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# An Open-source Computational Model of Neurostimulation of the Spinal Pudendo-Vesical Reflex for the Recovery of Bladder Control After Spinal Cord Injury

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***Abstract*—Spinal cord stimulation (SCS) could be used to restore control of the bladder after spinal cord injury, but substantial development is still required to tailor this technology for bladder function. Computational models could be utilized to accelerate these efforts enabling in-silico optimization of stimulation parameters. However, no model of the spinal pudendo-vesical reflex can simulate the effect of stimulation amplitude on neuron recruitment. This limitation hinders accurate prediction of bladder pressure changes for different stimulation configurations. Here, we implemented an open-source realistic spiking neural network model of the pudendo-vesical reflex enabling exploration of the impact of stimulation amplitude and frequency on bladder pressure changes. We used the o$^2$S$^2$PARC platform to design a parallel implementation of the bladder reflex circuits with NEURON. Our model successfully reproduced and expanded previous studies, producing a decrease in bladder pressure at low stimulation frequency (10 Hz) and excitation at high stimulation frequency ( ⩾33 Hz) in isovolumetric experiments. We then explored the effect of mixed nerve recruitment, simulating a common case of poorly selective spinal cord stimulation. We found that high recruitments of pudendal nerve axons are necessary to maintain this bi-modal behavior, regardless of stimulation specificity. Our framework is fully open-source and can be used to simulate any type of axon stimulations such as SCS and peripheral nerve stimulation.**

## I. Introduction

Neurogenic bladder dysfunction caused by spinal cord injury causes severe continence and micturition problems, which leads to significant and ongoing medical issues. Multiple studies suggested that electrical stimulation of pudendal afferents could be used to improve bladder function [1], [2]. In clinical applications, pudendal stimulation could be delivered by peripheral nerve implants or epidural spinal cord stimulation (SCS) that is known to recruit sensory afferents [3], [4]. However, substantial technological development is still required to refine these technologies to target continence and micturition. Computer models could speed up this development by enabling in-silico investigations, which expand the space of parameters beyond that which can be easily explored in experiments [5]. Unfortunately, existing computer models of the spinal pudendo-vesical reflex [6] utilize artificial representations of neural nodes as single elements. While useful for qualitative estimations, these models hinder the simulation of stimulation parameters such as current amplitude, since they can't reproduce the different population recruitment levels induced by varying current amplitudes. In this work, we extended an existing model of the pudendo-vesical reflex [6] into a spiking neuron network model integrating multiple neuron populations as well as the effects of axon stimulation. We developed our model with NEURON [7] in o$^2$S$^2$PARC, an open-source computational platform [8]. Our model can simulate changes in bladder pressure in response to stimulation of afferents and efferent axons at varying recruitment levels as well as stimulation frequencies. It is fully open source and available on o$^2$S$^2$PARC, thus easily enabling its use for any investigator in the field and adaptable to either peripheral or spinal cord stimulation.

## II. Methods

We designed our neural network using a parallel implementation of NEURON built on the reflex model proposed by Formento and colleagues [9] using python 3.8 and NEURON 8.0.

### A. Model topology and electrical stimulation

Our model is based on [6] and includes pudendal and pelvic nerve afferent fibers that receive sensory inputs from the urethra and bladder, dorsal interneurons (IND) that incorporate inputs from both pudendal and pelvic afferents, excitatory and inhibitory interneurons ($IN_{M+}$, $IN_{M-}$) that provide direct excitatory or inhibitory control of the sacral parasympathetic nucleus (SPN), SPN neurons that generate parasympathetic outputs to the bladder, pontine micturition center and periaqueductal gray (PMC/PAG) that provide descending excitation of IND, and feedback neurons (FB) that provide inhibitory control to IND to form a negative feedback loop. Our model (Fig. 1A) receives electrical stimulation inputs from pudendal and pelvic afferents which are implemented as virtual neurons whose firing rates are determined by sensory feedback and integrated with the defined stimulation frequency [9]. Specifically, stimulation-induced recruitment ratio can be adjusted from 0% to 100%. The number of afferents stimulated can be set by initial parameters. We included 30 cells for each neuron group. All other neurons were simulated as IntFire4 classes which generate quick excitatory and inhibitory post synaptic potentials that decay exponentially with predefined time

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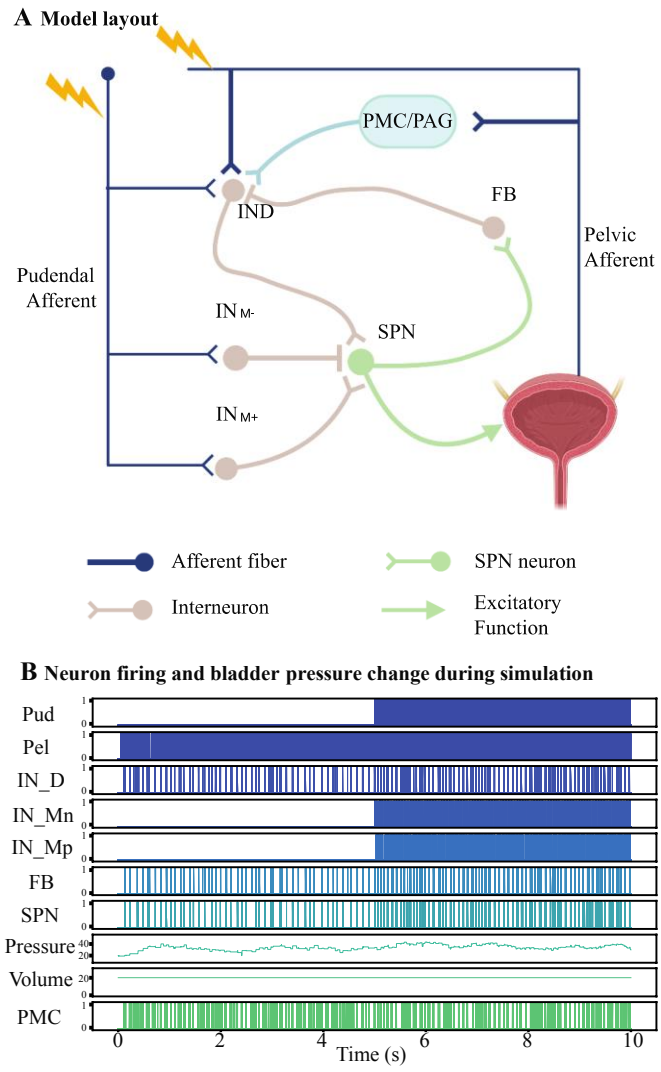


Figure 1. Computational model of pudendo-vesical reflex. **A** Illustration of model layout. Sensory afferents receive stimulation input and activate or inhibit the bladder through interneurons. **B** Recording of neuron spikes and bladder pressure change for 10 seconds of simulation. **C** Raster plot of the populational firing of an SPN group with 30 neurons and a higher density of SPN spikes after 5 seconds (the stimulation time point).

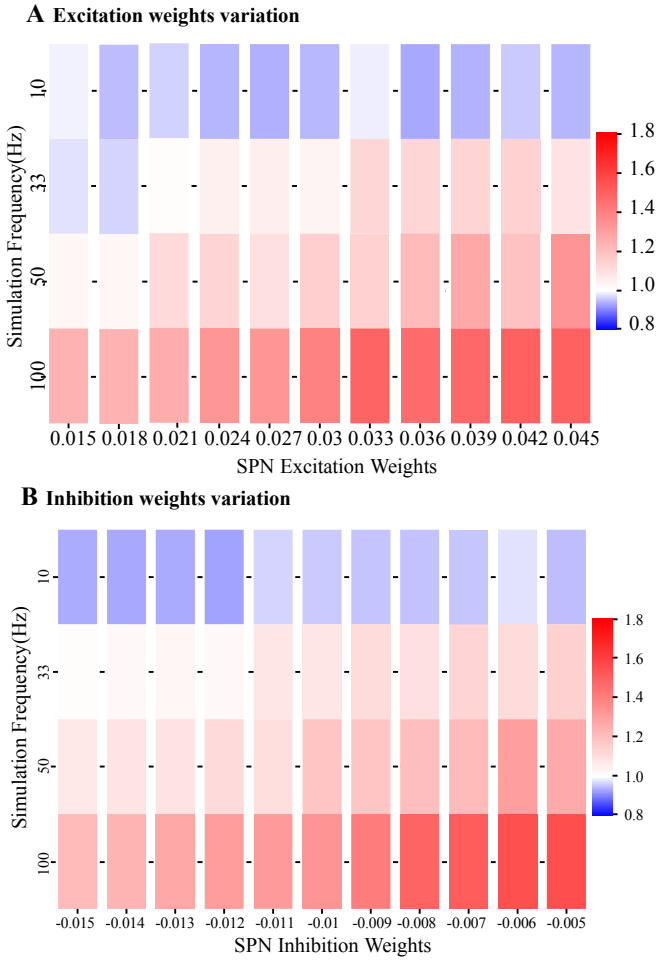


Figure 2. Parameter sensitivity analysis. Heatmap of bladder pressure ratio change representing a ±50% variation in excitation or inhibition weights. **A** Excitation weights variation. The original weight is 0.03. The excitation effect was cancelled when the excitation weight was smaller than 0.018. **B** Inhibition weights variation. The original weight is -0.01.

constants. All parameters can be found on (https://osparc.io/#/study/8eb58ade-3692-11ec-917d-02420a0b3377).

### *B. Estimation of bladder pressure at varying stimulation parameters*

In isovolumetric experiments, we defined the initial bladder volume at 20 ml and keep the bladder isovolumetric during the simulation (Fig. 1B). In our study, the total simulation lasted 10 seconds, and at the 5 second time point, a varying amount of pudendal or pelvic afferents from 0 to 100% were stimulated at 4 different stimulation frequencies: 10Hz, 33Hz, 50Hz, 100Hz. The bladder pressure was then estimated using a polynomial function of the averaged group firing rates of SPN neurons taken from [6], calculated with a 50-millisecond sliding window (Fig. 1C).

## III. Results

We used the change of bladder pressure ratio, which is the average pressure during stimulation divided by the average bladder pressure pre-stimulation, to examine the changes in

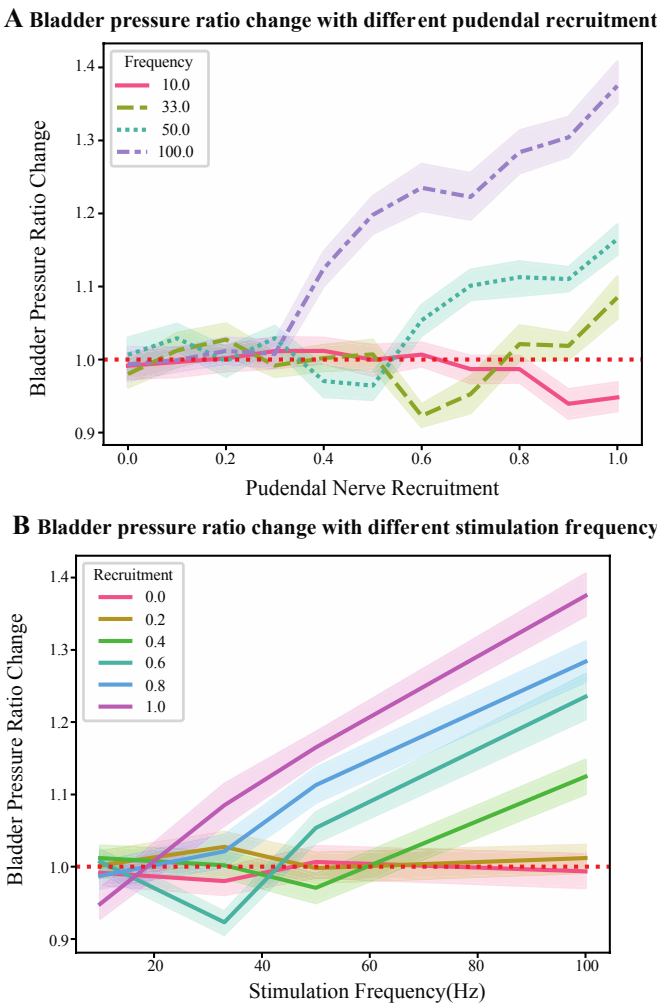


Figure 3. Bladder pressure ratio change with different pudendal nerve recruitment amplitude and input stimulation frequency. Bladder pressure ratio change with 95% confidence interval, recruitment amplitude ranged from 0% to 100%, stimulated with 10Hz, 33Hz, 50Hz, 100Hz. **A** Stable bi-model behavior was produced with high pudendal recruitment amplitude (>80%). **B** High stimulation frequency (>50Hz) supplement low pudendal recruitment amplitude to activate bladder.

bladder pressure caused by a specific set of stimulation parameters applied on the pudendo-vesical reflex.

### *A. Model robustness: parameter sensitivity analysis*

To validate the robustness of our model, we conducted a parameter sensitivity analysis to determine whether our model could produce the bi-modal continence (decreased bladder pressure) and micturition (increased bladder pressure) behaviors at 10 Hz and 33 Hz, respectively. We first investigated $IN_{M+}$ and $IN_{M-}$, the two interneurons directly providing excitatory or inhibitory control on SPN neuron by varying their connection weights to the SPN over a range of -50% to +50%.

Our model was robust toward synaptic parameter changes. Only when excitation weights were reduced by more than 40% was the excitation effect at 33 Hz stimulation canceled. In other cases, the bi-modal behavior remained after the parameter variation (Fig. 2A, 2B).

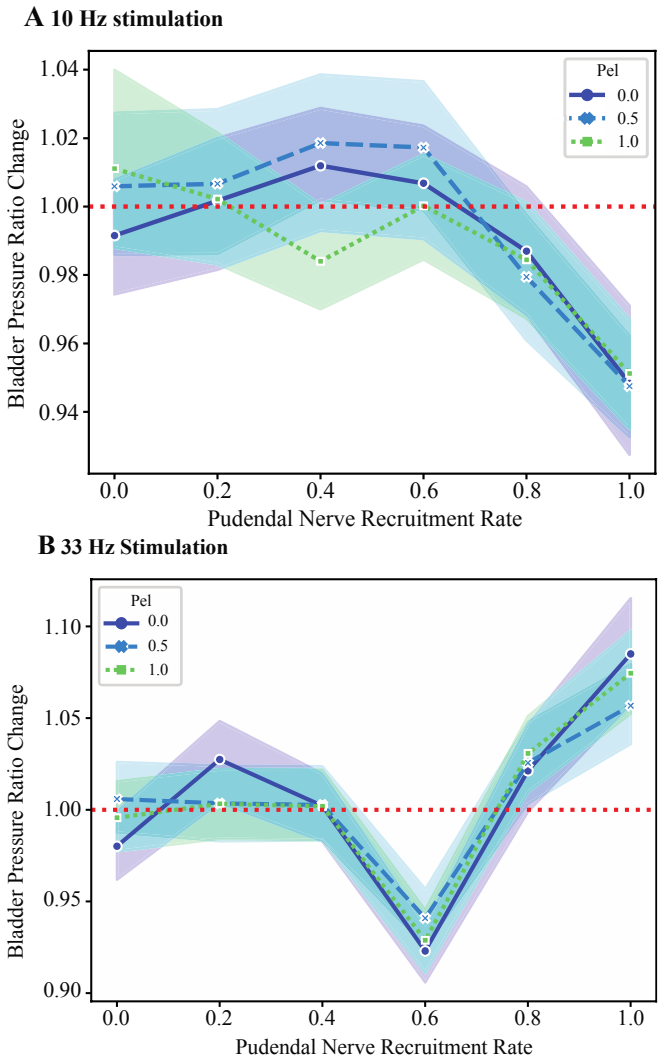


Figure 4. Varying pelvic afferents recruitment rate to see the bladder pressure ratio change. Pelvic afferents recruitment amplitude was 0%, 50%, 100%, while pudendal afferents recruitment amplitude ranged from 0% to 100% with a 20% step. Both pelvic nerve and pudendal nerve are stimulated at 5 second time point, with same stimulation frequency. **A** Recruited afferents stimulated at 10 Hz. **B** Recruited afferents stimulated at 33 Hz.

### *B. Effect of pudendal afferent stimulation intensity on bladder pressure*

To further explore the role of pudendal nerve activity in the bladder excitatory and inhibitory reflexes, we varied pudendal nerve recruitment rates. Indeed, electrical stimulation amplitude determines the number of axons recruited by each pulse [10].

In some cases, low pudendal nerve recruitment can be supplemented by high frequency electrical stimulation input (Stimulation frequency > 50Hz, recruitment rate > 60%) to generate the excitation effect (Fig. 3A). However, only high recruitment amplitude of pudendal nerve (> 80%) can sustain the excitation effect at 33 Hz and inhibition effect at 10 Hz (Fig. 3A, 3B) when pelvic afferents are not stimulated. In this case pelvic activity solely depends on sensory feedback.

### C. *Effect of pelvic afferent stimulation intensity on bladder pressure*

To examine the role of pelvic afferent recruitment in this pudendo-vesical reflex, we recruited 0%, 50% and 100% of pelvic afferents while varying the recruitment rate of pudendal nerve. Both pelvic nerve and pudendal nerve were stimulated at 10Hz or 33Hz. In both cases, the dynamics of bladder pressure changes were not significantly affected by the recruitment rates of pelvic nerve afferents (Fig. 4A, 4B). However, high pudendal nerve recruitment was necessary (> 80%) to preserve the bi-modal inhibition/excitation behavior, regardless of the recruitment amplitude of pelvic afferents.

## IV. Discussion

In this study, we aimed at implementing an open-source computational model of a spinal reflex regulating bladder function which can be generalized and adapted to study problems of peripheral or spinal electrical stimulation. Therefore, we developed a model based on [6] and equipped it with built-in mechanisms to study stimulation of afferents or efferents at different recruitment rates and stimulation frequency, enabling a variety of simulated experiments.

The results from the parameters sensitivity analysis indicated that our model was robust over a large parameter range, thus providing support for its validity in simulating large sets of parameters. In our example stimulations, we reproduced similar level of increase and decrease in bladder pressure to other modeling studies [6], [11], [12]. We then showed the capabilities of our model by simulating multiple stimulation frequencies as well as recruitment rates for pudendal and pelvic afferents. Our results suggested that under the isovolumetric conditions that maintain sufficient sensory input from pelvic afferents, then if sufficient recruitment of pudendal afferent is attained, crosstalk stimulation of pelvic afferents does not affect the capacity of stimulation to control the bladder, which showed the robustness of a potential stimulation system to poor specificity. This is consistent with experimental observations [3], [11], [12]. We also noticed a reversion of bi-model behavior at 33 Hz stimulation when pudendal recruitment was 60%, which may relate to the comparatively high SPN firing rate pre-stimulation due to high initial bladder volume [6].

## V. Limitations

Though our model reproduced the bi-modal behavior observed in previous publications and experimental investigations, it could be further improved by using realistic neuron models to simulate SPN behavior. Indeed, at present, our model doesn't have an intrinsic upper limit for SPN firing, which results in an unlimited bladder pressure increase with stimulation frequency. In future work, we will incorporate validated realistic neuron models [9], [13]-[15] to produce an intrinsic upper limit to SPN firings and make our simulations for high-frequency stimulation more realistic.

## VI. Conclusions

We presented an open-source computational model of the bladder reflex that can be used to simulate the effects of neurostimulation of pudendal and pelvic afferents on bladder pressure changes. Our example simulations shows that only high recruitment rates of pudendal nerve afferents can produce both increases and decreases in bladder pressure at varying stimulation frequency, regardless of the recruitment rates of pelvic afferents. While parameter sensitivity analysis shows significant robustness to model parameters, new experimental data exploring stimulation amplitude and frequency of pudendal and pelvic afferents is needed for further validation of our model.


## Acknowledgment

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