the need for animal models.

Computational spinal cord models have been built to study simplistic behavior, such as the stretch reflex [6], complex phenomena, such as gait and central pattern behavior [7, 8] and to study the role of therapeutics in controlling gait in animals etc [9]. However, models specific to human spinal anatomy are rare. Hence, the concepts of building human spinal connectome models using curated spinal neuroarchitecture and anatomical data with the capability of producing emergent phenomena are currently being explored [10]. This study introduces an automated approach to generate spinal sensory-motor connectome models using connection rules, neurons, and muscle data. The autogenerated model consists of simulatable spiking neurons, whose afferent and efferent activities can be synchronized with the musculoskeletal model, thereby enabling the testing and tracking of spinal pathways in the context of musculoskeletal functions. The current study explored the data pertaining to the generation of the spinal lumbosacral connectome and analyzed the connectome to build spinal proprioceptive-based lower limb muscle-muscle interaction reference maps. To demonstrate the usability of the connectome synchronized with the musculoskeletal *in-silico* setup, the implications of the autogenic Ia-excitation pathway on ankle angle were explored using stimulation experiments.
2. Methods

2.1. Spinal lumbosacral connectome generation

The lumbosacral connectome (L1-S3) model was generated using the 'sensory-motor circuit generation algorithm'. The algorithm relies on three categories of model description .xlsx sheets to automatically generate connectome (figure 2). The algorithm first segregates muscles into agonist and antagonist groups based on movement repertoire information; then, it applies connection rules between the specified neurons to produce all possible spinal connections pertaining to the muscle groups, resulting in a connectome (S_{ca}) (figures 2, 3). (refer supplementary—A (available online at stacks.iop.org/IOPSN/3/014001/mmedia)).
2.1.1. Muscles and their movement types

The list of 42 lower limb muscles for which the spinal infrastructure is to be built was obtained from an anthropometrically curated OpenSim\(^1\) based ‘lower-limb musculoskeletal model’ (hereafter called ‘MS’)\(^{[11]}\).

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**Definitions**

| Spinal neurons | Muscles |
|----------------|---------|
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A connection rule template is characterized by **Source spinal cell type(S)**, **Target spinal cell type(T)** type of **synapse** & type of muscle groups ("agonist", "antagonist", "self")

**Movements**

Library of human movement types and their antagonist movements are listed here

**Autogeneration algorithm**

1. Creates pool of spinal neurons \(N(0)\)
2. Groups muscles into agonists and antagonists pairs
3. For a given connection template, algorithm identifies \(S\) and \(T\) in the pool of \(N(0)\) i.e created in step 1
4. Using muscle groups information created in step 2, identifies the target muscle (i.e sub cell type) of \(S\) and \(T\), which satisfy the muscle group type ("agonist" or "antagonist") specified in the connection template.
5. Creates a connection/synapse
6. Repeats A,B,C until all the connection rules are applied among \(N(0)\)

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Figure 2. Schematic showing the auto-generation of connectome from the spinal neurons, connection rules, muscles and movement types data.

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Figure 3. Schematic of spinal proprioceptive feedback control. \(S_{\text{syn}}\): Synaptic connectivity matrix of connectome; \(E_{\text{m}}\): Motoneuron states and \(A_{\text{ax}}\): Afferent neuron states. \(A_{\text{ax}}\) receives proprioceptive feedback from muscles of the musculoskeletal model and triggers other spinal neurons specified in \(S_{\text{syn}}\) to obtain \(E_{\text{m}}\). \(E_{\text{m}}\) activates muscles causing limb movement. \(k,m,n\) are the total number of spinal neurons, motoneurons and afferent neurons.

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\(^1\) https://simtk.org/projects/opensim.
MS consists of excitable muscles that control the hip, knee, ankle, and joints of the lower extremity, and allows a total of 12 movement types per limb. Movement types coordinated by each of the 42 muscles were assigned based on the kinesiological information. This list is crucial for grouping the muscles into agonists and antagonists.

2.1.2. Spinal neurons

Three types of spinal neurons are involved in motor control: motor neurons, interneurons, and sensory neurons \[4\]. A list of neurons included in the connectome was prepared by specifying their type, location, and target muscle. Motoneuron localization data were obtained from a popular study \[12\] (figure 4).

2.1.3. Formulation of generic connection rules

The spinal cord consists of several pathways that start and end in the musculoskeletal system, thereby forming the spinal proprioceptive circuits. The spinal pathways/feedbacks over the last century have been explored using nerve stimulation studies in humans or cats, electrical stimulation in intact spinal preparations of animal models, and later using fluorophore or viral vector-based tracer studies. However, in the current study the ‘Stereotypical spinal connection rules’ are deduced from the works and reviews by Elzbieta Jankowska and David Burke and used as templates for automatic generation of circuit blocks in the connectome \[13, 14\]. Each connection in the spinal pathway (figure 1) was translated into connection rule i.e. defined by the ‘source’ and the ‘target’ neuron, and the ‘muscle group type,’ ‘spinal side’ and ‘synapse type’. (table 1).

2.2. In-silico stimulation experiments to demonstrate the effect of Autogenic Ia-excitatory feedback on the ankle

The connectome catering to ankle control was generated and synchronized with the MS to obtain a closed-loop spinal control system (figures 6(A), 3). Neuromuscular co-simulations were performed using the interfaced
setup of NEURON\textsuperscript{2} and OpenSim\textsuperscript{1} implemented in NEUROiD\textsuperscript{15}. The MS consists of muscle models that follow the Hill-type behavior of muscle contraction. The connectome consists of segmental alpha motoneurons and Ia-afferent neurons with Ia-excitatory connections. Motoneurons were modelled as spiking neurons and afferent neurons were modelled as artificial neurons. Ensemble motoneuronal activity was measured as the population firing frequency and scaled to a range between 0 and 1. The scaled output is fed to the MS for muscle excitation. The muscle spindle (Ia-afferent) activity of the muscles was estimated as peaks per second (pps) using the following formula\textsuperscript{16}.

\[
Ia = 4.3 \times V^{0.6} + 2(\Delta l)
\]

\(V\) and \(\Delta l\) are muscle stretch velocity and muscle stretch respectively.

In the current study, the role of autogenic Ia-excitatory feedback in ongoing movements was tested. For this, the soma of the tibialis anterior (ta) motoneurons located at the L4 segment was stimulated using presynaptic stimuli of 40 Hz for 100 ms to elicit a total dorsiflexion of 6°. Stimulation was performed with and without IA feedback. During the simulation, the ankle angle and muscle lengths of the soleus (sol), tibialis anterior (ta), gastrocnemius lateralis (gaslat), and gastrocnemius medialis (gasmed) were tracked, along with the voltages of the motoneurons (Refer Supplementary-B).

\textsuperscript{2} https://neuron.yale.edu/neuron/what_is_neuron.
3. Results and discussion

3.1. Lower limb muscle-muscle interaction maps

Automatically generated lumbosacral connectome for this study consisted of 848 unique spinal neurons and 21200 connections pertaining to the ipsilateral side of the lumbosacral spinal cord. Resultant connectome was

Figure 6. In-silico stimulation experiments: musculoskeletal behaviour. (A) (Left) Autogenerated spinal connectome model in NEUROiD window. (Right) Musculoskeletal model. (B) Voltage traces of ta motoneurons due to stimulation under no feedback. (C) Ankle angle during stimulation with and without autogenic Ia-feedback. (D) and (E) Muscle activation and Muscle length trajectories during stimulation. Note. The first initial peak in the ‘ta’ activity (on autogenic Ia feedback) (figure 6(D)) was due to passive stretch in ta muscles caused by passive fluctuations in the ankle. See posture and stability trends of the model in supplementary-B.

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3.1. Lower limb muscle-muscle interaction maps

Automatically generated lumbosacral connectome for this study consisted of 848 unique spinal neurons and 21200 connections pertaining to the ipsilateral side of the lumbosacral spinal cord. Resultant connectome was
analyzed to create Ia and Ib based spinal proprioceptive lower-limb muscle-muscle interaction maps (figure 5). Refer supplementary-codes to generate the connectome model and interactions maps [17]. Ia and Ib feedback from the muscle spindles and GTO, respectively, offer dynamic feedback control of muscles through their autogenic and heterogenic interactions [3, 18]. Autogenerated by the algorithm, each interaction in these maps represented the total number of pathways between a pair of muscles. Multiple counts of a particular pathway between a pair of muscles indicate multisegmental control of muscles, signifying the anatomical relevance of the connectome (figure 4). This enabled us to track segmental afferent and efferent activities during in-silico simulation studies (figure 6).

3.1.1. Autogenic control of muscles
Projection of proprioceptive information from a muscle to its own is called ‘autogenic’ interaction [18]. Interactions along the diagonals indicate autogenic ‘excitatory’ and ‘inhibitory’ interactions through the Ia and Ib pathways of the connectome, respectively (figures 5(A), (D)). The self-control of muscles through Ia and Ib feedback is perceived to offer ‘stretch resistance’ and ‘loading response’ respectively, thereby preventing muscles from excessive passive stretching or contraction. Muscles glumax (1, 2, 3), sol, bifemst, bifemlg, and semi-mem showed the highest number of Ia (figure 5(A)) and Ib (figure 5(D)), which could be due to their larger segmental control (figure 5(F)) (figure 4).

3.1.2. Synergistic control of muscles
Projection of proprioceptive information from one muscle to other muscles is called ‘heteronymous’ interaction [18]. This was mediated through Ia-excitatory (figure 5(A)), Ia-inhibitory (figure 5(B)), and Ib-excitatory (figure 5(C)).
For example, the agonist muscles vastus (vaslat, vasmed, vasint) and rectus femoris (recf) interact positively via Ia-excitatory to coordinate knee extension (figure 5(A)). This is because of the stretch information from the muscle spindles. Ia-inhibitory interactions of muscles generally demonstrate the opposite of Ib-excitatory interactions. For example, the knee extensors vastus (vasmed, vasint, valat), rectus femoris (recf), and knee flexors biceps femoris (bifemlg, bifemst) and semitendinosus (semmem) interact negatively by their Ia-inhibition and positively by their Ib-excitation pathways (figures 5(B), (C)). Because the stretch information from spindles negatively alters motoneuronal activity of antagonist muscles, while the loading information from GTO does the opposite. However, certain interactions, such as the gluteus maximus (glumax1,2,3) muscles with the gluteus medius (glumed1,2,3) and gluteus minimus (glumin1,2,3) are shown to interact by Ib-inhibitory, Ia-inhibitory, and Ia-excitatory pathways, due to overlapping roles of these muscles in their movement types (refer supplementary-A). However, the predominance of these interactions must be ascertained by dynamic simulation experiments using an in-silico setup.

3.2. Effect of autogenic Ia-feedback on the ankle angle

The ‘gaslat,’ ‘gasmed’ and ‘sol’ muscles contribute to ankle plantar flexion, while ‘ta’ contribute to ankle dorsiflexion. When the ‘ta’ motoneurons were stimulated in open loop without afferent feedback, those motoneurons were stimulated in open loop without afferent feedback, they contributed to ankle dorsiflexion and thereby ankle dorsiflexed by a maximum of 6 degrees (figures 6(C)–(E)). However, when stimulated with Ia-feedback turned on, the ankle initially dorsiflexed by 1.8° and then plantarflexed (figure 6(C)). Here, the dorsiflexion due to active ‘ta’ contraction has passively stretched ‘sol’, ‘gasmed’, and ‘gaslat’ muscles (figure 6(E)). This elicited segmental Ia-feedback ranging between 10 Hz–15 Hz from the muscle spindles of ‘gasmed,’ ‘gaslat,’ ‘sol’ muscles (figure 7(A)). This afferent activity excited their own motoneurons via the monosynaptic autogenic ‘Ia-excitation’ pathways in the connectome (figure 7(B)). Thus, resulting in simultaneous contraction in ‘sol,’ ‘gasmed,’ ‘gaslat’ muscles (figure 6(D)) which reduced the ongoing ankle dorsiflexion and caused plantarflexion (figures 6(D), 7(B)). In vivo experiments suggest that autogenic Ia-feedback from the soleus muscle contributes to reductions in ankle dorsiflexion [19]. Although the model successfully demonstrated the effect of Ia-afferent based stretch responses on ankle behavior, the clinical context may vary owing to subject-specific parameters. By and large, the synchronized connectome-MS model opens a window to build spinal connectomes of interest and study spinal feedback in the context of musculoskeletal functions and validate the same. Refer supplementary codes to run the model and generate the graphs [17]

4. Conclusions

The autogeneration of the connectome is data-driven; hence, it helps modify, update, and tune according to the hypothesis. In addition, the analysis of the lumbosacral connectome provided a plethora of physiologically relevant muscle-muscle proprioceptive interactions, which can help create in-silico test cases in the context of spinal and supraspinal pathologies. Anatomically tagged neurons in the simulatable connectome provide tracking of segmental spinal activity, which can be pivotal in identifying the correct electrode locations and stimulation frequencies for therapeutic spinal stimulation. In-silico testbeds allow the alteration of parameters and selectively turn on or off afferent feedback or ablate pathways to fit the context of the study. This has the potential to circumvent the challenges of in vivo spinal setups that require knockout animals, subject anesthetization, and ischemic blockage of afferent feedback.

Acknowledgments

We thank Raghu Sesha Iyengar and Avinash Kumar Singh of Spinal cord and movement labs, Department of Biomedical Engineering, IITH, India for their assistance in designing the simulation protocols and parameters. We extend our sincere gratitude to the anonymous reviewers for helping improve the study.

Data availability statement

The data that support the findings of this study are openly available at the following URL: https://github.com/madhaviith/iop_scinotes_codes.

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