

# Modeling of Activity-Induced Changes in Signal Propagation Speed of Mechano-Electrically Stimulated Nerve Fiber

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**Abstract.** One of the important questions in the research on neural coding is how the preceding axonal activity affects the signal propagation speed of the following one. We present an approach to solving this problem by introducing a multi-level spike count for activity quantification and fitting a family of linear regression models to the data. The best-achieved score is  $R^2=0.89$  and the comparison of different models indicates the importance of long and very short nerve fiber memory. Further studies are required to understand the complex axonal mechanisms responsible for the discovered phenomena.

**Keywords.** Microneurography, machine learning, spike count, neural coding, neuropathy

## 1. Introduction

Microneurography is an electrophysiological technique to study spontaneous and evoked activity in peripheral nerves of awake human subjects. This method helps to better understand human neural coding in axons of peripheral nerve fibers in general and, in particular, the differences between patients with peripheral neuropathies and healthy subjects [1]. Changes of the signal conduction speed caused by the preceding fiber activity are assessed via a standardized stimulation protocol, which includes a baseline electrical stimulation with a constant frequency (typically 0.125-2 Hz) combined with additional electrical, mechanical or chemical stimulations [2, 3, 4]. A number of results has been reported on the dependencies between the stimulation protocol and the resulting speed changes [5]. Those results include only relatively short-term history of the fiber

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activity but engaging the full potential of the data is limited due to the technical challenges with the preprocessing part, which requires a lot of manual work of the experimental researchers.

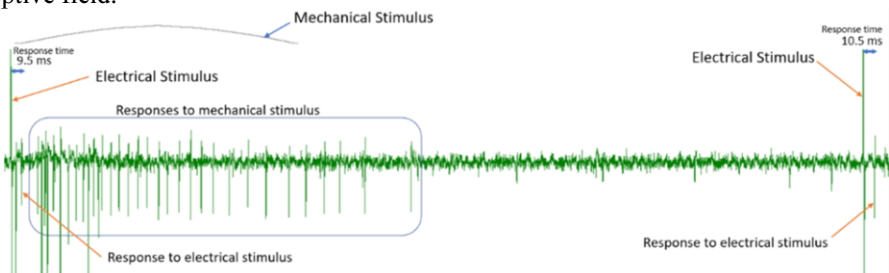
As part of the collaborative initiative on bringing new computational methods to support microneurography research and to make more efficient use of the large data collections, we are working on automatization of data preprocessing, but also on the more complex approach to model the dependencies between the history of activity of the axon and actual propagation speed changes. In this paper, we present the feasibility of our approach with data from an animal nerve fiber, obtained with a recording technique and stimulation protocols very similar to the ones used in human microneurography. The advantage of the chosen data is a better signal-to-noise ratio. It results in accurate assignment of actions potentials to their respective fibers and, in consequence, allows starting the modelling with minimal preprocessing.

To our best knowledge, this paper presents the first approach to building a machine-learning model of the effects of the history of neural activity on the signal propagation speed of peripheral nerve fibers. Due to the very high sampling rate of the data (c.a. 20,000 Hz) it is important to reduce the informational input dimension. Therefore, based on the state-of-the art research we hypothesized, that although the shape of the action potentials is important to identify the specific fiber producing the signal, the activity history of a single fiber is mostly influenced by the time stamps of the action potentials. As a result, the action potential is treated as a binary input with a timestamp, and the history of activity is represented by counts of action potentials in different time intervals, similarly to [6]. This approach allows to experiment with lightweight linear regression models [7] to get a better understanding of the underlying dependencies.

## 2. Methods

### 2.1. Data

**Tissue preparation and stimulation.** Skull of Wistar rat was divided in the sagittal plane, the brain was removed and the N. tentorius was freed of surrounding tissue. A glass electrode (ca. 20  $\mu\text{m}$ ) attached to the nerve was used for recording neuronal activity. A combined mechano-electrical stimulator was used to evoke action potentials in a receptive field.



**Figure 1:** Data interval between two baseline electrical stimulations. The delay between the stimulus and response is studied in the paper. Mechanical stimulus evokes additionally 28 spikes on the considered fiber.

**Experimental protocol.** Mechanical pulses (MP) (250 ms, 8-12 mN) were used to evoke an action potential burst every three minutes, paralleled by electric stimulation (ES) to control latency (5 MP + 0.1 Hz ES; 5 MP + 4 Hz ES; 1 MP + 0.5 Hz ES; 5 MP + 0.1 Hz ES and 10 minutes without any stimulation). Repeat the same protocol with 2 Hz ES instead of 4 Hz.

## 2.2. Data analysis

**Preprocessing.** The raw data was first analyzed in SPIKE2. Based on manually created templates, action potentials were detected and clustered into the groups corresponding to different neural fibers. One mechano-responsive [1] fiber was chosen for the further study. Figure 1 shows an exemplary data interval. The mechanical stimulation starts simultaneously with the baseline electrical stimulation. We can first observe the reaction to electrical stimulation, followed by a train of mechanically evoked potentials. The reaction to the next regular stimulus is visible as the rightmost spike. In Figure 2 we illustrated the reaction times (latencies) recorded as responses to the baseline electrical stimulation. At first, we observe relatively low (c.a. 9.25-9.50 ms) values corresponding to 0.1 Hz electrical stimulation, later the rapid growth of latencies is due to the change of the baseline protocol to 4 Hz. Regular rapid changes are the result of the mechanical stimulation, which causes 25 to 40 actions potentials on the fiber each time and this high activity causes rapid changes in propagation speed.

**Feature extraction.** The results from [1, 2] and the observations from the presented experiment suggest modelling latencies as responses to the fiber activity history. To quantify this history, we start by defining a time interval  $(t_1, t_2)$ , where  $t_2$  is the timestamp of the last electrical stimulus preceding the given response and  $t_1 = t_2 - n$ , where  $n$  is the considered history length in seconds. We call the number of action potentials within the interval  $(t_1, t_2)$  - “level 0” input. In order to improve the time precision, we can further subdivide the time interval into  $(t_1, (t_1+t_2)/2)$  and  $((t_1+t_2)/2, t_2)$ , call the spike counts in those two intervals “level 1” input and continue to divide the intervals until the desired precision is achieved. The higher precision in time comes at the cost of an exponentially increasing input dimension.

**Train-test data division.** The data is nonstationary [8], but since this property is directly related to the stimulation no further processing was done. Instead, the division into train and test sets was based on the intervals which are approximately stationary, as shown in Figure 2.

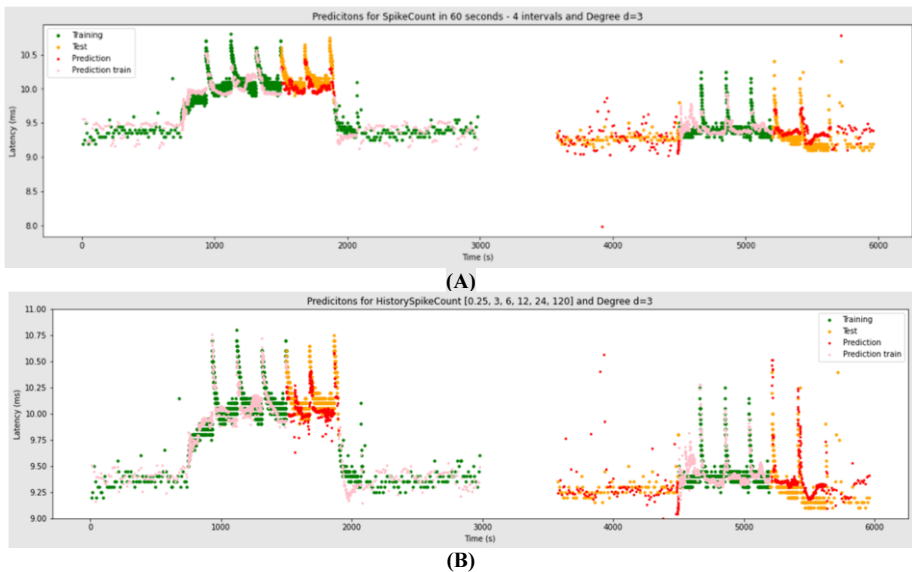
**Models.** We performed the exhaustive search through the following parameters: linear regression [7] up to cubic function; history length  $n = \{4, 12, 60, 120\}$  seconds, levels of division 0, 1, 2 (so up to 4 subintervals).  $R^2$  score was used to report the model fit.

## 3. Results

The model fit of a cubic polynomial, with a 60 second long history divided into 4 sub-intervals (input feature size 4), achieved a quite high  $R^2$  score of 0.89. However, we can see from Figure 2 (A) that the rapid changes caused by mechanical stimulation are not captured by this model. The reason for that issue is that the finest time scale is 15 seconds, which creates an almost identical history for the latency right after the mechanical

stimulation and the direct followers, particularly in the high frequency electrical stimulation range.

Therefore, we decided to change the input, so that both very short and long history could be incorporated. The experimentation with the models was based on the visually assessed ability to model the rapid changes and the  $R^2$  score. A very good result was achieved for the input based on the independent count of spikes in the preceding 0.25, 3, 6, 12, 24, 120 seconds and, again, the cubic polynomial. The  $R^2$  score for this model is 0.84 and therefore lower than for the previous model, but on Figure 2 (B) it is visible, that the rapid large changes are predicted much better.



**Figure 2:** Reaction times (latencies) corresponding to baseline electrical stimulation: experimental data (green for the train subset, yellow for test) and prediction (correspondingly pink and red). Large-scale changes are caused by varying frequency of electrical stimulations. Rapid local spikes (1/180 Hz) result from mechanical stimulation. **A:** Third order polynomial model on 60 sec history performs well overall ( $R^2=0.89$ ), but the rapid changes associated with mechanical stimulation are not fully captured. **B:** Despite the worse score ( $R^2=0.84$ ), the model accounting for short (0.25 s), medium (3, 6, 12, 24 s) and long (120 s) history handles rapid mechanically induced changes better.

#### 4. Discussion and Conclusions

The main purpose of the presented work was to test the combination of spike counting and predictive machine learning in modelling evoked speed changes of peripheral nerve fibers. The chosen approach showed promising results and additionally gave an important feedback for the further modelling process. The initial model chosen has a uniform timescale: the subintervals for spike count are homogeneously distributed over time. This results either in an exponential growth of the feature vector or a low temporal resolution. In order to handle higher sensitivity to more recent history we proposed here an alternative feature vector, which incorporated both long- and short-term spike counts

to capture both the fast and slow activity fluctuations. In future work, we will incorporate the logarithmic interval division scale to provide better short-time resolution with better control of the feature vector size.

The  $R^2$  score, which is a standard goodness-of-fit measure for linear regression models, was proved to be insufficient for the studied data type, as it is measuring primarily the large-scale fit. In our study, it is important to capture both large drifts resulting from accumulated latencies and rapid changes from additional short stimulation. Figure 2 (B) shows, that the second model is more suitable than the better scored first model. Therefore, there is a need to introduce an improved goodness-of-fit measure, which will be able to capture multiscale latency fluctuations.

In the proposed models, the influence of a very long history (scale of minutes) became apparent. The latency accumulation over time and thus the alternated excitability of the nerve fiber is a well-known neuroscientific phenomenon [4], but the extent of influences in microneurography data requires a more detailed study.

This feedback will be addressed in future work by a) modifying the feature selection process, b) considering more suitable to the multiscale data goodness-of-fit score and c) experimenting with different temporal scales to gain a better understanding about the multiscale interaction between the ion channels.

On the whole, evoked neural speed propagation changes, as assessed by tracking the fiber responses to regularly distributed electrical stimuli, can be successfully modelled by combining the fiber activity history measurement (spike count) and machine learning methods. Further levels of complexity, such as using the recovery time [1] and artificial neural networks will be added in the next steps.

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