Physiological Measurements Portfolio

IPEM Grade A Training Scheme

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Preface

During my six months of training in Physiological Measurements, I have been involved in all the aspects of the work carried out in different departments located both at the Southern General Hospital and at Gartnavel General Hospital at Glasgow.

During the first two months of my training I gained experience in instrumentation electronics, where basic concepts commonly used (i.e., gain, common mode rejection ratio, etc.) in electrophysiology were learnt on an experimental basis. I set up different experiments in order to study sources of signal artefacts, and also different techniques on how to overcome these artefacts were an object of study.

The following four months of the placement, were dedicated to building on the knowledge acquired in instrumentation to different areas of electrophysiology, that is: Intensive Care, Neurophysiology, Ophthalmology and Urodynamics. In each of these areas I spent a maximum of three weeks during which small projects were carried out to cover all the IPEM competencies. The main block of activities was centred on how to obtain and process different types of electrophysiological signals, and where applicable, pressure and flow measurements were produced.

Finally, I carried out several studies on patients with different pathologies, and additionally I have been involved in the interpretation of these clinical studies.
Chapter 1

Physiological Instrumentation

1.1 Introduction

Physiological instruments provide information to medical specialists about the function and performance of an organ, group of organs or system within the body of a patient by means of the physiological signal produced by them.

These physiological signals are characterised by standard values and features inferred from statistics made on a normal population.

Physicists performing these measurements should be aware of these characteristics of the signals and the electrical design of the equipment required to do such a measurement. The bulk part of their job will deal with the processing and interpretation of these signals. At the same time they will also contribute in the design, development and well functioning as well as the safe performance of the equipment used to detect, analyze and store these signals.

In this chapter I describe some of the experiments I performed on amplifiers, filters and signal processing. This experience helped me to understand the choice of equipment for the tests performed during my visit to the other sections of the department.
1.2 Instrumentation

Physiological parameters, such as temperature and pressure, produce very small signals when they are measured by electrical means (e.g. thermocouples: 40 $\mu$V/°C, pressure transducer produce figures in the order of the mV). Therefore, to acquire these signals to be recorded and analysed it will be necessary to amplify them.

At the same time, the size of these signals make them very susceptible to be obscured by the background noise. This means it will be necessary to filter the signal at some stage of the acquire process.

Finally, these signals (received in analogue mode) may be digitized so they can be processed and stored. In this role, an analogue to digital converter (ADC) will do the job.

The next diagram represents the major components of a electrophysiology recording system.

![Diagram of an electrophysiology recording system]

Figure 1.1: A physiological measurement recording system can be simply described as electrodes or leads, attached to a patient, which are connected to a recorder through a high gain differential amplifier with good common mode rejection. The resulting signal can be then displayed and analyzed previous to its recording. In some cases, the system may also incorporate filters (e.g. Notch filter) to subtract the signal of interest from background noise or from a mixture of signals. Finally, as a physiological measurement recording necessitates that an electrical connection is made to the patient, patient safety has to be assured. This can be achieved by isolating the pre-amplifier stages.
1.2 Instrumentation

1.2.1 Transducers

Types of transducers

The most useful form of transducer is one which converts energy to an electrical signal as this can be readily used and processed. Thus, a thermocouple for example, is more useful in instrumentation than a mercury in glass thermometer as the signal it produces is electrical and can be readily interfaced to other circuits for interpretation, display and recording.

Some transducers are used in a rather indirect manner. For example a displacement measurement transducer may be used to measure pressure. In this case a membrane is exposed to a pressure difference and its deformation is measured by a potentiometer.

Some measurements are made by active intervention to obtain a signal. The measurement of the blood flow in the circulation system is a good example of such measurements. The determination of the change of the temperature at a point downstream can be used to workout the flow rate at such a point.

In reality, there is a wide range of types of transducer. But their main common property is that they should be designed so their performance is safe at all times.

Desired attributes for a transducer

1. The amount of energy removed from a system should be small. All systems are changed when a measurement is performed. A thermometer needs a finite amount of energy, in the form of heat, to function

2. The system should be sensitive only to the desired signal.

3. The measurements should be minimally invasive: the transducer should cause as little damage as possible

Technical information on the transducers used to measure temperature and pressure

The following transducers were used in some of the experiments included in this portfolio.
1.2 Instrumentation

**Temperature**: A K-Type thermocouple, which is one of the most commonly used due to its wide range of applications. The conductor combinations typical of this type of thermocouple are:

+ *ve leg*: Nickel-Chromium  
− *ve leg*: Nickel-Aluminum (Magnetic)

Approximate figures for the generated EMG change per degree Celsius change with reference junction at 0°C are given below for different temperatures:

- 100°C: 42 µV/°C  
- 500°C: 43 µV/°C  
- 1000°C: 39 µV/°C

The approximate working temperature range of the measuring junction (NB. Not related to wire and conductor insulating materials) is:

**Continuous**  
0 to +1100°C  
**Short term**  
−180 to +1350°C

**Pressure**: The technical specifications of the pressure transducer used are summarised in the following table:

<table>
<thead>
<tr>
<th><strong>Uniflow™ Disposable Pressure Transducer</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating Range</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Nonlinearity and Hysteresis</td>
</tr>
<tr>
<td>Zero Offset</td>
</tr>
<tr>
<td>Zero Thermal Drift</td>
</tr>
<tr>
<td>Output Drift</td>
</tr>
<tr>
<td>Sensitivity Thermal Drift</td>
</tr>
<tr>
<td>Natural Frequency</td>
</tr>
<tr>
<td>Leakage Current</td>
</tr>
<tr>
<td>Volumetric displacement</td>
</tr>
</tbody>
</table>

*CHAPTER 1. Physiological Instrumentation*
1.2 Instrumentation

1.2.2 Amplifiers

Once a physiological signal has been converted into an electrical signal by a transducer, the next stage will be the amplification of such a signal. Amplification can occur in different ways:

1. one, could be a pre-amplification of the signal before its full amplification in the main amplifier of the equipment;

2. other, would be a direct amplification of the signal in the main amplifier.

I observed that most equipment used in clinics tend to pre-amplify the signal as it represents an advantage versus the amplification in only one stage (main amplifier). Some of these advantages are listed below:

- Remove noise from the signal, as it will be amplified through out the remaining stages of the amplifier.

- It is coupled directly to the electrodes to provide optimal low-frequency response at the same time that minimizes input bias current that would appear if they were coupled to capacitors.

- Often, for safety reasons, the preamplifier is electrically isolated from the remaining amplifier stages (and hence the power supply). This feature represents a safety feature of preamplifiers.

- It can be located near the signal source to minimize interference pickup on the high-impedance lead wires (head box).

In the next subsections we will present a review of the main features of the amplifiers based on experiments performed with operational amplifiers (OPAMPs).

General Characteristics of OPAMPs

Basically, an OPAMP is a device which amplifies a small signal by subtracting noise, distortion and nonlinear effects which obscure the signal. This subtraction might
be achieved using negative feedback: part of the output is coupled with the input to cancel the effects of the noise.

Most of the real OPAMPs have a very high gain (input) in open-loop mode\(^1\) and a low output impedance. Ideally, an OPAMP would have infinite open-loop gain and zero output impedance.

Some of the parameters measurable from an OPAMP are: its input/output offset voltage, input bias currents, input impedance, slew rate, common-mode rejection ratio (CMRR) and its gain-bandwidth product. Some of them were measured using a 741 OPAMP.

\(^1\)When an OPAMP does not have any external feedback, it is described as being used in an open-loop mode.
1.2 Instrumentation

Intrinsic Input Impedance

This is defined as the impedance ‘looking in’ at either input terminal with the remaining input grounded.

The next figure shows a schematic diagram of the circuit used to test this parameter.

![Schematic Diagram]

The elements used were:

- a signal generator which was set to generate a sine wave of 1 volt peak-to-peak at a frequency of 100 Hz;
- a 5-MΩ potentiometer;
- a 741C OPAMP; a breadboard where the circuit was wired up; and,
- an oscilloscope.

The circuit was wired as shown in the previous figure and powered. The input signal was then introduced in the circuit and checked on the channel 1 of the oscilloscope. Then, the potentiometer was adjusted until the input signal was reduced to one-half to its original value (i.e., 0.5 volts peak-to-peak on channel 2). When this point was reached, the power supply was disconnected from the breadboard and the potentiometer was removed without disturbing its setting. Its impedance was then measured using a voltmeter. This impedance is equal to the input resistance of the
OPAMP. The 741C OPAMP has an input impedance range between 300 kΩ and 2 MΩ. The input measured in our case was 1.1 MΩ.

The input impedance associated with an amplifier involved in the measurement of a small signal must be as high as possible. When a measurement system measures the voltage across a resistance, the measurement system becomes a potential divider itself, decreasing the voltage across the resistance (and therefore the signal). In order to avoid this effect, the intrinsic impedance of the measurement system should be high enough not to affect the signal being measured. Equivalently, if the intrinsic impedance of the measuring system is fixed, the same effect would be achieved by reducing the impedance of the connection made to the patient. For this reason the skin is rubbed and covered with conductive gel. Typical values for skin resistance (i.e. electrode impedance) before and after the patient preparation is > 50 K and 1 K respectively.

**Common Mode Rejection Ratio, CMRR**

When measuring an electrical signal with an OPAMP two different signals can be expected to arrive to its terminals. One, which is the signal of interest itself, will create a difference of potentials between the inputs. This will be called normal-mode input change. The other, which are normally external signals to our measurements, will be common to both electrodes. These are called common-mode input signals. An OPAMP has the characteristic of being able to reject these common-mode voltages, although the rejection will not be perfect. To quantify this imperfection it is used the term common-mode rejection ratio.

The CMRR is therefore defined as the ratio of the common-mode signal gain to the gain of a circuit. In practice, it is obtained by calculating the log of the voltage gain of the OPAMP and it is expressed in decibels (dB):

\[
CMRR = 20 \log \left( \frac{\text{signal gain}}{\text{common mode gain}} \right)
\]  

(1.1)

Electromagnetic signals generated by electronic equipment surrounding us are an example of sources of common-mode voltages.

The CMRR characteristic of the 741C amplifier was measured using the next setup:
After wiring up the circuit, the sine-wave generator was adjusted to generate a common-mode input voltage of 3.32 volts root mean square\(^2\) (rms) at 70 Hz. Then, the common-mode output voltage was measured, obtaining a reading of 0.285 volts rms. Therefore, the resultant common-mode gain was 0.0858 and the CMRR obtained was 81.3 dB.

Ideally, the common-mode output voltage would have been 0 volts as the OPAMP would have perfectly rejected the common-mode input voltage. In this case, from equation (1.1), \(V_{\text{out}} = 0\) and therefore \(\text{CMRR} = \infty\). However, the real situation is that only ideal OPAMPs will have an infinite CMRR. In practice, real OPAMPs will have imperfections that make them have a finite CMRR.

Any physiological measurement equipment is characterised by having a CMRR as high as possible. As the size of the signals is small, background noise produced by an electromagnetic source can totally obscure the signal. The most important source of noise comes from the mains power supply, which creates common-mode input voltage with a characteristic frequency of 50 Hz (in UK).

\[
V_{\text{rms}} = \frac{V_{\text{peak-to-peak}}}{\sqrt{2}}
\]
Gain and gain-bandwidth product

The gain of an OPAMP is defined as the ratio of the output voltage to the input voltage. In open-loop mode (no feedback) it has been said the gain is infinite. However, an OPAMP with feedback (negative or positive) will always have a finite gain as we will see from the results for the experiments I performed.

The gain of the 741C OPAMP was measured in two different configurations. First, a noninverting amplifier was assembled as shown in the next diagram.

\[ V_o = V_i \left(1 + \frac{R_B}{R_A}\right) \]  

(1.2)

The input signal was a sinusoidal wave with 1 volt peak-to-peak and a frequency of 400 Hz. The output voltage was calculated previous measurement from the equation.

Figure 1.3: Assembly of the non-inverting amplifier used in the experiment.

The feedback element, \( R_B \), was changed to higher values in order to study the behaviour of the OPAMP’s gain. It was observed on the scope that the output signal remained in phase with the input although with a larger amplitude. The next table summarises the values obtained.

Then, an inverting amplifier was assembled as shown in the next diagram.
1.2 Instrumentation

<table>
<thead>
<tr>
<th>$R_B$ (kΩ)</th>
<th>Measured $V_o$ (peak-to-peak)</th>
<th>Voltage Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>39</td>
<td>4.8</td>
<td>4.9</td>
</tr>
<tr>
<td>47</td>
<td>5.74</td>
<td>5.7</td>
</tr>
<tr>
<td>82</td>
<td>9.32</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Table 1.1: Behaviour of the circuit gain as a function of the feedback element, $R_B$, for a non-inverting amplifier.

![Diagram of an inverting amplifier](image)

Figure 1.4: Assembly of the inverting amplifier used in the experiment.

This time, a sinusoidal wave at 1 volt peak-to-peak and 500 Hz was used as the input signal. The output voltage was 0.9 volts peak-to-peak with its phase $\pi$ radians shifted with respect to the original signal. Again, the same set of feedback elements as in the noninverting amplifier was used to obtain different values of gain:
Table 1.2: Behaviour of the circuit gain as a function of the feedback element, $R_B$, for an inverting amplifier.

The next plot shows graphically the behaviour of the circuits gain when the feedback element is changed.

![Image](image.png)

**Figure 1.5:** Effect on the gain when the feedback element ($R_B$) is changed.

Inverting and non-inverting amplifiers are connected together to create more sophisticated amplifiers such as the differential amplifier and the instrumentation amplifier.
Instrumentation Amplifier

The value of CMRR obtained in the CMRR experiment is not adequate to cope with the small size of physiological signals. The voltage difference between the electrodes of the amplifier used to detect the signal is so small that the CMRR of the amplifier has to be specially high. This is achieved by using instrumentation amplifiers. The next figure shows the configuration of a classic instrumentation amplifier:

![Instrumentation Amplifier Diagram](image)

Figure 1.6: *Instrumentation amplifier*

To achieve high CMRR with standard differential amplifiers requires a very precise resistor matching. This is very difficult unless high precision resistors are used, which usually increases the cost of the amplifier.

In the instrumentation amplifier the resistor matching is still very important. To get a zero common-mode gain, the resistor matching in $U_3$’s circuit (Figure 1.5) has to be as high as possible; they still can be 5% precision resistors, but as long as they all have exactly the same value, $G_{CM} \approx 0$. In our circuit this was achieved by using a SIL resistor. This element consist of a resistor network connected to each other in series and surrounded by porcelain. Their nominal value was 22 kΩ, but even in the
1.2 Instrumentation

case they were 25 kΩ or 18 kΩ, their main characteristic is that they have exactly
the same value. Industrial instrumentation amplifiers are manufactured in such a
way that these resistors are internally mounted and trimmed by laser.

The gain, the CMRR and the input offset voltage of an instrumentation ampli-
plier were measured with different configurations. Each of these configurations
were different in the value of R₁ (Figure 1.5). The values used were: R₁ = 22 kΩ,
R’₁ = 2 kΩ and R”₁ = 200 Ω.

**Gain:** The overall gain of the circuit will be the product of the gain correspond-
ing to the input amplifiers and the output amplifier. As the output amplifier has a
unity gain as all the resistors attached to it have the same value, the gain will be
given by

\[ G = \left(1 + \frac{R₂}{R₁}\right) \]  

where \( R = R₁/2 \).

Therefore, the output amplifier does not contribute to the total gain of the
circuit, although, as it will be seen later, it will be fundamental to achieve a good
CMRR.

However, the gain of the total circuit will be different if the common resistor to
both input amplifiers changes. In order to obtain different outputs corresponding
to different gains, the board had jumpers which allowed to set the different values
of R₁.

The input and the output signals were made via screw terminal connection. The
power supply to the amplifiers was ±15 volts. The configuration used to measure
the gain of the instrumentation amplifier was the single-input amplifier. Then the
gain of the amplifier was obtained for the different setups of the common resistor
maintaining a constant output. It was observed that when the value of the common

---

3Note that the expression adopted in this case to calculate the gain correspond to the non-
inverting gain. This is due to the fact that the two input amplifiers are non-inverting amplifiers
and therefore the resultant gain will be a non-inverted gain. However, if one of the amplifiers or
the two of them were inverted, the expression of the gain should be considered would be the one
given by \( G = -\frac{R₂}{R₁} \).
resistor was increased the input increased proportionally decreasing at the same time the gain of the amplifier.

The voltages and gains obtained for the different setups are resumed in the next table:

<table>
<thead>
<tr>
<th></th>
<th>Input Voltage (V)</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>jumper at $R_1 = 22,\text{k}\Omega$</td>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>jumper at $R_1 = 2,\text{k}\Omega$</td>
<td>0.06</td>
<td>100</td>
</tr>
<tr>
<td>jumper at $R_1 = 200,\Omega$</td>
<td>0.006</td>
<td>1000</td>
</tr>
</tbody>
</table>

**CMRR:** As it was previously pointed out, the output amplifier ($U_3$ in figure 1.4) plays an important role to achieve a good CMRR. This is a differential amplifier characterised by having all the resistors connected to it of the same value. Under these circumstances the output voltage is given by $V_0 = V_2 - V_1$. Therefore, for common mode signals ($V_2 = V_1$), the output should be 0 volts.

The CMRR of the instrumentation amplifier was measured by introducing a common signal of 6.5 V. The measured output was 5 mV, so using the eq.(1.1) the CMRR obtained was 122 dB.

### 1.2.3 Active Filters

It is possible to make circuits that have very specific frequency characteristics by combining inductors and capacitors in different arrangements.

An active filter is constructed by a network of resistors and capacitors built around an opamp (active element). This network passes electric current at certain frequencies or frequency ranges while preventing the passage of others.

In the next subsection it is shown the results of an experiment I performed to study the frequency response of one of the most common active filter configuration: the *Notch filter*. 
Notch Filter

If the outputs of a low-pass and a high-pass filters are added together in equal weight, it is possible to create a notch, or band reject filter. Such a filter is extremely useful for minimizing the presence of noise such as the 50-Hz ‘hum’ produced by the mains.

A pre-fabricated Notch filter module (DCPB491c) was used to determine the main characteristics of a Notch filter: the pass-band gain \( \frac{V_{\text{out}}}{V_{\text{in}}} \) and the \( Q \) value.

The \( Q \) value (quality factor) is used to measure the sharpness of the peak response (notch) at the resonant frequency. The resonant frequency \( f_o \) of a RC circuit corresponds to the frequency at which \( V_{\text{out}}/V_{\text{in}} \) goes to zero as there will be an infinite attenuation of the signal in the RC network.

Therefore, \( Q \) is given by

\[
Q = \frac{f_o}{\Delta f_{3dB}}
\]

where, \( f_o \) is the resonant frequency and \( \Delta f_{3dB} \) is the width at the \(-3 \) dB points.

The next figure represents a classical example of an active Notch filter.
As it has been pointed out before, this filter is mainly used to remove interfering signals. The problem of this circuit is that its cut off characteristics are too gentle. At the same time, the twin-T filter works fine as a fixed-frequency notch, but it is difficult make it frequency tunable, since three resistors must be simultaneously adjusted while maintaining constant ratio. This was the case with our circuit as we will see in the next section.

*Equipment and Method*

A Parallel T 50 Hz Notch filter (circuit PCB DCPB491c) was used to measure its pass-band gain and $Q$ value.

The input and the output signal connections were made via screw connector. Test point were included on the board to facilitate connecting the test equipment, which consisted of a two channel oscilloscope and a sine wave generator.

The circuit had incorporated a Linear Technology Corporation’s LT1013 dual operational amplifier as the active component, fed with an external power supply of ±5 volts. This amplifier buffers the signal so the characteristics of the filter improve, e.g. deep filter null.

One of the most important features of this circuit is the three potentiometers (variable resistors) mounted on the board which allow to tune the filter to different

*Figure 1.7: A bootstrapped twin-T.*
notch frequencies. Two of the filters were initially set as shown in the diagram: P2 was set to 13.7 kΩ, while P3 was set to 7.65 kΩ. The third, P1 was set to its middle position. With this configuration the frequency response of the filter was studied by varying the input frequency and measuring the output with the oscilloscope. Once the filtering action with this configuration was studied, P2 and P3 were twisted in turn to monitor the effect on the filtering action. The same was done with P1.

Finally, another interesting feature of the circuit is the use of two capacitors in parallel (C2 and C8) instead of a single capacitor. Two capacitors were used for two reasons:

1. a better match in between capacitors is achieved if all of them are from the same batch.

2. It is more important that all capacitors have the same value than their absolute value.

3. Easier configuration than measuring and selecting values, as capacitors have a much wider tolerance than resistors.

Figure 1.8: Sketch of the Notch filter used during the experiment.
Results and conclusions

For the initial setup with an input signal of 1 Volt peak-to-peak, the filtering was found to occur at 44Hz. The next table shows the output voltage for the range of frequencies between 10Hz and 60Hz.
<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>$V_{out}/V_{in}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>0.357</td>
</tr>
<tr>
<td>22</td>
<td>0.355</td>
</tr>
<tr>
<td>25</td>
<td>0.350</td>
</tr>
<tr>
<td>27</td>
<td>0.340</td>
</tr>
<tr>
<td>28</td>
<td>0.330</td>
</tr>
<tr>
<td>32</td>
<td>0.300</td>
</tr>
<tr>
<td>35</td>
<td>0.260</td>
</tr>
<tr>
<td>38</td>
<td>0.200</td>
</tr>
<tr>
<td>39</td>
<td>0.180</td>
</tr>
<tr>
<td>40</td>
<td>0.150</td>
</tr>
<tr>
<td>41</td>
<td>0.100</td>
</tr>
<tr>
<td>42</td>
<td>0.070</td>
</tr>
<tr>
<td>43</td>
<td>0.035</td>
</tr>
<tr>
<td>44</td>
<td>0.001</td>
</tr>
<tr>
<td>45</td>
<td>0.035</td>
</tr>
<tr>
<td>46</td>
<td>0.080</td>
</tr>
<tr>
<td>47</td>
<td>0.100</td>
</tr>
<tr>
<td>48</td>
<td>0.150</td>
</tr>
<tr>
<td>50</td>
<td>0.200</td>
</tr>
<tr>
<td>52</td>
<td>0.250</td>
</tr>
<tr>
<td>54</td>
<td>0.250</td>
</tr>
<tr>
<td>54</td>
<td>0.250</td>
</tr>
<tr>
<td>56</td>
<td>0.280</td>
</tr>
<tr>
<td>58</td>
<td>0.300</td>
</tr>
<tr>
<td>60</td>
<td>0.320</td>
</tr>
</tbody>
</table>
Plotting these results, the filtering effect became clear.

![Figure 1.9: Plot showing the behaviour of the Notch filter at different frequencies of the input signal.](image)

From these results, it is possible to infer the quality factor, $Q$ of the Notch filter. Remembering the definition given in eq.(1.4), $f_0 = 44$ Hz and from the graph I estimated $\Delta f_{3dB}$ to be 15 Hz. Therefore, I measured $Q \approx 3$ for this circuit.

It was observed that when $P_1$ was increased, the quality factor increased linearly with the impedance. At the same time, with $P_1$ in its middle point, $P_2$ and $P_3$ were both twisted to their extreme values observing that when they were both at their maximum values the resonant frequency was smaller. On the other hand, at their minimum values the resonant frequency was higher.
1.2.4 Signal Processing: Averaging and signal-to-noise ratio

When physiological signals are measured, one of the parameters that will specify how reliable is the information obtained from the signal will be the signal-to-noise ratio (SNR). This ratio is a measure of signal strength relative to background noise and it is usually measured in decibels (dB). If the incoming signal strength in microvolts is $V_s$, and the noise level, also in microvolts, is $V_n$, then the signal-to-noise ratio, SNR, in decibels is given by the formula

$$SNR = 20 \log \frac{V_s}{V_n} \tag{1.5}$$

The higher the ratio, the more clear will be the signal. One way to increase this ratio would be amplifying the signal. However, in this case the noise accompanying the signal will be amplified too. It will be necessary to process the signal in some sort of way so $V_s$ becomes much greater than $V_n$, and therefore SNR gets bigger. At this stage, we already have seen in the previous section different ways to reduce noise: the noise can be reduced using differential amplifiers (high CMRR); or it could be filtered using the appropriate filter.

Nevertheless, there is still one more technique that can be applied to reduce noise and increase the SNR. This technique is the signal averaging. It is based on the fact that the random characterisation of the noise will make it increase at a slower rate than the signal when the measurement is repeated many times and the results are added together. If the number of measurements performed on a test is $N$, the signal being measured will increase by a factor of $N$, whereas the variance of the noise increases by a factor $N$, i.e. the noise amplitude increases by a factor of $N^{1/2}$. Therefore, the improvement in signal to noise ratio is $\frac{N}{N^{1/2}}$.

In the following sections we will see different types of potentials (EMGs, EEGs, VECPs, etc...) which were measured based upon the signal averaging principle. This filtering process was used to subtract from the signal the background noise, such as for example the one produced by the mains (50 Hz) of the equipment or those produced by another physiological process.
Chapter 2

Neurosurgical Intensive Care Unit

2.1 Introduction

The intensive care unit (ICU) is the postoperative destination for patients following surgical procedures that can be associated with complications in the acute phase (up to 48 hours post op). Head-injured patients or patients undergoing vascular procedures, are two of the largest groups among the patients who are admitted in an ICU. In the former case, a common complication of many serious neurologic conditions is an elevation of the pressure within the skull, the intracranial pressure (ICP). In adults, the average ICP ranges from $0 - 10$ mmHg. $20$ mmHg is considered to be the maximal upper limit of desirable ICP and pressures exceeding $40$ mmHg are considered extremely elevated [5].

The type of monitor used is dependent on a number of clinical factors and mainly they can be categorised into two groups: invasive and non-invasive. Intraventricular catheters or fiberoptic monitor (such as the Camino system) are examples of the first group. On the other hand, transcranial Doppler (TCD) ultrasonography is an example of the second group which is used to assess the cerebral blood flow velocity (CBF) and hence the risk of elevation of the ICP due to partial or complete blockage of the vessels supplying blood to the brain.

Clinical scientists will be involved in the quality assurance of these systems as well as in the management of the data collected with them from an ICU patient. During my visit to the ICU, I performed different experiments in each of these two
Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

Invasive hemodynamic monitoring refers to the measurement of blood flow and blood pressure via devices placed within blood vessels. A fluid-filled catheter records blood pressure through a transducer that converts the information into an electrical signal visible on a monitor. In order to reproduce the pressure signal with a high level of fidelity, the catheter-transducer system has to have a frequency response able to cover the frequency characteristics of the blood pressure signals.

It will be seen that any catheter-transducer system is able to reproduce the pressure signal within certain limits. Therefore the system is required to behave in such a way that distortion of the pressure information is within acceptable limits. The distortion that can occur may be divided into that related to static or very slowly changing pressures, and that connected with dynamic events. I was involved in the assessment of the static and dynamic response of different catheter-transducer system.

Static pressure requirements and calibration

Two main requirements are demanded when pressure is measured using a catheter-transducer system: the readings have to be linear and without hysteresis over the period of time they are taken. By linear it is understood that the proportionality between steady input pressures and the output electrical signal have to be constant over the range of pressures measured with the system. Hysteresis is the effect by which the output levels recorded when steps of increasing pressure are applied are not the same than the levels recorded as the steps decrease. These two requirements have to be tested under condition of minimum drift of the output during the period of time the pressures are measured. The drift of the pressure is mainly produced by the effect of temperature on the transducers together with the drift of the amplifier.

CHAPTER 2. Neurosurgical Intensive Care Unit
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

I performed a static calibration on a disposable Uniflow Baxter transducer before testing it under dynamic conditions to ensure the two requirements above were met. All the equipment used was always sitting in the same room, so thermal equilibrium between components was assumed.

Steady pressures were applied using a pressure generator that allowed to pump air into the catheter-transducer system manually. Before connecting the pressure generator to the transducer, the display of the generator was adjusted to 0 mmHg, so the atmospheric pressure was selected as the reference or zero point for the measurement. Then the generator was connected to the transducer through a three-way tap after filling the latter with water (at room temperature). Both, generator and transducer, were at the same height from the top of the table.

A Spiegelberg compliance monitor acting as a strain gauge amplifier was used to pick up the electrical signal produced by the transducer and to convert it into mmHg. Before starting the measurements, I adjusted the reading of the amplifier to 0 mmHg when the pressure generator was still at 0 mmHg. In this way I ensured that the reference (or zeroing) point of the catheter-transducer-compliance monitor system corresponded to the atmospheric pressure.

Figure 2.1: Arrangement to equipment used to perform the static calibration.
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

In an ideal system the pressure applied should stay steady as no drift would exist. However, in real systems, the pressure varies with time as some electrical drift is present. For the particular equipment I used to perform the measurement, the changing rate of the reading produced by the compliance monitor was negligible.

The Uniflow Baxter transducer is normally used for measuring systemic arterial blood pressure, so in this case, the maximum value of pressure to be measured will be around 40 mmHg. Thus, it is desirable that the transducer behaves linearly and without hysteresis at least between 0 and 50 mmHg. With the pressure generator still connected to the transducer, I set a pressure of 50 mmHg observing that the reading of the compliance monitor increased to 49.3 mmHg. Then, I re-set the pressure generator back to 0 mmHg to observe if any hysteresis was present in this interval. The reading obtained from the compliance monitor was 0 mmHg showing a correct behaviour of the system in terms of linearity and hysteresis. This same operation was repeated 5 times obtaining the following figures.

<table>
<thead>
<tr>
<th>Pressure Generator</th>
<th>0 mmHg</th>
<th>50 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIG1</td>
<td>0</td>
<td>49.3</td>
</tr>
<tr>
<td>SPIG2</td>
<td>0</td>
<td>49.5</td>
</tr>
<tr>
<td>SPIG3</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>SPIG4</td>
<td>0</td>
<td>49.5</td>
</tr>
<tr>
<td>SPIG5</td>
<td>0</td>
<td>49.2</td>
</tr>
</tbody>
</table>

Table 2.1: Results of the two point calibration.

One of the aims of the measurement was to compare the results obtained from a two point calibration with an eight point calibration method. Presently, ICU nurses apply a two point calibration method, so if any significant difference between the two methods is found, it would mean a reconsideration of the calibration procedures for the clinical practice. Therefore, the measurement described in the previous paragraph was repeated, but this time I took five sets of measurements for eight different pressures within the 0 and 50 mmHg interval. The resultant figures were:

CHAPTER 2. Neurosurgical Intensive Care Unit
## 2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

<table>
<thead>
<tr>
<th>Pressure Generator</th>
<th>0 mmHg</th>
<th>5 mmHg</th>
<th>10 mmHg</th>
<th>15 mmHg</th>
<th>20 mmHg</th>
<th>30 mmHg</th>
<th>40 mmHg</th>
<th>50 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPIG1</td>
<td>0</td>
<td>4.2</td>
<td>9.1</td>
<td>14.3</td>
<td>19.2</td>
<td>28.9</td>
<td>39.5</td>
<td>48.8</td>
</tr>
<tr>
<td>SPIG2</td>
<td>0</td>
<td>4.2</td>
<td>8.8</td>
<td>13.5</td>
<td>19.2</td>
<td>28.3</td>
<td>38.7</td>
<td>49.2</td>
</tr>
<tr>
<td>SPIG3</td>
<td>0</td>
<td>5</td>
<td>9.9</td>
<td>14.8</td>
<td>20</td>
<td>29.8</td>
<td>39.7</td>
<td>49.2</td>
</tr>
<tr>
<td>SPIG4</td>
<td>0</td>
<td>5</td>
<td>9.8</td>
<td>14.6</td>
<td>19.4</td>
<td>29.1</td>
<td>39.7</td>
<td>49.2</td>
</tr>
<tr>
<td>SPIG5</td>
<td>0</td>
<td>5.1</td>
<td>10</td>
<td>14.7</td>
<td>19.7</td>
<td>29.4</td>
<td>39.2</td>
<td>49.1</td>
</tr>
<tr>
<td>Mean</td>
<td>0</td>
<td>4.75</td>
<td>9.76</td>
<td>14.47</td>
<td>19.58</td>
<td>29.25</td>
<td>39.42</td>
<td>49.10</td>
</tr>
</tbody>
</table>

Table 2.2: Results of the eight point calibration.

The figures in Table 2.2, were plotted and a ‘best fit’ regression line fitted. In order to quantify the difference between the slopes of the five sets of lines for the two point calibration versus the eight point calibration, I applied the independent samples student t-test to both sets of slopes. This test assumes that the means of both data sets (expected and actual) are equal (Null Hypothesis). This hypothesis produced the following results.

<table>
<thead>
<tr>
<th></th>
<th>slopes-Expected data</th>
<th>slopes-Actual data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.990</td>
<td>0.984</td>
</tr>
<tr>
<td>Variance</td>
<td>$3.8 \times 10^{-5}$</td>
<td>$1.71 \times 10^{-5}$</td>
</tr>
<tr>
<td>Observations</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hypothesed Mean Difference</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>t(8)</td>
<td>1.511</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.084</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>1.859</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.169</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.306</td>
<td></td>
</tr>
</tbody>
</table>

These results suggest that, as $P(T<\=t)$ one-tail > 0.05, the hypothesis of no difference between the means of the expected and the actual measured pressures...
cannot be rejected. The next figure shows no difference between these means.

![Two-point versus Eight-point calibration method](image)

**Figure 2.2:** *Plot of the different sets of measurements made. SPIGX refers to the eight point calibration measurements, while two-x refers to the two point calibration measurements.*

The major consequence of this result is that the clinical staff will not have to spend valuable time in calibrating the system before using it. In fact, the common practice is that the clinical personnel establish the zero point and then technicians periodically calibrate the system to the top of the range of pressures the system will work in.

### 2.2.2 Dynamic pressure requirements and calibration

Fourier theory states that any signal is composed by a finite number of harmonics; so if these harmonics are known, one can reproduce the signal by just summing them. However, not all these harmonics are always required to reproduce the signal at a high level of accuracy. Obviously, the more complicated the signal is, the bigger
number of harmonics will be required to reproduce it.

In the case of human signals, the pressure pulse wave has different shapes at different places of the arterial/venous system, and therefore different number of harmonics will be required at each of these places to accurately represent the pulse wave. The next figure summarises the minimum number of harmonics found necessary to reproduce the pulse wave at different points of the circulatory system and the percentage amplitude contributed by each of these harmonics to the total amplitude of the signal.

Figure 2.3: Normalised amplitudes of harmonics of blood pressure curve. The numbers correspond to the following components of the circulatory system: 1, left ventricle; 2A, central pulse; 2B, peripheral pulse; 3, subclavian pulse; 4, arterial pulse; 5A, pulmonary artery; 5B, right ventricle; 6A, ascending aorta; 6B, abdominal aorta; 6C, femoral artery.
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

Therefore, from these curves, it is possible to conclude that, if the catheter-transducer used is able to reproduce the tenth harmonic of the signal measured, a maximum of 1.5 to 2% of the signal will be lost. An old rule of thumb to establish a boundary above which biological pressure variations may be ignored states that a good reproduction of the blood pressure wave can be achieved if the over-all system sine-wave frequency response extends linearly from zero to 10 times the cardiac frequency (see [6], pg. 48). For example, if the heart rate of a subject is 120/min (i.e. 2/sec = 2 Hz), a linear sine-wave frequency response extending from 0 to 20 Hz will give a good reproduction of the arterial pressure wave. In the following subsections I explain what is understood by sine-wave frequency response of a catheter-transducer system, and what are the parameters determining this response. These explanations are illustrated with the results of relevant experiments I performed on different catheter-transducer systems.

Frequency response and damping effect of a catheter-transducer system

The capability of a system to reproduce a number of harmonics of a physiological signal is called the sine-wave frequency response of the system. The natural (or resonant) frequency of a catheter-transducer system will represent the limit of the frequency range at which the catheter shows a linear sine-wave frequency response. Above this limit, the frequency response of the catheter-transducer system will behave non-linearly (see following diagram).

Figure 2.4: Resonant behaviour of a transducer near its natural frequency.
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

This diagram illustrates the sine-wave frequency response of a catheter-transducer system when the frequency of the signal applied is increased. The oscillation amplitude of the transducer diaphragm increases abruptly in the region of the resonant or natural frequency of the system. Above this frequency, diaphragm excursions fall and the system is unable to follow (transduce) the applied pressure. In this case, the bandwidth of the system is ‘flat’ to about 28 Hz - that is, it accurately reproduces waveforms up to this frequency.

This resonant frequency depends on the characteristics of the catheter-transducer system, such as length and diameter of the catheter, the volume displacement of the transducer and the density of the fluid used to fill the catheter. It has been shown ([6], pg.52) that the natural frequency of a catheter-transducer depends upon these parameters as follows:

\[ f_r = \frac{1.4 \times 10^3 d}{\sqrt{V_d L \rho}} \]  \hspace{1cm} (2.1)

where,

\( f_r \), is the natural or resonant frequency;
\( d \), diameter of the catheter;
\( V_d \), volume displacement;
\( L \), length of the catheter;
\( \rho \), density of the fluid filling the catheter.

Thus, a high natural frequency can be attained by using a transducer with a low volume displacement, connected to a short catheter of a large diameter that is filled with low density fluid.

Although achieving an adequately high natural frequency is one desirable goal, the other is the attainment of an appropriate degree of damping to obtain a uniform sine-wave frequency response. Because the transducer is hydraulically connected to the artery by a fluid-filled system with a characteristic compliance and a determined mass of fluid (inertial component), any change in pressure is not immediately transmitted to the transducer diaphragm (see Figure 2.5). This delay in response is known as ‘damping’. An ideally damped system should be about 70% critically damped.
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

Figure 2.5: The left hand trace illustrates an ‘under-damped’ system. - In this case, it has responded to a square wave applied at or near the natural frequency by becoming grossly overamplified. In contrast, a ‘critically damped’ system is shown on the right. The middle trace represents the best compromise - a system which is about 70% ‘critically damped’; here the overshoot during oscillation is about 7%, but the response amplitude is accurate at frequencies of up to 70% of the natural frequency.

Therefore, it is important to identify the factors which control the damping in the system. From [6] (pg. 54), these factors are related to the damping as follows,

\[
\beta = \frac{16n}{d^3} \sqrt{\frac{3L V_d}{\pi \rho 1.33 \times 10^8}}
\]

where, \(d, V_d, L\) and \(\rho\) represent the same than in Equation 2.1, and \(n\) represents the viscosity of the fluid filling the catheter.

From this last equation, an over-damping effect can be achieved by either using a long catheter (i.e., increasing \(L\)) with a small diameter (\(d\)) connected to the transducer.
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

Frequency and damping response characterisation of different catheter-transducer systems.

I tested the dynamic response of different catheter-transducer systems using sinusoidal and square electrical signals produced using a signal generator. With the sinusoidal waves I studied the sine-wave response of the system (sinusoidal method), whereas with the square signals I measured the damping factor of the system (transient method).

The catheters used were:

<table>
<thead>
<tr>
<th>Catheter</th>
<th>Diameter (mm)</th>
<th>Length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vygon 20 Gauge</td>
<td>0.9</td>
<td>38</td>
</tr>
<tr>
<td>Arterial Flow Switch</td>
<td>1.1</td>
<td>45</td>
</tr>
<tr>
<td>Baxter Quick Catheter</td>
<td>0.75</td>
<td>51</td>
</tr>
<tr>
<td>Arrow 18 Gauge</td>
<td>0.64</td>
<td>445</td>
</tr>
</tbody>
</table>

These catheters were connected to the transducer through a line and a three way tap as shown in the next picture:
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

Figure 2.6: Equipment used for frequency and amplitude measurement.
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

The arrangement of the components of the equipment used to measure the amplitude and frequency of the signal produced by the catheter-transducer system is shown in the next diagram:

![Diagram of measuring equipment](image)

Figure 2.7: Arrangement of the measuring equipment.

First, I measured the frequency response of each catheter using the sinusoidal method. The frequency of the sinusoidal signal applied was gradually increased, observing that at a certain frequency value the amplitude of the signal displayed on the oscilloscope start to decrease. This frequency is the resonant frequency of the catheter. The next figure shows the frequency response of the different catheter-transducer systems I used during the dynamic test.
2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

Figure 2.8: Frequency response of the different catheter-transducer systems.

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2.2 Assessing the static and dynamic characteristics of catheter-transducer pressure measurement system

From these diagrams the resonant frequency was obtained by measuring the frequency point at which the amplitude of the signal started to decrease \( f_{3D} \). The resultant resonant frequencies measured are shown in the next table:

<table>
<thead>
<tr>
<th>Catheter Type</th>
<th>Resonant Frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vyron 20 Gauge</td>
<td>13</td>
</tr>
<tr>
<td>Arterial Flow Switch</td>
<td>8</td>
</tr>
<tr>
<td>Baxter Quick-Cath</td>
<td>11</td>
</tr>
<tr>
<td>Arrow 18 Gauge</td>
<td>12</td>
</tr>
</tbody>
</table>

Once the sine-wave frequency response of every catheter-transducer systems was characterised, the transient test was performed to study the damping factor associated to each catheter. As we can see in Figure 2.1, the three-ways tap is connected to the transducer throughout an adjustable damping tap. This tap consisted of a screw, which could be turned clockwise or anti-clockwise changing the diameter of the tube to produce different damping effects, as predicted in Equation 2.2.

As it was impossible to know the diameter of the tube corresponding to each position of the screw, I measured the damping factor as a function of the number of turns of the screw. So, for each number of turns, the damping was obtained from the ratio \( D_2/D_1 \), where \( D_n \) represents the distance between consecutive peaks of the damping signal (see next figure).

![Figure 2.9: Measurement of the transient response to determine the amount of damping.](image)

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Once these distances were measured, the damping factor associated to the ratio \( D_2/D_1 \) was then estimated from tabulated data ([7], pg. 41–42). The next diagram shows the damping effect on the over-all system for different number of turns when a BD Arterial canule was used.

Figure 2.10: Results of the damping experiment on the catheters showing the damping factor for different catheter diameters.

The number of turns of the tap corresponding to an ideal damping factor of 0.64 was predicted using the function FORECAST of MS EXCEL, resulting 1.4 turns in the case of the short line catheter and 1.06 in the case of the long line. Nevertheless, as the tap was marked with 1/4 turn marks, the position of optimal damping for each line was difficult to be established precisely. Therefore, I determined this position experimentally, arriving at the conclusion that, for each catheter, one turn from the total closure position of the damping tap was the optimum position to obtain an appropriate degree of damping (\( \beta = 0.64, 7\% \) overshoot).
2.3 Electrical Safety in the Intensive Care Unit

Two pieces of equipment were tested to gain some experience in how to perform routine electrical safety tests. In particular: a patient monitor unit and an ICP Analyser were tested using a Biotek PRO 601 Safety Analyser.

In general, equipment should always comply with the standard EN60601 − 1 : 1990 (see [8]). But the objective of these acceptance tests is to check that the equipment complies with the HEI 95, titled ‘Code of practice for acceptance testing of medical electrical equipment’. This code of practice details inspection and test procedures that should be performed on medical electrical equipment before it is put into service.

Medical electrical equipment should be tested on the following occasions:

• On newly acquired equipment prior to being accepted for use (acceptance testing).
• During routine planned preventative maintenance.
• After repairs have been carried out on equipment.

A patient should never be connected to a piece of equipment, which has not passed a safety test.

The importance of visual inspection prior to all electrical testing cannot be overstressed. Most equipment, which has become hazardous or defective due to damage, exhibits visible signs of such, i.e. broken main cable. The main cable of the equipment tested was in perfect condition.

The test was focused on the safety of the:

1. protective earth resistance
2. insulation resistance
3. enclosure leakage current
4. patient leakage current
2.3 Electrical Safety in the Intensive Care Unit

The first test was made on the patient monitor unit, which was classified as a Class I type CF (see [9]). It presented external metal parts and an earth path where the tester probe was connected. Previous to any test, the resistance of the protective earth conductor is measured between the earth pin on the mains plug and a protectively earthed point on the equipment enclosure. The reading should not exceed 0.2 $\Omega$ at any point. The test is obviously only applicable to class I. If protective earth continuity is satisfactory then insulation tests can be performed. For class I equipment the insulation is measured at the mains plug between the live and neutral pins connected together, and the earth pin. Satisfactory earth continuity and insulation test results indicate that it is safe to proceed to leakage current tests.

This equipment is used for clinical use, being connected to the patient via metal leads. If by any chance, a current path is created from the monitor unit through the patient to the ground, current could flow through the patient causing cardiac fibrillation. Therefore, it is extremely important to check that no current can flow from the applied part/s of the equipment to the patient. Similarly, an operator in contact with any faulty equipment with broken protective earth conductor or with any point on the enclosure of the equipment not protectively earthed can become a current path and suffer similar physiological consequences. To ensure none of these two situations occur, earth and enclosure leakage current tests are performed. In particular, these tests were both performed under single fault condition (SFC), that is with the earth wire interrupted, or with the neutral interrupted, or with the live interrupted.

This unit passed all the tests, as we can see in Figure 2.11(a).

The other piece of equipment tested was an ICP analyser, which failed when its insulation resistance was tested (insulation resistance = 18.8 M$\Omega$ < 50 M$\Omega$). This equipment was classified as Class I Type B, so no earth connection appeared due to its double isolation. The reason of the fault was caused by a low resistance neon light across the L (live) and N (neutral) supply. Coupling the analyser to an isolation transformer solved the problem. The results of this test can be seen in Figure 2.11(b).
2.3 Electrical Safety in the Intensive Care Unit

Figure 2.11: (a) Failed test on an ICP analyser. (b) Successful test on a patient monitor unit. The results of the tests are given together with their limits in squared brackets. This limits are specified in HEI95.
2.4 Neuro-Intensive Care Monitoring

One of the main activities of the group of clinical scientists working at the Institute of Neurological Sciences, is the development and assessment of new forms of both invasive and non-invasive health care technology towards improving the management of brain injured patients. This group analyses data shared by multiple centres across the world joined all together in a neuro-intensive care monitoring research group called Brain-IT, which is co-ordinated from the Institute. Each member of the group contributes to a common Internet database with data collected according to a standard protocol. The use of this Internet based infrastructure has lead to the establishment of a large, standardised database of physiological monitoring data, demographic and patient treatment data which provides a powerful tool for post-hoc development of new data analysis and hypothesis generation methodologies. At the same time, medical device manufacturers will find this information useful to assess new technology, as the data should be collected using the same software and hardware in order to facilitate a faster data analysis.

I was involved in the monitoring of the arterial pressure of an ICU patient. Although the patient did not correspond to the group brain injured patients, the standard procedure to monitor the patient is still applicable. The arterial pressure of the patient was monitored using Baxter Quick Catheter connected to a three ways tap, which in turn was connected to a Disposable Baxter Transducer. The transducer was zeroed to the atmospheric pressure by opening the three ways tap to air. Then it was located at the same height of the heart and plugged to the monitoring unit which was constituted of a Spiegelberg Pressure Monitor, an A/D converter and a portable computer with a standard software package used by all the components of the Brain-IT group. The next two diagrams show how the equipment is set up and an example of the standard way the data monitored from the patient is presented.
2.4 Neuro-Intensive Care Monitoring

Figure 2.12: Upper: *Set up of the monitoring equipment (hardware).* Lower: *Standard presentation of data collected from bedside patient for consequent analysis.*
In the case of head injured patients, cerebral perfusion pressure (CPP) is a critical parameter that has to be continuously monitored as autoregulation may not occur. In a normal patient, cerebral blood flow (CBF) and CPP are paired for pressures between 60 mmHg and 140 mmHg, this is, autoregulation maintain these two variables independent in the mentioned interval. However, in brain injured patients, pressure autoregulation may be affected in such a way that CBF and CPP became impaired and changes in CBF produces dramatic changes on CPP. Therefore, if these patients have to lie inclined to reduce cerebral blood supply, this tilt can cause a hydrostatic gradient that can affect CPP, as we can see below.

Cerebral perfusion pressure (CPP) is the difference between mean arterial blood pressure (BP) and cerebral venous pressure (CVP).

\[ CPP = BP - CVP \] (2.3)

BP can be measured directly however CVP and CPP cannot. Intracranial pressure (ICP) is the pressure exerted by cerebral spinal fluid. It is approximately equal to the CVP and can be directly measured. So CPP can be derived from,

\[ CPP = BP - ICP. \] (2.4)

However there are some problems with this measurement. If the mean arterial pressure is zeroed at the height of the heart, the arterial pressure at the level of the head will be the blood pressure minus a hydrostatic pressure column due to the height of the head above the heart.

\[ CPP = MAP - (ICP - HPG) \] (2.5)

The effect of the hydrostatic pressure gradient (HPG) established due to the inclination of the bed is negligible if the patient is lying flat. However patients who have sustained head injuries often lie in an inclined positioned to enhance venous return of blood from the brain. I investigated the effect of the HGP by setting up a pressure transducer connected to a fluid filled line. I placed the transducer approximately at the level of the heart on a tilting couch and placed the top of the fluid filled line \( \approx 30 \) cm away on the incline of the couch. I then used an
inclinometer to incline the bed through a series of angles from 0° to 50°. The next diagram illustrates this last paragraph.

![Diagram](image)

Figure 2.13: *Diagram showing the arrangement of the components used to measure the effect of the hydrostatic pressure gradient produced by the inclination of the head injured patients bed.*

From here it is possible to understand that the HPG is calculated from the following,

$$ HPG = h \tan \theta $$(2.6)

The results I obtained from 2.6 are shown in the following table.

<table>
<thead>
<tr>
<th>Couch angle (°)</th>
<th>HGP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>3.96</td>
</tr>
<tr>
<td>20</td>
<td>8.18</td>
</tr>
<tr>
<td>30</td>
<td>12.98</td>
</tr>
<tr>
<td>40</td>
<td>18.87</td>
</tr>
<tr>
<td>50</td>
<td>26.81</td>
</tr>
</tbody>
</table>

The pressure figures were obtained from the strain gauge monitor. The most extreme angle for a patient to be tilted at is 30° which would mean a difference of ≈ 13 mmHg to the CPP measurement which is quite significant if HGP is not taken into account.

*CHAPTER 2. Neurosurgical Intensive Care Unit*
Chapter 3

Ophthalmic Electrophysiology

3.1 Electroretinography, ERG

The waveforms produced in electroretinography reflect the activity of different types of cells (rods and cones) within the retina. The most sensitive part of the retina is the fovea where the density of cones is much greater than the density of rods. However, around the fovea the density of rods exceeds the density of cones. Therefore, using different types of light stimuli\(^1\) it is possible to study the response of cones and rods separately and in conjunction. These different types of stimuli lead to five different responses which are analysed in different types of tests.

The ERGs can aid the diagnosis of a wide range of retinal conditions and when used in conjunction with electrooculography and visual evoked potentials, enables the clinician to isolate the site of dysfunction. Some of these dysfunctions are:

1. Retinal dystrophy, e.g. Retinitis Pigmentosa
2. Unexplained visual loss
3. Vascular conditions
4. Toxic or nutritional conditions
5. Retrobulbar neuritis

\(^1\)Each of these stimuli will be different in intensity and duration.
6. Glaucoma

An ocular electroretinography test was made in a healthy patient to observe the procedure followed to acquire data and its analysis.

The equipment used was: (i) a dome stimulator, where the light stimuli were produced. (ii) The physiological signals were collected using recording electrodes and reference electrodes. These electrodes were connected to two different amplifiers, one for each eye. (iii) Then, the amplified signal was sent to a computer where it was averaged and stored for later analysis.

Before starting the test, the patient’s pupils were dilated with one drop of 1% Tropicamide preparation in each eye. To achieve full dilation ISCEV recommends waiting for a minimum period of 10 minutes [11]. During this period, the reference skin electrodes were placed near each orbital rim. Together with these two reference electrodes, a ground electrode was placed at some point on the forehead half way from each of the reference electrodes. Before each electrode was fixed, the skin area was cleaned and rubbed with a conductive gel to ensure good electrical connection. Once these three electrodes were conveniently placed, their impedance was measured resulting in a reading of less than $4 \, k\Omega$ for every possible combination of electrode pair connection. These were within the range of $0 - 5 \, k\Omega$ recommended by the ISCEV protocol [11].

After the period of 10 minutes, the patient’s pupils were observed to be maximally dilated. Then the lights of the room were turned off in order to adapt the patient’s eyes to dark conditions (‘scotopic’ condition). This period lasted for 20 minutes.

After this period, it was explained to the patient that the active electrodes had to be placed under the lower eyelid touching the sclera in each eye. The discomfort can be reduced by applying local anaesthetic (1 drop of Benoxitate). The patient consented to use the anaesthetic and after a period of 2 minutes to let the anaesthetic have its effect, the ‘gold-foil’ electrodes (active electrodes) were inserted (see Figure 3.1).
3.1 Electroretinography, ERG

Figure 3.1: *Active electrodes for ERG.* From left to right: Burian-Allen, gold-lens, H-K loop and gold-foil electrodes.

Before insertion, electrodes were immersed in three different solutions, each one in different containers, to prevent irritation or infection of the eye. By order of immersion, the solutions used were: Chlorhexadine, sterile water and a saline solution. This last solution provides good ionic conduction in order to avoid attenuation of the signal amplitude.

As the extent of the area of retinal illumination is unknown for every individual patient and the stimulation should cover the full area of illumination, a chin rest was used to ensure the patient was in a central position. To ensure constant fixation of the eye, the patient was asked to look straight ahead and told to try not to blink in order to avoid signal artifacts.

As recommended in the local protocol, the cut-off frequency of the amplifiers and preamplifiers was set to 300 Hz, with a preselected gain of 1000. The signal was converted from analogue digital with a digitizer which had a sampling rate of 1200 Hz. The digitizer was connected to a computer where the sampled physiological response was displayed in real time so the operator was continuously monitoring the stability of the signal and making adjustments during the test procedure, i.e. changing the gain in case the signal was too small. The signal was averaged every time it was sampled, so the output signal was free of artifacts.

\(^2\text{See Section 1.2.4.}\)

CHAPTER 3. Ophthalmic Electrophysiology
3.1 Electroretinography, ERG

The test involved five different responses:

1. A rod response (in the dark-adapted potential)
2. A maximal response in the dark adapted eye
3. Oscillatory potentials
4. A cone response (in the light-adapted eye)
5. Responses to a rapidly repeated stimulus (flicker)

The first signal measured after dark adaptation was the rod response. The signal was measured at different stimulus strengths (brightness) by filtering the light flashes with neutral density filters that convert the white light into blue in order to emphasize the rod activity. The set of filters used allowed attenuation by 0.5 log units over a range of 0 to 5 log intensity units. Thus, the test was performed attenuating the standard flash\(^3\) (SF) strength by: 0 log, 0.5 log, 1 log, 1.5 log, 2 log, 2.5 log, 3 log, 4 log and 5 log intensity units\(^4\). The stimulus duration was selected to be considerably shorter than the integration time of any photoreceptor (≈ 5 ms). Finally, the stimulus wavelength corresponded to an approximate color temperature of 7000 K.

The critical parameters measured were the amplitude and the implicit time of the responses represented by the curves plotted in the insertion (a) of Figure \(\beta\). Each of these curves represents a ERG waveform. This waveform is constituted by the addition of two main components: the a- and the b-waves, which are electrical potentials of different polarity (a- wave negative and b-wave positive), amplitude, duration and absolute latency\(^5\).

\(^3\) A standard flash is the stimulus produced by a standard system, defined by the International Society for Clinical Electrophysiology of Vision (ISCEV) as: ‘one that produces a stimulus strength (in luminous energy per square meter) at the surface of the Ganzfeld bowl of 1.5 – 3.0 photopic \(\text{cd}\cdot\text{s}\cdot\text{m}^{-2}\) (candela-seconds per meter squared). This is equivalent to luminance-time, measured as \(\text{cd}^{-2}\cdot\text{s}\). Note that these are photometric units and that 3.43 \(\text{cd}^{-2}\cdot\text{s}=1\ \text{fL}\) (foot-Lambert)’. See [11]

\(^4\) In clinical practice only 2.5 log intensity units are used.

\(^5\) By absolute latency is understood the time interval between the flash and the response onset.
3.1 Electroretinography, ERG

Figure 3.2: Typical waveform of a dark-adapted (scotopic) ERG recorded in response to a high intensity flash. The a-wave amplitude is measured from the baseline down to the lowest point of the trace, and the b-wave amplitude is measured from the bottom of the a-wave to the highest positivity. In all succeeding figures, the calibration lines allow computation of duration (or peak times) in milliseconds and amplitude in microvolts of the ERG waves.

As can be seen in the set of curves of Figure β(a), the b-wave represents the largest contribution to the total waveform as its amplitude is always bigger than the a-wave amplitude. The difference in amplitude is measurable at low intensity stimulus, where only the b-wave appears. As the intensity of the flashes increases, the a-wave component starts to appear as well. This later appearance of the a-wave is due to the different origins of the a-wave and the b-wave. The a-wave is the leading edge of the receptor potential originated at the photoreceptor (outer) layer of the retina as a response to a diffuse flash. The b-wave is generated at the mid-retinal layer via Mueller-cell activation, as it is shown in the next figure which indicates the contribution of the different layers of the retina to the total ERG when the eye is dark adapted.
3.1 Electroretinography, ERG

Figure 3.3: Correlation of the different ERG components with the retinal structures that are associated with their generation.

Looking at this structure it is possible to understand how a second-order neural change such as the b-wave can obscure a primary one (the a-wave). The receptor potential of the photoreceptors is caused by an unbalanced influx of extracellular Na\(^+\) ions near to the site of quantal absorption. This effect produces a hyperpolarization of the entire receptor membrane (due to a much higher intracellular concentration of K\(^+\)) with the result of a negative-going potential. On the other hand, the b-wave is the result of an unbalanced concentration of extracellular K\(^+\) ions which produces a change of the membrane potential of the bipolar-Mueller cells. With a dim light the polarization of the photoreceptor membrane is slower than the bipolar cells, and only at high intensities are the photoreceptors excited quickly enough to contribute to the total ERG. At the same time, as each bipolar cell collects the signal from different photoreceptors, the amplitude of the signal corresponding to such cells will be bigger than the one of the photoreceptors. Due to all these reasons, the b-wave is used as a very accurate measure of the retinal sensitivity.

Previous studies [13] have shown that the parametric analysis of the ERG leads to a higher sensitivity in identifying patients who could develop rubeosis in central retinal vein occlusion (CRVO). I carried out an investigation of the retinal sensitivity using an ERG waveform obtained from one of my colleagues to measure: (i) the amplitude of the b-wave versus the flash log intensity (insertion (b) of Figure 3). This amplitude was measured from the a-wave through to the b-wave peak. And (ii),
the implicit time was measured from the flash onset to the peak of the correspondent wave.
3.1 Electroretinography, ERG

Figure 3: (a) Study of the evolution of the ERG waveform amplitude when the intensity of a dim white flash was decreased in steps of 0.5 log I. The two main components of the waveform are clearly delineated at high flash intensities; the a-wave is measured from the baseline downward to the very bottom of the negativity, and the b-wave is measured from the latter point upwards to the positive peak. The figure demonstrate why the a-wave, which is the leading edge of the receptor potential, does not appear in the complete ERG response at low intensities. Because the receptor potential is generated so slowly at low intensities, it is completely masked by the earlier-appearing b-wave. Only at high flash intensities (from 2 log I to the maximum response) does the receptor potential appear early enough to be detected in the complete ERG.

(b) Voltage versus log intensity (V log I) plot for the b-wave response. As it is shown in (a), the greater sensitivity of the b-wave to a flash of any intensity is particularly obvious at the lower values, where the V log I plot has its steepest slope.
In [13] is shown that the points in Figure $\beta$(b) describe a sigmoid curve with a plateau at high values of I. However, this plateau does not appear in the figure due to the intensity values used were not high enough.

After the maximal combined response, corresponding to the 0 log measurement of the rod response test, the next test was the measurement of the oscillatory potential. This time, the dark-adapted-eyes were stimulated each 15 seconds after setting the high pass filter cut-off to 75 Hz. The appearance of the oscillatory potential resulting from the test seems to be in perfect accordance with the description given in the standard: ‘... three major peaks often followed by a fourth smaller one’. However, this appearance is highly dependent upon stimulus conditions, adaptation and amplifier filter characteristics.

The aim of the last two tests performed was to study the cone response. In these two tests the patient was resting for 10 minutes with a low light background in order to allow the eyes to adapt to the light. Then, the first test performed was the single flash ‘cone response’, where a single white SF is applied several times to allow averaging (as in the rod test). The instant rod response to the flash is suppressed by the background light allowing the recording of a single peak corresponding to the cone response. As we can see in the report sheet, the first response -the cone response- will be represented by a peak signal.

Another way to check the cone response is by applying a stimulus that does not allow the rods to recover from their saturation state so the entire response becomes a cone response. This is the case when a 30-Hz high-intensity flash flicker is applied. In this case, and under the same conditions of light adaptation, the patient is exposed to stimulus of 30 flashes per second which produce a pure cone response due to the slow recovery of the rods (only able to recover to flash rates lower than 10 times per second). The first few responses were discarded in order to achieve a stable response to the excitation. As it is possible to observe in the report sheet, every single signal of the flicker response is related only with cone excitation.
3.2 Electrooculography, EOG

Principally, the EOG indirectly records the electrical activity that takes place in the retinal pigment epithelium (RPE). Therefore this test is useful in inherited retinal
dystrophies or degenerations such as Best’s or Stargart’s disease, where the RPE is specifically affected. One of the main disadvantages of this test is that it does require some patient participation and therefore is not entirely objective, being necessary to combine it with another test such as the ERG.

In this test the amplitude of the light response and the \textit{standing potential}, \( V_{sp} \), generated across the eye is measured when the eye is exposed to an intense light stimulus after being in complete darkness for a determined period of time.

The standing potential of the eye is the result of a voltage difference between the front of the eye (cornea), with positive charge; and the back of the eye (retinal pigment epithelium), with negative charge. This standing potential is measurable indirectly, using the fact that the change of the spatial orientation of a polarized eye will produce a voltage change which can be recorded by placing skin electrodes on the nasal and the temporal sides of the eyes, close to the eye rim. Thus, if a patient executes saccades between two fixed points under recording conditions, the changing potential will be represented by square waves of different amplitudes.
Two main factors determine the amplitude of the square waves: (i) the extent of the left or right eye-swings; and (ii), the light condition of the background. Obviously, if the fixation points remain equidistant from the centre of the visual field, the amplitude of the square waves will only depend on the brightness of the background light.

This test was performed using a full field dome stimulator with fixation targets constructed from red LEDs that induce eye movements of approximately 30° visual angle in the horizontal meridian. The electrical signals were collected using silver-silver chloride skin electrodes applied with a conductive paste on the region of the skin previously rubbed to ensure the best quality recording. The electrodes were positioned: 2 in the outer canthi (OC), 2 in the inner canthi (IC), and one (ground) on the middle of the forehead (Ref). The impedance of the electrodes should not exceed 10 kΩ.
3.2 Electrooculography, EOG

Figure 3.6: Left: Positioning of the electrodes. Right: Different types of electrodes. From left to right: silver silver-chloride, single use neurological and gold.

The amplifier used was set to a gain of 1000 with a high pass filter cut-off at 0.5 Hz.

After 20 minutes of dark adaptation, the patient was placed in front of the dome (at 30 cm from the red light) and the test was then started with the dark adaptation phase. The protocol used to measure the EOG was based upon the calculation of the Arden ratio, which is the ratio of light peak to dark trough. This dark trough was obtained by recording the EOG values while the patient was changing the direction of his eyes 10 times each two minutes. The amplitude of the signal was continuously decreasing until a minimum value was reached. This value corresponds to the trough of the curves shown in the Figure 3.7. Once the amplitude kept roughly constant at this trough value, the patient retina was exposed to a steady bright light, producing a steep rise of the amplitude of the EOG. After 3 minutes of light adaptation, the patient was asked to follow again the red lights. The saccades were repeated again every minute until the signal reached its maximum. This maximum amplitude will be the light-peak value required to obtain the Arden ratio. When the value of this ratio is under 1.7, the Arden Index is abnormal. If the Arden value is between 1.7 and 1.9, it is said to be equivocal; and a normal Arden index is any number above 1.9. In particular, the patient tested was within the normal Arden index, with an index value of 2.99 on the right eye and 2.37 on the left eye, as is observed in the sample report submitted. The meaning of the normal or abnormal value of the

CHAPTER 3. Ophthalmic Electrophysiology
Arden index refers to the integrity of the photoreceptors-RPE complex to generate the standing potentials which produce a recordable signal. In other words, the EOG light rise reflects activity from the mid-retinal layers which indicates the stimulation of the RPE cells. A disease of the macular area would affect most of the RPE, and no detection of EOG light rise would appear, giving as a result a Arden index below the minimum $1.7$.

Figure 3.7: EOG of the right and the left eye of the tested subject. Each point of these curves represents the average amplitude of 10 saccades each two minutes. The Arden ratio is obtained from the ratio light-peak/dark-trough.
3.3 Visual Evoked Cortical Potentials, VECP

This section discusses the technique used to assess objectively the integrity of the entire visual system. This assessment is based on the measurement of the electrical potentials generated in the occipital cortex when the retina is stimulated.

In order to record these signals, the ISCEV protocol ([12]) recommends the measurement of the electrophysiological signal using standard EEG techniques. The electrodes used to perform standard VECPs are standard silver-silver chloride electrodes. The electrodes were located on the scalp following the International 10/20 System. The skin was rubbed before the application of the electrodes to achieve a scalp-electrode impedance below 5 kΩ. To ensure good conductivity, a conductive paste was used to fix the electrodes to the scalp. The active electrodes were positioned 10% of the nasion-inion distance above the inion and the reference electrodes were placed 30% of the nasion-inion distance above the nasion; while the ground electrode was located elsewhere on the head. However, the exact positioning of the electrodes is fully described in the protocol.

Figure 3.8: Positioning of electrodes recommended by the ISCEV: (a) lateral view; (b) anterior view; (c) superior view.
The electrodes are then connected to a Biodata Amplifier. The cutoff values of the filter were set to 0.2 sec for low-pass and 100 Hz for high-pass. The input impedance of the preamplifiers was checked to be higher than 10 MΩ to allow good amplification of the signal in the main amplifier.

Most clinical VECP recordings involve placing a patient in front of a black and white checkerboard pattern displayed on a video monitor. The checks alternate black/white to white/black at a rate of approximately twice per second. Every time the pattern alternates, the patient’s visual system generates an electrical response that can be detected by the electrode on the back of the head. A typical VECP response (Figure 3.9) comprises a well-defined positive peak at around 100 milliseconds. Hence this peak is commonly called P_{100}.

![Figure 3.9: Standard shape of a typical VECP response](image)

However, it is important to note that ‘P_{100}’ is only a label for the positive peak of the VECP; although the latency of these peaks is about 100 msec after the stimulus onset in normal patients, this latency can be lengthened by several milliseconds by manipulation of stimulus conditions or the presence of many ocular diseases. Two stimulus conditions affect the latency of P_{100}: the size of the checks and the contrast of the monitor used to generate the stimulus. The smaller the checks or the pattern contrast, the bigger the P_{100} peak-time latency.

So far we have discussed the different aspects affecting the latency of the P_{100} and nothing has been said about its amplitude. The reason is because this amplitude does not give any relevant information unless one of the patient’s eyes is known to be abnormal. In this case there will be an interocular difference between the P_{100}.

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*Traditionally, in neurological literature the positives peaks of a VECP are shown ‘upside down’.*

**CHAPTER 3. Ophthalmic Electrophysiology**
amplitude of the eyes as a consequence of the disease. This difference is increased when the contrast of the monitor is decreased. This tool can be used as a sensitive indicator of ocular conditions other than optic nerve disease such as cataract, macular disease, and some types of amblyopia.

The ISCEV recommends that every laboratory establishes its own norms using its own stimuli, recording equipment and parameters. In the case of the Tennent Institute of Ophthalmology, at the Gartnavel General Hospital in Glasgow, the normal values of latency and amplitude were set for check sizes of 60’ (≈ 1°) and 15’ (≈ 0.25°). These values are shown in the next table.

<table>
<thead>
<tr>
<th></th>
<th>Normal Latency (msec)</th>
<th>Normal Amplitude (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60’</td>
<td>15’</td>
</tr>
<tr>
<td>MO</td>
<td>85-109</td>
<td>89-116</td>
</tr>
<tr>
<td>LO</td>
<td>82-120</td>
<td>88-126</td>
</tr>
<tr>
<td>RO</td>
<td>82-120</td>
<td>88-126</td>
</tr>
</tbody>
</table>

Table 3.1: Normal values of the latency and the amplitude of the VEP responses, where MO ≡ Mid-Occipital, LO ≡ Left-Occipital and RO ≡ Right-Occipital.

The next figure shows the results of a VECP obtained from a normal patient using monocular stimulation and placing the patient at 35 cm from the screen.
3.4 Optical Coherence Tomography, OCT

As can be seen, all the values are within the normal expected ranges.

3.4 Optical Coherence Tomography, OCT

Up to this point, all the techniques have been used to diagnose diseases of the eye have been based on the electrical signals following the exposure of the retina to light. All these techniques (apart from the multifocal ERG) give us information about the visual system as a block, based on the signals received outside the ocular glove (either from the occipital cortex or the orbital rim). But they do not provide specific anatomical information about the disease, which, on the other hand, would be very valuable.

Ultrasound imaging is being widely used clinically to perform routine checks...
of the back of the eye, giving us information such as intraocular distances. This technique provides cross-sectional images of intraocular structures based on the reflection of sound waves from these structures. This requires direct contact of the ultrasound measuring device to the cornea or immersion of the eye in a liquid which facilitates the transmission of sound waves into the glove.

Another problem involved in the use of ultrasound as a technique for imaging is its resolution. Compared with optical techniques which can provide a very high spatial and time resolution (10 microns and 30 fs respectively), ultrasound does not seem the best option. Recently, high resolution ultrasound imaging systems have being developed providing resolutions on the 20 micron scale; while standard ultrasound systems only provide 150 microns which is equivalent to a time measurement of 100 ns.

One of the advantages of the ultrasound is its ability to be transmitted into most biological tissues being therefore possible to obtain images of structures deep within the body. However, at high frequencies, the ultrasound is strongly attenuated in biological tissues. Consequently, imaging can be only performed to depths of only 4 to 5 mm, limiting the application of high resolution ultrasound to the anterior eye.

All these disadvantages present in ultrasound imaging are overcame when light is used for imaging. In this case, there is no physical contact between the measurement device and the cornea, minimizing the patient discomfort during examination. Besides, the resolution of the light imaging system is significantly higher than the ultrasound systems, allowing its use to image fine structures within the retina and the interior eye. However, light is highly scattered or absorbed within most biological tissues and therefore optical imaging is constrained to tissues which are optically accessible either directly or via an endoscope or catheter. For this reason OCT is ideally suited for Ophthalmology.

OCT is based on ‘low-coherence interferometry’. This technique is applied using an interferometer which can measure the time delays of optical echoes by comparing the reflected light beam from a specific structure within the eye, with a reference beam. The reference beam comes from a reference mirror. This is positioned at such distance from the detector that the reference pulse is delayed so that it coincides with an echo pulse from a particular structure in the eye.

CHAPTER 3. Ophthalmic Electrophysiology
Figure 3.11: \textit{OCT is based on optical interferometry}

The next figure shows the components of the Humphrey OCT System used to scan different parts of the eye.
Figure 3.12: A low-coherence light (diode or red laser) is used as a source light, and then decomposed in two beams the fiber coupler. After reflection of these two beams they are joined again together and then detected. The light detector is connected to a computer which analyzes the component of the detected light to perform an OCT image.

OCT has been shown to be clinically useful for imaging selected macular diseases including macular holes, macular edema, age-related macular degeneration, central serous chorioretinopathy, epiretinal membranes, schisis cavities associated with optic disc pits, and retinal inflammatory diseases. In addition, OCT has the capability of measuring the retinal nerve fiber layer thickness in glaucoma and other diseases of the optic nerve.

Following these lines are shown a set of pictures of different structures of the eye scanned from patients with different eye diseases using the Humphrey OCT System. These scans were performed as shown in the next diagram:
The optical beam is scanned in the transverse direction. Each of the axial measurements made along the transverse direction will provide two different parameters: distance and reflectivity. These data are then displayed in a false color representation where the reflected optical signal is represented on a logarithmic scale of brightness mapped onto a color scale using the standard ‘rainbow’ order of colors. High intensities are represented by red and white colors while low intensities are represented by blue and black. Thus, the image displayed is a true dimensional image of tissues with different scattering properties.

The next images were obtained using the Humphrey OCT System.

Figure 3.13: Left: Fundus surface of the eye with a glaucoma. The bright line represents the red laser used to scan the surface. Right: OCT showing the shape of the scanned surface.
Chapter 4

Neurophysiology

4.1 Introduction

During my visit to the Institute of Neurological Sciences, I had the chance to operate some of the equipment used in the department and to perform standard Neurophysiological tests on myself.

The aim of these tests is to obtain information from the nervous system of an individual with some neuropathology so a specific neurological disease can be diagnosed and treated.

Due to the small size of the signals measured, it is necessary to use specific equipment capable of receiving and recording very small signals.

4.1.1 Instrumentation

The main component present in this equipment is isolated biological amplifiers which are basically differential amplifiers characterised by:

- High input impedance and low source impedance. In general, the impedance of the electrodes (source impedance) will be much lower than the impedance of the amplifier itself (input impedance).

- High Common Mode Rejection Ratio (CMRR).
4.1 Introduction

Another issue related to instrumentation is the isolation of the equipment from the patient. This is achieved by using a 'head box' which provides galvanic separation of the biological amplifier(s) from the rest of the equipment. In this head box the power is transferred to the amplifier through a transformer which will provide isolation of the patient against high voltages (mains supplies). There is an increasing use of Digital Head boxes where an A/D converter follows the amplifier stage and the isolation is of the digital signal, which is transmitted to the main instrument.

4.1.2 Neural stimulation.

Neural stimulation is one of the most important physiological effects when a current is applied to the body. If a current of sufficient amplitude is passed between a pair of surface electrodes applied to the skin, then this current will have the biological effect of contracting a muscle. This effect is due to the excitation of the nerve fibres supplying the muscles.

A nerve is stimulated when the transmembrane potential\(^1\) at some point of the nerve (active region) is reversed by an externally applied current. If, where the current enters the nerve, the externally applied current flows from positive to negative, then the transmembrane potential will be increased, and where the current leaves the nerve, the transmembrane potential will be reduced. Stimulation will occur where the current leaves the nerve. If the positive electrode is called the anode and the negative the cathode, then the stimulation starts underneath the cathode.

If the current used is an alternating current then a graph can be drawn which shows the frequency of the current against the amplitude which is necessary to cause neural stimulation. The next figure shows such a graph and illustrates that the lowest threshold for stimulation is within the \(10 - 50\) Hz range. Above about \(200\) kHz (each cycle lasting \(5\) \(\mu\)s) stimulation is almost impossible. A current lasting at least \(50\) \(\mu\)s and preferably as long as \(20\) ms is needed to stimulate nerve fibres (see, [15]).

\(^1\)The transmembrane potential refers to the electrical potential created across the cellular membrane as a result of the displacement of positive ions (\(^+\)K) outwards the cell membrane while the negative ions (\(^-\)Cl) stay within the cell.
4.2 Neural stimulation tests

4.2.1 Electromyography, EMG

The first test in which I was involved was an Electromyography test practised on my right arm. The aim of this test was to record the electrical activity of the muscles of the arm in order to diagnose any possible muscular neuropathology.

The muscle is organised into a number of motor units each consisting of a nerve axon and the muscle fibres it innervates. Diseases affect the configuration of motor units changing the amplitude, duration and ‘shape’ of the action potentials they carry. The electrical signals can be taken from the body either by placing needle electrodes in the muscle or by attaching surface electrodes over the muscle. Needle electrodes are used where the clinician wants to investigate neuromuscular disease by looking at the shape of the electromyogram (looking for fibrillations and changes in the configuration of the motor unit). Surface electrodes are only used where the overall activity of a muscle is to be recorded. Both surface electrodes and needle electrodes only detect the potentials which arise from the circulating currents surrounding an active muscle fibre, and do not enable transmembrane potentials to

The reason there is a minimum time required to excite a nerve is due to the capacitance properties of the membrane surrounding the neural axon.
be recorded. Nerves and muscles produce electrical activity when they are working voluntarily, but it is also possible to use an electrical simulator to cause a muscle to contract and the electrical signal then produced is called an *evoked potential*. This is the basis of the nerve conduction measurements, which allow the speed at which nerves conduct electrical impulses to be measured (see following subsections).

![Figure 4.2: The tip of a bipolar needle electrode.](image)

Three types of lesions can be monitored by Electromyography:

(a) Nerve lesions

(b) Muscle lesions

(c) Neuromuscular transmission defects

*Nerve Lesions*

In normal muscle there should be no spontaneous activity at rest. Nerve diseases cause denervation of the muscle fibre. Small short duration potentials called fibrillation are found during the active process of denervation and this is caused by unstability in muscle fibres that have lost their nerve supply. These ‘free’ muscle fibres are then re-innervated by remaining motor axons. Thus there is a re-modelling of motor units with a decrease in their numbers and an increase in their size. The reduction of the number of motor units will affect the interference pattern: in a normal person, the EMG should show a full ‘interference pattern’ during strong
4.2 Neural stimulation tests

voluntary contraction of the muscle while this pattern is reduced in a patient with established neuropathy.

**Muscle Lesions**

In primary muscle disease (e.g. muscular dystrophies) muscle fibres reduce in size giving rise smaller polyphasic motor unit potentials.

**Neuromuscular Transmission Defects**

Inadequate release of transmitter (acetylcholine) or faulty receptors in the membrane can cause abnormal delays in or failure of activation of the muscle fibres. This can be investigated by measuring single fibre electromyographic (SFEMG) jitter or repetitive stimulation.

**Nerve Conduction Velocity (NCV)**

The following tests correspond to EMG signals I measured to assess the sensory and the motor nerve conduction velocity of a stimulus through the Ulnar nerve. This nerve is located in the arm and goes from the spinal cord through shoulder and elbow (funny bone) to the little finger. These tests were performed on one of my colleagues.

The equipment used was an electromyograph (Medelec MS20) with a set of surface electrodes connected to its pre-amplifier (see next figure).
The output from the pre-amplifier is taken to the main amplifier and then to the A-D converter and host computer. The signal is also usually taken to a loudspeaker as EMG signals fall within the audio band and the ear is very sensitive to subtle distinctions between signals.

Two different measurements were performed:

i. display of voluntary signals; and,

ii. measurement of conduction velocity using evoked signals.

Figure 4.3: Block diagram of the electromyograph Medelec MS20.
VOLUNTARY SIGNALS

In this case the connection between a muscle (the abductor digiti minimi - ADM) and pre-amplifier was made using three surface electrodes. The electrodes were placed in such way that the voluntary signal produced by the Ulnar nerve when moving the little finger was recorded (see Figure 4.2.1). That is, one connected to the positive input of the pre-amplifier was placed at the base of the little finger. Another connected to the negative input of the pre-amplifier was placed in the bulk of the muscle and a third surface electrode connected to a reference point. The latter can be placed anywhere as it is just a reference, but it is recommended to place it somewhere in between the electrodes and the stimulators. As it will be seen later (see Motor Nerve Stimulation), this will reduce the size of the stimulus artefact allowing an appropriate display of the signal.

In this case there was not any electrical stimulation to the muscle so the potential displayed on the screen of the EMG equipment was only the potential across the nerve due to a voluntary movement of the finger.

At complete rest no signal was observed, as there was no lesions in the muscle. However, single motor unit potentials were observed during slight voluntary contraction and full interference pattern (many motor units responding) at maximum contraction of the muscle.


**EVOKE SIGNS**

Nerve conduction velocities can be measured by recording the muscle action potential (MAP) by stimulating its nerve. This stimulation will generate a nerve action potential (NAP) which will be cascaded to the muscle fibres through the neuromuscular junctions (the motor end plates) producing a MAP and subsequently a twitch in the muscle fibres. The time between giving the stimulus and the start of the MAP - the latency - is noted. This time includes a delay in the neuromuscular junctions, which cannot be measured. The nerve is therefore stimulated in a second point and the latency difference and the distance between the two points is used to calculate the NCV. A reduced NCV indicates neuropathy. Measurement of NCV in different sections of a nerve can help in localising lesions.

![Figure 4.4: Measurement of the Nerve Conduction Velocity.](image)

Two different NCV measurements were performed on different types of nerve fibres:

1\textsuperscript{st}) Motor Nerve Fibre stimulation

2\textsuperscript{nd}) Sensory Nerve Fibre stimulation
4.2 Neural stimulation tests

I. Motor Nerve Fiber Stimulation.

In this case the motor nerve fibres of the Ulnar nerve were stimulated using a bipolar electrode together with the arrangement of the superficial electrodes specified in Figure 4.3. In this experiment the bipolar electrode were acting as the electrical stimulator. The stimulus used was a current pulse of 100 $\mu$s duration with a variable amplitude.

The two points of excitation were the right wrist and the right elbow (see Figure 4.4) of my colleague. Due to the longer distance from the elbow to the electrodes than from the wrist to the electrodes, the latency I obtained was longer in the first case than in the second. To compare these two latencies, I selected the same point on the traces that I thought corresponded to the start of the excitation (points $O_1$ and $O_2$). Then, the electromyograph provided me with the time corresponding to each of these points, which allowed me to calculate the velocity of transmission of the excitation along the nerve once I measured the distance between the elbow and the wrist. This calculation is nevertheless performed automatically by the computer of the electromyograph once the operator introduces the distance between the two points of excitation.
As can be seen in the right-bottom corner of the figure the response $O_1$ took place 2.98 ms after the artefact generated by the electrode (sharp peak at the beginning of the trace), when it was placed at the wrist. Similarly, $O_2$ took place 7.02 ms after the artefact when the electrode was placed at the elbow. The difference between the two times is also displayed, resulting in $\Delta t = 4.04$ ms. The distance between the two points of stimulation I measured was $\Delta e = 26$ cm, so the NCV was:

$$v = \frac{\Delta e}{\Delta t} = 64.3 \text{ ms}^{-1}$$  \hspace{1cm} (4.1)$$

The artefacts present at the beginning of each signal (sharp peak followed by a plateau right in the beginning of the traces) are due to the detection of the stimulus by the electrodes. This stimulus is spread over the volume of the arm, so the further the detection point from the stimulus, the smaller will be this artefact. Therefore, in Figure 4.5, this is why the upper trace,
which corresponds to the wrist, has a bigger peak size than the lower, which corresponds to the elbow.

Finally, we can observe there are regions on the traces were the signal is apparently cut off. The reason for this effect (artifact) is based on the voltage limit of the amplifier. The way these signals are clinically acquired is by increasing the stimulus until the amplitude of the signal does not change (and therefore its amplitude is maximal). Then, the gain of the amplifier is increased in order to make easier the recognition of the starting point of the motor action potential. This increment of the gain can produce an amplification of the signal over the voltage limits of the amplifier. As a result part of the signal is lost.

II. Sensory Nerve Fibres Stimulation

The last NCV test I performed was to measure the response of the sensory fibres of the Ulnar nerve to a stimuli. In this case the electrodes used were the reference, together with the stimulation electrodes, which were ring electrodes, located around the first phalanx of the little finger. The bipolar electrode was again used but in this case it was used as an impulse recorder instead of a stimulator. The stimulus, produced by the ring electrodes, consisted of a current pulse of 100 $\mu$s duration with a variable amplitude.

The recorded information was the time required for the stimuli to go from the negative ring electrode to the negative pole of the bipolar electrode, as well as the distance between the two. Such information can be observed in Figure 4.6.
In this figure, the lower trace (Mon 1) shows the response to a single stimulus. Because the signal is relatively small compared with the noise signal, averaging is used. The measurements were made on an average response to eight stimuli (Store).

In this case the latency of the first peak was not displayed but it was worked out from the velocity and the distance, resulting in a latency of 2.4 ms. The amplitude of the signal was 40 µV. Such a small signal can be easily lost in the background EMG, so the technique of signal averaging must be used to extract the response from the noise (see section 1.2.4).

4.2.2 Electroencephalography, EEG

EEG signals provide information about cerebral electrical activity. These signals arise from the neuronal potentials of the brain but, of course, the signals are reduced and diffused by the bone, muscle and skin which lie between the recording
electrodes and the brain. This attenuation and diffusion make these signals particularly difficult to measure. Different types of electrodes and systems on how to place these electrodes exist in order to overcome the difficult reception of such a small signal.

An EEG machine is basically a set of differential amplifiers and recorders. In particular the EEG units used in The Institute of Neurological Sciences at the Southern General Hospital in Glasgow, have 22 channels of EEG inputs. The combination of the electrodes to be connected to the differential amplifiers (or so called montage) can be established in different ways. When the EEG machine is connected to a computer to record and store the signals coming from every amplifier input (i.e., paper-less system), a convenient montage is the common reference montage. In this case, an amplifier will have connected one input to one electrode and the other input to a common reference electrode. This allows us to re-montage, which means the signal can be represented in different montages from the recorded signals. This is an advantage against the paper EEG systems, where the montages are determined at recording time, and it is not possible to change the montage once the recording has been made on paper.

Another type of EEG machine is the ambulatory EEG unit, which allows us to record EEG signals during the normal activity of the day. Besides, these portable units are provided with the facility of putting marks on the reading by pressing a button, so if the patient feels any symptom he will press the button and make an annotation of the time and the symptom felt in order to correlate to the EEG.

I had the opportunity to record my own EEG using an ambulatory EEG monitor. In this case the electrodes used were Ag-AgCl discs glued on to my scalp with collodion. The scalp was degreased with alcohol and abraded before the electrode was held in place. The collodion was run round the edge of the electrode and allowed to dry. Then electrolyte jelly was injected through a hole in the back of the disk electrode to form a stable scalp contact.

The electrodes were placed all over the scalp using the 10 – 20 International System, so named because electrode spacing is based on intervals of 10% and 20% of the distance between specified points on the head (see Figure 3.8). The next Figure shows schematically the position of the electrodes and an example of an Ag-AgCl discs used during the test.

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Figure 4.7: Right: 10-20 montage used in my EEG. The letters correspond to anatomical areas of the brain as follows: O, occipital; P, parietal; T, Temporal; F, Frontal; C, Central; FP, Frontal Pole. Left: Ag-AgCl disc electrode.

The number of electrodes used on this occasion was 14 (normally 22). The next plot shows the result of the test.
Figure 4.8: Traces produced by a portable unit showing electrical potentials produced by the Masseter and the eyelids.
4.2 Neural stimulation tests

As we can see on the bottom of the EEG page shown in Figure 4.8, the settings used to obtain this EEG are specified. In particular each number refers to:

- **Chart Speed**: 30.0 mms$^{-1}$
- **Gain Setting**: 100 µV/cm
- **Filter**: 70 Hz

The value quoted for the filter corresponds to the $-3$ dB point.

This EEG was downloaded into the EEG computer from a PC card inserted into the portable unit, where the data is stored until the moment of its discharge into the computer. Files with the EEGs are archived using optical or CD-recordable disks.

Although the EEG is normal, there are certain artefacts that can be observed. One is the contraction of the muscles during the chewing of food. One of the muscles involved in the chewing is the Masseter, a very strong muscle that produces a very big signal. Another artefact observed was the blinking of the eyes.

**Video EEG**

Some patients have to spend up to four nights in the hospital to be recorded in the ‘video EEG clinic’. During the clinic the patient is recorded using a colour video camera during the day and a black and white video camera at night with the help of an infrared light source. The video system records the images coming from the patient room and superimposed on these images (using some of the magnetic bands remaining free on the videotape) is also recorded the EEG and the ECG of the patient. So if the patient suffers a fit, these signals can be related with the situation of the patient at every time.

**Evoked Potentials**

Finally, a visual EEG evoked potential (VEP) test was performed on a real patient. The test consisted in seeing how the EEG of the patient changes due to a stimulus consisting of an alternating pattern of squares changing from dark to light. The patient has to focus on a red dot in the middle (fixation point) so the patient does not moves his eyes. In this way, a stable stimulus is created. It was explained that the response to the stimulus is very small and easily lost in the background of the
EEG, so to obtain this response it has to be extracted from the noise by increasing the signal to noise ratio. The technique used for this purpose is signal averaging the output of the EEG.

A delay of the response to the stimulus will mean demyelination.

4.3 Quantitative Sensory Testing (QST)

This is the collective name for a family of techniques that attempt to measure sensory function by testing the entire pathway from the receptor in the skin to the cortex using an appropriate physiological stimulus.

In this section is presented the results of measurements of thermal thresholds (heat and cold sensation), although the techniques are equally applicable to measure vibration sensation thresholds. By assessing thermal thresholds an index of the function in the small diameter thinly myelinated A\(\delta\) fibres (cold threshold) and unmyelinated C fibres (hot threshold) can be obtained. These thresholds detect neuropathies before the patient has any symptom (e.g. diabetic neuropathy).

Different methods can be applied to measure these thresholds, each one with different advantages and disadvantages. The aim is to reduce variability and enhance repeatability as well as to exclude patient bias from the threshold estimation in order to set an internal standard of measurement. In particular the results in this section are based on the ‘forced choice method’, where an stimulus and a null stimulus is presented in two periods (randomly ordered) and the subject has to select the period in which he felt or thought he felt the stimulus.

The equipment used (Thermal Threshold Tester, TTT) is self-contained. The operator selects the parameters of the test via a keyboard. These parameters are displayed in a liquid crystal display (LCD), which informs the operator about the progress of the test. A hard copy of the test results is available from a colour printer.

Reproducible stimuli are produced by a stimulating thermode. The stimulating thermode is constructed from arrays of semiconducting thermo-electric elements sandwiched between a thin metal plate (in contact with the skin) and a metal (brass) block.

The thermode operates under the Peltier principle: heat is ‘pumped’ from one

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side of the thermode to the other when a current passes through the thermoelectric elements; depending on the direction of the current, the surface of the thermode in contact with the metal plate will heat up or cool down. The amount of heat flowing into the patient can be quantified by the equation,

$$Q = S \cdot T_e \cdot I + 0.5 \cdot r_i \cdot I_2 - k dT$$  \hspace{1cm} (4.2)$$

Where:
4.3 Quantitative Sensory Testing

\[ S \] is the Seebeck coefficient;
\[ T_c \] is the absolute temperature of the cold junction;
\[ I \] is the thermode current;
\[ r_i \] is the internal resistance of the thermode;
\[ k \] is the thermal conductivity of the thermode; and,
\[ dT \] is the temperature difference between the metal junctions inside the thermode.

This equation is only used during stimulation and recovery. At other times the TTT operates as a servo system to maintain the temperature of the plate at the set level (basic skin temperature with default of 34°C).

The results shown in this section were obtained from a QST made on myself. The thermode was placed on the right and the left wrists. It was kept (by a restrainer) perpendicularly to the wrist in order to provide maximum contact between the metal plate and the skin. While having the thermode placed in one wrist, I was holding the patient control unit (PCU) on the other hand. This consisted of a remote control with two buttons which allowed me to answer the questions displayed on the LCD.
The operator starts the test keying in the date, the subject details, the test site and whether a hot or cold threshold is to be tested. Then, a calibration sequence is initiated in which the subject feels a stimulus. After the calibration, the stimulus is delivered during one of two periods, each indicated by illumination of one of two lights. At the end of the two periods the subject must indicate with the PCU in which time period he felt (or thought he felt) the stimulus (‘forced choice’ method). The microcomputer will then score a success (S) or a failure (F) in the case the answer was correct or incorrect respectively. The threshold temperature is determined by the *Up-and-Down Transform Rule*, which establishes that the stimulus level is reduced by one when the subject scores SSS or SSFS and will increase when the score is F, SF or SSFF. This rule will cause the stimulus level to oscillate around the threshold. The threshold is determined as the mean of the stimulus level after a pre-set, even number of changes of direction. The next figures represent the results of a cold and a hot tests where only two changes of direction were used to estimate.
the threshold temperature (the transform rule does not count on the first change of direction).
Figure 4.11: Charts containing the results of the QST. From up to down, the order is: 1. cold test in right wrist; 2. hot test in right wrist; 3. hot test in left wrist; 4. cold test in left wrist.
The values obtained were within the expected range of values characteristic of a healthy subject. The next table summarises the results.

<table>
<thead>
<tr>
<th>Site</th>
<th>Type of Threshold</th>
<th>Upper limit of normal[14] (Standard Deviation) (°C)</th>
<th>Actual Threshold (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right</td>
<td>Heat Threshold</td>
<td>0.40 (0.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Wrist</td>
<td>Cold Threshold</td>
<td>0.27 (0.05)</td>
<td>0.10</td>
</tr>
<tr>
<td>Left</td>
<td>Heat Threshold</td>
<td>0.40 (0.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Wrist</td>
<td>Cold threshold</td>
<td>0.27 (0.05)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

4.4 Autonomic Nervous System

The Autonomic Nervous System looks after functions of the body over which we have no voluntary control (respiration, blood pressure, sweating, vaso-dilatation). Investigation of some of these functions gives us information about the medulla (brain stem) which contains the vital centres controlling respiration, heart rate and blood pressure.

To investigate this we have to ask to the patient to make certain manoeuvres and look at the body’s responses. These manoeuvres are associated with different functions, but the results of the tests shown in this section are associated with the autonomic regulation of cardiovascular function. In this case the sympathetic and parasympathetic functions are assessed by a number of ‘provocations’ to the autonomic system. The equipment used is divided into different components:

- electrodes, to record the ECG of the patient and to observe the physiological reaction of the heart to the different provocation.

- NeuroScope, which provides a measure of cardiac vagal tone.

- Non-invasive blood pressure monitor (Colin BP-508).
4.4 Autonomic Nervous System

- A stretch-sensitive resistance plethysmograph

The next figure shows the arrangement of the equipment during an autonomic test.

![Figure 4.12: Set up of the equipment used to perform an autonomic test. Left: The subject lies on a couch vertically while the test is performed. Right: Detail of the Neuroscope.](image)

During this test, I analysed the behaviour of different parameters related to the automatic response of the cardiovascular system to various manoeuvres.

**Deep Breathing**

The test was performed positioning the patient supine, as this is the best position for relaxing and to get the autonomic system as stable as possible. Then she was asked to inhale deeply (for 4 sec) and exhale fully (for 6 sec) during periods of 60 seconds, i.e. 6 breaths/min.

The parameters monitored were the systolic blood pressure (SBP), the cardiac vagal tone (CVT) and the heart rate (HR).

The next diagram shows the SBP expected in a normal person during deep breathing.

*CHAPTER 4. Neurophysiology*
4.4 Autonomic Nervous System

Breathing modulates both HR and blood pressure; this process is traditionally called *Sinus Respiratory Arrhythmia*. On inspiration, the HR will increase and decrease during expiration. The deep breathing exercise performed by a normal person will accentuate the response and give rise to large oscillations in HR and BP. The vagal tone will show an average increase during the period of deep breathing.

The HR fluctuation with respiratory activity is determined by a number of factors:

1. Neural coupling from brainstem respiratory centre to cardiac centre.
2. Changes in baroreflex sensitivity.
3. Normal response to blood pressure changes (arterial baroreceptors).
4. Reflex involving stretch receptors in lungs.
5. Other reflexes.

Absence of Respiratory Sinus Arrhythmia during deep breathing is a sign of autonomic failure.

*Figure 4.13: Deep Breathing.*
**Isometric Exercise**

During the isometric exercise, the blood flow to the muscles involved is reduced or stopped if the contraction is strong enough and muscle acidosis (low pH) may result. In a normal person, both HR and BP will increase. Various mechanisms are involved in this.

1. Central command: brainstem receives a signal indicating that voluntary muscles are contracting. (This might cause an initial increase in HR and BP at the beginning of muscle activation. Not always seen in our isometric exercise.)

2. Arterial baroreflex: The carotid baroreceptors are reset to a higher level in anticipation of an increased need for blood. Higher blood pressure is allowed.

3. Ergoreceptors: Muscle acidosis will stimulate chemosensitive afferents located in the muscle (the body "screams" for more blood) and HR and BP increases gradually.

The following graph shows a rise in both HR (cardiac accelerator function) and systolic BP. There was also increase in diastolic BP (not shown) indicating an increase in sympathetic tone to resistance blood vessels.
4.4 Autonomic Nervous System

Figure 4.14: Response to isometric exercise.

Valsalva Response

In the Valsalva manoeuvre, the subject is asked to blow into a tube allowing only a small airflow and to maintain an air pressure at 40 mmHg for 15 sec. The response of HR and BP in a normal person is as follows:

1. **Phase I**: (from start of Valsalva manoeuvre) transient rise in BP due to increased intrathoracic and intraabdominal pressure causing mechanical compression of the aorta.

2. **Phase II**: The increased pressure prevents venous return to the heart causing fall in BP. The baroreflex mechanism tries to compensate for this by withdrawing vagal tone and thus increasing the HR.

3. **Phase IIc**: Total peripheral resistance increases as a results of increased sympathetic activity and during this phase the fall in BP is arrested and with further mobilisation of blood reserves (from liver, kidney and spleen) the BP increased to the level of pre-Phase I.
4. Phase III: (from end Valsalva manoeuvre) the sudden fall in intrathoracic pressure causes a drop in BP giving a further burst of sympathetic activity.

5. Phase IV: Venous return and cardiac output has been restored but blood vessels remain vasoconstricted, hence the overshoot in BP.

In a patient with sympathetic failure, the Phase II increase in BP is diminished or lacking.

An example of the valsalva manoeuvre made on me:

![Autonomic System Response to Valsalva Stimulus](image)

Figure 4.15: Valsalva response
Chapter 5

Urodynamics

5.1 Structure and physiology of the lower urinary tract

The lower urinary tract consists of two main organs: the ureters, which conduct the urine from the kidneys (higher urinary tract) to the bladder; and the bladder, where the urine is contained until its expulsion through the urethra to the outside world.

Clinical urodynamics is focused on the study of specific parameters (i.e. pressure) related to the behaviour of the musculature of the bladder and the urethra. Therefore it is important to know the muscular structure of these organs and how it is controlled.

The Bladder

The bladder is a hollow sphere which can have an internal radius of 5 cm. The wall of the bladder consists mainly of layers of smooth muscle called the detrusor.
The bladder joins the urethra through the bladder neck which consists of a sphincter (internal sphincter) which is voluntarily controlled. When the bladder is full of urine, sensory receptors in the bladder wall provoke a neurological signal that cause the simultaneous contraction of the detrusor and relaxation of the urethral and periurethral muscles. These simultaneous events are part of the so called micturition reflex (See Section 5.2).

The Urethra

The urethra is the last part of the lower urinary tract. The muscular structure of the inner part of the urethral wall is mainly smooth muscle longitudinally oriented, but these smooth muscles are surrounded –specially at the front– by striated muscle fibres, which run within the urethral wall in a circular direction. These striated muscles constitute the external or distal sphincter. Although striated muscles typically fatigue easily it seems that the muscles of the urethra are of a type which fatigue less and maintain urinary continence by means of sustained contraction. In fact, these muscles are under a constant stimulation to contract.

As it can be seen in Figure 5.1, the anatomy of the lower urinary tract of both sexes is different. The main differences are that in the female (Figure 1 left) the urethra is shorter and has a lower external sphincter pressure. In males (Figure 1 right) the bladder neck has a greater sphincteric function and there is a higher external sphincter pressure.
5.2 Neurological control: the Micturition Reflex

During the filling phase of the bladder, stretch receptors in the detrusor will produce a signal which is registered by the brain. However, the brain remains partially indifferent to the filling and there are two micturition centres (in the pons and sacral spinal cord) which will maintain continence. This is achieved via a constant innervation of the urethral sphincter and relaxation of the detrusor.

At a socially convenient time, and under a strong urge, the brain will allow the micturition reflex. But this will be the only involvement of the brain in the process as all coordination of voiding (e.g. relaxation of the urethral sphincter and contraction of the detrusor) will be controlled by the micturition centres. Thus, following from the decision to void, all the processes are involuntary and are controlled by the autonomic system.

Figure 5.2: Filling phase (suppression of micturition).
When voiding is desired the voluntary control of the reflex is removed and voiding should take place in a coordinated fashion. Therefore, an intact spinal cord is required for the voluntary control of micturition.

Figure 5.3: Voiding phase.

An involuntary micturition reflex will make the detrusor contract, causing leakage from the bladder. This phenomenon is known as unstable bladder.

5.3 Hydrodynamics of Micturition

5.3.1 Contractile behaviour of the complete bladder: The Bladder Output Relation, BOR

If the bladder is considered a perfect sphere, the tension developed by one of its muscle strips is related to the detrusor pressure by the so called bladder output
5.3 Hydrodynamics of Micturition

This relation predicts that at a given bladder volume the pressure generated by the detrusor depends on the flow rate out of the bladder. This dependence coming from the terms $P_{\text{det,iso}}$ and $Q^*$. It is an automatic geometrical consequence of the relation between force and speed of shortening from muscles and it tells us that, in the presence of obstruction leading to low flow, the normal detrusor will void at high pressure as it is possible to observe in the next figure.

Figure 5.4: The bladder output relation showing how the normal unobstructed detrusor empties at low pressure, but once obstructed (low flow) will move immediately to high pressure.

5.3.2 The Passive Urethral Resistance Relation, PURR

Another parameter involved in the hydrodynamic model of micturition is the urethral resistance, which is given by the passive urethral resistance relation, PURR.

$$p = p_{\text{uo}} + \frac{1}{2} \frac{Q^2}{A}$$ (5.2)
where \( A \) is the cross section area of the urethra. The second term on the right hand side of the equation comes from energy conservation. The factor \( p_{uo} \) is the opening pressure required to open the same cross sectional area \( A_1 \) as in a rigid outlet, as we can see in the next figure.

![Figure 5.5: The passive urethral resistance relation.](image)

From this figure it is possible to understand that the hydrodynamic model of micturition involves the solution of the BOR and PURR. The dotted lines are the BORs of different detrusor external powers. As the bladder empties the BOR moves from \( P_{\text{ext}2} \) towards \( P_{\text{ext}1} \) representing an increment of the detrusor external power.

### 5.4 Clinical Evaluations in Urodynamics

The main problems with which patient can present in a Urodynamic department are:

- Bladder outlet obstruction, as a result of a prostatic outflow obstruction.

- Unstable bladder, potentially as a result of a neurological disorder, causing a spontaneous contraction of the detrusor whilst the patient is attempting to inhibit micturition.
- Genuine stress incontinence (GSI), leakage of urine in the absence of a detrusor contraction due to raised abdominal pressure.

### 5.4.1 Bladder Outlet Obstruction Investigation

The micturition reflex as described above should result in a few millilitres left in the bladder. One of the reasons for this not to happen could be due to the swelling of the prostate gland with age in the male (i.e., *benign prostatic hyperplasia*, BPH) leading to BOO. In this case, since the urethra passes through the prostate, swelling of the prostate can impede flow. Although the detrusor may contract and the sphincter relax, the obstructive resistance increase due to the prostate may be too great for adequate emptying of the bladder.

The ideal investigation for BPH is the pressure flow study, where simultaneous flow and pressure measurements can be used to accurately diagnose bladder output obstruction. This technique requires a urethral or suprapubic catheter being inserted into the patient to measure pressure and flow simultaneously.

**The Pressure Flow study**

There are three principal problems which can arise with the process of micturition:

1. The urethra becomes obstructed usually due to the prostate BPH.
2. The detrusor-sphincter coordination is lost. This is called *detrusor-sphincter dyssynergia*.
3. Underactive detrusor muscle.

All can be investigated by the pressure flow study. For diagnostic purposes, the most informative way to present the data from a pressure flow study is to plot pressure against flow. This is the so called *Abrams Griffiths nomogram*.

The nomogram was created to separate obstructed from unobstructed bladder on the basis of the pressure flow loop. As mentioned previously, the micturion reflex initiates a contraction of the detrusor and a relaxing of the urethra muscles. Because the urethra is highly distensible, this enables a large flow for little rise in pressure in...
the normal case. The obstructed bladder leads directly to high pressure emptying. This derives from the bladder output relation (Equation 5.1). The obstructed urethra requires a very high detrusor pressure to initiate flow. This gradually decreases and the characteristic ‘D’ shape is seen.

![Graphs showing detrusor pressure vs. flow rate](image)

Figure 5.6: (a) High pressure low flow. If the normal detrusor is obstructed to give low flow rates it will produce high pressures. This has repercussions for the upper tracts. (b) Low pressure high flow. The normal urethra is highly distensible and opens at low pressures.

In the department of Urodynamics at the Southern General Hospital, pressure is normally measured by using a suprapubic catheter, so there is no obstruction of the flow as there would be with the urethral catheterisation. The flow is measured using the Lectromed gravimetric flowmeter (see section 5.5).

### 5.4.2 Investigation of GSI and Unstable Bladder

Cystometry is carried out to characterise the bladder stability during the storage and voiding phases of the micturition. This is done by measuring the pressure within the bladder (intravesical pressure) and the pressure within the abdominal cavity (abdominal pressure), using two catheters attached to pressure transducers via fluid filled lines. The rectal pressure responds to any changes of the abdominal cavity
due to straining or stress. This can be subtracted from the intravesical line to give the true intrinsic bladder pressure from the detrusor muscle (i.e. detrusor pressure).

Figure 5.7: *Stable bladder showing good cancellation between the abdominal and the vesicular lines.*

These traces are measured with a strain gauge transducer. A Wheatstone bridge with two pressure sensitive arms gives a voltage that is proportional to the pressure exerted upon the bridge via fluid filled lines. All pressure measurements are made relative to atmospheric pressure. The system is zeroed by balancing the Wheatstone bridge when the fluid filled line is at the same vertical height as the transducer.

Unstable bladder and genuine stress incontinence can be investigated through either a static or an ambulatory investigation. In both cases the patient is asked to empty their bladder prior to the investigation. The bladder is filled through the urethral catheter until the patient feels the bladder is full. In a stable bladder at filling rates below 100 ml/min, the detrusor pressure rises very little as the bladder volume rises from 0 up to several hundred ml. This is the case in physiological filling where filling rates are less than 20 ml/min. With filling rates greater than
100 ml/min, the detrusor pressure rises, then decays after filling has ceased. This decay is termed accommodation. A bladder in which large changes in pressure are seen (up to 50 cmH\textsubscript{2}O) is said to have low compliance. Compliance is defined as the change in volume per unit change in pressure and is dependent on the filling rate.

Figure 5.8: A low compliance bladder showing little accommodation.

In a static urodynamic investigation the patient will be asked to cough, stand up, jump, etc. to try to provoke GSI. At the same time the detrusor pressure is monitored for detrusor contractions. This technique is much noisier than the ambulatory technique as the patient causes artefacts and noise to appear by moving around and banging the fluid filled catheters. There is also a time constraint on the test as patients are seen as part of a clinic and there is a set time per patient.
GSI is the involuntary leakage of urine in the absence of unstable bladder. However, it can sometimes be confused with an unstable bladder which is triggered by a cough. Thus, the symptom is coincident with a stress event and is misdiagnosed as stress incontinence.

Ambulatory units are constituted of small catheter tip transducers and a portable recording system. Leakage is measured by a recording pad. Since ambulatory urodynamics also shows up leakage it is ideal for testing for genuine stress incontinence (GSI).

The next two figures show examples of unstable bladder and GSI tests I came across during my placement at the department of Urodynamics.
5.4 Clinical Evaluations in Urodynamics

Figure 5.10: (a) The normal detrusor, if filled slowly, accepts 300 – 600 ml without rise in pressure. If the bladder undergoes phasic contractions while the patient is trying to inhibit voiding this is called unstable bladder. Note the low bladder capacity. (b) Ambulatory trace over two minutes. The bladder is stable and there is a lot of movement. The patient is being down and up again. Because the stable is stable we can make the diagnosis Genuine Stress Incontinence.
5.5 Uroflowmetry

As indicated previously, pressure flow studies have the disadvantage of being invasive.

Alternatively, the free flow method is used which has the advantage of being non-invasive. In this case, the rate of flow of urine is recorded and plotted against time. However, its disadvantage is its low specificity with underactive detrusor producing false positives. Moreover, the patient has to evacuate a large amount of fluid (minimum of 150 ml) in order to study the flow mechanism at full power.

The department of Urodynamics has two different flow meters available for use:

1. Lectromed Gravimetric flowmeter; and,

2. Dantec Uro1000 rotating disc flowmeter.

The Lectromed Gravimetric flowmeter records the weight of urine voided and then differentiates the signal to obtain a flow rate. On the other hand, the Dantec Uro1000 rotating disc flowmeter has a spinning disc to which the urine is directed. The velocity of the disc is kept constant by a tachometer and a feedback circuit. As fluid hits the disc, more electrical energy is required to maintain the constant angular velocity and the measurement of the extra current can be used to give the flow rate.

A list of the advantages and disadvantages of each system is given below.
### Lectromed Gravimetric

**Advantages**
- Cheap (in comparison with Dantec)
- No moving parts

**Disadvantages**
- Subject to vibration
- Low frequency response
- Has to be zeroed and emptied between voids

### Dantec Uro1000

**Advantages**
- Excellent frequency response suitable for all physiological response
- No zeroing or emptying required between voids
- Immune to vibration

**Disadvantages**
- Motor corrodes and needs cleaned regularly as urine is an electrolyte
- Expensive in comparison with the Lectromed unit

Together with these factors, one of the main reasons which determines which flowmeter is used for each test is the need to have access to results in digital format. This format allows the recording of the data for computer analysis and to produce computerized records of the patients to be archived. In particular, the Dantec method does not produce digital data, only a paper chart where the flow is plotted versus time. The smallest graduation of the chart is $1 \text{ ml s}^{-1}$, and during the calibration, it was found difficult to read. As it is possible to observe in the next figure, the system provides all the relevant information at the end of the profile.
The Lectromed system produces a digital signal collected by a computer which samples and records the signal at 32 Hz, producing a profile such as that shown in the next figure.

The two diagrams above correspond to the same input signal. If both traces are compared it is observed the rounding of the edges of the Lectromed trace indicating its low frequency response compared with the Dantec system at the start and the end.

CHAPTER 5. Urodynamics
end of the void. Therefore, from this experiment, I arrived at the conclusion that the Dantec spinning disc has a better physiological response and is more accurate.

5.6 Calibration Checks

5.6.1 Investigation into Stability of Dantec Spinning Disc

I performed an evaluation of the flow rate response of the Dantec system using different flow rates of water.

Different constant flow rates were produced with the device shown below. These flow rates were calculated and then compared with the flow rate given by the uroflowmeter. From here, a calibration index was derived.

![Experimental set up: (a) General view, (b) Superior view.](image)

The equipment used consisted of a cylinder built in Perspex with a tap attached to its bottom which had an open/close valve. Each time, the water stream was directed towards the spinning plate to avoid artifacts, i.e. unconstant flow rate due to spilling of fluid out of the funnel. The different flow rates used for calibration were obtained from nozzles with holes of different diameters.

The uroflowmeter measures the flow rates which traverse a spinning plate mounted upon a flow transducer. The transducer transform the spinning velocity of the plate.
into a flow signal. Before the flow starts the velocity of the plate is constant, and this velocity is adopted by the system as zero flow. Then, when the flow starts, the velocity of the plate is reduced by an amount proportional to the flow. The system automatically starts recording and printing when the water flow starts, and stops recording automatically after flow is finished. The start criterion is: starts if flow rate $> 0.5 \text{ ml/sec}$, while the stop criterion is: stop if flow rate $< 0.5 \text{ ml/sec}$ for 20 seconds.

Together with the reading of the uroflowmeter, the flow rate was measured dividing the weight$^1$ of the water collector placed below the funnel by the time the flow lasted. This time was controlled with a stop watch. After each flow the water contained in the water container was weighed. The obtained flow rate was compared with the flow rate given by the uroflowmeter. The errors introduced in the measurement arose from:

i. The reaction time when using the stop watch.

ii. The amount of water that passed through the transducer but did not fall into the water container.

iii. The response time of the transducer. This response time has to be short in order to produce sharp edges on the trace. The effect of the edges of the trace given in the printout were however cancelled out by measuring a large amount of flow, so the amount of flow represented by the area under the edges was negligible.

The results are plotted in the next figure, where it is possible to observe the linear relationship between the results obtained from both methods of measuring the flow rate. The slope of the line obtained was 1.03 showing the consistency of the readings given by the uroflowmeter. The total combined error of the measurement was $\pm 0.67 \text{ ml/min}$.

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$^1$If $\rho(\text{water}) = 1 \therefore 1 \text{ kg}_w = 1 \text{l}_w$
5.6 Calibration Checks

Figure 5.14: *Calibration curve showing the agreement between the measured flow and the flow given by the Dantec flowmeter.*

### 5.6.2 Study of the stability of the Lectromed unit

I performed a measurement of the possible drift of the pressures measured with the Lectromed unit before and after the unit was calibrated. Any substantial difference between the two sets of measurements would mean the unit is not stable. The next figure shows the experimental set up.
Figure 5.15: *Lectromed unit with two pressure transducers attached to fluid filled lines.*
Pressures of 100, 80, 60, 40, 20 and 0 mmHg were applied to the Lectromed unit using a calibrated pressure generator and recorded. The corresponding pressure in cmH$_2$O$^2$ were,

<table>
<thead>
<tr>
<th>Applied Pressure (mmHg)</th>
<th>Recorded Pressure Lectromed</th>
<th>Mean Before</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>136,137</td>
<td>136.5</td>
</tr>
<tr>
<td>80</td>
<td>109,110</td>
<td>109.5</td>
</tr>
<tr>
<td>60</td>
<td>82,82</td>
<td>82</td>
</tr>
<tr>
<td>40</td>
<td>55,55</td>
<td>55</td>
</tr>
<tr>
<td>20</td>
<td>28,28</td>
<td>28</td>
</tr>
<tr>
<td>0</td>
<td>1,1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5.1: Pressure measurements before calibration

The unit was then calibrated following the in-house protocol where two pressures of 0 and 74 mmHg were applied to the system. The procedure was then repeated after the calibration, obtaining in this case the following readings,

<table>
<thead>
<tr>
<th>Applied Pressure (mmHg)</th>
<th>Recorded Pressure Lectromed</th>
<th>Mean After</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>134,134</td>
<td>134</td>
</tr>
<tr>
<td>80</td>
<td>107,107</td>
<td>107</td>
</tr>
<tr>
<td>60</td>
<td>81,82</td>
<td>81.5</td>
</tr>
<tr>
<td>40</td>
<td>53,55</td>
<td>53.5</td>
</tr>
<tr>
<td>20</td>
<td>27,27</td>
<td>27</td>
</tr>
<tr>
<td>0</td>
<td>-1,-1</td>
<td>-1</td>
</tr>
</tbody>
</table>

Table 5.2: Pressure measurements after calibration

In order to quantify the difference between the means of the before and after calibration results, I calculated the difference between the slopes of the ‘best fit’ regression line fitted to them.

$^2$Where 74 mmHg = 100 cmH$_2$O.
5.7 Urethral Pressure Profile Occlusion Investigation

The method used in the department to measure the urethral closure pressure is the Brown & Wickham method. This method consists of measuring the urethral wall pressure while a small flow rate is maintained through the holes of the catheter. In this case it has been observed that the pressure measured is very close to the actual urethral wall pressure with an error of ±1 cmH₂O/ml/min. This technique relies upon the fluid filled system being able to respond sufficiently quickly to any rise in pressure.

Figure 5.16: Results of the stability check performed on the Lectromed uroflowmeter unit.

The resultant slopes were, 1.356 before the calibration and 1.350 after the calibration. As the difference between these two slopes is so small, I concluded that the unit was stable.

5.7 Urethral Pressure Profile Occlusion Investigation

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in pressure in the urethra. As the urethral pressure rises temporarily, the catheter will be occluded. The pressure measured will begin to rise, but it will not read the correct pressure until the infusion system manages to inflate the fluid filled catheter to the urethral pressure. By this time, the moving catheter may have passed the high pressure region and so a low reading may be the result. This will depend on three variables:

- the compliance of the fluid filled system: \( C = \frac{\Delta V}{\Delta p} \)
- the infusion rate: \( Q_{inf} = \frac{\Delta V}{\Delta t} \)
- the catheter withdrawal rate: \( V_{cat} = \frac{\Delta x}{\Delta t} \)

If the holes of the catheter were suddenly blocked using the fingers\(^3\), the pressure measured would start to rise, as the pump continues to infuse. The rise of the pressure would have a finite gradient \( \frac{\Delta p}{\Delta t} \) dictated by the first two parameters above, which can be measured for any system. This gradient will be then the threshold rate measurable with this catheter and no attempt should be made to measure a urethral pressure rise at a rate greater than the threshold rate.

The effect of a poor speed of response is that if the recorded pressure can only rise at a rate of, say, 10 cmH\(_2\)O per second, then any pressure changes that move more quickly than this will not be recorded accurately. According to Brown \textit{et al.}[16], a figure of 200 cmH\(_2\)O per second is adequate at a profile withdrawal rate of 1 cm per second. If the speed of response of the catheter is not this fast, then compensation can be made by a slower withdrawal rate. In the Department of Urodynamics a servosystem withdrawal device is used to achieve a constant withdrawal rate of 1 mm s\(^{-1}\). At this rate the minimum required speed of response would only be 20 cm of water per second.

The next results correspond to a test performed on a catheter \textit{Rüsch} (Model 395766) in order to measure its speed of response. The method used was the finger occlusion method. The catheter acts as a fluid-filled tube infused with water and

\(^3\)This is the so called ‘finger occlusion method’. This method is easy to apply in order to study the speed of response to a rise of pressure. But to apply the method correctly the catheter eye should be occluded by sliding the finger over the hole and not by squeezing down on to it directly. Squeezing on the catheter eye will make the speed of response appear quicker than it really is.
coupled to a remote pressure transducer which converts the pressure signal into an analogue signal. A digitizer converts the analogue signal into digital which is processed and displayed by a monitor. The sampling rate of the digitizer is 32 Hz.

The profile obtained is shown in the next figure:

![UPP Pressure Occlusion Investigation](image)

Figure 5.17: Profile of the UPP occlusion investigation.

The y-axis represents the pressure measured, and the x-axis corresponds to the points sampled every 1/32 seconds. The pressure rise between A and B is $\Delta p = 150\text{cmH}_2\text{O}$. The number of sampled points between A and B is 115, so the lapse of time between A and B will be $115/32 = 3.6$ seconds. Therefore, the rate of the pressure rise between these two points will be

$$
\frac{150}{3.6} \cdot \frac{\text{cmH}_2\text{O}}{\text{seconds}} = 41.7 \text{cmH}_2\text{O s}^{-1}.
$$

From the figure given by Brown, it is possible to conclude that the catheter has a good speed of response. The only source of error of this reading will come from the possibility of having squeezed the eye of the catheter instead of sliding the finger over the hole, as mentioned above.

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