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Automated Testing System for Safe Peripheral Nerve Stimulation

Master's thesis in Applied Physics

JASMIN BENTLER

Department of Physics
Chalmers University of Technology
Gothenburg, Sweden 2017

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JASMIN BENTLER

Contact: bentler.jasmin@gmail.com

Supervisor: Max Jair Ortiz Catalan, Integrum AB
Examiner: Bengt Lennartson, Systems and Control, Electrical Engineering

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Department of Physics
Chalmers University of Technology
SE-412 96 Gothenburg
Telephone: +46 31 772 1000

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JASMIN BENTLER
Department of Physics
Chalmers University of Technology

Abstract

Current research at Chalmers University of Technology and Integrum aims to give prosthesis users artificial sensory feedback. This thesis discusses stimulation parameter restrictions to allow for safe neurostimulation and a non-damaging daily life prosthesis use. Emphasis is put on the lack of experimental human tissue results on peripheral neurostimulation and approaches to transfer animal result data are proposed. An automated testing system for a neurostimulator model used by Integrum is presented. In particular, noise treatment and different analysis approaches are utilized to optimize the testing process. Individual stimulus parameters can be analyzed by the testing system as well as long time functionality over multiple hours of stimulation. Finally, by means of a basic functionality test the integral software of the neurostimulator type can be verified.

Keywords: safe neurostimulation, peripheral neurostimulation, sensory feedback, prosthesis, automated testing system

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Introduction

Intuitive control is currently the main limitation for a functional restoration by artificial limbs. Sensory feedback is not implemented in commercially available prosthesis but has shown to enable patients to handle delicate objects, to perform daily life activities and to strongly inhibit phantom limb pain. Work done at Chalmers University of Technology, Sahlgrenska University Hospital and Integrum AB, has produced technology to interface an artificial limb to the patient's bone, nerves and muscles. Analog and digital electronics have been combined to acquire and process bioelectric signals, decode motor intention, and restore sensory feedback. This embedded controller for artificial limbs is connected to implanted neuromuscular interfaces and the prosthesis itself. It is therefore of foremost importance to secure the safety and proper functioning of the device. Special importance lies on the long-term functionality of neurostimulation without damaging the nervous system of the patient.

Due to the currently existing lack of safety guidelines on electrical peripheral nerve stimulation, the first part of this thesis is dedicated to identifying safe stimulation parameters while acknowledging shortcomings of the current research state. Despite the lack of specific research, numerous sources were reviewed in order to identify parameter tendencies and to gain insight on parameter effects.

The second part of this thesis presents a developed automated testing system able of recording stimulus pulse packages and of performing three different test types: A detailed individual pulse analysis, a long time analysis and a basic functionality test aimed at testing the integrated neurostimulator model.

Part I

Safety Considerations on Electrical Peripheral Nerve Stimulation

The safety requirements for electrical peripheral nerve stimulation are very little researched. In fact, up to date the only specialized research was done around 1990 by Agnew and McCreery which will be presented in the following sections. Moreover, a recommended stimulation pulse profile and electrode type are described. Furthermore, safety considerations concerning the stimulation electrode and the stimulated tissue are presented. Finally, an estimate for safe peripheral nerve stimulation parameters is made. In particular, these estimates are derived to enable safe daily stimulation of, for example, the ulnar nerve by an arm prosthesis.

1 Pulse Profile

For electrical stimulation it is safer to employ a charge-balanced biphasic pulse shape instead of a monophasic one as shown by Mortimer et al. (1980). The intention of using a pulse with zero net charge is to reverse the reactions occurring during the main phase stimulation on the electrode surface after the excitation has spread. Figure 1 explains the variable parameters of stimulation: amplitude, pulse width, interphase delay and frequency.

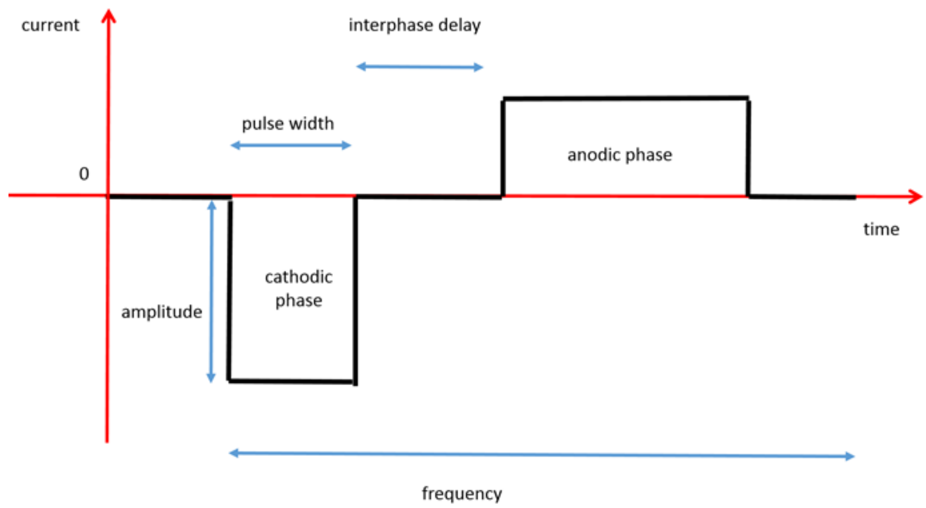

Figure 1: A biphasic square pulse profile.

2 Electrode Safety Considerations

2.1 Electrode Type

Various different electrode models exist for neurostimulators with a main difference being whether the electrode is extraneural (non-penetrating) or intraneural (penetrating). For instance, Kim and Romero-Ortega (2012) provides a description and comparison of the most relevant electrode models (see Table 2). Invasive multi-contact electrodes enable very selective stimulation, as, for example, demonstrated with the Utah Slanted Electrode Array Clark et al. (2014). However, they induce strong tissue reactions like scarring Christensen et al. (2014). In contrast to that, extraneural cuff electrodes allow less selectivity but keep the perineum intact which is important to maintain the chemical balance of the nerve and thus to preserve the normal nerve function as described, for example, by Tyler (2015). It is therefore clearly favorable to employ non-invasive cuff electrodes for long time nerve stimulation.

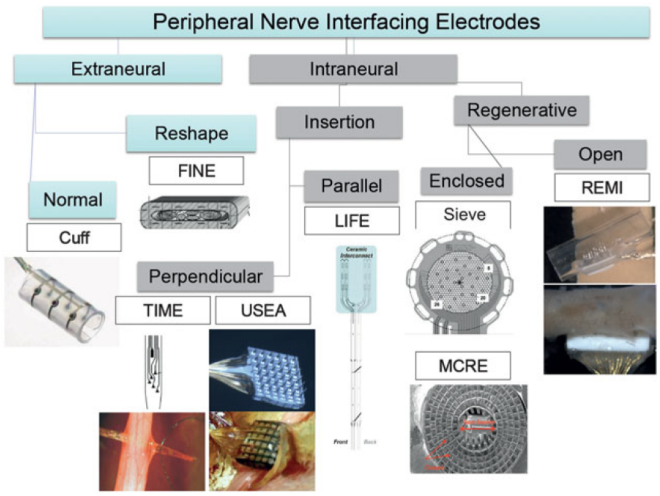

Figure 2: Classification of electrode types by Kim and Romero-Ortega (2012).

Furthermore, Durand et al. (2005)) derived that an electrode with a surface area of ≤ 1 mm^2 has to be treated as a point source, meaning that the induced electrical fields differ greatly from larger electrodes and would require different safety measures. Cogan et al. (2016) emphasized how this fact is mainly disregarded in modern neurostimulation.

2.2 Damage to Electrode

Aside from causing tissue damage, continuous stimulation can also be harmful to the electrode. Brummer and Turner (1977) describes in detail how stimulation of organic tissue may cause among other reactions hydrolysis and possibly toxic dissolution of the electrode demonstrated for platinum. Stimuli without causing hydrolysis were used to define safe charge injection capacities for electrodes by Robblee and Rose (1990).

Merrill et al. (2005), Cogan (2008) and Kim and Romero-Ortega (2012) list and compare charge injection capacities of commonly used viable electrode materials like platinum, activated iridium, stainless steel and platinum-iridium.

Experiments with platinum electrodes by Leung et al. (2015) yielded that while the different in vivo tissues surrounding the electrode had little effect on the charge injection capacity, the in vitro results obtained by means of phosphate buffered saline strongly falsified the result (see Figure 3). Accordingly, it is important to use in vivo data instead of relying on in vitro results when choosing an electrode material.

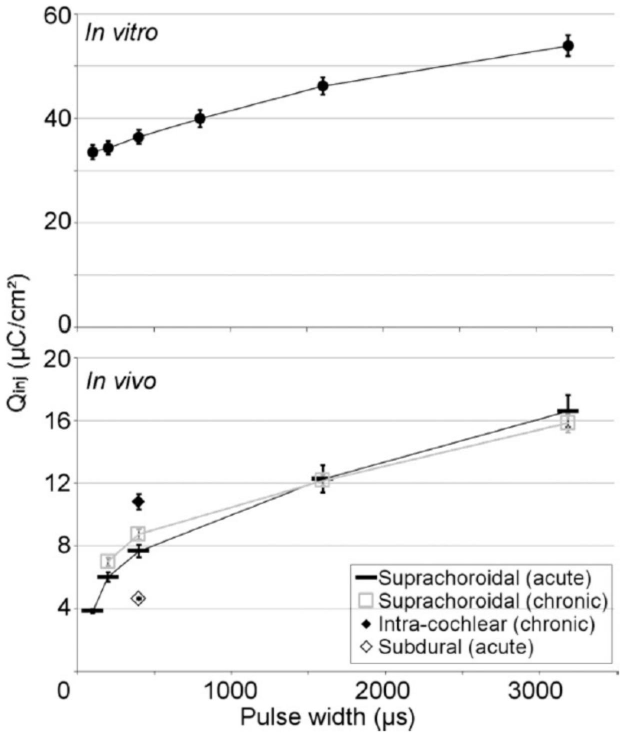

Figure 3: Comparison of in vitro and in vivo charge injection capacities of platinum macro electrodes by Leung et al. (2015).

3 Tissue Safety Considerations

3.1 Charge per Phase and Charge Density

Shannon (1992) developed the only mathematical model describing safety limits of electrical stimulation:

$$\log\left(\frac{Q}{A}\right) = k - \log(Q)$$
$$Q = I \cdot PW$$

with Q = charge per phase, I = current, PW = pulse width, A = electrode area and k = constant, with k indicating which relation of charge density and charge equals safe stimulation.

Since the model is based only on in vivo cat cortex stimulation with disk electrodes at 50 Hz by McCreery et al. (1990) it is reasonable to assume that the model does not necessarily hold for different electrodes, target tissue and stimulation frequencies.

Nonetheless, Merrill et al. (2005) was able to match the Shannon model to different target tissue results at same frequency for different electrodes as depicted in Figure 4.

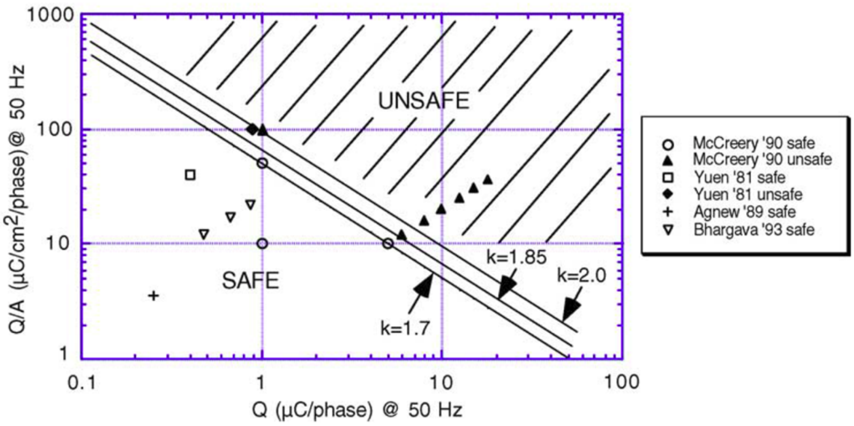

Figure 4: Application of the Shannon model to experimental results with different target tissues and electrodes at 50 Hz documented by Merrill et al. (2005).

3.2 Pulse Width and Current

When considering only the pulse width instead of the product of pulse width and current, a longer pulse width equals a longer reaction time on electrode surface which theoretically can cause a greater amount of harmful byproducts as described by Merrill et al. (2005) and Brummer and Turner (1977)).

Despite that, Butterwick et al. (2007) found that a longer pulse width resulted in a lower current damage threshold and identified a behavior typical of electroporation. Furthermore, Gorman and Mortimer (1983) and Prado-Guitierrez et al. (2006) reported lower activation current thresholds for longer pulse widths implying that long stimuli with low amplitude are equally effective as short high amplitude pulses.

3.3 Frequency

While the Shannon model and considerations of pulse width and current are common when it comes to safety considerations, research by Agnew et al. (1989), Agnew et al. (1999) and McCreery et al. (1995) has shown that indeed the frequency is a parameter that has a larger impact on the safety of neurostimulation. Table 1 lists examples of experimental results that emphasize the effect of high frequency stimuli.

McCreery and Agnew experimented on cat sciatic nerves with the frequencies 20 Hz, 50 Hz and 100 Hz and the pulse width of 100 μs for stimulation times between 4 and 16 h. Figure 5 indicates how the low frequency stimulation at 20 Hz remained constantly harmless to the nerves even at stimulation currents eight times as high as required for full nerve recruitment of 2 mA. At two times the full recruitment current 0.2 % damaged axons in three out of eight stimulated nerves were detected. Higher frequencies on the other hand caused damage scaling approximately linearly with the applied current and are only safe at low stimulus currents.

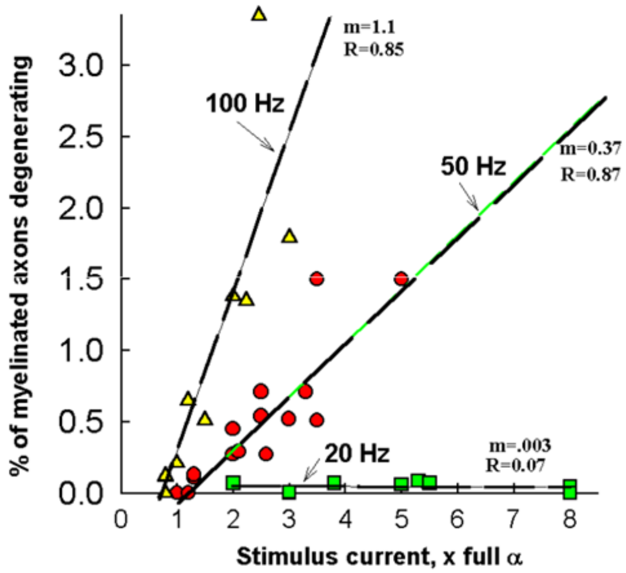

Figure 5: Percentage of damaged axons versus applied stimulus current in multiples of full recruitment current α at different frequencies (PW = 100 μs) as found by McCreery et al. (1995).

The experiments on chicken retina and choroallontonic membrane by Butterwick et al. (2007) also demonstrate a dependence between safe frequency and charge density. Butterwick found that lower currents (at constant pulse width) cause damage if the frequency increases until a damage threshold is reached at which all further tested frequencies (0.16 - 33.33 Hz) cause damage at the same current, respectively charge.

Supplementing damaging effects of frequency were also documented by Tykocinski et al. (1995) who experimented on guinea pic auditory nerves. Slight reductions in the auditory nerve's excitability became apparent after stimulation with comparably low frequencies at 1.0 μC/phase. In contrast to that, stimulation with higher frequencies resulted in signification reduction of the nerve excitability at 0.16 μC/phase.

Thus, it is evident that the frequency is an important factor in safe neurostimulation. Especially in comparison to stimulus current and pulse width, this parameter appears to have the greater effect allowing a large variation in stimulus current and thus charge if the frequency is chosen low enough.

Table 1: Frequency related safety discoveries.

Reference	Frequency	Target tissue	Discovery
Agnew 1989,99	20 Hz	Sciatic nerve (cat)	Safe
	50 Hz		Damage lasting for 60 days
	100 Hz		Irreversible damage
McCreery 1995	20 Hz	Sciatic nerve (cat)	Safe
	50 Hz		Damage
Tyokocinski 1995	100 Hz	Cochlear (guinea pig)	Slightly reduced excitability
	200-1000 Hz		Significantly reduced excitability
Butterwick 2007	$>$ 0.16 Hz	Retina (chicken)	Constant charge damage threshold

3.4 Interphase Delay

Inserting a phase delay between the main and reversal phase of the stimulus pulse serves the purpose to prevent action potential inhibition by the reversal phase as reported by Mortimer et al. (1980). This only increases the efficacy and not the safety of the stimulation. On the contrary, McCreery et al. (1992) found that the introduction of a 400 μs interphase delay lowered the current damage threshold in comparison to stimulation without interphase delay. If an interphase delay is necessary it is therefore recommended to use a smaller value. Both Prado-Guitierrez et al. (2006) and Maciejasz et al. (2015) reported efficient nerve activation with smaller interphase delays (0 - 100 μs). More precisely, they reported that the interphase delay lowered the required activation current. It is possible that the lower activation current justifies the implementation of an interphase delay when considering the safety of the stimulation.

3.5 Duty Cycle

The duty cycle corresponds to a stimulus signal alternating between on and off. That is, continuous stimulation is a duty cycle of 100% whereas the alternation of stimulus and equally long pause corresponds to a duty cycle of 50%.

Table 2 lists experiments on different target tissues which uniformly yielded that the introduction of a 50% duty cycle improves the safety of the stimulation. Of particular importance is the discovery by Agnew et al. (1989) that stimulation at originally deemed unsafe 50 Hz can be executed safely by implementing a 50% duty cycle. Tykocinski et al. (1995) monitored the excitability of auditory nerves after high frequency stimulation and found that the excitability recovered completely if 50% duty cycle stimulation was used. This was true for even twice as high charge densities than classified safe by prior research.

Other examples for safe stimulation with duty cycle are the 2000 h long stimulation of the cochlear by Xu et al. (1997) and Gabi et al. (2010) who were able to stimulate in vivo rat muscle tissue for 21 days without cell death.

Table 2: 50 Percent Duty Cycle related safety discoveries.

Reference	Frequency	Cycle	Target tissue	Discovery
Agnew 1989	50 Hz	5 s	Sciatic nerve (cat)	Significantly reduced damage
Tykocinski 1995a	200 Hz	0.01 s	Cochlear (guinea pig)	Significantly better recovery
Xu 1997	2-8 kHz	0.5 s	Cochlear (cat)	2000 h safe stimulation
Gabi 2010	0.2-0.4 Hz	2.5 s	Muscle tissue (rat)	21 day safe stimulation

3.6 Stimulus Duration

Finally, the duration of continuous stimulation has been shown by Agnew et al. (1989) to have a large influence on the axon health. Whereas 8 and 16 h long stimulation of cat sciatic nerves at 50 Hz caused irreversible nerve damage, for instance, endoneurial endema, to more than 1 % of the axons, stimulation for 4 h at the same frequency has proven to be harmless to the nerve.

4 Target Tissue Considerations

4.1 Transferability Between Target Tissues

Undoubtedly, differences based on chemistry and anatomy of the target tissue exist and specific stimulation is therefore required. For example, Kim and Romero-Ortega (2012) and Weber et al. (2012) list the dissimilarities between brain and peripheral nerve stimulation and Polasek et al. (2009) compares motor versus sensory stimulation.

4.2 Transferability Between Animal and Human Test Results

Since research focusing on nerve survival is problematic to perform on humans, no research on safe electrical stimulation of (peripheral) human nerves exists. Instead, animal nerves are used. For instance, Güven et al. (2005) and Colodetti et al. (2007) performed animal retina stimulation experiments expecting these results to be applicable to humans in the future. Agnew et al. (1999) tested in vivo cat sciatic nerves as an alternative to human peripheral nerves but stated uncertainty about these results being directly transferable.

This indicates that direct comparison research is required before animal experiments are a complete replacement for human tests. Possible indicators of comparability could by conduction velocity, diameter, axon count and myelination. Information on human nerves is, for example, provided by Sunderland and Walshe (1968) while some data on the cat sciatic nerve can be obtained from Boyd and Kalu (1979) and data on the rat sciatic nerve by Lu et al. (2008).

4.3 In Vitro vs. in Vivo

Previously, when discussing the charge injection capacity, the disagreement between in vivo and in vitro results was noted by Leung et al. (2015). Similarly, Butterwick et al. (2007) and Gabi et al. (2010) observed strong discrepancies in their in vivo and in vitro results. These disagreements, however, might also be due to the tested tissues stemming from different body parts or animals. In particular, Gabi et al. (2010) observed for the tested rat tissues that in vivo cells were more durable under stimulation which could imply that in vitro experiments would result in too low safety limits for stimulation parameters.

4.4 Dependence of Purposeful Safe Stimulus Range on Patient

Finally, one has to consider that each person can have individual safe stimulation ranges. For example, research by Ortiz-Catalan et al. (2014) and Tan et al. (2014) showed very small ranges between eliciting feeling and pain which could indicate that small deviations from the individual ideal stimulation parameters could already harm the patient. The individuality of test subject stimulus thresholds is also emphasized by McCreery et al. (1992) and McCreery et al. (1995) and it is therefore reasonable to test which stimulus parameters are comfortable for the patient before inflicting continuous neurostimulation .

5 Conclusion: Safe Peripheral Nerve Stimulation

The reviewed literature strongly indicates that safe peripheral neurostimulation is theoretically possible and can therefore be used to supply a prosthesis user with artificial feedback. Especially, strict control of frequency, introduction of a duty cycle and restrictions on the total stimulation period were shown to significantly improve the safety of electrical stimulation.

Due to the lack of specific research only an estimate can be made concerning suitable stimulation parameters. Assuming sufficient similarity between human peripheral nerves (such as the ulnar nerve) and the cat sciatic nerve as well as the use of an electrode comparable to the helical platinum cuff electrode employed by Agnew et al. (1989), Table 3 lists the concluded safe stimulation parameters. It is important to keep the parameter interactions in mind. For example, higher frequencies can be employed if lower stimulus currents are utilized. Low frequency, duty cycle and a restriction on the continuous stimulation period individually transforming otherwise unsafe stimulation parameter settings to non-damaging stimulation. Hence, without longer continuous tests than 16 h stimulation being available (for a suitable target tissue), a simultaneous implementation of all three parameters appears to be the safest approach.

Table 3: Safe Stimulation Parameter Estimate.

Parameter	Recommendation
Frequency	20 Hz
Current	4 mA
Pulse width	100 μs
Interphase delay	$0 \leq \text{delay} \leq 100\ \mu$s
Duty cycle	50 %
Stimulation duration	4 h

Part II

Automated Neurostimulator Testing System

In this part of the thesis an automated testing system consisting of an experimental setup with a neurostimulator and developed software is presented. The software allows the management of data acquisition and analysis with emphasis on different stimulation properties: single pulse details, long time parameter changes and test of integral neurostimulator software.

6 Experimental Setup

6.1 Pulse Profile

The stimulus pulse profile employed in this thesis corresponds to a biphasic square pulse (see Figure 6) with zero net charge. That is, the anodic reversal phase corresponds to a ten times smaller amplitude but ten times longer phase width than the cathodic main phase. Between the main phase and the reversal phase is a 50 μs interphase delay to allow the excited action potential to spread instead of immediate suppression by the reversal phase.

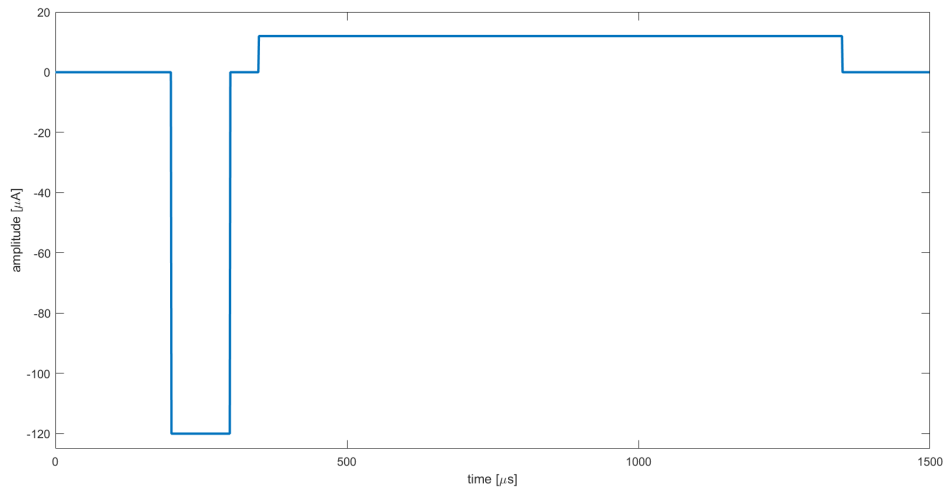

Figure 6: The charge balanced pulse profile.

6.2 Neurostimulator

The utilized neurostimulator by Synergia Medical and Integrum consists of a non-penetrating cuff electrode with three platinum-iridium stimulation channels. It is possible to request a stimulation amplitude between 10 μA and 500 μA in increments of 10 μA, a pulse width between 10 μs and 500 μs in increments of 10 μs, a frequency of 1 to 100 Hz in increments of 1 Hz and lastly, the number of pulses between 1 and 100 pulses per pulse package of the same parameter settings.

In the results section, this neurostimulator will be referred to as ”NS1”.

6.3 Testing Setup

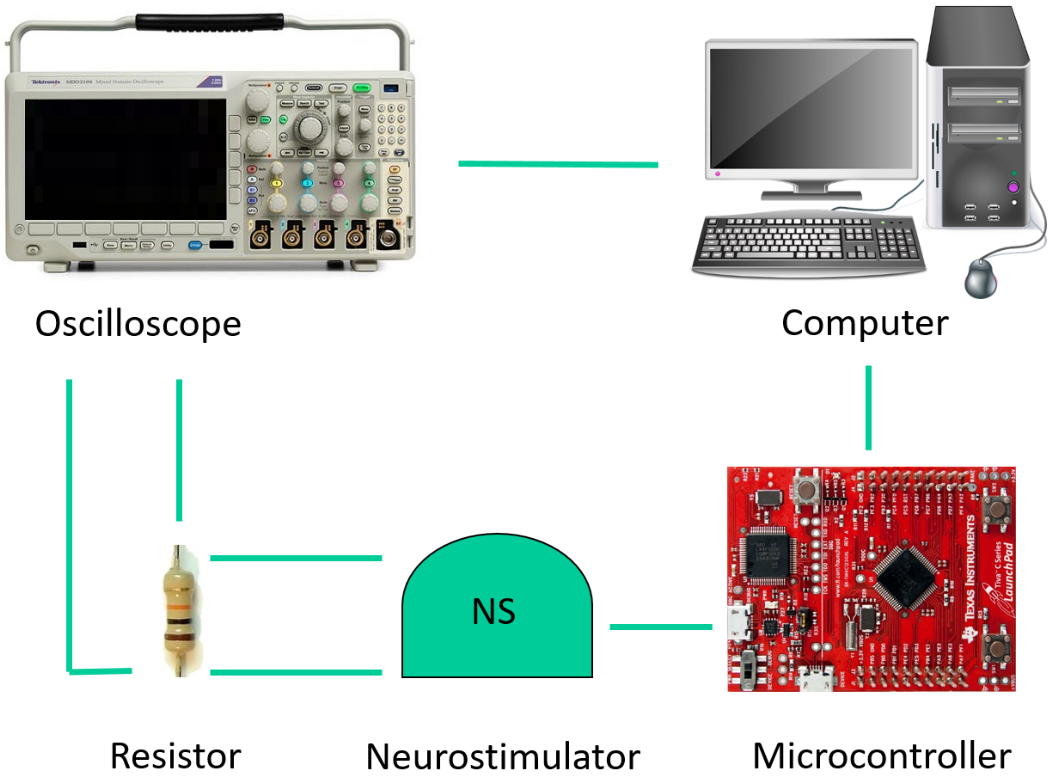

Figure 7: Experimental setup for data recording.

Figure 7 shows a simplified schematic of the data recording setup. The whole testing process is controlled by a computer (Windows 10, 64 bit). In particular, graphical user interfaces (GUI) were created in Matlab 2016a to manage data acquisition and analysis. To generate electrical pulses commands are sent via USB cable from the computer to a micro-controller (Tiva Launchpad) which then conveys the commands to the neurostimulator. After the signal is outputted at a resistor (10 kΩ) it is detected by an oscilloscope (MD3014 by Tektronix) which is also controlled by Matlab. For the experiments a battery powered differential probe (manufactured by Manson) was utilized for the oscilloscope data sampling to significantly decrease the background noise from 20 μA to 12 μA.

In this setup, both the oscilloscope and the micro-controller are connected to the computer via USB cables. In case of the micro-controller, this also serves as its power source. The neurostimulator, however, needs to be externally powered. During the data recording of the parameter test, the neurostimulator was powered by 9 V batteries while during the long time test the neurostimulator was supplied with 6 V from a voltage generator.

The oscilloscope control was based on Matlab's Quick-Control Oscilloscope [1] of the Instrument Control toolbox using the TKdpo2k3k4k IVI Driver 1.2.0 and the National Instruments Compliance Package 14.0.

[1] https://se.mathworks.com/help/instrument/using-quick-control-oscilloscope.html

6.4 Recording Data with Matlab GUI

The automated testing can be controlled by a recording and an analysis GUI. In total, three types of tests exist: a parameter test (high detail, various short samples), a long time test (low detail, one parameter setting, 8h of run time) and a basic functionality test which focuses on the specific software integral to the neurostimulator. The GUI screens and manual can be found in the appendix.

Selecting the test type from the options "Parameter Test", "Long Time Test" or "Basic Functionality" and pressing start will start the recording of the respective test or, in case of the basic functionality test, start a real time analysis.

The parameter test corresponds to various parameter settings being stimulated by the neurostimulator in a random order. Depending on frequency, differently long pulse packages are stimulated for a 1 sec recording sample as to fit the sample into the 1 sec time frame. In case of 1 and 2 Hz only 1 pulse is outputted. The higher the frequency, the more pulses are stimulated: Frequencies higher than 2 Hz will be stimulated as package of 2 pulses, frequencies higher than 5 Hz as a package consisting of 5 pulses and finally frequencies higher than 10 Hz will be stimulated as 10 pulses long packages. In order to collect comparable information, the pulse packages are stimulated at least twice and up to twenty times. Accordingly, 20 pulses are stimulated for each parameter setting with the data being distributed over multiple files.

Each recorded sample was named in a way that allows to retrieve the employed parameter setting for the subsequent analysis. That is, parameter test file names are of the form

`para_`*amplitude_pulse width_frequency_number of pulses_channel_recording number*`.mat`.

For instance, `para_100_150_30_10_0_5.mat` corresponds to a stimulation with main phase amplitude 100 μA, main phase pulse width 150 μs, frequency 30 Hz and 10 pulses within the stimulated package. Finally, the last numbers indicate that neurostimulater channel 0 was used and that this is the fifth recorded sample of the same stimulation setting.

The long time test examines whether the NS can flawlessly supply a fixed parameter set for a time interval long enough to mimic daily use by a patient.

Since the neurostimulator does not react to new commands while outputting a pulse package, at most 100 pulses can be requested at once. Accordingly, the long time data collection is not truly continuous but takes place in successive 10 second recording samples. Furthermore, each 10 second sample contains several pulse packages of fixed length in order to fill the 10 second interval and to create a variation in the number of stimulated pulses. Per sample 266 pulses in a fixed pulse package pattern of 100, 75, 50, 25, 10, 5 and 1 pulses are stimulated. This pattern of different pulse packages is chosen as such to make the best use of a 10 second interval resembling complete continuous stimulation. Naturally, true continuous stimulation would be the most taxing case for the neurostimulator and it is thus reasonable to aim for this ideal situation.

For this reason duration of stimulation is favored over accuracy by using the sampling rate 100 kHz instead of the best possible 1 MHz (for more details see next section).

The overall recording time for one channel takes approximately 8h. This was selected as total testing time because it corresponds to regular working hours per day during which a patient would need his prosthesis. Recording and saving each 10s file corresponds to 10.15s or less total time consumption. Thus, 3000 10s samples are recorded to achieve 8h of nearly continuous stimulation. Concerning patient use it is also realistic that the prosthesis feedback is not demanded 100% of the time.

Similarly to the parameter test, long time tests are saved as
`long_`*amplitude_pulse width_frequency_channel_recording number*`.mat`. Here, the number of pulses is not listed in the name since it is always 266.

Table 4: Brief Overview Test Types

	Parameter Test	Long Time Test	Error Messages Test
focus on	correctness of individual pulses	change of NS output over time	functionality of integrated NS software
analysis start	after recording	after recording	real time
recording duration	approx. 2 h/channel	approx. 8 h/channel	arbitrary
sample length	1 sec	10 sec	/
sampling rate	1 MHz	100 kHz	/

If either ”Parameter test” or ”Long Time Test” are started ten warm up measurements will be made and shortly displayed to the GUI user. This is supposed to serve as an initial functionality check and the files are stored with their name being of the form `initial_*.mat`. Furthermore, the measurements are used to warm up the oscilloscope and thus suppress recording errors.

6.5 Matlab and Oscilloscope Communication

Matlab's Quick Control oscilloscope allows to set the sampling rate by choosing the sample time and the number of data points. The allowed sampling intervals are small times below 1 s and the discrete values 1s, 2s, 4s, 10s whereas the allowed number of data points are 10k, 100k, 250k and 1M. Although the oscilloscope can be manually set to record 10^7 data points during any of the allowed time intervals, using Matlab's Quick Control limits the maximum value to 10^6 and reduces the data points to that value if 10^7 data points were selected before. Thus, the highest possible sampling rate is 1 MHz. The MDO3014 has a voltage resolution of 0.004 V.

First, in order to be able to manage the oscilloscope, its resource name has to be determined. Then, the oscilloscope channel has to be enabled and its recording properties set. Finally, data can be recorded by using the function getWaveform(resource).

Calling getWaveForm(resource) basically corresponds to taking a screenshot of the current oscilloscope screen. Accordingly, recording the data requires the Matlab program to pause for approximately the duration of the stimulation to guarantee that the full signal is captured. The length of the required pause depends on the performance of the computer, respectively Matlab, to neurostimulator communication speed and the expected signal length. This variable has been found to be very consistent over ten thousands of recordings given that at least one (unused) ”warm up” recording was done at the beginning of data collection.

6.6 Other Tested Recording Devices

Before deciding on the final recording method described in the Testing Setup and Matlab and Oscilloscope Communication section, three other recording methods were tested.

The first considered recording method was an instrument amplifier controlled via the Tiva Launchpad. The sampling rate was impeded by the serial port communication rate limit and thus the instrument amplifier did not yield useful recordings. Figure 8 and 9 show examples of the obtained recordings. One can see that the low sampling rate of 25 kHz does not allow for the identification of the interphase delay.

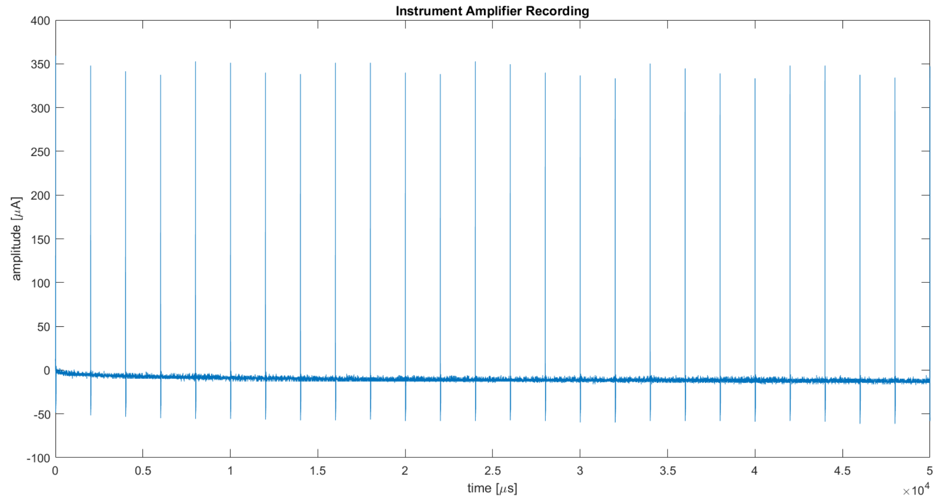

Figure 8: Pulse package sample recorded with instrument amplifier.

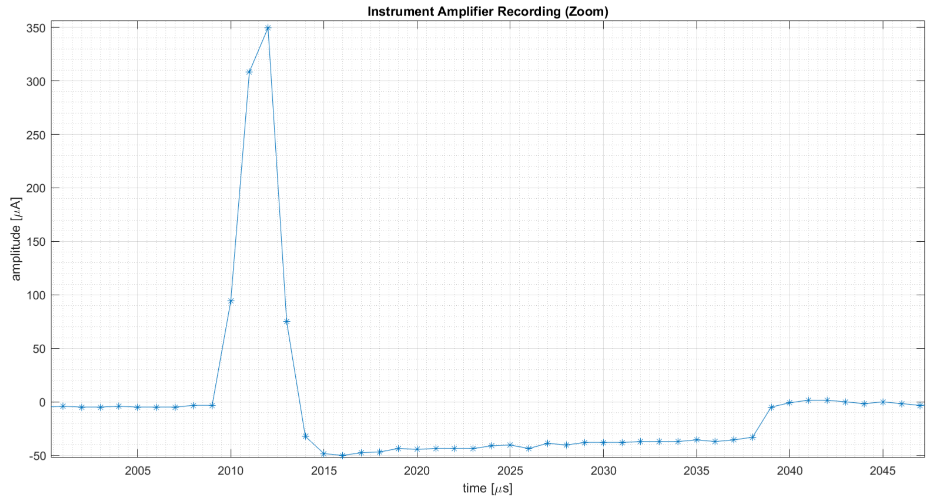

Figure 9: Manual zoom on single pulse recorded with instrument amplifier.

Then, the Analog Discovery by Digilent [2] was tested. Despite exhibiting a good sampling rate of 300 kHz and a very good amplitude resolution (see Figures 10 and 11) this method was not chosen because of its significant drawback of not being able to detect stimulations consisting of only a single pulse or, respectively, the initial pulse of a pulse package. Analog Discovery fails to detect these initial pulses because if a neurostimulator command is sent too much time passes before start of the data acquisition to reliably record all pulses. Matlab pauses while acquiring data with the Analog Discovery and thus starting the acquisition before sending the neurostimulator command is not on option. Parallel programming approaches with the ”parpool” function of Matlab resulted in the error message that ”parpool” cannot be used for acquisition processes. Alternatively, this recording device could be used if an artificial pause would be implemented in

[2]https://se.mathworks.com/help/daq/examples/getting-started-acquiring-data-with-digilent-analog-discovery.html

the neurostimulator software thus delaying the nerostimulator output until the data recording can be started by Matlab.

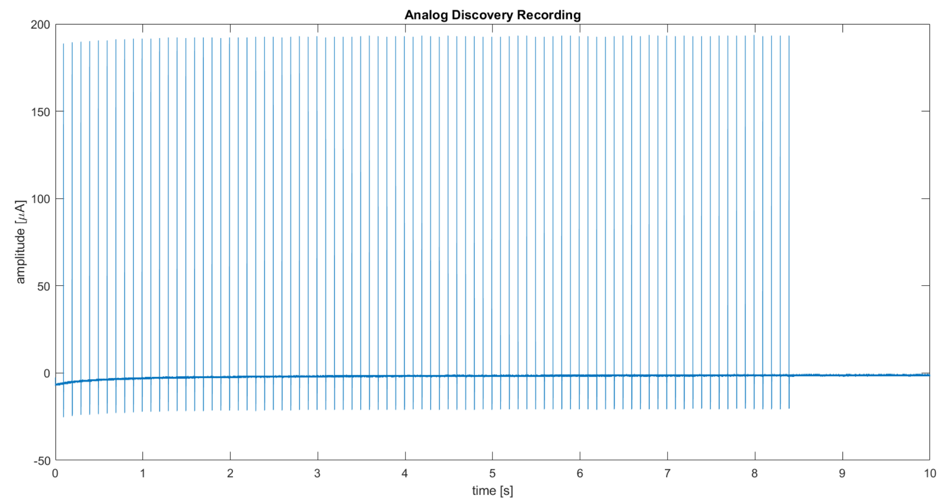

Figure 10: Pulse package sample recorded with Analog Discovery.

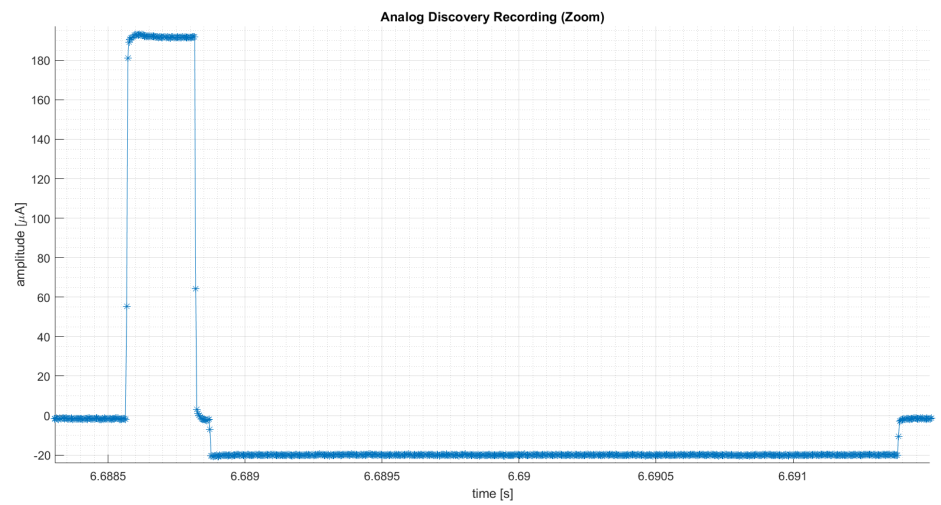

Figure 11: Manual zoom on single pulse recorded with Analog Discovery.

Lastly, another Tektronix oscilloscope model TS2004C was considered. In contrast to the more modern MDO3014 this model can be controlled by Matlab by means of a TekVISA-driver. Because of this Tektronix model being able to only record only 10k data points the newer MDO3014 and the IVI-driver was favored.

6.7 Summary: Experimental Setup

In this project, a setup consisting of a MDO3014 Tektronix Oscilloscope, a differential probe, a suitable resistor, a computer and the three-channel neurostimulator developed by Synergia Medical and Integrum was used to execute parameter, long time and software tests. A Matlab GUI served as testing interface and allowed control of electrical pulse output, recording and analysis.

7 Initial Data Processing

7.1 Exclusion of Faulty Recordings

Due to insufficient warm-up and other random errors, an oscilloscope recording might be unusable for further analysis. Cases like these (shown in Figure 12) are documented as failed recordings and not further processed. During testing phases oscilloscope errors occurred in approximately 0.02% of recordings.

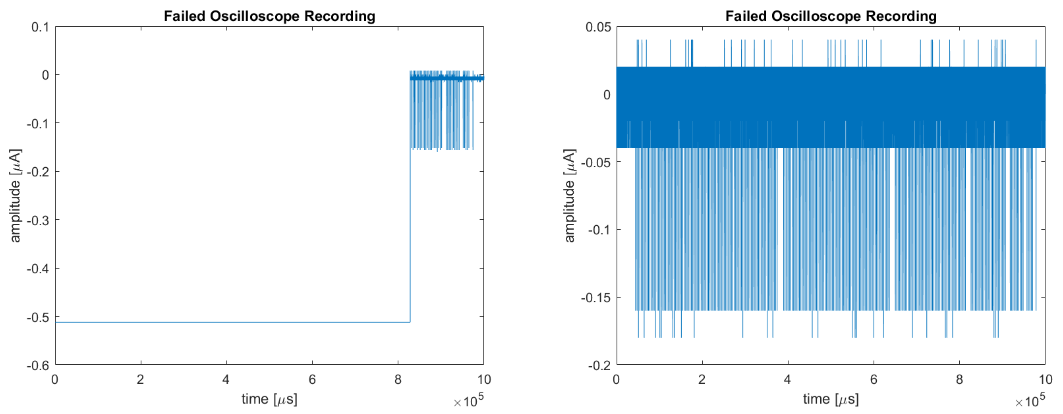

Figure 12: Two examples of unusable oscilloscope recordings. Left: Insufficient warm-up, right: randomly occurring strong noise.

7.2 Data Calibration

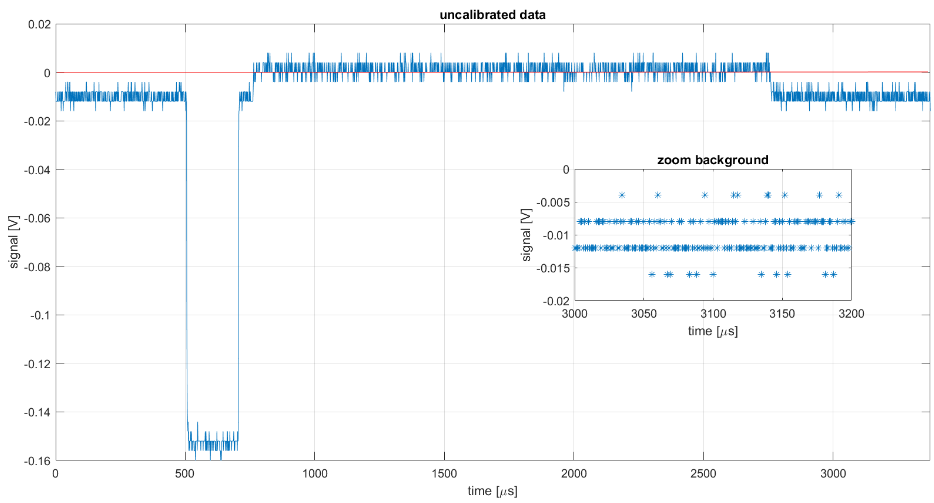

Figure 13: Raw data in voltage with visible offset.

The oscilloscope provides data in voltage which has to be translated in μA by means of the resistor value of the testing circuit. In theory, all data should be centered around 0 with noise levels given by the oscilloscope accuracy 4 μA or multiples of that. However, a falsification by a non-consistent offset which is created by the employed sampling probe requires correction to allow the analysis of the data. Figure 13 and 14 show sampling data before and after the corrections have been made. In particular, one can see the calibration of the y-axis as well as the offset correction in Figure 14.

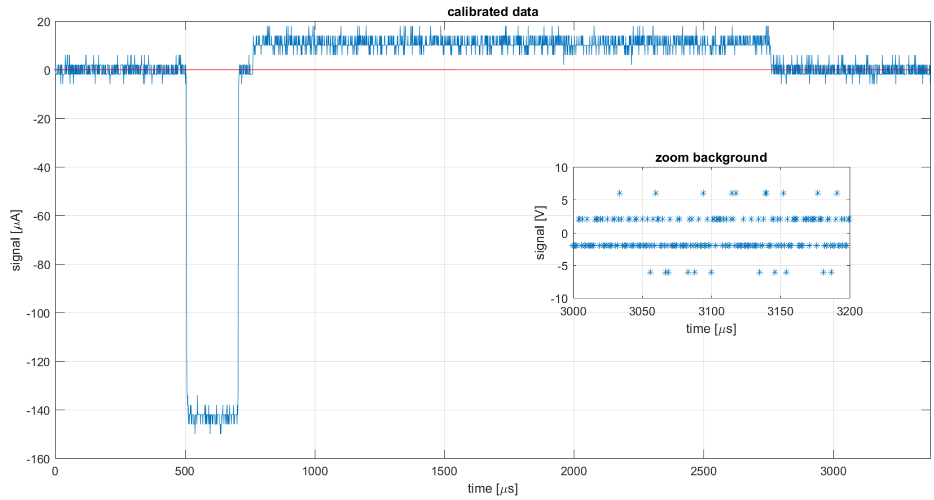

Figure 14: Calibrated data after offset correction in μA.

A noteworthy fact is that the offset varies seemingly random over multiple measurements. Additionally complicating is that the sampling probe does not filter the noise in a consistent manner: For instance, the amount of values smaller than the median can be significantly less than the amount of values larger than the median when the probe systematically suppresses negative noise more than positive noise. Systematic filtering like this can occur for long times like a second or minutes. Examples of such systematic noise backgrounds of individual measurements are depicted in Figure 15. As a consequence, the mean of the background noise does not always equal the correct offset. An additional problem is that rarely a few larger noise values appear. For example, for millions of data points the noise is ±16, ±12, ±8, ±4 and 0 μA but then also two points with -20 μA occur in a one million data point sample. Therefore, neither the mean nor median can be used to determine the offset reliably for all data samples.

Considering the variety in possible noise backgrounds created by the differential sampling probe, the individual offsets are determined by first calculating the offset as the mean of 2000 background data points and then readjusting the result by the mean of only the two discrete values centered around this offset. This readjustment is meant to reduce the influence of an imbalanced noise most likely purely caused by the probe. In case of balanced noise the readjustment is accordingly 0.

This procedure is done prior to the analysis of each record sample and is limited to so few data points as to not factor in a stimulus pulse. Trial inclusion of more data points did not yield a better result.

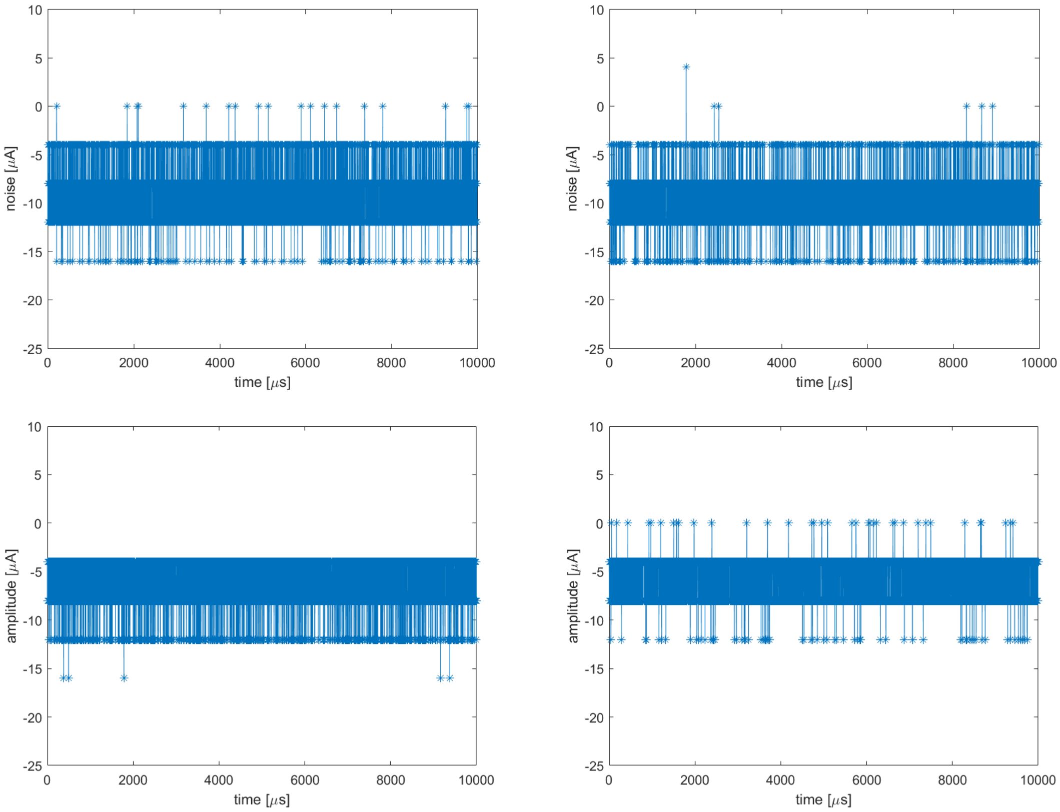

Figure 15: Examples of noise backgrounds of four individual samples.

7.3 Noise Filtering

Correct analysis of the reversal phase whose amplitude equals only one tenth of the main phase amplitude requires a prior smoothing of the raw data in order to help distinguish the small reversal phase from noise.

First, simple thresholding is used to remove values that correspond obviously to noise (see Figure 16; same example as 13 and 14). Due to the difference in magnitude for the main and reversal phase, the threshold for the main phase is twice as large as that for the reversal phase. For the employed devices and settings, the reversal phase threshold was chosen as 5 μA (barely above the smallest noise level) and the main phase threshold as -10 μA accordingly. Values of smaller magnitude than those thresholds are set to zero.

Then, more precise filtering is done by reading the data from left to right and setting all values to zero whose next four neighboring data points exhibit at least one data point that is zero.

Since this also leads to the removal of data points belonging to a phase, in particular, the last four values, the erosion of those values is undone in one final step: The data is read from left to right again and all values who are zero but whose four previous neighbors are unequal to zero are restored to their value before erosion. To summarize, this removes all noise outside a phase but keeps the phase intact. In cases like Figure 17 all non-phase noise was perfectly eliminated.

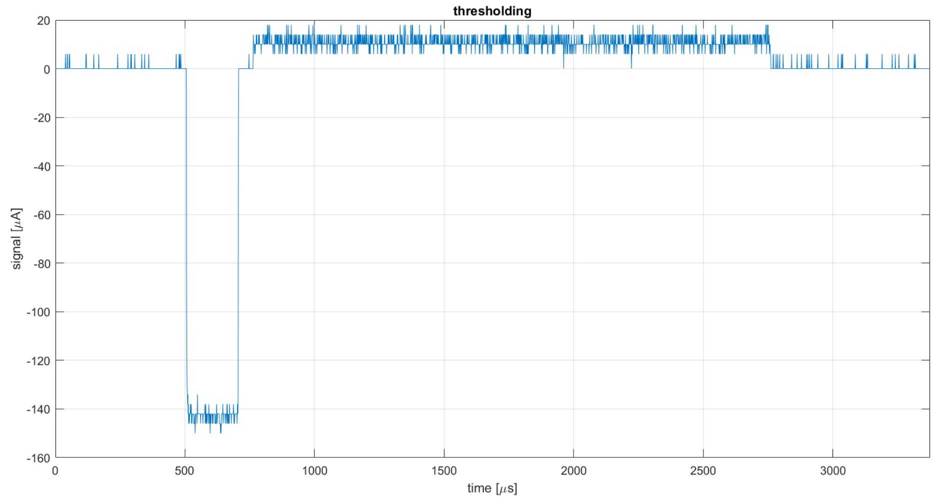

Figure 16: Data after thresholding with thresholds 5 μA and -10 μA.

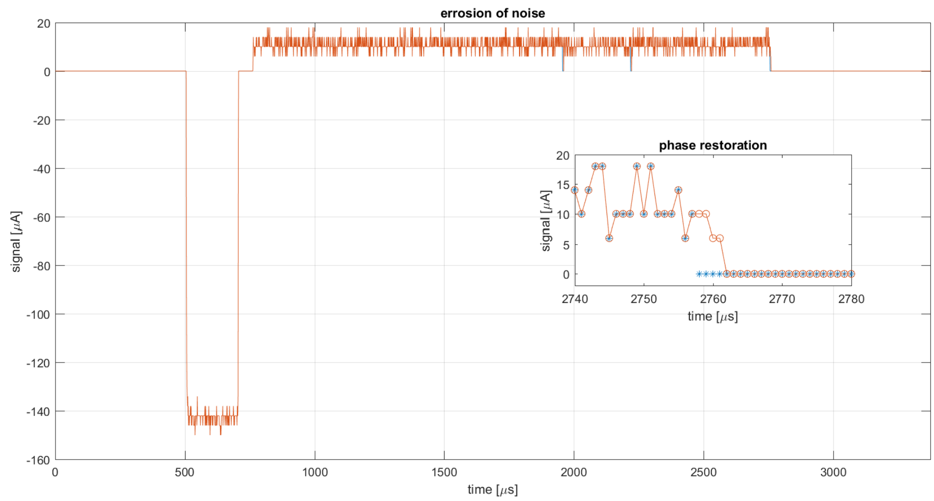

Figure 17: Smoothed data. The excerpt of the end of the pulse shows in blue (stars) the data after erosion and in orange (circles) the data after phase restoration.

Small clusters of high noise level can sometimes lead to not completely smoothed data exhibiting a few remaining noise peaks. Therefore, the noise filtering procedure is performed twice in a row on the data. In addition to that, the analysis programs processing the smoothed data perform an additional selection by classifying remaining clusters of one or two data points or clusters of a user defined length as noise and larger ones as a phase.

8 Noise Data Classification

The following examples shall demonstrate how the analysis treats clusters of data diverging from the expected square pulses. Figure 18 depicts the special cases that need to be considered when distinguishing stimulation signal from noise. Some of the clusters are treated by applying the noise filter as described in the previous section whereas more difficult cases require additional classification during the analysis.

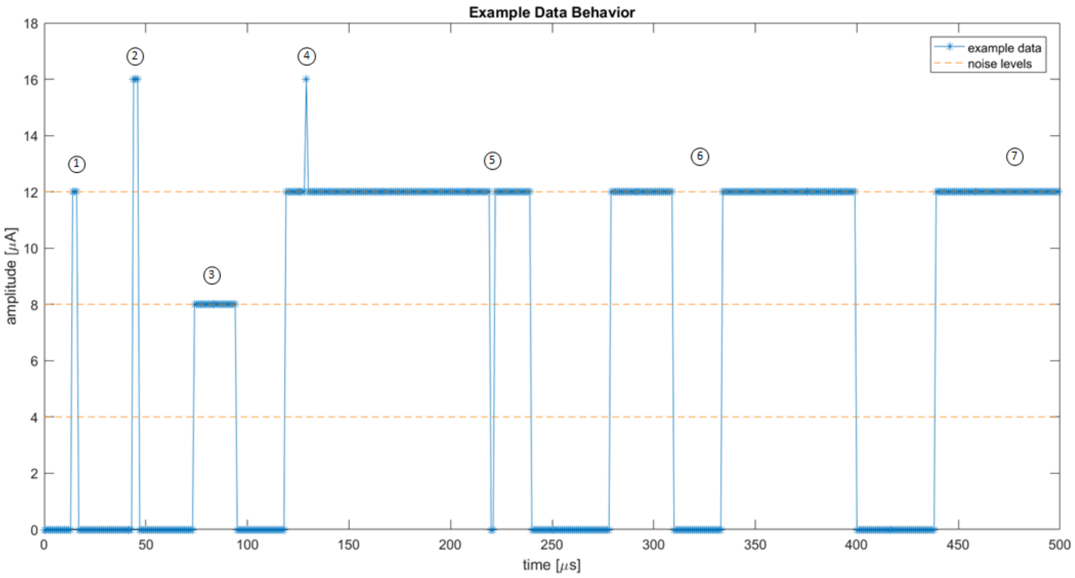

Figure 18: Examples of data point behavior that requires classification. 1: Noise peak, 2: Large noise peak, 3: Wide noise peak, 4: Mid-phase peak, 5: Interrupted phase, 6: Long interrupt, 7: Cut-off phase

1. Noise Peak

A simple noise peak which will be eroded when applying the noise filter.

2. Large Noise Peak

Both small and large noise data points get removed by the noise filter before the phases are analyzed. However, if a noise peak is too large, as in this case, it will be documented since a stimulation error is possible. This example will be referred to as a stray peak in the following.

3. Wide Noise Peak

Long noise peaks are left intact during the data smoothing because of their resemblance to a phase. Nonetheless, they will be classified as noise instead of a phase if their length and mean amplitude are both small compared to an expected phase (for more details, see Section Parameter Test).

4. Mid-Phase Peak

Another type of stray peak. In particular, if a single value within a phase is significantly larger than its mean it may correspond to a dangerous stimulation and is therefore treated as an error.

5. Interrupted Phase

Since the reversal phase usually is of the same amplitude as common noise data points some phases can be interrupted if a smaller value is measured mid phase. As long as the interruption of a phase is short, it will be ignored and the phase parts treated as one phase.

6. Long Interrupt

However, if a phase exhibits an non-negligible interrupt it is registered at two phases due to a stimulation error being likely.

7. Cut-Off Phase

If a data sample does not fully record a phase resulting in this phase being cut off, it is not used in the analysis.

9 Parameter Test

The purpose of the parameter test is to detect deviations between a single pulse and the expected biphasic square pulse. Errors in single pulses are reported and general error dependence on parameter magnitude itself as well as dependence on the other parameters is examined. Table 5 and Figure 19 illustrate the different analysis processes.

Table 5: Overview Parameter Test

Input	Output	Purpose
All *para*_*.mat files	Log_Parameter_Test_*.txt Log_Large_Errors_Parameter_Test_*.txt error_*type*_*.fig error_*type*_*.png	Report of errors in pulse packages and single pulse in specific file
Selected *para*_*.mat files	histo_*.mat histo_*parameter*_*.png ratioBy*parameter*_*.png	Value distribution of parameters and monitoring of ratio main phase / reversal phase
Mandatory *para*_*.mat files	APFColormap_*.mat PAFColormap_*.mat FAPColormap_*.mat *parameter*ErrorVS*parameter*_*.mat *parameter*ErrorVS*parameter*_*.png colormap_*parameter*_error_tendency_*.fig colormap_*parameter*_error_tendency_*.png colormap_*parameter*_error_percentage_*.fig colormap_*parameter*_error_percentage_*.png	Monitoring of error dependence on parameter magnitude and other parameters; correction matrices

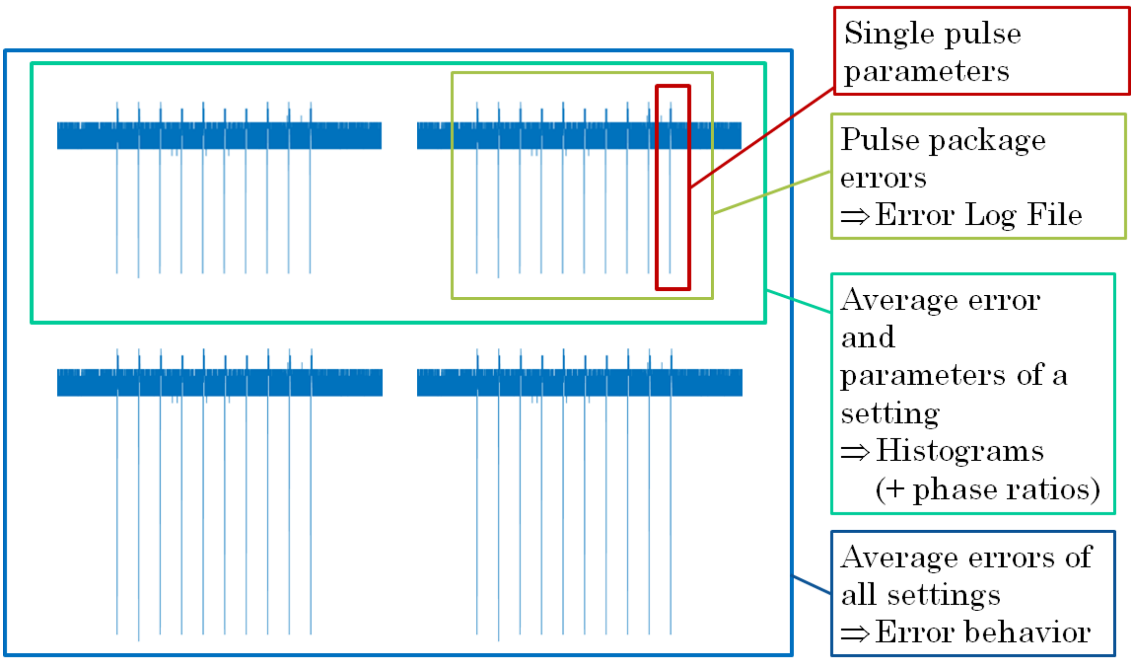

Figure 19: Illustration of file processing. Single pulses are checked for errors, parameters of all files of a setting are used to create histograms and the average error of all files matching the mandatory range are used to determine the error dependencies.

9.1 Parameter Determination

This test considers individual pulses with high time resolution. For each pulse in each 1 second long measurement, the parameters main phase amplitude and main phase pulse width are examined. Depending on the amplitude value the reversal phase parameters and finally the interphase delay are also tested. Additionally, the frequency is calculated for the whole pulse package.

9.1.1 Main Phase Amplitude, Pulse Width and Frequency

The main phase amplitude, its pulse width and the frequency are always determined due to the main phase being easily distinguishable from background noise.

In order to identify the main phase the user has to set approximate amplitude thresholds separating noise from phase. Since the reversal phase is most often at noise level it is most effective to choose the reversal phase threshold 5 μA which corresponds to being just above one unit of oscilloscope accuracy which is given by 4 μA. By means of this, thresholding is performed to identify the start and the end of a main phase. Naturally, the pulse width corresponds to the time between those points and, similarly, the amplitude to the mean value of this interval. This is determined for each pulse separately and each phase is counted for further calculations.

Due to the noise filtering not always being able to smooth the data 100 percent, an additional noise check is implemented: when identifying the phases, small peaks consisting of only one or two data points are classified as noise and therefore not factored into the phase calculations.

The frequency, in contrast to the other parameters, is calculated for the whole pulse package as the number of pulses per time between the start of the first pulse and that of the last pulse in the package, given that the pulse package contains at least two pulses. Measurements with 1 or 2 Hz are not checked for frequency. However, these frequencies are not that important for the intended application of the neurostimulator and can therefore be neglected.

9.1.2 Reversal Phase Amplitude, Pulse Width and Interphase Delay

In case of the stimulation amplitude being higher than a by the user defined ”Threshold 1”, for instance 95 μA , the reversal phase is considered, too. Moreover, a second amplitude ”Threshold 2”, for instance 165 μA, is used to the method of testing the reversal phase (both thresholds concern the main phase amplitude instead of the reversal one). This means, if the reversal amplitude is higher than ”Threshold 2” each pulse is examined individually like the main phases. As before, the pulse length is defined as the time between exceeding the reversal phase threshold and falling below it. Then, the amplitude is given by the mean of those data points. Furthermore, the interphase delay is retrieved as the distance between end of main phase and beginning of reversal phase.When using this analysis method both main and reversal phases are counted.

As before, small peaks shorter or equal to two data points are assumed to be noise and not counted as reversal phases. In addition to that, peaks less than a defined cluster size are also classified as noise as long as their mean value is less than four times the oscilloscope accuracy. This condition originates from experimental observations where similar noise peaks occurred.

If the main phase amplitude is between ”Threshold 1” and ”Threshold 2”, the reversal phase amplitude is estimated by classifying all data points greater than zero as part of a reversal phase and then dividing by the number of those data points. Thus, an average reversal phase amplitude is calculated as the mean of all values greater than zero. The reversal phase length is not determined because of the noise filter being prone to erode parts of the reversal phase due to its very small magnitude. This method does not allow for the determination of the inter phase delay and reversal phase length but nonetheless gives information on all other parameters.

Due to the future possibility of different sampling probes or recording devices being used, all thresholds are adaptable by the user in order to be adjustable to different noise backgrounds, meaning, that lower noise levels would allow for the reversal phases to be tested individually at smaller amplitudes.

9.1.3 Number of Phases

Despite being determined as described in the previous paragraphs, the number of phases is not compared with the expected number of phases. This is because of the recording method corresponding to capturing the displayed data of the oscilloscope which may lead to fewer pulses being recorded than outputted by the neurostimulator.

9.2 Error Analysis

For each individual pulse the determined parameters are compared to the expectation value and classified as an error if the difference exceeds the allowed error selected by the user. In case of the error being even 2.5 times or larger than the allowed error it will be classified as a large error. Additionally, the analysis tests for stray peaks within and outside of phases.

The basic error documentation is divided in a summarized part and complete part. The summarized part highlights only the large errors in a specified log file and figures depicting the whole pulse package plus a zoom on the error region. The other part is a complete documentation of all errors sorted by file name yielding a possibly lengthy text file.

9.3 Parameter Value distribution (histogram data)

For selected parameters all settings including at least one of these parameters are used to create histograms yielding a mean value and standard deviation for all files corresponding to this parameter setting. That is, a mean and standard deviation are calculated from the data of multiple files.

These histograms also serve the purpose to evaluate the noise filtering and classification since single values strongly deviating from the mean may correspond either to a filtering or a stimulation error. In addition to the value distributions the ratio of main phase amplitude divided by the reversal amplitude, respectively the ratio of the reversal pulse width and the main pulse width are monitored depending on main phase amplitude value. These values are obtained by using the mean values from the histograms and by error propagation of their standard deviations.

9.4 Error Behavior Analysis (color map data)

One important issue is to monitor the average parameter error and its sign versus the specific parameter. Therefore data matrices (so called color map files) are employed storing the average error and the error percentage for all parameter combinations in chosen ranges. This information is then used to discover dependencies of the average error on the parameter magnitude itself and on the other parameters. Calculating the average error rather than the standard deviation directly provides the tendency of the error meaning whether the neurostimulator tends to output too low or too high amplitudes. That is, if the error is purely statistical, the average error would be zero.

The error dependence on the specific parameter is depicted in two dimensional plots whereas the error dependence on other parameters are saved in three dimensional figures as to better depict the tendencies that would be difficult to discern in multiple two-dimensional plots. Both histograms and color maps provide information on how much the neurostimulator output would require to be corrected to yield the targeted parameter value.

10 Example: Parameter Test Results

10.1 NS1 Results

To demonstrate the functionality of the parameter analysis real results of NS1 are shown in the following. The employed settings for this analysis are listed in table 6.

Recordings with amplitudes lower than 40 μA were not used due to the possibility of the pulses being overshadowed by noise. Example pictures of stimulation amplitude 10 to 30 μA can be found in the appendix on page 66.

Table 6: Settings for Parameter Test Result Example 1

Mandatory Amplitude	50:10:200 μA
Mandatory Pulse Width	100:50:300 μs
Mandatory Frequency	1:1:30 Hz
Only Main Parameters	< 95 μA
Almost All Parameters	95 - 165 μA
All Parameters	> 165 μA
Allowed Error Amplitude	$\pm$ 10 μA
Allowed Error Rev. Amplitude	$\pm$ 5 μA
Allowed Error Pulse Width	$\pm$ 5 μs
Allowed Error Rev. Pulse Width	$\pm$ 10 μs
Allowed Error Frequency	$\pm$ 1 Hz
Allowed Error Delay	$\pm$ 10 μs
Hole Size	8 μs
Cluster Size	10 μs
Phase Peak Height	20 μA

10.2 Error Analysis

The parameter test of NS1 concluded that every stimulated pulse is smaller than the expectation resulting in a long error log file. Therefore, only the large error results of the mandatory range will be discussed in completion here. Some result figures of the non-mandatory amplitude range will also be employed to gain understanding of the stimulation behavior of NS1. For the complete error log file and figure set please refer to the appendix.

10.2.1 Mandatory Range

According to the analysis results, 13 large errors were found in the mandatory range. All errors correspond to a parameter being smaller than expected. In particular, one case of too small pulse width, one case of too small inter phase delay and the rest corresponding to too short reversal phases. None of the large errors are amplitude errors and all phase length errors are below 50 μs. Figures 20 to 22 show the the three types of error in detail as they are provided by the program. The remaining figures of reversal pulse width errors can be viewed in the appendix.

Parameter Test: Large Errors Log File (NS1)

```
Begin of parameter measurement analysis: 14-Nov-2016 18:10:20

120_250_17_10_0_1.mat
wrong main phase pulse width [us]: [250;250;250;250;250;250;250;218;250;250]

170_150_29_10_0_1.mat
wrong reversal phase pulse width [us]: [1496;1498;1497;1465;1498;1495;1496;1498;1497]

170_200_6_5_0_3.mat
wrong reversal phase pulse width [us]: [1964;1997;1998;1996;2000]

170_300_20_10_0_2.mat
wrong reversal phase pulse width [us]: [3000;3000;2968;3000;3001;3001;2999;2999;2998]

180_200_27_10_0_1.mat
wrong reversal phase pulse width [us]: [1998;1998;2000;1997;1999;2000;1997;1997;1966;1998]

180_200_7_5_0_4.mat
wrong reversal phase pulse width [us]: [2001;1968;1999;2000;1999]

190_150_18_10_0_1.mat
wrong reversal phase pulse width [us]: [1499;1500;1497;1499;1497;1498;1500;1498;1466;1499]

190_250_5_2_0_10.mat
wrong interphase delay [us]: [29;55]

190_300_16_10_0_2.mat
wrong reversal phase pulse width [us]: [3004;3002;3001;3000;3004;2969;3000;3001;3000]

200_150_9_5_0_2.mat
wrong reversal phase pulse width [us]: [1466;1498;1496;1498;1497]

200_250_6_5_0_1.mat
wrong reversal phase pulse width [us]: [2467;2498;2498;2500;2502]

200_300_29_10_0_2.mat
wrong reversal phase pulse width [us]: [3004;3001;3003;3001;3003;3002;3002;3001;2970;3002]

200_300_9_5_0_2.mat
wrong reversal phase pulse width [us]: [2969;3001;3000;3000;2999]

End of parameter test: 14-Nov-2016 19:27:10

10400 pulse packages tested, 13 large error(s) found.
```

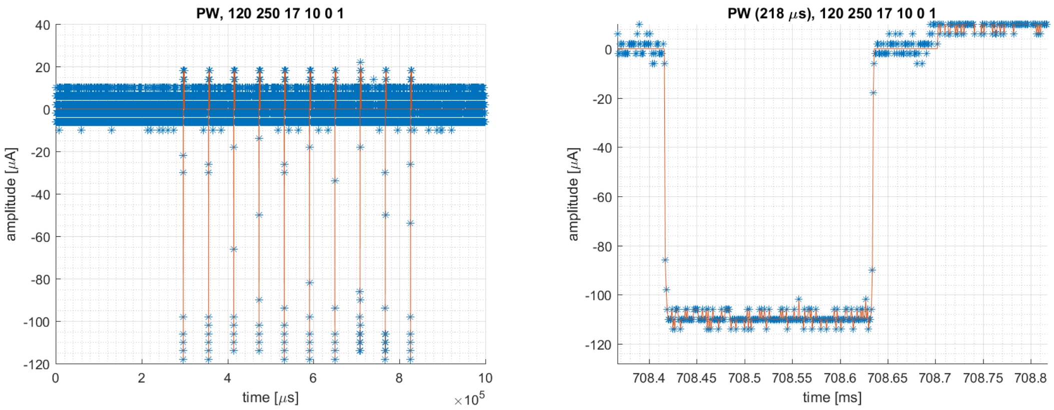

Figure 20: Pulse package and individual pulse with too short pulse width.

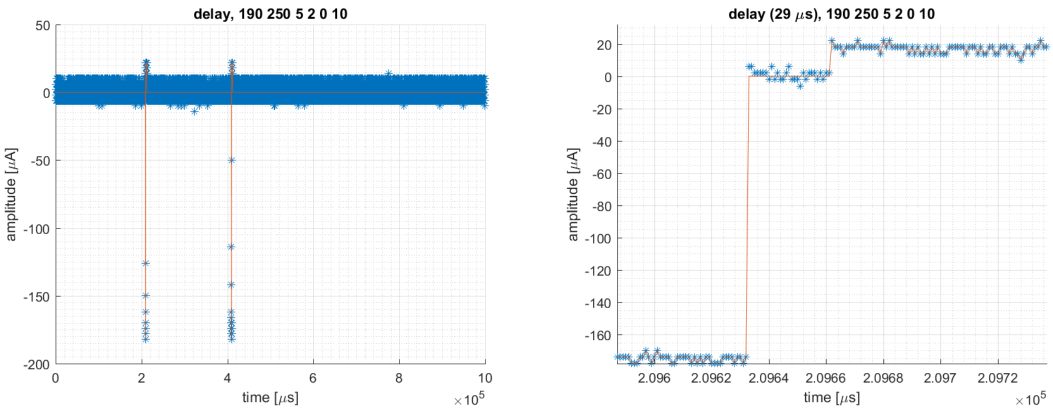

Figure 21: Pulse package and individual pulse with too short interphase delay.

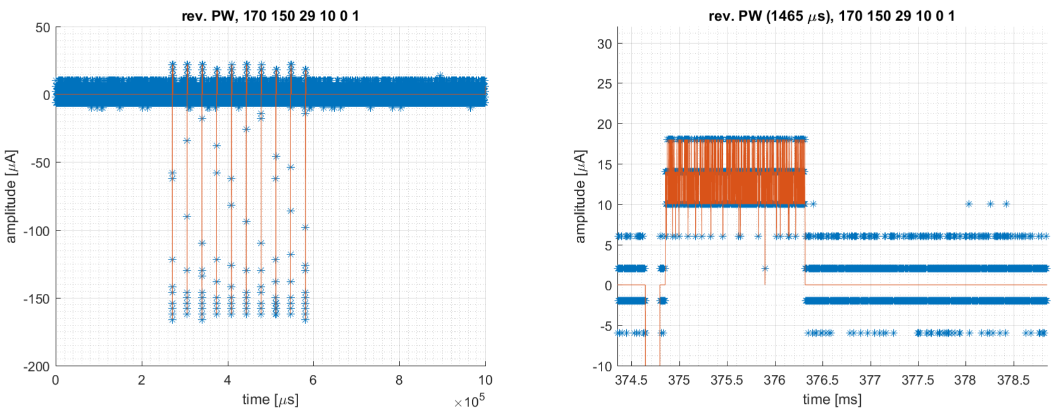

Figure 22: Pulse package and individual pulse with too short reversal pulse width.

10.2.2 Non-Mandatory Range

The NS1 measurements outside the mandatory range exhibit additional stimulation errors. Mainly, the amplitude deviation from expectation value increases causing the analysis program to report them as large errors starting at main phase 220 μA. This behaviour is exemplified in Figure 23. However, it appears that in this special case the average amplitude is mostly diminished by the short pulse width and the slope values below the target amplitude. Nevertheless, the maximum amplitude of the discussed phase is still below expectation. A behavior that will become more grave the higher the amplitude is. Figure 24 shows the extreme case of 500 μA with a discrepancy of 75 μA between expected and recorded amplitude. Additional figures documenting this tendency of lower amplitudes above the mandatory range can be found in the appendix.

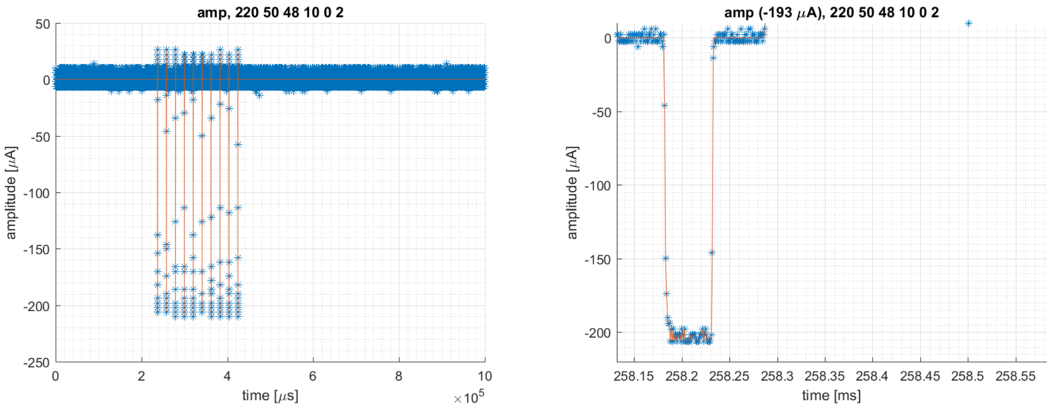

Figure 23: Pulse package and individual pulse with too low amplitude.

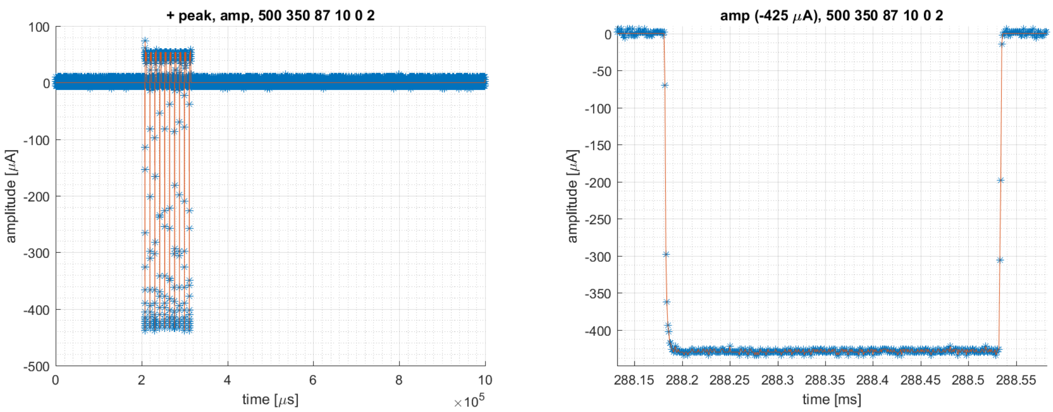

Figure 24: Pulse package and individual pulse with too low amplitude.

Another exhibited error is the occurrence of stray peaks within the main phases as shown in the example Figures 25 to 26. As before, this behavior is exclusive to high amplitudes. Negative peaks occur in the range 320 to 500 μA and positive phase peaks are detected between 430 to 500 μA. The positive peaks appear to be identified as such since the amplitude average is lowered by the phase rising remarkably slowly to its average amplitude. In contrast to that, the positive peaks clearly surpass the expectation value and appear to be a stimulation flaw of the neurostimulator rather than harmless oscillation. Furthermore, whereas the negative peaks mostly appear in the middle of the negative phase, the positive peaks exclusively appear at the beginning of the reversal phase. In total, about 60 pulse packages consisting of 1 to 10 pulses contained one of these peak extrema. Although the peaks seem limited to high amplitudes, one has to note the relatively high condition of 20 μA peak height, that is, a peak is registered as such when the difference to the average phase amplitude is 20 μA or more. It is therefore possible that the peaking behaviour starts to occur at lower amplitudes but is not detected due to the small peak size. Additional supplementing figures are printed in the appendix.

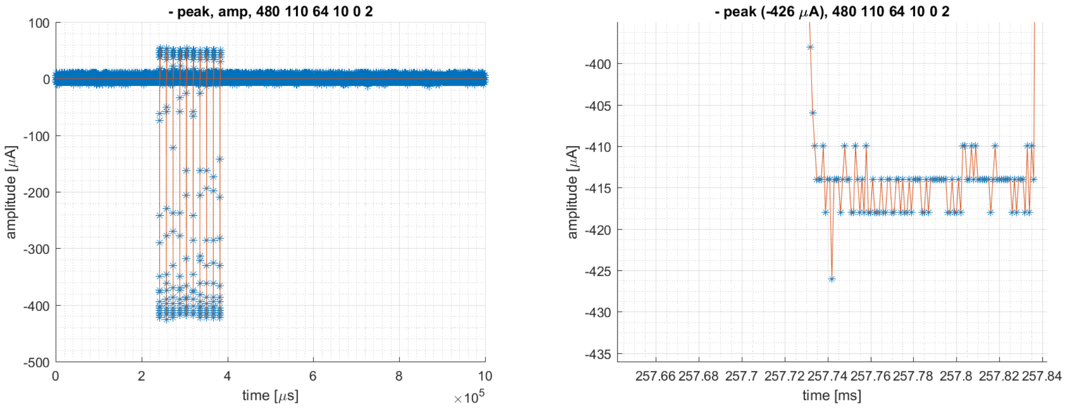

Figure 25: Pulse package and individual pulse with negative phase peak.

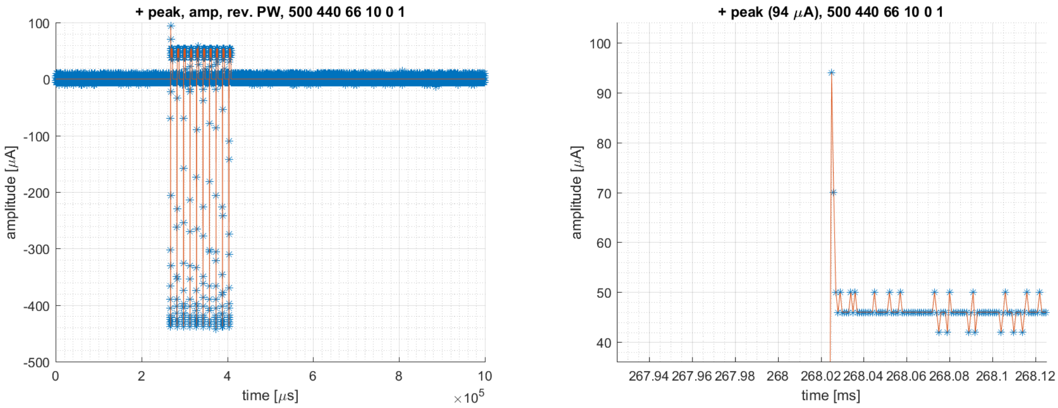

Figure 26: Pulse package and individual pulse with positive phase peak.

The final detected error behavior is that the NS1 does not output pulse widths below 50 μs. Instead, the last stimulated pulse width is outputted again as depicted in the example Figure 27. Additional figures can again be viewed in the appendix. This cut at 50 μs is in disagreement with the product description by the manufacturer which states 0 μs as the lowest forbidden pulse width.

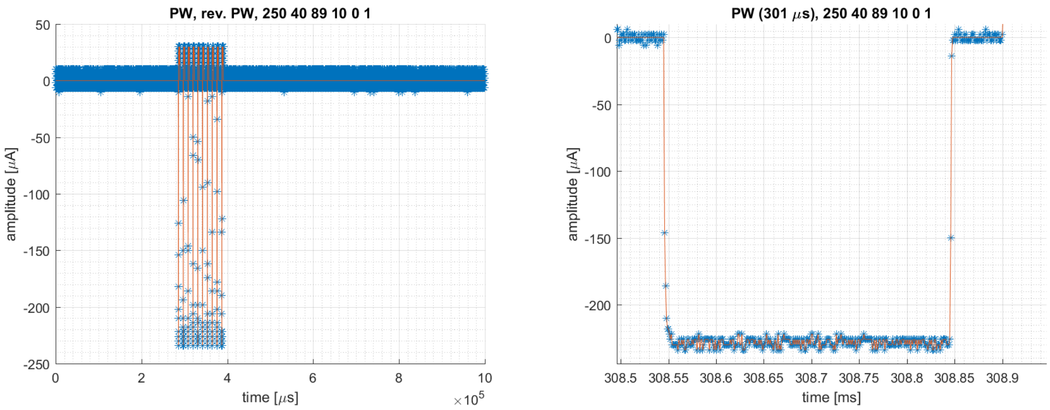

Figure 27: Pulse package and individual pulse with false pulse width.

10.3 Parameter Value Distribution (histogram data)

By means of the created histograms one can gain insight on the value distribution of a parameter, that is, how consistently the neurostimulator outputs the same parameter setting.

Since, depending on the main phase amplitude (respectively "Threshold 1" and "Threshold 2"), different parameters are determined, different histograms are created for a parameter setting. Below "Threshold 1", for example, the setting 50 μA, 100 μs, 30 Hz (see Figure 28), only the main phase amplitude and pulse width data is collected. Between "Threshold 1" and "Threshold 2", for example, the setting 120 μA, 250 μs and 15 Hz (see Figure 29) information on main phase amplitude, pulse width and reversal phase amplitude values are stored. Finally, for high amplitude settings (above "Threshold 2") like 200 μA, 150 μs and 30 Hz (see Figure 30) histograms for the main phase amplitude, main phase width, reversal phase amplitude, reversal phase width and interphase delay are created.

It appears that the NS stimulates pulses that are consistent for a given parameter setting. This observation is supported by the small standard deviations.

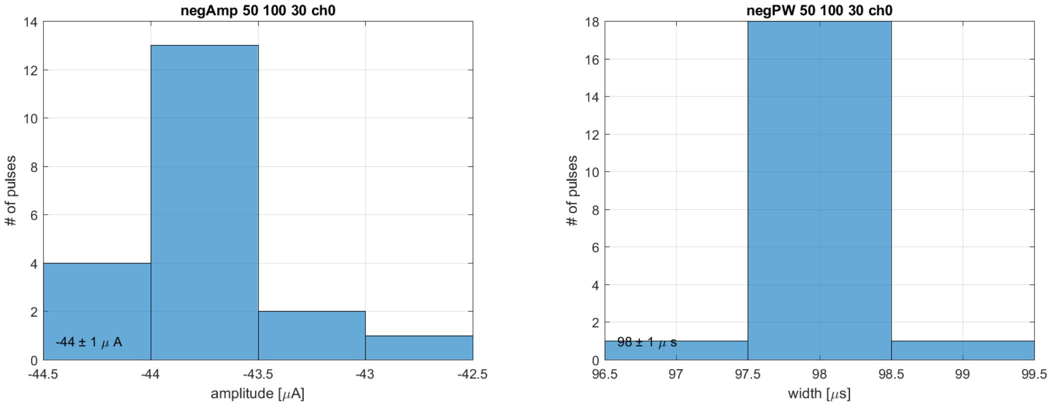

Figure 28: Main phase amplitude and phase width of a low amplitude setting.

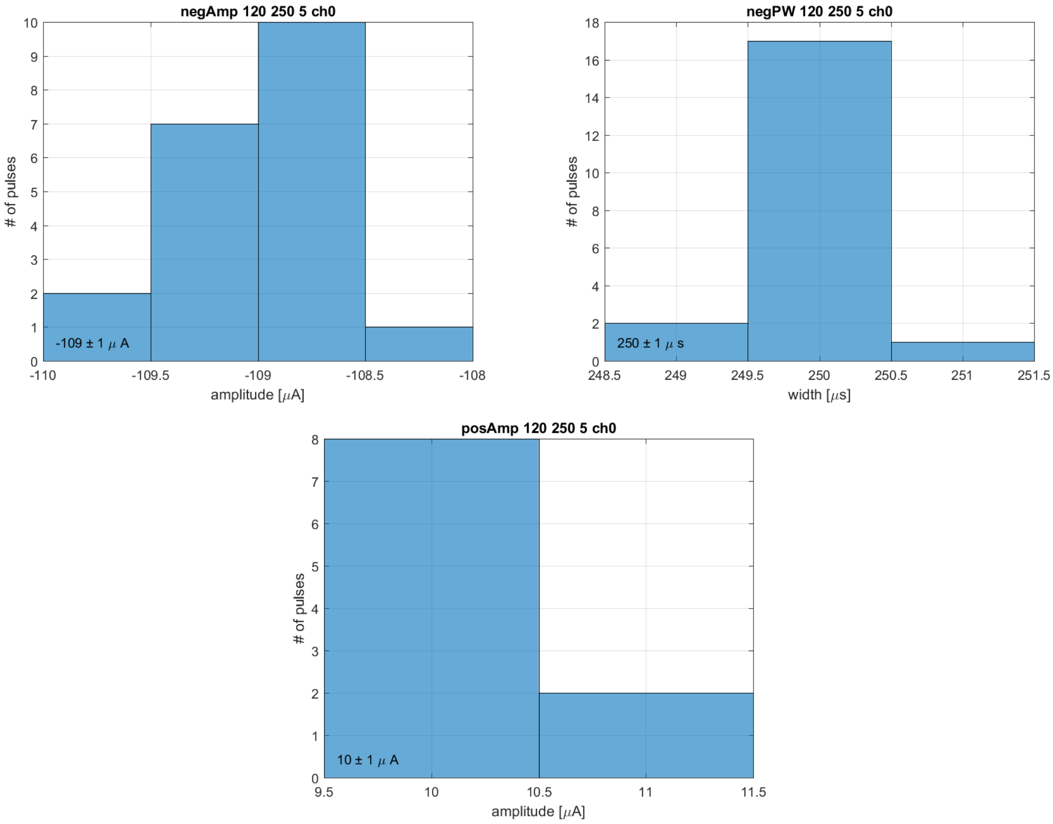

Figure 29: Main phase amplitude, phase width and reversal amplitude of a median amplitude setting.

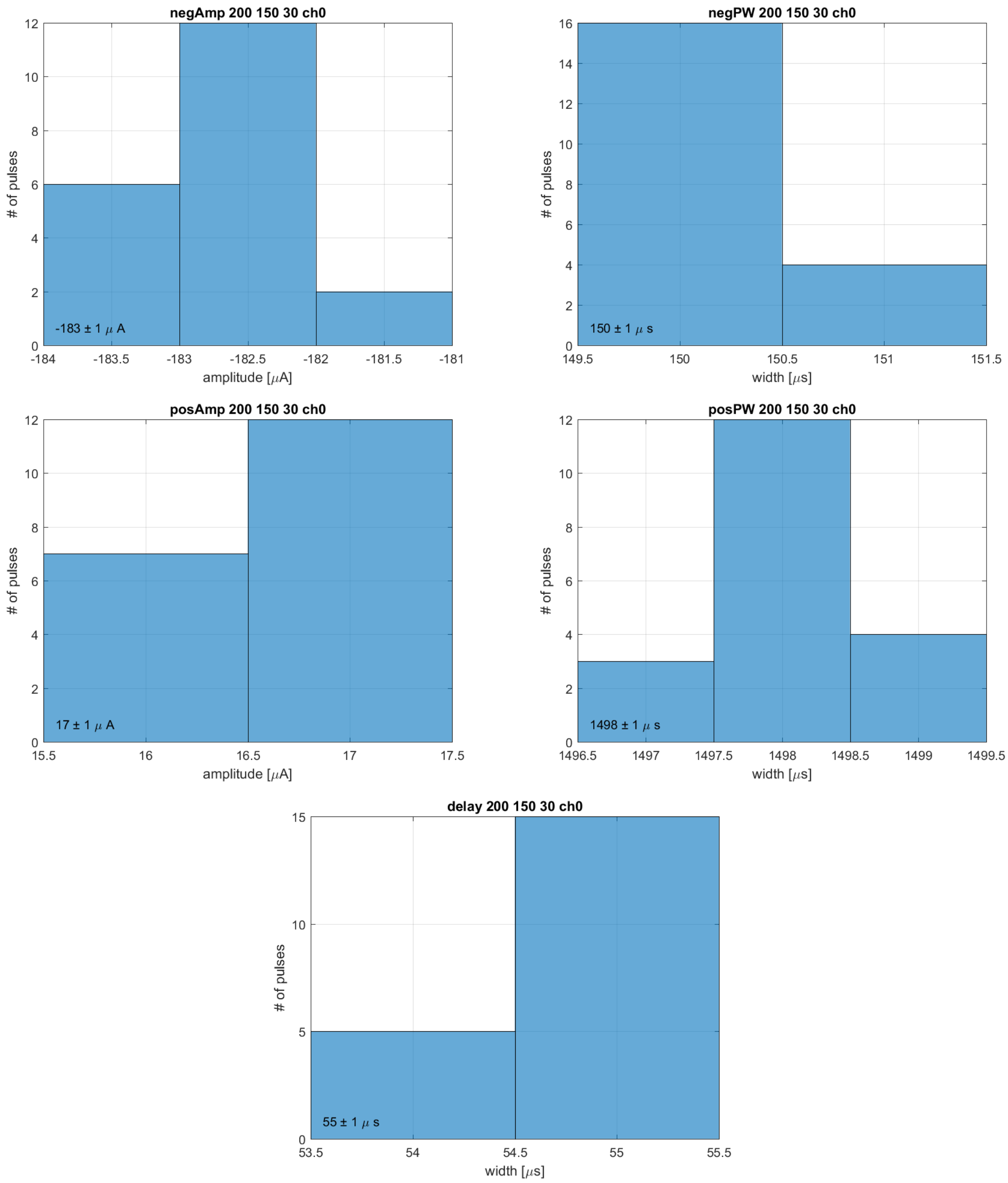

Figure 30: Main phase amplitude, phase width, reversal amplitude, reversal phase width and interphase delay of a high amplitude setting.

10.4 Phase Parameter Ratios (histogram data)

Another interesting variable is the ratio of main and reversal phase because they convey information about the net charge of the stimulus. If the quotients main phase amplitude divided by reversal phase amplitude and reversal phase pulse width divided by main phase pulse width of the histogram means and standard deviations are calculated one obtains the graphs shown in Figures 31 to 33. The amplitude ratio oscillates significantly more than the pulse width ratio meaning that the neurostimulator controls the latter more successfully. It is apparent that neither the stimulated pulse width nor the frequency have a noticeable impact on those ratios. On the other hand, the ratios sorted by amplitude seem to slightly approach the ideal value 10 for increasing amplitude.

The most probable explanation would be that the small reversal phases cannot be detected successfully due their closeness to the noise level. Again, it is also possible that the neurostimulator cannot output the small reversal phases correctly. The amplitude ratio most likely also suffers from the oscilloscope accuracy of 4 μ A. Said accuracy combined with the offset correction may be an explanation for the ratio being 10 at 190 μA and worse again for 200 μ A.

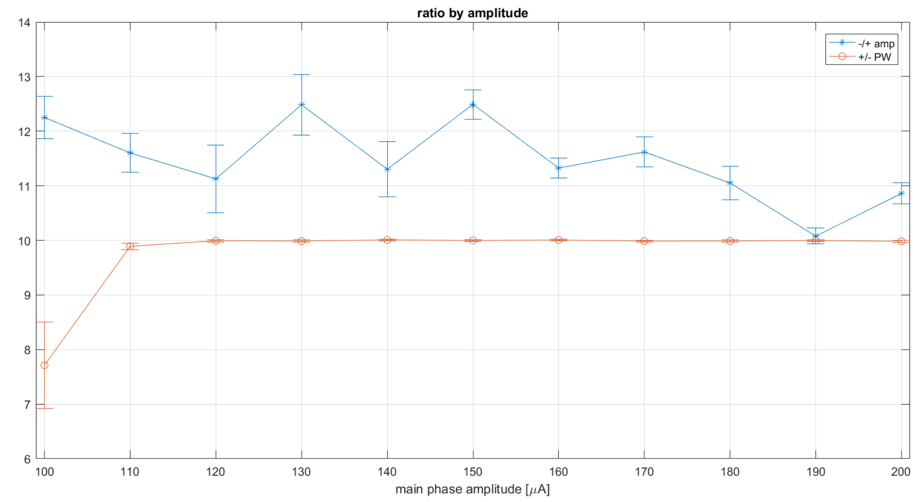

Figure 31: Ratio of amplitudes and pulse widths sorted by amplitude (PW = 250 μs, f = 30 Hz).

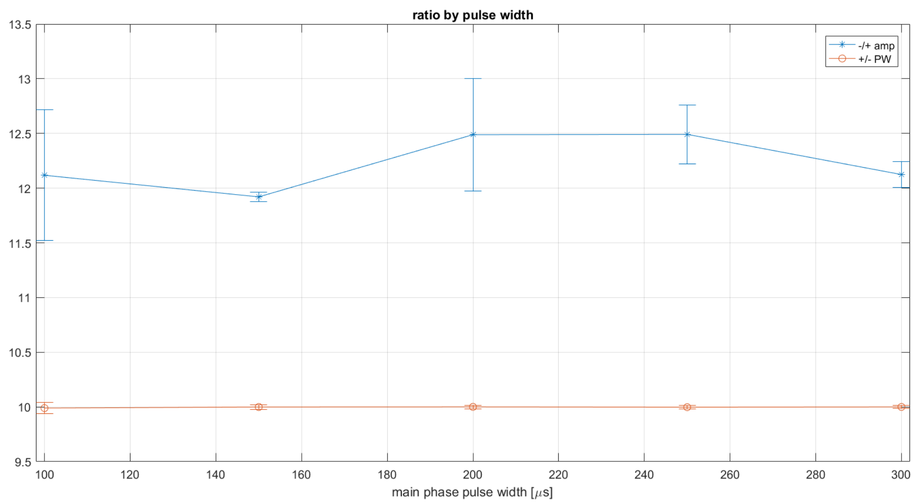

Figure 32: Ratio of amplitudes and pulse widths sorted by pulse width (A = 150 μA, f = 30 Hz).

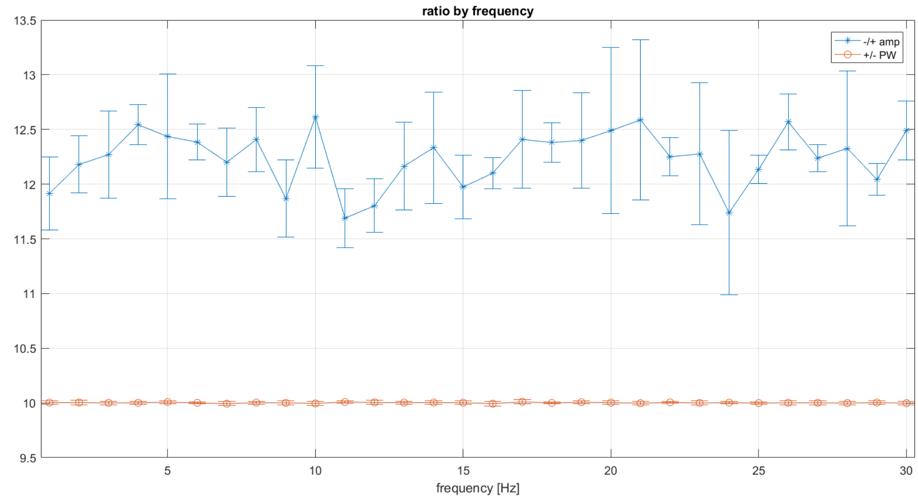

Figure 33: Ratio of amplitudes and pulse widths sorted by frequency (A = 150 μA, PW = 250 μs).

10.5 Error Behavior Analysis (histogram data and color map data)

10.5.1 Error Dependence on Parameter Magnitude

When considering the influence of a parameters magnitude on its error, one can find an approximately linear increase with increasing magnitude. This is the case for all three considered parameters, main phase amplitude, main phase pulse width and frequency (see Figures 34 to 36).

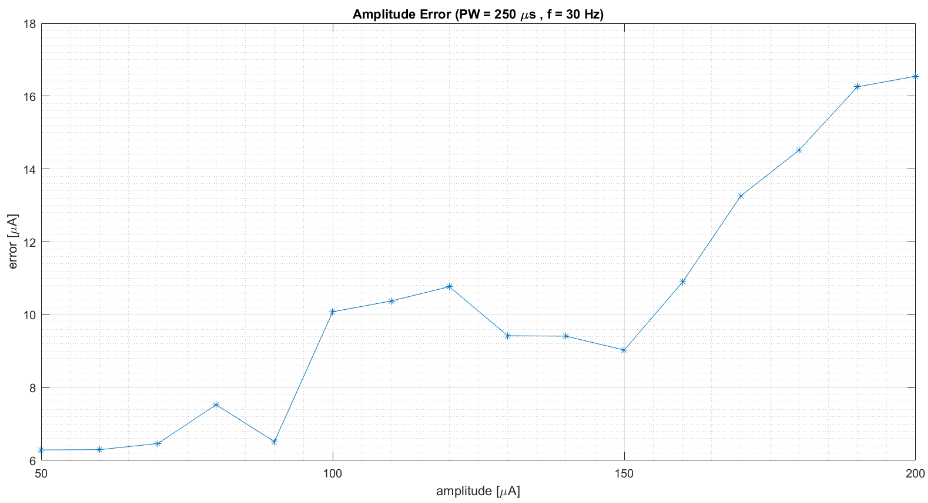

Figure 34: Amplitude error dependence on amplitude at constant pulse width and frequency.

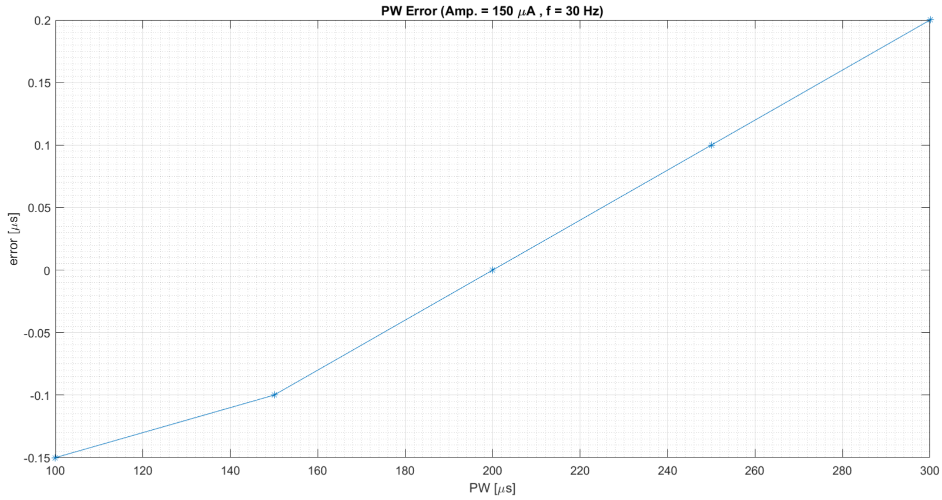

Figure 35: Pulse width error dependence on pulse width at constant amplitude and frequency.

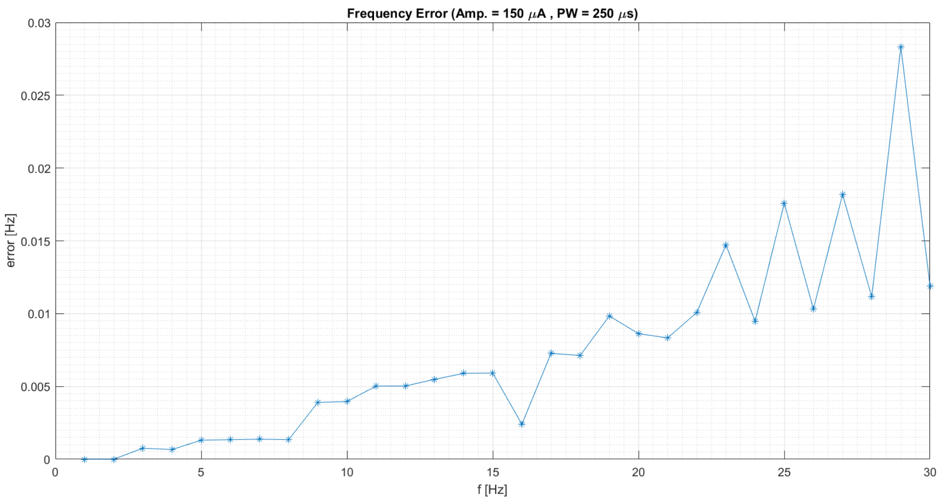

Figure 36: Frequency error dependence on frequency at constant amplitude and pulse width.

10.5.2 Error Dependence on Other Parameters

To test whether the error does not only depends on the respective parameter value but also on the other parameters, three-dimensional color map plots are employed. Additionally, two-dimensional plots provide information on how many pulses were stimulated incorrectly (within the allowed error). Figures 37 to 43 show an excerpt of the color maps created for every value combination of the mandatory ranges.

Amplitude

The first Figures 37 to 39 demonstrate the dependence of main phase amplitude error on pulse width and frequency. At low amplitude (example: 50 μA) no error exceeds the allowed value which is 10 μA. The error tendency plot reveals that on average every pulse is incorrect nonetheless. One can see the error decreases slightly for larger pulse width. This behavior could stem from a larger pulse width contributing more values for the average. Especially, the values corresponding to the rising or falling slope have a greater weight if the pulse width is small. This, however, classifies nonetheless as a stimulation error because the pulse shape differs from a (perfect) square pulse.

Larger amplitudes correspond to an increasing number of pulses that exceed the allowed error. Remarkably, this implies that the neurostimulator NS1 has the tendency to output all pulses incorrectly small which becomes more apparent the larger the amplitude is. This observation agrees with the those made when considering error dependence on parameter magnitude itself. But, here, one can also recognize a dependence on pulse width. The frequency does not appear to influence the amplitude error.

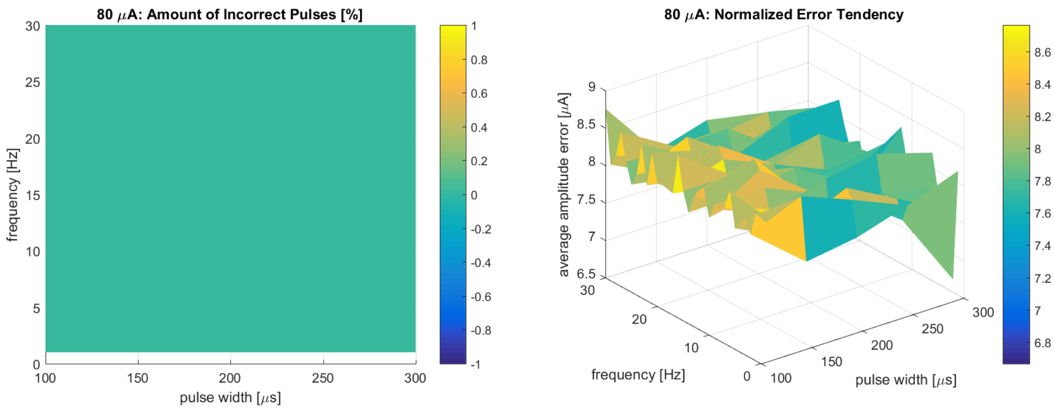

Figure 37: Error dependence of A = 80 μA on pulse width and frequency.

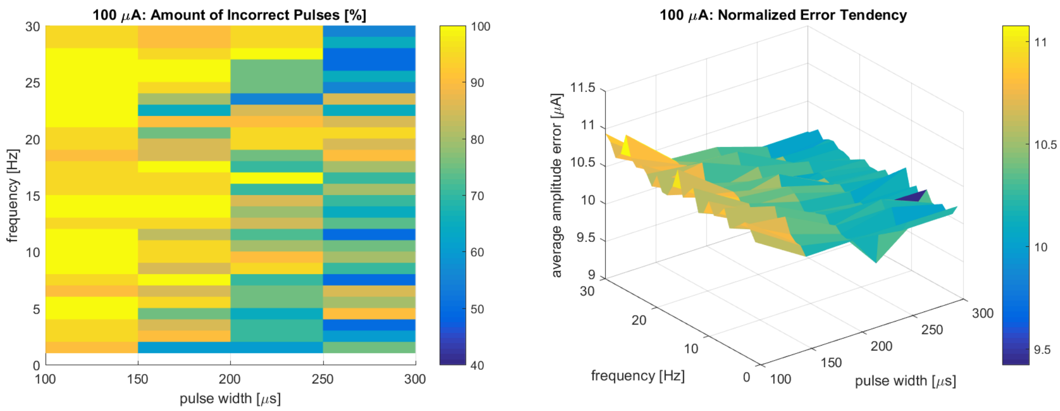

Figure 38: Error dependence of A = 100 μA on pulse width and frequency.

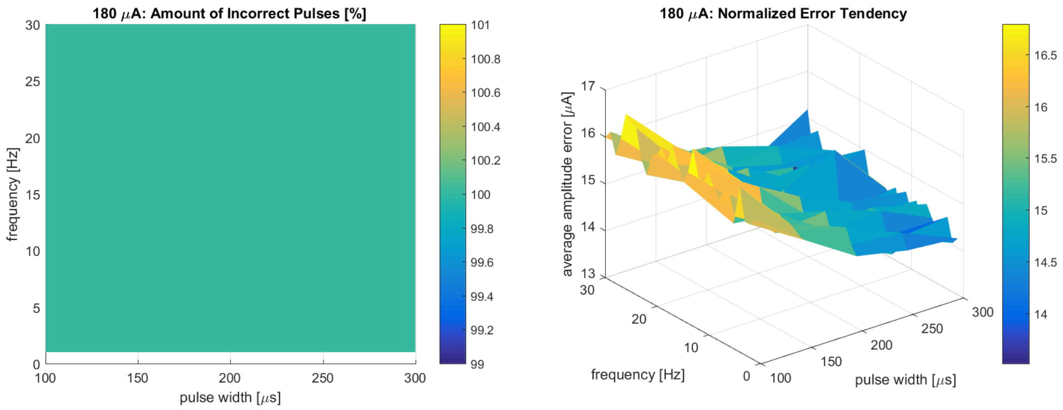

Figure 39: Error dependence of A = 180 μA on pulse width and frequency.

Pulse Width

In contrast to the amplitude, the pulse width is outputted very precisely by the neurostimulator since the maximum detected deviation from the expected value (in the mandatory settings range) is around 2 μs. While frequency does not seem to influence pulse width, a clear tendency is visible concerning the dependency on amplitude: the larger the amplitude the larger the detected pulse width. It most likely that this behavior is caused by the noise filter being more prone to falsely erode a phase at noise level than an easily discernible phase. Nevertheless, the errors stemming from noise filtering are confirmed to be small by these results.

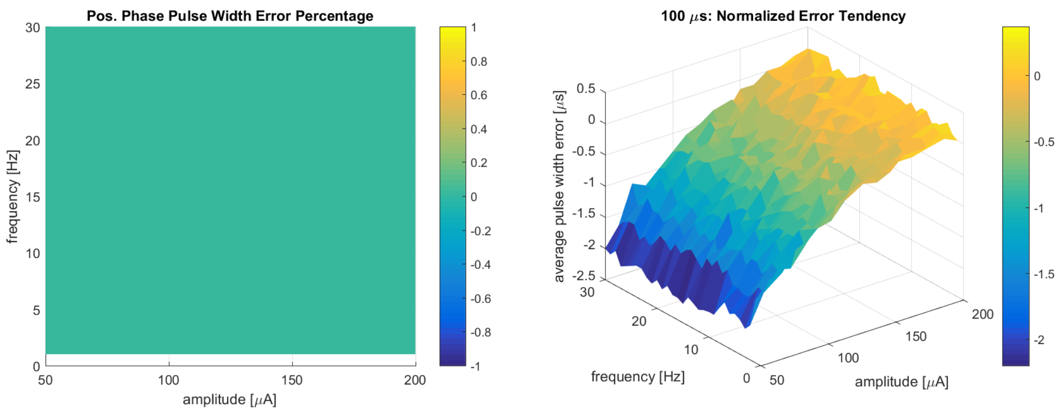

Figure 40: Error dependence of PW = 100 μs on amplitude and frequency.

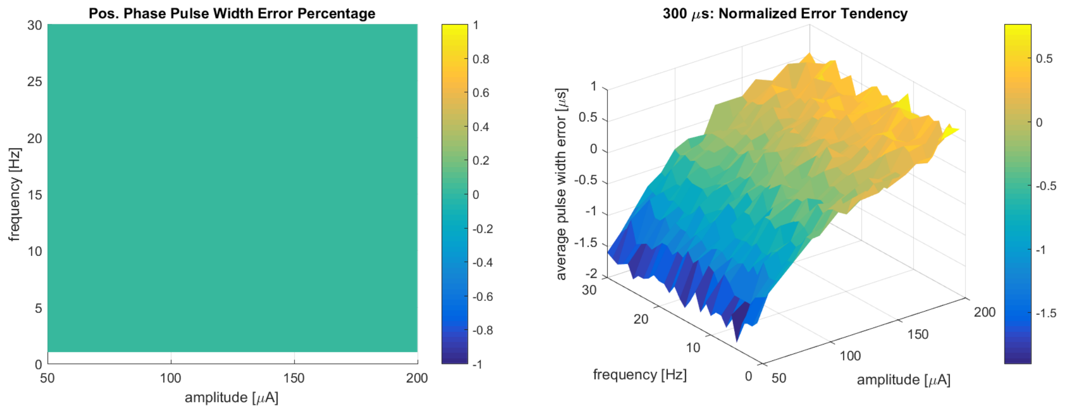

Figure 41: Error dependence of PW = 300 μs on amplitude and frequency.

Frequency

The frequency Plots 42 to 43 indicate that no obvious dependence on other parameters exist. Moreover, the frequency error is of the magnitude 10^{-4} and thus notably below the allowed error 1 Hz. Accordingly, no frequency errors were reported.

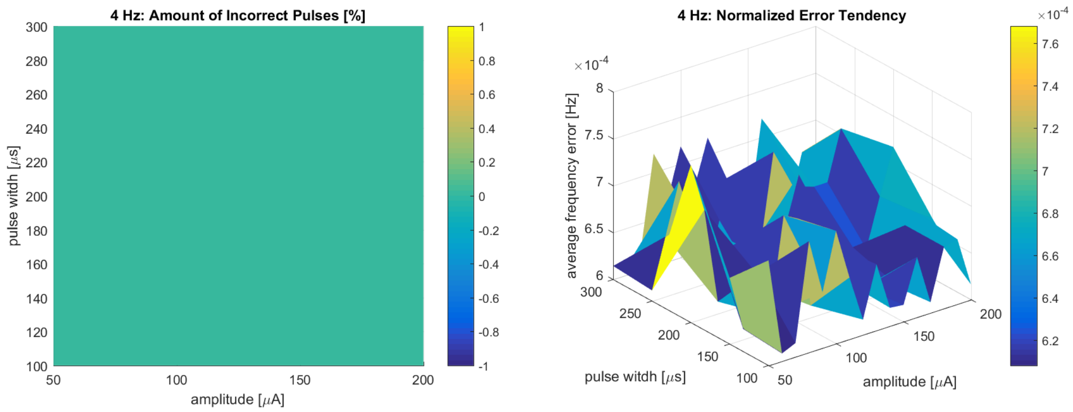

Figure 42: Error dependence of f = 4 Hz on amplitude and pulse width.

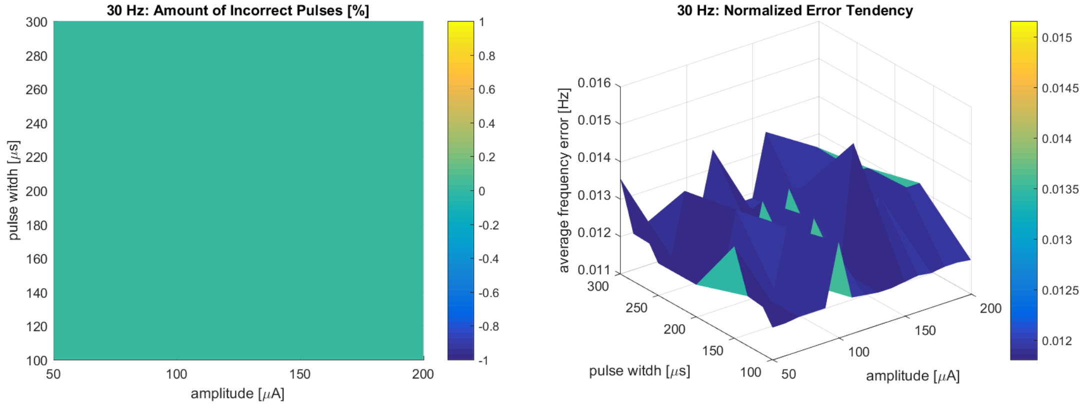

Figure 43: Error dependence of f = 30 Hz on amplitude and pulse width.

10.6 Conclusion: Parameter Test Results

Due to the allowed error magnitude being adjustable, the parameter test strictness is mainly defined by the user. With allowed error values defined as in the previous section, the NS1 produced only about 0.026% false pulses in the mandatory range intended for patient use whereas outside of the mandatory range approximately 11% of the pulses were incorrect. While the high amount of stimulation flaws in the non-mandatory range indicates technical flaws in the neurostimulator, they can be deemed irrelevant because these parameter magnitudes are inherently not to be used due to the health risk they pose.

In general, the NS1 exhibits the behavior to output a parameter the more incorrectly the larger its magnitude is which is especially true for high amplitudes.

For a compact and detailed overview of the results of all tests, including individual parameter behavior and dependencies, see Section 15.

11 Long Time Test

Table 7: Overview Long Time Test

Input	Output	Purpose
All long_*.mat files	Log_Long_Time_Test_*.txt error_long_*.fig error_long_*.png	Report of stimulation or recording errors in specific file
	longtimeResults_*.mat LongTime*parameter*.fig LongTime*parameter*.png	Time development of parameters

11.1 Parameter Determination

Whereas the parameter test examines single pulses at highest possible accuracy, this test focuses on testing if the neurostimulator is able to output the same parameter setting reliably over a time. Despite the real patient use corresponding to manifold parameter settings, only one parameter setting is chosen to better monitor the possible changes.

A significant difference to the parameter test is the mix of differently long pulse packages in one measurement sample. This mix was implemented to not only test the phases but additionally the reliability to output a certain number of pulses. Because of this a slightly different approach is used to determine the parameters of a sample.

After the data is calibrated and smoothed as described above, the phase parameters are calculated. Per sample the average main phase amplitude, average main phase pulse width, average reversal amplitude, average frequency determines as well as the number of cathodic, respectively anodic, phases are identified. To simplify the analysis, the interphase delay is considered to be of less importance and is therefore neglected.

11.1.1 Number of Phases and Frequency

First, the number of cathodic and anodic phases as well as the frequency are determined. To accomplish this, thresholds (called positive and negative noise level in the GUI) are used to identify the start of a pulse. Then, the elapsed time to the start of the next pulse is used to establish the frequency between those two pulses which in total will be used to calculate an average frequency for the whole 10 sec sample. As to not falsify this value by accidentally considering the time lapsed between two separate pulse packages, the frequency is not calculated if the elapsed time exceeds a threshold of 50000 data points. Furthermore, when distinguishing the small reversal phase from the noise, the thresholding examination is paused an estimated phase length after the reversal phase start was identified. This prevents one phase from being identified as multiple phases without suppressing the detection of possible stray peaks after the reversal phase is finished.

11.1.2 Mean Amplitude and Pulse Width

Again thresholding is used, that is, the smoothed data is divided into positive and negative values. Thus, the amount of values divided by the number of respective phases corresponds to the pulse width while the mean of these values corresponds to the average phase amplitude. Furthermore, the average charge per phase is determined as average amplitude per phase times average phase width. When calculating the pulse width, the data point distance of 10 μs is considered.

11.2 Error Analysis

Despite mostly calculating averages, the long time test is able to check for erroneous stimulation. In particular, stray peaks are distinguished from regular phases by the data either having an unexpected minimum, respectively maximum, or by a total pulse number exceeding 266. In order to classify extrema they are compared to the stimulation amplitude, respectively reversal amplitude. Similar to the parameter test, a figure is outputted should a stray peak occur or the number of detected phases differ from 266.

Additionally to the stored figures, an error log file is created stating the duration of the analysis, the number of tested files, the number of files excluded due to oscilloscope errors, the number of detected phases versus number of expected phases and finally the number of files showing an unexpected peak.

11.3 Time Development Analysis

In contrast to the parameter test, possibly false amplitudes or pulse widths are not registered as an error. Instead, the overall average parameter versus time is considered. The long time test yields figures showing all calculated parameter averages which indicate if a parameter was constantly outputted as the same value or if changes occurred. Accordingly, no non-negligible information on the parameters is lost. In addition to the aforementioned parameters also the sum of the absolute values of both amplitudes is monitored to provide a variable that is not affected by random offset shifts of the data.

12 Example: Long Time Test Results

12.1 NS1 Results

12.1.1 Error Analysis

The following example results stem from the analysis of the negative phase first neurostimulator NS1. In total, 2850 10 second samples were recorded with the differential sampling probe to approximate 8h of run time. The resulting error log file is printed on page 45. It states that the first three files were were unusable due to faulty recording by the oscilloscope and that no stray peaks or unexpected extrema were stimulated.

Most importantly, the log file conveys that in five cases no negative phase was outputted by the neurostimulator. By looking at the supplementing figures outputted in addition to the log file, it becomes apparent that what the program classified as five missing negative phases are in reality three missing phases and two incidents were the stimulated negative phase consists of only one data point. Although the negative phase is not completely omitted in those latter cases it is nonetheless insufficient stimulation. To be precise, one data point means that the phase is at most 10 μs long with the sampling rate being set as such. With the oscilloscope detecting reliably for all prior tests with varying pulse widths and sampling rates, it is reasonable to assume that this is indeed a stimulation error instead of a detection problem.

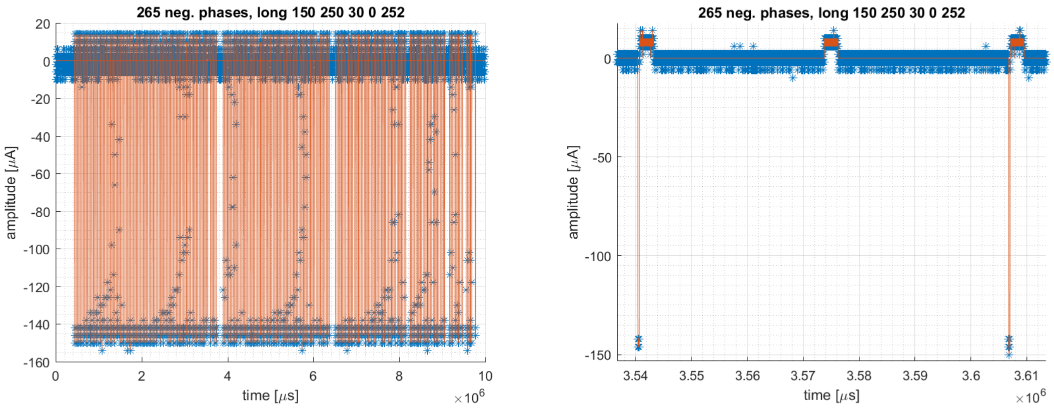

Figure 44: Missing negative phase in first pulse package (100 pulses).

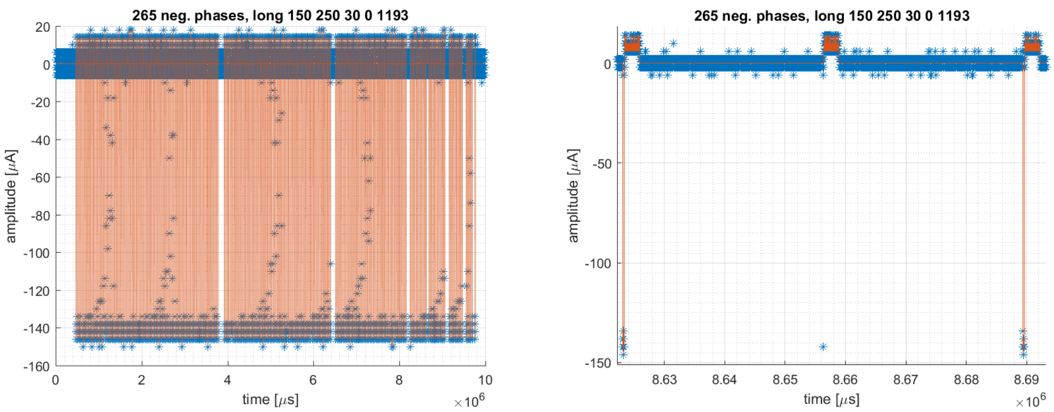

Figure 45: Too short negative phase in fourth pulse package (25 pulses).

Figures 44 illustrates an example of a missing phase. A close look at the left picture reveals a missing negative phase located close to the end of the first pulse package. This area is shown as a zoom in the right picture. Here, one can see three stimulated pulses out of which the middle one consists only of the positive phase whereas the two outer pulses are correctly stimulated as main and reversal phase. Similarly, an example of a too short negative phase (visible as only one data point) is shown in Figure 45.

The remaining faulty negative phase outputs can be viewed in Figures 79 to 81 in the appendix.

Long Time Test: Log File (NS1)

```
Begin of long time measurement analysis: 26-Oct-2016 00:40:41

long_150_250_30_0_1.mat:
Oscilloscope error suspected, file excluded.

long_150_250_30_0_2.mat:
Oscilloscope error suspected, file excluded.

long_150_250_30_0_3.mat:
Oscilloscope error suspected, file excluded.

long_150_250_30_0_252.mat
wrong number of negative phases: 265

long_150_250_30_0_390.mat
wrong number of negative phases: 265

long_150_250_30_0_1193.mat
wrong number of negative phases: 265

long_150_250_30_0_1258.mat
wrong number of negative phases: 265

long_150_250_30_0_1398.mat
wrong number of negative phases: 265

End of long time measurement analysis: 26-Oct-2016 01:01:35

2847 of 2850 files tested, 3 excluded due to oscilloscope errors.
0 of 2847 files exhibit one or more possible error peaks.
757297 negative phases detected, 757302 expected.
757302 positive phases detected, 757302 expected.
```

12.1.2 Time Development Analysis

Besides the previously portrayed stimulation error documentation, the analysis program also monitors the change of parameters over time. The corresponding results are depicted in Figures 46 to 50.

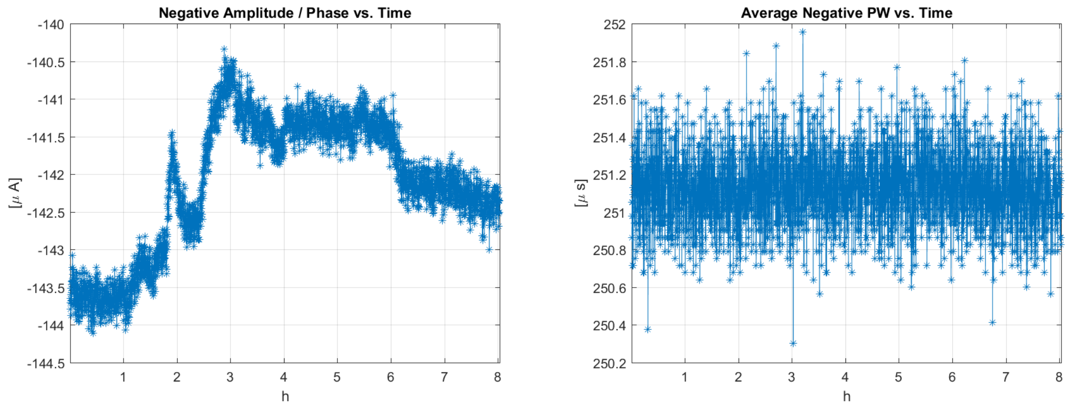

Figure 46: Negative main phase amplitude and pulse width over time.

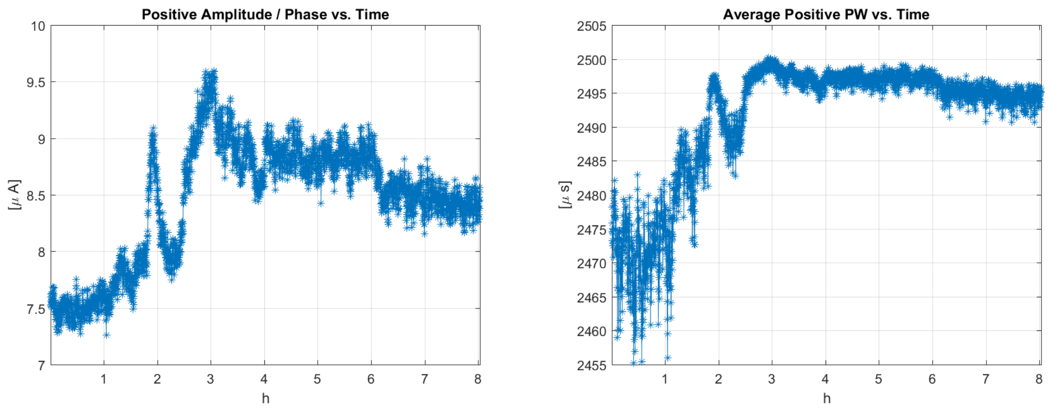

Figure 47: Positive reversal phase amplitude and pulse width over time.

Figure 46 shows a change in the amplitude but an approximately constant pulse width of the main phase. The next figure corresponds to the respective results of the positive reversal phase. In contrast to the easily discernible main phase the small reversal phase has been detected with varying pulse width over time. Possible explanations for this change in pulse width could be false offset correction or change in noise over time. In particular, the amplitude over time figure exhibits the same tendencies as that of the main phase meaning an increase in main phase amplitude occurs simultaneously to an increase in reversal phase amplitude. Changes in the data offset are therefore plausible.

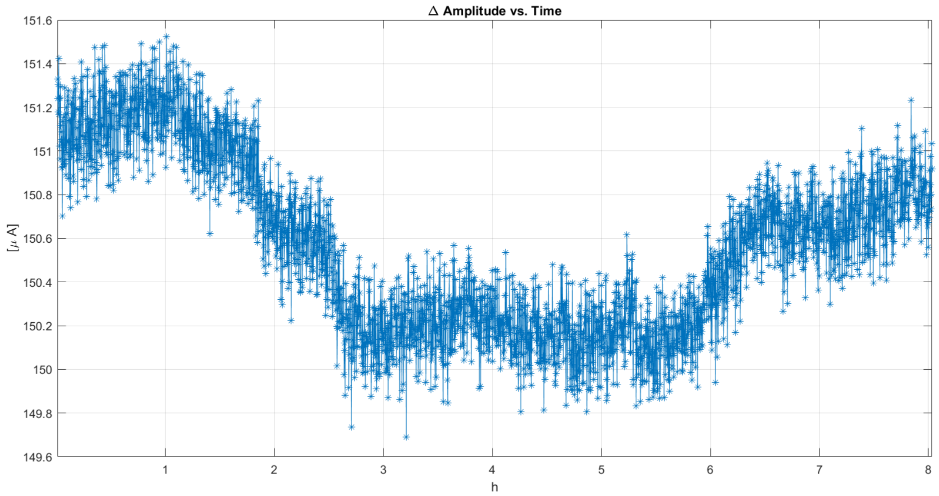

Figure 48: Delta of both amplitudes (positive phase amplitude minus negative phase amplitude).

To clarify, Figure 48 shows a variable that is independent of offset correction, that is, the total amplitude length meaning the positive amplitude minus the negative amplitude. Because an offset induced increase in reversal amplitude is accompanied by an increase in main phase amplitude this variable should be constant over time. However, small changes of this variable can be seen, implying that the neurostimulator outputs slightly different magnitudes over time. However, this behaviour seems to be oscillating around a constant value indicates that no dangerous tendencies, for example linear increase of amplitudes over time, exits.

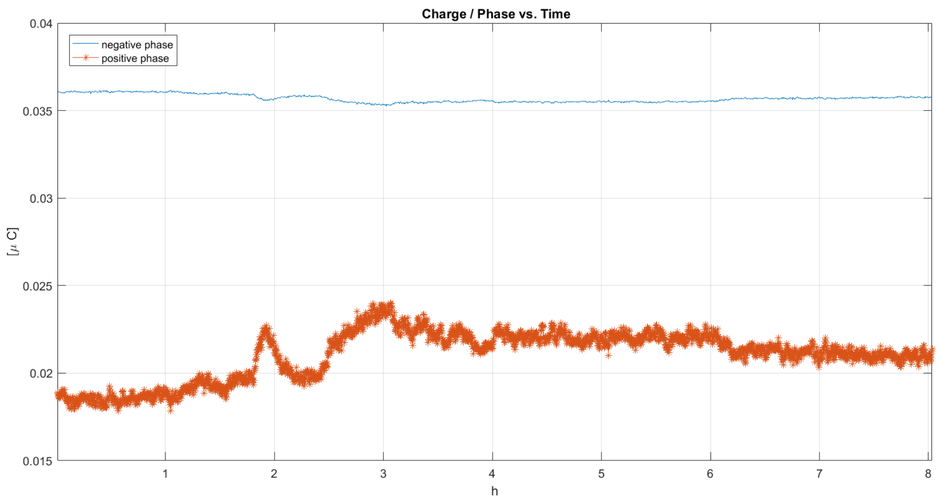

Figure 49: Absolute value of main and reversal phase charge/phase over time.

Figure 49 depicts the absolute value of the charges per phase over time. In the ideal case the net charge of both phases equals zero. Here, the main phase charge is consistently larger than that of the reversal phase. This situation may correspond to the neurostimulator not being able to output reversal phases in smaller increments than 10. That is, it could possibly only output 10 or 20 μA if the correct reversal phase value is a value between these limits. An alternative conclusion could be that this difference originates from the reversal phase pulse width not being detected correctly. When comparing the pulse width of the reversal phase with its expectation value of 2500 μs one can see in Figure 47 that this value is detected at approximately 3h. However, it is apparent that even at this time point the charges do not match. Another important factor could be that the filtering of the negative noise is more successful than that of the positive noise meaning that when dividing the data in positive and negative values the resulting positive mean factors in more noise values than the negative mean. That is, the calculated reversal phase amplitude is to some extent falsified by noise which is a lower value than the reversal phase amplitude.

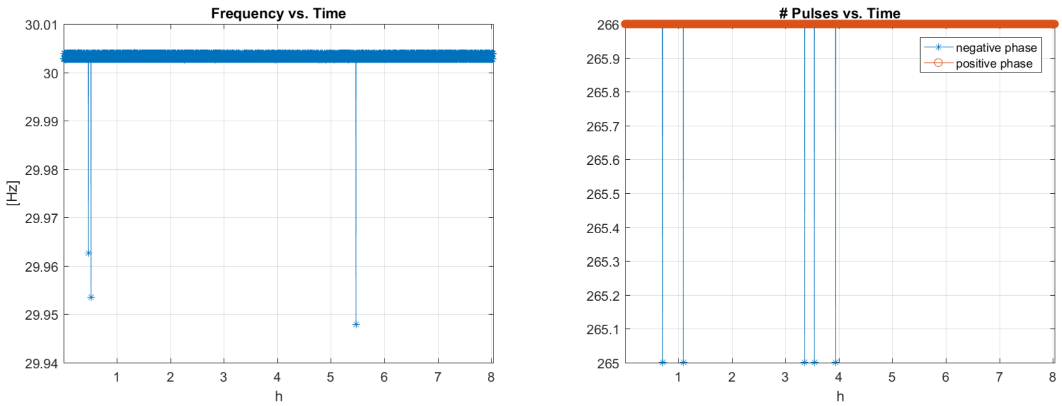

Figure 50: Frequency and number of phases over time.

Finally, Figure 50 shows the change in frequency and the detected number of phases during the 8h recording. One can see that the long positive phases were always stimulated whereas five negative phases were omitted or falsely outputted as previously discussed.

12.2 Conclusion: Long Time Test Results

Despite variations in the stimulation parameters over time, no theoretically dangerous tendency like constant increase was detected. Instead, the fluctuations appear to be statistical and thus not dangerous. The most interesting stimulation error is the lack of several main phases which is theoretically dangerous due to the imbalanced charge. However, with only about 0.001% of pulses exhibiting this error, daily life use should be possible without risking the patient's safety. Especially, if limits on the very relevant parameter stimulation duration per action, for example, grasping a cup, are implemented in the signal output software.

13 Basic Functionality Test

Table 8: Overview Basic Functionality Test

Input	Output	Purpose
none (real-time analysis)	`Log_Error_Messages_Test_*.txt` `Result_Error_Messages_*.png`	Monitoring of error messages returned by NS

Whereas the prior tests analyzed the correctness of electrical signals outputted by a neurostimulator, here, the firmware of the neurostimulator which was used during this Master thesis is tested. That is, if the neurostimulator receives a command that is deemed dangerous or impossible to execute it is expected to output an error warning instead of performing the command. The gist of the basic functionality test is thus to send commands that are expected to trigger an error warning and to document the responses.

The user can decide on the number of tests of a certain error message and thereupon a randomly ordered set of all possible error message tests is sent to the neurostimulator. That is, in total the variable amount of *test number* x 14 tests will be performed. Table 9 lists the possible error message types. The respective commands consider that amplitude and pulse width can only be outputted with increment 10 μA, respectively μs, while the frequency and number of pulses have an increment of 1 Hz respectively 1 pulse.

Table 9: List of Error Codes

Code Name	Description	Test Command
0xAA	no error	A = 200 μA, PW = 200 μs, f = 20 Hz, N = 50, channel 0
0x80	wrong byte structure	not testable
0x81	command does not exist	command hex2dec(FF) missing
0x82	wrong channel number	channel = hex2dec(00)
0x83	not implemented by manufacturer	-
0x84a	amplitude = 0 μA	A = 0 μA
0x84b	amplitude > 500 μA	A = 510 μA
0x85a	pulse width = 0 μs	PW = 0 μs
0x85b	pulse width > 500 μs	PW = 510 μs
0x86a	frequency = 0 Hz	f = 0 Hz
0x86b	frequency > 100 Hz	f = 101 Hz
0x87b	number of pulses = 0	N = 0
0x87b	number of pulses > 100	N = 101
0x88	charge is higher than allowed maximum	allowed charge = 0.1 μC, A = 500 μA, PW = 500 μs
0x89	allowed maximum charge is set > 1.5μC	allowed charge = 2.0 μC

The expected error messages correspond to codes from 0xAA to 0x89. However, code 0x80 which refers to a wrong byte structure could not be tested due to the neurostimulator serial port communication coming to a halt in case of an insufficient byte structure being sent. Furthermore, code 0x83 was not assigned to an error yet at the time of testing. All other tests can directly be done by sending a wrong command, for instance, amplitude 0. The exception is error message code 0x88 which corresponds to the charge per phase being greater than the highest allowed value according to the software. Originally, this value is set to 1.5 μC which cannot be created due to the already existing restrictions on amplitude and pulse width. Therefore, in order to cause the neurostimulator to respond with this code, the software maximum has to be reduced first. After having set the allowed charge to the maximum amplitude and pulse width are requested exceed that limit. Afterwards the allowed maximum charge is reset to its original value.

13.1 Error Analysis

Similarly to prior tests, the results are documented in a text file. In this text file the number of total tests, the total number of correctly and falsely outputted error messages as well as a list of the false error messages are documented. That is, in addition to indicating a faulty error warning it is also shown as which code the incorrect error warning was returned. For better visualization, the results are saved as a bar diagram depicting which error code was correctly returned or not.

14 Example: Basic Functionality Test Results

14.1 Simulation Results

In this section simulated example results are used to demonstrate possible results of the basic functionality test which was not performed on the NS1. In practice, the test has been proven to function with a different neurostimulator which was not intended for patient use due to broken channels. Since the basic functionality test of that specific neurostimulator yielded no software errors, simulated results are shown here to emphasize the capability of this test in detecting different errors.

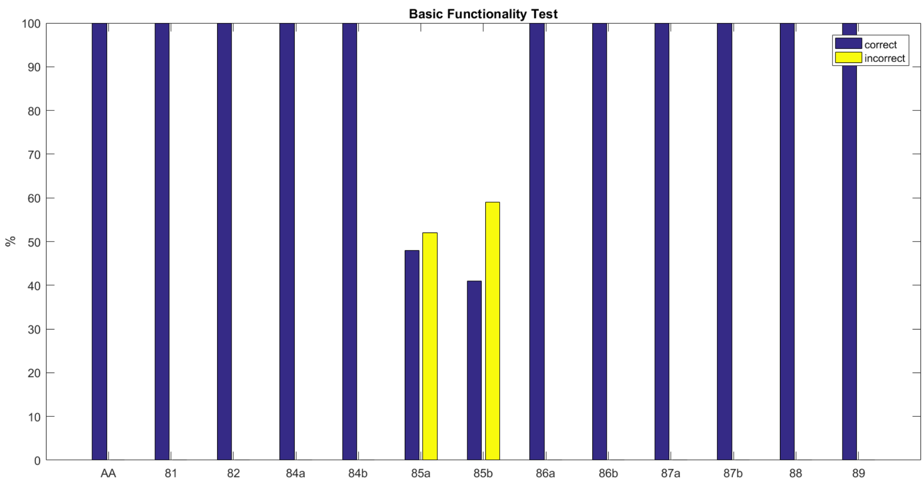

Figure 51: Example basic functionality test bar diagram depicting the amount of correctly and incorrectly returned error messages (simulation).

Figure 51 shows a bar diagram of a simulated result of a neurostimulator returning all error messages correctly except for 0x85a and 85b. Instead, when the corresponding commands (pulse width = 0 μs and pulse width = 500 μs) are sent, the neurostimulator returns 0xAA (no error) and 0x81 (non-existing command). The percentage of correct answers is depicted in blue while the incorrect answer percentage is shown as a yellow bar. Here, 100 times 14 error messages were tested in total.

The log file corresponding to that bar diagram is printed on the next page and shortened to improve readability.

Basic Functionality Test Log File (excerpt)

```
Begin of basic test: 17-Nov-2016 12:22:04
End of basic test: 17-Nov-2016 12:24:05


0xAA:  100 correct, 0 false error messages.

0x81:  100 correct, 0 false error messages.

0x82:  100 correct, 0 false error messages.

0x84a: 100 correct, 0 false error messages.

0x84b: 100 correct, 0 false error messages.

0x85a: 48 correct, 52 false error messages.

0x85b: 41 correct, 59 false error messages.

0x86a: 100 correct, 0 false error messages.

0x86b: 100 correct, 0 false error messages.

0x87a: 100 correct, 0 false error messages.

0x87b: 100 correct, 0 false error messages.

0x88:  100 correct, 0 false error messages.

0x89:  100 correct, 0 false error messages.


Error log:

Error 0x85 falsely displayed as code 0xAA.
Error 0x85 falsely displayed as code 0xAA.
Error 0x85 falsely displayed as code 0xAA.
Error 0x85 falsely displayed as code 0x81.
Error 0x85 falsely displayed as code 0x81.
Error 0x85 falsely displayed as code 0x81.

[...]

Error 0x85 falsely displayed as code 0x81.
Error 0x85 falsely displayed as code 0xAA.
Error 0x85 falsely displayed as code 0xAA.
Error 0x85 falsely displayed as code 0xAA.
Error 0x85 falsely displayed as code 0x81.
```

14.2 Conclusion: Basic Functionality Test Results

The shown simulated results were manufactured on purpose to illustrate the capability of the testing program and do therefore conclude an erroneous product. That is, these test results would correspond to a neurostimulator whose software cannot correctly respond to commands that request a non-existing or too long pulse width. This product would be too dangerous for patient use.

15 Compact List of NS1 Results

15.1 Parameter test

15.1.1 Error Analysis - Mandatory Range

- 13 large errors in 10400 pulse packages of (on average) 5 pulses
- 1 pulse width, 1 interphase delay and 11 reversal pulse widths too short

15.1.2 Error Analysis - Non-Mandatory Range

- 1054 large errors in 1092 pulse packages of (on average) 5 pulses
- increasingly shorter amplitudes and reversal amplitudes, from A = 220 μA reported as large error
  - 15 μA shorter at A = 220 μA
  - 75 μA shorter at A = 500 μA
- from A = 320 μA on: scattered positive phase peaks 20 μA larger than phase amplitude
- from A = 430 μA on: scattered negative phase peaks 20 μA larger than phase amplitude
- below PW = 50 μs cannot be stimulated (in contrast to product description)

15.1.3 Parameter Value Distribution (histogram data)

- pulses of same parameter setting very similar (standard deviation about 1 μA, resp. 1 μs)
- interphase delay consistently 55 μs (in contrast to 50 μs in product description)

15.1.4 Phase Parameter Ratios (histogram data)

- amplitude ratio = 12
- pulse width ratio = 10
- amplitude ratio value approaches 10 for increasing amplitude
- pulse width and frequency no notable influence on ratios

15.1.5 Error Behavior Analysis - Dependence on Parameter Magnitude

- all parameters exhibit an error that increases with the magnitude
- increase appears to be linear or slow quadratic
- but: amplitude error is the only significant one

15.1.6 Error Behavior Analysis - Dependence on Other Parameters

- amplitude error depends on pulse width (most likely because slope values having lager weight)
- pulse width error very small and slightly dependent on amplitude
- frequency error very small and independent of other parameters

15.2 Long Time Test

- 5 cases of missing main phases (or PW = 10 μs) in 757302 pulses
- main phase amplitude changes in range of 4 μA
- reversal phase amplitude changes in range of 2 μA
- main phase pulse width constant and corresponding to expectation
- reversal phase amplitude fluctuating in range of 40 μA but approaching expectation, noise influence likely
- net charge larger than zero, possible causes: NS error, noise level or oscilloscope accuracy of 4 μA insufficient

15.3 Basic Functionality Test

Not performed with the NS1.

15.4 Conclusion: NS1 Results

The neurostimulator NS1 works reliably within the mandatory ranges but behaves increasingly erroneous in the non-mandatory range. While it can correctly generate pulse width and frequency, it fails to output the requested amplitudes, rendering them too low. The outputted inter phase delay is consistently 5 μs too long but shows no other errors. The main concern is the incorrect amplitude ratio of 12 (instead of 10) which might be result of the oscilloscope accuracy of 4 μA falsifying the ratio but could be caused by the neurostimulator not being able to stimulate the small reversal phase amplitude. To minimize possible damaging effects and in agreement with the literature research it is highly recommended to restrict the neurostimulator use to 4 or at most 8 hours per day.

16 Conclusion: Automated Testing System

The developed automated testing system was able to successfully record stimulation data and to perform the parameter, the long time and the basic functionality test. In particular, numerous different types of stimulation errors could be identified for the tested neurostimulator: Erroneous main phase amplitude, main phase width, interphase delay length, reversal phase amplitude, reversal phase width and suppression of phases. The testing system showed that no frequency errors occurred. Therefore, the testing system has been proven to being able to detect all possible parameter stimulation errors and thus allows the user to judge the safety of a neurostimulator concerning long time patient use.

Besides determining stimulation errors, the analysis program provided insight on the error dependence on parameter magnitude and the remaining parameters. Especially, the error tendency matrices can serve as correction matrices if implemented in the neurostimulator software in order to adjust the outputted stimuli to match the inputted command.

Moreover, detailed Matlab GUIs allow easy adjustment of analysis parameters and are additionally flexible for future changes, for instance, a different recording method.

In addition to the already existing tests, possible future improvements could be to combine the neurostimulator testing system with an artificial limb controller and sensory system thus mimicking the complete prosthesis and all integrated processes during tests. Additionally, one could further develop the testing system by including a heat dependency test to determine if the neurostimulator behavior changes according to internal or external temperature.

Part III

Appendix

A Recording GUI - Manual

A.1 General

Open the GUI by executing `NS_recording_GUI.m` in Matlab (version 2016a). The initial screen is depicted in Figure 52.

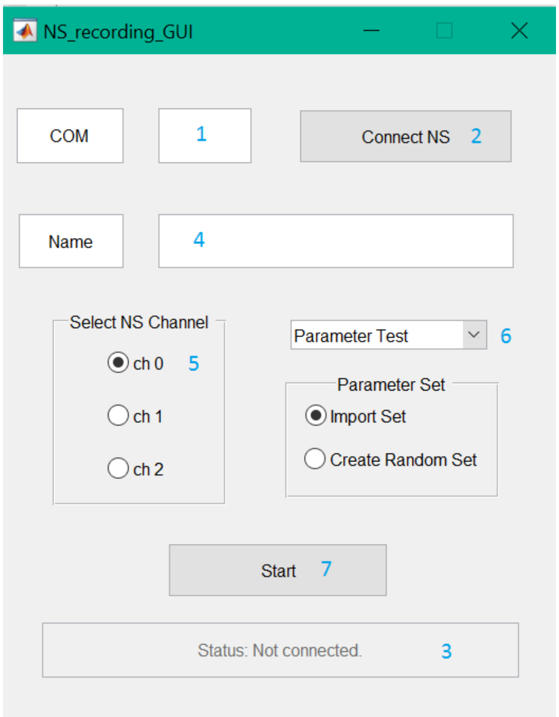

Figure 52: Recording GUI initial screen.

1. Com Port Field

Enter the com port number at which the neurostimulator is connected.

2. Connect NS Button

Press "Connect NS" to establish a connection between Matlab and the neurostimulator.

3. Status Text Field

Displays whether the connection attempt was successful.

4. Name Field

Enter a name which will be used to create a folder of that name in which the recordings will be stored. The neurostimulator channel will automatically be added to the folder name as "_ch_number".

5. Select NS Channel Button Group

Select one of the three neurostimulator channels to be used.

6. Test Type Pop-Up Menu

Select the test type for the recording. The options are "Parameter Test", "Long Time Test" and "Basic Functionality Test".

7. Start Button

Press "Start" to begin with the recording.

A.2 Parameter Test

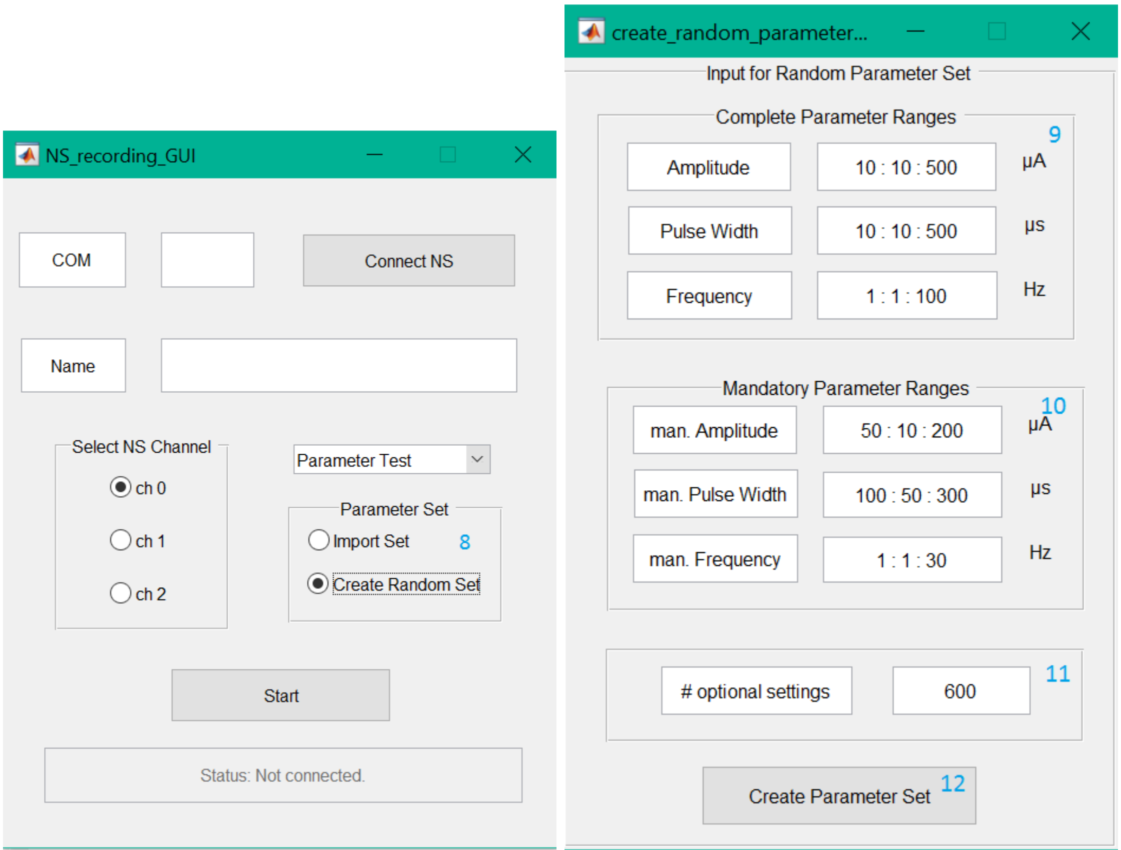

Figure 53: Recording GUI with the parameter test secondary GUI.

8. Parameter Set Button Group

Selecting the option ”Import Set” will load an already existing parameter set ”parameterSet.mat”. It consists of 3 000 randomly ordered settings. In particular, 2400 settings correspond to all possible combinations of the parameter ranges A = 50:10:200 μA, PW = 100:50:300 μs and f = 1:1:30 Hz and 600 random combinations of the unused parameters of the ranges A = 10:10:500 μA, PW = 10:10:500 μs and f = 1:1:100 Hz. In addition to the mandatory ranges for which all combinations are created, the maximum setting A = 500 μA, PW = 500 μs and f = 100 Hz is also included.

Selecting the option ”Create Random Set” will open a secondary GUI to create a new ”parameterSet.mat” file (see Figure 53).

A.3 Parameter Test - Secondary GUI

9. Complete Range Fields

Enter the maximum ranges of the new parameter settings.

10. Mandatory Range Fields

Enter the ranges for which each possible parameter combination will be created.

11. Optional Settings Field

Enter the number of random setting out of the complete range that will be included in the settings file.

12. Create Parameter Set Button

Press ”Create Parameter Set” to overwrite the existing ”parameterSet.mat” file with a new one agreeing with the chosen settings.

A.4 Long Time Test

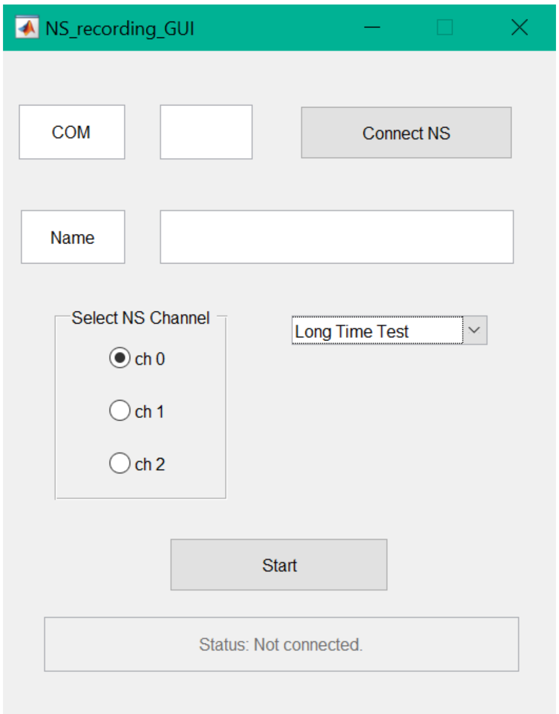

Figure 54: Recording GUI selection of long time test.

The long time test requires only the selection of ”Long Time Test” in the test type pop-up menu. The stimulated parameters are A = 150 μA, PW = 250 μs and f = 30 Hz. The total test duration is approximately 8 hours with 3000 10.15 seconds samples. Each sample consists of 266 pulses in pulse packages consisting of 100, 75, 50, 25, 10 , 5 and 1 pulses.

A.5 Basic Functionality Test

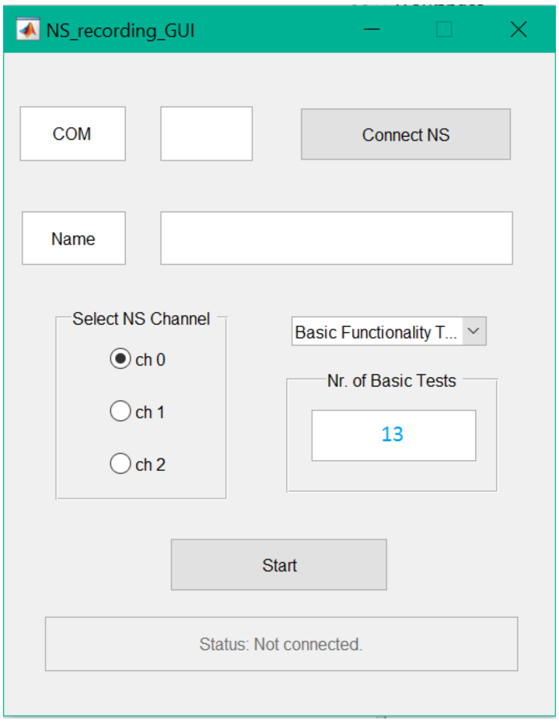

Figure 55: Recording GUI selection of basic functionality test.

13. Number of Basic Tests Field

Enter the number of tests to be performed per error messages. With thirteen tested error messages, the resulting test number is 13 x user input.

B Analysis GUI - Manual

B.1 General

The ”Analysis GUI” processes the parameter and long time data files created with the ”Recording GUI” after the recording is complete. Both parameter and long time analysis require the input of the general GUI.

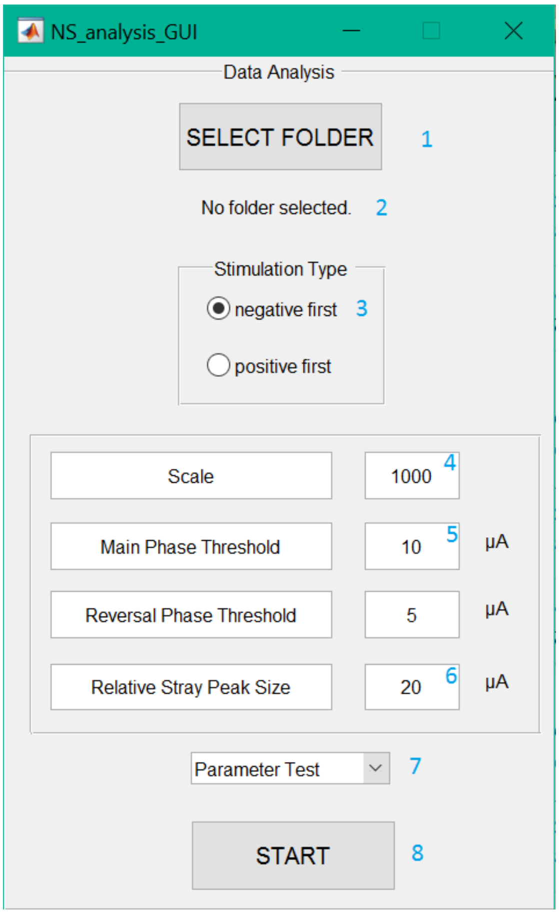

Figure 56: Analysis GUI initial screen.

1. Select Folder Button

Press the ”Select Folder Button” to open the directory and select a folder containing measurement files created by the recording GUI.

2. Folder Name Display

Here, the name of the previously selected folder is displayed.

3. Stimulation Type Button Group

Select the polarity of the first phase of the bi-phasic stimulation. (Not yet implemented)

4. Scale Field

Enter the necessary multiplication factor to convert oscilloscope voltage into μA. This value changes with the resistor of the recording circuit.

B.1.1 5. Threshold Fields

The main phase and reversal phase thresholds will be used for noise filtering and to identify the start and end of a phase. The thresholds need to be entered without sign.

6. Relative Stray Peak Size Field

Mid-phase peaks[3] equal or larger than the entered value compared to the average of the phase (parameter test), respectively the expected value (long time test), will be treated as erroneous stimulation by the analysis program. For instance, if a phase mean is -200 and the relative stray phase peak size is 20 , a single data point with the value -220 will be considered an error. The relative stray phase peak size needs to be entered without sign.

7. Test Type Pop-Up Menu

Select the option "Parameter Test" to open a supplementary second GUI to change additional settings. The second option "Long Time Test" does not require additional input.

8. Start Button

Press "Start" to start the selected test type analysis.

B.2 Parameter Test - Secondary GUI

9. Hole Size Field

The "Hole Size" corresponds to the maximum length of a noise phase interrupt before the analysis identifies an interrupted phase as two phases.

10. Cluster Size Field

The "Cluster Size" corresponds to the maximum length of a non-phase noise cluster before the the analysis identifies the cluster as a phase.

11. Mandatory Parameter Range Fields

Enter the ranges for which each parameter combination was recorded. The mandatory ranges need to be entered in Matlab syntax.

[3]Peaks outside of phases are unaffected by this value and treated differently in the analysis.

12. Threshold Fields

Based on these threshold values different analysis methods are chosen to determine as many parameters as possible of a data sample. Below ”Threshold 1” only the main phase amplitude, main phase pulse width and frequency are determined by means of the thresholds entered in the main analysis GUI. Between ”Threshold 1” and ”Threshold 2” the main phase parameters and frequency are determined as before but additionally an estimate reversal phase amplitude is obtained by taking all remaining values after applying the noise filter that are of the polarity as the reversal phase into consideration. Above ”Threshold 2” the main phase amplitude, main phase pulse width, reversal phase amplitude, reversal phase pulse width, frequency and interphase delay are determined according to the thresholds entered in the main GUI.

13. Allowed Error Fields

Enter the maximum allowed deviation to the expectation values before a determined parameter is treated as falsely stimulated. If the deviation is exceeded, the analysis classifies it as a small error. If the deviation is 2.5 the entered value, the analysis classifies the stimulation as a large error.

14. Histograms Tick Box

If the option ”Histograms” is selected histogram .mat files are created. Those files are a requirement for.

15. Color Maps Tick Box

If the option ”Color Maps” is selected histogram .mat files are created. Those files are a requirement for.

16. Apply Button

Press ”Apply” to save the parameters for the main GUI. Return to main GUI and press ”Start” to begin the selected analysis.

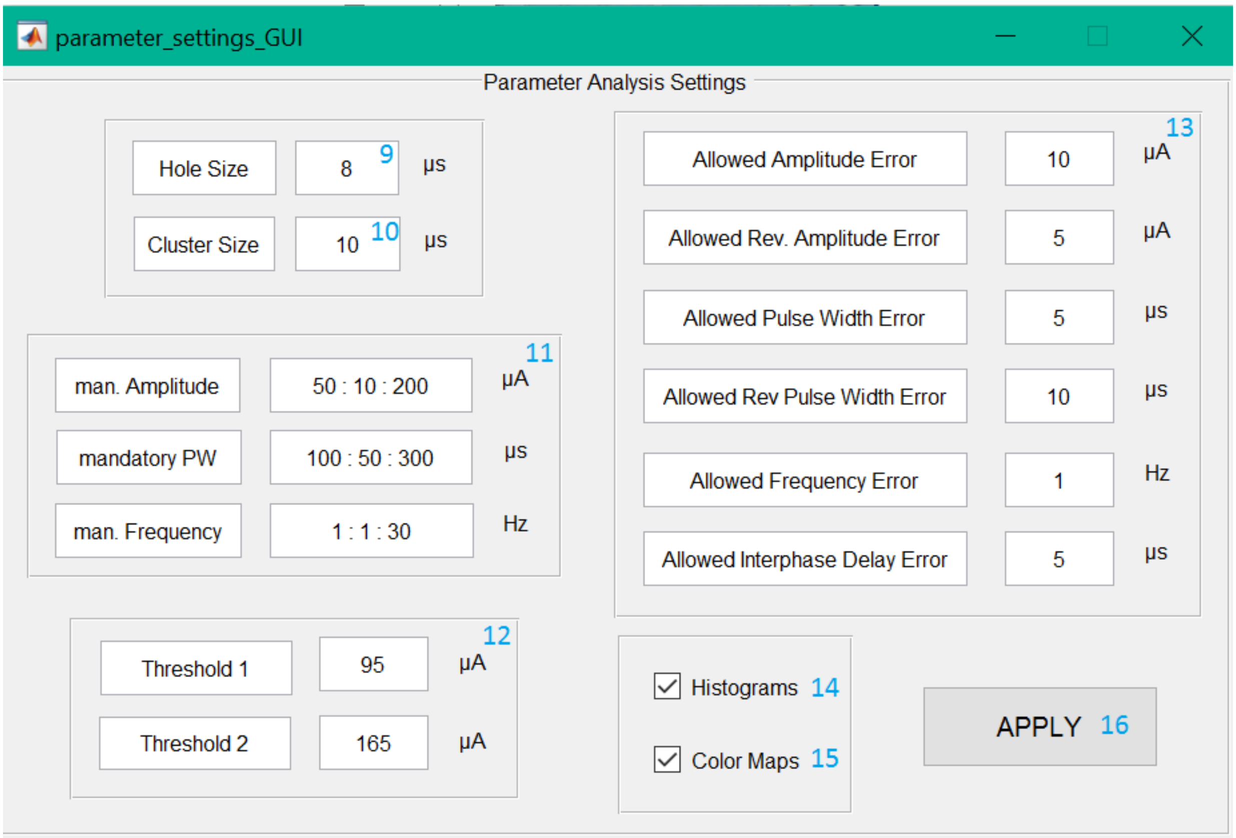

Figure 57: Secondary GUI for specification of parameter test analysis.

C Parameter Test - Figures

C.1 Excluded Files (excerpt)

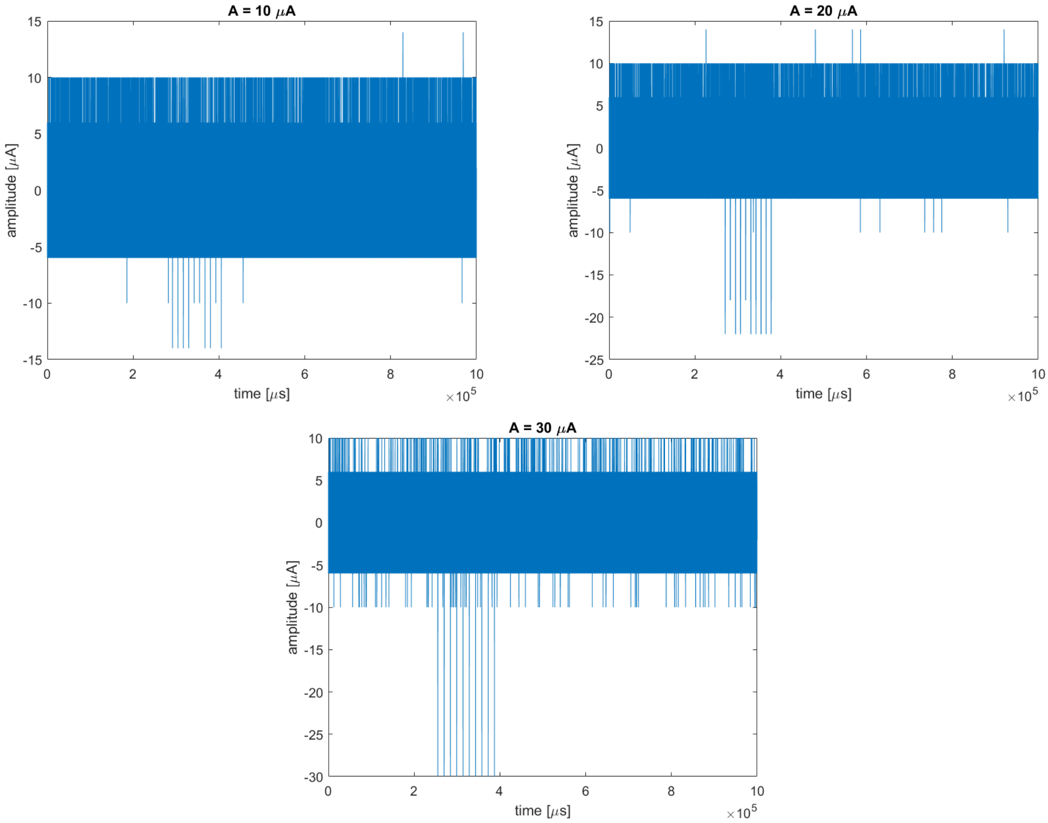

Figure 58: Files that were not analyzed because of their low amplitude.

C.2 Error Analysis - Mandatory Range (complete)

C.2.1 Too Short Reversal Pulse Width

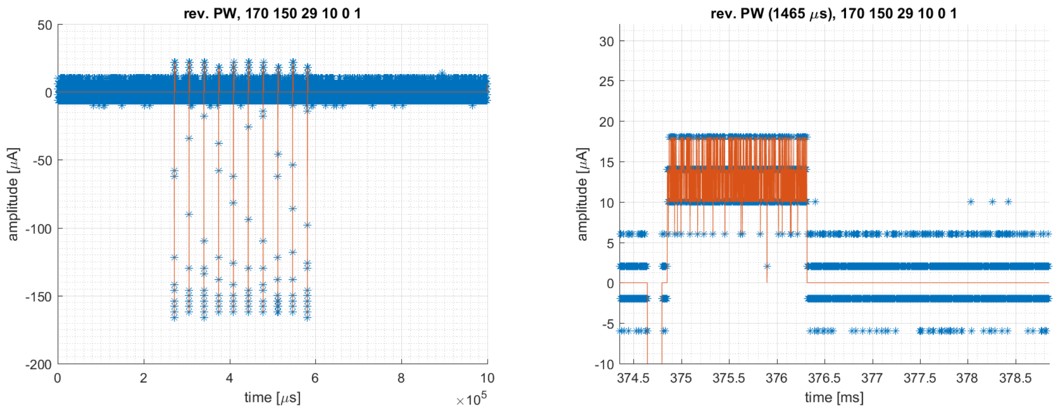

Figure 59: Pulse package and individual pulse with too short reversal pulse width.

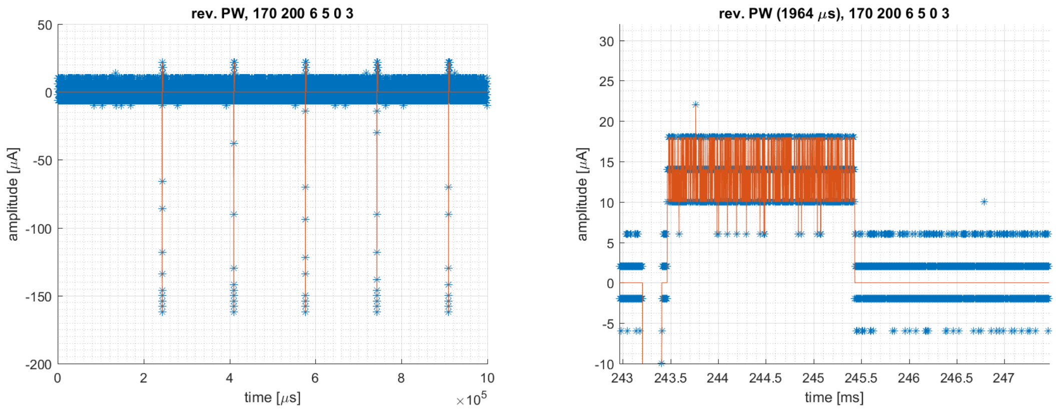

Figure 60: Pulse package and individual pulse with too short reversal pulse width.

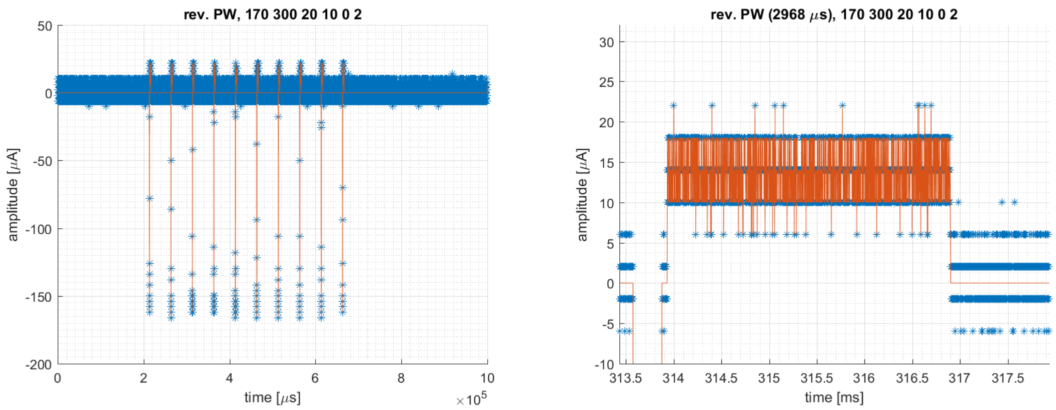

Figure 61: Pulse package and individual pulse with too short reversal pulse width.

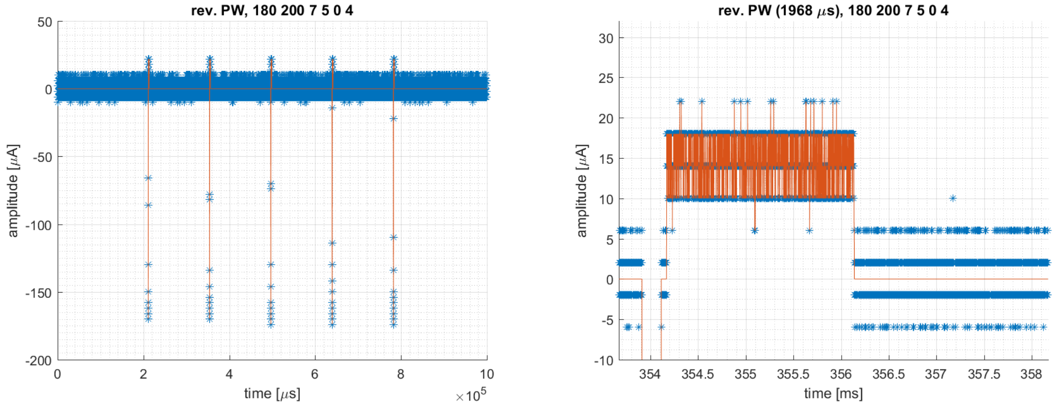

Figure 62: Pulse package and individual pulse with too short reversal pulse width.

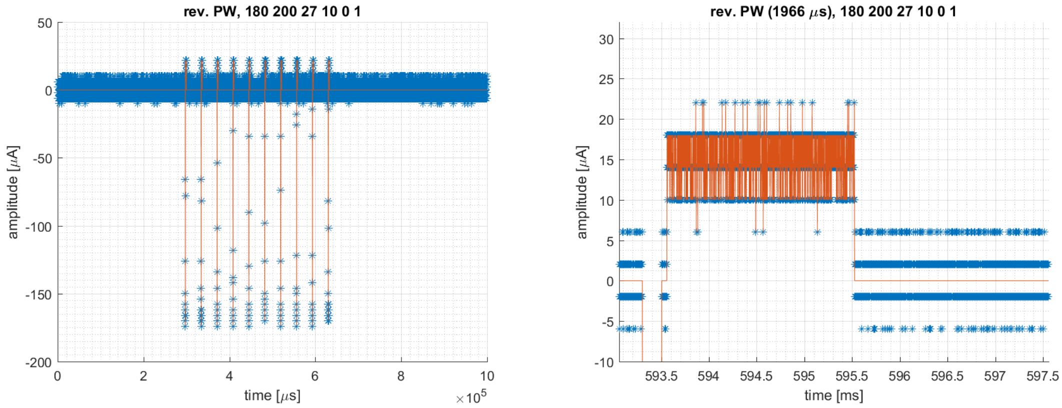

Figure 63: Pulse package and individual pulse with too short reversal pulse width.

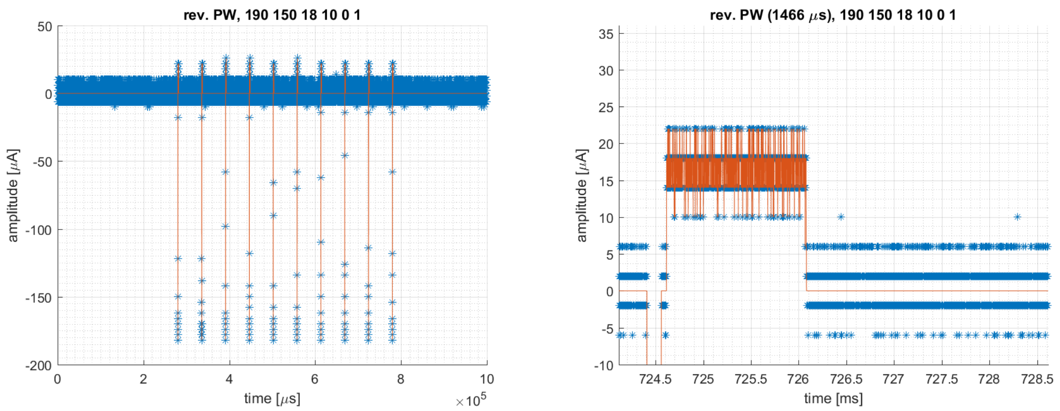

Figure 64: Pulse package and individual pulse with too short reversal pulse width.

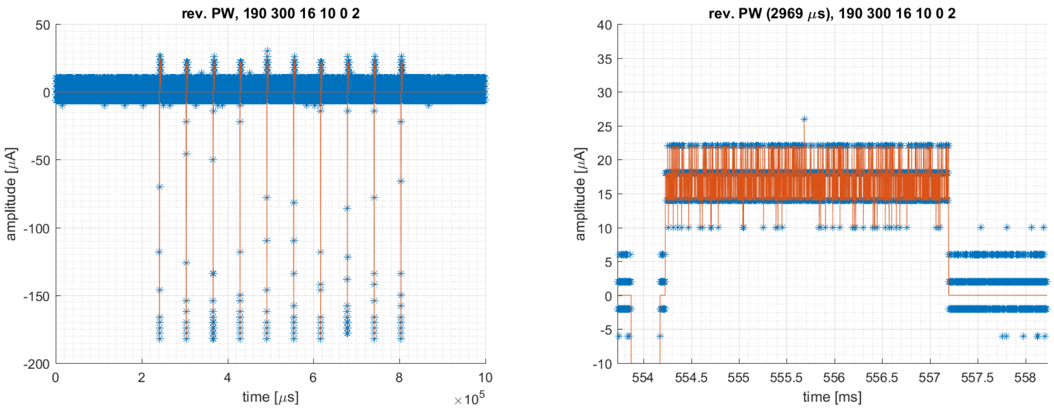

Figure 65: Pulse package and individual pulse with too short reversal pulse width.

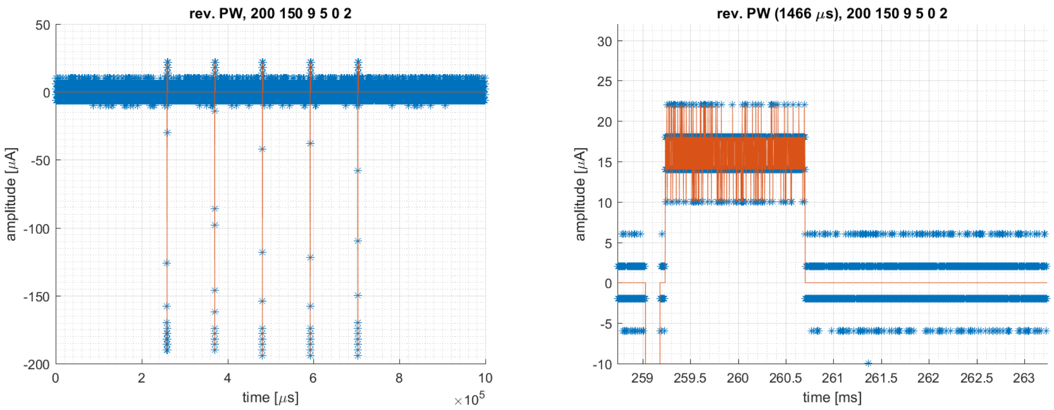

Figure 66: Pulse package and individual pulse with too short reversal pulse width.

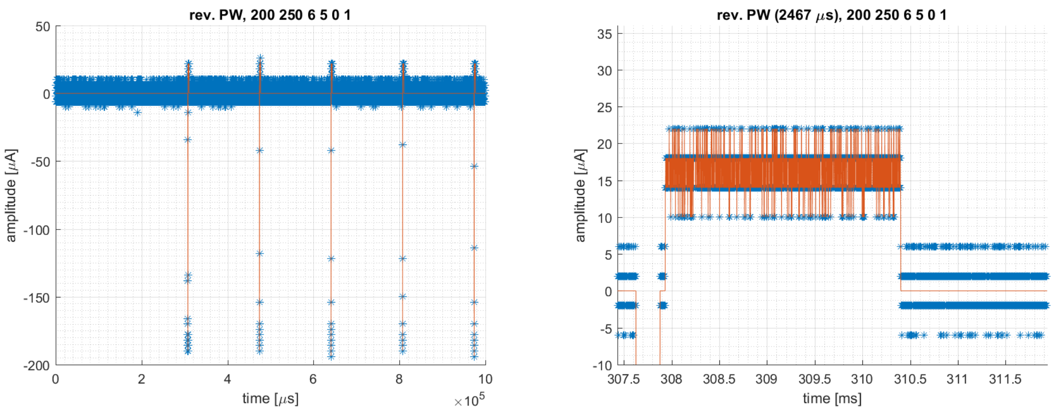

Figure 67: Pulse package and individual pulse with too short reversal pulse width.

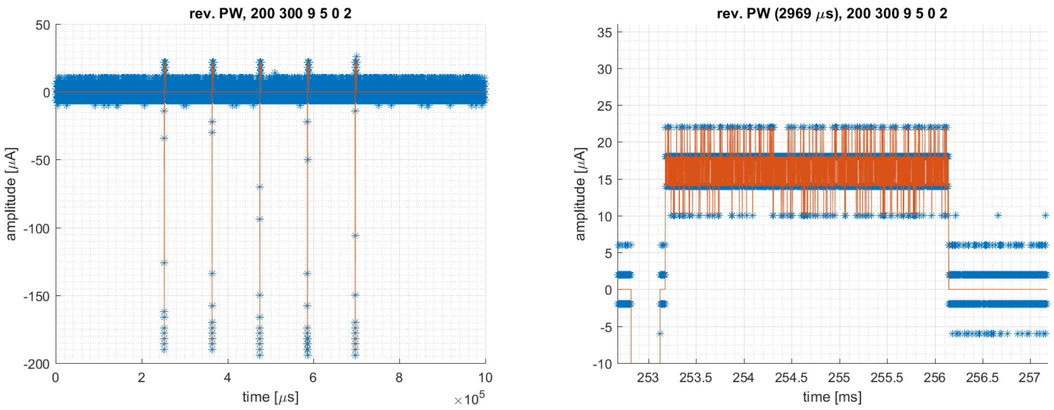

Figure 68: Pulse package and individual pulse with too short reversal pulse width.

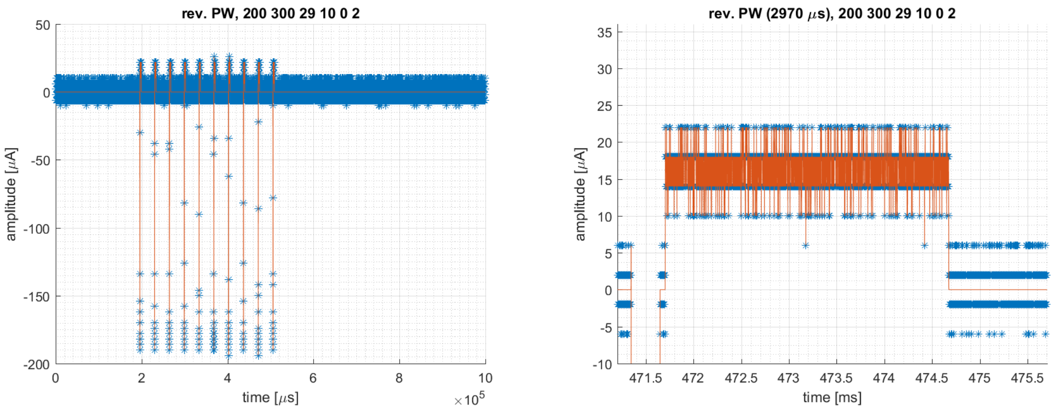

Figure 69: Pulse package and individual pulse with too short reversal pulse width.

C.3 Error Analysis - Non-Mandatory Range (excerpt)

C.3.1 Too Low Amplitude

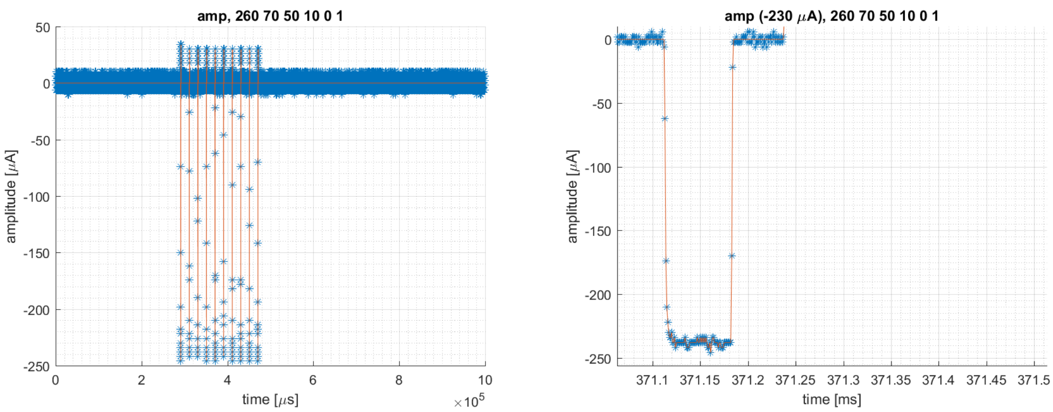

Figure 70: Pulse package and individual pulse with too low amplitude.

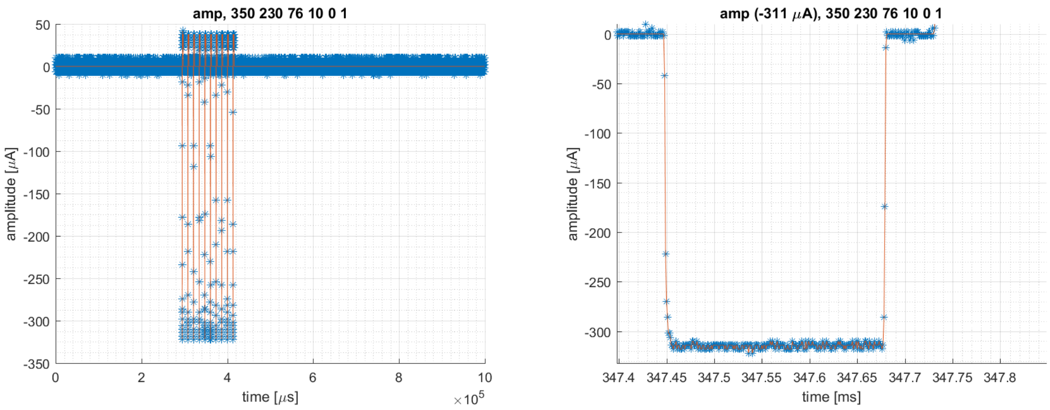

Figure 71: Pulse package and individual pulse with too low amplitude.

C.3.2 Negative Phase Peak

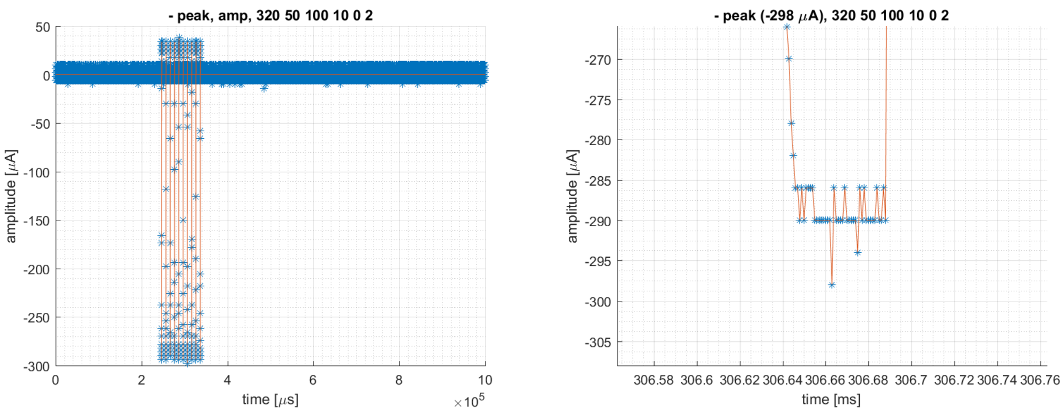

Figure 72: Pulse package and individual pulse with negative phase peak.

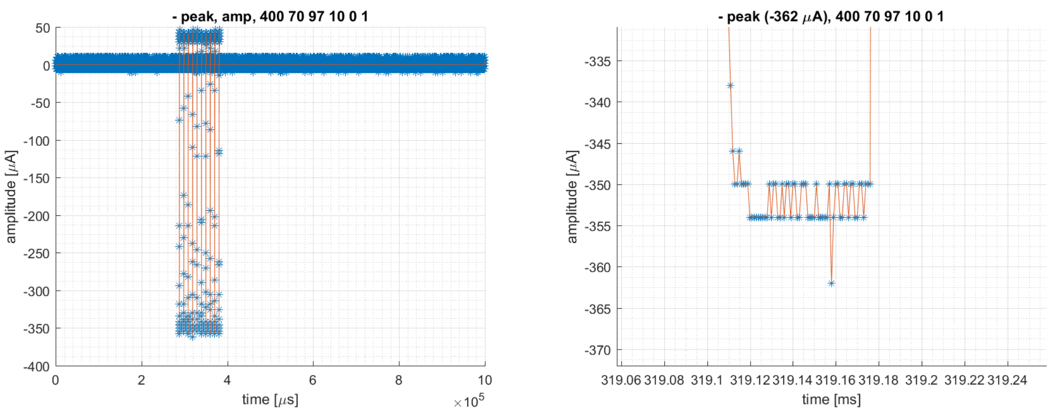

Figure 73: Pulse package and individual pulse with negative phase peak.

C.3.3 Positive Phase Peak

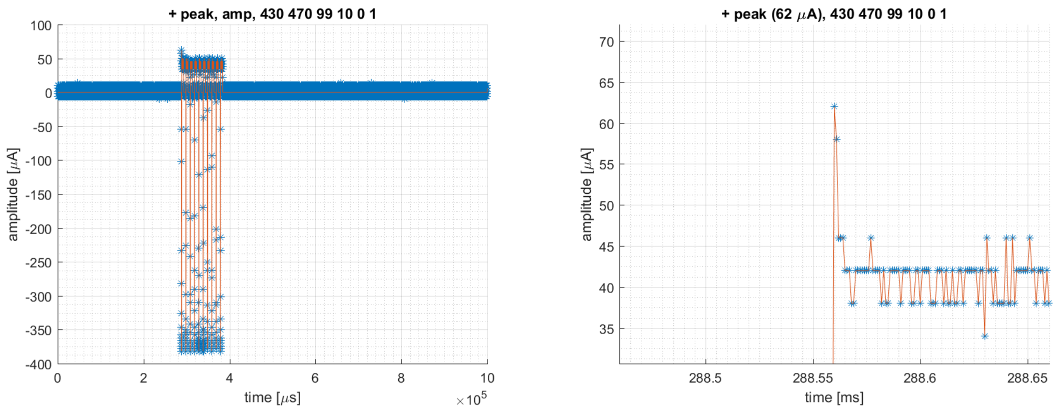

Figure 74: Pulse package and individual pulse with positive phase peak.

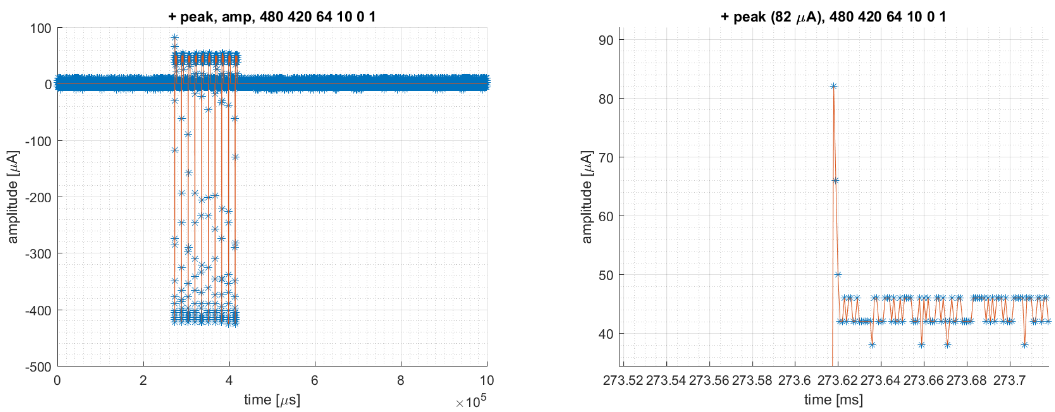

Figure 75: Pulse package and individual pulse with positive phase peak.

C.3.4 False Pulse Width

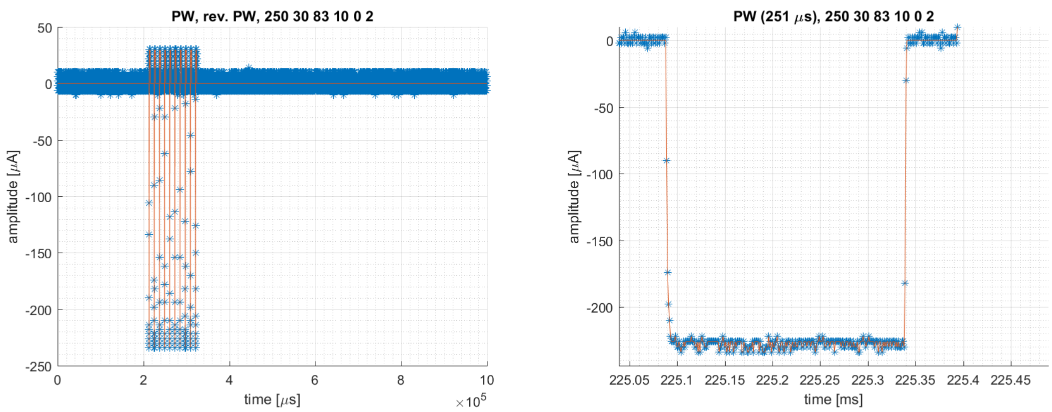

Figure 76: Pulse package and individual pulse with false pulse width.

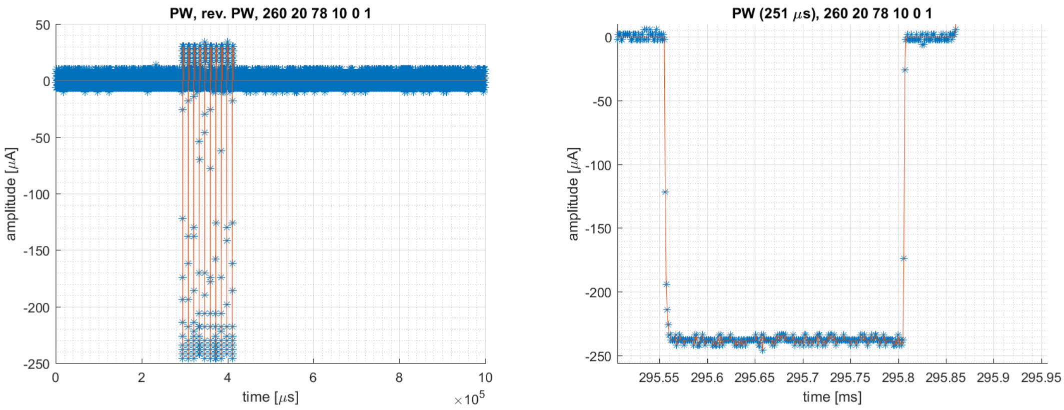

Figure 77: Pulse package and individual pulse with false pulse width.

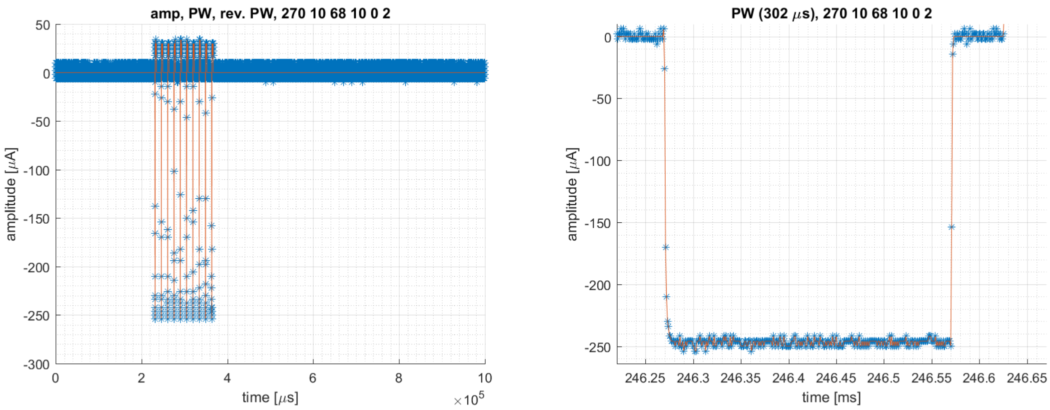

Figure 78: Pulse package and individual pulse with false pulse width.

D Parameter Test - Log Files

D.1 Mandatory Range

D.1.1 Error Log File (excerpt)

Parameter Test: Large Errors Log File (NS1)

```
Begin of parameter measurement analysis: 14-Nov-2016 18:10:20

100_100_10_5_0_1.mat
wrong main phase amplitude [uA]: [-89;-89;-89;-89;-89]

100_100_10_5_0_2.mat
wrong main phase amplitude [uA]: [-89;-89;-89;-89;-89]

100_100_10_5_0_3.mat
wrong main phase amplitude [uA]: [-90;-88;-89;-89;-89]

100_100_10_5_0_4.mat
wrong main phase amplitude [uA]: [-89;-89;-89;-89;-89]

[...]

150_100_30_10_0_1.mat
wrong main phase amplitude [uA]: [-140;-140;-140;-140;-140;-139;-140;-140;-140;-141]

150_100_30_10_0_2.mat
wrong main phase amplitude [uA]: [-139;-138;-139;-138;-137;-139;-138;-139;-138;-139]

[...]

200_300_9_5_0_1.mat
wrong main phase amplitude [uA]: [-184;-184;-184;-184;-184]

200_300_9_5_0_2.mat
wrong main phase amplitude [uA]: [-184;-184;-184;-184;-184]
wrong reversal phase pulse width [us]: [2969;3001;3000;3000;2999]

200_300_9_5_0_3.mat
wrong main phase amplitude [uA]: [-183;-184;-184;-184;-184]

200_300_9_5_0_4.mat
wrong main phase amplitude [uA]: [-184;-183;-184;-183;-184]

90_100_9_5_0_1.mat
wrong main phase amplitude [uA]: [-80;-80;-81;-81;-80]

End of parameter test: 14-Nov-2016 19:27:10

10400 pulse packages tested, 13 large error(s) found.
```

D.2 Non-Mandatory Range

D.2.1 Error Log File (excerpt)

Parameter Test: Large Errors Log File (NS1)

```
Begin of parameter measurement analysis: 15-Nov-2016 19:06:17

210_10_70_10_0_1.mat
wrong main phase amplitude [uA]: [-190;-191;-191;-192;-191;-191;-191;-191;-191;-191]
wrong main phase pulse width [us]: [101;100;100;100;100;100;100;100;100;101]
wrong reversal phase pulse width [us]: [997;997;997;996;998;998;997;998;997;998]

210_10_70_10_0_2.mat
wrong main phase amplitude [uA]: [-191;-191;-190;-190;-190;-191;-191;-191;-191;-190]
wrong main phase pulse width [us]: [100;100;100;100;100;100;100;100;100;100]
wrong reversal phase pulse width [us]: [999;998;998;998;1000;998;999;998;998;1000]

[...]

350_500_81_10_0_1.mat
wrong main phase amplitude [uA]: [-315;-315;-315;-315;-315;-315;-315;-315;-316;-315]
wrong reversal phase amplitude [uA]: [29;29;29;29;29;29;29;29;29;29]

350_500_81_10_0_2.mat
wrong main phase amplitude [uA]: [-312;-312;-312;-312;-312;-311;-313;-312;-312;-312]

[...]

500_80_38_10_0_2.mat
unexpected minimum [uA]: -438
wrong main phase amplitude [uA]: [-419;-411;-420;-415;-420;-415;-415;-416;-416;-416]

500_80_49_10_0_1.mat
unexpected minimum [uA]: -438
wrong main phase amplitude [uA]: [-415;-416;-416;-415;-420;-415;-414;-415;-415;-420]

500_80_49_10_0_2.mat
unexpected minimum [uA]: -438
wrong main phase amplitude [uA]: [-415;-414;-414;-420;-415;-419;-414;-414;-419;-413]

End of parameter test: 16-Nov-2016 04:34:34

1092 pulse packages tested, 1054 large error(s) found.
```

E Long Time Test - Figures

E.1 Missing Negative Phase (complete)

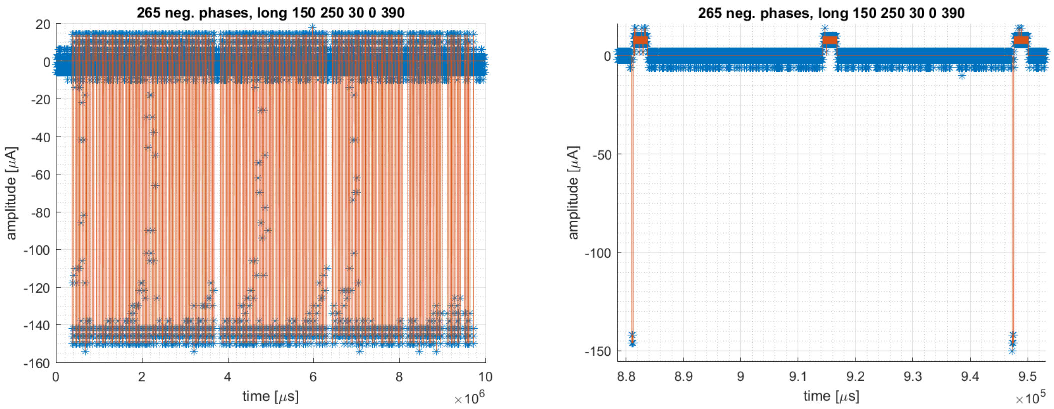

Figure 79: Missing negative phase in first pulse package (100 pulses).

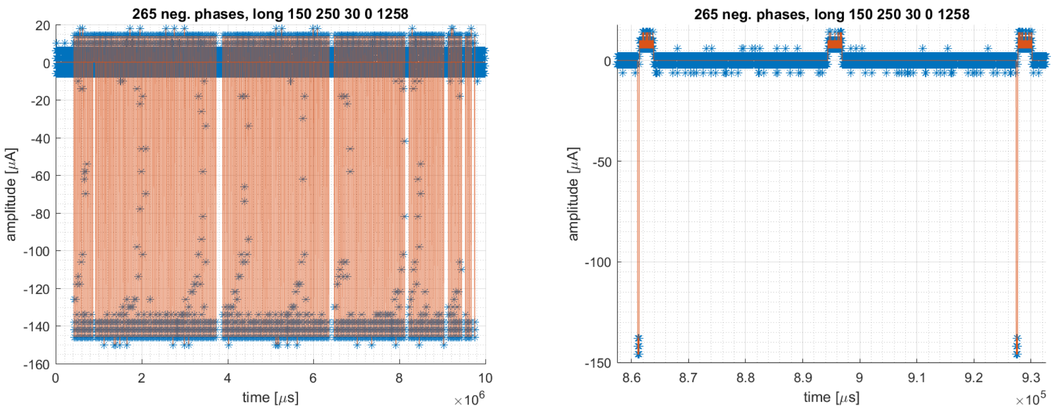

Figure 80: Missing negative phase in first pulse package (100 pulses).

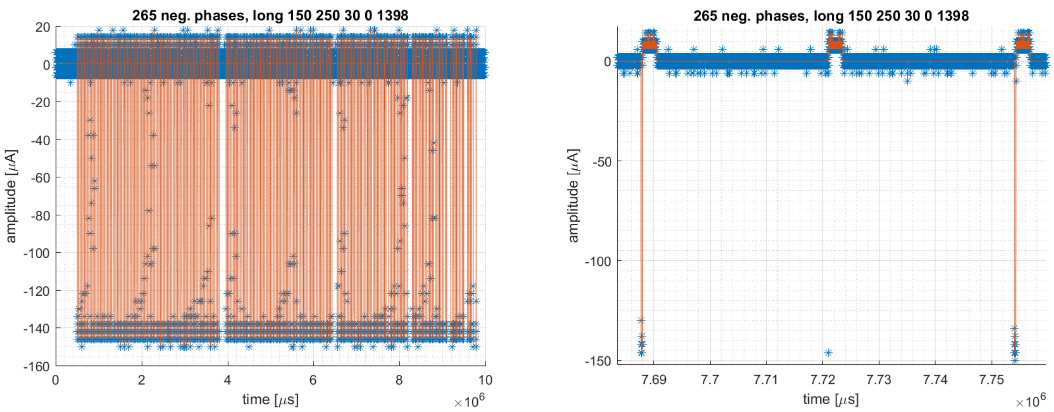

Figure 81: Too short negative phase in third pulse package (50 pulses).

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W. F. Agnew, D. B. McCreery, T. G. Yuen, and L. A. Bullara. Evolution and resolution of stimulation-induced axonal injury in peripheral nerve. *Muscle & nerve*, 22(10):1393–1402, 1999.

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