KATHOLIEKE UNIVERSITEIT LEUVEN
FACULTY of ENGINEERING

Industrial Internship: Biomedical Engineering

Final Report

A synchronized intestinal electrical stimulation system for treating diabetes

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October 04, 2020

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1. Introduction

The following report will discuss the 6-week internship (from 06/07 to 14/08) that I have conducted in collaboration with Transtimulation Research Inc that is based in Oklahoma, USA. I was initially going to travel to the USA to work on site at the company, however, the coronavirus pandemic has made it impossible to travel to the USA. The internship plan was adjusted to focus on a project that could be done remotely. My two supervisors for this project were Professor Chen and Chris Zhu.

The focus of the project was to develop an algorithm for the online detection of the peaks of the slow wave intestinal stimulation to deliver an intestinal electrical stimulation (IES) in real-time. IES has been proven to treat diabetes since it accelerates intestinal transit and reduced nutrition absorption. An IES that is delivered in synchronization with the intrinsic slow wave of the intestine is more potent in accelerating intestinal transit than IES delivered at random phase. Hence the need to build an online peak detection for detecting slow waves and delivering stimulation in real-time.

The first part of this report will provide a brief introduction on the company: the company's main product, its position in its sector and the different departments of the company. The second part will focus on the project that has been assigned to me and the materials and methods I have used for the development of the algorithm and a reporting on the achieved accuracy. The third and last part will conclude with a personal reflection on my experience working with the company.

2. Company overview

2.1. Organizational structure and collaborators

Transtimulation Research Inc is a research-based company founded by Dr Jiande Chen. The company's main research area is in the field of electrical simulation with a focus on gastro-intestinal systems for treatment of digestive disorders. The company was founded about 10 years ago and employs around 10 people. Although the number of people currently employed varies depending on the project and available funding. The company has a principle office in Oklahoma City, OK and another office in Houston, Texas. The company also performs contracted research at university laboratories and hospitals. Any research that is conducted in the hospital is the hospital's property and need to be bought as a patent before it could be used by the company.

The company itself works with two other branch companies located in Ningbo, China known as MedPace. MedPace consists of the main manufacturing company MedKinetic and the translational medical research centre Pace. Those three companies collaborate in the following manner:

- Transtimulation research Inc is responsible for initiating new projects and conducting the research needed to actualize the project into a developable product. The end stage is a prototype that is ready for development and testing.

- MedKinetic is responsible for the production of the proposed porotype, quality control, legal affairs, marketing and sales. Medical doctors are also hired to provide training to other medical professionals on the developed products.

- Pace Performs additional clinical research studies to validate the produced prototype and conduct the needed clinical trials that are needed for introducing the product to the market.

Medpace consists of around 40 to 50 employees that might further expand in the future as the product range of Transtimuation research Inc widens and more products are available for market release.

Besides the close collaboration with these branch companies, Transtimulation Research Inc. also performs research for or together with bigger companies, like they did with Medtronic in the past. Medtronic is also one of the main competitors of the company. Its neuromodulation business unit also contains gastro-intestinal stimulation systems. Other competitors like Laborie and Medical Measurement Systems (MMS) focus more on manometry systems.

2.2. Resources and Financing

Since the company is still conducting clinical trials and does not have yet a fully developed product on the market, it receives its main source of income from external grants and the sale of patents. The main buyer of patents is MedKinetic. On a few occasions, patents are sold to other partners if MedKinetic doesn't end up purchasing a certain patent. Grant applications are usually written by Dr.

Jieyun Yin most often in collaboration with Prof Chen. When the grant is approved and awarded, the company can start working on the target project and hire more people needed for the job.

The government grants come from the National Institutes of Health (NIH) that has a program to support Small Business Innovative Research (SBIR). The program is divided into three different phases. First, the feasibility of the new concept should be proved.

For this, a time span of six months and $ 150,000 is available. The second phase is intended to make the actual product. This phase takes about two years and a grant of $ 1,000,000 is awarded. The third and last phase of the grant focusses on the commercialization of the product.

As for MedKinetic, they do not rely on grants for their funding: the revenue is generated from the sales of the products that have already been deployed in the market.

2.3. Research

The company's focus of research is on neuromodulation concerning the gastro-intestinal (GI) track. A new research study is synthetized by first proposing a valid hypothesis. Then the required device for testing and trials are developed at Medkinetic or purchased from external companies to perform clinical trials on animals in the laboratory. The company is one of the biggest leading groups working on research in the field of neuromodulation for the GI tract and many of the publications in that domain are published from the company. One of the company's biggest competitive advantages is in the fact that is highly specialized in this field as opposed to carrying out research in the applications of neurostimulation in other areas than the GI tract. This plays out to the advantage of the company since the field of neuromodulation in GI tract is still relatively young compared to other application of neuromodulation (Spinal cord, deep brain, etc..) and there is still a fair amount of research that needs to be conducted before deploying a final solution in the market.

Neurostimulation of the Gastro-intestinal tract can be divided into three different sub-categories where the company conducts research in all those categories:

2.3.1 Stimulation at the level of the skin surface

Includes Electroacupuncture (EA) and transcutaneous electroacupuncture (TEA) which are largely inspired by traditional Chinese medicine where needles are inserted into specific acupuncture points for pain relief. EA uses needles to deliver an electrical stimulation whereas TEA uses a set of electrodes. The advantage of both of those methods is that they are minimally invasive since they only need to be applied at the surface skin level and it does not require any surgery as compared to the other stimulation techniques. It has been found that the use of those techniques can change the intestinal motility for treatment of reflux and constipation. One TEA solution named ST36 where a stimulation is applied just below the knee level has proven effecting in treating constipation related symptoms and rectal sensations. [1]

2.3.2 Stimulation at the level of the nerve

The two different nerves that are stimulated for treating GI tract related diseases are the vagal nerve and the sacral nerve. The company group is currently conducting research on the effects of vagal nerve stimulation. The vagal nerve is responsible for parasympathetic activity and is usually stimulated in the neck or below the heart. The aim of its stimulation it to activate the parasympathetic response of the nervous system in order to counteract diseases and symptoms that are related to sympathetic overactivity such as diabetes and inflammation.

2.3.3 Stimulation at the level of the organ

- *Electric stimulation of the gastric fundus or distal oesophageal sphincter:* The gastric fundus is located in the proximal area of the stomach *(Figure 1).* Stimulating this area can be used to treated gastroesophageal reflux diseases (GERD) since the stimulation induces a pressure that prevent the nutrients from traveling back through the oesophagus.

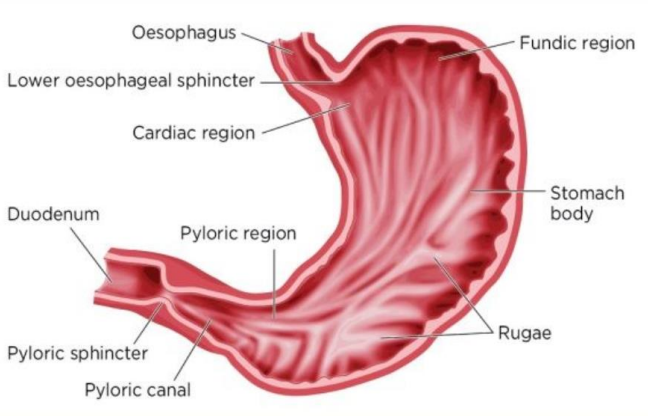

Figure 1: Anatomy of the stomach [2]

- *Gastric electric stimulation (GES):* This stimulation is applied directly to the stomach body and is used to alleviate nausea and vomiting in patient with gastroparesis. It can also be used to treat obesity.

- *Intestinal electrical stimulation (IES):* A stimulation that is applied directly in the intestines can help in normalizing intestinal dysrhythmias and delay stomach emptying to induce a feeling of "fullness" for obese patients. At the intestinal level, it can reduce food intake, reduce blood glucose levels due to its hypoglycaemic effect (this will be further discussed in section 3) so it is a potential treatment for type 2 diabetes. IES that is delivered in synchrony with the peak of the intrinsic intestinal myoelectrical activity (called slow wave) is termed Synchronized Intestinal Stimulation (SIES). SIES enhances the effects of IES where the stimulation is delivered at a random phase for a constant frequency since it enhances the contractility of the intestines and further accelerates the intestinal transit in comparison to IES

2.4. Product range

2.4.1 MEGG4 measuring device

This product was developed by MedKinetic has already been deployed on the market and is used for diagnostic purposes to measure the electrical activity of the of the stomach also known as electrogastrogram (EGG) which gives an indication on the activity of the muscles of the stomach and the internal pressure. Those two biomarkers can be used for diagnosis of different type of gastric diseases.

The device consists of 6 electrodes placed at different locations on the stomach where the EGG signal is collected and sampled at a rate of 10 Hz. 4 of those electrodes are used to measure the signal and the other two electrodes are ground and reference electrodes. The electrodes should be places at a fixed location for establishing a clinical reference *(*
Figure 2*)*.

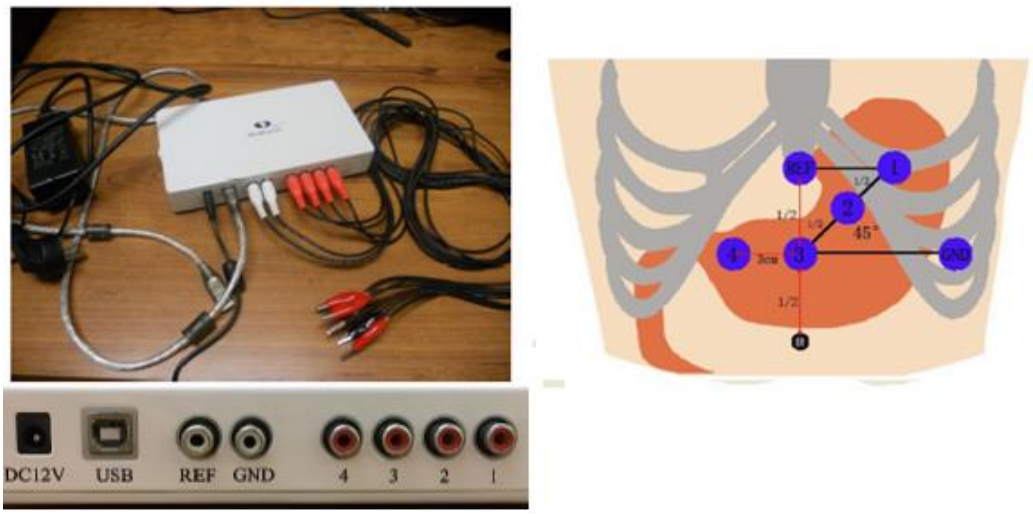

Figure 2: MEGG4 diagnostic device (left). Reference placement of electrodes on stomach (right).

The device is connected to a computer via USB and has a software with a user interface for physicians to use. Real time display of the signal measured from the 4 electrodes can be visualized. Additional features included in the software is the possibility to perform a spectral analysis to analyse different spectral features that can be used for diagnostic purposes.

2.4.2 GI motility device

A diagnostic device that measure the motility of the gut with the use of a manometer system. It can be used to assess the functions of the gut and sphincter and check for any potential abnormalities.

2.4.3 TEA neuromodulation device

A transcutaneous electrical acupuncture (TEA) device that is used to deliver electrical pulses to acupuncture points for treatment of different diseases *(Figure 3).* It is possible to control this device through a smartphone and to vary the amplitude and the length of the electrical pulses according to the medical professional's choices for a certain patient.

Figure 3: TEA Neuromodulator device

2.4.4 Other devices

Other types of devices include a PH sensor for the gut and a recorder for the electrocardiogram to assess the heart rate variability (HRV) of an ECG signal. A future device will include an implantable intestinal stimulator device that is assembled on an IPG chip for SIES applications which will include an electrode for detecting the slow wave of the intestines and a neurostimulator to stimulate the intestines when a peak is detected.

3. The project

3.1. Theoretical introduction

Obesity is defined as the accumulation of excess body fat deposition in relation to height and sex. The epidemic of obesity has seen a rise in numbers throughout the last decades owing to an increase economic growth, industrialization, the adoption of a sedentary lifestyle and the increased consumption of processed food. It affects around a third of the current world population. It is estimated that by 2030, 38% of the worldwide population will be overweight and another 20 % will be obese [3]. Obesity increases risk factors of a variety of chronic diseases such as cardiovascular, immunological and neurological problems and an increased risk of developing type 2 diabetes (T2D).

While there are many current existing medical solutions for treating and reducing diabetes such as drugs that inhibit food intake and diets. It has been shown that there is a tendency for people to regain weight after a certain time since the body can build tolerance to the drugs rendering them ineffective after a certain time [4]. In addition, it has been shown that those medications may cause potential harmful side effects such as kidney failure [5].

In some cases, bariatric surgery is used to treat obesity and diabetes. In one meta-analysis study consisting of 3188 patient who underwent Bariatric surgery, it has been shown that obesity was resolved 78% of patients and resolved or improved in 87% [6]. There are various physiological and endocranial mechanisms that explain why Bariatic surgery is effective in treating diabetes and obesity [7]:

- The small gastric pouch that is created and related directly to the intestines reduces the meal size required to induce a feeling of satiety.

- Bypassing the small proximal intestines reduces the absorption of nutrients.

- By excluding the distal part of the stomach, Ghrelin also termed the hunger hormone (a negative regulator of insulin release) is inhibited.

- Bypassing the proximal small intestines allows a rapid delivery of nutrients to the smaller lower intestines which increases the release of GLP-1 hormone. GLP-1 increases glucose stimulated release of insulin

While the surgery is effective in most cases, its drawbacks is that the surgery is irreversible, invasive, expensive and may lead to infection or bleeding in the patient requiring a secondary surgical intervention [8].

IES has been suggested as an alternate method of treating gastric problems which aim is to address the potential drawbacks associated with bariatric surgery since it is:

- *Adjustable:* The strength and duration of the IES can be adjusted to be patient specific and prevent potential adaptation as a result of long-term use.

- *Less invasive than bariatric surgery:* A surgical intervention is still needed for electrode placement and chip implant, but this can be done with a laparoscopy surgery that lasts approximately 30 min.

- *Reversible:* Can be easily removed if deemed inefficient for a certain patient.

- *Safe:* Electrical stimulation for the stomach has been performed in many patients with minimal surgical complication during or after the surgery.

-*Less costly:* The procedural and hospitalization costs of the IES therapy will be substantially lower than the bariatric procedures for diabetes. That is because the laparoscopic surgery for the administration of the stimulator and the electrodes is much shorter and there is only an overnight stay at the hospital unlike bariatric surgery which requires more time for care and hospitalization.

Preliminary studies of IES have demonstrated the hypoglycaemic effects associated with that method making it a suitable candidate for an alternative technique of treating diabetes and obesity [9].

In IES, only the function of the GI tract is altered unlike bariatric surgery which changes the anatomy of the GI tract. IES can be thought of as an electrical bypass. The mechanism by which it acts as a potential solution for treatment of obesity has a lot of similarities to that of the bariatric surgery and it can be summarized as follows [10]:

- A reduction in food intake due to its inhibitory effect on gastric emptying (satiety effect).

- A reduction intestinal absorption due to its accelerative effect on intestinal transit since the electrical stimulation enhances the contractility of the intestinal smooth muscles.

- An increase in GLP-1 release since the intestinal transit is increased and more nutrients are arriving at the distal intestine where GLP-1 is secreted.

- A decrease in Ghrelin (the hunger hormone), due to delayed gastric emptying, causes more insulin to be secreted in the blood,

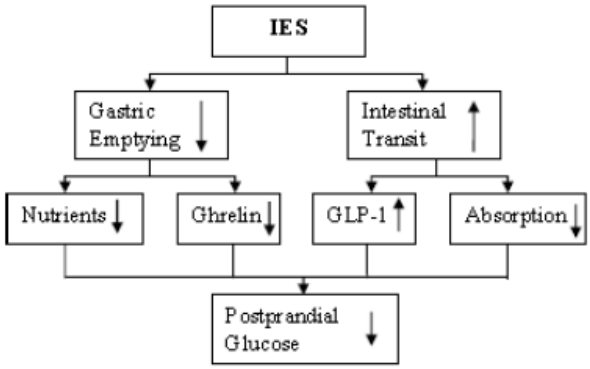

Figure 4: Summary of biological factors by which IES reduces postprandial blood glucose

IES has been initially proposed to treat intestinal dysmotility but then it was proposed to expand its application for treatment of diabetes after observing its potential as an alternative method to conventional surgery. Since IES is still novel there are many areas of its application that need to be investigated before releasing it as a solution in the market such as the optimal set of parameters for the stimulation (duration and type of pulse), automated detection of food intake for activation of IES only in the post-prandial state to avoid tissue fatigue and adaptation, and finally a synchronized (IES) termed SIES where a stimulation is delivered in synchrony with the intrinsic intestinal slow waves to accelerate the effect of IES and make the solution more potent against diabetes [11].

The myoelectrical activity of the intestines (also termed slow wave) is characterized by periodical signal that varies in frequency depending on the animal *(Figure 5)*. For rats, the slow waves have cycles per minute (cpm) that ranges between 35 and 49 cpm [12]. The normal range for humans is between 9 and 12 cpm [13].

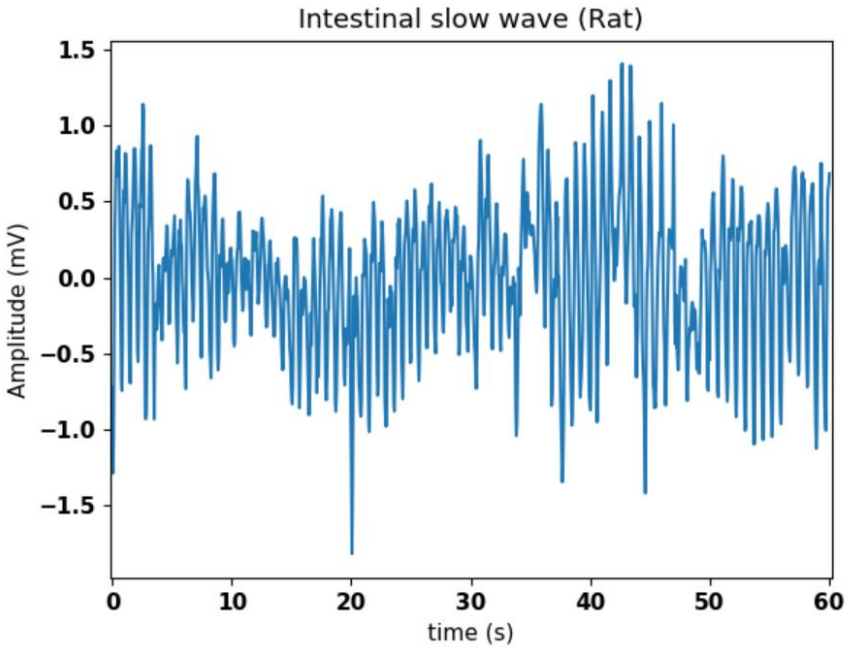

Figure 5: Intestinal slow wave signal (Rat)

3.2. Project goals

The main goal of this project is to develop a real-time system that can delivered synchronized IES to small animals in order to run clinical trials on the validity of SIES as a treatment method for diabetes.

The project is divided into two major sub-tasks that are needed to achieve the final goal of the project:

3.2.1 Optimization of the online peak detection algorithm

The current implemented algorithm for peak detection algorithm is the automated multi-scale peak detection algorithm (AMPD) which enables the detection of the peaks is noisy and quasi-periodic signals [14]. While it may be optimal for detecting the peak given the nature of the signal. It does not run in real-time and only works for static signals and its computationally expensive. Since the algorithm is going to be integrated on an implantable chip. It is required to find an alternative algorithm that is less computationally expensive and runs in real time in order to minimize power detection and provide an electrical stimulation that is synchronized with the slow peaks.

The aim of this subtask will be as following

- Get familiar with the current existing peak detection algorithm (AMPD) and look for an alternative or improve upon the existing one to make it real time and easy to implement

- Write the algorithm in C code to integrate it on the IPG chip. This requires memory management of the different parameters to avoid overloading the memory as well as minimizing the calculation steps for power conservation.

- Implement an adaptive algorithm where the threshold of detectability is adjusted depending on the inherent cpm changes

3.2.2 Integrate the algorithm in a real-time system

Experimental trials will be conducted on rodents for the current neurostimulator systems. Hence, a testing real-time must be implemented for testing on rodents. The whole external setup consists of a recorder with an implemented amplifier that will pick up the intestinal slow wave signal and amplify it. The signal will be sent to a computer which is connected to a stimulator that will deliver a stimulation in synchrony with the detected peaks.

The aim of this sub-task will be the following:

- Integrate the whole system together (detector, peak detection algorithm, stimulator).

- Develop a control algorithm for the system for delivering the stimulation in synchrony with the detected peaks.

- Test that the whole system functions properly on rodents and modify it/ improve it if necessary.

Since the internship was conducted remotely, the hardware necessary for completing the second part could not be obtained from the company and it was impossible for me to test my algorithm on the whole integrated system. However, after discussing with the company they mentioned that it would be possible to follow up on the results of the algorithm once they integrate the algorithm and start the experimental trials. Thus, they will give me feedback on the performance and inform me if any changes are needed. For those reasons, I shifted my focus on optimizing the first part of the project.

3.3. Previous work

In order to present a novel solution for the peak algorithm. I first consulted a few reports of students who have previously worked on projects related to mine in order to acquire more insight about the project and build upon their ideas.

3.3.1 Signal acquisition and pre-processing

In order to reduce the computation of peak detection algorithm, the available rat slow wave datasets were resampled from 200 Hz (acquisition frequency) to 10 Hz. An analogue bandpass filter with cut-off frequencies of 0.2 and 2.5 Hz is implemented in the acquisition device to remove high frequency noise and baseline drift. The natural range of frequencies for a rat with slow wave ranging in normal cpm range (35-49 cpm) corresponds to frequencies of 0.58-0.82 Hz whereas for the dog the cpm range is (18-22 cpm) which corresponds to frequencies of 0.15-0.2 Hz [15]. The wide margin was used in order to not exclude too slow or too fast peaks. It was investigated whether an additional filter needs to be implemented in the software but later it was deemed unnecessary since all the digital filters are associated with a certain delay which widens the gap between the time of peak detection and the delivery of stimulus. In addition, it was observed that the signals acquired by the acquisition device were smooth enough for peak estimation [16].

3.3.2 Peak detection algorithm

The algorithm that was chosen for peak detection is the AMPD. As mentioned previously, it work well in static signal since the scalogram method estimates a certain number of peaks before and after the peak while in real time we are restricted by a few datapoints for detecting signals after the current peaks where there might be a trade-off between accuracy and delay (this will be further discussed in section 3.5) . Additionally, there was a search-back algorithm that is used to determine whether few peaks were detected (according to the expected peak number defined by the cpm) within a certain time range and tries to find the additional missing peaks. This method won't work in real-time since detecting for missing peaks in a certain window will not provide any added benefit because it will already be too late to deliver a stimulus. The improved missed peak algorithm for real-time that I ended up implementing will be further discussed in section 3.4.2.

The offline accuracy was estimated for a limited range for 6 datasets each spanning 1 minute for a reported accuracy of 90 % of accuracy for a 10 Hz signal. The detected peak is considered accurate if it is detected within 0.2 ms from the ground truth peak [16]. Further details about the criteria that is used for the manual annotation of the ground peaks can be found in the appendix.

3.4. Materials and methods

3.4.1 AMPD

It was previously reported that the existing peak detection algorithm was written in Visual Basic and had AMPD integrated in it in addition with other search back methods. However, it has not been tested to work on an online signal [17]. In addition, the algorithm needs to be written in C in order to run on the IPG chip. For those reasons, I decided to start writing the algorithm from scratch in C. The first step of action was to investigate the AMPD algorithm that was previously used for peak detection in order to get acquainted with the algorithm and observe its limitations.

AMPD is a technique that works well on periodic and quasi-periodic signal. Its main advantage over other currently existing peak detection algorithms is that it does not require setting up many free parameters such as windows length or threshold value and it is robust against and low and high frequency noise [18]. AMPD achieves that by using a multiscale technique to detect all local maxima scalograms in a signal.

The steps that I used for implementing the peak detection algorithm can be summarized as follows:

1) Detrend the signal to remove the linear trend in the signal $x = [x_1, x_2, \dots, x_i, \dots, x_n]$ by subtracting the least square fit from the signal. While this step is crucial for the proper estimation of the different scalograms, I did not observe any significance in the result estimate for the given datasets of slow waves that were provided to me. It seems that there are no linear trends present when acquiring the signal.

2) Set a threshold for the maximal scale to be computed in accordance with the lowest expected frequency of the signal (minimum range of cpm of a certain animal in case of slow waves) to minimize the computational time.

$$k_{max} = f_s \frac{cpm_{min}}{60}$$

The local maxima will be calculated by using a moving window with different scales that vary in window length (w_k)

$$w_k = 2k \mid k = 1,2, \dots, k_{max}$$

3) Initialize the local maxima scalogram (LMS) matrix with zero values. The columns correspond to the total number of datapoints in the signal (N) and the rows span up to k_{max} where the k-th row contains the value for the window length w_k

$$\mathrm{M} = \begin{pmatrix} m_{1,1} & m_{1,2} & \cdots & m_{1,N} \\ m_{2,1} & m_{2,2} & \cdots & m_{2,N} \\ \vdots & \vdots & \ddots & \vdots \\ m_{k_{max},1} & m_{k_{max},2} & \cdots & m_{k_{max},N} \end{pmatrix}$$

The LMS matrix is filled according to the different local maxima scales as follows:

$$m_{k,i} = \begin{cases} 1 & x_{i-1} > x_{i-k-1} \wedge x_{i-1} > x_{i+k-1} \\ 0 & \text{otherwise} \end{cases} \quad \text{for } i = k+2, \ldots, N-k+1$$

Figure 6 provides a visual representation of the process used to fill the LMS matrix. In the figure it is assumed that $k_{max} = N/2$ which is the maximum scale that can be reached for a certain dataset. In reality, k_{max} is set up to a threshold as previously mentioned.

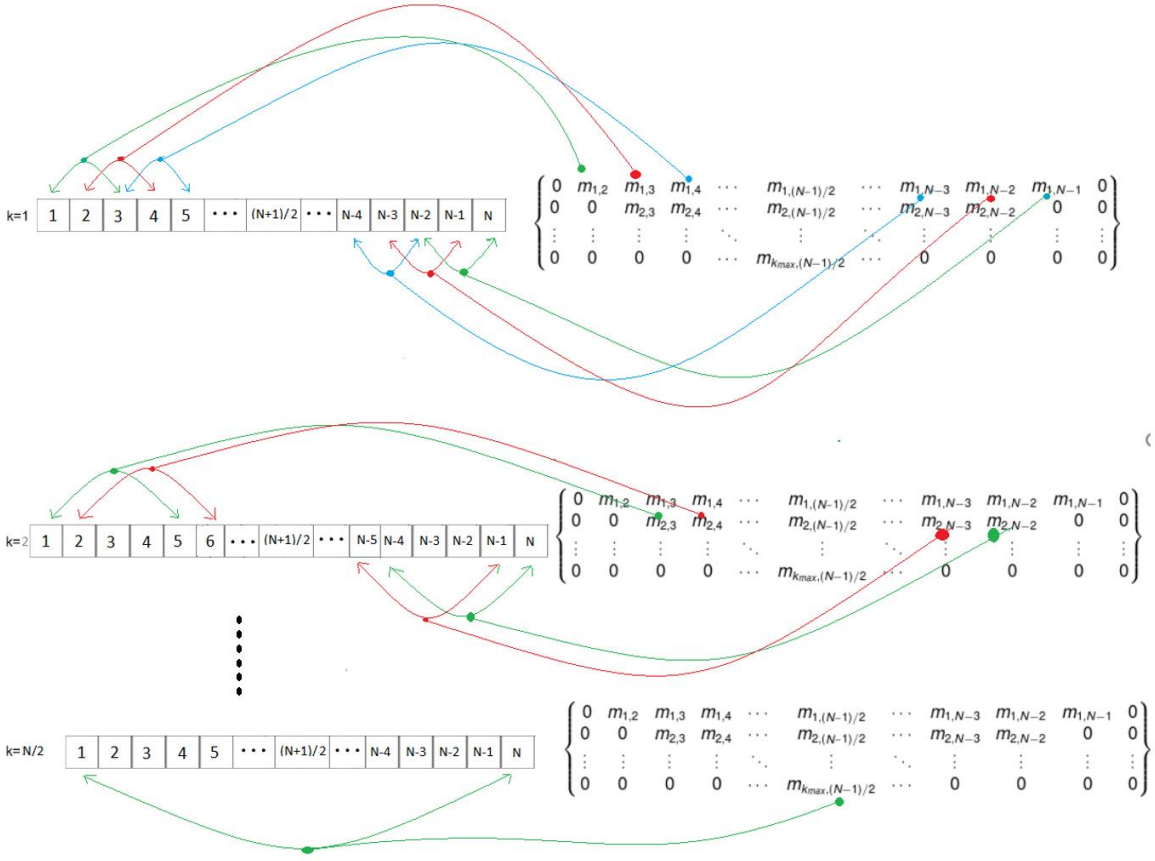

Figure 6: Illustration of the estimation of the LMS matrix for different scales

4) Perform a column wise summation of the LMS matrix to find the scale with the most local maxima

$$\gamma_k = \sum_{i=1}^{N} m_{k,i}, \text{ for } k \in 1, 2, \ldots k_{max}$$

The vector $\gamma_k = [\gamma_1, \gamma_2, \dots, \gamma_{kmax}]$ contains the information about the scale-dependent distribution of the local maximum.

$$\lambda = \arg\max_k(\gamma_k)$$

The index of the global maximum (λ) of γ_k is the scale with the most local maximum.

5) The peaks correspond the datapoints in the LSM matrix where a local maximal scalogram was detected for all the different scalograms up λ.

$$j = \begin{cases} peak & argmin(m_{k,i}) = 1 \quad for \quad k = 1,2,..,\lambda \\ No\ peak & argmin(m_{k,i}) = 0 \quad for \quad k = 1,2,..,\lambda \end{cases}$$

Where $j = 1,2,..,N$

Figure 7 shows the output of AMPD when used on the intestinal slow wave signal of a rat (offline mode). The algorithm performs well as expected since the signals are quasi-periodic. The peaks that are estimated always correspond to the highest peak in the cycle in case the cycle is characterized by a double peak.

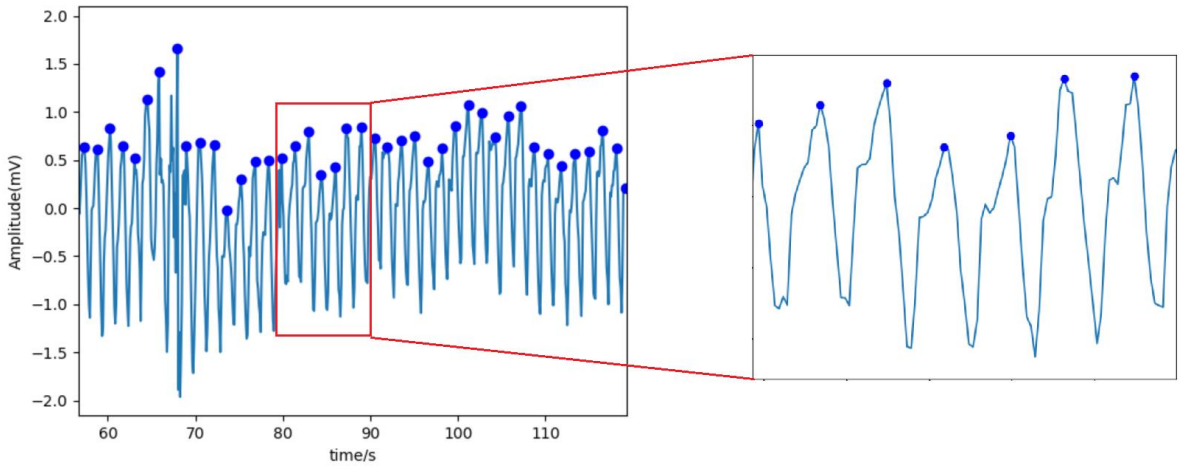

Figure 7: Peaks detected using AMPD for intestinal slow wave signal of rat

The maximal scale detected by AMPD provides the optimal scale used to perform left and right-hand side comparison to for peak detection. AMPD cannot be used to detect the signal in online mode since the right hand-side comparison will introduce a substantial delay between the time of peak detection and the stimulation delivery. However, the maximal scale can still be used to perform left-hand side comparison (early datapoints comparison) with no delay. This part will be incorporated in the online peak detection as further explained in S*ection 3.4.2*.

The maximal scale can be derived in offline mode and then used in online estimation since it was found that is constant for a certain animal regardless of the eating phase (fasting, feeding, post-prandial). For example, the maximal scale in a rat was found to be 700 ms which means that a

datapoint is considered a peak if its bigger than all the datapoints at a distance of ± 700 ms from the datapoint being evaluated as illustrated in *Figure 8.* As for dog data, it was found to be 1500 ms.

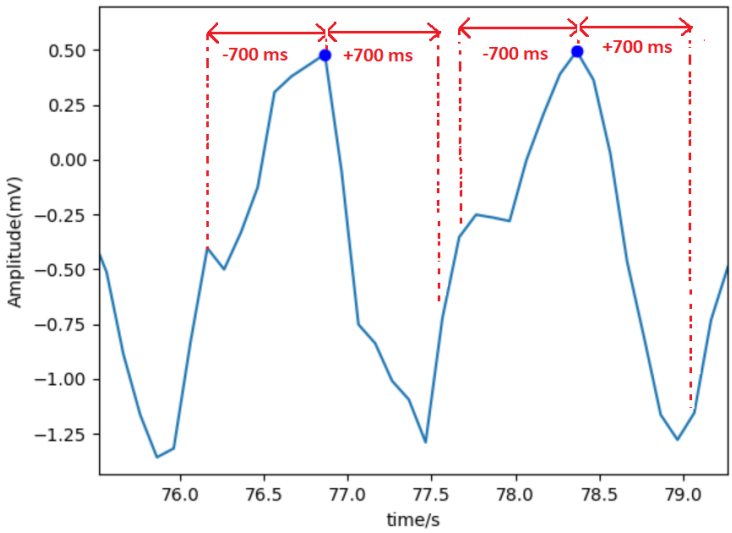

Figure 8: Illustration of the peak estimation method for the maximal scale derived from the rat intestinal slow wave

3.4.2 Online algorithm

After testing AMPD for peak detection algorithm. The next step is to develop an algorithm for detecting the peak in real time. Since I did not have access to the necessary hardware for acquisition of slow wave. I simulated the real-life scenario by artificially feeding the algorithm one datapoint at a time.

The algorithm needs to be accurate, have low computational load and provide minimal delay between the onset of the peak and the time of detection. Two different versions were developed for this application and both will be tested throughout the experimental trials. The non-adaptive version assumes that the there is no fluctuation in the cpm range for a certain animal thus the signal is perfectly periodic. The adaptive version is slightly different and will assume that the cpm fluctuates slightly overtime. The two versions have the same method for estimating whether a certain datapoint is a peak or not but differ in the way the define whether a peak was detected too early or too late as further explained below.

3.4.2.1 Non-adaptive

Figure 9 Illustrates the block diagram of the non-adaptive peak detection algorithm. Since we are assuming that there isn't any significant fluctuation of cpm over time, the average cpm value is constant and it is calculated as the average of the lowest and highest possible cpm that can be detected for a certain animal: 42 cpm for rat and 20 cpm for dog. The average cpm is used to estimate the detection range of which to search for a peak. The detection range prevents the early detection of a peak (with reference to the last detected peak): when a peak is detected, the next

peak that is to be detected is in distance range between 75% and 125% of the average cpm from the last peak. If a peak is detected within the detection range, then the detection range is re-initialized with reference to the newly detected peak. On the other hand, if no peak is detected within the detection range then the detection range is re-initialized to start from the last point of the previous detection range where no peak was found (missed peak range). In addition, the detection range is relaxed to detect nearby peaks (starts from the last point of the previous detection up to 75% of the average cpm).

For estimating whether a certain datapoint within the detection range is a peak or not. The datapoint must be larger than all the previous datapoint up to the range defined by the optimal maximal scale (MS) derived from AMPD (previously denoted as λ). In addition, it must be larger than all the subsequent datapoint up to a range defined by the positive lag (PL) parameters:

$$x_i \begin{cases} peak & x_{i-m} < x_i \quad \& \quad x_i > x_{i+p} \quad where: \quad \forall m \in \{1,..,MS\}, \forall p \in \{1,..,PL\} \\ No\,peak & otherwise \end{cases}$$

Unlike the MS which is derived from AMPD, there is no explicit method to derive the optimal PL. Increasing the PL will increase the number of datapoints will increase the overall accuracy of the peak estimation method at a cost of increase lag between the onset of the peak and the actual time when the peak was detected making the pulse delivery less synchronous than required. Hence, there is a trade-off between accuracy and lag that will be further discussed in *section 3.6.*

The datapoints are all stored in a buffer with a size equivalent to the upper range of the detection window (1.25 *average cpm). The buffer is essential for memory conservations and to avoid overflow.

All the operations in the algorithm are restricted to 1 dimensional array which are less power consuming than operations on a 2-dimensional array such as filling up the LSM matrix in AMPD. In addition, the detection range time window also plays a role in reducing power consumption by restricting the peak estimations operations to a certain range of datapoints.

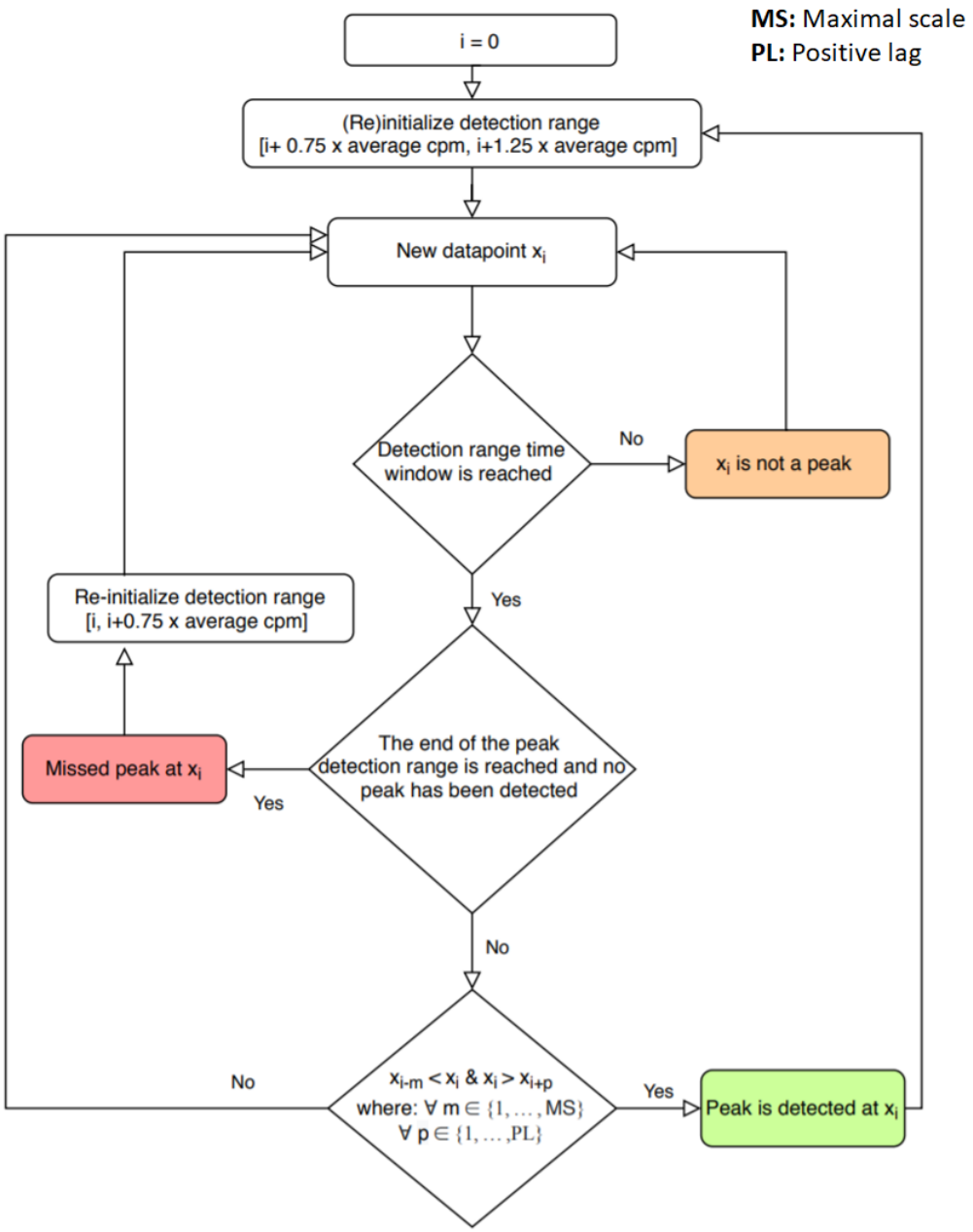

Figure 9: Block diagram of the non-adaptive peak detection algorithm

3.4.2.2 Adaptive

The aim of the adaptive algorithm is to consider the fluctuation in frequency (cpm) of the intestinal slow wave for peak detection estimation. Unlike the non-adaptive where the average cpm is the only parameter that defines the detection range, the adaptive version combines both aspects of a constant cpm (as defined by the average cpm) and an adaptive average cpm (as defined by the moving average cpm window) in order to deliver a stimulation at a relatively constant rate which varies slightly according to the changes in cpm of the intestinal slow waves.

The moving average window stores the values of the instant cpm (estimated from the distance between the last two peak) of each of the previously detected peaks. Each time a peak is detected, the instant cpm is stored as the last element of the moving average window and the “average

adaptive cpm" is estimated. This average is used to re-initialize a new time detection range to detect the next peak.

When a peak is detected in a certain within the detection window, the instant cpm is estimated and compared to the upper and lower limit of the possible cpm range of a certain animal to ensure that the cpm is within the acceptable range. The estimated peak is categorized into three different categories:

1) *Early peak:* when the instant cpm is larger than the upper limit of the cpm for an animal (ex: estimated instant cpm for a rat is 56 cpm is larger than 49 cpm which is the upper limit of the cpm of an animal). Then the estimated peak is classified into an early peak. In that case, the stimulation is not delivered at the instance of peak detection but at a distance of "average adaptive cpm" from the last peak.

2) *Late peak:* This is triggered when the end of the detection window as defined by the "average adaptive cpm" is reached. Then the estimated peak is classified into a late peak and the stimulation is delivered at that point.

3) *Acceptable peak*: when the peak has an instant cpm within the detection window of the "average adaptive cpm". The stimulation is sent at that peak.

There is an additional safety mechanism that prevents the "average adaptive cpm" to fall to low or too high in order to keep the distance between the electrical stimulations within the acceptable range of the natural cpm of the animal. The block diagram of the adaptive algorithm is illustrated in *Figure 10.* There are two variable parameters that need to be tested and optimized for the adaptive algorithm (in addition to the PL as described in the non-adaptive version):

1) *Standard deviation (std):* defines the upper and lower limit of the cpm range to which the instant cpm range will be compared to. Too large of a standard deviation allows the range to be more relaxed and more peaks will be classified as "acceptable peak". Whereas a small standard deviation restricts the range and more peaks will be classified as "Early" or "late". The default value is 0.1 (10%).

2) *Moving average (MA) window size:* Too large of a moving average window stores more cpm values from previous peaks making the "average adaptive cpm" more consistent (stimulation at stable cpm). Whereas a small window only considers the latest cpm values. The default size is 3.

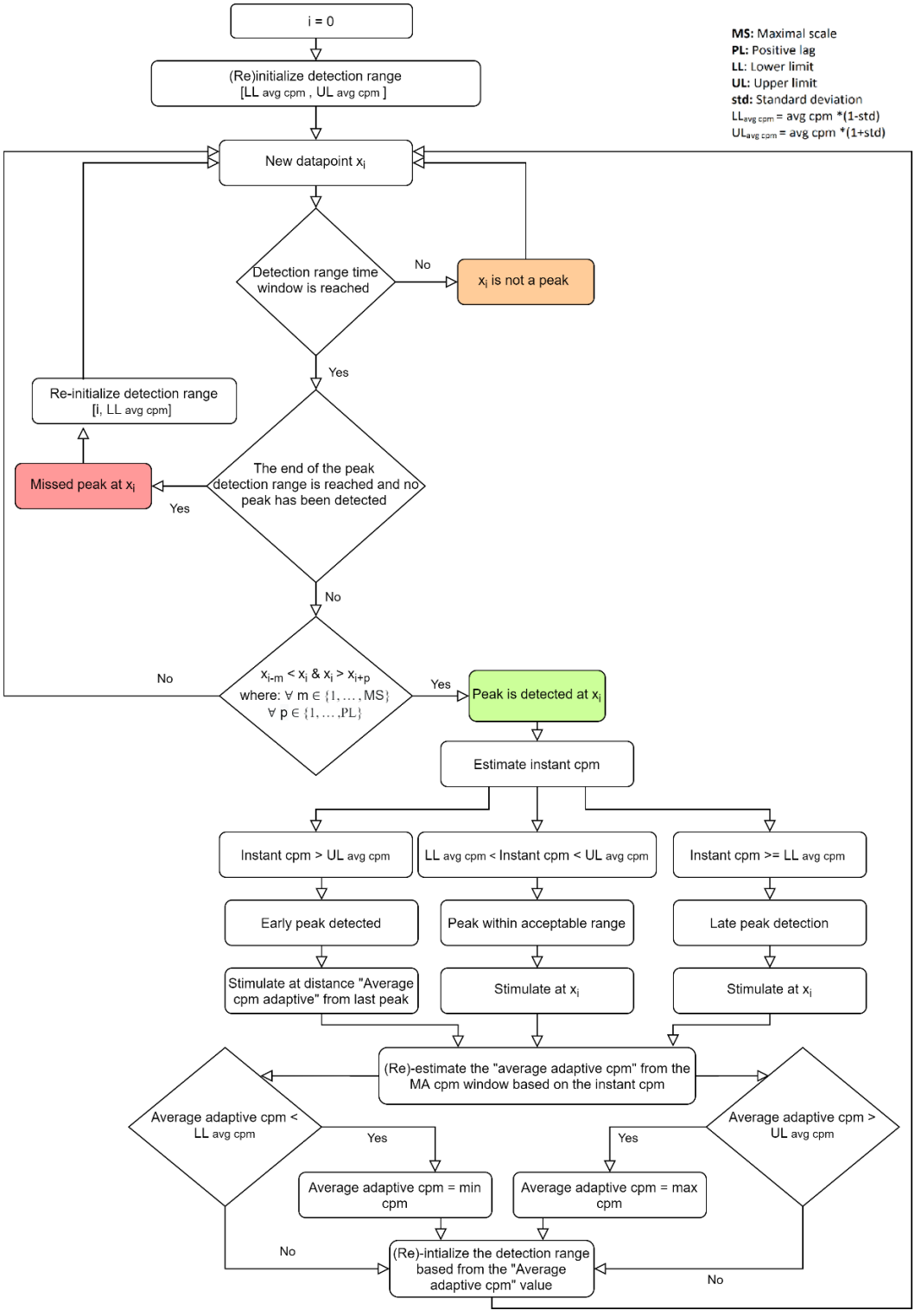

Figure 10: Block diagram of the adaptive peak detection algorithm

3.4.3 Accuracy estimation

The accuracy of the peak detection method will be estimated as the number of detected peaks that are at ≤ 10% of the average cpm distance from the ground truth peaks. For the rat, this corresponds to a maximum distance of 150 msec from the ground truth (average distance between two peaks is

1500 msec). The peaks that were derived from AMPD were used as the ground truth to estimate the accuracy. In addition, the number of missed peaks will be assessed where the missed peaks are the percentage of total number of detected peaks to the total number of ground truth peaks. White noise was added to the signal to quantify the efficiency of the online peak detection estimation at different SNR levels.

The slow wave was recorded using an EOG amplifier (EOG100C by BIOPAC® Systems,Inc) that interfaces with the MP150 data acquisition and analysis platform and AcqKnowledge software (version 3.9). The amplifier filters the signal with a bandpass filter (0.02 -35 Hz). The filters have a high degree of phase linearity to keep the distortion level as minimal as possible. The available dataset were 10 recordings for rat and 8 recording for dogs with varying recording lengths (30-60 min). The data was decimated to 20 Hz (low pass filter before down-sampling in order to avoid aliasing).

The accuracy estimation of the peak detection estimation was only tested on the non-adaptive algorithm. The non-adaptive algorithm requires testing on a real-life scenario since its aim is to keep the cpm in bounded limits whereas the dataset is static and of varying frequency. To test the non-adaptive algorithm, an actual clinical setup needs to be setup and the behaviour of the signal upon stimulations needs to be observed. This will be tested later when the company will start the experimental trials.

3.5. Results and discussion

Figure 11 illustrates the accuracy of the peak detection method for different noise levels and different delays as defined by the PL parameter for rat slow wave (average accuracy for all dataset). A PL of 3 for a 20 Hz signal corresponds to 150 msec of delay (10% of the average cpm). As expected, the accuracy increases with an increase of delay for the clean signal and the signals with the different noise levels. For signals with SNR at 25 and 30 dB there seems to be a decrease of accuracy as the delay is increase from 100 msec to 150 msec (PL=2 to PL=3) possibly due to noise contamination that makes some datapoints after the peak appear to have a higher amplitude than the peak itself which in turn fails to classify the actual peak.

This effect is more prominent in *Figure 12* for the dog dataset as the delay increases from 150 msec to 300 msec (PL=3 to PL=6) since there are more datapoints to be compared with and the probability that the noise will contaminate the peak detection will be higher.

The accuracy of the peak detection is higher for the dog slow waves than the rats since the cpm of a for two reasons:

1) The cpm of the dog is about half of that of the rat: 20 cpm (≈3 seconds) compared to 42 cpm (≈1.5 seconds). This enables us to compare more datapoints after the peak when estimating whether a datapoint is a peak or a not for a dog compared to a rat before reaching 10% of cpm (6 datapoints vs 3 datapoints for a 20 Hz signal) as illustrated in *Figure 13.*

2) The slow wave of the dog is rarely characterized by two neighbouring peaks and is less noisy compared to slow waves of rats (*Figure 13)* making it easier to estimate peaks in real time.

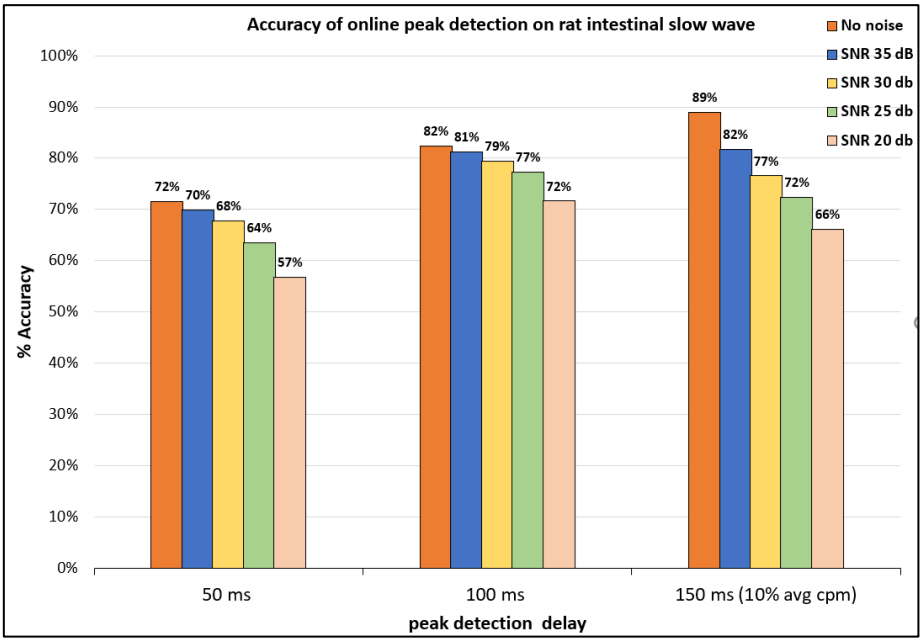

Figure 11: Accuracy estimation of the online peak detection algorithm on intestinal slow wave of rats for different delays and SNR levels

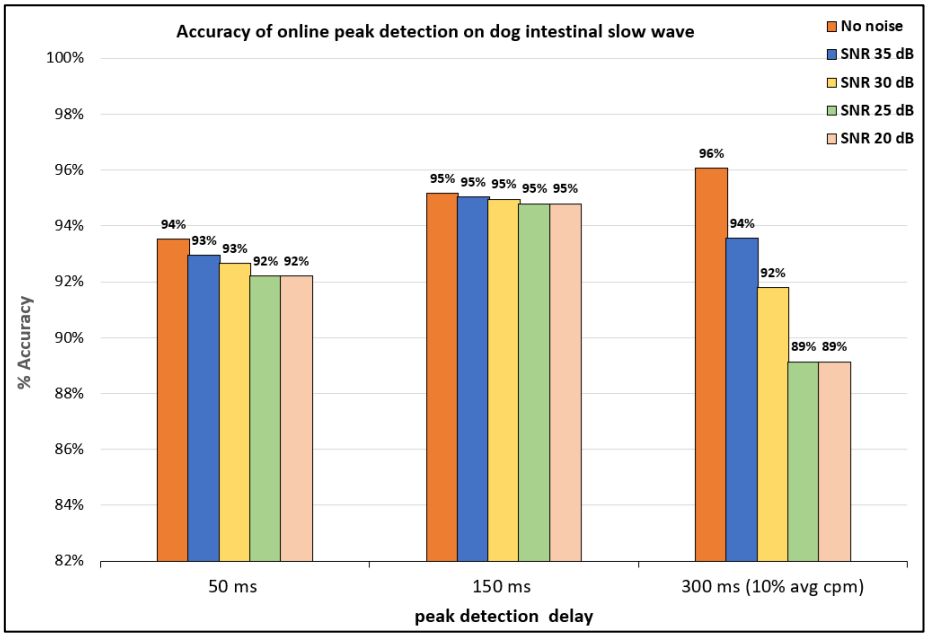

Figure 12: Accuracy estimation of the online peak detection algorithm on intestinal slow wave of dogs for different delays and SNR levels

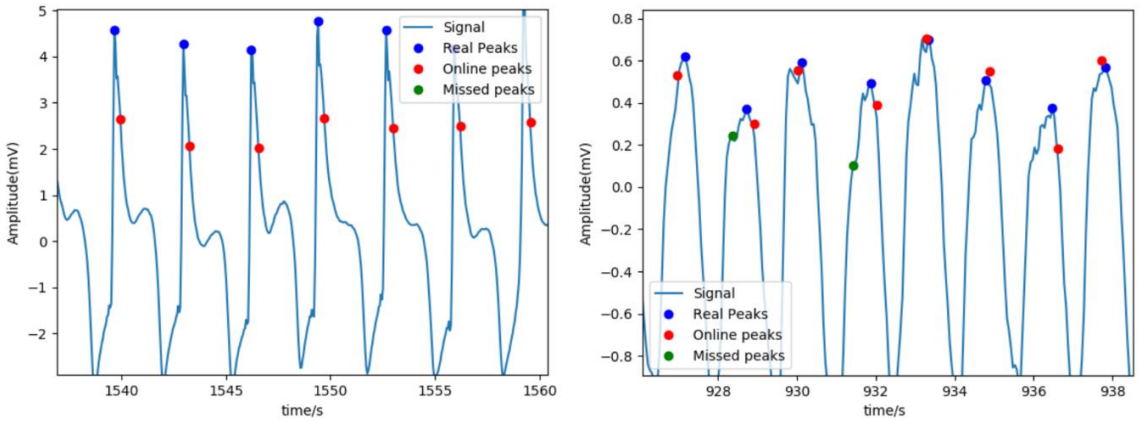

Figure 13: online peak detection result on intestinal slow wave of dog (left) and rat (right)

For real life scenario during clinical trials on rats, the optimal parameters to be set for a 20 Hz acquisition is a PL of 3 (150 msec) and a MS of 14 (700 ms) to achieve an accuracy of 89 %. As for the dog slow waves, the PL can be set to 1 (50 msec) since there is minimal improvement as the PL increases (+1% when the delay is increased from 50 msec to 150 msec for a clean signal). A similar delay could be expected for humans since the cpm range is even lower than the dog slow wave (9-12 cpm) making the peaks "easier" to detect with a minimal delay. However, this still requires further validations (no human recordings are available yet). The overall "missed peaks" for both cases does not exceed 2%.

Although the accuracy is higher for dog's slow wave peak estimation is higher than that of the rats, it requires almost double the amount of datapoints (as defined by the MS) it more power consuming. The choice of 20 Hz respects the Nyquist criterion and provides a good balance between obtaining an acceptable number of samples to run the algorithm with good accuracy and limiting power consumption. The code in C stores all the data in a buffer with a size of (PL+MS+1) that is updated on each iteration of a new datapoint: the limited size of the buffer plays a part in memory conservation to avoid overloading the memory on the IPG chip.

The overall delay should consider both hardware and software limitations (online peak detection algorithm). The former is the delay between the moment of peak detection and the stimulation delivery, and it should be accounted for when estimating the overall delay.

3.6. Conclusion

This project involved an experimental validation of an online peak detection algorithm for the detection of peaks in intestinal slow waves. The newly implemented algorithm is defined by an explicit parameter (maximum scale derived by AMPD) and an experimental parameter (positive lag). The integrated code fulfils the required criteria of power and memory conservations and can be made integrated on an IPG chip. The achieved accuracy is relatively high (89 % and 96% for rats and dogs respectively) and is adequate for the desired application. The adaptive version still needs to be tested in an actual clinical scenario and the accuracy results need to be reported.

Certain limitation should be acknowledged for this project, the ground truth peaks were derived from applying AMPD offline on the new signal. While the peak's locations seem to be acceptable by mere visual inspection *(Figure 7),* it might not reflect the actual criteria for the actual peak estimation (see Appendix). Previous interns were able to manually annotate the peaks based on those criteria since they were dealing with small recordings (2-3 min). For my project, I wanted to validate on datasets with long recordings to obtain a generalizable accuracy estimate. Manually annotating the peaks for those recordings would have been a tedious task.

As mentioned previously, it was impossible to integrate the whole system together since the hardware was unavailable for me to experiment on. However, the team informed me that they will keep me informed about the latest updates for the experimental trials in order to follow through on the conclusion of the study.

4. Reflections

The 6-week internship that I conducted with Transtimulation Research Inc was a very pleasant and instructive experience. I managed to expand my knowledge in the field of neurostimulators, signal processing, programming and communication skills. I also got additional exposure on medical industries in R&D and the stages required for a product development. Because of the coronavirus pandemic, I had to conduct the internship from home and did not get the chance to travel to the USA and work on-site at the company. This hindered the execution of the last part of the project which would have been an additional valuable learning opportunity. Although working from abroad has its challenges, it has taught me to be more independent and pro-active in my work and to communicate my questions and report on my results more effectively since I did not always have the chance to communicate with the company on a daily basis.

I spent most of the project programming in C since the code will be implemented on an IPG chip. Learning C was quite challenging in the beginning due to its low-level nature and additional consideration that need to be considered such as memory conservation and proper variable initialization. This was quite departure for me since I was used to high level languages (Python, Matlab). For this reason, I was initially building my test code in Python and then translating in into C since Python code is easier to write and the data can be visualized easily. Visualizing the data was quite necessary for me to come up with a scheme for the block diagram of the online peak detection algorithm. I lost a bit coding the AMPD code in C since it will not be used for the online detection. It would have been enough to just have it in python in order to derive the MS. Looking back I should have thought of the general scheme of the algorithm that I wanted to develop before writing separate parts of it that won't be needed.

Most of the meetings that we had were on Zoom meetings and we occasionally had quick communications on WeChat. The general attendees for the meeting was Dr Chen, Dr Pikov and Chris Zhu and sometimes other engineers from China joined in. Before organizing a meeting, I would generally report on my latest results and ask questions via email so that the team has time to investigate my work and consider answers to my questions prior to the meeting. Otherwise, it would

have taken to report and ask questions especially that most of the meeting are from 3 different time zones (Belgium, USA and China). Most of the feedback and tips that I received regarding the coding part was from Chris Zhu since he is the software engineer that will oversee the integration of the algorithm into the IPG chip.

Some previous courses that I followed throughout my Bachelor and Master of Biomedical Engineering proved to be useful. The course of “Human system physiology” helped me to understand the general concept behind SIES and its physiological and neurohormonal effects that contribute to treating diabetes and obesity. The course “Biomedical Data processing” also provided me with solid knowledge about working and interacting with data and the intuition needed to synthetize an algorithm to solve a certain problem. Although all the signals that were treated in this course were static and there were no computational constraints, it was interesting to see the additional requirements that need to be fulfilled when an algorithm has to run in real-time on an implantable chip. The “Design in Medical Technology” course also helped me quite a bit since I spent most of the course coding in Python to develop a clinical workflow which taught how work with large amounts of datasets and automate tasks more efficiently.

Overall, this internship was a great opportunity for me to acquire additional experience as a future biomedical engineer and gain exposure in the neurostimulation industry sector. I am grateful for everyone who made this internship possible given the coronavirus pandemic and I would recommend applying for an internship at Transtimulation research Inc for any future biomedical engineer interested in developing their technical and communication skill.

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6. Appendix

6.1. Criteria for peak annotation

- Two peaks can only be detected if they are at least separated by one second (maximal 60 cpm) and a peak is said to be missed if the distance between two peaks equals more than two seconds (minimal 30 cpm).

- The peak should be higher than the mean of the signal. To calculate the mean of the signals, extracts of one minute of the signal were used.

- The peak is the highest point in the interval [-0.25 0.25] seconds around it.

- There can be maximal one peak between two points that intersects with the line drawn at the height of the mean of the signal.

- When deciding about the correct location of the peak, the periodicity of the intestinal slow waves was considered. For example, if more possible peaks are visible, but only one can be selected because they are too close to each other, choose the peak that best keeps the periodicity of the previous peaks.

- If two peaks are separated from each other, but too close, choose the widest peak (previous rule has priority to this one).

- If two peaks are visibly belonging to the same slow wave:

    - If (lowest peak - mean) > 0.5 * (highest peak - mean):

        - Choose the peak that maintains the periodicity the best
        - If hard to decide which one maintains the periodicity the best, choose the largest peak.
        -If both peaks also have the same height, choose the first peak.

    -Otherwise, choose the largest peak.

6.2. Logbook

Sunday 05/07

- 20:00 – 21:00
  Introductory meeting to get acquainted with the topic. The AMPD code was provided to me in Visual Basic language along with data for 2 different recordings of slow wave intestines for animal models. It was reported that the algorithm can indeed detect peaks but there was a problem in detecting the last peak which is needed for delivering the stimuli from the electrode. An additional report was provided to me from a student (Emiel Vereycken) who was working on this project last year: *"Development of a synchronized intestinal electrical stimulation system".*

Monday 06/07

- 14:00 – 16:30
  - First day of industrial internship (working from open computer room in Mechanical Engineering department).

  - Literature review: Emiel's report to get more acquainted with the structure of Transtimulation and the previous works that was done along with the outline of the peak detection algorithm that includes AMPD and other models that are integrated in it (search back methods, finding last peak…)

  - Sent emails to Professor Chen and Chris to ask for the internship reports of students who previously worked on implementing AMPD for peak detection

  - Mention of Matlab coder app that can generate C code from Matlab functions, could be helpful when implementing the peak detection algorithm.

- 16:30 – 17:30
  - Search for different peak detection algorithms and their corresponding literature review. Algorithms that I found are: "AMPD" (as recommended previously by Professor Chen) and "Smoothed z-score algorithm). I will investigate both and try to list their advantages and disadvantages.

Tuesday 07/07

- 10:00 – 13:00
  - Literature review: reports of two different students (John Fredy Morales Tellez & Sofie Tilborghs) to get more acquainted with the previous work that was done concerning the previous implementation of the AMPD algorithm and the challenges of detecting the first and last peak.

- 14:00 – 17:30
  - Literature review: AMPD algorithm two papers :
    "An Efficient Algorithm for Automatic Peak Detection in Noisy Periodic and Quasi-Periodic Signals" and *"Peak Detection Implementation for Real-Time Signal Analysis Based on FPGA"*

Wednesday 08/07

- 10:00 – 13:00

  Continue literature review for AMPD algorithm

- 13:30 – 17:00

  Implementation of AMPD algorithm in python for a random generated signal. Investigation of the algorithm for the two given datasets (Dog & Rats). Algorithm works well for static signal. Further feedback needed on the quality of the detected peaks (in case of a hill with two peaks close to each other) + figure out a way to properly detect

for the last peak (possible solution would be to detect a peak only when the mean rate has been already detected and then apply the different scales for left hand side evaluation).

Thursday 09/07

- 10:00 – 11:00

  Reviewing previous reports for additional insight on peak detection

- 11:00 – 12:00

  Setting up environment for C (Codeblocks IDE and MinGW compiler)

- 13:00 – 17:00

  C tutorials: (basic syntax, functions, logical conditions, etc...)

Friday 10/07

- 10:00 – 12:00

  C tutorials: (arrays, pointers, dynamic memory management)

- 12:00 – 13:00

Setting up WeChat on phone and laptop. Revising of literature review from previous students for additional insight on peak detection algorithm and which peaks need to be chosen.

- 14:00 – 17:30

Started implementing AMPD algorithm. Figure out how to read the recordings (stored in .txt format) and store them in the memory (need dynamic memory since array is going to be changing constantly). Read more tutorials on pointers and dynamic memory allocation.

Monday 13/07

- 9:30 – 12:00

  Tried installing a package for plotting the data in C using <graphics.h> however it does not seem to be working after trying to install it using different tutorials. I am going to plot everything generated in C in python (matplotlib) for now and then try to reinstall if needed.

- 12:30 – 17:00

Implemented first steps in AMPD (detrending the data, setting maximum scale of scalogram according to the minimum cpm, initializing LSM matrix)

Tuesday 14/07

- 9:00 – 12:00

  Wrote algorithm to fill out the LSM matrix according with the different scale estimation. Setup the code into 2 different segments for right- and left-hand side comparison to account for the edges.

- 13:00 – 17:00

  Wrote segment to find maximal scale that accounts for the most detected peak. After testing it turned out that additional normalization steps are needed to make the algorithm function properly

- 17:00 – 18:00

  Zoom meeting with Professor Chen, Dr Pikov and the rest of the team from China and the USA to discuss matters related to the internship. I will receive additional data to test my algorithm from different animals. I got the chance to ask questions about doubts that I have.

  Additional recommendations were given to me about testing the accuracy algorithm on data with different sampling frequencies (by artificially down sampling the signal) to figure out what could be an acceptable sampling frequency (possible trade-off between high power consumption of the IPG chip and intestinal stimulation delay → figure out a threshold for an acceptable range. All the filters are implemented in the hardware of the IPG chip, no need to filter the signal in the code.

  Since I do not have access to the IPG chip, it was recommended to me to stimulate the "online recording" of the signal artificially by cutting the signal and feeding it to the algorithm one data point at a time.

Wednesday 15/07

- 9:00 – 12:00

  The debugger in Codeblocks was not breaking at the given flag points. After investigation it turns out to be a problem with compatibility between the compiler and the debugger. Problem fixed by installing a new executable debugger.

- 13:00 – 16:00

  Cleaning up the code and organizing some part of the codes into functions for memory management

Thursday 16/07

- 9:00 – 12:00

  Finalizing the code of AMPD (finding the optimal scale and extracting the relevant peaks)

- 13:00 – 17:00

Further code cleansing and optimization (printing info about the signal after running the algorithm). AMPD is now fully implementable in C, the next steps are to make it iterative.

I Sent an email to Chris to ask for possible plotting packages in C or source code. The current workaround is to extract the generated peaks in C and plotting them in python using matplotlib.

Problem with estimating signals with lots of data points in the C code (30 min recording of rats with 30,000 datapoints) → probably due to memory and array restrictions in C. Need to cut the signal into smaller segments which is still fine sice AMPD was shown to work properly on a 2-minute recording).

Friday 17/07

- 9:00 – 12:00

  Wrote a python script for splitting up the data into multiple text files for large recordings (30 min) → easier to analyse and visualize smaller recordings. Other recordings could be used as ground truth

- 13:00 – 17:00

  Wrote a script to extract the peaks indexes from the C code implementation of AMPD

  Wrote a script to visualize the extracted data from C implementation of AMPD to python

Monday 20/07

10:00 – 12:00

Wrote an email to the team with all the scripts that I have written so far (AMPD in C, splitting large recordings and the plotting in C) and briefed them about the current work I have done in the last two weeks). Additional check-up on the script revealed that there is still a bug that needs to be fixed

13:00 – 18:00

Fixing the current bug for the C implementation of AMPD: problem with initializing the LSM matrix when the recordings consists of large data points. It turned out that I initialized the array in the stack memory which has limited capacity for data storage → stack overflow. Solution: initialize the array in the heap dynamic memory using malloc function. Sent the updated version of the script to the team asking to check on it and provide potential feedback for improving/optimizing.

Now that AMPD is fully implantable on static signal → try to make it work on-line. I will implement the solution in python since it's easier for visualization and testing different solutions and then will translate the chosen solution to C. I simulated an online scenario in python by splitting a recording into two parts and adding one data point each second to the first part. Using matplotlib I managed to create plots that also keep updating → online visualization is now ready. Next steps is to try different methods for detecting the last peak

being generated (use peaks that were already detected previously through AMPD as ground truths).

Tuesday 21/07

National Belgian Holiday

Wednesday 22/07

9:00 – 12:00

Started implementation of a method to detect the last peak. My initial approach it to use AMPD to detect peaks for 60 s and then use a heuristic approach to detect the last peak. I will write the script in python since its easier to visually assess the algorithm and then translate it to C when ready. I wrote a python script that takes as input one segment of a script and then the graph is updated each second with new data points.

13:00 – 17:00

Wrote an algorithm that detects new peaks on last peaks (so far trying on a static signal with ground truth AMPD peaks). I reviewed again (z-score algorithm) and it does not work on the slow wave dataset due to many false positives. It seems like a heuristic approach is the only valid way to approach this problem (in combination with AMPD). I developed an initial approach that compares the current datapoints to previous datapoints (depending on the optimal scale defined by AMPD) and checks if the datapoint is bigger than the two next datapoints (ideally it would be one datapoints of delay, I still have to check whether one datapoint is sufficiently accurate). The initial implementation seems to be working well and I can build on it. Next steps → test it on more datapoints and optimize it if necessary, figure out a way to report on the accuracy and delay for different methods and make it iterative (peaks appear in real time).

Thursday 23/07

9:00 – 12:00

Further modification of the C code after I found a bug upon returning peaks for dog slow wave signal

13:00 – 17:00

Organized the python code into many functions for plotting, resampling, animated plotting in order to make it easier to process many files with different configurations and report on the optimal configuration so that it could be implemented in the C code.

Friday 24/07

9:00 – 12:00

Reviewed reports from previous years to figure out the methods used to assess the accuracy of the peak detection algorithm. I am going to include the detected peaks and real peaks that were already included by Sophie, however, the reporting may slightly differ since I do not have the ground truth file that was annotated manually. I am going to use the output of AMDP as my GT and in addition I am going to include a histogram that includes the accuracy of detection for different lags up to 1ms since sometimes a big peak has a small peak preceding it (at least for rats → dog signals still needs to be investigated)

13:00 – 17:00

Creation of Excel sheet and python script to report on the accuracy of different methods and procedures. Things that will be tested are number of samples after the signal (1 or 2), the sampling frequency (so far it looks like 10hz is ideal), the number of samples to be compared before the peak. Python script still needs to be modified a bit before the final testing → implement that next week. I am bit behind the actual schedule; I might take space from last week which I previously dedicated for writing the report to finish the tasks (if necessary) and then proceed to wrap up the report after the end of the internship.

Monday 27/07

Tried different configurations for the online peak detection algorithm and documented the reports in excel (created bar charts for detected, real and missed peaks + histogram for real peaks detected at different time lags). So far, the best configuration seems to be 10 hz (acts a bit as a low pass filter compared to 20 hz since 20 hz is quite noisy which negatively affects the accuracy of the online peak detection), also with 10 hz the number of datapoints to be compared is halved which decreases computation time. The maximum scale that is to be used is the one derived from AMDP (tough we only do left hand side comparison with it) and right hand side is only comparing whether the current value is bigger than the next value.

Tuesday 28/07

Further documentation of the results implemented an algorithm in Python to visualize an animated version of the algorithm. Sent a mail with all the derived results to the team for tomorrow's meeting

Wednesday 29/07

Viktor sent me a mail suggesting trying a smoothing window for 20hz rat signal in order to obtain a better detection. I further tried windows of different sizes and documented the results. The accuracy seems to get higher as a result of a smoother signal which remedies for the spikiness in the rat signal.

Team meeting: Professor Chen suggested to further improve the accuracy (currently at about 80% for 150 msec of delay for 20 hz rat signal) → more datasets will be provided to me by Shiying Li and we will organize a zoom meeting for him to explain to be the results.

Prof Chen suggested trying out different sampling frequencies to detect the signal. However, a filter needs to be applied first to filter signals $1/4^{th}$ below the sampling frequencies (ex: IIR LPF at 10 hz for 40 hz signal) before downsampling the signal → perform a spectral analysis to study the signal. The IPG has an inherent filter between 0.5 and 150 hz.

Chris asked to send the current online peak detection in Python for him to investigate. Also suggested to omit AMPD since the only thing that needs to be extracted is the optimal scale and the cpm, but I use the last peak detected in AMPD as a starting peak for the online implementation → figure out if there is a way around it.

Thursday 30/07

I re-organized the python code which includes my online peak detection and other functions (decimate, accuracy estimation depending on Positive lag, reading data and saving peaks..) and sent it to Chris for validation.

I received more rats datasets from Shying Li for accuracy estimation. I have tried using a butterworth filter for low-pass filtering before down sampling to avoid aliasing with a cut off frequency at ¼ of the desired down-sampled frequency (ex: 10 hz cut-off before down-sampling a signal from 200hz to 20hz) but the accuracy did not differ. I concluded that I was using the decimate function (from scipy package) to downsample my signal which uses an anti-aliasing filter before downsampling so that my previous approach was correct.

I wrote a script to test the accuracy of all the datasets that I have for a combination of different window sizes and positive lags.

Friday 31/07

Documented and plotted the result to derive the best parameters. The optimal parameters results were consistent for a certain animal regardless of the dataset (accuracy is distance at 10% of CPM):

Dog: a) Positive lag of **1** b) smoothing window size of **2** c) maximum scale of **30** for 20 hz as per AMPD with an accuracy of 95% for 6 different analyzed datasets.

Rat: a) Positive lag of **3** b) smoothing window size of **3** c) maximum scale of **15** for 20 hz as per AMPD with an accuracy of 90% (as per my evaluation criteria) for 8 different datasets.

Sent an email to report on the results → accuracy is satisfactory. I will start implementing the whole algorithm in C code.

Monday 03/08

Implementation of the online peak detection in C code

Tuesday 04/08

Implementation of the online peak detection in C code

Wednesday 05/08

Finalizing the implementation and tried to reduce any expensive computations. I figure out that I can omit AMPD from the implementation since I was only using it to derive the last peak and the optimal scale →

1) optimal scale is constant and only changes for a certain animal and sampling frequency but not depending on the dataset

2) Last peak could be replaced by any datapoint at the start of the signal and will lead to similar accuracy results

Omitting AMPD reduces the computation substantially (no more LSM matrix calculation)→ Online algorithm only contains 1D array calculations.

Thursday 06/08

I found a bug in the code for the way that the accuracy was being estimated. Fixed the code and analysed the dataset again to derive the optimal parameters.

Skype meeting, now that the algorithm is complete need to implement an adaptive version that tries to stimulate at a constant cpm while taking into account the fluctuation of the cpm in the slow wave.

Friday 07/08

Implement the adaptive algorithm in Python.

Monday 10/08

Continue Implementing the adaptive algorithm in Python.

Tuesday 11/08

Translating the final online adaptive algorithm into a C code

Wednesday 12/08

Finalizing the code in C and double checking that everything is functioning properly.

Thursday 12/08

Documenting all the deliverable codes and make sure that there are no bugs.

Friday 13/08

Last official day of internship. Last deliverable was both the adaptive and non-adaptive version of the online peak detection algorithm written in C and in Python.

Sunday 30/08

Zoom meeting to conclude the internship and provide further explanation on any questions related to the final deliverables. Next step for the company will be to implement the algorithm in the clinical trial set-up and test its implementation. I will be contacted when that happens and will be given feedback on the results.