ABSTRACT

Verma, Parul Ph.D., Purdue University, May 2020. Towards Understanding Neuropathy from Cancer Chemotherapy and Pathophysiology of Pain Sensation: An Engineering Approach. Major Professor: Doraiswami Ramkrishna.

This thesis addresses chemotherapy-induced peripheral neuropathy (CIPN)- a form of pain sensation and a prevalent dose-limiting side-effect of several chemotherapy agents such as vincristine, paclitaxel, and oxaliplatin. These agents are used for treating various cancers such as leukemia, brain tumor, lung cancer. Peripheral neuropathy is a numbing, tingling, and burning sensation felt in the palms and feet, which occurs due to damage to neurons (nerve cells). Prolonged CIPN can impact the quality of life of cancer patients. Occasionally, severe CIPN can result in termination of chemotherapy treatment altogether. Currently, there are no established strategies for treating CIPN due to a lack of understanding of its mechanisms. Moreover, different patients react differently to the same treatment; a subgroup of patient population may never experience CIPN, while another may experience severe CIPN for the same dose. In addition, there are no established strategies for predicting CIPN either. This thesis addresses both prediction and mechanisms of CIPN.

The following paragraphs reflect the organization of this thesis. Each paragraph introduces a research problem, the approaches taken to investigate it, and states the key results.

First, a metabolomics-based approach was used to investigate CIPN prediction. Blood samples of pediatric leukemic cancer patients who underwent treatment with a chemotherapy agent - vincristine were provided. These blood samples were analyzed at different treatment time points using mass spectrometry to obtain the metabolite profiles. Machine learning was then employed to identify specific metabolites that

can predict overall susceptibility to peripheral neuropathy in those patients at specific treatment time points. Subsequently, selected metabolites were used to train machine learning models to predict neuropathy susceptibility. Finally, the models were deployed into an open-source interactive tool- *VIPNp*- that can be used by researchers to predict CIPN in new pediatric leukemic cancer patients.

Second, the focus was shifted to the pathophysiology of pain and the pain-sensing neuron; specifically: (i) investigating pain sensation mutations and the dynamics of the pain-sensing neuron, and (ii) exploring chemotherapy-induced peripheral neuropathy mechanisms.

While pain is a common experience, genetic mutations in individuals can alter their experience of pain, if any at all (certain mutations yield individuals insensitive to pain). Despite its ubiquity, we do not have a complete understanding of the onset and/or mechanisms of pain sensation. Pain sensation can be broadly classified into three types: (i) nociceptive, (ii) neuropathic, and (iii) inflammatory. Nociceptive pain arises due to a noxious external stimulus (e.g., upon touching a hot object). Neuropathic pain (which is felt as a side-effect of the aforementioned chemotherapy agents) is the numbing and tingling sensation due to nerve damage. Inflammatory pain occurs due to damage to internal tissues. Pain in any form can be characterized in terms of electrical signaling by the pain-sensing neuron. Signal transmission regarding pain occurs through generation of an electrical signal called the action potential- a peak in neuron membrane potential. Excessive firing of action potentials by a pain-sensing neuron indicates pain of a specific form and intensity. In order to investigate this electrical signaling, a mathematical modeling approach was employed. The neuron membrane was assumed to be an electrical circuit and the potential across the membrane was modeled in terms of the sodium and potassium ions flowing across it via voltage-gated sodium and potassium channels, respectively. Generation of a single action potential followed by a resting state corresponds to a normal state, whereas periodic firing of action potentials (an oscillatory state) corresponds to pain of some form and intensity *in vitro*. Therefore, an investigation into the switch from a resting

state to an oscillatory state was proposed. A bifurcation theory approach (generally useful in exploring changes in qualitative behavior of a model) was used to explore possible bifurcations to explain this switch. Firstly, genetic mutations that can shift the pain sensation threshold in the pain-sensing neuron were explored. The detected bifurcation points were found to be sensitive to specific sodium channels model parameters, implying sodium channels sensitivity towards the pain sensation threshold. This was corroborated by experimental evidence in existing literature. Secondly, a theoretical analysis was performed to explore all possible bifurcations that can explain the dynamics of this pain-sensing neuron model. The mathematical modeling simulations revealed a mixture of small amplitude and large amplitude membrane potential oscillations (mixed-mode oscillations) for specific parameter values. The onset and disappearance of the oscillations were investigated. Model simulations further demonstrated that the mixed-mode oscillations solutions belonged to Farey sequences. Furthermore, regions of bistability- where stable steady state and periodic solutions coexisted- were explored. Additionally, chaotic behavior was observed for specific model parameters.

Finally, this thesis investigated the role of voltage-gated ion channels in inducing CIPN using the same mathematical model. Repetitive firing of action potentials in the absence of any external stimulus was used as an indicator of peripheral neuropathy. Bifurcation analysis revealed that specific sodium and potassium conductances can induce repetitive firing without any external stimulus. The findings were supplemented by recording the firing rate of a sensory neuron culture. Next, a chemotherapy agent - paclitaxel, was introduced in the model to investigate its potential effects on the firing behavior. It was seen that a medium dose of paclitaxel increased repetitive firing. This was supported by the firing rate recordings of the sensory neuron culture.

In summary, this thesis presents a prediction strategy for CIPN. Moreover, it presents a bifurcation theory-based framework that can be used to investigate pain sensation, in particular, genetic mutations related to pain sensation and chemotherapy-induced peripheral neuropathy. This framework can be used to find potential voltage-

gated ion channels that can be targeted to control the pain sensation threshold in individuals, and can be extended to investigate various degeneracies in CIPN mechanisms to find therapeutic cures for it.