A strategic approach for data processing and structural management in physiological studies

Python proof-of-concept implementation
with breath-hold experiments

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Abbreviations

$\Delta s^{e}_{\mathrm{PPG}}$	Deflection amplitude of the pulse wave measured in the ear lobe.
$\Delta s^{f}_{\mathrm{PPG}}$	Deflection amplitude of the pulse wave measured in a finger.
Δs_{BP}	Deflection of blood pressure pulse wave.
Δs_{PPG}	Deflection amplitude of the pulse wave.
$\overline{\tau}_{\mathrm{m}}$	Arbitrary interval at the end of an apnea.
$\overline{b}$	Baseline Interval of signal.
$\overline{r}$	Recovery Interval of signal.
τ	Time variable for apneic duration.
τ_{m}	Time instant at the end of an apnea.
τ'_{m}	Time instant close to the end of the apnea correlating with a minimum or maximum value..
f_{C}	Heart rate.
$pa_{\mathrm{CO_2}}$	Partial pressure of carbon dioxide in expired air.
$pa_{\mathrm{O_2}}$	Partial pressure of oxygen in expired air.
$pb_{\mathrm{CO_2}}$	Partial pressure of carbon dioxide in blood.
$pb_{\mathrm{O_2}}$	Partial pressure of oxygen in blood.
s	Continuously measured (bio)signal.
s^{e}_{SO2}	Continuous signal of the blood oxygen saturation, measured at the ear lobe.
s^{f}_{SO2}	Continuous signal of the blood oxygen saturation, measured at a finger.
s_{BP}	Continuously signal of the blood pressure wave.
s_{DIA}	Continuous signal of the diastolic blood pressure.
s_{ECG}	Continuously signal of the electrocardiography.
s_{EMG}	Continuously signal of the electromyography.
s_{HR}	Continuous signal of the heart rate.
s_{HS}	Continuously signal of the heart rate.
s_{MAP}	Continuous signal of the mean arterial blood pressure.
s_{PPG}	Continuous signal of the photoplethysmography.
s_{RE}	Continuously signal of the respiration effort.
s_{SO2}	Continuous signal of the blood oxygen saturation.
s_{SYS}	Continuous signal of the systolic blood pressure.
s_{cHb}	Oxygenated and deoxygenated cerebral hemoglobin.
$\mathrm{AP_E}$	Apnea event starting after expiration.
$\mathrm{AP_I}$	Apnea event starting after a regular inspiration.
BHD	Breath hold diving or breath hold diver.

BP	Blood pressure.
CO_2	Carbon dioxide.
DAO	Data access object.
DR	Diving reflex.
ECG	Elecrocardiogram.
GUI	Graphical user interface.
HRV	Heart rate variability.
MAP	Mean arterial blood pressure.
MCV	Mean coefficient of variance calculated from apneas sharing the same duration.
MVC	Model, view and controller.
O_2	Oxygen.
OS	Oxygen saturation of blood.
R'pa_{CO_2}	Relative production of partial pressure of carbon dioxide per minute.
R'pa_{O_2}	Relative consumption of partial pressure of oxygen per minute.
RQ	Respiratory quotient.
T'pa_{CO_2}	Total production of partial pressure of carbon dioxide per minute.
T'pa_{O_2}	Total consumption of partial pressure of oxygen per minute.
T'pb_{O_2}	Reduction of partial pressure of oxygen in the blood per minute.
T's_{SO2}	Reduction of oxygen saturation per minute.
VC	Vital capacity.

Abstract

The essential objective of physiological studies is the measurement and evaluation of various biosignals, which are often acquired continuously and simultaneously. The investigated characteristic physiology is usually concealed within the recorded signals or their interrelation and has to be extracted by the use of various data processing methods. Revealing this *internal* information of a signal (e.g. the heart rate from an electrocardiogram) alone, however, is not sufficient to receive the desired results. *External* information, describing the specific context (e.g. events, study group, etc.), has to be assigned to the data as well to allow meaningful comparison and evaluation. Unfortunately, this task is hindered by the lack of comprehensive solutions and unified procedures.

To address this issue, a strategic approach was developed in order to improve efficiency and deepen the understanding of data processing and organisation management in physiological studies and experiments. Based on the specific requirements of *internal* information management, a layer model was designed defining four distinct stages in data processing in order to standardise common procedures of this task. These layers are (1) data acquisition (e.g. recording of signals), (2) validation (removal of artefacts), (3) preprocessing (calculation of physiological parameters) and (4) statistics (extraction of tendencies). In addition, a concept of a server-based software architecture, that is capable of handling the identified challenges of *internal* and *external* information management on a large scale, was created.

A standalone prototype, focusing on *external* information management, was implemented and applied to data, which was obtained from five previously published experimental studies. It could be demonstrated, that the structure and overview of physiological studies can be greatly improved by this systematic approach. Furthermore, data, sharing similar *external* information, could be retrieved fast and efficiently for further processing. The full potential of this novel concept, however, has yet to be discovered in future implementations focusing on the aspects of centralization and data processing.

Kurzfassung

Das Hauptziel physiologischer Studien ist die Erfassung und Auswertung von verschiedensten Biosignalen, welche meistens kontinuierlich und simultan aufgenommen werden. Da die gemessenen Signale oft keinen unmittelbaren Eindruck in die charakteristische Physiologie geben, müssen meist mehrere Analyseschritte durchgeführt werden, um weitere Information freizulegen (z.B. die Berechnung der Herzrate aus einem Elektrokartiogramm). Diese *interne* Information alleine ist allerdings nicht ausreichend, um aussagekräftige Ergebnisse zu erhalten. Vielmehr bedarf es auch die Zuordnung von *externer* Information, welche den Kontext der Daten beschreibt (z.B. Ereignisse, Studiengruppe, etc.), mit dem Vergleiche und umfassende Auswertungen ermöglicht werden. Eine einheitliche Softwarelösung oder standardisierte Abläufe existieren für diese spezielle Aufgabe derzeit nicht, hätten aber immenses Potenzial die beschriebenen Vorgänge zu vereinfachen.

Aus diesen Überlegungen folgt die Notwendigkeit einer strategischen Herangehensweise, die die Effizienz und die Struktur von Datenverarbeitung und organisatorischem Management innerhalb physiologischer Studien und Experimenten verbessern soll. Im Speziellen wurde, basierend auf den extrahierten Anforderungen des *internen* Informationsmanagements, ein Schichtenmodell entworfen, welches verschiedene Ebenen der Datenverarbeitung definiert. Diese Ebenen sind im speziellen (1) Datenerfassung (z.B. Messung von Signalen), (2) Validierung (Entfernung von Artefakten), (3) Vorverarbeitung (Berechnung von physiologischen Parametern) (4) Statistik (Aufzeigen von Trends). Zusätzlich wurde ein Konzept für eine Server-basierten Systemarchitektur gestaltet, welche die identifizierten Herausforderungen von *internem* und *externem* Informationsmanagement systematisch behandelt.

Abschließend wurde ein Prototyp implementiert und auf die Daten früherer experimenteller Studien angewandt. Es konnte gezeigt werden, dass die Übersichtlichkeit und die Struktur dieser Daten deutlich verbessert wurde. Des Weiteren konnten Daten mit übereinstimmender *externer* Information schnell und effizient abgerufen werden womit die Weiterverarbeitung deutlich vereinfacht konnte. Das volle Potenzial des vorgestellten Konzepts muss allerdings noch in zukünftigen Implementationen, die auch die Aspekte der Zentralisierung und des *internen* Informationsmanagements berücksichtigen, festgestellt werden.

Acknowledgements

I would like to thank all those, without whom the present work would not have been possible. Eugenijus Kaniusas, supervisor of this work and head of our research group, who introduced me to Biomedical Engineering and supported me with his scientific, physiological and biomedical expertise throughout the last years. Stefan Kampusch who frequently shares his insights and knowledge with me. All the participants who invested their time for the sake of science. In particular Christopher Friedrich who, additionally from participating in our studies, constantly provided new input and ideas from a freedivers perspective. Boris Wrubel for his friendship and enjoyable collaboration. Michi Wiezcorek, Clemens Punzengruber and, in particular, Radl Rabe for their comprehensive proof-reading.

My sincere thanks go to my father who patiently supported me both mentally and financially throughout my whole studies. Most of all, I want to thank Kathi Mitterer for her unlimited support and her relentless search for perfection.

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Chapter 1

Introduction

1.1 Overview

Data management in physiological studies and experiments poses countless challenges to the scientific personnel in charge, implying expert knowledge in multiple application fields. Data of diverse sources has to be (I) acquired, (II) characterised and (III) analysed in order to achieve valid and consistent results. In the context of physiological studies, this data is represented by (mostly) continuous recordings of multiple biosignals, which reflect internal mechanisms of the body. As described in section 2.2, a continuous biosignal s can be obtained by various means and techniques, demanding specific knowledge about measurement devices and the features of the specific signal. The recording and storing the data, however, establish only the basic conditions for further evaluation since the raw data itself does not always provide the desired physiological information but solely displays the sensor's response to physical changes inside the body. In order to obtain physiological and interpretable information from such signals, its *internal* information has to be extracted (see also section 2.4). One commonly calculated parameter is the heart rate, which can be derived from the electrocardiogram signal. Even though the processing of signals is often considered to be the core challenge in a study, characterisation, classification and organisation of data is of, at least, equal importance. Only by assigning this *external* (i.e. descriptive) information to data, researchers are able to compare the obtained parameters according to their physiological event (e.g. rest, breath hold, etc.) or subject group. However, especially when considering academic environments, limited resources often lead to insufficient and unclear *external* data organisation and will in turn not only impair ones ability to communicate results and progress of a study amongst colleagues, but also the evaluation of *internal* parameters.

1.2 Current Solutions

An efficient and structured management and evaluation of recorded data is essential for a positive and high-quality scientific outcome but requires additional effort and resources which are not always available. Bearing in mind that studies are often conducted by a scientific team, data manipulation is commonly performed in isolation on local machines and by different people. Without a centralised storage and a well accessible system, the risk of corruption or loss of synchronisation requires additional verification and therefore even more resources. This does not only hold true for *internal* but also for *external* information which is essential for the interpretation of the former.

It has already been shown in [1] and [2], that efficiency and resource capacity can be increased by deploying a strategic and centralised management system. The accessibility of data is not only beneficial for the current study, but can also help to improve future projects by reusing existing data. Furthermore, sharing data via a common interface with other research groups can obviously help to expand local and global cooperation and has been reported to greatly improve citation rate [3], indicating greater research quality. Even though world-wide availability of computational power, storage capacities and network bandwidth have strongly improved over the last decades, until now, no standardised centralised framework was developed to manage and process both, *external* and *internal* data within a scientific physiological study. Current software solutions either do not offer sufficient flexibility and sophistication for such a complex and specialised task or they go vastly beyond the scope. Hospital Information Systems (HIS) [4], for instance, (e.g. AKIM at the Vienna General Hospital [5]), are primarily specialised on patient management as well as personnel and budgetary administration but they still come with a special set of frameworks which enables researchers to perform clinical studies. This includes mostly patient history modules which are either implemented into the HIS or offered as a standalone solution. A common example for the latter is Caisis [6], a web-based framework for data management in the field of cancer research that has become more popular during the last decade [7]. Such systems are capable of delivering statistics from different patients and various medical values (biopsy, blood tests, etc.) but lack the ability to store, manage and analyse datasets of continuous physiological signals. Another popular study management tool is NVivo [8], which focuses mainly on qualitative data analysis and survey execution, respectively. Similar to HIS and Caisas, LabKey [9] offers a management platform for medical data and diagnosis evaluation related to chemical analysis[1].

A field of application, which is closely related to physiological studies in terms of structure and data management, is that of distributed health care. Physiological data is recorded by patients, stored into a centralised system and reviewed later by physicians remotely. In [11], a centralised health care system is proposed, which stores and processes data in a cloud[2] and allows authorised users to browse this data.

[1] LabKey is currently also deployed in the search for ebola treatment[10].

[2] Cloud computing or cloud databases describe a configuration of servers which provides services and disk

However, the main focus of this framework (as of many others) lies on diagnostics and not on signal processing in the context of scientific evaluation. In summary it can be said, that while these tools are great at tracking single values and simple events and some even offer sophisticated data storage and presentation possibilities, they still fail to meet the combined requirements of (I) scientific state of the art data analysis and (II) processing of complex and often interrelated continuous biosignals while also (III) allowing management of *external* information.

It should be noted that solely data processing requirements are covered by an already existing framework, called PhysioNet [12]. It contains a large collection of recorded physiological signals in the PhysioBank component, while the PhysioToolkit contains open source software and algorithms in order to analyse physiological signals. PhysioNet is a powerful platform for the search of existing data and applicable algorithms and is accessed more than 45.000 times a month [13]. However, it offers no real interface to assign study related information or meta-data to signals and therefore also cannot satisfy all requirements of a comprehensive physiological study management framework as described earlier.

1.3 A Novel Approach

This work introduces a novel and strategic approach to the management and processing of *external* and *internal* signal information, acquired in physiological studies. To complete the picture of fundamental processes and requirements of physiological study management, Chapter 3 presents the conducted studies with their specific background, method and result. This excursion is essential to the understanding of the deeper motivation for this work, since it provides insights into the background and practical experiences which resulted in the presented approach. The particular implementation was done in several steps starting with the analysis of common data processing procedures and characteristics, described in Chapter 2. By abstracting usual requirements of this task, a layer model was created in order to define the separate stages that signals have to pass during analysis. This will help to establish well defined and concrete work packages for scientific personnel, software developers and other users. Due to the arising demands, the outline of a specialised and centralised client-server architecture was designed (Chapter 4). The proposed system provides the necessary features to manage *external* and *internal* information in a practical way. In order to evaluate the validity and benefits of such a strategic approach on a smaller scale, a standalone prototype was implemented (see Chapter 5). For this specific tasks, a Python client for local *external* data management was developed and applied to data from already finished studies.

storage via simple interfaces while being individually invisible to the user or developer. By only providing access to the particular interface, administrators can easily scale the system horizontally, i.e. deploying more servers, and therefore adapting to a growing system.

Chapter 2

Data Processing Model

2.1 Introduction

This chapter covers the abstraction and classification of data processing stages which are required to extract *internal* information from recorded data. For this purpose, a four layer model[1] was designed according to common processing demands, which have been acquired from the research group Biomedical Sensors at the University of Technology, Vienna. It should be noted, that even though the described model can be used for various fields of data processing, the herein specific focus will be on tasks and stages explicitly related to physiological data.

Such models and abstractions are already well established in many different application areas like network communication [14] or software development [15], where they have greatly promoted a deeper understanding of processes and interrelations for involved researchers and developers around the world. Inspired by such effective simplifications and abstractions of widely used practices and principles, a model was created in order to describe daily challenges of data processing in physiological studies. Similar to other models, a better understanding and division of processes will also help scientific personnel and software developers to concentrate their energy effectively on specific tasks by improving the organisation of work distribution and clarifying interfaces between different data processing stages. These stages themselves represent another crucial aspect of this approach. Knowing the current state of data allows a study to be executed in a clearer and well structured environment. An obvious and simple way to specialise in different aspects and concrete problems of *internal* information processing can strongly increase efficiency and output of a study. For instance, in a separated study environment according to the presented model, statisticians could use data provided by the preprocessing layer to perform their own evaluation while personnel without specialisation could tag data with *external* information.

[1] Even though the first appearance of this model was in [A6], where it could only be discussed briefly, it requires a more detailed description, provided in the present document.

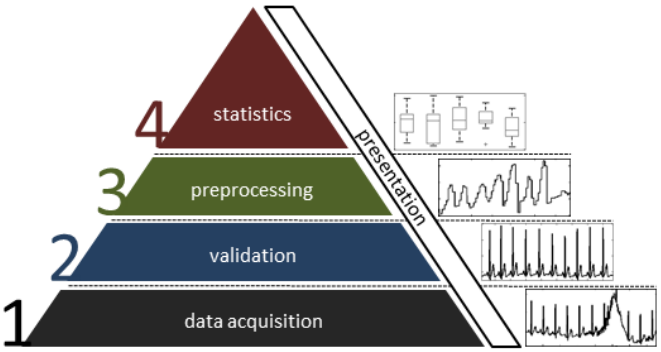


Figure 2.1: The data-processing model with four main layers and an example of their related (bio)signal representation. This representation of data is also indicated by a fifth presentation layer, covering the whole model. The abstractions of common processing steps helps to improve the understanding of essential requirements of data processing. Next to the layer model exemplary data originating from an Electrocardiogram in the particular processing state can be seen.

In Fig 2.1 the proposed layer model is depicted. Four separated primary layers were extracted, representing different challenges of common data processing. These are (in order of their typical chronological appearance during a study):

1. Data Acquisition
2. Validation
3. Preprocessing
4. Statistics

Additionally, a secondary Presentation layer provides necessary user interaction for data manipulation on top of each primary layer. In following sections these layers, their functions and associated data states, will be discussed in detail, focusing on their particularities in the context of physiological data processing. Examples from previous studies and collected data will be provided for each layer to assemble a complete picture of the specific requirements.

2.2 Data Acquisition

The basis of all data processing is data acquisition. In most cases, this involves highly sophisticated and specialised hardware and software which is capable of gathering data from various sights of interest and storing it in a reusable and comfortable way. Note that many biomedical sensors can also be build very fast and cheap using some basic circuit engineering tools and components. Such implementations however, are prone to produce artefacts and low signal to noise ratios leading to unreproducible signals of low quality, further increasing efforts in the later stages of the study. It is therefore highly recommended to use professional equipment to establish a reliable basis. The correct

(a) (b) (c)

Figure 2.2: a) Simultaneous assessment of multiple biosignals from the right hand. Depicted sensors (from bottom to top) are: Oxygen saturation, blood pressure, transmission photoplethysmography and reflection photoplethysmography. Data acquisition unit Biopac MP36 can be seen in the background. In (b) a typical experiment setup is shown. A subject, as shown in (c), lies down on the bed and is monitored by multiple devices while performing different maneuvers (e.g. apneas).

operation of such devices can be quite challenging considering the variety of parameters available for sensors and devices. For instance, one can choose between different sampling rates, filtering options, offsets, presets of derived signals, calculations, output methods, file formats, etc. Depending of these settings, the output can strongly vary even within the same device, risking the loss of important signal features. The heart rate variability (HRV), for instance, cannot be sufficiently calculated from an electrocardiogram recorded with a sampling rate below 100 Hz [16][2]. Even more severe consequences can arise from a wrong filter setting. Characteristics like the dycrotic notch in the pulse wave or important offset, i.e. direct current (DC) values can easily be cut-off by filters, rendering further analysis impossible. Aside from these adjustable parameters, another aspect of increased complexity is the use of multiple devices. Usually a single measurement device alone will not be able to record all desired biosignals[3]. Even multi channel devices like the Biopac System MP36 (Biopac Systems Inc, Santa Barbara, CA) can only cover four different simultaneous recordings. This can exponentially increase the complexity of a study since each device has to be administered and operated correctly by a qualified person in order to yield the desired signal. Figure 2.2 displays a few devices and sensors which can be combined in a complex physiological study. Proper knowledge of the functionality of all devices is essential, along with the means to forward data from the device to a computer. This digitalisation often requires customised interfaces and cables to account for the particular specification of analogue outputs. Even if a signal can be read digitally from a device, a variety of file formats - including easy readable MATLAB files as well as complex binary files - complicates the consistency of file storage and management. Finally, the financial effort of using multiple devices should also not be underestimated due to required maintenance and possible rental charges. Figure 2.3 shows a schematic view of a multiple device configuration and the specific channel sequence.

[2]The recommended sampling rate is 250-500 Hz but this threshold can be reduced to approximately 100 by applying appropriate interpolation.

[3]In one of our recent studies we used six different measurement devices, to obtain 16 biosignals from various sources of the body.

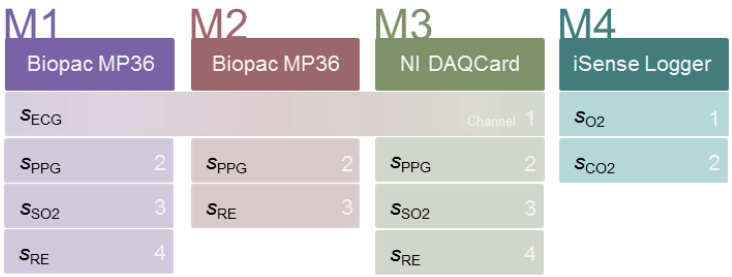


Figure 2.3: Schematic overview showing a study setup deploying three measurement devices. Note that the first channel (ECG) is acquired by a sensor from device M1, but is carried through all devices using an analogue output. This is done in order to synchronise data before performing further analysis steps. M4 on the other side only provides discrete values at specific time instants and is not connected with the other devices.

2.2.1 Biosignals

In this section biosignals (in particular those which will be of relevance to this work), denoted as s, and their specific characteristics and physiological significance will be described while also discussing their origins and different assessment methods. Biosignals can derive from various sources inside the body revealing vital information about the health state of a person. They reflect physiological processes occurring inside and travelling through the body. By application of sensors on various sites outside (non-invasive) or inside (invasive) the body, physiological mechanisms can be measured and converted into visible and analysable data, i.e. s. Certain alternations of well known patterns and waveforms can be used to identify pathologies or normal physiological responses to external stimuli. It should be noted, that even though a more precise classification using e.g. by nature (electrical, mechanical, acoustical, and more [17]) or physiological origin (e.g. cardiovascular, pulmonary, etc.) is possible, the present collection's purpose is to give an overview of commonly measured biosignals. A short overview of this classification is provided by table 2.1. Additionally, some sensor's assessment is not limited to a single location of the body, e.g. pulseplethysmography at the finger or the earlobe. If required, this information will be provided in the superscript of a variable, e.g. s^e for a signal applied to the ear. A typical sensor assessment configuration with multiple devices attached to a subject is depicted in Figure 2.4. It should be emphasised, that only the initially acquired biosignals will be explained whereas derived and calculated signals and parameters will be described in section 2.4.2. This arbitrary separation was done to highlight the importance and independence of the layer structure of the proposed data processing model. Additionally, the focus lies on actual signals that can be acquired and stored, which might result in a mix up of measurement technique and physiology which is fully intentional at this point in order to establish a focused perspective of the requirements and preconditions of data acquisition and processing in physiological studies.

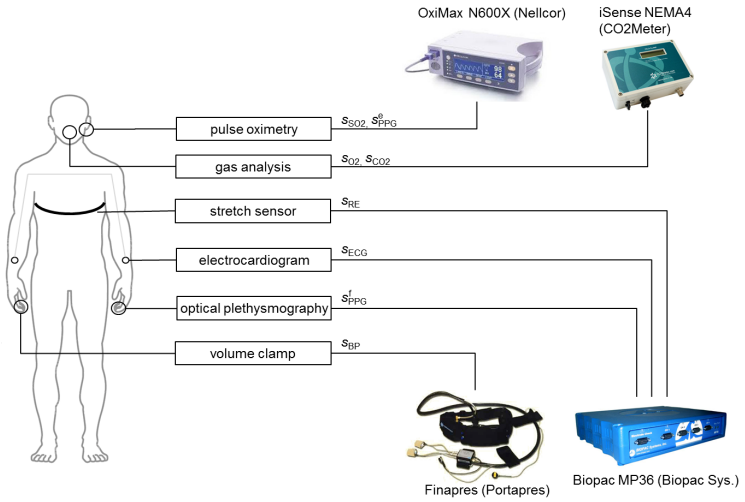


Figure 2.4: Assessment of various biosensors and their resulting biosignals are shown. Note that some sensors provide multiple signals (e.g. pulse oximetry) while multiple sensors can connect to a single device (e.g. Biopac MP36). Based on these signals, further analysis can be performed.

2.2.1.1 Electrocardiogram

The electrocardiogram (ECG) is recorded by measuring the electrical activity of the heart. During each heart beat, different regions of the heart are excited[4] successively, yielding a characteristic electrical potential waveform [18], as s_{ECG}. (see Figure 2.5a as the biosignal). A healthy ECG cycle is composed of several distinct features denoted as P, Q, R, S and T wave whereas the QRS complex represents the most dominant feature. The ECG is regularly used by physicians as a clinical diagnostic tool to detect cardiac diseases and irregularities. It should be noted, that depending on the position of applied electrodes, this waveform can strongly vary while revealing information about the state of different regions of the heart. The typical application uses 12 leads, positioned semicircular around the heart allowing to visualise the electric behaviour of the whole heart. However, for many applications (e.g. many physiological studies as discussed later) a much simpler derivation with only three electrodes can be utilised. The so-called Einthoven derivation, for instance, will still sufficiently visualise the key characteristics and waves in order to analyse important physiological phenomena. The s_{ECG} is measured in Volt with usual values in the range of few mV.

2.2.1.2 Photoplethysmogram

The photoplethysmography (PPG) is a widely used optical measurement technique. The derived biosignal, s_{PPG}, correlates with fluctuations of the blood volume inside blood vessels. With each heart beat, blood is ejected into the aorta and the systolic system

[4] Anatomically, the electrical excitation is initiated in the so-called sinotrial node, the primary pacemaker of the heart which in turn excites the Atrio-ventricular node, the His-bundle and finally the ventricular muscle cells.

	Biosignal	Origin	Sensor
Biopac MP36 (Biopac Systems)	s_{ECG}	heart	electrical
	s_{EMG}	muscle	electrical
	s_{RE}	lungs	mechanical
	s_{HS}	heart	acoustic
	s_{PPG}	blood vessels	optical
OxiMax N600X (Nellcor)	s_{SO2}	vessels	optical
	s_{PPG}	vessels	optical
iSense NEMA4 (CO2Meter)	$pa_{\mathrm{O_2}}$	lungs	electro-chemical
	$pa_{\mathrm{CO_2}}$	lungs	electro-chemical
Portapres (Finapres Medical Systems)	s_{BP}	vessels	mechanical-optical

Table 2.1: Measurement devices, with relevance for the present work, are listed with a selection of available signals. Signals are further classified by physiological origin, the their sensor type.

leading to a periodic change of the vessels diameter, i.e. a pulse wave(in Fig. 2.5b a typical pulse wave is depicted). This pulse wave can be registered by a photodiode responding to infrared light which illuminates a region of the body, often the finger or the earlobe. Light that is reflected by or transmitted through tissue and blood vessels experiences attenuation which can be measured by a photodiode. Since blood and tissue have different absorption coefficients for infrared light and the volume of tissue does not change, only modulations of the blood volume account for changes of the total absorption. However, slow variation in the signal can also provide information about the total perfusion level, i.e. the venous blood volume.

2.2.1.3 Oxygen Saturation

The oxygen saturation (SO_2) of the arterial blood, i.e. bound oxygen to haemoglobin, is measured by the application of two PPG sensors with different wavelengths. The resulting absorption coefficients for these specific wavelength (e.g. 660nm and 910nm) are different for oxygenated and deoxygenated haemoglobin offering the parameters to calculate the total oxygenation. Equation 2.1 shows the necessary formular resulting in SO_2, and in succession to the continuous signal s_{SO2} which is shown in Fig. 2.6a.

$$SO_2 = \frac{HbO_2}{HbO_2 + Hb} * 100\% \tag{2.1}$$

HbO_2 represents oxygenated haemoglobin whereas Hb defines the deoxygenated blood. The most common implementation of the detection is called pulse oximetry where influences from constant absorbers like tissue or venous blood are eliminated by detecting and using only the pulsating arterial blood component for the calculation of the saturation. Since the majority of oxygen in the blood will be consumed by the tissue near the capillaries, arterial oxygen levels at the sensors location (often a finger or earlobe) will almost match values near the pulmonary artery. In [19], pulmonary

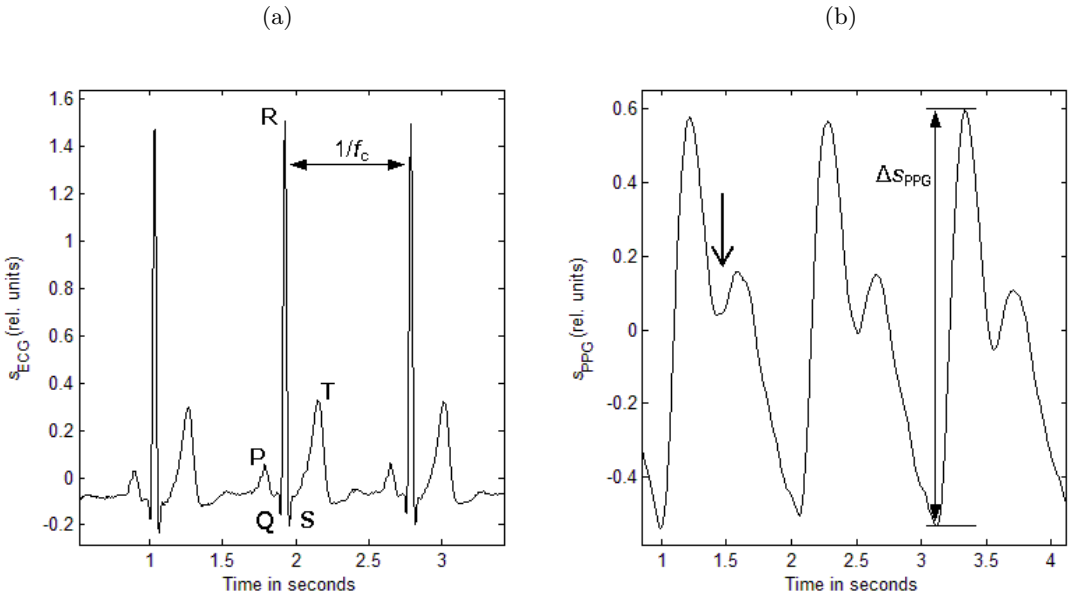


Figure 2.5: Typical biosignals recorded from a male subject of age 23. a) depicts a typical ECG signal with labelled waveform characteristics. Note that the most prominent feature of the s_{ECG} is the so called R wave (see text). In (b), the PPG signal s_{PPG} is presented with the dicrotic notch highlighted.

oxygen levels are reported to be close to 100 mmHg[5] whereas arterial oxygen pressure is still at 95 mmHg. In contrast, blood that has passed demanding tissue and has entered the venous system is desaturated to about 40mmHg. Note that due to methodical averaging procedures, the relatively slow behaviour of the gas exchange cycles and the proximal location of the sensor, s_{SO2} values can experience delays of about 20 seconds [20].

2.2.1.4 Blood Pressure

There are various methods to measure the blood pressure (BP), from inflatable cuffs (e.g. Sphygmomanometry) to invasive (intra-arterial) techniques used in intensive care. The method which should be explained in more detail since it is also of relevance later in this work, is a combination of different techniques. To be precise, a cuff containing a PPG sensor is applied around a finger, therefore combining mechanical and optical measurement techniques. The cuff applies pressure to the tissue while the PPG sensors registers the amplitude of the pulsewave. When the transmural pressure is equalised, i.e. the applied pressure is equal to the blood pressure, the pulsewave amplitude reaches its maximum. Using this loop, the cuff can readjust in order to get the correct BP recording

[5]Blood oxygen saturation and partial pressure of oxygen in the blood can be correlated with a non-linear sigmoidal function, also called hemoglobin's oxygen-dissociation curve. The exact shape of this curve varies with numerous chemical parameters, e.g. pH value or CO_2 concentration.

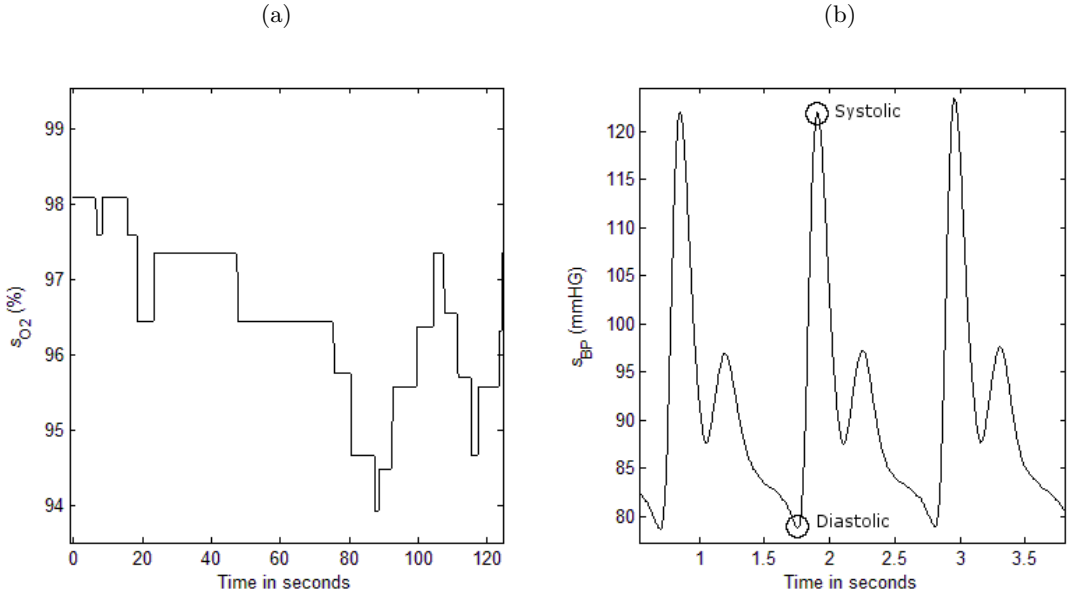


Figure 2.6: Typical biosignals recorded from a male subject of age 23. a) depicts the course of the blood saturation over 120 seconds as the signal s_{SO2}. In (b), the blood pressure wave, s_{BP} is shown.

(measured in mmHg). This principle is called volume clamp method [21] and while it sometimes struggles to show perfectly correct absolute values[6], the relative changes in the signal provide important informations about systemic changes. It combines the benefits of a non-invasive (easy to use and apply) and a invasive (continuously with pulse wave) measurement technique yielding the signal s_{BP} (shown in Figure 2.6b).

2.2.1.5 Respiration

In order to measure the respiratory efforts (RE) a simple mechanical sensor is put on a stretching belt and applied around the chest. With each inspiration and expiration the belts length changes, inducing the signal s_{RE}. Detecting the respiration efforts is especially important for the apnea related studies discussed in this work.

2.2.1.6 Gas Concentration

Lastly, two chemical parameters should be mentioned since they too are of crucial importance for apnea related studies. Namely, carbondioxide (glsco2) and oxygen (O_2) concentrations of the expired air, i.e. the lungs[7] are measured for example by using a

[6] As discussed in a recent meta study[22], non-invasive blood pressure measurement techniques still cannot compete with classic invasive methods in terms of accuracy and precision.

[7] It should be noted that even though expired air analysis gives a good estimate for the gas concentration inside the lungs, air which is present in the upper airways (trachea, bronchi, etc.) does not participate in the gas exchange of a breathing cycle but is mixed inside the expired air.

non-dispersive infrared sensor and a zirconium dioxide oxygen sensor respectively. These sensors provide the gas concentration signals, pa_{CO_2} and pa_{O_2}. Note, that while the recording itself can be done continuously, measuring gas concentration of the expired air with the quoted devices requires a specific setup, also called Douglas bag, allowing only to record discrete value. To be more precise, air is exhaled into a bag which contains a tube running to the sensors.

2.2.2 Sources of Signal Errors

Mistakes made during data acquisition will have severe consequences for the next layers since even minor errors carried through the first layer will require detailed investigation during validation. While the detection of errors can be performed automatically in many cases, many correction actions require manual attention from trained personnel increasing the efforts of a study significantly. In a worst case scenario, collected data might get lost due to severe contamination. Therefore thoughtfulness and conscientiousness in this early stage of a study is essential for a proper and continuous workflow.

Each signal requires a special sensor and its proper application so it can be used in the further processing steps. Regular maintenance of these devices and sensors are crucial in reducing sources of errors. Old ECG electrodes for instance can produce high noise since the electrode gel degrades over time leading to a loss of conductive properties. In terms of sensor application, the applied pressure, location and angle of the sensor has to be considered. A good example of an incorrectly placed sensor can be depicted by looking at a PPG sensor. Too much or to little pressure on the sensor will distort the signal, while the sensor is only working properly on the finger tips. But even after a careful application, a measurement can easily be compromised by artefacts (e.g. induced by movement).

2.3 Validation

The second layer comprises processes, necessary to validate the acquired data. Even if no errors have been produced during data acquisition, most of the time, the acquired raw data does not meet all the requirements to be analysed on a physiological or statistical basis. Artefacts in particular can contaminate such a signal and have to be removed systematically in order to ensure signal quality and validity. An artefact is an anomaly, partly or completely shadowing the signal and its desired features. Possible sources of such artefacts include electrical coupling (e.g. power line or stronger electrical signals inside the body[8]), movement or accidental detachment of a sensor and calibrations of devices during a measurement. Additionally, periods in which the study protocol could not be performed sufficiently (e.g. too short apnea duration) or

[8]For instance, the excitation of muscle cells during movements will produce an electric signal which is much stronger than the ECG signal.

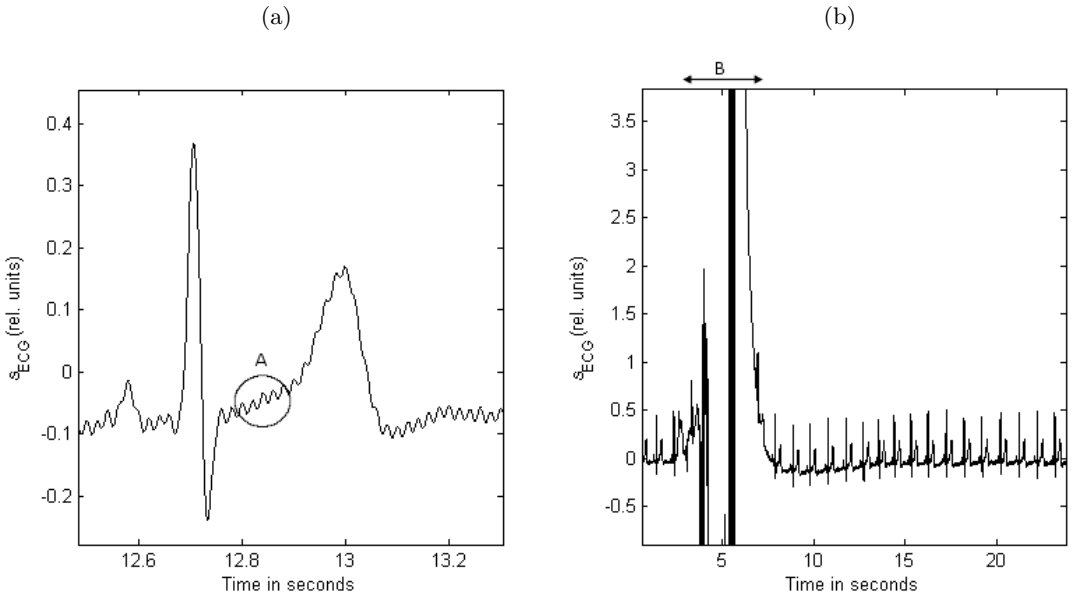


Figure 2.7: Different types of signal irregularities are presented. In (a) mild 50 Hertz noise (marked also as A) from the power line can be seen on top of s_{ECG}. b), depicts a heavy movement artefact in another s_{ECG} over the period B. The original signal can hardly be seen anymore.

environmental parameters were alternated (e.g. change in temperature) should be marked to be ignored in further steps.

To clean the signals and validate them, the application of filters as well as manual and automatic detection of such irregularities and artefacts is necessary. In addition, and most important for the correlation between signals, it has to be ensured that signals acquired from different devices are synchronised in the time domain. All these measures are required to prepare the data so it can be used as input for the preprocessing layer. In some cases with very strong signal corruption, reconstruction of the original signal and its characteristics will not be possible sufficiently. To account for destroyed data segments, these sequences have to be marked or interpolated to ensure that they are not used for later analysis.

All errors and noise within the signal, which are not removed after this stage will produce further (often manual) efforts in the proceeding stages of the study.

2.3.1 Filtering

Probably one of the most effective ways to clear up a signal from superimposed noise, unwanted characteristics or artefacts is the application of a filter. Quite often, acquired data will contain strong noise components resulting from conductive coupling with the powerline. Depending on the quality of sensor and cable shielding, the signal quality might be insufficient for further processing algorithms. Due to the quite narrow banded

nature of this noise, most of the time a 50Hz notch filter is enough to remove it. Another use of filters lies in the removal of unwanted signal components like baseline drifts. An ECG for instance often includes a varying DC offset which complicates the detection of desired features but can easily be removed by a high pass filter. Additionally, filters also represent a powerful tool for signal processing which will be discussed in section 2.4.1.

While it is easy to eliminate interfering components, designing a filter incorrectly can just as easily remove or alter desired features.

2.3.2 Synchronisation

One issue of the utilisation of multiples devices lies in the ensuring of synchronisation throughout all devices. A consistent time vector is essential for identification and analysis of complex interrelations between different signals and their features which often represent a crucial aspect of a high quality study. Additionally, maneuvers and events have to be matched to their respective physiological response at the correct time in all signals. Unfortunately, it is usually not possible to start a measurement at the exact time instant at all devices involved. Another divergence can arise from different internal clocks, which can be of importance in longer measurements. Therefore, signals should be synchronised afterwards throughout all devices by

- elimination of possible starting offsets,
- interpolation of signals with different sampling rate and
- adjustment of minor time divergences (resulting from variations of the internal clock of the devices).

While it is possible to do the first two steps manually, it neither very practicable nor accurate. Also, minor time divergences are hardly noticeable by the human eye and therefore need computational assistance. One practical way to automatically and successfully accomplish this synchronisation is by looping a specific signal with distinctive features (e.g. the ECG) through all devices. This signal can then be used as a reference to run synchronisation and merging algorithms based on correlation.

2.4 Preprocessing

This section will explain the third abstraction layer in which algorithms and calculations are used on the validated signals in order to achieve the signals and parameters, i.e. *internal* information that actually represents the targets of the specific study and will lead to comparable results. Generally, the acquired and validated signal will not show sufficient information that can be used to obtain the desired information. Only after analysing their specific waveforms and characteristics, further statistics can be performed which are required to draw conclusions from a study setup. This may be as simple as taking the mean value of a signal but can quickly become incredible complex if indices

(e.g. breath holding index [23]) have to be calculated by combining features of different signals. Some signals and methods which can be used to obtain these derived signals will be introduced and explained here.

While most artefacts are produced by external sources, some physiological events originating from a subject can also cause irregularities in the signal which also have to be marked similar to artefacts. Usually artefacts do not hold information which can be used to interpret and analyse physiological events, irregular physiological characteristics are only subjectively useless for the particular study. This is of importance because several analysis methods are valid only for typical physiological behaviour but fail to interpret special events correctly without additional information. A good example is the so-called ectopic beat[9] recorded in the ECG that can lead to false R-peak detection by algorithms, yielding incorrect heart rates. Another physiological influence on the signal quality can arise when people suffer from cold hands, i.e. reduced perfusion. Especially for PPG and BP measurements, the baseline perfusion can severely weaken the signal's strength and quality. Note that the border between artefact and physiological event can be vague and depends strongly on the hypothesis and requirements of a particular study.

2.4.1 General Signal Analysis

Signal processing can take many forms in a huge variety of professional fields, like electrical engineering, communication engineering, audio engineering, and many more. Such processing methods require complex mathematical calculations in time and frequency domain revealing countless additional (and invisible to the human eye) features and characteristics of a signal. Here, some general tools and methods used in signal processing will be introduced, in order to give a brief overview of the possibilities of such analysis while also explaining the relevance for scientific studies.

2.4.1.1 Fourier Transform

Probably one of the most common used transform method to obtain information about the frequency domain characteristics of a signal is the Fourier transform. Basically, it uses sinusoidal functions to decompose a signal into its frequency components.

Especially the Discrete Fourier Transform is indispensable in modern digital electronics and signal processing and is usually deployed by fast Fourier transform algorithms. It should be noted here, that the Fourier transform is reversible, allowing features or noise to be deleted in the frequency domain which will remove them also in the original signal after inverse Fourier transform. Considering physiological signals, the composition of the frequency spectrum contains various information about the physiological state since changes of the frequency might indicate pathological changes

[9] An ectopic beat, or premature ventricular contraction, is a (often) non-pathological event in which the electrical excitation of the heart is not initiated by the sinotrial node but by heart muscle cells. As a consequence, an instantaneous heart beat occurs regardless of the regular heart cycle (mostly shortly after the last regular one).

in the physiology. As stated in [24] for instance, by analysing the frequencies present in the first heart sound, acute myocardial infarct situations can be distinguished from the normal state, but also from an already healed infarct.

2.4.1.2 Peak Detection

Generally, each signal is composed of various features which make them unique and give information about the specific characteristics of the signal. Since there are uncountable features and methods to acquire them, only one example should be given here. This specific feature which is frequently of interest (in physiological studies) is a peak, represented by a local minimum or maximum in a signal. The detection of these peaks is required in many different fields reaching from analytical chemistry (e.g. mass spectrometry) to electrical engineering. Depending on the signal and the extend of such peak, different detection algorithms can be utilised, reaching from simple threshold algorithms to complex filtering or the combination of several methods.

2.4.2 Biosignal Analysis

Based on general signal processing methods, specialised analysis algorithms have been developed to decipher physiological events inside biosignals and their characteristics. While the method itself is often quite similar to those used in other fields of application, the parameters and combinations are adapted for the particular challenges.

In this section, common signal processing methods and some possible implementations will be introduced. It should be noted, that even though many algorithms used for biosignal analysis (especially in diagnostic applications) require online (on-the-fly) execution, this is not necessary for most physiological studies. The examples examined below therefore focus on offline calculations.

Unfortunately, even with the use of sophisticated and adaptive algorithms on a noise free signal, certain physiological mechanisms or measurement induced events may lead to signals which cannot be analysed correctly, either in part or completely. Manual controlling of the resulting parameters after the execution of an algorithms is therefore highly recommended. Figure 2.8 shows a semi-automatic tool which enables the user to add or remove peaks in s_{ECG}.

2.4.2.1 Heart Rate

The leading parameter that can be extracted from s_{ECG} is the heart rate f_{C}, describing the interval between two successive heart cycles. In particular, the inverse of the distance between two heart beats is multiplied by 60 to calculate the beats per minute (bpm). While f_{C} can also be calculated from characteristics occurring in other signals, including s_{PPG}, s_{BP}, s_{HS} and even s_{RE}, the most accurate basis for calculation is the s_{ECG} and therefore will be the focus of this section. Putting all s_{ECG} of an signal together to an array will yield a new signal, s_{HR} including information about the cardiac frequency. In

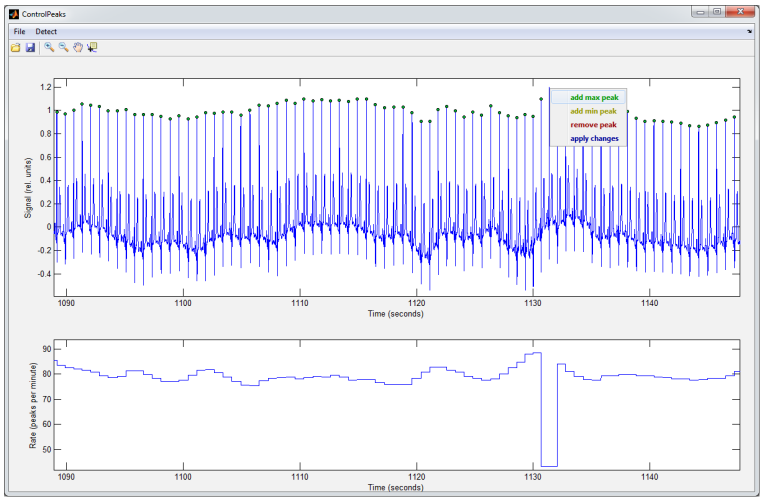


Figure 2.8: A semi-automatic tool for heart rate calculation. While most peaks were detected correctly by the algorithms (see upper plot), due to a irregularity, one peak has been overlooked (as can be seen in the jump of the heart rate and has to be added manually afterwards.

order to receive the time between two heart beats (the RR interval) in the first place, a distinctive feature has to be detected within each cycle. Most algorithms use the QRS complex for this purpose, utilising the sharp form of the R peak. This detection can be implemented through various different algorithms. Simple threshold detection is in many cases viable after the removal of the baseline. However, since other features of the ECG (especially the T wave) may reach this threshold too, the square of the derivation of the signal can be taken to emphasise the rapid increase of the R peak while ignoring high (but not so steep) characteristics. Additionally, chest movements (as being performed during apnea events), may lead to significant changes in the level of the R peak requiring constant adaptation of the threshold and sequential processing. In order to further reduce the impact of other ECG features, more sophisticated algorithms can be used. In [25] an QRS detection algorithm is proposed, using a weighted and squared first-derivation operator before applying a moving averaging filter. The rate can then be easily extracted using simple threshold algorithms.

The heart rate is the most basic and at the same time probably most important parameter that can be extracted from an s_{ECG}. It reflects the adaptability of the heart to external or internal stimuli, like stress or exercise.

2.4.2.2 Heart Rate Variability

One of the vital abilities of the cardiovascular system is adaptability. Depending on the current needs of the body, the system can change the stroke volume, f_{C} or vascular resistance in order to efficiently satisfy the demands. Considering the heart, this adaptation is done by alternating the heart rate and therefore increasing or decreasing oxygen supply. This vital mechanism can be seen not only during exercise but also in the resting state and is known as the heart rate variability (HRV). Probably the most

prominent and immanent representation of this variation can be observed during respiration as the so-called sinus arrhythmia[10], shown in Figure 2.10. The HRV can be calculated from the s_{ECG} by looking at the time differences between successive RR intervals[11] or by looking at features of s_{HR}. More sophisticated methods in the time-domain include (among many others):

- SDNN; the standard deviation of RR intervals.
- RMSDD; root mean square of successive differences
- SDSD; standard deviation of successive differences
- NN50; number of successive differences (paired) that differ more than 50ms

Additionally, evaluations can be performed in the frequency-domain, where high, low and very low frequency components of the RR intervals can be compared. These frequencies reflect parasympathetic (high frequency) and sympathetic (low frequency). Note that for most HRV calculations to be valid, at least 5 minutes (for some parameters even 24 hours) of measurement data has to be available.

2.4.2.3 ECG Waveform Analysis

The ECG offers various and crucial information about the physiological state of a body. Due to the direct reflection of the heart's electrical activity, each feature in the wave of an ECG can be mapped to certain excitation patterns of the heart while also revealing positional information about the axis of the heart. Additionally, changes of ionic concentrations are also reflecting in the s_{ECG}. For instance, an increase in potassium (>6.5 mmol/l) is known to sharpen the T wave while elongating the PQ-interval due to transmission faults [19].

2.4.2.4 Systolic/Diastolic Blood Pressure

Among the various parameters which can be obtained from the BP , the systolic (BP_{sys}) and diastolic (BP_{dia}) values are the best known. They give information about the pressure inside the arterial vessels during excitation (systolic) and relaxation (diastolic) phases of the heart cycle. As can be seen in Figure 2.6b, BP_{sys} is

[10] Inspiration introduces a negative pressure gradient in the thorax, allowing air to enter the lungs. As a side effect, also venous blood is drawn increasingly back to the heart, particularly into the right atrium and subsequently into the right ventricle. Since the pericardium is a relatively rigid structure which cannot expand outwards, the increasing volume in the right ventricle presses on the left ventricle and reduces its volume and therefore the ejected blood volume. To account for this reduced stroke volume, the heart rate has to increase in order to ensure constant blood flow.

[11] Generally, the beat-to-beat intervals used for the calculation of the HRV can originate from various biosignals and are therefore referred to as NN ("normal") intervals. Since this work uses an ECG signal as a basis (since it offers the most accurate time instant for a heart beat), the term RR interval will also be further used in the context of HRV calculation.

represented by the peak values, whereas BP_{dia} can be found at the minimums. Again, a specialised peak detection algorithm will be able to find these two values. Putting them together to arrays, the signals s_{SYS} and s_{DIA} are created. Additionally, mean arterial pressure (MAP) and systolic to diastolic deflection (Δs_{BP}) are common parameters that can be extracted from s_{BP}.

2.4.2.5 Pulsewave Amplitude

Similar to Δs_{BP} , the deflection of the pulse wave in a s_{PPG} can also be calculated as indicated in 2.5b. The resulting Δs_{PPG} parameter correlates partly with the peripheral blood volume and vasoconstriction.

2.4.2.6 Gas Parameters

Gas analysis as described in 2.2.1 already produces parameters, which could be directly used without further analysis and compared with other measurements. However, a clearer picture can be drawn by calculating

- the exhaled in relation to inhaled concentrations to obtain production or consumption of a gas
- evaluating the exhaled concentration in relation event durations

Additionally, the relation of $pa_{\mathrm{O_2}}$ to $pa_{\mathrm{CO_2}}$ can be calculated as the respiratory coefficient (RQ), which is commonly used to determine metabolic rates.

2.4.2.7 Blood Oxygenation

Similar to exhaled gas, also s_{SO2} can be related to event duration or to a baseline value to receive the relative oxygen consumption. Additionally, due to the correlation between oxygen saturation and partial pressure of oxygen in the blood $pb_{\mathrm{O_2}}$, it is possible to approximate the partial pressure of oxygen in blood using the modified equation 2.2 (based on the works in [26]).

$$SO_2 = \frac{K_{O_2} * p^n_{O_2}(bl)}{1 + K_{O_2} * p^n_{O_2}(bl)} * 100\% \tag{2.2}$$

with K_{O_2} representing the hill Coefficient (= 1.3933 * 10-4) and n being Hill exponent (for human blood $n = 2.7$). It should be noted, that this value is just just an approximation, since the oxygen dissociation curve is influenced by various parameters (e.g. CO_2, pH value, temperature, etc.) as described in [19].

test	samples	tested variable	prerequisites
t-test	one	X	normal distribution
	two (dependent)	X - Y	normal distribution
	two (independent)	X and Y	normal distribution, same variance
Wilcoxon	one	X	symmetric distribution
	two (dependent)	X - Y	symmetric distribution
Welch	two (independent)	X and Y	normal distribution
U-test	two (independent)	X - Y	same distribution

Table 2.2: Overview of different tests commonly used in medical and biomedical studies. Number of tested samples, variables and prerequisites are listed (partly taken from [27]).

2.5 Statistics

After the desired basis of physiological parameters has been established, statistics have to be applied in order to compare and evaluate the data. This is the actual process in which a hypothesis is validated or falsified. Since all data has been verified and parameters have been already extracted and stored, future hypothesis based on the same data will only require changes of the statistic, highly improving the performance of future works. Note that this tasks actually combines both, *internal* and *external* information to generate the desired outcome. While statistics can be quite simple for single measurements by comparing mean (or median) values for periods with different maneuvers, the effort and complexity increases rapidly with additional measurements, subjects and events. In particular, the right tools and tests have to be chosen depending on the prerequisites of the data (an overview of common tests is shown in 2.2). Several characteristics of a study, subjects and events and their physiological influences should be closely investigated in terms of independence, distribution shape and desired outcome. For instance, data samples are often assumed to be normally distributed and that a two sided t-test can be applied for data comparison. However, this is not always the case and the application of incorrect tests will yield incorrect results, normality tests should be performed as a precaution. As a general consequence of finding other than normal distributions, more data samples will be needed in order to receive a result with the same significance.

Another way to find similarities in recorded data is by by calculating the correlation coefficient r by dividing the covariance by the product of the individual variances. The resulting value (between -1 and +1) provides a good measure for any linear connection between two variables. It can however be misleading in some cases and is likely to show false high values if outliers are present. Other statistics frequently used are regression analysis (to determine the connection between two quantitative features) or empirical mode decomposition. Latter decomposes a signal into so-called intrinsic mode functions revealing instantaneous frequency information allowing trend forecasts. Finally principal component analysis should be mentioned as a statistical procedure which shows how variables of a sample can influence other variables.

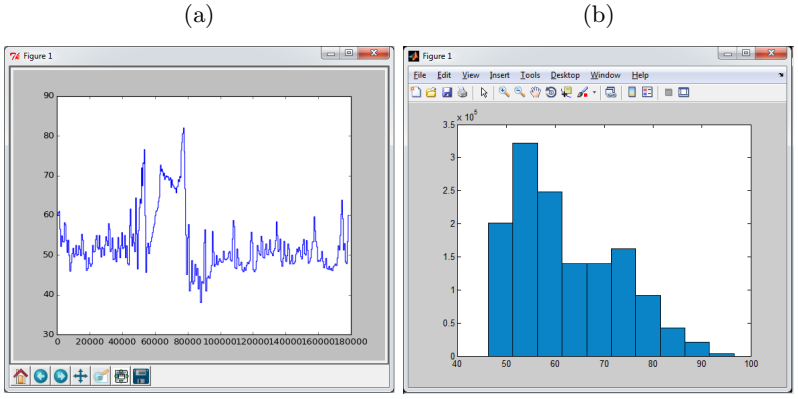


Figure 2.9: Two standard plotting methods. a) shows a basic plot of an signal in Python, whereas in (b) a histogram plot of a signal in MATLAB gives information about the distribution of values.

2.6 Presentation

Over the course of a study, acquired data, algorithms and the final parameters and their statistics have to be evaluated. This has to be done via some kind of user interface in order to allow operators to visually or numerically control the performed actions and the results. It is also very important to verify if a study setup has any flaws which might need attention or if the acquired data unexpectedly does not offer sufficient information to answer the hypothesis. There are several ways to display data in its current stage, like Excel or simple text editors which might help to verify the mere existence of the desired data. The standard way to take a closer look especially at data arranged in arrays is by plotting them. MATLAB and Python offer various plotting functions like a line plot or a histogram (see Fig 2.9). Note that different layers of the data processing model will impose different challenges on the presentation technique. That is, while data acquisition and most of validation will probably require only the presentation of data after executing functions from the command line, more complex operations in preprocessing might need extensive user interaction, as already seen in Fig. 2.8. Presentation is probably most important in statistics, since data has to be displayed in a comprehensible way by the use of various tests and statistical evaluations. This can be particularly tricky if several parameters and events have to be combined for different subjects and groups over multiple measurements. The simultaneous viewing of all signals of one measurement is also essential for the first evaluation of a recording and allows the basic communication of results. The saying: "a picture is worth a thousand words" also applies here. A presentation of a simultaneous recording of multiple validated and preprocessed biosignals is shown in Figure 2.10. Note that some biosignals which are in some way related are merged in a single plot (e.g. s_{BP}, s_{SYS} and s_{DIA}) to minimise the total size of a plot and allow for direct comparison.

Depending on the number of parameters which are to be analysed, the presentation

techniques should be adapted accordingly. In particular, small numbers will probably only require simple plotting methods whereas clinical trials, involving several operators and measurement personnel will benefit from distributed solutions with complex visual preparation techniques.

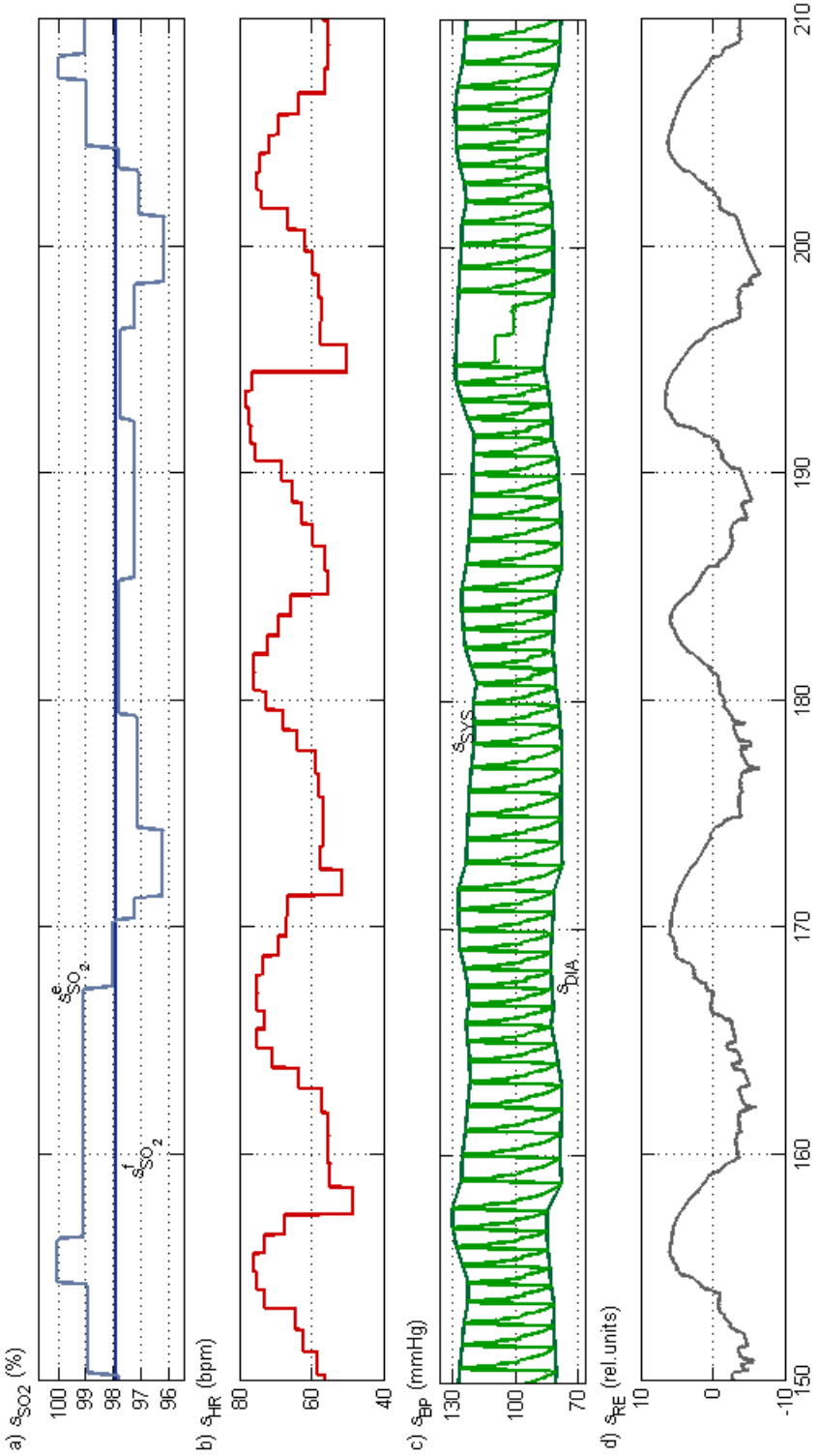


Figure 2.10: Simultaneous and continuous recording of various biosignals and some derived signals/parameters. a) oxygen saturation s_{SO2} (from the earlobe and from the right index finger), (b) heart rate s_{HR} (calculated from the s_{ECG}), (c) blood pressure as s_{SYS} and s_{DIA} enwrapping s_{BP} and (d) respiration efforts s_{RE}. It can be seen, that the (central) s^e_{SO2} behaves differently to the (proximal) s^f_{SO2}. The correlation between s_{RE} and s_{HR} can be visually noticed while the respiratory fluctuations in s_{BP} are harder to detect by humans. The artifact in s_{BP} at t=195s is interolated in s_{SYS} and s_{DIA}.

Chapter 3

Studies and Experiments

3.1 Introduction

In this Chapter, essential information about typical experimental designs and signal processing in the context of a physiological study[1] will be provided. In particular, utilising investigations of breath-holds in human [A5, A4, A3, A2, A1] (see appendix for full works), *internal* and *external* information management will be examined from a more practical perspective. That is, a variety of physiological processes, important biosignals, specific methods, study protocols and results will be presented. The aim of this excursion into specific physiological studies is to convey the entire complexity of considerations which are necessary for a complete execution of such study. It will be shown, that multiple analysis levels are required to efficiently extract information from continuous biosignals (denoted as s) according to their characteristic and background.

3.1.1 Respiration

Respiration is one of the fundamental bases of aerobic metabolism, by transporting and processing oxygen. These two vital functions are defined as physiological respiration and cellular respiration. Latter describes the process of energy production inside a cell, in particular the generation of adenosine triphosphate (ATP) which is required for the majority of cellular functions while physiological respiration can be considered as the sheer method of oxygen transportation into an organism. In humans physiological respiration is performed via breathing but to simplify matters, breathing and respiration will be used as synonyms subsequently. Without oxygen, the citric acid cycle is interrupted and (for a limited time) anaerobe processes start to take over energy production. However, but due to various substitute reactions, more waste products are generated while the energy outcome is reduced, eventually causing cell

[1] Please note that these studies were conducted by the research group Biomedical Sensors at Vienna University of Technology, of which I was a team member. As a consequence, the first person plural will be used at several occasions to refer to this specific research group.

damage. Furthermore, respiration does not only ensure a constant oxygen supply but also removes produced carbon dioxide (CO_2) from the circulatory system. While most animals have chemical and physical buffers (hemoglobin and hydrogencarbonate[19]) that can store oxygen and carbon dioxide and therefore balance small fluctuations, long lasting apneas will cause tissue damage, e.g. due to hypoxia. However, short breath holds are vital to stop water or dangerous gases from entering the respiratory tract.

3.1.2 Physiology of Apneas

3.1.2.1 Involuntary Apneas

Unfortunately, the cessation of breath is often not a deliberately act but can arise from pathologies or stressful situations. In particular so-called sleep apneas (i.e. recurring periods of ceased breathing longer than 10 seconds during the night) are climbing higher in the ranking of lifestyle diseases. It has been observed [28, 29], that an increase in cardiovascular and cerebrovascular morbidity and mortality can be linked to people suffering from involuntary sleep apneas. Unexpected irregularities in oxygen and carbon dioxide levels can lead to severe unbalances in biochemical processes, e.g. acidification of blood. These sleep apneas can be divided into different types according to their physiological origin. In particular,

- Obstructive sleep apnea (OSA),
- central sleep apnea (CSA) and
- mixed sleep apnea (MSA)

can be distinguished. OSAs result from collapsing airways mainly caused by obesity or augmented relaxation (e.g. due to alcohol intoxication) of airway muscles. As a result respiration efforts are blocked, creating an involuntary Valsalva maneuver[2]. As a result, cardiovascular parameters are thrown off balance with temporal decreased blood pressure and increased heart rate. Aside from mechanical closure of the airways as in OSAs, central sleep apneas (CSA) are produced by a pathology inside the respiratory control center. Respiration efforts are stopped due to a lack or reduction of neurological feedback from carbon dioxide receptors. MSAs are characterised by the combination of obstructive and central apneas. During all types however, gas exchange is inhibited which leads to an accumulation of carbon dioxide CO_2 and decrease of oxygen O_2 during a night of repetitive sleep apneas. A decrease of OS values down to 82% in individual apneas has been observed by [30] while investigating various degrees of this disorder. In accordance to voluntary apneas, blood pressure (BP) also increases strongly throughout these apneas (up to 240 mmHg for systolic BP [31]).

[2] Antonio Maria Valsalva, an 17th century Italian physician and anatomist, found out that by inducing a strong exhalation against closed airways, he could examine the state of the Eustachian tube. Interestingly, this maneuver is also performed by divers in order to equalise pressure in the middle ear during descent.

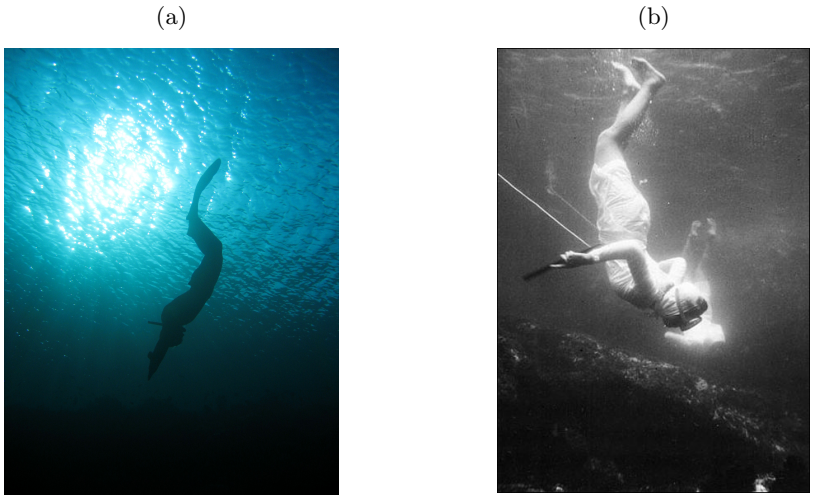


Figure 3.1: Breath-hold diving in pictures. a) Freediving athlete descending into the deep (©Markus Einweiser). b) Picture of a female Ama diver from Japan (Retrieved from http://houseofpomegranates.com/).

Interestingly, breathing can also stop involuntarily during full consciousness. When experiencing intensive or stressful situations (e.g. during a dental procedure), respiration is often inhibited. Recent studies show that even reading emails can produce periods of apneas [32]. In preliminary data of a recent experiment, this phenomenon could even be observed during competitive gaming with multiple drops in arterial oxygen saturation (up to 87%). It can be assumed, that humans stop breathing more frequently than we currently are aware of.

3.1.2.2 Breath Hold Diving

In humans, breath hold diving (BHD) was performed throughout the history of mankind due to various reasons, though primary for survival purposes. Hunting for seafood, which has a long tradition around the world is probably the most basic motivation to hold ones breath. But also the search for water itself in some regions of the world promoted breath hold diving. That is, inhabitants of deserts are generally in need of reliable water supply which is often provided by oasis' fragile wells, requiring dangerous digging and maintenance underwater. Other cultures have found treasures in the sea, like pearls and shells, which were used as cultural accessories or currency. A famous example of such culturally developed breath hold diving can be found among the Japanese and Korean Ama pearl divers[3] (see Figure 3.1) who traditionally perform apnea diving since almost 2000 years [34].

With increasing social complexity and securing of basic needs, these original apnea

[3]Interestingly, mostly women are involved in this tradition while men tend to stay on the boat. A possible explanation for this seemingly cultural development was given by [33] describing a significantly higher temperature tolerance in the female population.

diving purposes have been adapted and obtained a more sporty character. The earliest development of freediving started during the 50th and 60th of the 20th century in Italy where pioneers like Enzo Maiorca initiated the first deepdiving competitions [35]. Maiorca himself was the first man to reach a depth of 50m in 1962 something that was thought impossible at that time. With an increase in popularity[4], freediving as a sport was born and specialised disciplines were created each with different approaches and physiological needs, pushing the limits of human physiology. Freediving has opened new frontiers by establishing different competitive disciplines[5]. Officially, basically three different breath hold diving disciplines can be distinguished:

Static Apnea
The principle behind static apneas is actually pretty straightforward. The athlete lies motionless in a pacified pool with his face down. The motivation is to overcome the human respiratory reflex and sustain apnea times as long as possible. (The current world record for men lies at 11 min 35 s according to [35])

Dynamic Apnea
Competitions in this discipline are also carried out in pools but the primary success metric is not pure time but the travelled distance under water. Even though this distance is partly also determined by the sustained breath hold duration, muscle efficiency, diving technique and CO_2 tolerance are additional factors influencing the final performance. It should be noted, that dynamic apnea consists of two sub-disciplines, one with and the other without the support of fins.

Deep freediving
As the name already suggests, going as deep as possible (usually in open water) is the desired goal of this discipline. Even though deep diving shares several characteristics with dynamic apneas, the essential challenge is to manage the increasing ambient pressure. A striking example is demonstrated by an extreme type of deep diving, the so-called no-limits apnea, where athletes are pulled down by a sled reaching speeds of up to 7 ms^{-1}. (The official world record for men is 214 m[6])

3.1.2.3 Diving Reflex

In order to adapt to their environment or to exploit new food sources, some animals have developed physiological strategies to sustain short periods of ceased breathing

[4]Luc Bessons's motion picture The Big Blue highlights this progression.
[5]In fact, apneic periods are also frequently observed in other water sports, e.g. water ball, underwater rugby or synchronised swimming.
[6]Herbert Nietsch, an Austrian freediver, attempted to set a new record in June 2012 and actually reached the depth of 254 meters. Unfortunately he experienced serious symptoms of decompression sickness during his ascend, requiring immediate medical care and therefore disqualifying his attempt.

without taking any harm. The so-called diving reflex (DR) [36] is known to be of vital importance for diving birds, reptiles and mammals by reducing oxygen consumption and carbon dioxide production. This physiological mechanism can also be observed in humans [37, 38, 39], even though with diminished characteristics, allowing unaided diving without oxygen unit. Even though the term suggests full water immersion, it can also be observed in dry experiments [40][A2]. The diving response, as a cardiovascular mechanism, comprises

1. selected vasoconstriction and
2. bradycardia,

consecutively leading to several beneficial reactions. Firstly, vasoconstriction in the periphery results in a reduction in blood supply in non vital skeletal muscles. Since muscle tissue is a strong oxygen consumer, an undersupply of peripheral muscles provides additional oxygen to the vital organs (i.e. the heart and the brain). The combination of vasoconstriction and reduction of heart rate (f_{C}) yields a reduction of cardiac output which in turn limits blood supply and oxygen consumption. Experiments in the hyperbaric chamber have revealed that this mechanism can reduce cardiac output to less than 3 litres per minute [41]. It is still not completely clarified, whether this bradycardia is produced directly from the breath hold as a primary component of the DR [38], or by a complex feedback loop triggered by baroreceptors in the periphery responding to the increased BP [42]. However, it can be speculated, that both effects might coexist. Figure 3.2 depicts the course of s_{HR} during a breath hold dive. While the assessment of sensors is limited under water, s_{HR} shows the typical caridac component of the DR. It has been reported by [37], that the extent of bradycardia and increase in arterial BP is directly related to the reduction rate of arterial oxygen saturation during breath-holding with exercise (presumably also in static apneas). It has also been shown by [43, 38, 39], that face immersion can strongly augment bradycardia by the activation of thermal receptors. Full body immersion were reported to have an even stronger impact on the heart rate (reduced to 26% compared to face immersion) but nevertheless reduced total apneic duration to 55% due to an increased oxygen consumption caused by counter measures against hypothermia (e.g. shivering) [44].

It should be emphasised, that even though this physiological mechanism still exist in humans, diving animals are by far better adapted to this environment. This is especially striking if considering that diving mammals generally initiate their dive by exhaling while still sustaining an aerobic metabolism[45]. Evolution has adapted these animals by allowing them to store oxygen mainly in their blood and muscles increasing not only buoyancy control but also preventing pressure related injuries. That is, hydrostatic pressure applied to a body increases with increasing depth[7] and will in consequence

[7]This is often demonstrated by the famous experiment with a balloon, where its volume is halved at 10 meter under water. In particular, a 10 meter water column exerts a hydrostatic pressure of 1 bar.

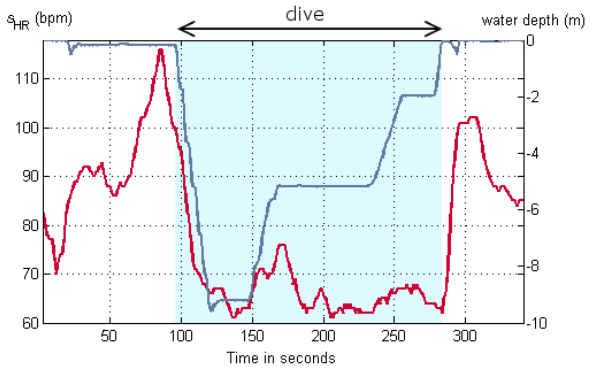


Figure 3.2: Basic measurement of heart rate s_{HR} (red) and water depth (dark blue) during a breath hold dive (light blue area) utilising a dive computer (Galileo SOL, Scubapro) connected to a heart rate belt. s_{HR} initially increases due to excessive inhalation and then rapidly decreases during descent. During the dive, a relatively constant s_{HR} was maintained while it stabilised shortly after surfacing.

compress peripheral tissue and vessels. This effect is also passed on to the lungs and to its smallest structure, the alveole. In their normal state alveoli are approximately 0.1 (expiration) to 0.4 mm (inspiration) in size [46] but exposure to external pressure can lead to rupture and collapse, inhibiting further gas exchange. This is also one of the main sources of injuries in breath-hold divers who have artificially adapted to the diving environment (others include inner ear traumas and decrompression sickness).

3.1.2.4 Breath Hold Duration

It is important to understand how the human body can be trained in order to ignore essential survival instincts and delay the respiratory reflex as long as possible. In particular the training mechanisms of the most extreme (in terms of apnea duration) discipline, the static apnea, should be discussed since it is closely related to the apneas performed in the conducted studies. The ability to sustain an apnea is basically determined by

- O_2 storage,
- O_2 consumption,
- CO_2 tolerance.

In order to prolong the apneic duration, these aspects have to be improved by athletes. Some techniques and physiological principles will be explained in the following.

Oyxygen storage:
The lungs represent the most flexible and largest storage of O_2 in the human body [46] and can also function as a CO2 storage. Various training exercises used by freediving athletes derive form yoga, which is known to improve vital capacity (VC) [47]. As a

consequence, freedivers often have a VC of 8 liters or even more [38], which is an enormous improvement compared with the usual 5 l of the average human. Additionally, even more air can be pressed into the lungs by a special respiratory maneuver, the glossopharyngeal insufflation (also called lung packing [38]). Utilising the glossopharyngeal muscles, additional air is pumped on top of the VC to recruit even the most isolated lung parts and therefore increasing the available air storage by another 2-4 l[8].

The complexity of oxygen storage in the human body can be demonstrated with a short derivation. Assuming an O_2 concentration of 21% in the inspired air, a freediver with 12 l lung volume (2 l residual volume, 8 l vital capacity and 2 l lung packing) has efficiently 2.1l of O_2 inside his lungs. Additional O_2 storages in the body are hemoglobin (Hb) and myoglobin (Mb) in the blood and in the muscle, respectively. Considering that former has a O_2 capacity of approximately 1.35 ml O_2/g 0.203l O_2/l blood and blood has 150 g Hb/l, the maximal storage volume of O_2 in one l blood is 0.203 l. Since this represents the maximal capacity, i.e. with 100% OS, values will be lower for arterial and venous blood with approximately 97% and 76% OS. With an assumed distribution in the blood system of 4 l and 1 l for venous and arterial blood, the total storage of O_2 in Hb is about 0.81 l (0.61 l + 0.2 l). Note that dissolved O_2 (with approximately 3 ml O_2/l blood) in blood plasma is neglected at this point. Numbers were extracted from [19]. In average the male body contains 42% muscle tissue [48] which correspond to 29.4 kg in a 70 kg individual. With a density of 1.06 kg/l this results in a volume of 27.7 l. Myoglobin concentrations of 0.70±0.09 mM for type I fibers and 0.46±0.08 mM for type II fibers where reported in [49] with an assumed ratio of one, resulting in myoglobin concentrations of approximately 0.58 mM, i.e. 0.58*10$^-$3 mol/l or 0.0161 mol for 27.7 l. Since one mol of myoglobin can store 1/4 of one mol of hb (which binds to 4 mol or 4*24.6 l O_2 [19]), 0.0161 mol will be able to bind 0.36l O_2. The assumed freediver has therefore a total O_2 storage of approximately 3.27 l (2.1 l + 0.81 l + 0.36 l).

Another work [50] calculated a total of 2.395 l but did not consider myoglobin storage while also suggesting a breaking point of 25 mmHg pb_{O_2}, limiting the actual usable O_2. Influences of hypercapnia effects on the dissociation curve or possible spleen contractions were also not taken into consideration. The immanent influence of different lung volumes on s_{SO2} is clearly depicted in Figure 3.5 (at the end of this Chapter) showing signals of an elite diver who performs two apneas after full exhalation and one after inhalation plus lung packing.

Oxygen consumption:
Considering the oxygen consumption, values of humans at rest have been reported to be about 250 ml min^{-1} [51]. Endurance training is therefore very common in freedivers, not only to reduce basic oxygen consumption but also to increase oxygen storage in type I muscle fibers. Additionally, mental training (active relaxation) and special diets

[8]This procedure can also be reversed in order to completely empty the lungs in order to train CO_2 tolerance and reduce the residual volume.

can further decrease O_2 consumption. Many freedivers, especially in the static apnea discipline, radically reduce intake weeks before a competition in order to reduce O_2 consumption of the stomach and digestive tract. Food can also be used to increase the pH value and therefore shifting the dissociation curve to the left, which decreases the transport of oxygen from the blood to the tissue. Furthermore, it has been reported by [38] that when the human body burns fat to produce energy it uses 8% more oxygen than when metabolising carbohydrates (glycogen) while producing 30% less CO_2. For freedivers trying to go "Where no man has gone before", such minimal improvements might be the difference between a new record or a tragic incident.

Carbon dioxide tolerance:
Finally, the accumulation of CO_2 represents the primary trigger of the respiration reflex by stimulating central and peripheral chemoreceptors. While those receptors are also influenced by a decrease of partial pressure of O_2 (pb_{O_2} values below 97 mmHg will increase impulse frequency [19]) and the pH value of blood and of liquor, pb_{CO_2} plays the major role. However, it is possible to reduce the effect of these receptors by frequently performing apneas (this is also the reason why patients suffering from sleep apneas often sense a diminished urge of breathing) and therefore increasing the tolerance level to CO_2. An immanent technique to prolong breath hold duration is hyperventilation. By excessive exhalation of CO_2 the initial level will drastically decrease, providing a longer duration until critical levels are reached[9].

3.2 Apnea Studies

3.2.0.5 Motivation

In the following section, our recent contributions to the understanding of physiological events during apneas will be presented. The thematic roots of our research group, Biomedical Sensors at Vienna University of Technology, can be found within the field of physiology of involuntary sleep apneas. Due to its increasing impact as a lifestyle disease, a better understanding of physiological mechanisms and consequences of nightly apneas is essential for proper diagnosis and effective treatment. However, recording valid data from patients suffering from sleep apneas proved to be quite complex and time-consuming. In particular, sleep laboratories often have a tight schedule that allows for only limited flexibility in the selection and assignment of subjects. Moreover, measurements recorded in sleep labs are often compromised by the unusual environment and abundance of sensor application. Both inducing unwanted stress in a subject or patient and may therefore lead to disadvantageous physiological behaviour (e.g. increased heart rate, blood pressure and reduced sleep quality)

[9]Unfortunately, this technique can be quite dangerous for divers since O_2 is further consumed while the breathing urge is delayed by the reduced initial CO_2 level. This can cause so-called shallow water blackouts, often with lethal outcome.

suggesting wrong conclusions. As a consequence, our efforts were moved towards voluntary induced apneas in a controlled environment aiming to explain fundamental physiological responses during a breath hold. Eventually, this led to a closer cooperation with national and international elite breath hold divers who were eager themselves to unveil physiological responses to apneas. Their ability and intention to expose their bodies to extreme conditions was the inspiration for the following works.

3.2.0.6 Method and Study Population

Over the course of several studies and experiments, 8 professional divers (two female) and 25 non divers (7 female) have performed various breath holds under different conditions. This section will explain in detail how these conditions were varied in order to extract specific physiological information from our subjects. Please note that in order to maintain consistency within this work, some symbols for signals or parameters in the following text might not match its complement in the mentioned study. Furthermore, since measurement devices and their produced signals were already discussed in section 2.2.1, associated devices will not be quoted here. In [A1] the influence of different apnea intensities on subjects without breath hold diving experience was investigated. For this purpose nine subjects (three female) were recruited with BMI, 23±2 kg/m^2 (mean±standard deviation) and age 24±3 years. In total, four voluntary maximal duration apneas - maximal apnea time τ_{m} was only limited by the capability of a subject - were performed after different initial breathing states. The first two apneas started after inspiration $\mathrm{AP_I}$ whereas the others started after expiration $\mathrm{AP_E}$ yielding mean τ_{m} of 1.2±0.6 min and 0.9±0.6 min, respectively. During these maneuvers s_{BP}, s_{ECG}, s_{PPG} and s_{RE} were measured and the parameters s_{SYS}, s_{DIA}, s_{HR} and Δs_{BP} extracted.

In the proceeding work [A2], the concept of intensity related differences within apneas from [A1] was refined by introducing three different starting conditions. Namely, apneas could start after a normal inhalation A1, after a deep inhalation A2 or after a deep inhalation preceded by a short breathing technique which is used by freedivers to prolong their apneas. Additionally, τ_m was limited to 45s in order to reduce the variability of the physiological responses and multiple apneas of each type were performed on three different days yielding a total of 12 apnea recordings (see Fig. 3.3a). Also, in addition to the previous recorded signals, s_{SO2} was measured and s_{MAP} calculated. Study population was recruited from divers (two male and one female) as well as non-divers (11 male and 4 female) in order to compare the influence of apnea training on the maneuvers. BMI of the divers and non-divers was 27.7± 2.1 kg/m^2 and , 22.8± 2.3 kg/m^2 respectively. Mean age was 27.3±5.8 (divers) and 24.6±5 (non-divers) years.

As an extension to [A2] a short trial including three professional freedivers was conducted in [A3]. One essential enhancement of this study was the acquisition of $pa_{\mathrm{CO_2}}$ and $pa_{\mathrm{O_2}}$ from the expired air and $pb_{\mathrm{O_2}}$ and s_{SO2} from the blood as discrete values at time instant τ_{m}. Note that for some signals (e.g. s_{BP} , s_{SO2}) τ_{m} was not consistent with the highest or lowest value, respectively. Therefore variable τ'_{m} was introduced,

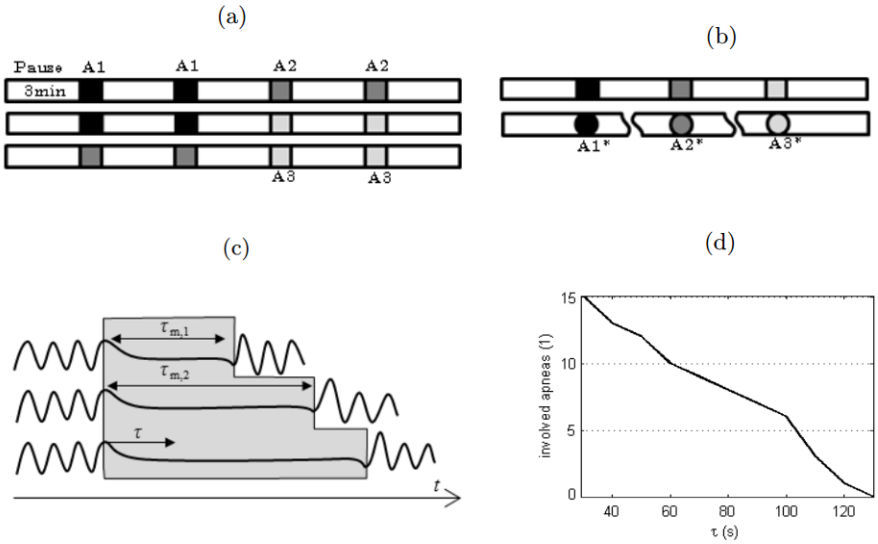


Figure 3.3: Schematic display of experiment designs in different studies. a) shows a setup introducing three different apnea types with 45s duration. In particular A1 started after normal inhalation, A2 after a deep inhalation and A3 after a deep inhalation preceded by a short breathing exercise. The slightly adapted protocol depicted in (b) additionally includes apneas A1-3* which are not artificially limited in their duration. Each row represents a different measurement day. c) shows schematic apneas with varying duration limit whereas (d) the total number of representations for these apnea durations τ illustrates.

describing the time of maximal expression in a signal near to τ_{m}. The ratios of the relative changes of $pb_{\mathrm{O_2}}(\tau'_{\mathrm{m}})$,$pa_{\mathrm{O_2}}(\tau_{\mathrm{m}})$ and $pa_{\mathrm{CO_2}}(\tau_{\mathrm{m}})$ to τ_{m} were calculated to establish a measure for production and consumption rates T'$pa_{\mathrm{O_2}}$, T'$pa_{\mathrm{CO_2}}$ and T'$pb_{\mathrm{O_2}}$. Additionally, apneas A1*, A2* and A3* were introduced, representing the described apnea types A1-3 without duration limit, i.e. a maximum try (see also Fig. 3.3b). In this work we realised the importance of standardised breath-hold preconditions (e.g. inhaled air volume and mental preparation) on the comparability of samples which was also the inspiration for our next work. In [A5], a single professional diver performed 15 apneas of varying durations (τ_{m} 137.7±62 s) on different days as illustrated in Figure 3.3c,d. The uptake of oxygen was controlled and limited to 5 l and no physical preparation was allowed before an apnea. Additionally, the subject did not know the duration of an apnea until the very end, therefore also limiting mental preparation effects. We connected the acquired end tidal $pa_{\mathrm{O_2}}(\tau_{\mathrm{m}})$, $pa_{\mathrm{CO_2}}(\tau_{\mathrm{m}})$ and $pb_{\mathrm{O_2}}(\tau'_{\mathrm{m}})$ of these various recordings in order to create a map of gas parameters for different τ_{m}. For physiological signals, segments of apneas sharing the same τ vectors were then compared to each other in order to describe the reproducibility of measurements. Note, that in every study the subjects were measured in a supine position without face immersion. If multiple apneas were performed in the same session, an adequate pause (3-10 min) was introduced between maneuvers to account for fatigue and adaptation effects.

The statistical evaluation was focused on relative changes of a signal to an averaged baseline in the interval [t_0, t_1]. In some cases this baseline was located in a different measurement but generally, the period right before an apnea was used (between 60 and 360s) and will be denoted as $\overline{b}$. Similar, a recovery period $\overline{r}$ describing signals shortly after the end of an apnea was utilised in the interval [t_2, t_3] (again, the total duration was not consistent over different studies). Additionally, (usually) also the changes in the signal were not given as discrete values, but were also averaged in a certain interval, i.e. [τ_0, τ_1] and are abbreviated with $\overline{\tau}_{\tau_0,\tau_1}$. For instance, the interval in an apnea from beginning to second 20 is defined as $\overline{\tau}_{0,20}$. In some cases, relative times were more advantageous requiring an alternative, quantile based, interval description, e.g. apneic time from half of its duration to its end is defined by the deciles of this interval e.g. [d_0, d_m] or $\overline{\tau}_{d0,m}$. Finally, intervals at the end of an apnea which are used to describe the mean end apneic values will be referred to as $\overline{\tau}_m$.

3.2.0.7 Result

Various studies have been conducted aiming to improve the understanding of physiological events during apneas. The performed measurements did not try to directly explain pathological phenomenons of such apneas, but rather explored general physiological mechanisms which help the body to sustain vital functions during periods of ceased breathing. In this section, the results of our effort will be summarised and compared to existing findings in literature. Note that specific figures can be found in the respective work located in the appendix and are not reprinted in this section. However, in order to demonstrate some results, typical courses of physiological signals are illustrated at the end of this Chapter in Figure 3.4 and Figure 3.5.

Cardiovascular Parameters
Even though the protocols of all our studies did not involve face immersion, which is known to augment the diving reflex [38, 39], the physiological effects of this mechanism were still visible in s_{BP}, s_{HR} and Δs_{PPG}. In [A1], $s_{SYS}(\overline{\tau}_m)$ was 18±5% higher than $s_{SYS}(\overline{b})$ in AP_I and 15±5% higher in AP_E. s_{HR} was observed to be lower at $\overline{\tau}_m$ compared with values from $\overline{b}$ for both apnea types with stronger changes in AP_I (-9±7% vs. -1±8%). A similar effect can be seen in Figure 3.5a in BH1 (after expiration) and BH3 (after inspiration). Parameter Δs_{PPG} showed a dominant decrease in both, AP_I (28±11%) and AP_E (53±8%) indicating ongoing peripheral vasoconstriction. Observations in [A2] showed a small increase of s_{MAP} for apnea types A1 and A2 (12.3±12.8% and 3±8%). In A3 no significant trend could be seen for s_{MAP} (0.7±10.3%). Considering s_{HR} a decrease could be seen in A1 and A2 but not in A3 (10.4±9.6%, 7.4±10.3% and 3.5±9.7%). We concluded, that starting conditions could strongly influence the intensity of an apnea on the body and therefore trigger different extends of physiological mechanisms. As discussed in [A5], also τ strongly influences the intensity of an apnea. A steady increase in s_{SYS} was observed throughout all apneas while it reached its peak in the apnea with the highest τ (τ_m=222s). Subsequently, s_{SYS} increased up to 217% compared to $s_{SYS}(\overline{b})$ in

the longest apnea and Δs_{BP} even up to 266%. This course was very stable throughout all measured apneas with a mean coefficient of variance (MCV) of 8±2.6% and 15.6±5.2% in s_{SYS} and Δs_{BP}, respectively. Note that the actual maximum of BP related parameters occurred after the apnea during $\bar{r}$. Strong changes were also seen in $\Delta s^{f}_{\mathrm{PPG}}$ and $\Delta s^{e}_{\mathrm{PPG}}$ with a decrease over τ to 21±7% and 53±13%, respectively. As expected from the more distal location of $\Delta s^{f}_{\mathrm{PPG}}$, the vasoconstriction effects were more distinct than in the proximal location of $\Delta s^{e}_{\mathrm{PPG}}$. Both Δs_{PPG}, finger and ear, showed very high values in MCV, 53.6±17.1% and 59.7±23.2%, respectively. Interestingly, s_{HR} increased over τ up to 40±9% with a MCV of 10.6±2.7%.

Gas Parameters
Parameters describing the behaviour of gas concentrations are highly relevant for the evaluation of apneas. In particular, changes in s_{SO2}, $pa_{\mathrm{O_2}}$ and $pa_{\mathrm{CO_2}}$ can be directly linked to apneic events. We observed this interrelation in [A5, A3] showing a decrease of s_{SO2} and $pa_{\mathrm{O_2}}$ and an increase in $pa_{\mathrm{CO_2}}$ with increasing τ. End tidal $pa_{\mathrm{O_2}}$ and $pa_{\mathrm{CO_2}}$ dropped to 38 and 60 mmHg for τ_{m}>200, which is similar to observations in [52]. s_{SO2} dropped under 80% in several measurements and were reported in [40] to frequently go below 60%. The immanent influence of different lung volumes on s_{SO2} is also depicted in Figure 3.5 showing signals of an elite diver who performs two breath holds after full exhalation (BH1,2) and one after full inhalation plus packing (BH3). BH1 and BH2 showed very low $s_{\mathrm{SO2}}(\tau'_{\mathrm{m}})$ (57% and 42%) and high T's_{SO2} (11% min^{-1} and 14% min^{-1}) compared to BH3 with 65% $s_{\mathrm{SO2}}(\tau'_{\mathrm{m}})$ and 4% min^{-1} T's_{SO2}.

Interestingly, T's_{SO2} in other measurements was usually higher in apneas with higher τ_{m} indicating a steeper decrease in later phases of an apnea. Contrary, T'$pa_{\mathrm{O_2}}$ and T'$pa_{\mathrm{CO_2}}$ showed reduced values with increasing τ_{m} as shown in [A3]. However, this behaviour could only be partly reproduced in [A5], since although T's_{SO2} tend to decrease for τ_{m}<180 s (3.27% min^{-1} for τ_{m}=164 s) it started to increase again for longer apneas (5±1.5%min^{-1} for τ_{m}>180s. A closer look at T'$pa_{\mathrm{O_2}}$ and T'$pa_{\mathrm{CO_2}}$ also showed that per minute values are only reducing over time if regular end tidal T'$pa_{\mathrm{O_2}}$ and T'$pa_{\mathrm{CO_2}}$ (appr. 16 and 4%) is not considered. By prior subtraction of these values from $pa_{\mathrm{O_2}}$ consumption and $pa_{\mathrm{CO_2}}$ production, relative T'$pa_{\mathrm{O_2}}$ and T'$pa_{\mathrm{CO_2}}$ can be calculated. These new parameters, R'$pa_{\mathrm{O_2}}$ and R'$pa_{\mathrm{CO_2}}$, hardly showed any variation for different τ_{m} (2.5±0.7% min^{-1} and 1.5±0.4% min^{-1}). Looking at absolute end tidal values, Finally, it was observed in [A5] that the ratio between $pa_{\mathrm{O_2}}$ and $pa_{\mathrm{CO_2}}$ decreased with a higher τ_{m} eventually yielding a RQ of 0.58 at τ_{m}=222 s.

3.2.0.8 Discussion

Considering s_{BP}, we observed an increase in all of our studies that correlated with τ. This was also reported by other works investigating voluntary apneas [53, 39, 50] and sleep apneas [54, 31]. In combination with the decrease in Δs_{PPG} these parameters suggest strong selected vasoconstriction. A specific increase of brachial artery resistance in dry apneas was reported in [40]. It should be noted, that changes in Δs_{PPG} were not as

consistent as those in s_{BP}, since several measurements showed a clear increase towards τ_{m}. Possible explanations for this higher variation are given by [55] with a hypoxic induced vasodilitation of under supplied vessels and by [53] with the direct inhibition of vasoconstriction by hypercapnia. Another explanation can be found in the full course of s_{BP}, which is illustrated in the compilation of Figures 3.4b and 3.5b. As noticed also by [53], s_{BP} and Δs_{BP} vastly decreases at the onset of an apnea due to changes in the intrathoracic pressure similar to a Valsalva maneuver. After a deep inspiration, the filled lungs will demand more space in the thorax than usual, therefore squeezing venous vessels. Consequently venous return is inhibited leading to a decrease of stroke volume and in turn of s_{BP}, as described in [17]. This phenomenon is especially dominant after lung packing due to the introduction of an almost unphysiological lung volume. This might lead to a severe undersupply of the brain, in the worst case, can cause syncopes[10] (i.e. the so-called packing blackout). The apneas shown in Figures 3.4 and 3.5 (BH3) were initiated after lung packing and correspondingly show a vast decrease of BP derived signals. The reduction of BP related parameters by a decreased stroke volume is followed by a temporal increase of s_{HR} in order to restore the cardiac output [18] (see Figure 3.4a (B*)). These mechanisms also seem to interfere with the usual observed bradycardia [38] which was already attenuated [43] in our experiments due to missing face immersion. We also observed stronger signs of the diving response in BHD than in non-divers suggesting the trainability of this reflex.

The complex interrelation between gas metabolism and cardiovascular parameters can be analysed to obtain information about the health state of a person. In particular, the adaptability of an organism to stressful or unusual situations, e.g. periods of oxygen undersupply, is a potential property for the development of reasonable health markers or indices. Voluntary short apneas, i.e. an induced physiological imbalance, might therefore comprise an alternative to current cardiopulmonary fitness evaluations which rely mostly on exercise, inducing cardiac stress (e.g. Harvard step test, see also [56]) as described in [A4]. The time delay until full recovery of physiological values should be further investigated. Additionally, cerebrovascular behaviour is also closely linked to the balance of different gas concentrations inside the blood. Especially CO_2 is known to have vasodilatory influences on cerebral vessels [40] while also highly affecting vital autoregulatory mechanisms inside the brain [57]. In Figure 3.4d a slight increase in total cerebral Hemoglobin, s_{cHb} over the course of the apnea can be observed. However, at marked time S*, this rise was rapidly increased while also introducing pulsating variations which seem to correlate with involuntary breathing efforts. [58] suggested that the breathing movements actually might help to improve O_2 supply to the brain.

[10] In a recent experiment with one elite BHD, we were able to produce a short lung packing induced blackout under medical supervision. The diver experienced a temporary decrease of systolic BP to 53mmHg while the systolic to diastolic amplitude was reduced to approximately 5mmHg.

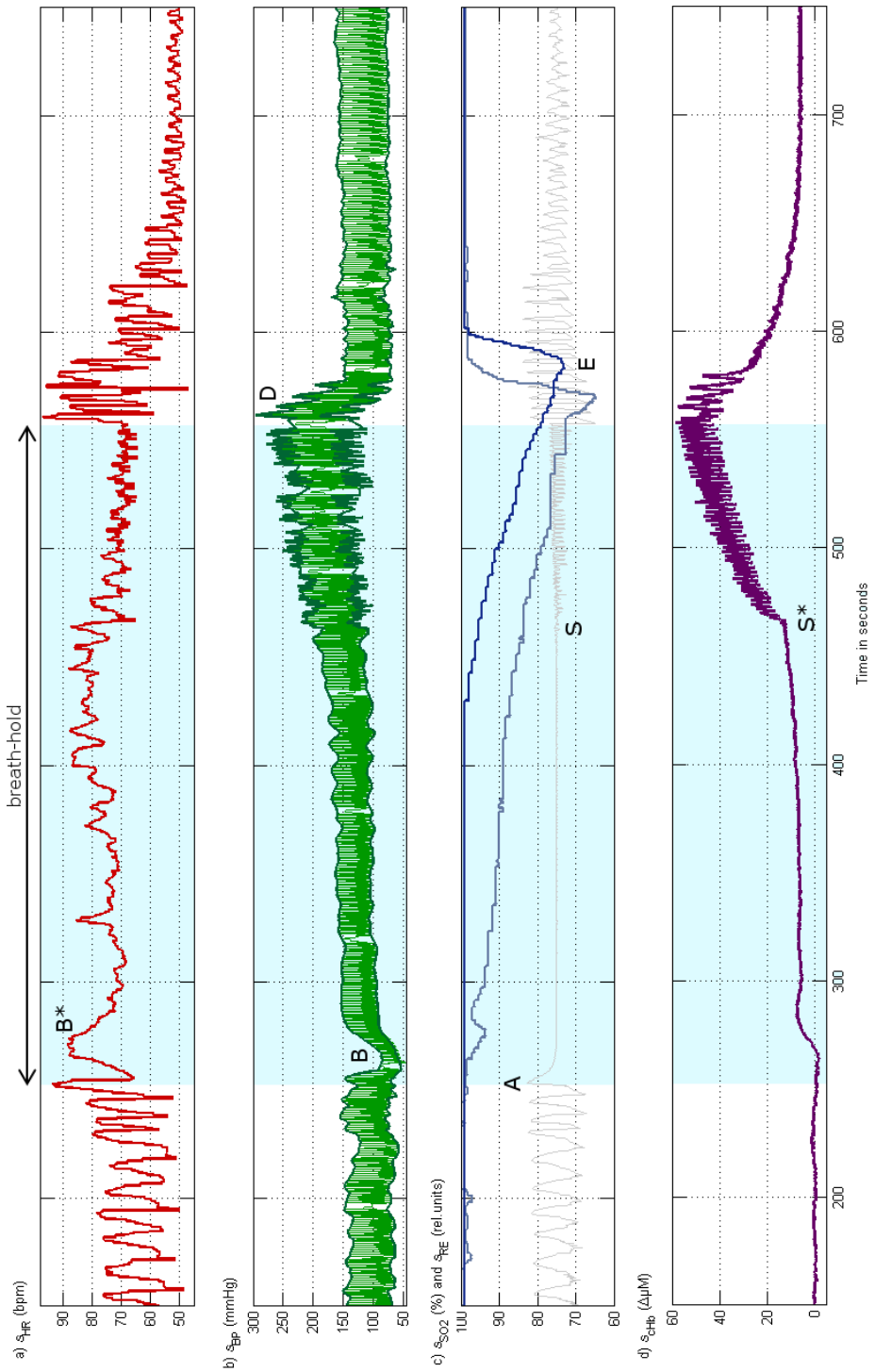


Figure 3.4: Simultaneous recording of multiple biosensors during a breath hold (blue area). Displayed signals are (a) heart rate s_{HR}, (b) blood pressure wave s_{BP} (c) oxygen saturations s^{f}_{SO2} (dark blue) and s^{f}_{SO2} (light blue) and respiration s_{RE} and (d) relative changes of cerebral hemoglobin s_{cHb}. The apnea starts with a deep inhalation (A) which is accompanied with a slightly delayed reduction in s_{BP} (B) and a subsequent increase of s_{HR} (B*). With prolonging apnea, s_{SO2} starts to decrease and the breathing urge gets stronger. At (S) the struggling phase begins and causes involuntary chest movements which induce flucuations of s_{cHb} (S*). Shortly after onset of breathing, s_{BP} and s_{SO2} reach their maximum (D) and minimum (E), respectively.

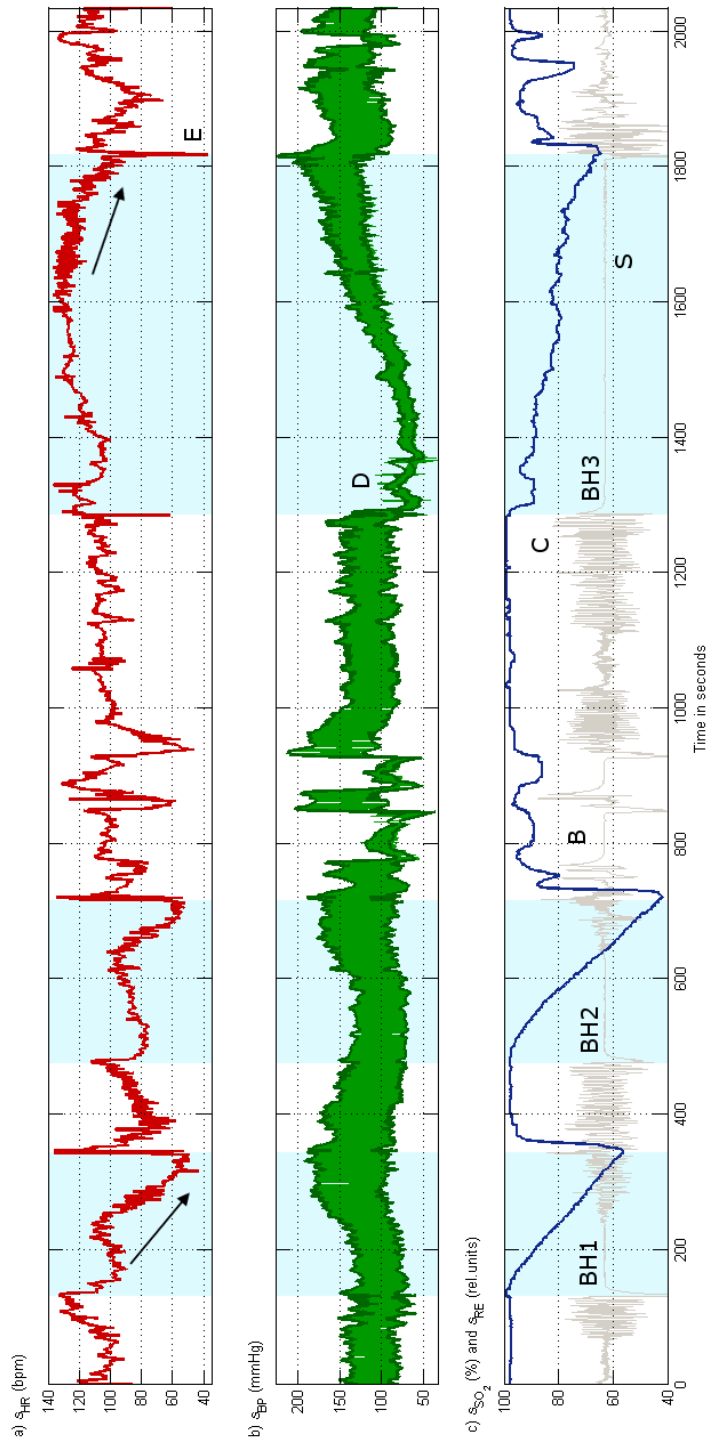


Figure 3.5: Simultaneous recording of multiple biosensors during a series of three breath holds performed by an elite BHD. Displayed signals are (a) s_{HR}, (b) s_{BP} and (c) s_{SO2} and respiration s_{RE}. s_{RE} gives some information about the nature of the particular apneas. In particular, BH1 and BH2 are initated after reverse lung packing while BH3 is started after lung packing. The reduced O_2 capacity in BH1,2 result in a much stronger decline of s_{SO2} compared to BH3. Note that the diver performed additional breath holds at B and excessive hyperventilation at C in order to prepare for BH3 which lasted 8min and 51s. Note that s_{BP} strongly declines at the beginning of BH3 apnea (D) and steadily increases from there. Considering s_{HR}, the expected bradycaria was visible in BH1,2 and at the end of BH3.

Chapter 4

Software Design

4.1 Introduction

In this chapter, the proposed system architecture with its underlying modules will be described. The chosen programming languages, frameworks and tools will be introduced while also explaining their specific application in the context of a study management tool. It is important to note, that this work only introduces an innovative design that has not been implemented yet. The database structure, on the other hand, already exists in the final version and was also used for the prototype. Section 4.3 will give insights into the database structure and its particularities. It should be noted, that the proposed framework does not offer any interface to external monitoring devices and therefore is not capable of data acquisition itself. Its functionality includes data storage and *external* information management, but starts at the validation layer of the data processing model.

It has already been discussed in Chapter 1 that existing frameworks do not cover the requirements of management and processing in a physiological study. The alternative approach is the developement of an individual solution. Generally, such implementations are done for smaller projects in which scripts and small functions can easily be adapted to the needs of the particular objective. Most of the challenges in this scope can be covered well using MATLAB [59], which comes equipped with an incredible toolbox of algorithms, data analysis frameworks and numerical computing. Its popularity amongst engineers and researchers around the globe is not without reason and although alternative open source programming languages like Octave [60] or Python [61] have spread in the last years, MATLAB is undoubtfully one of the big players. However, aside of all its advantages several weaknesses remain in the context of requirements of a modern object oriented programming language. While it is based on C, C++ and Java, it offers only little support for software development issues of a more complex scale like database interfaces, web services or even mobile applications. When thinking about the implementation of a tool to administer physiological studies, these aspects could be essential for an efficient *external* and *internal* information management. To address these challenges, well established programming languages like

Java or Python offer a much more versatile and highly sophisticated platform. Java for instance, has the highest global distribution and has even been awarded top 1 programming language in 2014 by IEEE Spectrum [62]. Although there are not many tasks which cannot be efficiently addressed by Java, unfortunately signal processing is one of them. Performance issues and the lack of specialised analysis frameworks strongly inhibits Java to conquer this field of application. While MATLAB and Java on their own cannot provide the required features for a comprehensive study management design that also includes data processing, theoretically, there are ways to combine both strengths. This could be done either by calling Java classes or functions (packed in jar files) from a MATLAB Tool or by creating a MATLAB Runtime inside a Java Program. Even though both methods are functionally valid, there are severe trade-offs in terms of performance and development simplicity. A program structured this way, would require different Integrated Development Environments (IDE), a complex debugging strategy and detailed knowledge of the interaction between both languages. Despite offering sufficient functionality, this solution was also not practical for this project.

Based on these findings, the general-purpose programming language Python seems to be most suitable. Amongst its open source libraries and frameworks the necessary tools for database access, graphical interfaces, internet connectivity as well as signal processing can be found. Furthermore, the open source licence is an additional benefit considering financial efforts as well as community support. Python has also been reported to be one of the most popular scientific programming languages [63] in computer science and is, according to [62], among the 5 most popular programming languages. The potential development of data access, data distribution, user interaction and scientific features provides the basis for a sophisticated centralised analysis and management system.

4.2 Server-Client Architecture

The core structure and basis design of the whole system is formed by a centralised server-client architecture. The server holds the methods to access information located in the database and can provide this information over the network to individual clients. Additional to already stored data, signals and data can be analysed by the server to produce derived signals, statistics and scientific results. In order to ensure high compatibility between different operating systems and software, the client side is represented by a Webview or a front-end implementation. While meta-data is stored in the database, data files are located on the servers filesystem and only its path is registered in the database. Even though modern database systems are already capable of holding large files (e.g. LONGBLOB in MySQL, see [64]), it is recommended to store files larger than 1MB in the filesystem [65]. As already mentioned, files recorded in physiological studies using continuous measurement systems, will most likely be a hundred times larger than the recommended threshold. A possible solution, also described in [66], would be to break down data into smaller data junks (<1MB) which

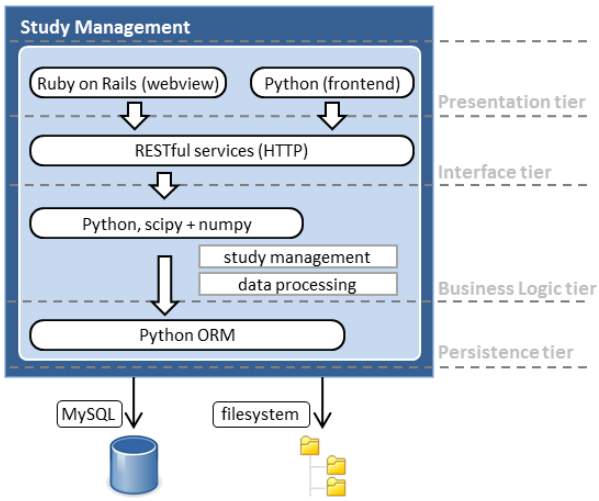


Figure 4.1: System architecture of a study management software structured by its module tiers. From top down: Presentation (User interface), Interface (Network connection), Business (data processing) and Persistence Tier (Database and Filesystem Connection)

are merged again later on request. However, since using the servers filesystem comprises a viable and comparable simple option, it was preferred as data storage method.

In order to give a clearer overview of the systems architecture, an abstraction of different modules can be seen in Fig. 4.1. Four major modules (or tiers) were introduced to demonstrate separate function groups of the software. The following sections will cover their characteristics and the proposed frameworks.

4.2.1 Presentation Tier

On this level methods are located which present data to the user. This includes user friendly presentation of *external* as well as *internal* information. The underlying implementation can be both, webview and classic client software. The former offers a higher portability and compatibility with different devices and operating systems, which is highly advantageous not only when considering different computer systems but also mobile phones and tablets. Even though this might not be an immanent goal, future applications may rely on mobile usability. For this approach Ruby on Rails [67] is suggested as programming language for this module. This open source developing framework fulfils all requirements to implement the required features while combining the best from other heavily used web programming languages like PHP (quick) and Java (clean and solid) [68]. Using a webserver could further help to separate logic and presentation implementations. A client software approach on the other hand would give the user more control while also offering a symbiosis between scripts and stand-alone tools (i.e. MATLAB) which are operating locally on the users computer. The integration of such individual implementations are much easier to develop having

easy access to the local storage and runtime integration (but can also be done for instance by uploading Python or MATLAB scripts to the server). Eventually, Python was considered as the most suitable framework for these features, whereas Java could also be a viable option.

4.2.2 Interface Tier

Aside from presentational (and possible processing) capabilities, the previously mentioned programming languages also have to communicate with the server over the network and vice versa. It should be noted here, that for several reasons (which have partly been discussed in 1 and will be further examined in 4.2.3) the core server implementation is also based on Python.

This communication is defined within the Interface Tier, describing how data is transferred through the network. Nowadays, there exist various protocols [69] which standardise the way computers and other devices interact with each other. Probably the best established is the Hypertext Transfer Protocol (HTTP) [70], representing also the basis for data communication in the World Wide Web. It is also applying principles defined as Representational State Transfer (REST) [71] services, allowing an easy and standardised development of web services. Especially web Application Programming Interfaces (API) play a crucial role in order to access network services in a comfortable and consistent way. Additionally, using JavaScript Object Notation (JSON) [72] as interchange format further improves simplicity and clarity of software development. Besides the information, also large data will have to be transferred. For this purpose, File Transfer Protocol (FTP) can be used alternatively to HTTP.

4.2.3 Business Tier

The core functionality (in terms of data management) of the framework is described in this tier. In the current design[1], most features will be processed on the server and only the resulting information and graphs are then transferred to the client side as described earlier. Meta information organisation and data processing is located here. As already been pointed out, these core features are based on Python, including several open source packages. In particular, Scipy and Numpy [73] should be mentioned since they offer the majority of functions required for state of the art mathematical and scientific programming (e.g. manipulation of arrays and matrices, integration, differential equation solvers, statistics, and many more).

4.2.4 Persistence Tier

The server stores information and data in a database (see 4.3 for further description) and its filesystem, respectively. The connection to the database is implemented using

[1] In future implementations, specialised individual data processing could be embedded into the client with an integration interface which allows users to to access their own functions.

the Python SQL toolkit, SQLAlchemy [74]. Being an Object Relational Mapper (ORM)[2], it allows for easy and fast development of complex SQL queries that can be easily embedded into any object-oriented structure. The file-system is accessed over standard Python libraries. Signals are stored on the server in a directory hierarchy, mapping the relationship between studies, subjects and measurements. Each signal of a measurement is then stored as an individual file. The resulting paths for one measurement will therefore look something like this:

```
..\data\Phys. Unbalance during Apnea(2013)\am\20141021_2057\ecg.mat
..\data\Phys. Unbalance during Apnea(2013)\am\20141021_2057\bp.mat
..\data\Phys. Unbalance during Apnea(2013)\am\20141021_2057\resp.mat
```

Code excerpt 4.1: Server side path structure of stored data.

4.3 Database

The database design is based on the open source relational database management system MySQL[4] [76] which is one of the most widely used database management systems (currently rank 2 according to [77]). With excellent support and general compatibility, MySQL is also one of the easiest database management systems to install, manage and access via software. It is used in countless applications around the world and fulfils all requirements of a scientific study management tool. In the next section, the particular data base structure will be described in context of these requirements. In Fig. 4.2 the complete enhanced entity–relationship (EER) model is shown.

The biggest challenge for the database design was the feature for creating individual setups of studies and devices. The option to create completely dynamic designs implies numerous complex interrelations between the stored information. These relations hold the real information about the state and connections of a study. Some specific relationships should be explained in detail to give a clear picture of the databases particularities (note that italic names indicate that these items are represented in the database as tables). *Devices* for instance hold information about all their available *Modes* and *Inputs*. When creating a *Configuration* the user can then choose a specific *Mode* and *Input* for this *Device*, thus creating new relations between tables. The similar principle is used for *Applications* and *Inputs* which are also connected over a relation to a *Configuration*. In accordance, *Events* are created and can be connected to a *Study*. Then a specific *Event* is connected to a *Measurement* using an association table where also begin and end of the event is stored. Another

[2] An Object Relational Mapper forms a bridge between classic query based database connection (i.e. Selects, updates, deletes, etc. [75]) and object-oriented programming. In particular, database tables are represented by objects, whereas their attributes are mapped to columns of this table. This allows a clear and very comfortable access of database tuples[3] while also keeping a clean program structure.

[4] SQL stands for Structured Query Language, which is a specialised programming language developed for managing data held within a database.

particularity is the table *signals* which can refer to itself when a calculation method is used on them to generate a new *signal*.

4.3.1 Tables

The most crucial tables (no association tables are listed) will be described in detail with their attributes and specific function. Note that tables are listed alphabetically, since a logical structure is not possible due to their countless relations with each other. Furthermore, due to these relations, data can not be easily removed from the database without violating constraints or losing information about former elements. To account for this issue, important tables contain a *deleted* field marking the time and date of its removal. For the sake of completeness it should also be noted, that all but association tables will include an autoincremented numerical id field.

Alias Over this table an instance of a device is mapped to a specific configuration. This ensures, that one device can be added several times to the same study (which is quite often required). The device receives an alias name which helps to identify the same device within different setups.

Application Many sensors used in a study can have different application locations. For instance: Finger, Earlobe in case of s_{PPG}.

Configuration A configuration is defined by a combination of available elements. It is unique for a study and basically describes the setup that is being used for data acquisition. In particular, this means a composition of devices (i.e. alias) with a specific arrangement of channels each mapped to another input signal with its own sampling rate and application site.

Device This table holds descriptive information (i.e. name, description, number of channels, etc.) about the available devices.

Event In most studies, an event will trigger changes relative to the normal state. These events and their attributes are stored here.

Group Another measure to compare physiological phenomenona is the recruitment of different study groups. Some examples are: control group, divers or diabetics.

Input Here, all signals (input channel) that can be recorded are stored. Name (e.g. Electrocardiogram) and description of the signals can be saved.

Measurement When a session is recorded for a subject it is represented in the database in this table with its date and its correlating signals and events.

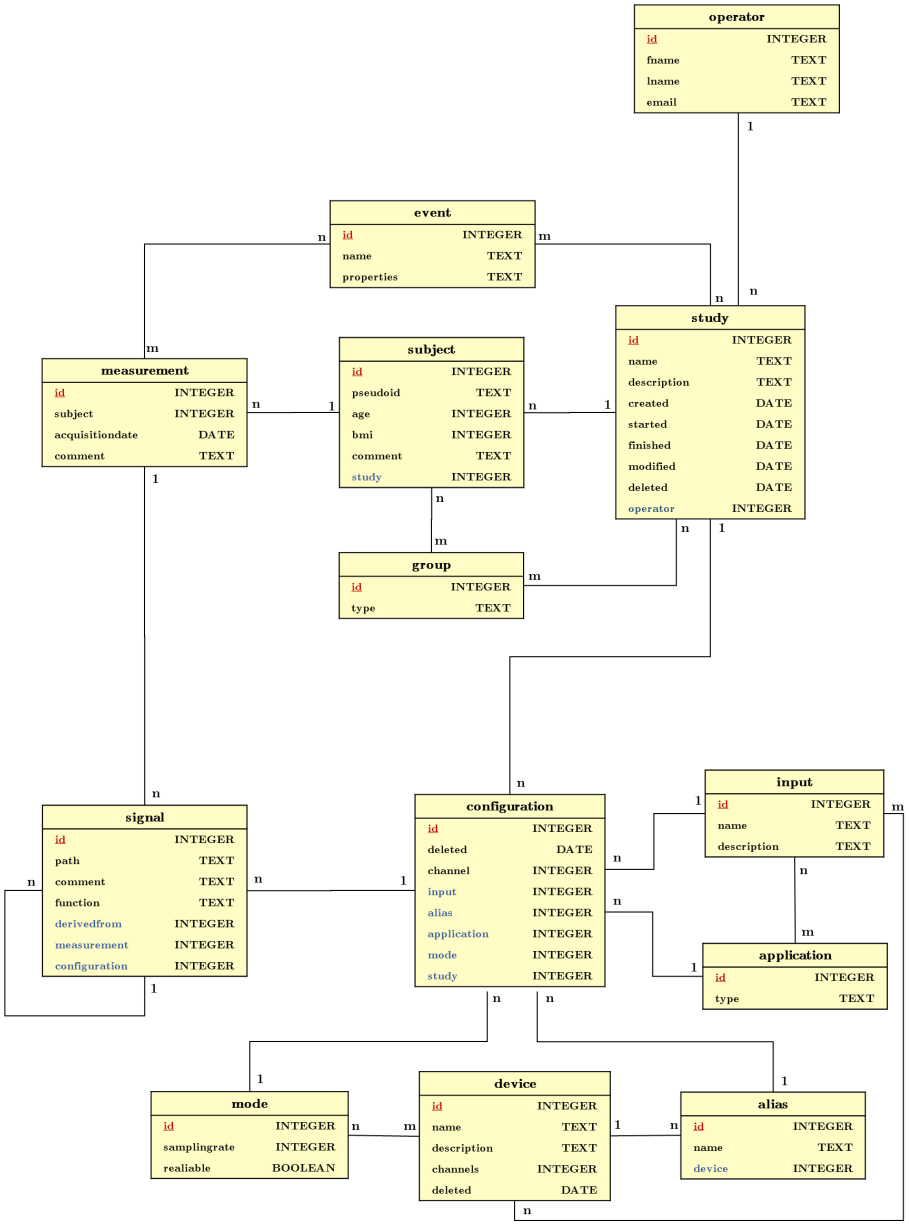


Figure 4.2: The EER model of the database. Tables, their attributes and the relations are shown. Primary and foreign keys are coloured in red and blue, respectively. Note that basic association tables (without additional attributes) are missing and only indicated by an m-to-n relationship. The central table *Configuration* combines various information of a study and its characteristics in order to create a unique setup.

Mode Devices can operate with sampling rates. While most can constantly sustain this rate, other devices show tiny variations over the course of a measurement. These information is stored in this table.

Operator Studies have at least one operator, who is responsible for the organisation and management of the study. His contact information is stored in this table.

Signal The signals represent an actual measurement of an assigned input channel, i.e. of a biosignal. Therefore, when creating a measurement, for each input assigned to a device, a signal with actual data has to be created. The data is stored in the file system while its path is saved in this table.

Study Studies have several attributes in order to make them unique in the system. This include its name, start, ending and description. They can also be considered as the top level of *external* information.

Subject Subjects have a pseudonym, age, bmi and are assigned to a specific study.

Chapter 5

Prototype

5.1 Introduction and Overview

Based on the data processing model (Chapter 2) and the proposed software architecture (Chapter 4), a prototype was implemented to show basic functions, principles and work flows. It should be emphasised, that this client only represents a proof of concept realisation of the presented architecture. The main focus was set on study management aspects and data management (i.e. *external* information) whereas the data processing was left for future developments. That is, a study with specific attributes can be created and then executed by adding (in subsequence) subjects, measurements and the associated signals. The recorded data can then be accessed by applying various filters to receive a customised data set for further analysis. Section 5.2 will give an overview of the defined requirements, i.e. user stories for this prototype.

As already discussed in Chapter 4, one of the most appropriate programming languages for the implementation of such a multi functional study management tool is Python and in particular, version 3.3.5 was used for the developed prototype.

5.2 User Stories

Here, the requirement coverage of the prototype will be listed. For this purpose, user stories (see [78] for a detailed explanation) are utilised to list the intended features. Two different user roles were defined for this purpose, in particular: *operator*, and *researcher*. Former is responsible for the design of a study, whereas latter will use the provided structure to collect and store data. Both can then access the acquired data to apply local analysis algorithms. Even though those user classes are assigned to specific user stories, in practice they are often represented by the same person. Note also that mostly basic user stories are defined, to give a short overview of the prototypes features.

These user stories will be referred to later in section 5.3, when discussing their actual implementation within the prototype.

5.2.1 Study Management

In order to initialise a study, a design has to be created. User stories associated with these tasks are found in the table below.

US-SM-01	As an *operator* I want to create a new study with its properties.
US-SM-02	As an *operator* I want to create a new device.
US-SM-03	As an *operator* I want to create a new signal.
US-SM-04	As an *operator* I want to create a new mode.
US-SM-05	As an *operator* I want to create a new group.
US-SM-06	As an *operator* I want to create a new event.
US-SM-07	As an *operator* I want to assign signals to a device.
US-SM-08	As an *operator* I want to assign modes to a device.
US-SM-09	As an *operator* I want to assign events to a study.
US-SM-10	As an *operator* I want to assign groups to a study.
US-SM-11	As an *operator* I want to create a new configuration with different devices and signals.
US-SM-12	As an *operator* I want to define specific modes and applications for devices and signals in a configuration.
US-SM-13	As an *operator* I want to edit study properties and configurations.

Table 5.1: Overview of user stories related to study management and organisation.

5.2.2 Study Execution

All user stories related to the execution of a study, e.g. data management, are listed here.

US-SE-01	As a *researcher* I want to contact a *operator* of a study.
US-SE-02	As a *researcher* I want to create a new subject and assign him/her to a study.
US-SE-03	As a *researcher* I want to create a new measurement and assign it to a subject.
US-SE-04	As a *researcher* I want to add data to a measurement.
US-SE-05	As a *researcher* I want to display data of a measurement.
US-SE-06	As a *researcher* or *operator* I want to download data directly a study.
US-SE-07	As a *researcher* or *operator* I want to download data directly a subject.

Table 5.2: Overview of user stories related to study execution.

5.2.3 Data Access

User stories describing data access requirements in the prototype are shown below.

US-DA-01	As a *researcher* or *operator* I want to find and download data associated with specific studies.
US-DA-02	As a *researcher* or *operator* I want to find and download data associated with specific signals.
US-DA-03	As a *researcher* or *operator* I want to find and download data associated with specific devices.
US-DA-04	As a *researcher* or *operator* I want to find and download data associated with specific groups.
US-DA-05	As a *researcher* or *operator* I want to find and download data associated with specific events.
US-DA-06	As a *researcher* or *operator* I want to find and download data associated with specific sensor applications.
US-DA-07	As a *researcher* or *operator* I want to combine filters to find and download a specific data set.

Table 5.3: Overview of user stories related to data access.

5.3 Graphical User Interface

In this section the graphical user interface (GUI or UI) of the prototype will be introduced. The implemented features will be shown using research related examples and actual measured data. Tkinter, which is Pythons standard GUI framework and easy to use for most applications, was chosen as GUI implementation package.. The class structure is based on the Model-View-Controller[1] (MVC) [80] design pattern to assure re-usability and clarity of programming code. In the last section 5.3.3, the GUI components will be shown and described in order to give an overview of the possibilities and limitations of the prototype.

5.3.1 Model-View-Controller

The MVC architecture is one of many approaches for developers to deal with increasing complexity in GUI programming. A strategic system design can strongly improve readability and clarity of code which in turn lowers programming efforts. Its main principle is the separation of presentation, data and functions. Therefore in a MVC architecture, a GUI implementation requires the following interacting classes:

- Model: stores information and data of a view.
- View: describes the elements and arrangement of a GUI.
- Controller: holds the logic and functions used by the view.

[1] As already noticed by [79], MVC implementations (like most software implementations) often also include other architecture styles. Even though this work tries to stay conform to the MVC concept, some classes might not meet all requirements of a "real" MVC architecture.

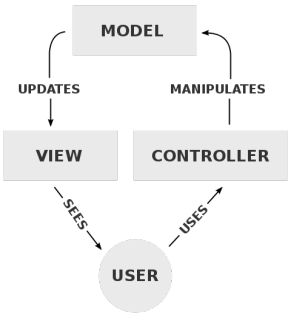


Figure 5.1: A schematic display of the Model-View-Controller architecture. The user interacts with views use functions of controllers to manipulate data stored in models. A full cycle is completed if these changes in data trigger an update of the view (image from [81]).

As indicated in Figures 5.1 and 5.3, each class comprises their own special functionality and interaction between other MVC classes. The user only sees views and can manipulate and change their elements. By doing so, functions are called that are stored in the controller and are mapped to the GUI. These functions are not only used for data manipulation and calculations, but also represent the interface to external data sources like webservices or databases. The controller in turn updates the data stored in the model and triggers a refresh of the GUI which will then display the updated data. However, this relationship can have multiple connections, e.g. one controller can be added to multiple views. On user interaction, an update is then triggered in both views via the controller. The implementation of such complexly interconnected and dependent structure is (especially in Python) not quite simple and is explained best with a minimal example:

```
model = Model()
controller = Controller(model)
model.controllers.append(controller)
view = View(controller)
controller.views.append(view)
```

Code excerpt 5.1: MVC architecture in Python.

As shown above, a model has to be created and given to the controller upon construction . The controller itself has then to be added to the models controller to complete this mapping. Creating a view requires a controller as input parameter, while the view then has to be added then to the controller.

5.3.2 Customisation

This section will show some selected extracts and examples of customisations developed for this prototype. It should be noted, that while Tkinter offers mostly all necessary GUI elements, it strongly lacks the possibilities to customise them. For instance, it is really simple to implement an ordinary option menu using the *Tkinter.OptionMenu* Method as shown in the following code segment(see Figure 5.2a for the resulting element):

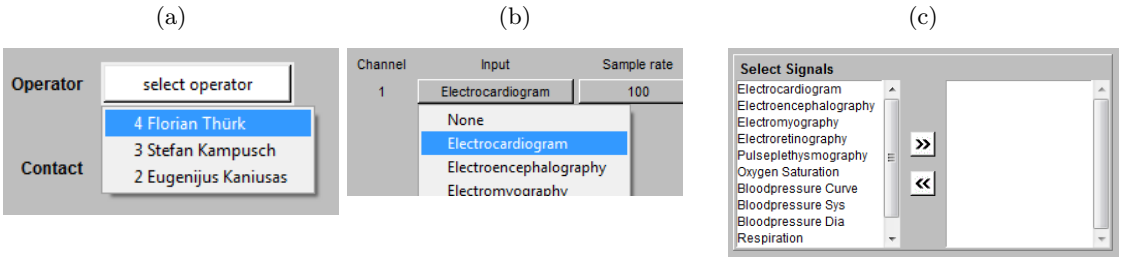


Figure 5.2: Customisations of GUI controls are shown. a) depicts the standard implementation of Tkinter, whereas b) presents a slimmer customised option menu. Additionally, c) shows a custom selection box, enabling the user to add and remove elements from a selection.

```
self.option_operator = tk.OptionMenu(self, self.operator,
        *list(self.operator_dict.keys()),
        command=self.select_operator)
```

Code excerpt 5.2: Adaptation of a Tkinter option menu GUI element.

Whereas *self.operator* being the textvariable that defines the default value ('select operator'), **list(self.operator_dict.keys())* being a pointer to the list of operators received from the database and *command=self.select_operator* setting the command which is triggered when changing the selection. The first parameter (*self*) defines the parent of the OptionMenu (i.e. the current info frame).

While this standard method includes all basic features of such element, the possibilities of customisation are very limited. For instance the height of the OptionMenu can not be defined as pixels but only in terms of a relative numeric value, whereas 1 (the minimum) being the height of one text line. Even though this is usually no issue if the view offers enough space, the appearance can be clumsy and bulky for small windows and graphic components (such as the configuration view). Also, reassigning values to a standard OptionMenu, a feature which is needed quite often, is somehow quite complicated. While a simple and default implementation of OptionMenu is quite easy, as shown above, even minor customisation (like absolute element height) implies quite complex workarounds. One example to achieve such individualisation is by using a *Tkinter.Label* element linked to a custom *Tkinter.Menu*, that is opened and filled dynamically by additional functions. The basic code snippets of this workaround are shown below in 5.3.

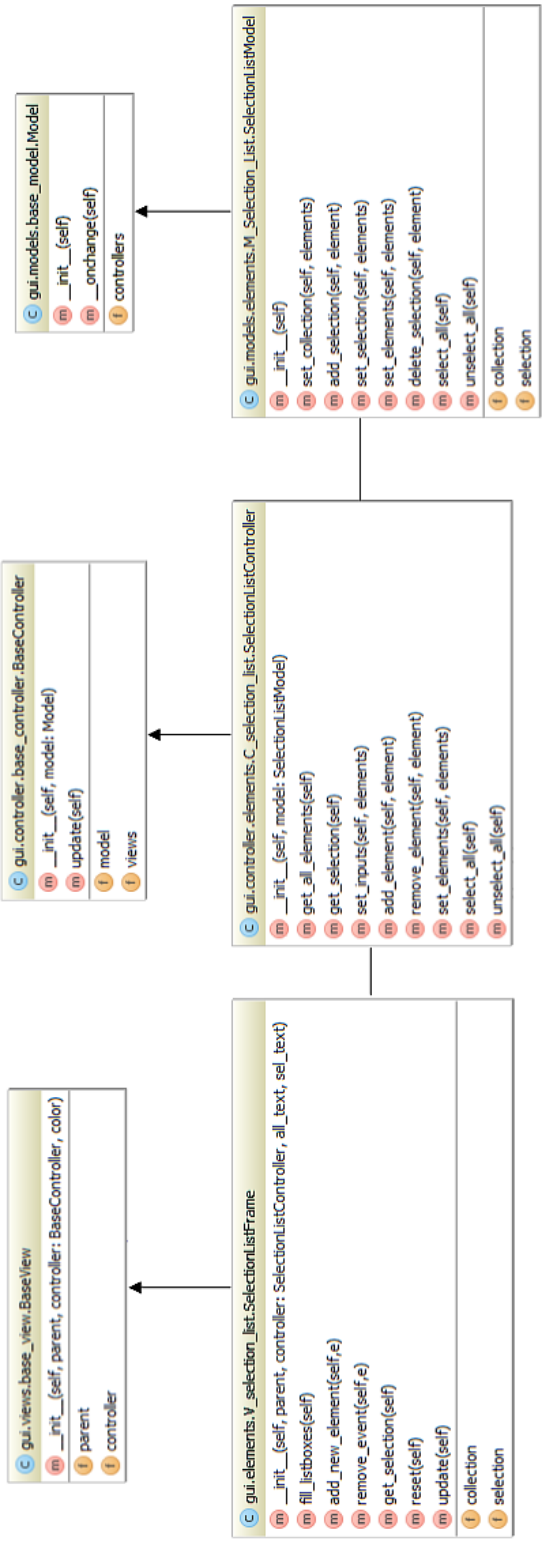


Figure 5.3: The Class model of a customised listbox GUI element is shown. Each class is subclass of a basic model, view or controller. Note that it the colored chars describe different elements. The blue **c** denotes a class, the red **m** a method and the yellow **f** a field or class attribute. Note that the user interacts only with the view, which in turn calls methods from the controller that modify information of the model. Changes inside the model trigger an update of all involved controllers and consequently of the view elements. While this approach more complex than a usual form design, it allows to divide interface, functionallity and data.

```
input_menu = tk.Menu(self.tframe, tearoff = 0)

text_input = tk.Label(parent, textvariable = dev_input_var,
        background ="grey", font = CustomFonts.small_label,
        relief = RAISED, width = self.input_rowsize[1])
text_input.bind("<Button-1>", lambda event: self.pop_up_menu(event, input_menu))

def pop_up_menu(event, menu):
    menu.post(event.widget.winfo_rootx(),
    event.widget.winfo_rooty()+event.widget.winfo_height())
```

Code excerpt 5.3: Adaptation of a Tkinter menu GUI element.

With the *tk.Menu* method, a new menu can be created. The menu is filled again with elements from the database (not shown) and is opened when the *pop_up_menu()* function is called. The position is dynamically calculated relative to the *Tkinter.Label* from which the function was called. This binding has to be done for every label using *text_input.bind()*. The result can be seen in Fig. 5.2b, where a element is drawn that is more compact and versatile than the standard OptionMenu.

All in all, the individual element needed more than four times the lines of code of the standard element, even requiring additional functions and deeper knowledge of internal behaviours of Tkinter. It should be emphasised, that similar issues appeared throughout the program and strongly increased its complexity.

Additionally, certain custom GUI controls were predefined to increase individualisation and re-usability. A good example for such control is the custom list box (see Figure 5.2c) that enables users to select and add various elements. This customised selection list utilises its own MVC structure, making it an independent GUI element. The implemented classes for this specific element are shown in the class diagram of Figure 5.3. Note that since all MVC classes share common fields and methods, superclasses for models, views and controllers are provided. Again it should be emphasised that Tkinter offers solid basic functionality with the *Tkinter.Listbox* method but makes it quite difficult to customise individual elements.

5.3.3 Components

The prototype basically consists of three sections (**Design**, **Execution** and **Data**)[2] that should be run in succession. The component currently active will be indicated by the color of the status bars (top and bottom) correlating to the color of the associated navigation bar item. For instance switching to the Design tab will show blue status bars (see also Fig. 5.4a). Each component comprise different challenges and features, while guiding the user through the crucial work-flow of a study. Always visible on the top left side of the window is the navigation bar that allows the user to quickly switch between components.

[2]In this section, actual GUI elements mentioned will have their display name formatted **bold** to clarify classifications of terms and ease orientation of figure to text mapping.

5.3.3.1 Design

The **Design** component includes all features necessary to create a study and its basic conditions. Already persisted studies and devices are displayed in a treeview structure and can be selected for editing. Fig. 5.4a shows the (i) navigation bar, (ii) the treeview and (iii) the main view of the study view, i.e. **General Information**. Latter is accessed by simply clicking on the headline of the treeview, **Studies**, and is used to create a completely new study and define its basic information. This consist of name, description and operator but also include events and groups, which can be created and assigned to the study. Aside from these directly editable fields, in this first view also information about the state of a study is displayed. **Status** refers to the progress of the study, i.e. Design, Running and Finished. **Created** and **Modified** give information about the date the study was created and edited, respectively. It covers user stories US-SM-01/05/06/09/10 (see section 5.2).

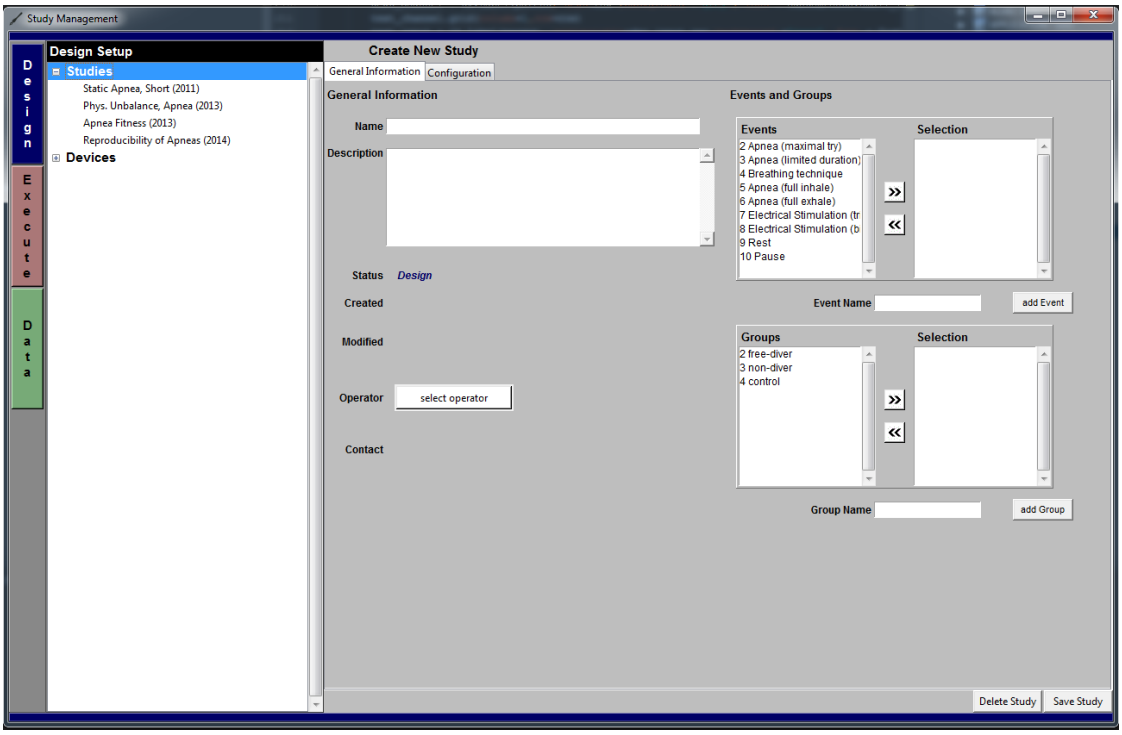
The second, study related, tab contains the **Configuration** view which is used to define the composition of devices and sensors and their particular configuration. Devices loaded from the database are displayed in a table with their essential attributes. Multiple devices can then be selected and added to the configuration. A device can be described by a unique alias (the default value of the **Alias** field is its name and is also a valid option) and new channels can be added. Each channel represents a potential signal, characterised with its particular parameters (**Input**, **Sample rate** and **Application**) which can be also set by the user. Additionally, channels and devices can be removed again, if requirements changes while a study is still in status design. Configuration related user stories US-SM-11/12/13 are implemented in this tab.

Another feature provided by the Design component is the management of devices. The structure of this view (not shown) is very similar to the **General Information** tab of the study creation view. **Name** and **Description** can be defined while it is also possible to assign signals and supported modes (sampling rate) to a device. New signals and modes can also be created in this view. Signals also have a description field of their own. Additionally, already existing devices can be edited or deleted as needed.

5.3.3.2 Execution

After the setting of a study is completed, it enters the running state and can be further managed in the **Execution** component. All running studies are listed in the treeview and can be selected to process user stories US-SE-01 to US-SE-07. As depicted in Figure 5.5a, the first view (**Information** tab) contains an overview of the previously defined settings of a study. This includes values that were assigned in the **General Information** tab of the **Design** view, e.g. **Name**, **Groups**, **Events**, etc. Additionally, the date of the **Latest Measurement**, a count of all measurements and the number of subjects assigned to this study are stated. Aside from displaying the characteristics of the study, this view provides a basic data access tool. All data assigned to a study can be downloaded as compressed Matlab files. Finally, a message can be sent to the operator of the study via

(a)



(b)

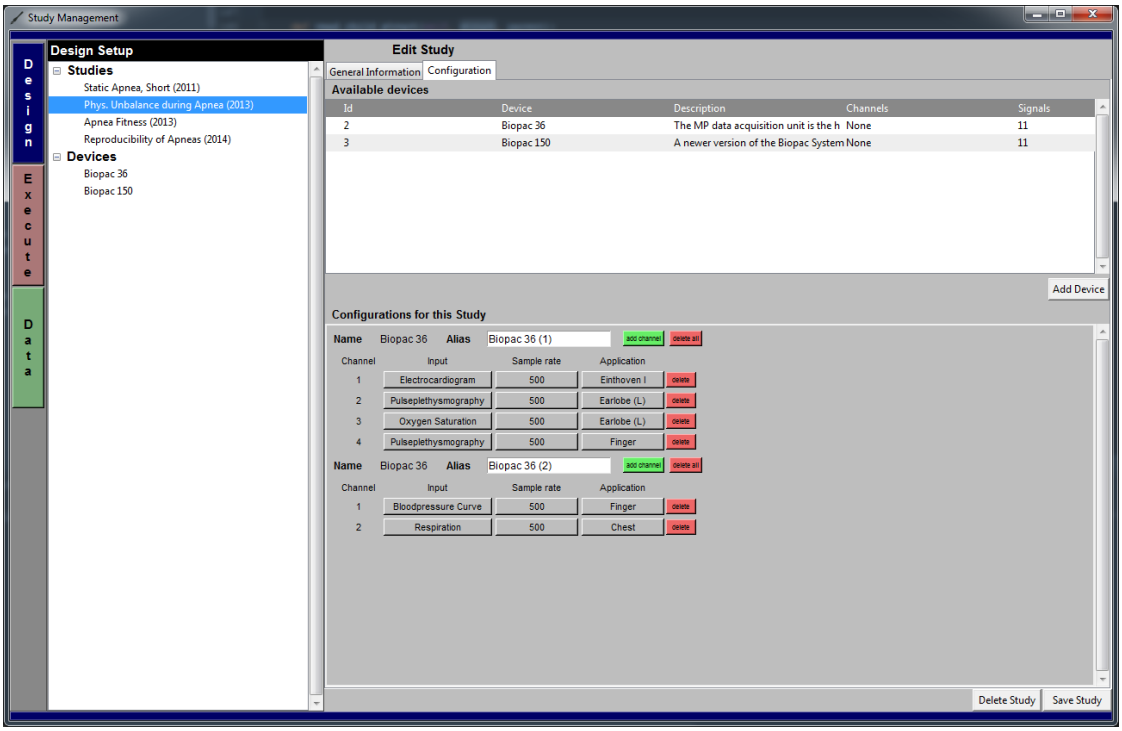


Figure 5.4: a) The main window of the **Design** component is depicted. It can be distinguished into three frames containing: (from left to right) navigation bar, treeview and data frame. The treeview shows already existing studies and devices which can be selected to open the **General Information** view in the data frame. Crucial UI fields are shown with all necessary information about the state of a study. In (b), the **Configuration** tab is shown where new devices and signals can be defined and assigned to the study. Note that while a) shows an empty form for a new study, b) has already elements inserted to give a better overview.

a contact form.

In the next tab, **Add new subject**, (shown in Fig 5.5b), new subjects can be created and added to the selected study. For the creation process it is necessary to define **Pseudo Id**, **Age**, **BMI** and optional any **Additional Information** as well as the associated groups of which the subject is member of. Once the subject has been added to the study, it will be shown in the treeview and can be selected. By doing so, similar to the study **Information** tab, general parameters of the particular subjects are shown as depicted in Fig. 5.6a. In particular, these parameters are **Pseudo ID**, **Age**, **BMI**, **Additional Information** and associated **Groups** which have been defined earlier. In addition, the count of **Total Measurements** of the subject is displayed while also allowing a batch download of all these measurements.

The core features of this component will now be described. Namely, the previously defined configuration can now be mapped to actual recorded data and signals in the **Add new Measurement** tab. This can be done by loading MATLAB files, assigning loaded signals to the specific configuration channel and saving the measurement. Figure 5.6b shows an already partly assigned (indicated by a green border) measurement. The assignment itself is done by a drag-and-drop operation from the list of loaded **Variables** to the according configuration slot. The file which will be loaded can be selected by a standard open file dialogue and is shown in the **Current File** label. However, extracting individual signals from a MATLAB file can be quite complex due to the various data types that can be used to store and encapsulate a continuous signal (e.g. array, matrix, struct[3], etc.). The Python package scipy was used for this purpose since it offers the basic interface for MATLAB connectivity. However, adaptations to the file loading function had to be implemented in order to account for different MATLAB data structures. The particularities in the loading function can be seen in Code excerpt 5.4 below:

```
def load_matlab_file(self, file):
    mat = scipy.io.loadmat(file, struct_as_record=True)
    meta = ['__version__', '__globals__','__header__'];

    for var in mat.keys():
        if not var in meta:

            s = mat[var]
            element = MatVariable(self.mat_tree_root,s, var)

            if type(s) is numpy.ndarray:
                self.read_child_struct(s, element)
```

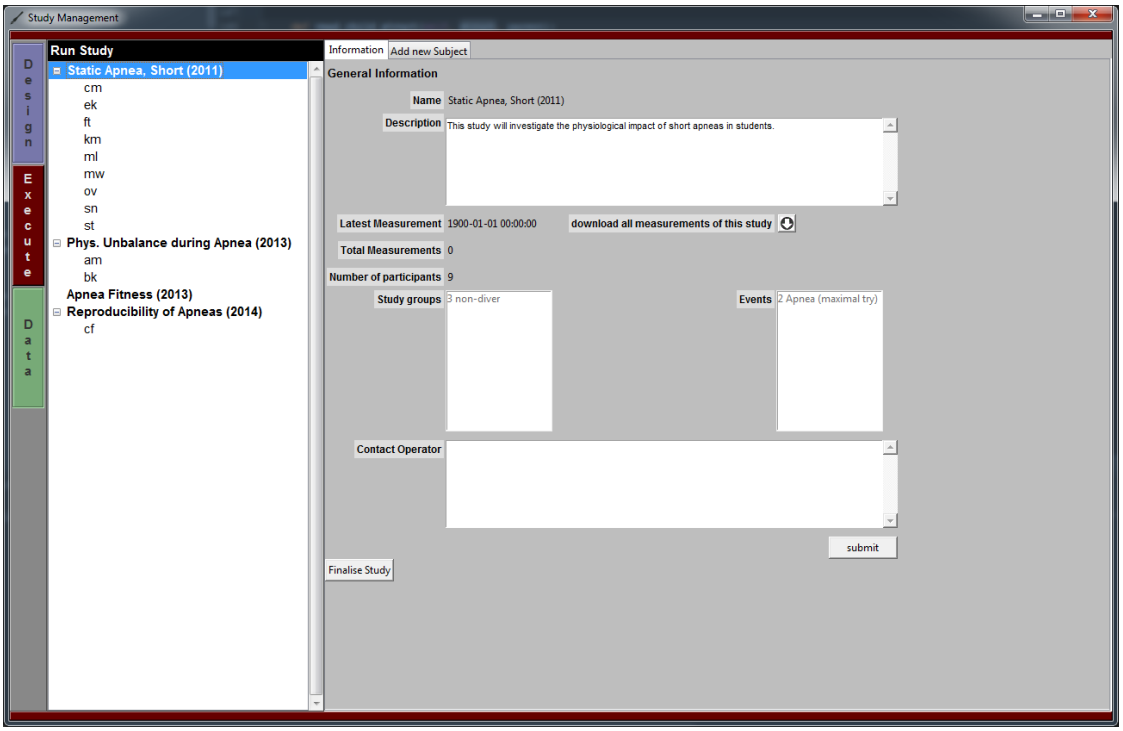
Code excerpt 5.4: Basic import of a class.

The function loads the *file* given as parameter with the *scipy.io.loadmat* function. The data is received as a map[4] data type. One particularity of Matlab is the addition of

[3]A struct in Matlab is basically an object with attributes (i.e. names and values) in terms of object orientation.

[4]A map (or dict in Python) is an abstract datatype composed of a unique key and its associated value.

(a)



(b)

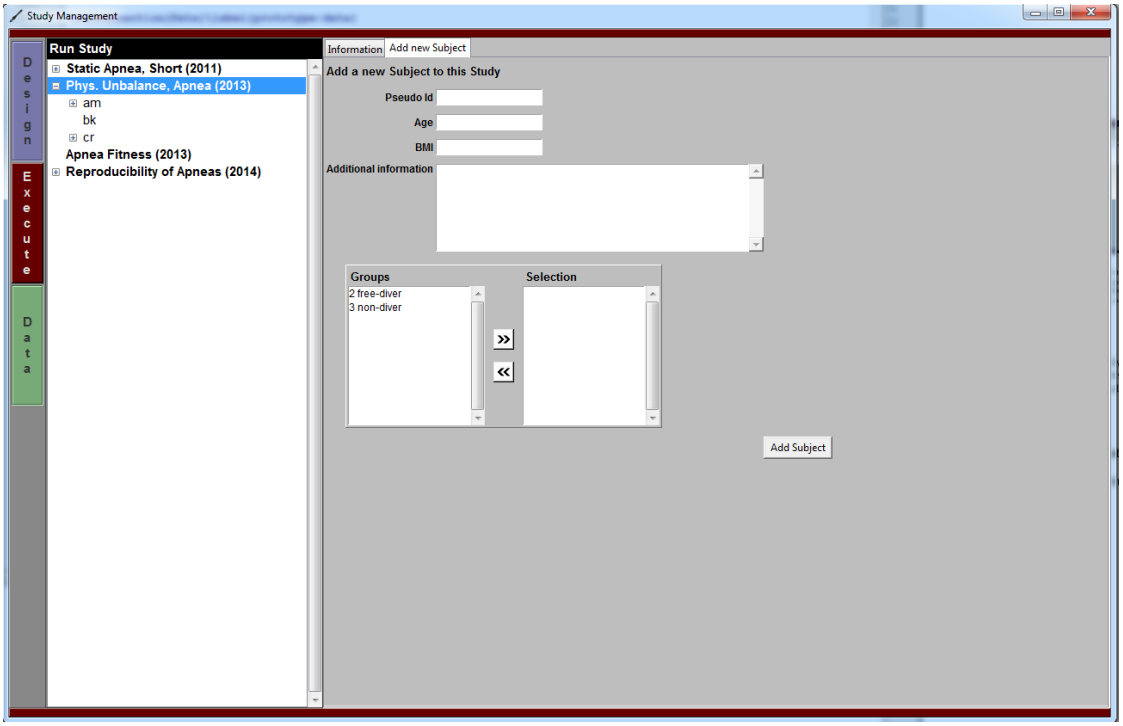
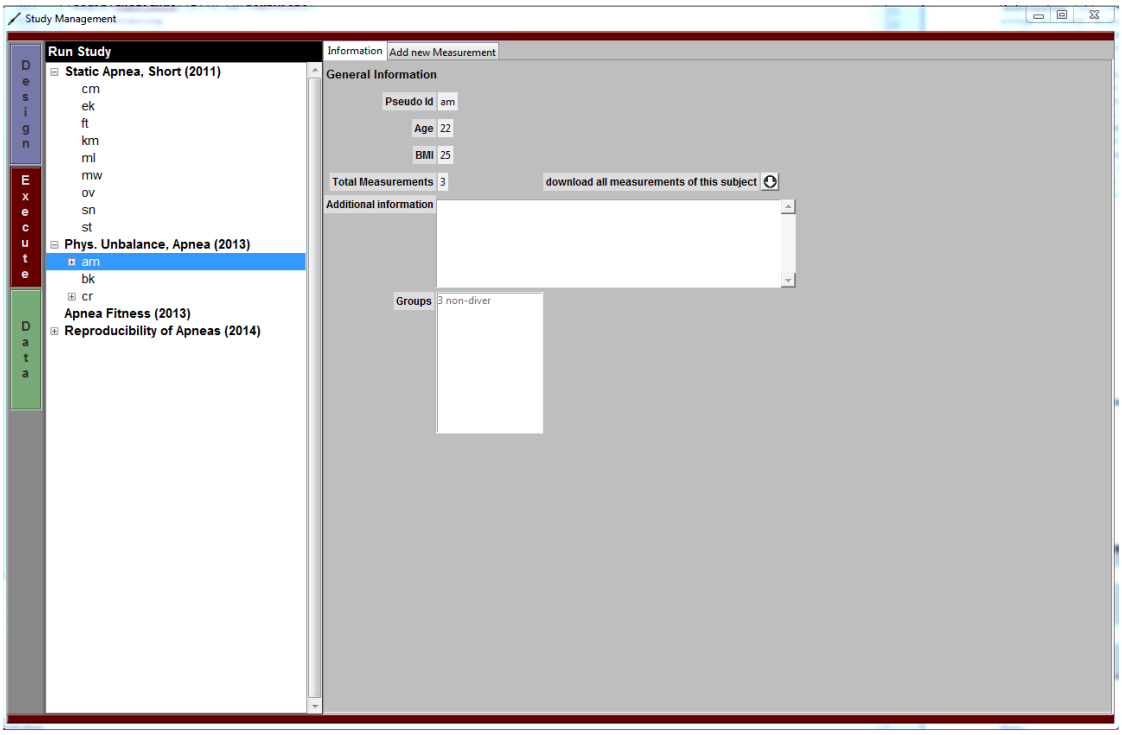


Figure 5.5: Essential views of the **Execute** component are shown. a) illustrates the main window, which gives an overview of running studies. Similar to the design window, three parts of the window can be distinguished, i.e. (from left to right) navigation bar, treeview and data frame. The treeview shows existing studies in the running state with their assigned subjects while the data view reveals important information about the selected study. In (b), the **Add new Subject** tab can be seen, in which a subject is defined by his attribute and added to the particular study.

(a)



(b)

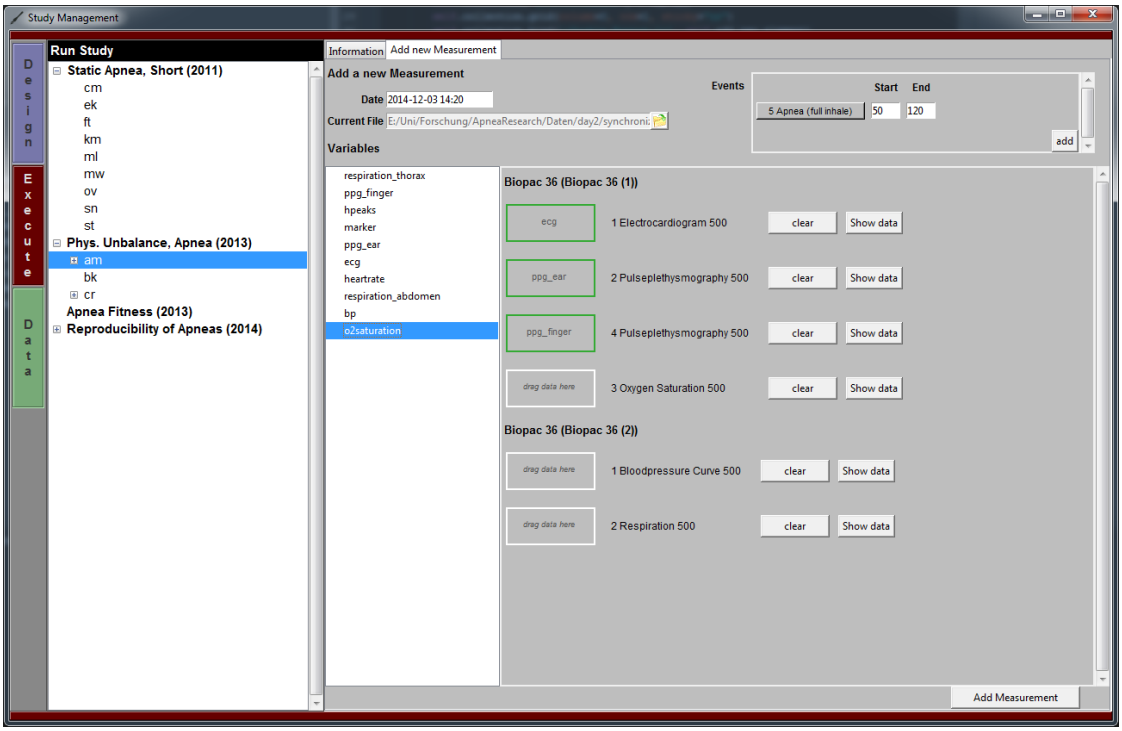


Figure 5.6: a) shows the main view of the subject related UI in the **Execute** component. Previously added fields are shown along with the possibility to download all data associated with this subject. In (b) the **Add new Measurement** is illustrated with data assignment in progress. For this purpose a MATLAB file can be opened and relevant signals can be chosen from its variables using a drag and drop function. To each configuration channel one signal can be assigned. A measurement can also include one or multiple events which can be dynamically added (top right).

header variables (e.g. __version__) to a .mat file. While these fields are not visible when working with the Matlab environment, Python does not distinguish between header and ordinary variables. Consequently they have to be filtered or at least detected in order to load only correct signals. The remaining variables are then analysed and processed according to their data type. Since each signal is saved individually in the file system, the loaded signal should be extracted from the Matlab file as a one dimensional array. Therefore, loading normal arrays is quite easy and can be easily achieved by simply accessing the value of the specific key of the map. Structs and matrices[5] on the other side have to be decomposed due to their hierarchical and multidimensional structures. For this purpose the recursive function *read_child_struct* (not shown) was implemented, which scans a struct or matrix for child elements. If a child element has children itself, it will call *read_child_struct* again until an array or single value is found. Note that *MatVariable* is an individualised tree class, which has a parent *MatVariable*, array or single numerical data and a variable name as attributes. It is used later to hierarchically fill the structure of the**Variables** listbox (see Fig. 5.6b). After assigning a signal to a device channel of a configuration, it can be plotted using the **Show data** button. This feature enables users to quickly check loaded data before saving the measurement.

A loaded matrix will display one main entry with the name of the variable with its rows or columns one level lower. In accordance, a struct will also have one main entry with the name of the variable whereas its attributes will be displayed one hierarchic layer below. Successive attributes of these attributes will in consequence will be even lower in the tree.

Note that also the **Date** of the measurement can be set, with a default value of the current date. Additionally, multiple **Events**, which are available for this study, can also be added to the measurement with a particular **Start** and **End** time. Finally, the measurement can be added to a subject and will be listed in the treeview below the specific subject.

5.3.3.3 Data

In order to easily access stored signals of measurements, the **Data** component was implemented. It provides complex search filtering options which can be customised to receive only the required data. Particular data can be searched for according to their study, signal type, device, associated subject group, involved events or point of application (see Fig. 5.7). The basis of each filter is the previously introduced custom listbox element. A composition of requested data can be created by selecting the desired fields in the listbox (empty selection will be handled as empty filter, i.e. * wildcard). From the acquired data, a set can be selected to download only relevant data. For instance, data from a specific study including only the non-diver group and at least one apnea event can be included. Furthermore, data across multiple studies

[5]Loading a matrix is insofar of importance, since the software of one device (Biopac MP36) regularly used in studies exports recorded data into a matrix with each row representing a single signal.

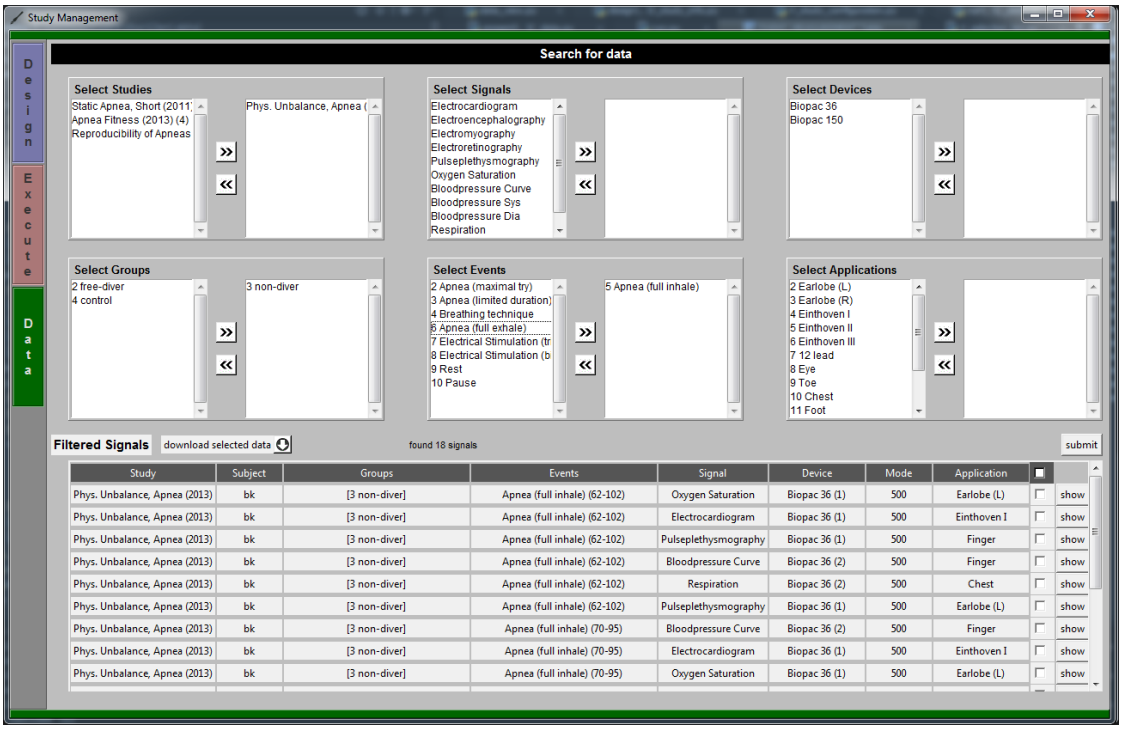


Figure 5.7: In the **Data** component, various filters can be applied to receive a customised set of signals for further analysis. Note that an empty listbox indicates a * wildcard, therefore searching for all data in this category. Found signals are displayed in the bottom and can be individually plotted.

can be gathered to concentrate on similar events or sensor applications occurring throughout all studies. For instance, all s_{ECG} signals could be selected regardless of their study. Additional information about this data is displayed (e.g. device, sampling rate, etc.) and individual signals can be plotted to preview the result. Note that while the access of data is provided by this component, custom data analysis has to be separately performed locally.

5.4 Database Interface

This section will take a closer look on the classes and implementations responsible for the interaction with the database. In this prototype (unlike in the proposed architecture of 4.2), the client requests data directly from the database using SQL as a basis. The particular toolkit used for this implementation is the Python framework SQLAlchemy, allowing the realisation of the full potential and flexibility of SQL in Python. It should be noted, that while the pure use of SQL statements for database manipulation can be viable for small projects, its complexity rapidly increases with database size. Additionally, processing the received data can not be done intuitively as shown in the following minimal example:

```
for row in c.execute('SELECT * FROM device'):
        print(row)
----------------------------------
(2, 'Biopac 36', 'The MP data acquisition unit is the heart of all Core Packages.
    [...]', None, None)
(3, 'Biopac 150', 'A newer version of the Biopac System. [...]', None, None)
...
```

Code excerpt 5.5: Basic SQL implementation in Python

While the SQL statement itself is very simple and can implemented with minimal efforts, the resulting data is poorly formatted. The return value is an array, holding no meta information about the table or its specific attributes. In consequence, the implementation effort increases since the tables resulting from each SQL query have to be known very well in order to access its elements. For the example above for instance, accessing the *name* field of an tuple of the device table requires one to know 1) the selected attributes and 2) the position of the desired field in this selection. In the example above, requesting the name of the device would be achieved by calling *row[1]*. While this is manageable, lets introduce a more complex example while also considering the need of using the results for further queries.

```
for row in c.execute('SELECT * FROM configuration'):
        print(row)
----------------------------------
(2, 2, 2, 1, 4, 14, 3)
(2, 3, 6, 1, 4, 15, 3)
...
```

Code excerpt 5.6: Complex result of a sql statement on Configuration.

Since this table combines multiple tables and therefore only contains their ids as foreign key, minor changes in the SQL statement or in the database can completely mess up the expected data. Additionally, the explicit definition of keys in sql statements is also very impractically and vague in terms of code clearness. Without any a priori knowledge of the data base design, code refinement or development of further features becomes very difficult. It should also be mentioned that debugging the output of these statements can be quite frustrating and difficult. To avoid these limitations, an Object-relational mapping (ORM) toolkit was integrated to allow easier access of tables and their interrelations. In particular, SQLAlchemy was used, supporting two common principles which greatly improve the interaction with a database.

5.4.0.4 Data Access Objects

First, the use of Data Access Objects (DAO) creates an abstraction layer combining session handling, data base connection and SQL queries. Each table is associated with its own DAO, allowing for a clear differentiation of functions and data access. However,

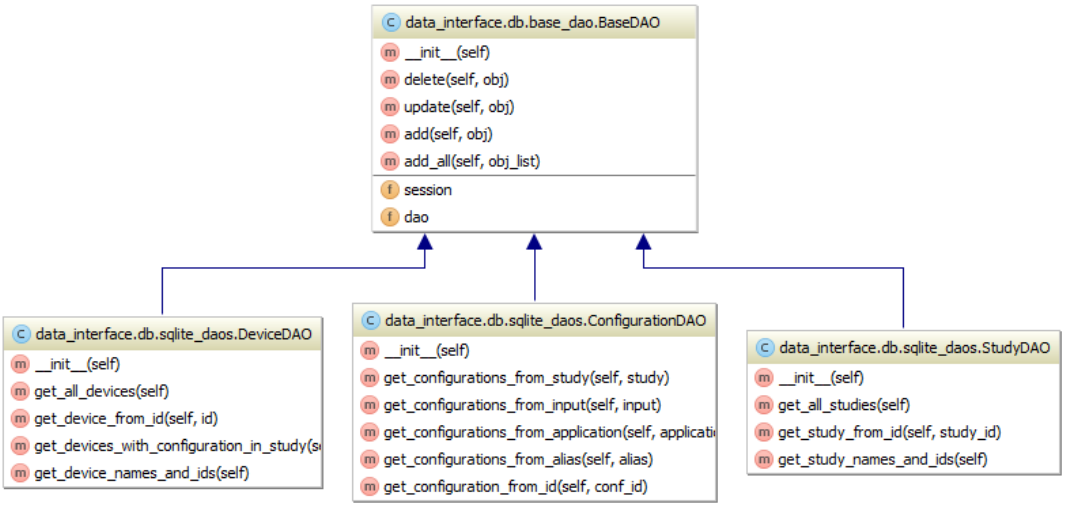


Figure 5.8: Data access objects for tables Device, Configuration and Study are shown. While each class has specialised methods to access and alter data for their specific table, basic database manipulation methods and the session are inherited from the BaseDAO superclass.

some methods for basic data access are shared throughout all DAOs, which emphasises the use of a superclass as shown in 5.8. Due to the use of an ORM toolkit, these functions do not need explicit SQL queries, allowing for clearer object oriented programming. Additionally the superclass allows a better use and manipulation of the *session*, which handles the communication with the database. While the *session* is initialised empty, calling one of the functions decorated[6] with *@session* will dynamically manage the session handling (i.e. open, close, commit, rollback, etc.) before and after running the functions code.

```
@session
def update(self, obj):
        return self.session.merge(obj)
```

Code excerpt 5.7: Data acccess object implementation.

Looking at the code and the UML model, the *obj* parameter which holds the information that is persisted to the database seems to be rather unspecified. However, this little object represents the second vital ORM principle, as we will see in the next section.

5.4.0.5 Data Beans

While the implementation of DAOs on their own can vastly increase structure and function of database related programming code, another practice can do even more. So

[6] A decorator (or wrapper), allows to extend functions and objects by dynamically calling additional functions when the initial objects are called. This design pattern does not change the behaviour of the object itself, but adds independent functionality.

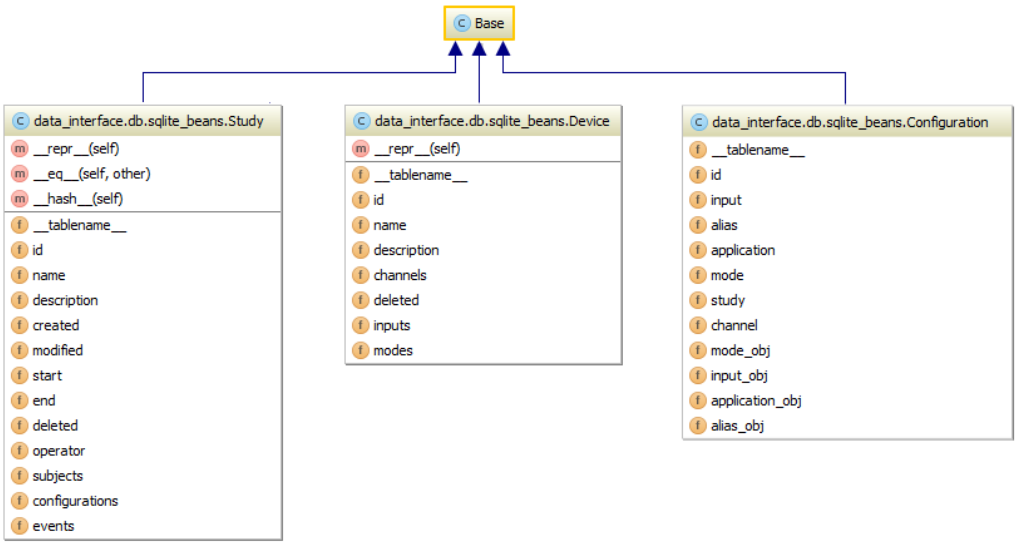


Figure 5.9: Data objects (beans) are shown for selected tables. The table name and its specific attributes have to match its database counterpart. In Study and Device, some methods were overwritten to improve comparison and representation functionality (see text). Note that all beans inherit from the declarative_base class provided by SQLAlchemy.

called beans[7] offer a direct mapping from database tables to objects, connecting their columns directly to attributes. A class model of selected data objects are shown in Figure 5.9. Note that the inheritance of properties from the SQLAlchemy class *declarative_base* (instantiated as *Base*) is required. In order to compare the derived objects based on arbitrary criteria (e.g. by identical id, or name) and not by the hash value of the object, default methods *eq* and *hash* had to be overwritten. Additionally, the *repr* method which defines the way a function is represented if printed (by default its hash value), has been modified in some cases to show only the name and id of an object to improve code quality and readability.

Although the implementation is quite simple for most tables, complex relation will yield certain particularities as shown in the following example describing the mapping of the association table that connects event and measurement table.

[7]The term bean actually originates from JavaBeans, describing a class which hold objects and properties inside a single object. Especially in database implementations (e.g. Java Hibernate, Spring) this definition is widely used and recommended. Since Python works quite differently from Java (i.e. serialisation, getters, setters) the use of this term here can be misleading and will be simply defined as a database object encapsulating various properties without a constructor.

```
class EventMeasurement(Base):
    __tablename__ = 'event_measurement'
    event = Column(Integer, ForeignKey('event.id'), primary_key=True)
    measurement = Column(Integer, ForeignKey('measurement.id'), primary_key=True)
    start = Column(Integer, primary_key=True)
    end = Column(Integer, primary_key=True)
    event_obj = relationship("Event", backref="measurement_assoc")
    measurement_obj = relationship("Measurement", backref="event_assoc")
```

Code excerpt 5.8: Bean like class in Python.

Columns of the table are defined as attributes with a specific data type (e.g. String, Integer, etc.) and various possible properties. The present class representation of the *event_measurement* table links predefined events with new measurements, while also adding start and end values. Even though relations to other tables can be implemented solely by the foreign keys parameter, a more sophisticated way is offered by the relationship method which automatically generates a *backref* attribute in the referenced object. For the above example, this means that by loading an *EventMeasurement* object from the database, also an *Event* object is received and stored as *event_obj* attribute. Vice versa, the *Event* object will hold a *measurement_assoc* object referencing to the associated *EventMeasurement*. If required, this loading chain can be extended to include not only directly related tables but also those related to the related table(e.g. the query receiving an *Event* can load *EventMeasurement* through its direct relation but also *Measurement* through the chain relation). However, using this functionality too excessively can strongly impair the performance of a query.

5.4.1 Code Structure and Deployment

Finally some words shall be added to explain the structure and arrangement of classes and packages of the project while also introducing the method used for the deployment of an executable. The main packages are *gui* and *data_interface*. Former contains all classes and further packages that implement and control views, controller and models which actually form the three subpackages of *gui*. Each of these packages in turn, branch into subpackages related to the main components (i.e. design, execute, data) and into one additional package containing customised elements that are used throughout all gui classes. The final package paths describe the assignment of classes to their particular views. An example of a full path is shown in code excerpt 5.9 using a particular import command.

```
from gui.views.design.data.study_data_view import StudyDataView
```

Code excerpt 5.9: Basic import of a class.

Here, the class *StudyDataView* is imported from the study's data package *study_data_view* located in the design component.

In order to create a generally usable program, the user should not be bothered with the structure of packages and classes but should simply intends to run a single file. While this can be done on any computer having Python and the required packages and toolkits installed, the setup of these should not be demanded from a common user of a program. For a computer running on Microsoft Windows, a more sophisticated deployment can be achieved by creating a single executable. For this purpose, the Python package py2exe was used, which enables a developer to define an individualised *setup.py* file and in consequence to create a runnable executable.

5.5 Evaluation

5.5.1 Overview

In this section, the implemented Python prototype is tested and evaluated using data collected in previous studies. In the studies, data management and processing consumed the majority of the invested time. Even though the final evaluation should be the main focus, a lot of time was wasted for non-essential or redundant tasks. The main reason for this overhead was the individual software solution implemented for each study which was very loosely structured and contained various interacting scripts. Additionally, scripts read and processed data in a specialised way according to the specific measurement configuration and study properties. Consequently the same evaluation features were implemented for different studies. Even though a lot of effort was put into this organisation, no sustainable solution could be established[8]. In the process to improve *external* information management, several tools have been deployed. This included word documents, MATLAB variables and even xml files in order to find and compare the desired signals. Furthermore, data was only stored on the local filesystem with different file formats and path structures which greatly inhibited the combination of signals gathered from different studies. Simply receiving all electrocardiograms involved in an apnea event from all studies required individualised scripting and data preparation.

5.5.2 Application of the Prototype

As described in section 5.3 the presented prototype allows users to create studies, assign devices, add subjects and measurement and store its associated signals. In the process of embedding all data acquired by the previously conducted studies into this design, four studies, involving 33 subjects and almost 1000 individual signals have been digitalised. Even though the whole process required approximately four hours (partly because of the variety of data formats) actually inserting a single measurement with all its data took only about one minute. Since each individual signal possesses its own *external*

[8]The main reason for this circumstance can be lead back to a lack of resources and time. A comprehensive tool might have needed more time to be implemented than a new script based evaluation.

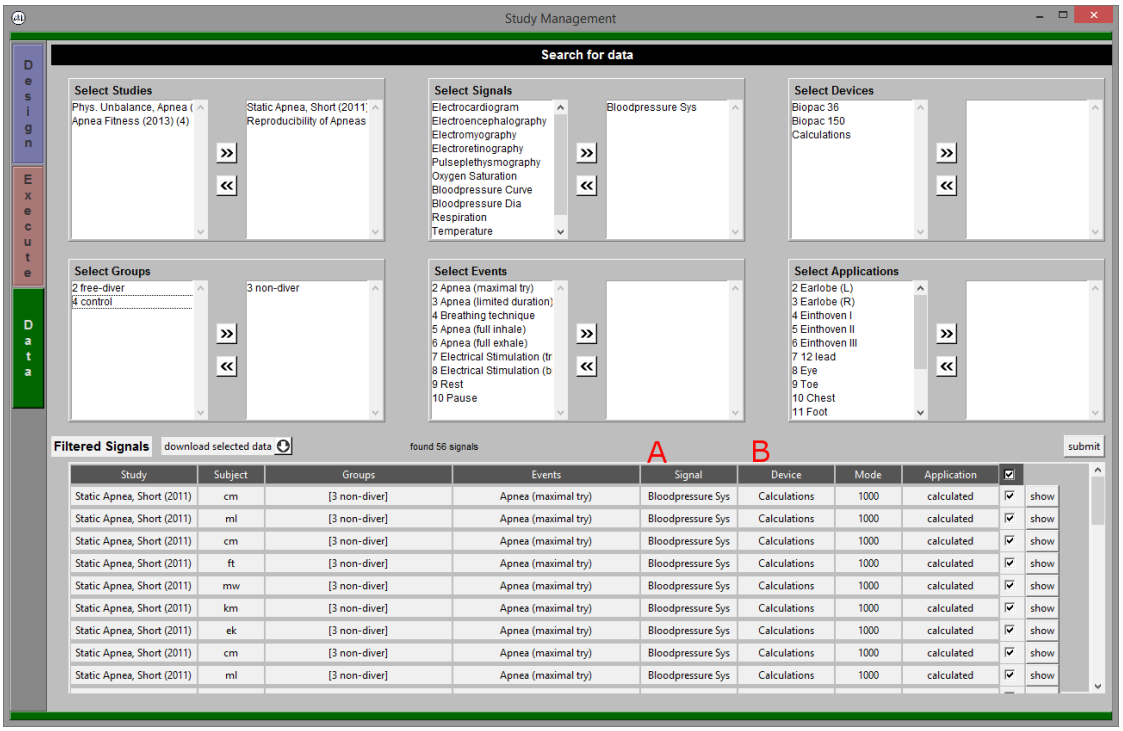


Figure 5.10: Data component with a sepecific filter setting (s_{SYS} in two studies for the non-diver group). Note that the selected signal (A) is not produced by a physical device but from *Calculation* (B). This enables the prototype to manage precalculated signals similar to primary biosignals.

information, desired signals of specific origin could later be received effortless (within seconds) and without further programming.

While the prototype was not designed to manage *internal* information or derived signals, it is still possible to store this calculated data similar to primary biosignals which are acquired directly from a device. By introducing a new device "Calculations" derived signals (e.g. s_{SYS}, s_{DIA} or s_{HR}) can be assigned to input channels of a running study similar to primary biosignals. It should be noted that this requires an additional (offline) analysis step prior the insertion of the data. This additional effort, however, greatly reduces the final evaluation by providing all necessary data each time a specific signal is required. Figure 5.10 shows an example of this particular approach. s_{SYS} signals from two studies, but only for the non-diver group, are selected for this purpose yielding 56 individual signals. The signal type is denoted as *Bloodpressure Sys* and the associated device as *Calculation*.

Even though the output of the data filter was not directly linked to MATLAB but instead provided in a compressed file, further analysis of *internal* information could be easily performed after importing the data into the MATLAB environment. This procedure is shown in Figure 5.11, depicting the collection of the selected s_{SYS} from the previous example. These variables represent the basis for further signal processing as also indicated by a histogram plot, which summarises the distribution of mean baseline

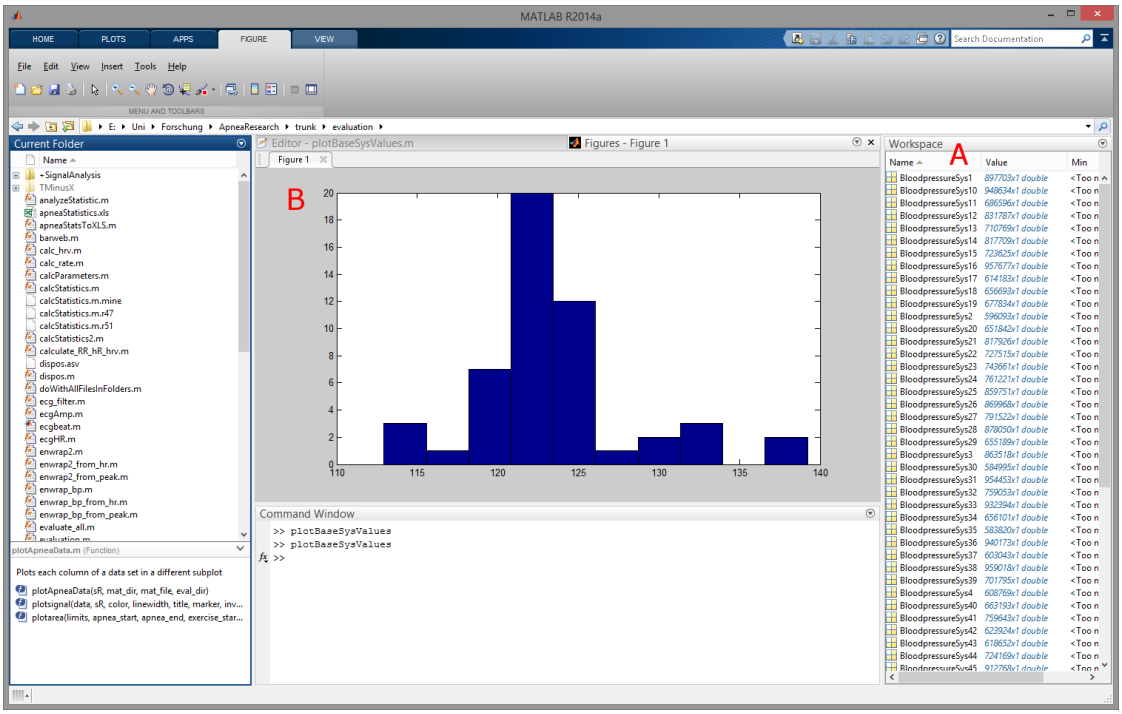


Figure 5.11: The MATLAB environment with loaded s_{SYS} variables (A), which have been received from a prototype selection. These signals can be used for further analysis as indicated by the histogram plot (B) showing the distribution of mean baseline values throughout all 56 signals.

values throughout all s_{SYS}.

Overall, the prototype produced a coherent view of the conducted studies and provided a consistent and satisfying browsing experience. Signals could be easily inserted and the assignment of *external* information allowed for fast and structured access. The possibility to dynamically design a study, its involved devices and signals allowed to reproduce all configurations of the investigated studies.

Chapter 6

Discussion

6.1 Conclusion

Common physiological data processing practices used in physiological studies have been analysed based on the published works [A5, A4, A3, A2, A1]. The acquired experiences in the field of multiparametric measurements and data processing supported the design of a novel layer model, describing abstract stages of biosignals and its *internal* information. In particular, four separate layers were extracted according to their distinct processing requirements and their expected result. Based on this classification, a systematic and centralised framework was designed, providing the individual interfaces to these layers via state of the art information technologies. This framework not only offers a solution for the management of *internal* information, but also allows the administration and organisation of descriptive, i.e. *external* information. Figure 6.1 depicts the interrelation of these two information types in physiological studies. In order to evaluate this systematic concept, a stand-alone prototype with basic functionality was implemented and tested with various studies conducted in the field of breath-hold diving. Since this was the first time, this particular combination between requirement abstraction, software design and physiological studies was performed, several limitations and considerations should be discussed.

6.2 Model and Software Design

While the objectification of common processes is a specialised field on its own and has created various abstraction models so far, a lot of effort is often required to enforce its use. That is, scientific personnel and developers have to receive uniform training in order to consider the designed interfaces and layers. Therefore such a model has to be widely accepted by the specific community in order to achieve the desired outcome. Since this work was limited to a single institute, research for the particular requirements and classification of functions might be biased and may not be applicable for studies using different processing approaches. In order to fully evaluate such a layer model, thorough

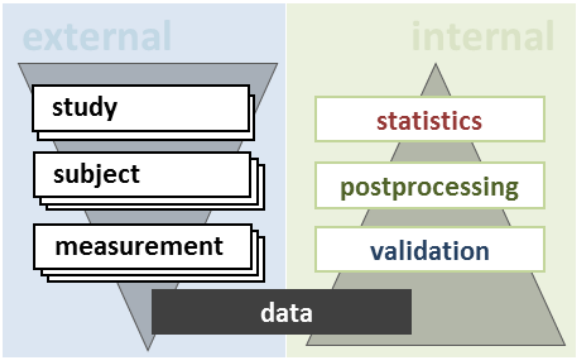


Figure 6.1: From study design and organisation to data processing and finally statistics. According to the requirements of a study organisation and the hereby proposed data processing model, the complete course of a study design to its final evaluation is indicated. On the left: *exteral* information in hierarchic structure attached to recorded data. On the right: This data represents the basis for *internal* information processing.

surveys and analyses at multiple data processing research groups should be performed to optimise acceptability. Due to limitations in time and personnel this was not done in the present work.

However, the model can be assumed valid for the requirements presented in this study and can, at least, be considered as a suitable basis for the presented software architecture. The concrete implementation has to be discussed shortly since there are countless technologies existing, offering different pros and cons compared to the chosen one. The most fundamental design alternative is probably located at the server site. While the present design is based on a classical dedicated server architecture, the vulnerability to single point of failures and its low scaling possibilities could be disadvantageous for bigger implementations. The necessity to upgrade storage and computational capacities could be of crucial importance when considering the huge amount of data that can be recorded from physiological sensors. Even though vertical and horizontal[1] scaling can be achieved in a traditional system, the adaptation of software and integration of hardware can often become tricky, time consuming and may cause annoying downtimes of the service. A cloud based approach offers more flexibility for fast growing systems while also eliminating the classic single point of failure issue. Today, public clouds solutions are provided by several companies (e.g. Amazon, Google, Microsoft, etc.), enabling people around the globe to easily outsource services, applications and storage. Even though this allows systems to scale almost unlimited, it also introduces disadvantages, e.g. transfer bottlenecks [82] and loss of server control. A complete pro and con comparison between dedicated and (public) cloud architecture is displayed in Tab 6.1. Aside from technical difficulties, a cloud based design is also questionable in terms of data privacy. Especially when physiological information about people has to be stored, this kind of outsourcing limits the control and therefore

[1] In a classic architecture, the performance of a service can be improved by adding components to a single node (vertical scaling) or by adding more nodes to the system (horizontal scaling).

	Pro	Con
Dedicated Server	full control	paying for maximum power
	initial disk space	limited scaling
	cheap bandwidth	configuration/management
	high performance	single point of failure
Cloud	no hardware to buy	often lower performance
	pay for actual usage	bandwidth limited
	unlimited instance scaling	lack of control
	unlimited disk scaling	disk space expensive

Table 6.1: Pros and cons in the consideration of a dedicated server versus a cloud based architecture.

presents new security issues on an ethical level. A more secure approach would be the implementation of a private cloud, running on hardware inside an internal network. Such a private cloud might be considered for future implementations since it offers the same scaling advantages as a public cloud but with control and security mechanisms of a dedicated server architecture. The downside is a significant increase in financial effort, development time and administrative complexity. However, if the proposed architecture is accepted by a wider scientific community, this will definitely be the technology of choice. Until then, a simple dedicated server is probably sufficient to cover the demand.

Similar to the issue concerning the requirement analysis for the proposed software architecture, also the design and evaluation of the prototype were biased since they relied on the scientific personnel and experiences of our research group. It should also be noted, that only studies with one particular physiological background have been analysed and that it was demonstrated that the prototype can provide the means for this specialised application, additional studies in other fields and research facilities would be required to further validate the design. Additionally, even though an intense research was performed prior to designing the proposed architecture, it cannot be ruled out that a similar system already exists covering the required features.

In order to facilitate open source data and algorithms, a modular interface to common databases and platforms should strongly be considered. Such connection could save time and efforts in the development of new algorithms while also enhancing the possibilities of data analysis. In particular a comprehensive link to Physionet would be highly advantageous.

6.3 Prototype

The prototype was developed to display basic functions of *external* information management and highlight the need for a sophisticated solution. In particular, organisational information of previously conducted studies and their specific measurement setups were digitally captured while the recorded signals were embedded and assigned to measurements of subjects. Python as a programming language proved

to be a good selection for a client based software. However, the GUI implementation based on the Tkinter package provided not the desired functionality. The limitation of customisation possibilities along with the clumsy default appearance and its sometimes weird element placing disqualified this package for further consideration. Since a comprehensive design would heavily rely on data centralisation and access via a web interface this might not be relevant for future developements. It should be noted, that the software was also not extensively tested by any external parties but only by specific scientific personnel with prior knowledge. Ideally, complex implementations should be tested according to testing standards (e.g. ISTQB) to ensure flawless performance and requirement coverage and should be considered for future implementations. In conclusion, this basic prototype clearly demonstrates the potential of a comprehensive system and how it could shape the structure and performance of future physiological studies.

6.4 Perspectives and Future Directions

Given the potential that the present approach offers for the management of physiological studies, the main target of future works will be on the development of a centralized system for *external* and *internal* information management. Especially the separation of presentation and business module should be focused since this will be essential to implement portable solutions which can be accessed from multiple locations e.g. via an internet browser. While the present evaluation did not require massive amounts of storage space a cloud based approach for the persistence module should be considered. Prior further implementation, however, a comprehensive survey, including also other fields of application (e.g. electrical engineers), should be conducted in order to adapt the requirements and features to additional needs of the scientific community. Although the implementation of a comprehensive solution is only at its beginning, the question is not whether such a system will emerge, but when and how.

Appendix

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Cardiovascular Response to Static Apneas

Impact of static apneas of different severity on mechanoelectrical biosignals in humans

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***Abstract*—While holding one's breath the human body experiences complex but meaningful changes of different cardiovascular parameters. During the so-called static apnea compensatory mechanisms of mechanical and neuronal nature are involved. Two types of apnea have been investigated and compared while blood pressure, vascular constriction, and heart rate have been estimated in parallel. One type of voluntary apnea AP_I began after the end of inspiration, whereas the other type AP_E after the end of expiration. Nine young and healthy subjects were recruited for the study. In both cases of AP_I and AP_E an increasing systolic blood pressure was observed (118±5% in type AP_I at the end of apnea relative to preceding baseline versus 115±5% in type AP_E). A more dominant vascular constriction was seen in AP_E (46±8% versus 71±11%). A slightly decreasing heart rate was observed during the apneic period, with stronger changes given in AP_I (90±7% versus 98±8%). Duration of voluntary apneas was shorter in AP_E (0.9±0.6min versus 1.2±0.6min). The study has shown that apneas AP_E of higher severity level have a less distinct diving reflex and are accompanied by stronger changes in blood pressure and heart rate.**

Keywords: static apnea, breath hold, blood pressure, heart rate, vasoconstriction

I. INTRODUCTION

In contrast to normal respiration, a complete temporal cessation of respiration constitutes an abnormal stressful situation. The arising cardiovascular interrelations are highly complex and convey valuable information about the health state. In general, bodily defense mechanisms will attempt to maintain an appropriate level of blood flow.

Static apneas, as given for instance in voluntary breath hold during diving, comprise a special bodily state worth of discussion. On the other hand side, sleep apneas comprise involuntary breath holds, being studied in detail [1], [2].

In case of voluntary apneas, a decrease of the heart rate f_C at the end of an apnea is reported in [3], which is interrelated with the so-called diving reflex [4], [5]. Increased parasympathetic activity may prevail in order to reduce oxygen consumption in the heart muscle while f_C is being reduced and diastolic filling prolonged [6]. Selected vasoconstriction may take place to redirect blood to vital organs. An acceleration of the sympathetic activity may progressively arise because of ongoing hypoxemia and hypercapnia [7], [8].

In terms of biosignals, cardiovascular biosignals are of special interest because of their tight interrelation with the respiratory activity. The level of f_C tends to decrease at the beginning of the apnea and increase with accelerated sympathetic activity. A temporal increase of systolic and diastolic blood pressure has been reported up to 25% [1-3], [9], [10]. The peripheral vasoconstriction may increase because of the sympathetic activation, which can be easily detected by diminished pulsation of the optical tissue absorption [11]. After resumption of breathing, the blood pressure usually drops and the blood flow in the periphery increases because of initiated vasodilatation [3].

Most phenomena are clearly visible in elite divers [12] as well as in untrained persons [3]. The aim of the given study is to analyse the impact of static apneas of different severity on mechanoelectrical biosignals in humans. As a novelty, the severity was specified by voluntary apnea type, as described in the following. A proper understanding of the cardiovascular response as a function of apnea severity may facilitate health assessment, support of apnea divers, or even to create models for involuntary apneas occurring in diving accidents. Our hypothesis was that a more severe apnea would cause a higher sympathetic activity.

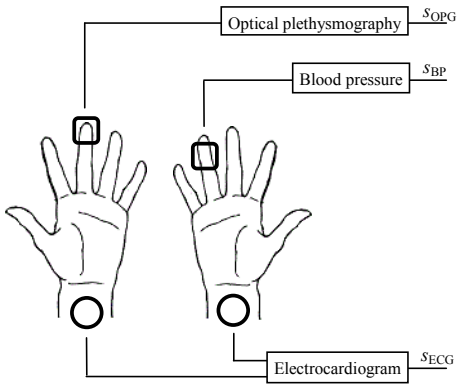

Fig. 1. Assessment of cardiovascular response using multiple sensors: Optical plethysmography , continuous finger-pulse PG for measurement of the blood pressure and standard electrocardiogram yielding s_{OPG}, s_{BP} and s_{ECG}, respectively.

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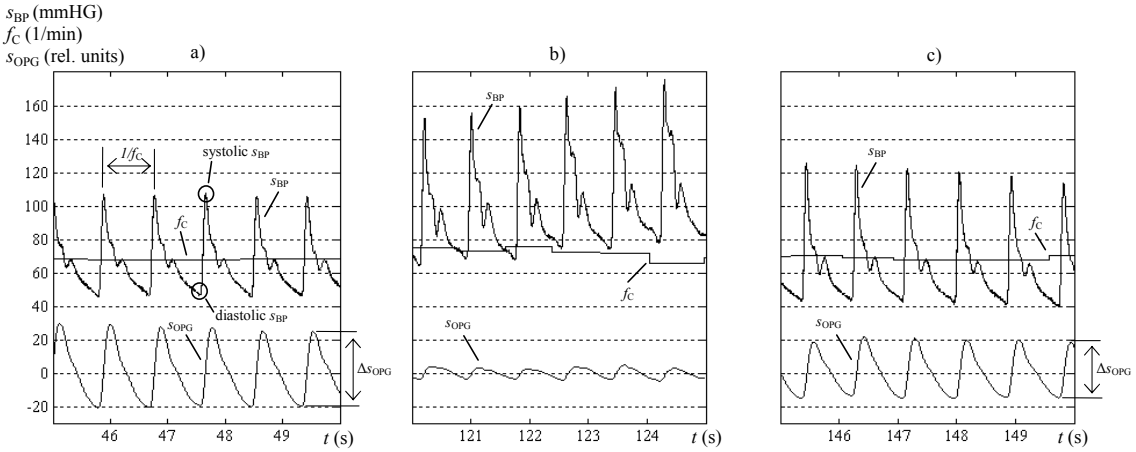

Fig. 2. Synchronous recordings of blood pressure s_{BP}, heart rate f_C and optical plethysmography s_{OPG} (with removed baseline) during voluntary apnea of type AP_E. The biosignals are shown (a) immediately before AP_E, (b) right before the end of AP_E and (c) during recovery period.

II. METHODS

A. Study Population and Protocol

Nine healthy and young subjects (six males) volunteered for the study, showing normal body mass index (around 23kg/m^2 for males and females) and being free of any cardiovascular diseases. Overall the subjects had no individual experience or previous training on static apnea and they didn't exercise any professional sports.

The subjects were studied awake in supine position. Each volunteer completed four trials of static apnea of maximal duration and maximal try. Between the apneas there was a recovery period of about 3min in between trials to minimize the effects of fatigue. The first two trials comprised voluntary apnea AP_I which began after the end of regular inspiration event, i.e., with inhaled air. The next two trials comprised voluntary apnea AP_E which began after the end of expiration, i.e., with exhaled air. Actually, apneas AP_E imposed a larger load on the volunteers than AP_I.

B. Measurements

During the experimental study, three different biosignals were recorded in a noninvasive way, as depicted in Fig. 1. The blood pressure s_{BP} was continuously monitored by the use of the volume clamp principle [13]. Here Portapres device (Finapres) was used with the finger cuffs on the right hand (Fig. 1). The optical transmission plethysmogram s_{OPG} was applied on the middle finger from the left hand; here multifunctional Biopac System (Biopac Systems) was utilized. Both hands were used to avoid mutual artifacts. Also we used the finger for optical plethysmography measurement instead of the ear because changes in arterial diameter can be expected to be more distinct in peripheral sympathetically controlled vessels. In synchrony, the electrocardiogram s_{ECG} was recorded via Biopac with two electrodes on both hands (lead I Einthoven). Also a thorax belt (Biopac Systems) was used to monitor respiratory activity s_R, which offered a reference for respiration and the different apnea types.

In the given study, the changes in systolic blood pressure s_{BP}, peripheral vasoconstriction and f_C were analyzed. While the systolic pressure is given by maximal amplitude of s_{BP} within a cardiac cycle (compare Fig. 2a), the peripheral vasoconstriction is reflected by both pulsatile amplitude Δs_{OPG} of s_{OPG} and the base level of s_{OPG} (compare Fig. 2a/2c). That is, with progressing vasoconstriction, Δs_{OPG} tends to diminish because the width of the arterial pulsatile deflection is reduced and the artery stiffens. The level of f_C was determined as the distance between two neighboring R peaks in s_{ECG}.

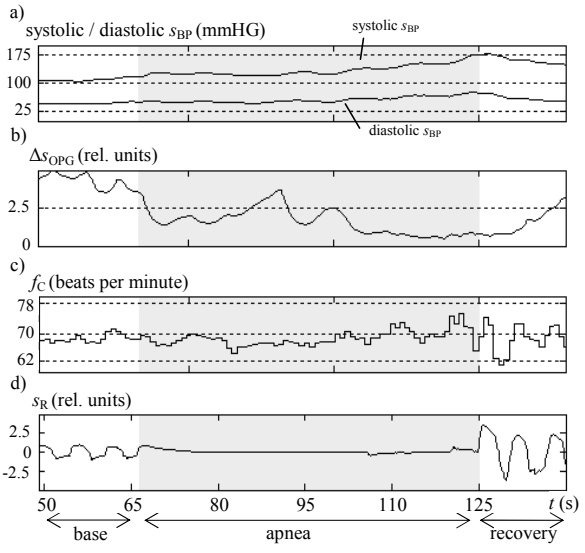

Fig. 3. Multiparametric mechanoelectrical biosignals before, during ☐ and after AP_I. (a) Systolic and diastolic blood pressure s_{BP}, (b) Pulsatile deflection Δs_{OPG} of the plethysmogram. (c) The corresponding heart rate f_C. (d) Thoracic circumference changes s_R.

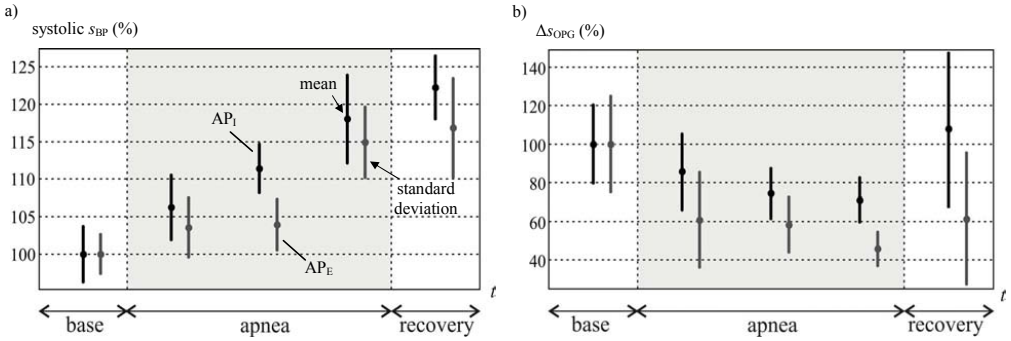

Fig. 4. Average and standard deviation characteristics of amplitude related parameters (a) systolic s_{BP} and (b) pulsatile amplitude of optical plethysmography Δs_{OPG} (compare Fig. 2c) during AP_I and AP_E of all subjects. The shown values are relating to values of the baseline (at 100%).

Basically five regions have been defined within a single trial for signal analysis. That is, a baseline period was introduced which precedes the apnea and lasts for 15s; an immediate recovery period which follows the apnea and lasts also 15s. Both baseline and recovery periods serve for reference aims. During the apnea, three successive periods have been defined, which divides apnea into three equal parts. It should be noted that the respective duration of the latter parts is different for different apneas, because apnea duration varied among trials and subjects.

III. RESULTS

A. General tendencies

Typical waveforms of multiparametric mechanoelectrical biosignals in the course of AP_I are illustrated in Fig. 3. As detailed in Fig. 2, the blood pressure s_{BP} temporary increases during the apneas, including its systolic, diastolic, and systolic-diastolic values. In parallel, the level of f_C increases slightly in the given case while the deflection amplitude Δs_{OPG} diminishes. It should be noted that the base level of s_{OPG} was removed in Fig. 2 for presentation reasons.

Tendencies of the latter changes over the apneic period for all trials and subjects are depicted in Fig. 4 and Fig. 5. In case of the systolic s_{BP}, a temporal increase of about 15% over the apneic period was observed in all cases. In all trials the peak of the systolic s_{BP} was observed either at the end of the apneic period or even up to 9s after the breathing was resumed. The deflection amplitude Δs_{OPG} predominantly decreases by about 40%, whereas inverse behaviour was observed in two male subjects. The heart rate f_C slightly decreases by only about 5%, whereas some subjects have even shown increasing tendency of f_C.

In general, the systolic s_{BP} was the biosignal with the most inertness in comparison with Δs_{OPG} and f_C. In contrast, Δs_{OPG} showed the fastest and most pronounced response after the end of apneas.

B. Comparision between different apneas

The changes of the systolic s_{BP} are more pronounced in AP_I than in AP_E and raise by about 18% over the apneic period with a standard deviation of 5% versus 15±5% (Fig. 4a). The difference is consistent over all regions and is particularly obvious in the middle of the apneas. Concerning Δs_{OPG}, the difference between AP_I and AP_E is less distinct, even though stronger changes have been observed in case of AP_E (54±8% at the end of apnea), see Fig. 4b. The changes in f_C are more dominant in AP_I (10±7%) than in AP_E (2±8%), (Fig. 5).

Duration of voluntary apneas was shorter in AP_E with 0.9±0.6min than in AP_I with 1.2±0.6min. The shortest apnea lasted 20s whereas the longest 150s. However, it is interesting to note that two male volunteers showed longer AP_E than AP_I.

IV. CONCLUSION

The impact of static apneas of different severity on mechanoelectrical biosignals in humans has been analyzed. Consequent changes have been observed in the systole s_{BP}, Δs_{OPG}, and f_C throughout apneas. In case of Δs_{OPG} its decrease

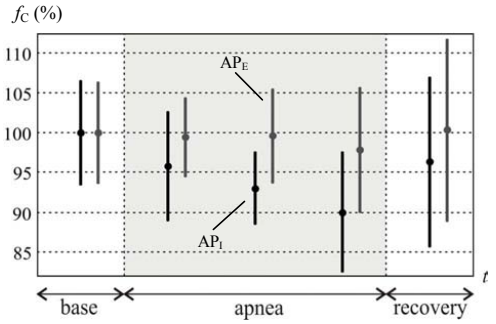

Fig. 5. Changes in heart rate f_C in response to AP_I and AP_E of all subjects. The shown values are relating to values of the baseline (at 100%).

during AP_E (more severe apnea) was stronger than in AP_I. Regarding systole s_{BP}, its increase during AP_I was slightly stronger than in AP_I. Lastly, when examining f_C, its decrease was noticeable only during AP_I.

While the interpretation of s_{BP} is quite obvious, the physiological meaning of f_C and Δs_{OPG} should be discussed.

The difference between both apnea types concerning f_C could be due to a possible compensation of the diving reflex by sympathetic activity due to a higher stress level at the beginning and throughout AP_E. This effect may be related to the phenomenon seen in professional divers during competition where mental stress impairs bradycardia occurring during apneas [14]. Also [15] found that mental arithmetic (i.e. increased stress / sympathetic reaction) during apneas has a negative influence on the diving reflex related changes of f_C.

Concerning Δs_{OPG}, it is actual proportional to the pulsatile deflection amplitude of the arterial cross-section which is a function of the arterial stiffness and the stroke volume. In particular, a significant decline of Δs_{OPG} was noticed at the end of apneas. It acknowledges the current interpretation of the diving reflex, in which a stronger vasoconstriction supports the oxygen saving strategy [14]. After resumption of breathing a strong rise of Δs_{OPG} immediately followed to reestablish the usual oxygen supply in the periphery tissues. On the other hand, since the arterial stiffness is controlled by the sympathetic activity and the consequent vasoconstriction, Δs_{OPG} can also be interpreted as a function of stress [16]. A less distinct fall of f_C and a stronger decline in Δs_{OPG} were observed during AP_E compared to AP_I. Thus it is more likely to conclude that the above changes are due to an increase in sympathetic activity rather than due to a stronger diving reflex.

Limitations of the study should be mentioned. Because of the low number of volunteers no statistical conclusions could be drawn, only tendencies have been shown. The study has not accounted for the particular duration of the apnea and the sequence of the trials.

For more detailed analysis the study will be extended to confirm the presented observations at a statistical level.

ACKNOWLEDGMENT

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Physiological unbalance during dry static apneas: effects of preceding preparations

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***Abstract*—The aim of the present study was to determine whether, and to what extent, breathing preparations right before a voluntary apnea influences the characteristics of the diving response. To validate the impact of such breathing exercise on the diving response, sixteen non-divers and three diving athletes performed short apneas of 45 seconds with alternating starting conditions. We found that while the diving response in non-divers was observed during apneas after normal inspiration (mean arterial pressure, MAP, increased by 12.3±12.8% and heart rate, HR, decreased by 10.4±9.6%), the effects of the response decreased during apneas after deep inspiration (MAP 3±8%, HR 7.4±10.3%) and were hardly noticeable during apneas following a short breathing exercise (MAP 0.7±10.3%, HR 3.5±9.7%). Similar effects could also be seen in professional divers with stronger expressed diving response. Apneas with larger load on the body were accompanied by a stronger diving response. We also found that apneas without any preceding preparation but one normal inspiratory breath were subjectively hard to sustain even for diving athletes. This was also displayed in a prominent drop of oxygen saturation in both groups of divers and non-divers.**

Keywords: static apnea, breath hold, blood pressure, heart rate, diving response

I. INTRODUCTION

Naturally, the human body requires oxygen in order to produce adenosine triphosphate which is the main carrier of chemical energy within cells. A prolonged shortage of oxygen supply as well as excessive accumulation of carbon dioxide will result in inhibition or loss of functionality of cells, organs or the whole organisms. Therefore a constant supply of oxygen and disposal of carbon dioxide via breathing are vital. However there are several physiological mechanisms that enable the human body to sustain periods of ceased breathing, known as apnea.

Involuntary apneas which can occur during the sleep can severely influence the personal health and are related to cardiovascular and cerebrovascular morbidity and mortality [1],[2]. In contrast, voluntarily induced apneas during diving have been reported to increase heart rate variability and overall fitness [3]. Apnea athletes (or freedivers) have shown that it is possible to endure episodes without breathing for time periods even longer than 11 minutes (the world record is currently at 11min 35sec according to [4]). Such extreme durations can only be achieved in the discipline static apnea, in which the athlete stays completely relaxed in water during the whole apnea time. The proficient understanding of the mechanisms that enable the human body to reduce oxygen consumption during such extreme apneic periods has gained increased attention from the scientific community in the recent years. The physiological responses involved may be the key to develop new clinical treatments for sleep apneas and to find novel ways for health assessment.

It is known that during breath holding the so called diving response [5], [7], [8] is of crucial importance for the conservation of oxygen in the body to ensure a proper function of vital organs (heart and brain) as long as possible. Therefore blood flow to non-vital muscular tissue in the periphery is inhibited by selected vasoconstriction, which results in increased blood pressure [10]. Another phenomenon which can be observed is a significant decrease in the heart rate. It is still unknown whether this is another autonomous contribution to the diving response [5] or just part of a complex cardiovascular feedback loop [6]. Considering the first possibility it could be argued, that an increase in parasympathetic activity could influence the heart to reduce its oxygen consumption [7], [9], i.e. decelerate the heart beat. In the latter case, baroreceptors in the transverse aortic arch and carotid artery would sense the increasing blood pressure emerging from the constricting vessels in the periphery. Consequently, the brain signals the heart to decrease blood output by slowing down the heart rate.

It should be noted that the aforementioned physiological parameters are continuously regulated during normal breathing. For instance, blood pressure decreases during inspiration and increases during expiration [12]. However, the effects of involuntary and voluntary apneas interfere with breathing-related mechanisms in the body and therefore produce a stressful situation for the body.

Frequent exposure of the human body to voluntary apneas can enhance the diving response and therefore extend breath hold periods [10], as used by diving athletes. A reinforced diving response can also spontaneously be achieved by face immersion into cold water [5], [11].

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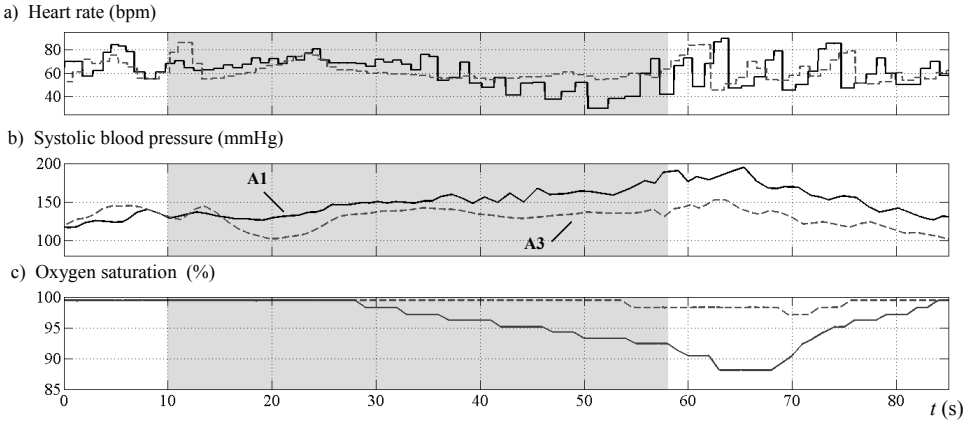

Fig. 1. Individual comparison of various physiological parameters during A1 versus A3 in a non-diver. Changes in heart rate, systolic blood pressure and oxygen saturation were more prominent in A1 than in A3.

The training of freedivers is different from that of most other sport's. Since the main point of interest in static freediving is the effective air capacity, an intense stretching of thoracic muscles and tissues surrounding the lungs has to be regularly performed. The stretching increases the vital capacity and thus also the air capacity. Another apnea-prolonging factor is a decreased consumption of air. Therefore mental training is important in order to relax as many muscles as possible. Aside from those regular exercises each static apnea attempt is initiated right after several short-term preparation exercises which also increase the lungs compliance.

This study's aim was to evaluate how a simple breathing technique before the apnea can influence the diving response. Since its effect is mostly seen in the cardiovascular system, a multiparametric measurement was performed focusing on those biosignals. Fig. 1 offers an overview over recorded signals.

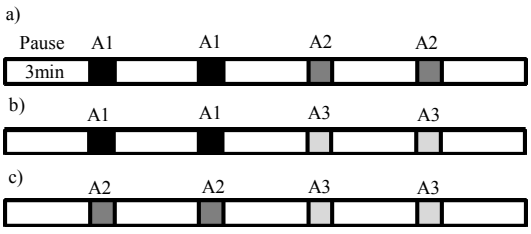

Fig. 2. Schematic representation of the experiment design. Measurements were recorded on three different days with different setups (a), (b) and (c). Each measurement started with three minutes of baseline followed by four apneas of 45 seconds duration with breaks of three minutes in between. Apneas started with normal inhalation (marked as A1), deep inhalation (A2) or deep inhalation after a short breathing exercise (A3).

II. METHODS

A. Study Population and Protocol

A total of 15 non-divers, 11 male and 4 female with age 24.6 ± 5 years (mean ± standard deviation) and body-mass-index 22.8 ± 2.3 kg/m^2, were recruited for the study. Non-divers had none or only little experience in apnea diving and weren't involved in any professional sport. The divers group consisted of three diving athletes (2 male and 1 female with age 27.3 ± 5.8 years and body-mass-index 23.7 ± 2.1kg/m^2) who regularly participated in apnea competitions. Written informed consent was obtained from each subjects before the study.

Each participant performed a total of twelve apneas in supine position and without face immersion, each 45 seconds long, as illustrated in Fig. 2. The apneas were initiated at the end of a normal inspiration (type A1), at the end of a deep inspiration (A2), or at the end of a deep inspiration 1min after a simple breathing exercise (A3). The breathing exercise consisted of six slowly performed breathing cycles, in which chest breathing alternated with abdominal breathing. The three apnea types (A1-A3) were performed four times each to reduce artifacts and the influence of the participant's condition from day to day (Fig. 2). Between two apneas there was a pause of three minutes in order to avoid exhaustion effects. In addition, the measurements were executed on three different days, whereas the particular time of the day did not significantly vary. No food, caffeine or cigarettes were consumed at least one hour before the measurements. Divers were not allowed to do any other preparation than those defined in the protocol.

B. Measurements

Multiple physiological parameters were recorded during the measurements. The blood pressure was continuously monitored by Portapres (Finapres) using the volume clamp principle. The cuff was applied to the ring finger of the left hand. Electrocardiogram (Einthoven I), and pulse

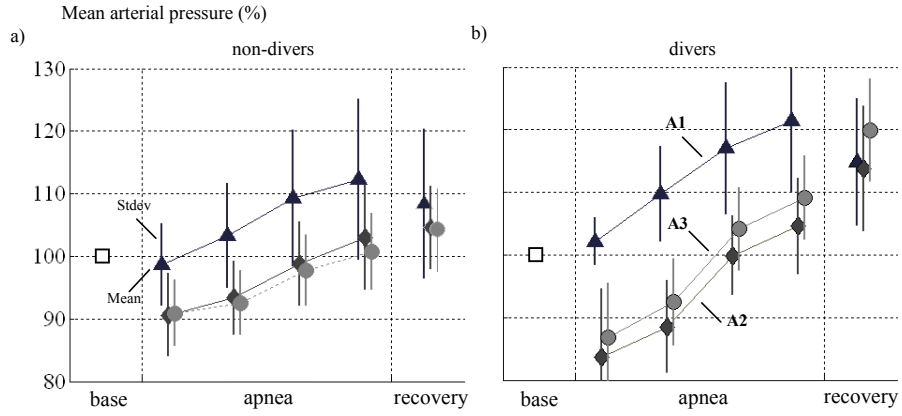

Fig. 3. Relative change of mean MAP is shown for the three different apnea types (A1-3) in (a) non-divers and (b) divers. Values were calculated relatively to a fifteen second baseline preceding the apnea. During all apneas, a strong increase in MAP was seen in non-divers and divers.

plethysmography (applied on the middle finger of the right hand) were monitored using a multifunctional Biopac System MP36 (Biopac Systems). Oxygen saturation OS of the blood was measured with a pulse oximetry (Nellcor) from the left ear.

Mean arterial pressure MAP was calculated from blood pressure, heart rate HR from electrocardiogram by R peak detection. Statistic values were averaged for each apnea type (A1-3). In particular, six episodes were evaluated in the course of the apnea; namely, the baseline, 15 seconds before an apnea, the apnea itself with four overlapping episodes ranging from 0-40%, 20-60%, 40-80% and 60-100% of the total apnea time (45s), and the instant recovery, 15s right after the apnea. For MAP values, we introduced a new parameter MAP_{MM} for comparison aims, which accounts for the difference between maximum and minimum value of MAP during an apnea.

We excluded data from six apneas (4 A1 and 2 A2) because the corresponding participants could not sustain the apneas for the whole 45 seconds.

III. Results

A. General tendencies

As displayed in Fig. 3, MAP increased in almost all test subjects and all apnea types (A1-3) even though there is a decrease in A2 and A3 at the beginning of the apnea. Similar responses were also observed in [5], [10] (increase in MAP) and [11] (temporal drop in MAP). The drop in OS was significantly larger in A1 than in A2, A3.

TABLE I. Increase of MAP during apneas

Apnea Type	divers		non divers	
	MAP_{end} (%)	MAP_{MM} (mmHg)	MAP_{end} (%)	MAP_{MM} (mmHg)
A1	21.4 ± 11.6	35 ± 8.9	12.3 ± 12.8	31.8 ± 20.1
A2	4.5 ± 7.6	40.5 ± 10	3 ± 8.4	32 ± 12.6
A3	9.1 ± 6.7	41.3 ± 13	0.7 ± 6.1	26.4 ± 12.1

Values are mean ± standard deviation; MAP_{end} = change of MAP relative to baseline (comparable to last values during apnea in Fig. 3); MAP_{MM} = maximal increase of MAP during apnea.

B. Apneas in comparison

Concerning non-divers, an increase in MAP could be observed in all apneas (Fig. 3a). A1 showed the strongest response with a relative rise of 12.3 ± 12.8% at the end of the apnea related to the baseline. This effect was less pronounced in A2 (3 ± 8%) and was not noticeable in A3 (0.7 ± 10.3%). The HR decrease was most prominent in A1 with a drop of 10.4 ± 9.6% (similar to the changes in MAP), less expressed in A2 (7.4 ± 10.3%) and the least in A3 (3.5 ± 9.7%); see Fig. 4. In comparison with the baseline, there was only little change in HR (Fig. 4a). An individual comparison of HR, MAP and OS in A1 and A3 can be seen in Fig. 1.

C. Non-Divers and Divers

As shown in Fig. 3, divers showed a higher increase in MAP than non-divers; compare also Table I. Similar observations concerning the difference in arterial resistance between divers and non-divers can be derived from [8]. However, at the beginning of A2 and A3 there was a drop in MAP which was more prominent in divers (16.3 ± 10.9 % in divers vs. 9.4 ± 6.6 % in non-divers in A2, related to the baseline). The maximal increase of MAP during apnea was higher in divers than in non-divers and does not vary much from A1 to A3; see Table I. The HR of divers increased strongly at the beginning of apnea and tended to decrease towards its end. In non-divers, however, a small drop in HR was seen throughout the apnea but only A1 showed an clear decrease. It should be noted that due to the low number of divers, only approximate tendencies could be drawn without any statistical conclusions.

IV. Conclusion

For the first time, the influence of simple preparation maneuvers on the diving response has been investigated. In addition, a selective comparison is established between divers and non-divers with respect to those preparations and to general impact of apnea on physiological parameters. MAP increased in all participants while HR decreased only to a

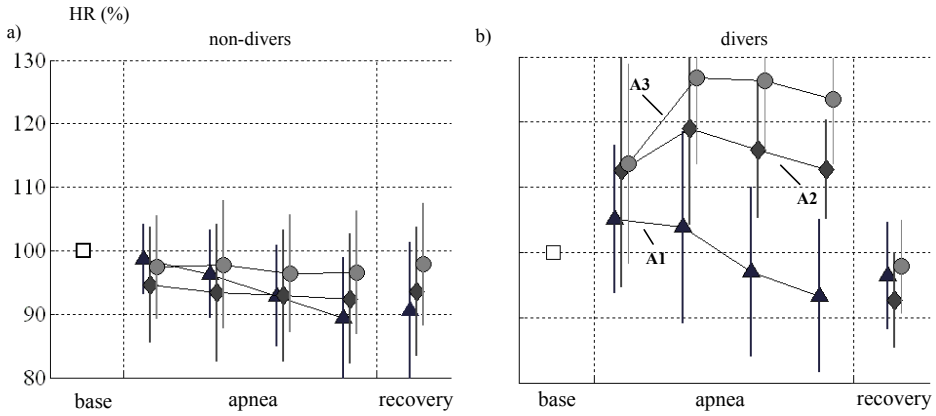

Fig. 4. Relative change of HR in (a) non-divers and (b) divers. Only small changes can be seen in (a) while (b) shows an initial increase followed by a mild decrease.

minimal degree in non-divers and even increased in divers. The OS clearly declined only in A1.

The increase of MAP reflects the increase of peripheral resistance caused by the (selective) vasoconstriction in the course of the diving response. Although this could be seen in all subjects, MAP increased stronger in divers probably because of their improved diving response.

It is important to note, that at the beginning of A2 and A3 a drop in MAP was observed in all measurements. This temporary decrease is caused by increased air pressure in the lungs (at the end of inspiration), which compliant veins inside the chest are exposed to. Venous vessels are squeezed by the enlarged lungs, which inhibits blood supply to the heart. Consequently, the stroke volume SV decreases and thus MAP - as a function of SV - decreases as well. The observation that this effect is more prominent in divers than in non-divers can be probably explained by larger vital capacity in divers.

Only little changes could be seen in the HR in non-divers throughout all apneas. A1 experienced a mild decrease in HR,

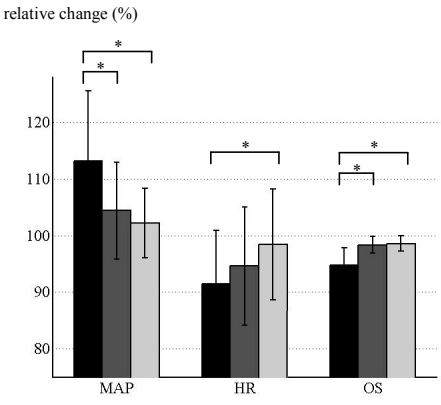

Fig. 5. Comparison of changes in (a) mean arterial pressure MAP (b) heart rate HR and (c) oxygen saturation OS, changes from the end of the apnea to the baseline in A1 (black), A2 (dark grey) and A3 (light grey). The statistical differences between the bars are indicated by asterisks "*" based on t-test to reach error probability $p < 0.01$.

whereas HR hardly changed in A2 and A3. On the other hand, divers displayed high variations in HR with a strong initial increase which was followed by a gentle decline over the rest of the apnea. The initial rise of HR can be explained by the discussed drop of MAP or SV. Since the body aims at constant cardiac output (=HR*SV), HR has to increase when SV decreases.

Interestingly, apneas of the type A1 were even hard to sustain not only for non-divers but also for divers. This was also indicated by a strong temporary decrease of OS, which was almost the same for divers and non-divers. Considering A3 versus A2 in non-divers and divers, only small improvements of the unbalance of physiological parameters were observed. Concerning the diver athletes, it can be concluded that not only their long-term practice and training, but also their short-term preparations seem to determine their (possibly) extreme diving performance.

Limitations of the study include a low number of divers and the specific regulation of apnea time. A study containing more professional divers could provide necessary information about the differences in physiological behavior in apneas with and without preparation. Concerning the limited apnea time (45s), it has to be noted that important effects could be missed which usually appear before the end of much longer apneas (maximum try apneas). Since A2 and A3 were quite easy to sustain, the participants may have not reached those effects. As stated in [13], the apneic duration can be basically divided in two phases: the easy going phase and the struggle phase. Many phenomena, such as involuntary diaphragm contractions, can only be seen in the struggle phase when the urge to breath can not be easily overruled and the stress in the body increases.

It also has to be noted that there are various breathing techniques, long-term and short-term, which have the potential to influence the diving responses to an apnea. Even though we chose a quite common technique a broader study focusing on different preparations could reveal more information about training possibilities and adaptability to apneas.

Our next work will investigate the possibility of a novel quantitative health state evaluation which originates from the individual unbalance of physiological parameters during an apnea. Such evaluation methods could also be used to determine the effectiveness of freedivers training.

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Conference "Biomedical Engineering"

Effects of preceding preparation in breath-hold divers: gas analysis in expired air and blood

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Introduction. Cessed or dysfunctional breathing can strongly influence personal health. Recent studies give evidence that periods of involuntary apneas during sleep show high prevalence and are related to cerebrovascular and cardiovascular morbidity and mortality [1]. On the other hand, apnea divers are known to endure breath holds longer than 11 minutes [2], while having an increased fitness [3]. The main mechanism which enables animals and humans to sustain episodes without breathing is the so called diving reflex [4], [5]. By reducing blood perfusion in non-vital tissue and organs (except heart and brain) with selected peripheral vasoconstriction, more oxygen remains to ensure the proper function of the body. In addition the heart rate slows down in order to reduce oxygen consumption and to increase the efficiency of the heart beat. It is important to note that not only oxygen is consumed in tissue during apneic periods, but also carbon dioxide accumulates there due to the lack of expiration. Individual manifestation of the diving reflex can give important information about the apnea-diving related fitness as well as the general health state of a person. One way to evaluate how efficient the body can react to an apneic phase by reducing oxygen consumption is to measure the arterial oxygen saturation [5], [6]. The analysis of expired air preceding an apnea gives also useful information about the efficiency of the oxygen consumption [7]. In addition, carbon dioxide concentration can be easily measured and used to further investigate the characteristics of the diving response.

The presented approach to assess the diving reflex combines volumes of expired oxygen and carbon dioxide with our method used in previous works to simulate and assess the apnea severity [8]. In particular, different breathing preparations were performed before starting with the apneas, and, in addition, limited and maximal apnea durations were applied.

Method. Three professional divers (2 male and 1 female) participated in the study. The group performed a total of 6 dry apneas in supine position without face immersion. Three different breathing exercises were performed two times each. In particular, we distinguished between apneas after a normal inspiration (a1), a deep inspiration (a2), and a deep inspiration following a simple breathing exercise (a3) [8]; likewise, the apnea severity decreased from a1 to a3. Each apnea was performed twice, once with a limited duration of 45 seconds (denoted as $a1_{lim}$ to $a3_{lim}$) and once without temporal constraints with a maximum possible duration ($a1_{max}$ to $a3_{max}$).

No food, caffeine or cigarettes were consumed at least one hour before the measurements. Divers were not allowed to do any other preparation than those defined in the protocol. Blood pressure (Finapres Medical Systems), electrocardiogram (Biopac Systems) and blood oxygen saturation (BOS) (Nellcor) were continuously recorded. Carbon dioxide (CO2) and oxygen (O2) volume concentration were measured (Datex Ohmeda Capnomac Ultima) in a plastic bag to collect the expired air after an apnea.

Consumed oxygen $O2_C$ was calculated by subtracting the recorded O2 values from atmospheric oxygen concentration (21%). Oxygen consumption over apneic time $O2_{CA}$ represents the ratio between $O2_C$ and the corresponding apnea duration (AD). The produced carbon dioxide $CO2_P$ represents the absolute value of CO2 (CO2 concentration in the inspired air can be neglected), whereas $CO2_{PA}$ relates $CO2_P$ to AD. In addition, the maximum consumption of oxygen in the blood related to AD was assessed and quantified as BOS_{CA}, namely, as the difference of BOS before apnea and minimum BOS, related to AD.

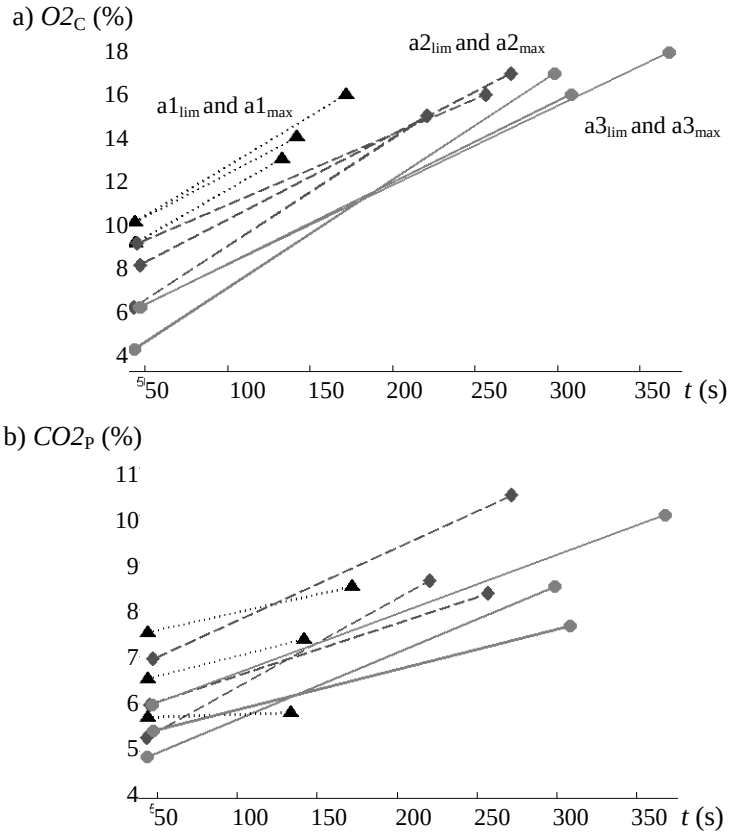

Fig. 1. Data points of (a) oxygen consumption $O2_C$ and (b) carbon dioxide production $CO2_P$ during apneas with limited apnea duration of 45s and maximal apnea duration. Black triangles indicate apneas $a1_{lim}$ and $a1_{max}$, dark gray diamonds $a2_{lim}$ and $a2_{max}$, and light grey circles $a3_{lim}$ and $a3_{max}$.

Results. Data points of $CO2_P$ and $O2_C$ are shown in Fig. 1. Throughout all apnea types (a1 to a3), $CO2_P$ and $O2_C$ tend to increase with increasing apnea duration. During apneas with limited duration of 45s, $O2_C$ clearly decreased from a1 to a3, in contrast to less pronounced tendency for the decrease of $CO2_P$ from a1 to a3. Oxygen consumption per minute $O2_{CA}$ in the air, oxygen consumption per minute BOS_{CA} in blood, and carbon dioxide production $CO2_{PA}$ in the air are shown in Fig. 2. A decrease in $O2_{CA}$ and $CO2_{PA}$ can be observed from a1 to a3 as well as with increasing apnea duration (e.g., $O2_{CA}$ and $CO2_{PA}$ decrease from $a1_{lim}$ to $a1_{max}$, see the arrow in Fig. 2a). BOS_{CA} also dropped from a1 to a3. However, BOS_{CA} tend to increase with increasing apnea duration, which is surprisingly in contrast to the behaviour of $O2_{CA}$.

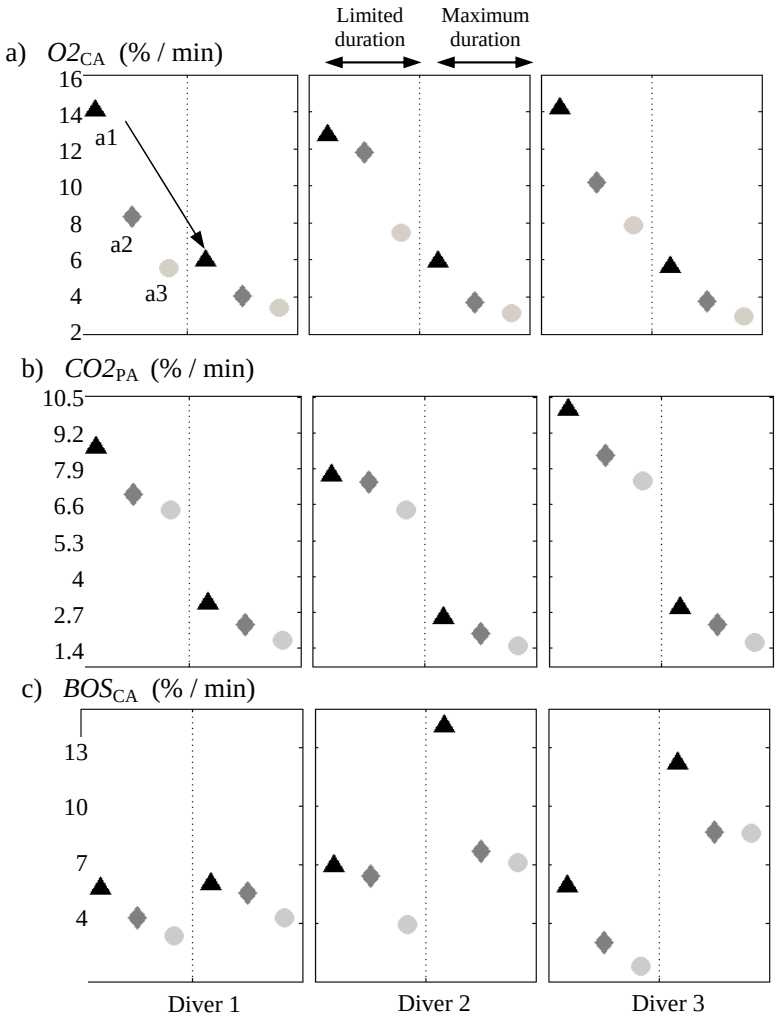

Fig. 2. (a) Oxygen consumption per minute, $O2_{CA}$, (b) carbon dioxide production per minute $CO2_{PA}$, and c) oxygen consumption in blood per minute BOS_{CA} during

different apnea types ($a1_{lim}$ to $a3_{lim}$ and $a1_{max}$ to $a3_{max}$) for apnea symbols see Fig. 1.

Discussion. A novel approach was introduced to simulate the intensity of voluntary apneas and to evaluate the diving reflex via the gas analysis in the expired air and blood. CO2 production and O2 consumption showed a high correlation with AD. We observed that $O2_{CA}$, $CO2_{PA}$, and BOS_{CA} decrease from a1 to a3, i.e. with decreasing apnea intensity. One possible explanation for this could be the fact that the total volume of air in the lungs in a2 and a3 is larger than in a1, i.e., the total O2 supply could cover the O2 needs in the body in a2 and a3. However, by decreasing apnea intensity sympathetic activity might also be reduced, which could lead to a higher relaxation during the apnea and therefore to an increase in the efficiency of the oxygen-storing diving reflex.

$O2_{CA}$ and $CO2_{PA}$ decreased for longer AD. A possible reason for this phenomenon might be different mental preparation. That is, even though the initial parameters were the same for the AD of 45 s and the unlimited AD breath holds, the diver's efforts to hold the apnea might be different when the diver knows how long the apnea will last. Since apnea divers are trained to actively relax muscles to save oxygen during an apnea, they will probably choose to concentrate more on this relaxation when facing a maximal try apnea.

On the other hand, BOS_{CA} did not decrease - as expected from $O2_{CA}$ - with prolonged AD but instead increased. This opposite behaviour indicates possible non-linearities in the O2 diffusion from the air in the lungs into the blood. It may indicate an impaired diffusion and exchange of O2 with increased AD.

In our next work we will investigate the possibility of a novel quantitative health state evaluation for divers, which facilitate the individual unbalance of physiological parameters during an induced apnea. Such evaluation methods could also be used to determine the effectiveness of freedivers training.

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Effects of preceding preparation in breath-hold divers: gas analysis in expired air and blood

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Expired gas composition and blood oxygen saturation were measured in professional breath-hold divers during 45s and unlimited apneas. Different preparation breathing techniques were executed before apneas to vary the severity and intensity of an apnea. The results show that oxygen consumption and carbon dioxide production in the expired air correlated with the duration of the apnea. Interestingly, the latter consumption and production related to the apnea duration decreased for longer apneas and for better preparation. In contrast, the consumption of oxygen in the blood increased for longer apneas but decreased for better preparation only.

VOLUNTARY APNEA FOR THE FITNESS ASSESSMENT OF DIVERS AND NON-DIVERS

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Introduction

Physiological fitness is relevant not only in terms of personal fitness but also determines suitability as operator under difficult ambient or operational conditions. Fitness can be assessed using passive methods, such as estimation of body mass index, or active methods, such as treadmill tests [1]. However, such general tests do not usually account for the particular aim of the fitness assessment and may miss important features. For instance, marine divers need special procedures for the appraisal of their fitness, procedures which specifically consider their unique mission under water and the physiological stress they are subjected to during the mission. In particular, the abilities to hold breath and withstand high ambient pressure (apnea diving) comprise important fitness factors for divers [2].

Methodology

Short voluntary apneas lasting for only 45s are proposed here for the estimation of the diver's fitness. In fact, ceased breathing disrupts breathing cycle and thus the stationary equilibrium for pulmonary gas exchange and for other regulatory processes in the body. The relatively short duration of these apneas insures that both fit and less fit persons can still withhold their urge to breath. That is, the persons under investigation are not excessively stressed and do not enter the struggle phase with ongoing contractions of the diaphragm.
As described in [3],[4] in detail, young divers and non-divers were asked to stimulate apnea for 45s, whereas different physiologic parameters were continuously registered [5]. The parameters included

blood oxygenation, blood pressure, peripheral vasoconstriction, heart rate, and chest excursions; compare Fig. 1. Voluntary apneas with and without preceding preparation were simulated. Preparatory measures which preceded apneas were chest stretching and a single reinforced inhale before each apnea.

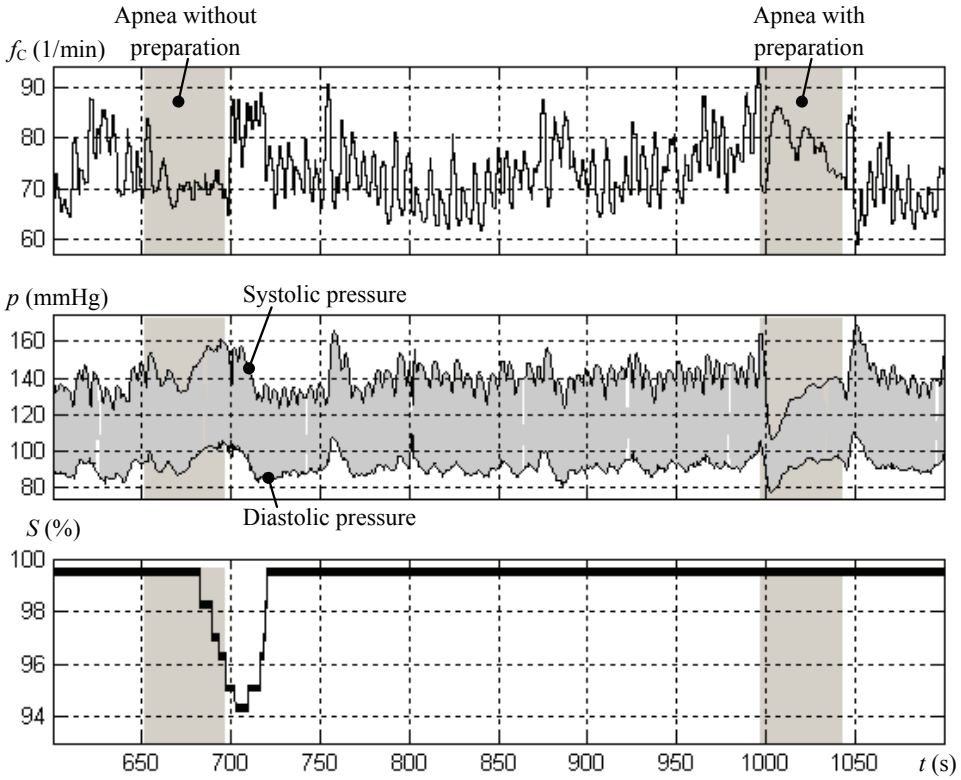

Fig. 1. Multiparametric recording of a non-diver during two voluntary short apneas (of 45s) including heart rate f_C, blood pressure p, and oxygenation level S of blood

Results

An excerpt of recorded data of a non-diver is shown in Fig. 1. Temporary unbalance of the shown physiological parameters can be observed during apneas. In particular, almost missing desaturation results during the apnea with preparation, which indicates the vital impact of the initial preparation on the apnea performance.

A comparison of the latter unbalances in the registered parameters between professional divers and non-divers yielded a surprising similarity for apneas without preparation. In contrast, differences between divers and non-divers were obvious for apneas with preparation. Consequently, it follows that the diver's fitness can only be assessed via apneas with preparation. Likewise, reasonable procedures for the assessment of fitness should necessarily include diver specific measures such as the aforementioned preparation.

Conclusions

The present paper offers first evidence on the reasonability of apnea-based tests to assess the personal fitness of divers. That is, the diving fitness is revealed if subjects are allowed to prepare for the following apnea. It is well known that preparatory measures before apnea such as chest stretching and hyperventilation improve significantly the apnea performance [2] and thus the personal expertise of divers with such preparatory measures is crucial for their diving fitness. Likewise, an apnea-based test without any initial preparation before the apnea does not reflect the diving fitness but rather the general fitness. Voluntary short apneas - as proposed in this short paper - could become standard procedure in the fitness assessment of divers and sailors in the marine sector.

Acknowledgements

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Summary

VOLUNTARY APNEA FOR THE FITNESS ASSESSMENT OF DIVERS AND NON-DIVERS

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Abstract: Personal fitness can be assessed using various passive and active tests, which do not usually account for the specific aim of fitness assessment. The marine sector, especially divers, need special procedures for the appraisal of their fitness, procedures which specifically consider their unique mission and the physiological stress they are subjected to during the mission. To achieve this, short voluntary apneas are proposed here for the estimation of the diver's fitness. Apneas comprise a temporary unbalance of the otherwise stationary equilibrium in the body. The formation of this unbalance and its dominance throughout the apnea are expected to reveal personal fitness of divers and non-divers. Preliminary results offer first evidence on the reasonability of such apnea-based tests which show a high potential to become a standard procedure in the fitness assessment of divers and sailors.

Reproducibility of cardiovascular and gas parameters in voluntary apnea related to apnea duration

A case study

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***Abstract*—The physiology and pathophysiology of voluntary apnea is an important issue not only for recreational and professional apnea diving, rescue and military diver, but also for the genesis of the involuntary sleep apnea. Numerous physiological mechanisms are involved to counteract the induced unbalance in the body's homeostasis. Even though cardiovascular effects are qualitatively similar in humans (such as diving reflex) the extent and temporal course can strongly vary from person to person. The present work discloses for the first time the behaviour of vital cardiovascular and gas parameters (in blood and air) as a novel function of the apnea duration. Blood pressure and heart rate increased for increasing apnea durations while pulsatile amplitude of the pulse wave in the finger and in the ear decreased. It is shown that carbon dioxide production per minute was quite stable independently of the voluntary apnea duration, whereas oxygen consumption per minute increased with increasing duration. The estimated respiratory quotient declined for longer apneas since the produced carbon dioxide in the lungs tended to increase slower than the consumed oxygen in the lungs. The oxygen saturation in blood exhibited a non-linear behaviour over the apnea duration, whereas the estimated partial pressure of oxygen decreased almost linearly over the duration. In addition, the reproducibility of cardiovascular parameters for apneas of different durations was quantified, given standardized conditions before apnea. Reproducibility, i.e. variation of a signal, for heart rate, systolic blood pressure and oxygen saturation was 10.6%, 8% and 1.4%, respectively, attained over different days of apnea recording. Higher variability in the heart rate and the blood pressure indicates their relevance as a regulatory parameter to counteract the physiological imbalance due to apnea.**

Keywords—apnea; expired air; breath hold; cardiovascular

I. INTRODUCTION

Even though free diving becomes more and more popular, many physiological mechanisms enabling the human body to sustain relatively long periods of ceased breathing are still unknown (the world record in static apnea is currently at 11min 35s [1]). Even though oxygen is an essential resource in the human body, professional divers are trained to endure periods of its under-supply. The so-called diving reflex [2], [3] is one of the most important inborn physiological mechanisms aiming to promote an efficient use of the residual oxygen in the body. It describes a decrease of heart rate and an increase of blood pressure along with the peripheral vasoconstriction [4]. The main focus of these actions is to sustain the function of vital organs by reducing oxygen consumption and perfusion of non-vital tissue. It should be noted, that face immersion into cold water strongly augments the effects of the diving reflex [2], [5]. By recurring exposure of the body to apneas the extent of the diving reflex can be increased [6]. Additionally to natural mechanisms, professional freedivers have developed even more strategies to optimize oxygen consumption. Mental training, for instance, strongly augments muscle relaxation and therefore decreases metabolic activity, whereas physical endurance training decreases oxygen consumption by muscles in the resting state and increases muscular oxygen storage; all of them leading to increased apnea times [6]. Additionally, special nutrition and diets can be chosen to influence the metabolism and the blood pH-value and have been shown to favorably influence the apnea duration [7].

Advancing in this field of research is not only important for professional sport athletes but also reveals essential interrelations between vital physiological processes inside the body. In addition, rescuer and military divers as well as patients suffering from involuntary sleep apneas could strongly benefit from new findings in the physiology of voluntary apneas.

To evaluate the physiology during breath holding, multiparametric data was collected and analyzed in our previous studies [8], [9]. We observed that not only there was a high variability in the response to apneas between different subjects, but also within individuals. In particular, it seems that differences in the inhaled air volume and mental preparation can strongly influence the body's reaction to an apnea. Although all subjects were instructed to inhale approximately the same amount of air before apneas, it was subjectively impossible to exactly control the inhaled volume. Even after a full inhalation the air volume will never be the same due to different vital capacities. Consequently, larger air reserves will decrease the perceived intensity of an apnea which goes in parallel to the reduced the body's response. With respect to this, this paper introduces a novel approach to quantify several cardiovascular and expired gas parameters by controlling the basic condition (e.g., the exact volume of inspired air) prior an apnea and evaluating data - for the first time - as a function of apnea duration but not of absolute time.

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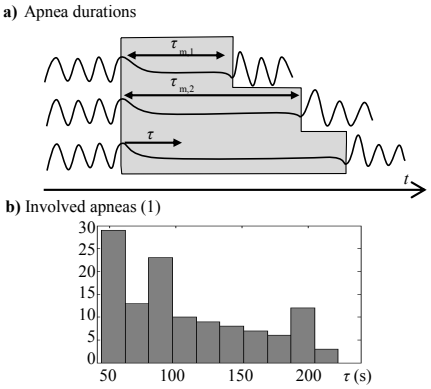

Fig. 1: a) Apneas within schematic breathing cycles and the assessment of the apnea duration τ and the maximum apnea duration τ_m. (b) The distribution of collected apneas as a function of τ_m with the granularity of 17s..

II. METHODS

A. Study Population and Protocol

One professional freediver (male, age 24) was recruited for the study. He frequently participates in freediving competitions and was in training at the time of the study. Written informed consent was obtained before the study.

All apneas were performed in supine position without face immersion. The measurements were scheduled in the forenoon at approximately the same time of day and no food or caffeine has been consumed. Additionally indoor climate and illumination was regulated.

A total of 15 breath holdings (n = 15) were performed with different durations on different days with a minimum interval of at least 2 days between breath holding events. The subject was instructed to mentally prepare for a relatively long apnea of 220s duration. The effective duration of the apnea was announced by the operator only a few seconds before the intended end. This was done in order to prevent different preparation states (e.g. muscle relaxation) for apneas with different durations. To account for typically different volumes of inhaled air, a plastic bag filled with a controlled volume of 5 liters was used for the last inspiration event prior the apnea. In addition, the diver had to perform a complete exhalation right before the last inspiration event to reduce the variability in the amount of the remaining air inside the lungs across the apneas of different duration. In contrast to non-divers, an almost complete exhalation can be easily performed by professional freedivers.

B. Measurements

Various physiological and physical parameters were acquired. The blood pressure was continuously recorded by Portapres (Finapres) with the cuff applied on the ring finger of the left hand. In addition, electrocardiogram, pulse plethysmography of the middle finger of the left hand, and breathing efforts were recorded using a Biopac MP36 System (Biopac Systems). A standard pulse oximetry (Nellcor) was used to measure blood oxygen saturation S_{O2}.

Volume ratios of end-tidal carbon dioxide Pa_{CO2} and oxygen Pa_{O2} were acquired using Datex Ohmeda Capnomac Ultima CO2 Monitor.

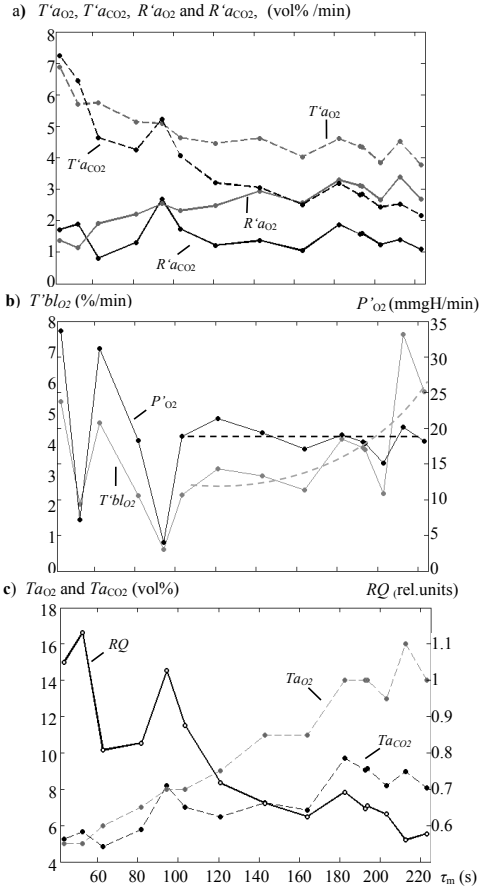

Fig. 2: a) The course of apnea duration as related to gas parameters. Absolute values of oxygen consumption $T'a_{O2}$ and carbon dioxide production $T'a_{CO2}$ are compared to their relative counterparts $R'a_{O2}$ and $R'a_{CO2}$, respectively. b) The courses and relation between consumed oxygen in blood per minute Tbl'_{O2} and decline of per minute P'_{O2}. Linear and non-linear behavior is indicated by dashed lines. c) Total values for oxygen consumption and carbon dioxide production in the first expiration after the apnea. Their unequal characteristics over the apnea result in a decrease of the respiratory quotient.

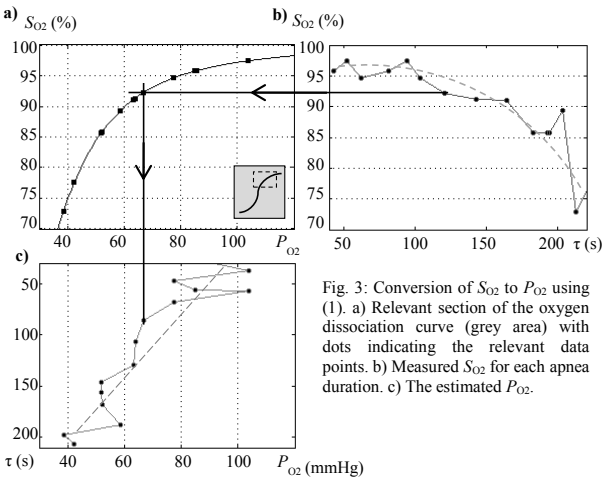

Fig. 3: Conversion of S_{O2} to P_{O2} using (1). a) Relevant section of the oxygen dissociation curve (grey area) with dots indicating the relevant data points. b) Measured S_{O2} for each apnea duration. c) The estimated P_{O2}.

C. Parameters and Statistics

Apneas of different duration τ_m were carried out, as illustrated in Fig.1a. Considering apneic segments for the apnea time τ ($< \tau_m$) of different apneas, it is obvious that segments of smaller τ occurred more often than those of larger τ. The particular distribution of τ is shown in Fig. 1b.

S_{O2} and Pa_{O2} were related to their base values (the baseline of Pa_{O2} was considered to be 21vol% in the inspired air) to acquire total consumed oxygen Tbl_{O2} (in %) in the blood and consumed oxygen Ta_{O2} (in vol%) in the lungs, respectively. Since the base value of carbon dioxide in the inspired air can be neglected (only ~0.04vol%), the corresponding Ta_{CO2} was equal to Pa_{CO2}. Since Ta_{O2} and Ta_{CO2} of a regular expiration of the diver (both Pa_{O2} and Pa_{CO2} were in the range of 4vol%) can be considered to account for expiratory gas volumes prior to the apnea, the relative consumed oxygen Ra_{O2} (= Ta_{O2}-4vol%) and produced carbon dioxide Ra_{CO2} (= Ta_{CO2}-4vol%) can be estimated. These relative values depict the difference in the gas balance between normal breathing and apnea. Total values T and relative values R were divided by their particular apnea duration to get their associated changes T' and R' relative to time, the respiratory quotient RQ in the lungs was estimated as the ratio between Ta_{O2} and Ta_{CO2}. See Fig. 2 for an overview of recorded and calculated gas parameters.

Mean arterial pressure p_M, systolic blood pressure p_S and the deflection $p_{S,D}$ between the systolic and diastolic values were calculated using the blood pressure signal. Heart rate f_C was obtained from the electrocardiogram, whereas the deflection width of the pulse wave was obtained from the pulse plethysmography at the ear pw_E and at the finger pw_F. Partial pressure of oxygen in the blood P_{O2} was approximated using (1) derived from [10]. Calculated values can be seen in Fig.3.

$$S_{O_2} = \frac{K_{O_2} P_{O_2}^n}{1 + K_{O_2} P_{O_2}^n} \quad (1)$$

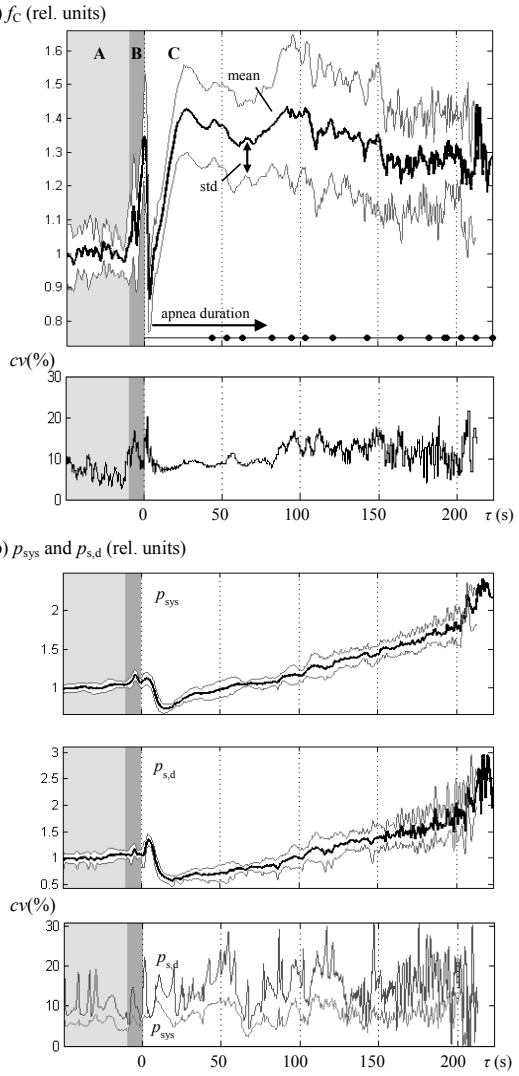

Fig. 4: a) Heart rate f_C,as a function of the apnea duration τ. The values of f_C are related to their baseline (the region A, as indicated by the light grey area) as averaged over all measurements. The dark grey area B represents the time interval excluded from the baseline. Apneic time in the region C is depicted inside the white area. The experimental apnea durations, τ_m are indicated by black points. In the lower subfigure, the corresponding coefficient of variance cv is shown. (b) Blood pressure p_S and $p_{S,D}$ as a function of the apnea duration τ and the corresponding coefficient of variance cv in the lower subfigure.

With K_{O2} being the Hill coefficient (= 1.3933 * 10^{-4}) and n the Hill exponent (for human blood 2.7). For statistical evaluation baseline values (e.g. $\overline{f_C}$) were calculated using the median of 60 to 10 seconds before the start of an apnea, see Table I. The last 10 seconds before the apnea were not

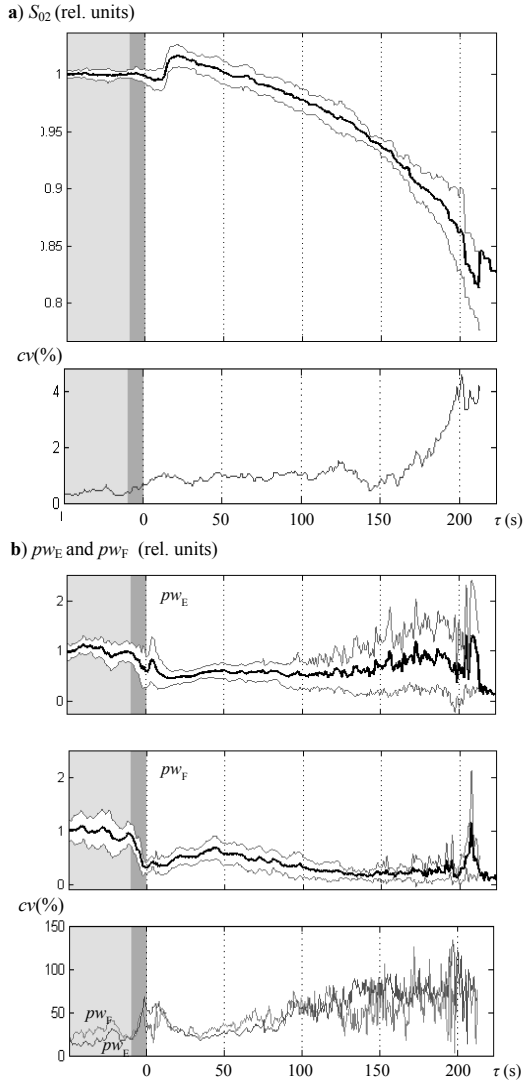

Fig. 5: a) The oxygen saturation S_{O2} and (b) the pulsatile deflection pw_E and pw_F a function of the apnea duration τ and the corresponding coefficient of variance *cv* in the lower subfigure.

considered as baseline since moving the bag to the mouth and exhaling would have influenced the data.

This baseline was then used as a reference for further analysis. In particular, all values during individual apneas were first related to their respective baseline to account for different starting conditions. The resulting ratios were then averaged for the respective τ, i.e., averaged over all measurements. Correspondingly, the resulting means and the standard deviation of the summarized values can be seen in Fig.4 and 5. Additionally, coefficients of variation, *cv* of each signal was calculated by calculating the ratio of the standard deviation (note that n-1 degrees of freedom were chosen to account for diminishing sample number for increasing τ) and the associated mean value.

TABLE I. ABSOLUTE BASELINES

$\overline{f_C}$(bmp)	$\overline{p_S}$ (mmHg)	$\overline{p_{S,D}}$ (mmHg)	$\overline{pw_F}$ (rel.)	$\overline{S_{O2}}$ (%)
51.7±5.2	117±10.6	51.1±5.2	1.5±0.7	98.2±1.4

All values mean ± standard deviation

III. RESULTS

A. Cardiovascular parameters

As shown in Fig. 4a, a short increase in f_C in synchrony with the forced expiration followed by a decline and a further strong increase during final inspiration to $1.3\overline{f_C}$ can be observed. After dropping to a minimum (=$0.8\overline{f_C}$), a steady increase throughout the first 20s of an apnea to a plateau of $1.35\overline{f_C}$ followes. During the apnea, a mild continuous decline to $1.25\overline{f_C}$ can be noticed The pressures p_S and $p_{S,D}$ - see Fig.4b - increase mildly during forced expiration followed by a relatively strong peak in $p_{S,D}$ a few seconds after the onset of the apnea. Both parameters rise strongly throughout the apnea to $2\overline{p_S}$ and $2.5\overline{p_{S,D}}$, respectively. The deflections pw_F and pw_E generally decrease during the apnea, whereas pw_F by trend decreases stronger over apnea time as compared to pw_E. The deflection pw_E increases with increasing apnea duration, see Fig.5b; pw_E also shows a temporary increase at the beginning of apneas. A high variability can be observed in all cardiovascular parameters with increasing apnea duration.

Concerning the reproducibility of collected data, *cv* strongly differs in between signals. As shown in Fig. 4, *cv* was relatively low and constant throughout the apneas in f_C (10.65±2.72%) and p_S (8.08±2.64%), whereas $p_{S,D}$ showed higher values (15.63±5.2%, mean of *cv* ± standard deviation). Even though S_{02} showed only very small variation between apneas, a strong increase of *cv* can be seen towards the end of the apnea (see Fig. 5a). The highest *cv* could be seen in pw_F and pw_E with 53.58±17.13% and 59.66±23.17%, respectively; an increase throughout the apnea could be observed in both signals (Fig. 5b).

B. Chemical parameters

In Fig. 5a the saturation S_{O2} increases mildly at the beginning of an apnea and then decreases over the course of apnea to a minimum of $0.84\overline{S_{O2}}$.

As shown in Fig. 2b, the levels Ta_{O2} and Ta_{CO2} both increased over the apnea duration, resulting in a decrease of *RQ*. Considering values as related to time, $T'a_{O2}$ and $T'a_{CO2}$ decrease with apnea duration, whereas $R'a_{O2}$ increases. The level of Ra'_{CO2} remains relatively constant across the apnea duration (1.5±0.4 vol%/min). For apneas with shorter duration than 100s, the courses of $T'bl_{O2}$ and P'_{O2} showed no clear pattern. For increasing apnea durations, P'_{O2} seems to level off, whereas $T'bl_{O2}$ rises.

IV. Discussion

A novel approach for the acquisition of physiological data and expired gases is presented, in the framework of a case study. In addition, cardiovascular and gas parameters were analyses as a function of apnea duration. One professional free diver was recruited to perform 15 apneas of different duration, given identical starting conditions. Our data show that heart rate, blood pressure and oxygen saturation are quite reproducible for different apneas within the same subject (Figs. 4a,b and 5a). The amplitude of the pulse wave on the other side varied strongly between apneas (Fig. 5b). A higher variability might reflect a stronger regulatory importance of the signal, i.e. heart rate, blood pressure and pulse wave amplitude. Deoxygenation of blood on the other hand is depending on those regulatory mechanisms during an apnea.

Considering the strong changes of blood pressure and heart rate at the beginning and prior the apnea, the changes of intrathoracic pressure during the preceding complete expiration and the following deep inhalation before apnea change the effective pressure applied on the (venous) vessels inside the thorax [11]. This change in the intrathoracic pressure induces the aforementioned variability of the blood pressure and heart rate. This phenomenon can be seen most clearly shortly after onset of the apnea (See Fig. 4). Pressure changes similar to a valsalva maneuver [11] during inspiration which result in a drop of blood pressure and increase of heart rate. The high variability of cardiovascular parameters is also clearly visible in the so-called struggle phase [12] (approximately after 120s) and could be attributed to involuntary rapid chest movements during this phase. Such movements are accompanied by abrupt pressure changes in the thorax. Similar pressure changes can be observed during respiration, which strongly impact cardiac output and stimulate baroreceptors in terms of the thoracic pump [13], [11]. During the apnea the blood pressure tends to increase while the deflection of the arterial vessels decreases; both due to diving reflex [2]. After reaching its maximum because of the previously mentioned mechanisms the heart rate tends to decrease over apnea duration.

Interestingly an increase in blood oxygen saturation was observed in all measurements at the beginning of an apnea. Since the peak appears approximately 20s after the last deep inspiration it is likely that the deep inhalation temporary increased the distally assessed saturation. In addition, the averaging function of the pulse oximeter may delay the registered oxygenation.

With respect to the end tidal gas parameters, it was shown that for longer apnea duration oxygen consumption per time increased, whereas carbon dioxide production per time remained relatively constant. This is also visible in a decrease of the respiratory quotient (Fig. 2c). Even though the consumption of oxygen in the blood seems to increase non-linearly, an estimation of the associated partial pressure of oxygen revealed a relatively linear reduction of the partial pressure (Fig. 3). This is a result of the sigmoid shape of the oxygen dissociation curve.

Limitations ans Future Works

The aim of this paper is to introduce a new evaluation method for physiological and end tidal gas parameters during voluntary apnea. No statistical significant conclusions could be made due to the limitation of this single case study. Since no face immersion was performed, the diving response cannot be expected to be highly dominant.

In our future work, a larger diving group will be investigated using similar methods to account for statistical significance and prove validity of the proposed measurement methodology, whereas the face immersion will be considered within the study protocol.

Acknowledgment

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Strategic framework for management of hybrid biosignals from study design to statistics

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Abstract — A centralized framework for management of hybrid biosignals is proposed in order to design experimental studies, store hybrid biosignals and the associated metadata, view, validate, synchronize, and evaluate all data in a flexible and obvious way. Different studies performed at different times with different subjects, physiological maneuvers, applied devices and heterogeneous biosignals require a strategic and centralized framework to offer an individualized perspective on available data for a researcher to answer current research-related questions. Especially, administration of metadata of different studies and performed experiments require this centralized approach. When considering biomedical studies with large data quantities accumulated by regionally separated teams, data synchronization and their consistency inspection can significantly increase global efforts and thus costs and duration of scientific projects. For the first time, we present a server-client based design that enables users (researchers) to easily manage recorded data and the related meta-information via a website or a client software. A prototype is already implemented as a first proof of concept.

Keywords—data management; data analysis; biomedical research

I. INTRODUCTION

When thinking of the efforts one have to put into designing, running, storing and evaluating an experimental study, it is often surprising how many man-hours have to be spent on data validation and organization. Since availability of computer power and storage capabilities have increased over the last years, data quantities are also scaling up. This is especially true for studies or experiments that involve large data recordings like imaging methods, genetic databases, or multiparametric measurements of physiological signals. Considering the latter, biosignals originating from mechanical, optical, acoustic and electric sources [1] are of main interest and are hereby referred to as hybrid biosignals. The collection of such signals from the body with high sampling rates (in the range of kHz) can often yield overwhelming data quantities. Aside from pure data management it is also crucial to store and administrate the associated meta-data about a study like subject groups, clinical histories, time and date of recordings, special events during measurements and many more.

While the focus of research activities should lie on evaluating this data using statistics and algorithms, quite often a lot of the productive time has to be spent on data synchronization, validation, processing and organization. In many cases this implies a decline of analysis quality due to limited time/budget and increasing complexity.

Another important issue is the accessibility of the stored data. Considering a research group with several researchers focusing on different tasks, a user level system is required which enables each researcher to access the data he or she requires in a simple way. This also allows for a better access control when dealing with interns joining research groups for a short term as well as for a more efficient distribution of scientific labor. In our experience, scientific work at universities often involves students and short term interns that require attention and time in order to help them developing their own analysis tools or use existing ones. Additionally, even though similar challenges arise in different projects, algorithmic software is frequently written from scratch without using existing code. It is obvious, that different tasks in biomedical studies may require different approaches but significant similarities exist in the structure of physiological studies and applied algorithms.

In general, the basic structure of most biomedical studies and experiments can be described by some key states. In order to prove a scientific hypothesis, subjects are recruited and have to perform various maneuvers while being monitored by specific biomedical devices yielding numerous biosignals (see Fig 1). After analyzing data and comparing their characteristics in different subject groups or during different maneuvers, the hypothesis-related conclusions can be drawn. Our research group, for instance, uses a large variety of biomedical sensors, able to measure and record hybrid biosignals like electrocardiogram (ECG) or continuous blood pressure. In a recent study we acquired 18 different biosignals obtaining about 180MB for a single measurement session. However, since this data only represent the raw data, each analysis performed on it will require additional storage space. With several subjects, all examined several times, the amount and complexity of data exponentially rises.

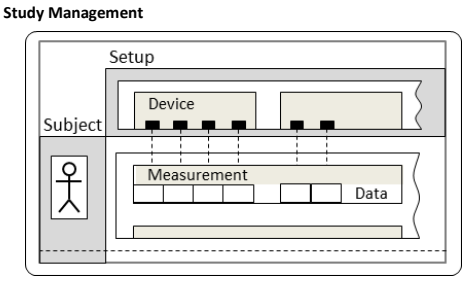

Fig. 1.The basic meta-information that can be mapped to a biomedical measurement is the subject that is investigated and the setup of devices and their signals (indicated by black squares) that are used in a study. Using this information, data can be easily mapped and filtered.

In order to illustrate these issues, imagine a team working on such data without central data management. Since the data is very large, the easiest way for distribution will be the physical one, requiring the team to work at the same location. From now on, all modifications and process made on each dataset will require tedious synchronization while small mistakes may result in data loss or their corruption. Minor changes in evaluation scripts can also account for severe differences between the evaluated datasets which are hardly noticeable. Even if these issues are solved, the access of the data in future might comprise another tough challenge. Thinking of the various information linked to each subject and measurement (i.e., meta data related to special incidents, event times, artifacts, etc.), missing that information might render those recordings useless. In our experience relying solely on MATLAB® or other data processing frameworks for the whole project organization can often lead to inconsistencies and corruption of data.

While similar centralized systems exist for clinical trials and patient histories [2] [3], hospital information systems [4], qualitative data analysis and surveys [5], discrete biomedical data [6], sole biosignal analysis [7] and data storage [8], combining the administration of both meta-data and hybrid biosignal within one tool - to our knowledge - has not been successfully developed yet. Such a system would be highly advantageous as already shown in [9] introducing a biomedical image management system. It has already been shown that a centralized system is capable of greatly improving efficiency and research capacity [10]. Another benefit, maybe more subtle, of such a system is the improvement of data distribution. The ability to access data from different studies and sharing extracted parameters and meta-data with other research groups is strongly dependent on a universally accessible platform. As described in [11], sharing data is also beneficial for the citation rate which indicates paper quality.

We propose a server based framework providing a network interface for the strategic management of both raw data and meta-data (organizational data). Data sets will be stored at a single location accessible for users via a website or a frontend. Additionally, meta-information and the state of the stored data can be easily tracked, which allows for a comfortable data access not only for the current measurements but also for records used in previous studies.

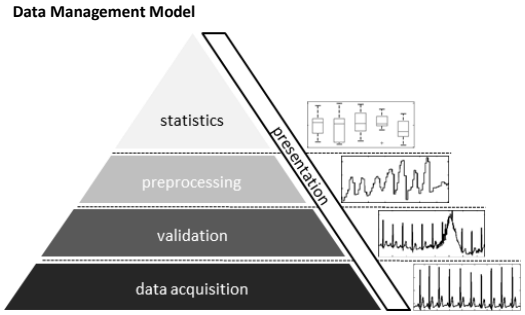

Fig. 2. Proposed data management model, describing the different stages a signal passes through before physiological information can be extracted. Each layer represents separated challenges throughout this process. After collecting the data (data acquisition) it has to be cleared for artifacts and other irregularities (validation) before the associated parameters are derived (preprocessing) and summarized in statistics (statistics). All layers are framed by a vertical presentation layer which enables users to interact individually with data in different layers as indicated by examples on the right side.

We propose an abstract layer model describing fundamental data management and processing levels. As inspired by other layering models [12], which have already greatly improved handling and understanding of interrelated processes, we aim to clarify and simplify the data management process.

II. Data Model

In order to improve the management of hybrid data and of the associated workflow, we introduce a layer model with separated sections each having unique challenges and requirements for analysts and developers. As depicted in Fig. 2, four main layers describe different processing states of biomedical data:

- Data acquisition layer: The basis for further processing is the raw data acquired from biomedical devices. This might be an ECG like shown in Fig. 2.
- Validation layer: Almost every biosignal received from a measurement device will contain artifacts and invalid data segments (for an ECG, for instance, this could be an ectopic beat when aiming at the heart rate variability analysis), and needs to be synchronized with other signals. Such periods need to be identified before further analysis can be performed.
- Preprocessing layer: In this layer, data analysis is executed in order to achieve study relevant parameters. In case of the ECG signal, heart rate or heart rate variability can be derived.

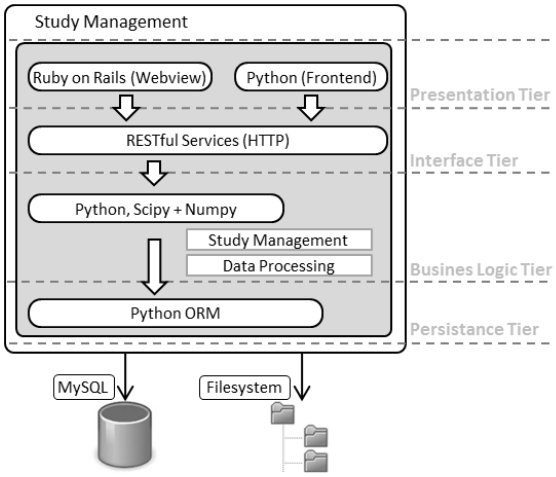

Fig. 3. Architecture of the proposed management software. A webservice provides the interface to access data on a remote server based on RESTful services. The server stores recorded data and its associated meta information in a filesystem and SQL database, respectively. On request, data can be processed and displayed to the user via a webview or graphical interface.

- Statistics layer: After obtaining all necessary physiological parameters, statistics can be run to compare different groups, subjects, events, and even experimental studies.
- Presentation layer: In each aforementioned layer, the requirement to display data exists to enable user an interaction and possibly an individual assessment of the data quality.

Definition and isolation of these layers not only provides a clearer workflow and better overview over the general state of a study but also enables developers and users to be easily assigned to subprojects and modules according to their specialization. For instance, short term interns could start at lower layers by recording and verifying signals (acquisition and validation) while experienced employees can focus on the evaluation of the data (preprocessing and statistics).

III. System Architecture

The proposed software architecture consists of different modules with separated functionalities. As shown in Fig. 3. the basis of data storage is provided by a MySQL database holding metadata of studies while measurement data is stored on the servers filesystem. This separation is highly reasonable since storing large datafiles (>40MB) directly inside a database is not viable in most database implementations. The persistence tier represents the connection to the database and the filesystem. The open source Python toolkit SQLAlchemy was chosen for the purpose of database interaction due to its simplicity and functionality. In the next tier, the business logic layer, data and metadata are processed (i.e. study management and data management as illustrated in Fig. 1 and Fig. 2). This information can then be distributed via RESTful services [13] over the HTTP protocol (Interface Tier). Data processing (as described in the precious section) is based on Python frameworks, providing functions similar to MATLAB® while study meta-data management is basically facilitated through data base access. The provided network interface can then be accessed over various different implementations and displayed (Presentation Tier). A web-service based on the open source web application framework Ruby on Rails could account best for needed portability issues, which provides a widely accessible platform A Python implementation, on the other side, might give more freedom to users in terms of development.

Due to the broad spectrum of functionalities such a framework has to provide (e.g., database interaction, network communication, data processing and statistics) Python was preferred over Matlab and Java for the core server and standalone client programming language. Considering the increasing presence of Python in the scientific community and its open source availability, its acceptance and support can also be expected to be high.

IV. Realisation

A Python based graphical interface was developed to demonstrate basic functionalities in a proof of concept. In this first step the focus lied on the organization of meta information as well as the accessibility of recorded biomedical data. In accordance to Fig. 1 studies can be created and individualized by adding devices, signals, events, groups and so on. While the study is carried out, new subjects can be assigned with their individual information (e.g. bmi, age, associated group, etc.). Based on this established structure, measurements and their data can then be easily uploaded and are stored in the filesystem while meta information is stored in the database.

The software has essentially three sections covering the functionality described above. In particular, a distinction between

- Design,
- Execute and
- Data views

was implemented. In the first step of the creation process of a biomedical study the design view enables the user to create new studies and define the frame conditions. Additionally, devices can be customized by defining features like supported signals or sampling rates. The device configuration or setup (see Fig. 1) can be individually defined for each study offering the user a completely modular design tool. After a study was composed that way, its state changes to running and it can be further administrated in the Execute view, where subjects and measurements can be added. The latter measurements are appended to subjects according to the configured setup of the study (i.e., used devices and signals). For this purpose, MATLAB® files can be loaded including variables or structures which can be assigned individually to biosignals as

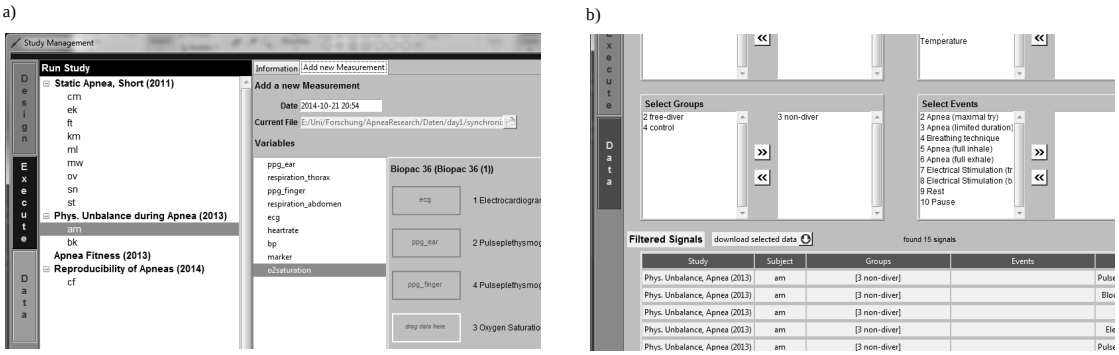

Fig. 4. The prototype implementation with (a) the Execute view and (b) the Data view. The former shows an overview of currently running studies in the system and its associated subjects (listed by pseudo-identification, such as sm, ek etc.). For each subject new measurements can be added by opening a Matlab file containing arrays, matrixes or structs that hold the recorded data. This data can be assigned to their counterpart channels of the device. In (b), the previously stored data can be accessed by setting various filters for data selection.

depicted in Fig. 4a. The data will then be uploaded and saved on the filesystem. All meta-information associated with this data set is stored in the database. Fig. 4b shows the Data view which allows users to apply complex filters and easily access data from the storage.

V. Discussion

In our proposed framework for hybrid biosignals management, studies can be administered not only at an organizational level but also at a data processing level. Combining principles already implemented in other tools [2] [7], a server based storage for meta-information and hybrid biosignals has been designed with the intrinsic possibilities for the user to easily access and process data. The anticipated model for implementation and workflow (Fig. 2) clarifies the current process-state of hybrid data (and meta-data) and realizes an efficient separation of study development and data analysis.

Based on this design, a proof of concept prototype was developed focusing mainly on meta-information and data storage. However, the current database structure and database access implementation is scalable to the proposed full implementation of the architecture (see Fig. 3) and can be reused in future developments.

An essential improvement that has to be made is the protection of sensitive subject data. Even though the current design does not allow for an individual mapping of data to real persons, sophisticated encryption and anonymisation methods have to be implemented to account for privacy and ethical standards. As stated in [8] centralized raw data storage might also be a problem due to ethical issues. As described in [14], access issues for distributed systems - due to e.g. firewall configurations - should be accounted for when implementations are considered on a larger scale. Access to servers might be restricted because of security policies.

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