2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Predicting Wide-Dynamic Range Neuron Activity from Peripheral Nerve Stimulation using Linear Parameter Varying Models

Claire A. Zurn, Christine Beauchene, Wanru Duan, Yun Guan, and Sridevi V. Sarma, *Member, IEEE*

***Abstract*— Neuromodulation treatments for chronic pain are programmed with limited knowledge of how electrical stimulation of nerve fibers affects the dynamic response of pain-processing neurons in the spinal cord and the brain. By modeling these effects with tractable representations, we may be able to improve efficacy of stimulation therapy. However, pain transmitting neurons in the dorsal horn of the spinal cord, the first pain relay station in the nervous system, have complex responses to peripheral nerve stimulation (PNS) with nonlinearities and history effects. Wide-dynamic range (WDR) neurons are well studied in pain models and respond to peripheral noxious and non-noxious stimuli. We propose to use linear parameter varying (LPV) models to capture PNS responses of WDR neurons of the deep lamina in the dorsal horn in the spinal cord. Here we show that LPV models perform better than a single linear time-invariant (LTI) model in representing the responses of the WDR neurons to widely varying amplitudes of PNS current. In the future, we can use these models alongside LPV control techniques to design closed-loop PNS stimulation that may accomplish optimal pain treatment goals.**

***Clinical Relevance*— Electrical nerve stimulation as a therapy for chronic pain is in need of a more informed approach to programming. By describing the effects of stimulation on the pain system with tractable mathematical models, we may be able to titrate the stimulation to more effectively treat chronic pain.**

I. Introduction

Chronic pain is a significant burden to public health, with estimates of 11-40% prevalence in the United States[1]. Opioids have been used as the primary treatment in the past but can be extremely addictive and have overdose potential. Meanwhile, neuromodulation by electrically stimulating nerve fibers has shown promise as a replacement with fewer side effects[2]. FDA approved targets for stimulation include the spinal cord, dorsal root ganglion, and peripheral nerves of the trunk[3]; but many more are being investigated in clinical trials. Across all applications, most programming (selective delivery of frequency, pulse width, and spatial pattern) of the electrical stimulation is done by trial and error and is held constant for weeks to months at a time in patients. This type of neuromodulation has limited efficacy for patients, with generally about 60% of patients reporting greater than 50% reduction in pain score, and therapeutic effects often decrease over time[4]. There is a need to better understand and characterize the dynamic effects of stimulation on the pain system for the further development and improved programming of neuromodulation for chronic pain treatment.

When you damage tissue, such as a paper cut, a primary sensory neuron specific to pain (nociceptor) fires a series of action potentials down its axon and synapses in dorsal horn neurons, including WDR neurons (often in the deep lamina) and nociceptive specific neurons (more in the more superficial laminae). The WDR neurons, of which many are projection neurons, integrate information from primary sensory neurons and interneurons to act as the first major relay station in the pain pathway, sending their axons, along with others, to the thalamus in the brain. The thalamus then relays this information to cortical areas to sense, think about, and emotionally respond to the painful stimulus.

The WDR neuron is particularly interesting for receiving both non-noxious A-fiber and noxious C-fiber inputs, encoding pain intensity and showing dynamic changes in excitability after repeated noxious stimulation, and has been well-studied in rodents and non-human primates. Under healthy conditions, its response largely consists of two components in response to a single high-intensity electrical stimulus, first as it receives information from large-diameter Aβ fibers (non-noxious) and medium-diameter Aσ fibers (A-component) and second as it receives nociceptive information from the small-diameter C fibers (C-component, Fig. 1). In chronic pain models, the separation between the two components become less clear and often there is an increase in the underlying base firing rate (spontaneous activity)[5], [6].

In the past, efforts to mathematically characterize the WDR neurons responses have spanned very complex, mechanistic models, to very simple linear time-invariant (LTI) models[7], [8]. Mechanistic models can become too complex

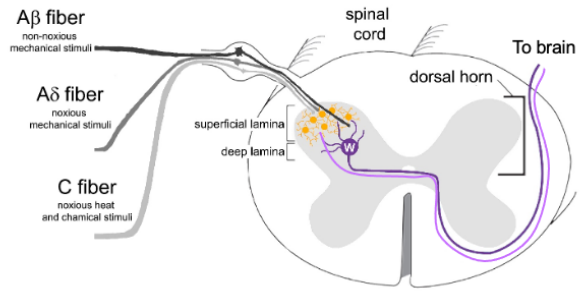

Figure 1. Anatomy of peripheral nerve fibers entering the spinal cord and transmitting information through wide dynamic range neurons (marked W).

*This work is funded by the NIH/NINDS T32 NSO70201 to CB, NIH/NCCIH R01AT009401 to CZ and SVS, and R01NS110598 and R01NS117761 to YG.

C. A. Zurn, C. Beauchene, and S. V. Sarma are with Johns Hopkins University, Baltimore, MD 21218 USA (phone: 952-303-1178; e-mail: czurn1@jhu.edu).

W. Duan and Y. Guan are with Johns Hopkins Medicine, Baltimore, MD 21287 USA.

to be used for therapeutic stimulation development; on the other hand, LTI models fail to capture the nonlinearities produced by the different activation thresholds for pain and simple touch receptors. By definition, a LTI model creates one response that scales with the amplitude of the input. Thus, it is unable to capture these nonlinearities and history effects observed in dorsal horn neuron responses.

In this study, we aim to create a tractable computational model to represent and predict the WDR firing responses to varying amplitudes of peripheral nerve stimulation (PNS). Specifically, we hypothesize that a linear parameter varying (LPV) model will outperform a single LTI model and will be able to more accurately represent and predict responses of WDR neurons to PNS. LPV models are simply a set of LTI models across a space of scheduling parameters. These scheduling parameters can vary with time and input[9]. There exists theory to utilize these LPV models in control design, allowing for future development of pain therapeutics[10], [11].

II. Methods

A. Data Collection and Preprocessing

All procedures were approved by the Johns Hopkins Animal Care and Use Committee. One male Sprague-Dawley rat underwent spinal cord injury at T10 vertebra level to generate a central neuropathic pain model. After recovery, the rat underwent anesthesia and a single WDR neuron was isolated in the deep layers of the dorsal horn near level lumbar L4. Single unit extracellular electrophysiology was recorded at 10 kHz (Fig. 2A). Ipsilaterally, bipolar PNS was delivered to the peripheral receptive field of WDR neurons in the hind paw. A stimulus response (SR) curve was generated by stimulating with 0.2-10 mA of current over 10 pulses, allowing transient of carryover effects of the simulation in the pain system to diminish between pulses (about 30 seconds interval); this was repeated for a second trial (10-minute interval). Single action potentials were isolated from the WDR recordings by filtering the data between 300-3000 Hz before applying a simple thresholding method. Firing rate curves were then generated by down-sampling to 1000 Hz, applying a 100-point Gaussian distribution to each spike location, and smoothing further where firing was sparse. The two trials' firing rate curves were then averaged.

The resulting firing rates (Fig. 2B) display the typical increasing SR behavior and match with previous literature[12]. When electrical stimulation is delivered at small amplitudes (0.2 mA – 2 mA), only low-threshold A fibers are activated, and the WDR neuron shows firing in a simple A component (peak). As the amplitude of the stimulation is increased, more action potentials appear in the A component before the stimulation becomes painful. At that point, an additional C-component of responses can be recorded. As current continues to increase, more action potentials occur in the C component.

B. Linear Time-Invariant Model Fitting

As mentioned above, a linear time-invariant (LTI) model quantifies the input-output relationship between the current delivered and the resulting WDR neuron firing rates. In the transfer function realization of an LTI model (1), *H(s)* provides the Laplace domain relationship in terms of coefficients a_0 through a_z and b_0 through b_p, where z is the number of zeros, p the number of poles, and s the Laplace variable.

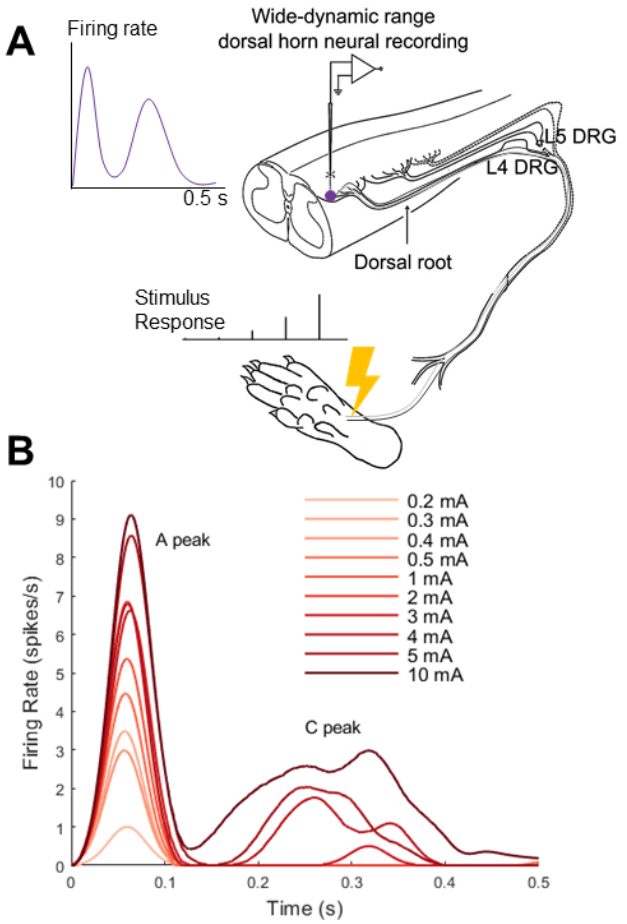

Figure 2. A) Data collection scheme, in which the paw is stimulated with electricity of varying amplitude and wide-dynamic range (WDR) neuronal firing is recorded. B) Average firing rate responses of a WDR neuron for 0.2 to 10 mA of current.

$$H(s)=\frac{a_0 s^z+a_1 s^{z-1}+\cdots+a_z}{b_0 s^p+b_1 s^{p-1}+\cdots b_p} \quad (1)$$

Specifically, the transfer function (TF) representation was utilized in two different scenarios. First, a single LTI TF was determined to serve as a reference model with minimal complexity. Additionally, a set of LTI TF models were used as components to construct the linear parameter varying (LPV) model. To generate multiple LTI models, input-output pairs of time-series were generated. Then strictly proper TF models relating these input-output pairs were generated using MATLAB's built-in subspace methods, enforcing stability. Poles could range from 3 to 10, and zeros could range from 2 to 9, with the condition that there were fewer zeros than poles.

C. Linear Parameter Varying Model Fitting

We propose that a linear parameter varying (LPV) model can capture the nonlinearities in the WDR PNS responses as opposed to a single LTI model. In the state-space realization of LPV models, a scheduling parameter determines the state-space matrices used to predict the WDR response (Fig. 3).

To develop the LPV models, the strictly proper LTI TFs (described in *II.B)* were identified for each individual stimulation amplitude using their respective responses. This generated a set of LTI TF models, one for each stimulation amplitude, which were then transformed into state-space

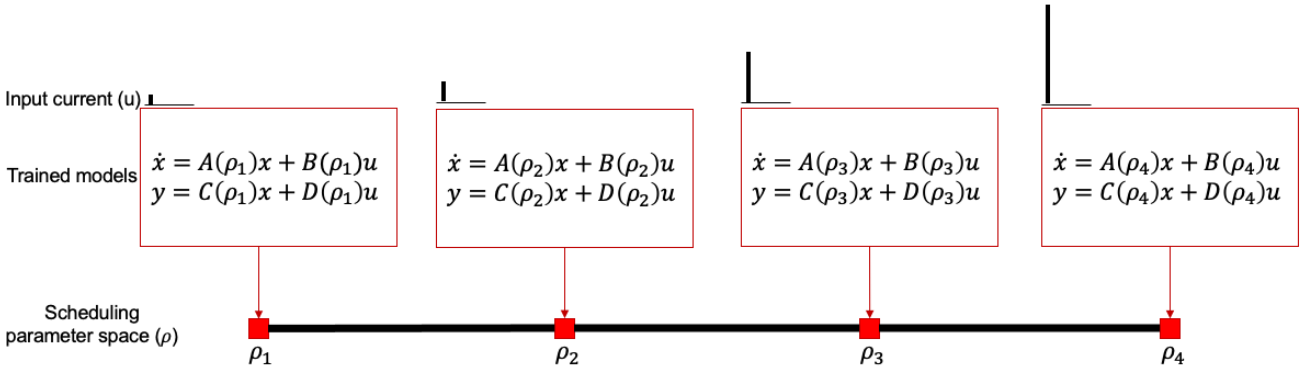

Figure 3. Linear parameter varying model schematic for the stimulus response curve (varying the input current amplitude). Each model is trained with a different input-output pair and stored at the proper point in scheduling parameter space. Any point between two models in scheduling space (thick black line) can be interpolated using the two nearest models (red blocks).

representations. Therefore, our final LPV model was created by using the set of LTI models and a scheduling parameter, ρ, which determined the state-space model evaluated for that instant in time. We chose our scheduling parameter, ρ, to be the **integral of current delivered over the last 20 seconds**, effectively giving us the amplitude of the single pulse as our parameter but allowing for history effects due to more complex inputs in future work.

D. Identifying and Selecting the LPV Model Order

To evaluate and select a best-fit LPV model, a root-mean-squared error (RMSE) was calculated between the firing rate curve and model-predicted curve for every stimulation amplitude and every pole-zero combination. The average RMSE was then evaluated over all SR pulses. Further, the order of the model (number of poles) was penalized to prevent overfitting. By minimizing a weighted combination of the RMSE values and model order, we identified a single pole-zero combination to be used going forward. To evaluate the performance of the LPV model, we also identified a single LTI model of the same pole-zero combination to act as a reference.

E. LPV Interpolation Scheme and Evaluation

For constructing the LPV model, an interpolation scheme is needed to estimate the response for any value of the scheduling parameter without an associated trained LTI model. Common methods include using the nearest neighbor (in scheduling parameter space) and linear interpolation. We chose a linear interpolation scheme, whereby the A, B, C, and D matrices of the state space model are linearly interpolated from the two nearest neighbor models. For this work, we utilized the interpolation scheme built into MATLAB's LPV Block in Simulink.

We evaluated this LPV model with a linear interpolation scheme by systematically leaving out each of our eight internal grid points (0.3-5 mA) and simulating the response using interpolation of the two nearest neighbors. For example, to find the interpolated model for 3 mA we interpolated between the state-space systems for 2 mA and 4 mA. The same inputs were simulated using the LTI model generated with equal poles and zeros. Two metrics were used to evaluate and compare the two model fits relative to the recorded firing rate data: R-squared (R^2) coefficient of a linear fit and a root-mean-squared error (RMSE).

III. Results

The optimal combination of poles and zeros for the fitted LTI models used for the LPV model was found to be 8 and 6, respectively. Across the whole time-series of 10 SR pulses, the models fit the data well with an R^2 coefficient of 0.998 and a RMSE of 0.0364. In addition to time-series quantification metrics, we can also look at the set of LTI models in the frequency-domain. Fig. 4 displays the Bode plots of the models, showing a decreased gain with increased amplitude, as expected. While the firing rate response increases with increased current amplitude, that change is significantly smaller than the change in current. Additionally, an altered shape can be seen between 2 and 10 Hz for the three greatest amplitudes of stimulation; all three of these display a second activation peak, indicating pain transmission. The same can be seen in the Bode plot of the all-pulse LTI model.

Fig. 5 shows examples of the LPV and LTI simulated responses overlaid with the data. The single LTI model (in blue) shows two peaks across every pulse, scaled by the input amplitude. Meanwhile, the LPV model (in red) shows just one main peak at small amplitudes (< 1 mA), two distinct peaks at high amplitudes (> 3 mA), and a transition period between the two (1-3 mA), showing that only the LPV model captures the nonlinear transition between non-noxious and noxious stimuli.

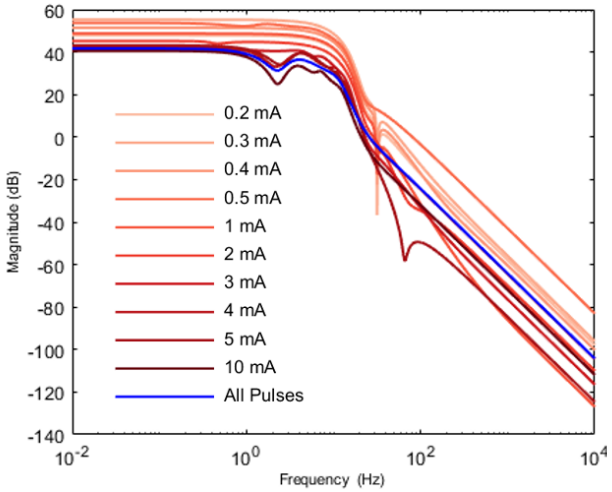

Figure 4. Bode plot of the set of 10 individual LTI models fit for the 10 amplitudes of peripheral nerve stimulation, along with the LTI model for all 10 amplitudes together.

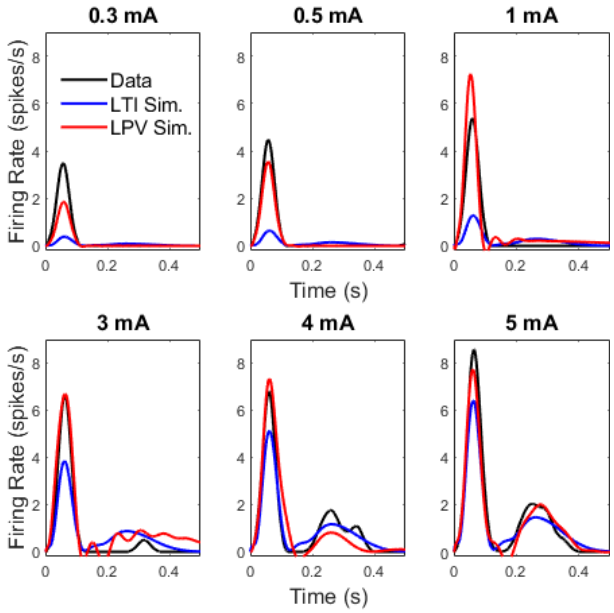

Figure 5. Simulated results for eighth order linear time invariant (LTI) and linear parameter varying (LPV) models. LPV results simulated using a two-nearest-neighbor linear interpolation scheme. Interpolation appears to perform best at small and high amplitudes and less well where the system transitions from one to two peaks.

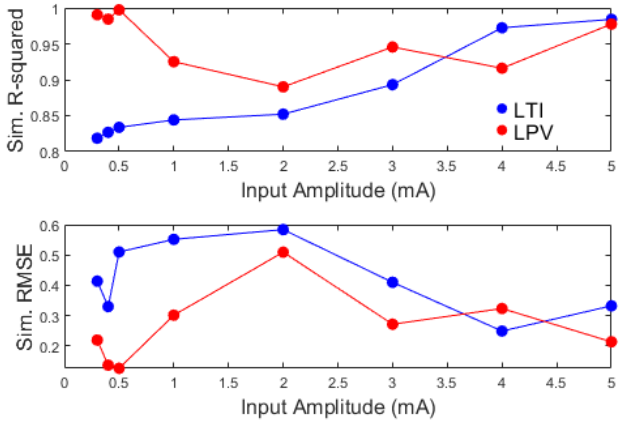

Figure 6. Comparison of simulated results using an eighth order linear time invariant (LTI) model and linear parameter varying (LPV) model. R-squared value taken from a linear fit with recorded data. Root mean squared error similarly calculated relative to recorded data.

The high oscillations observed in the 3 mA LPV response (Fig. 5) is an example of this transition, which does not match the data as well as in the non-transition cases. This suggests that the linear interpolation scheme works well in cases where it was interpolating between similar-shaped responses. At small amplitudes, the size of the A fiber response was changing but the C fiber response was zero. Meanwhile, the 5 mA response was simulated using 4 mA and 10 mA responses, both of which showed well-defined A and C fiber responses.

Finally, the R^2 and RMSE values were analyzed for each stimulation amplitude and compared between the LTI and the LPV simulations. As seen in Fig. 6, the LPV model almost always performs better than the LTI model across stimulation amplitudes, except at 4-5 mA. The time-domain response of the single LTI model has both A and C fiber peaks at every input amplitude, making the high amplitude responses fit best. However, both the shape of the response and linear decrease in amplitude makes the fit much worse at low current amplitudes. Therefore, the results in Figs. 5 and 6 highlight the strength of the LPV model, which can accurately capture the nonlinearities that the single LTI model cannot.

IV. Discussion

In this work, we showed that we can successfully represent the nonlinear dynamics of the WDR neuronal responses in the dorsal horn in response to stimulation using an eighth order LPV model. We also showed that we can estimate the unsampled space of stimulation amplitude (within 0.2-10 mA) of parameter ρ with success. In contrast, the LTI model failed to capture the variable thresholds for noxious and non-noxious stimuli.

The LPV framework is easily extendable to allow for multi-dimensional scheduling parameter space. We hope to use this in the future to capture the nonlinear dynamics of repetitive stimulation at different frequencies in addition to this example of varying stimulation amplitude. Finally, we eventually will use these models and extensive scheduling parameter space to design peripheral nerve stimulation controllers to treat chronic pain.

References

[1] R. L. Nahin, "Estimates of Pain Prevalence and Severity in Adults: United States, 2012," *J. Pain*, vol. 16, no. 8, pp. 769–780, Aug. 2015.

[2] Z. Chen *et al.*, "The Impact of Electrical Charge Delivery on Inhibition of Mechanical Hypersensitivity in Nerve-Injured Rats by Sub-Sensory Threshold Spinal Cord Stimulation," *Neuromodulation Technol. Neural Interface*, vol. 22, no. 2, pp. 163–171, 2019.

[3] M. Hofmeister *et al.*, "Effectiveness of Neurostimulation Technologies for the Management of Chronic Pain: A Systematic Review," *Neuromodulation Technol. Neural Interface*, vol. 23, no. 2, pp. 150–157, 2020.

[4] J. Grider *et al.*, "Effectiveness of Spinal Cord Stimulation in Chronic Spinal Pain: A Systematic Review," *Pain Physician*, p. 22.

[5] W. Maixner, R. Dubner, M. C. Bushnell, D. R. Kenshalo, and J.-L. Oliveras, "Wide-dynamic-range dorsal horn neurons participate in the encoding process by which monkeys perceive the intensity of noxious heat stimuli," *Brain Res.*, vol. 374, no. 2, pp. 385–388, May 1986.

[6] J. Wallin, A. Fiskå, A. Tjølsen, B. Linderoth, and K. Hole, "Spinal cord stimulation inhibits long-term potentiation of spinal wide dynamic range neurons," *Brain Res.*, vol. 973, no. 1, pp. 39–43, May 2003.

[7] C. Beauchene, P. Sacré, F. Yang, Y. Guan, and S. V. Sarma, "Modeling Responses to Peripheral Nerve Stimulation in the Dorsal Horn," in *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Jul. 2019, pp. 2324–2327.

[8] A. Farajidavar, S. Saeb, and K. Behbehani, "Incorporating synaptic time-dependent plasticity and dynamic synapse into a computational model of wind-up," *Neural Netw.*, vol. 21, no. 2, pp. 241–249, Mar. 2008.

[9] J. S. Shamma, "An Overview of LPV Systems," in *Control of Linear Parameter Varying Systems with Applications*, J. Mohammadpour and C. W. Scherer, Eds. Boston, MA: Springer US, 2012, pp. 3–26.

[10] C. Briat, "Control of LPV Systems," in *Linear Parameter-Varying and Time-Delay Systems: Analysis, Observation, Filtering & Control*, C. Briat, Ed. Berlin, Heidelberg: Springer, 2015, pp. 93–119.

[11] M. Sato and D. Peaucelle, "Gain-Scheduled Output-Feedback Controllers with Good Implementability and Robustness," in *Control of Linear Parameter Varying Systems with Applications*, J. Mohammadpour and C. W. Scherer, Eds. Boston, MA: Springer US, 2012, pp. 181–215.

[12] Y. Guan *et al.*, "Spinal Cord Stimulation-induced Analgesia: Electrical Stimulation of Dorsal Column and Dorsal Roots Attenuates Dorsal Horn Neuronal Excitability in Neuropathic Rats," *Anesthesiology*, vol. 113, no. 6, pp. 1392–1405, Dec. 2010.