UNIVERSITY OF BELGRADE
SCHOOL OF ELECTRICAL ENGINEERING

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METHODS FOR ASSESSMENT OF ELECTRICAL ACTIVITY OF SMOOTH MUSCLES

Doctoral Dissertation

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УНИВЕРЗИТЕТ У БЕОГРАДУ

ЕЛЕКТРОТЕХНИЧКИ ФАКУЛТЕТ

Ненад Б. Поповић

МЕТОДЕ ЗА ОЦЕНУ ЕЛЕКТРИЧНЕ АКТИВНОСТИ ГЛАТКИХ МИШИЋА

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Big wish of mine was that the part of the research is oriented towards hardware, which resulted in construction of the device for electrogastrography recording. Enormous support and help in that endeavor I have received from Prof. Dr. Predrag Pejović. I am very thankful for it, as well as for the wholesome cooperation during my PhD studies.

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During my scientific research, I have been employed by Abbott Company – maintaining a balance between working duties and duties regarding the research could sometimes become a real challenge. Because of that I must mention my Abbott colleagues, who by their positive attitudes, understanding and working environment they create, made my time and devotion to scientific work more effective.

As a technical consultant for implantation of Pacemakers and Implantable Cardioverter Defibrillators, I have the opportunity to collaborate and learn from many medical doctors from Serbia and surrounding region. I am obligated to mention Prof. Dr. Goran Milašinović particularly, the Director of Pacemaker Center of Clinical Center of Serbia, who greatly helped me understand the multidisciplinarity of biomedical engineering field by his comprehensive knowledge of medical and technological principles, in treating cardiac arrhythmias. Working alongside him, as well as other doctors and medical staff of the Pacemaker Center, who share their great knowledge selflessly, is an opportunity for personal growth and improvement, for which I am immeasurably thankful.

The support given by closest friends as well as time spent with them, affected my work to a large degree. My appreciation goes to all of them, especially to Milica Milinković, Svetislav Vasović, Milan Antić, Lazar Simončević and Matija Tripković, without who previous years of my life and work I would not perceive as halfway meaningful and successful as they are. My further thanks go to Svetislav, whose help in formulating certain contents in English language was more than welcome.

Throughout my entire education, I could have leaned on unreserved support of my parents, Mirjana and Boško, as well as my sister Dunja. Examples they had set motivated me, words they had directed guided me – and for that, there is no end to my gratitude.

It is almost impossible to bring to light the thankfulness feeling towards my wife Emina. It is my strong belief that without her support it would be much more strenuous for one to generate energy and find motivation for working on this dissertation. Emina, for every day, hour and minute spent beside me – I truly thank you.

In Belgrade, February 2021

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Nenad B. Popović

ЗАХВАЛНИЦА:

Од завршне године основних студија, па све до данас, највећи утицај на мој научни рад имала је професорка др Надица Миљковић, која је и ментор ове дисертације. Током заједничког рада, њено знање и искуство представљали су ослонац за сва спроведена истраживања. На њеном примеру, схватио сам шта израз да наука стреми ка откривању истине заиста значи, и да су први предуслови за успешно бављење њоме, непоколебљива радна етика и моралне врености. Како саветима, тако и примедбама, обликовала је моје критичко размишљање и научила ме педантном и темељном приступу у научно-истраживачком раду. Велика ми је част што имам прилику да сарађујем са њом. Овим путем јој се неизмерно захваљујем.

Велику захвалност дугујем и проф. др Томиславу Шекари, од кога сам имао прилику да научим пуно о фракционом диференцијалном рачуну, којег смо повезали са облашћу биосигнала, те сазнања преточили у релевантне научне радове.

Моја велика жеља била је да део истраживања буде оријентисан ка хардверу, што је резултовало конструкцијом апарата за снимање електрогастрографије. Велику подршку и помоћ на том путу имао сам од проф. др Предрага Пејовића. Захвалан сам му на томе, као и на целокупној сарадњи током докторских студија.

Део истраживања приказаног у овој дисертацији реализован је на Факултету за Електротехнику Универзитета у Љубљани. Највећу захвалност за ту веома успешну сарадњу дугујем проф. др Јаки Соднику. Консултације са њим у великој мери су утицале на стварање идеја и формиање закључака ове дисертације. Желео бих додатно да се захвалим и осталим колегама из Словеније, Кристини Стојменовој, Греги Јакушу и Тимотеју Грудену на сјајној комуникацији, сарадњи и размени идеја.

Захваљујем се и проф. др Мирјани Поповић на свим консултацијама и саветима који су ми били од велике помоћи на самом почетку бављења обрадом електрофизиолоских сигнала.

Додатно, свим члановима комисије захваљујем на корисним саветима при обликовању докторске тезе.

Колегиници Милани Проданов и колеги Марјану Проданову сам веома захвалан на сардањи током специфичних делова истраживања.

Посебно захвалност дугујем свим испитаницима укљученим у истраживање, на вољи да учествују, стрпљењу и излагању бројним протоколима. Без њиховог доприноса, значај добијених резултата био би далеко мањи.

Током мог научног истраживања, био сам запослен у компанији Abbott – одржавање равнотеже између радних и истраживачких обавеза некада је било прави изазов. Због тога, морам поменути своје колеге из Abbott -а, које су, својим позитивним ставом, разумевањем и радном атмосфером коју стварају, учинили моје време и моју посвећеност научном раду знатно ефективнијим.

Као технички консултант при уградњи имплантибилних пејсмејкера и кардиовертер дефибрилатора, имао сам задовољство и прилику да сарађујем и учим од многих лекара из Србије и региона. Посебно бих издвојио проф. др Горана Милашиновића, директора Пејсмејкер центра Клиничког Центра Србије, који ми је својим свеобухватним знањем медицинских, али и технолошких принципа лечења срчаних аритмија помогао да боље разумем мултидисциплинарност коју носи област биомедицинског инжењерства. Рад са њим, али и другим лекарима и медицинским особљем

Пејсмејкер центра, који несебично деле велико знање које имају, прилика је за стални развој и напредовање, на чему сам им неизмерно захвалан.

Подршка најближих пријатеља и време проведено са њима, имали су снажан утицај на мој рад. Захвалио бих се свима, а посебно Милици Милинковић, Светиславу Васовићу, Милану Антићу, Лазару Симончевићу и Матији Трипковићу, без којих претходних пар година живота и рада не бих сматрао ни упола значајним и успешним као сада. Светиславу додатно захваљујем на помоћи у формулисању одређених делова текста на енглеском језику.

Током целокупног школовања могао сам рачунати на безрезервну подршку родитеља, Мирјане и Бошка, као и сестре Дуње. Њихови примери су ме мотивисали, а њихове речи усмеравале. Бескрајно сам им захвалан на томе.

Тешко налазим речи којима бих описао захвалност коју осећам према мојој супрузи Емини. Верујем да бих још теже налазио енергију и мотивацију за рад на овом докторату да нисам имао њену подршку. На сваком дану, сату и минуту који проведеш крај мене – хвала ти.

У Београду, фебруар 2021.

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Ненад Б. Поповић

Title: Methods for assessment of electrical activity of smooth muscles

Summary: Recording of the smooth stomach muscles' electrical activity can be performed by means of Electrogastrography (EGG), a non-invasive technique for acquisition that can provide valuable information regarding the functionality of the gut. While this method had been introduced for over nine decades, it still did not reach its full potential. The main reason for this is the lack of standardization that subsequently led to the limited reproducibility and comparability between different investigations. Additionally, variability between many proposed recording approaches could make EGG unappealing for broader application.

The aim was to provide an evaluation of a simplified recording protocol that could be obtained by using only one bipolar channel for a relatively short duration (20 minutes) in a static environment with limited subject movements. Insights into the most suitable surface electrode placement for EGG recording was also presented. Subsequently, different processing methods, including Fractional Order Calculus and Video-based approach for the cancelation of motion artifacts – one of the main pitfalls in the EGG technique, was examined.

For EGG, it is common to apply long-term protocols in a static environment. Our second goal was to introduce and investigate the opposite approach – short-term recording in a dynamic environment. Research in the field of EGG-based assessment of gut activity in relation to motion sickness symptoms induced by Virtual Reality and Driving Simulation was performed. Furthermore, three novel features for the description of EGG signal (Root Mean Square, Median Frequency, and Crest Factor) were proposed and its applicability for the assessment of gastric response during virtual and simulated experiences was evaluated.

In conclusion, in a static environment, the EGG protocol can be simplified, and its duration can be reduced. In contrast, in a dynamic environment, it is possible to acquire a reliable EGG signal with appropriate recommendations stated in this Doctoral dissertation. With the application of novel processing techniques and features, EGG could be a useful tool for the assessment of cybersickness and simulator sickness.

Keywords: electrophysiology, smooth muscles, biosignals, electrogastrography, EGG instrumentation, EGG protocol, EGG processing, EGG features, sickness, virtual reality, driving simulation

Scientific area: technical sciences, electrical engineering

Specific scientific area: biomedical engineering

Наслов: Методе за оцену електричне активности глатких мишића

Резиме: Снимање електричне активности глатких мишића желуца може се реализовати употребом електрогастрографије (ЕГГ), неинвазивне методе која пружа значајне информације везане за функционисање органа за варење. Упркост чињеници да је откривена пре више од девет деценија, ова техника још увек није остварила свој пун потенцијал. Основни разлог за то је недостатак стандардизације који условљава ограничења у смислу поновљивости и упоредивости између различитих истраживања. Додатно, варијабилност која је присутна у примени различитих препоручених поступака снимања, може смањити интерес за употребу ЕГГ-а код широког опсега потенцијалних корисника.

Наш циљ је био да пружимо евалуацију поједностављене методе мерења тј. протокола који укључује само један канал током релативно кратког временског периода (20 минута) у статичким условима са ограниченим кретањем субјекта тј. у мировању. Такође, приказали смо наше ставове у вези најприкладније позиције површинских електрода за ЕГГ снимање. Презентовали смо и резултате испитивања метода, на бази обраде видео снимка као и фракционог диференцијалног рачуна, за отклањање артефаката помераја – једног од највећих изазова са којима је суочена ЕГГ метода.

За ЕГГ је уобичајено да се користе дуготрајни протоколи у статичким условима. Наш други циљ био је да представимо и оценимо употребљивост супротног приступа – краткотрајних снимања у динамичким условима. Реализовали смо истраживање на пољу оцене активности желуца током појаве симптома мучнине изазване виртуелном реалношћу и симулацијом вожње. За потребе методе за оцену електричне активности желуца, предложили смо три нова параметра за квантификацију ЕГГ сигнала (ефективну вредност амплитуде, медијану и крест фактор) и извршили процену њихове прикладности за оцену гастроинтестиналног тракта током коришћења виртуелне реалности и симулатора вожње.

Закључак је да ЕГГ протокол у статичким условима може бити упрошћен и његово трајање може бити редуковано, док је у динамичким условима могуће снимити одговарајући ЕГГ сигнал, али уз праћење препорука наведених у овој тези. Употребом нових техника за процесирање сигнала и прорачун одговарајућих параметара, ЕГГ може бити корисна техника за оцену мучнине изазване коришћењем симулатора и производа виртуелне реалности

Кључне речи: електрофизиологија, глатки мишићи, биосигнали, електрогастрографија, ЕГГ инструментација, ЕГГ протокол, ЕГГ процесирање, ЕГГ параметри, мучнина виртуена реалност,симулација вожње

Научна област: техничке науке, електротехника

Ужа научна област: биомединско инжењерство

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Abbreviations

%SWC	Percentage of Slow Wave Coupling
A/D	Analog-to-Digital
BMI	Body-Mass Index
CF	Crest Factor
CT	Computerized Tomography
DF	Dominant Frequency
DFIC	Dominant Frequency Instability Coefficient
DS	Driving Simulators
ECA	Electrical Control Activity
ECG	Electrocardiography
EEGG	Enhanced Electrogastrography
EGG	Electrogastrography
EMD	Empirical Mode Decomposition
EMG	Electromyography
EMI	Electromagnetic Interference
ERA	Electrical Response Activity
FC	Fractional Calculus
FFT	Fast Fourier Transform

GEA	Gastric Electrical Activity
GI	Gastrointestinal System
GMA	Gastric Motility Assessment
HR	High-Resolution
IBS	Irritable Bowel Syndrome
IC	Instability Coefficient
ICA	Independent Component Analysis
M-EGG	Multichannel Electrogastrography
MF	Median Frequency
MRI	Magnetic Resonance Imaging
OGD	OesophagoGastroDuodenoscopy
PR	Power Ratio
RMS	Root-Mean-Square
RSA	Running Spectrum Analysis
SG	Savitzky-Golay filter
SNR	Signal-to-Noise Ratio
SS	Simulator Sickness
SSQ	Simulator Sickness Questionnaire
VR	Virtual Reality

Preface

Research in the area of electrophysiological signal acquisition, focused on gastric electrical activity, in the past four years resulted in this Doctoral dissertation entitled “**Methods for Assessment of Electrical Activity of Smooth Muscles**“. It was conducted at the School of Electrical Engineering – University of Belgrade, under the mentorship of Assoc Prof. dr Nadica Miljković. The main topic of this Dissertation is the investigation and application of the procedures for the recording and analysis of biosignals originating from the smooth muscles of the stomach. It included a detailed review of existing scientific contributions, development of the hardware equipment for the recording, recommendations for the recording protocol and conditions, and proposal of novel techniques for analysis and interpretation. The specific focus was on applying non-invasive electrogastrography technique for the recording of gastric electrical activity, especially in non-standard conditions.

Motivation

Almost 100 years passed since the discovery of the method for detection of the smooth stomach muscles electrical activity – Electrogastrography (EGG) by Alvarez (1922) [1]. Since then, this procedure has advanced in many aspects, including recording apparatus, procedures, and analysis, but its clinical application remained limited to this day. The main reason for this is the lack of standardization in EGG, which produces many controversies among physicians regarding its usefulness and effectiveness. Although technological progress in electrophysiological methods in the past few decades offered several opportunities for additional improvement, substantial questions remained unanswered. It is believed that the pathway towards standardization and broader use of EGG could be through detailed investigation of existing recommendations and proposal of novel techniques with valid evaluation approaches. Additionally, the paradigm shift from a long-term static recording of EGG towards short-term recording in a dynamic environment with a specific subject stimulus could increase interest in this method. For example, the occurrence of sickness symptoms in healthy volunteers, as a consequence of different stimulus, could be evaluated by EGG.

Overall, the possibility for further improvement of the methods for evaluation of the stomach smooth muscles via non-invasive cutaneous recording and its promising applications inspired this research.

Aim and Research Questions

This research aimed to propose and evaluate novel approaches for EGG recording and analysis in the context of the overall improvement in the field. Simplification of recording protocol via custom-made apparatus was marked as groundwork for further advancement towards EGG application in a dynamic environment such as driving simulation and virtual reality. The performance and relevance of such applications are highly dependable on suitable processing and analysis methods proposed and evaluated in this Doctoral dissertation. Based on that, the initial two hypotheses were:

1. *With the appropriate instrumentation and clearly defined post-processing and signal analysis methods, it is possible to reduce and simplify the protocol for EGG recording for suitable adaptation of the EGG method to a wider application in clinical practice and for the research. In addition, such protocol should enable high-quality EGG acquisition with decreased noise presence.*

2. *Electrogastrography as a non-invasive method can provide useful information regarding gastric electrical activity alterations in healthy subjects during driving simulation and virtual reality experiences.*

Evaluation of the hypothesis was done by providing answers to the following research questions:

1. Is it possible to acquire a reliable EGG signal via a custom-made open-source device by employing a simplistically designed short-term recording protocol with one recording channel?

2. What are the perspectives of completely automated processing algorithms for artifact cancelation?

3. Is it possible to record EGG in the dynamic environment, and what are the main guidelines that need to be followed?

4. Which parameters should be used to quantify the EGG signal recorded in a dynamic environment?

5. Is there a correlation between EGG alterations and the occurrence of nausea symptoms in a dynamic environment?

Scientific Contributions

During the research following scientific contributions stood out:

1. Design and realization of custom-made open-source hardware for the recording of an electrogastrographic signal. The device was tested in the two studies published in journals with impact factor [2], [3] in 33 subjects, and used in overall more than 70 different protocols.

2. Recommendations for simple short-term single-channel EGG recording, evaluated in 20 healthy subjects during fasting and postprandial phase of the gastric cycle.

3. Proposal of automatic algorithms for denoising EGG signal by application of fractional calculus and video recording, evaluated in two case-studies.

4. Evaluation of EGG recordings in a dynamic environment (in 16 subjects overall), with the corresponding discussion regarding recommendations that need to be fulfilled to obtain suitable signals.

5. Assessment of three novel parameters for the description of EGG signal – median frequency, crests factor, and root-mean-square value. The parameters were evaluated in 16 subjects overall.

6. Application of EGG for the assessment of sickness induced by driving simulator and virtual reality in healthy subjects. Overall, the assessment procedure was tested in 16 subjects [3].

Dissemination of the Results

Main results of the research described in this Doctoral dissertation are presented in following articles published in Journals with impact factor and conferences.

Publications in Journals with Impact Factor:

Popović N.B., Miljković N., Stojmenova K., Jakus G., Prodanov M., Sodnik J.: Lessons learned: Gastric motility assessment during driving simulation, *Sensors (Basel)*, vol. 19, no. 14, 2019. ISSN: 1424-8220, DOI: 10.3390/s19143175 **(M21, IF2019: 3.275)**

Popović N.B., Miljković N., Popović M.B.: Simple gastric motility assessment method with a single-channel electrogastrogram, *Biomedical Engineering / Biomedizinische Technik*, vol. 64, no 2, pp. 177-185, 2019 (online 2018), ISSN: 0013-5585, DOI: 10.1515/bmt-2017-0218 **(M23, IF2018: 1.007)**

International Conferences:

Popović N.B., Miljković N., Šekara T.: Electrogastrogram and electrocardiogram interference: Application of fractional order calculus and Savitzky-Golay filter for biosignals segregation, *2020 19th International Symposium INFOTEH-JAHORINA (INFOTEH)*, March 17-19, 2020, East Sarajevo, Bosnia and Herzegovina, pp. 1 - 5 **(M33)**

Miljković N., **Popović N.B.**, Prodanov M., Sodnik J.: Assessment of sickness in virtual environments, *Proceedings of the 9th International Conference on Information Society and Technology ICIST*, March 10-13, 2019, Kopaonik, Serbia, Vol.1, pp. 76-81 **(M33)**

Popović N.B., Miljković N., Papić V.: Video-based extraction of movement artifacts in electrogastrography signal, *Book of Abstracts, Belgrade Bioinformatics Conference (BelBi)*, June 22, 2018, Belgrade, Serbia, Vol. 40, No. 1, pp. 126, ISSN: 2334-6590, DOI: 10.13140/RG.2.2.19753.29280. **(M34)**

Gruden T., **Popović N.B.**, Stojmenova K., Jakus G., Miljković N., Sodnik J.: Electrogastrography as a tool for sickness detection in autonomous vehicles, *Proceedings of the 1st International Congress on Motion Sickness and the collaborative 15th European Society for Clinical Evaluation of Balance Disorders Meeting*, July 7-10, 2019, Akureyri, Iceland pp. in - print **(M34)**

Related research that provided some useful insights and experiences for the Doctoral dissertation is published in following Journal articles and conferences.

Publications in Journals with Impact Factor:

Miljković N., **Popović N.B.**, Djordjevic O., Konstantinović Lj., Šekara T.B.: ECG artifact cancellation in surface EMG signals by fractional order calculus application, *Computer Methods and Programs in Biomedicine*, vol. 140, pp. 259-264, 2017, ISSN: 0169-2607, DOI: 10.1016/j.cmpb.2016.12.017 **(M21, IF2017: 2.674)**

International Conferences:

Popović N.B., Miljković N., Djordjevic O., Šekara T.B.: Artifact cancellation using median filter, moving average filter and fractional derivatives in biomedical signals, *Proceedings of the International Conference on Fractional Differentiation and its Applications*, July 18-20, 2016, Novi Sad, Serbia, pp. 150-161, ISBN: 978-86-7892-830-7. **(M33)**

Cimeša Lj., **Popović N.B.**, Miljković N., Šekara T.B.: Heart rate detection: Fractional approach and empirical mode decomposition, *Proceedings of the 25th Telecommunications forum*, November 21-22, 2017, Belgrade, Serbia, pp. 1-4, ISBN: 978-86-7892-830-7, DOI: 10.1109/TELFOR.2017.8249358, IEEE. **(M33)**

National Conferences:

Popović N.B., Miljković N., Šekara T.B.: Two applications of fractional calculus on biosignal processing, *Proceedings of the 2nd Conference on Measurement Information Technologies (Konferencija merno-informacione tehnologije, MIT)*, December 7, 2018, Novi Sad, Serbia, pp. 1-2, ISBN: 978-86-6022-132-4. **(M61)**

Structure of the Doctoral Dissertation

This Dissertation consists of six chapters. Each of them provides descriptions and explanations of the related topics with state of the art perspective, enhanced with suitable illustrations and graphical presentations of the essential aspects. This Dissertation consists of six chapters. Each of them provides descriptions and explanations of the related topics with state of the art perspective enhanced with suitable illustrations and graphical presentations of the essential aspects. As previously mentioned, this work is primarily based on the two publications in the scientific journals with impact factor [2], [3] and four conference papers [4]-[7]. The Dissertation structure does not follow corresponding publications separately since the aim was to present the Author's overall scientific work. Chapter 1 is introductory, and it aims to provide basic knowledge of the EGG methodology. It is followed by the Chapter dedicated to an explanation of suitable apparatus for EGG recording (Chapter 2). The essential step in acquiring an electrical signal from the stomach smooth muscles is adequate instrumentation. Therefore, in Chapter 2 development process of the custom-made EGG device is presented. With the proper EGG instrumentation, the next step is a definition of the recording protocol described in Chapter 3 with key considerations regarding measurement protocol described in the following subchapters: 3.1. Duration of the Recording Session, 3.2.

Subject Posture, 3.3. Electrode Placement, and 3.4. Fasting or Postprandial? Each of them offers an overview of the current status from the literature, followed by the presentation of published contributions of this Dissertation and corresponding discussions. When EGG signal is suitably recorded, it should be properly analyzed and interpreted, which is the topic of Chapter 4. The main concerns are described in four subchapters: 4.1. EGG Signal Evaluation, 4.2. Artifact Cancelation, 4.3. EGG Signal Feature Extraction, and 4.4. EGG Interpretation. In Chapter 5, one of the most challenging issues in the EGG area is addressed – recording of an EGG signal in a dynamic environment. That was done by presenting the results of two investigations being result of this Dissertation [3], [6], regarding EGG application in a virtual reality environment and during application of driving simulation. The overall conclusion of the research presented in this Doctoral dissertation is presented in Chapter 6.

In Chapter 1. Introduction a brief overview of the anatomy and physiology of the gastrointestinal tract is presented. Bases for the understanding of gastric electrical activity are also provided. A comprehensive historical overview, current status, and perspectives for future work in EGG are presented.

Chapter 2. Instrumentation for EGG recording is written as a guideline for designing and realizing open-source hardware for EGG acquisition. It includes critical considerations, discussion regarding EGG recording with non-dedicated devices, review of commercially available devices, device development procedures, and proposals for further improvement.

The main aspects of the recording protocol are presented in Chapter 3. Recording protocol. It is divided into four subchapters covering the following topics: duration of the recording session, subject posture, electrode placement, and meal intake. Each subchapter incorporated an overview of published results and discussion on possible improvements and a requirement for standardization. In this chapter, important considerations regarding the simplification of the protocol are presented.

In Chapter 4. Analysis and Interpretation of EGG signal essential guidelines for the evaluation, artifact cancelation, and feature extraction of EGG signals are provided. Discussion regarding differences between visual and automated evaluation approach is offered. Existing methods for the processing with the detailed explanations of novel video-based and fractional-based approaches are presented. In addition to the description of commonly used parameters, median frequency, crest factor, and root-mean-square value are introduced as promising quantification techniques.

Chapter 5. Assessment of Gastric Myoelectrical Activity in Dynamic Environment, key takeaways regarding recording in a dynamic environment are provided. Subsequently, studies that included EGG assessment of smooth stomach muscles in healthy subjects during virtual reality and driving simulation experiences were presented and discussed.

The conclusion of the research described in this Doctoral dissertation with suggestions for future work is presented in Chapter 6. Conclusion.

In the Appendix A. Anatomy and Physiology of Gastrointestinal System, a medical basis for the understanding of the processes that take place in the stomach and can be evaluated using an electrogastrography is provided.

Appendix B. Methods for the Assessment of GI System includes an overview of clinically used methods for GI functionality evaluation.

1. Introduction

Smooth muscles are present in many organs of the human body, and they have an important role in processes that happen in the organism. The scope of this Doctoral dissertation is an assessment of the smooth muscles that are the functional part of the gastrointestinal system (GI), more precisely - the stomach.

As a part of GI, the stomach is a hollow organ which main function is storage and mixing of gastric content prior to its digestion and absorption that primarily takes place in the bowels. It can be stated that the mechanical part of the digestion process takes place in the stomach, which is why motility is its core property. Two layers of smooth muscles, circular and longitudinal, that can be found between serosa and mucosa, are responsible for rhythmical contractility of the gut. The question arises: What is the control mechanism behind this rhythmical activity? [8]–[10]

The answer to this question lies in Gastric Electrical Activity (GEA) phenomena, which originates from the pacemaker region of the stomach. This area is populated with specialized cells called Interstitial Cells of Cajal (ICC), which can spontaneously generate electrical current. This automaticity is responsible for periodical contractions of the smooth muscles and the overall motility of the stomach. GEA can be divided into two superimposed components: 1) Electrical Control Activity (ECA) or slow waves, and 2) Electrical Response Activity (ERA) or spike potential. ECA presents as a slow periodical variation of resting potential (period around 20 seconds), while ERA is composed of the action potentials that can only occur when slow wave activity reaches appropriate amplitude. Spike potentials correlate with gastric contractions in a one-to-one manner, whereas ECA controls the maximum rate of those contractions. A detailed overview of GI anatomy and physiology with a specific focus on GEA is presented in Appendix A. [11]–[13]

As described, electrical activity is the control mechanism for the smooth stomach muscles. Its recording and analysis could provide valuable conclusions regarding the functionality of GI. While there are many different GI assessment techniques (see Appendix B), the only non-invasive one that could provide an insight into GEA is Electrogastrography (EGG).

1.1. What is Electrogastrography?

There is a need for a safe and easy way to get a perception of the electrical signals from the gastrointestinal system. The solution can be found in a technique called Electrogastrography. It is a non-invasive method for the recording of the stomach electrical activity via surface electrodes placed on the abdomen [14]. Adjacent terms, electrogastrogram, and electrogastrograph, both abbreviated by EGG, stand for the signal recorded by this technique and the device used for it, respectively (see Figure 1.1.) [15]. Resulting EGG waveform represents slow wave activity, and it correlates with the invasively measured signal from the serosal and mucosal surface [16]. Its frequency in a healthy organism is about 3 cycles-per-minute (cpm) or 0.05 Hz, while the amplitude varies from 0.1 mV to 0.5 mV [2]. Frequency content of EGG signal is discussed in many articles, and in subchapter 1.3.1 overview of this topic will be presented. For the research described in this Dissertation, it was adopted that EGG frequency ranges from 1 cpm to 10 cpm with three sub-bands: 1) bradygastric (1-2 cpm), 2) normogastric (2-4 cpm), and 3) tachygastric band (4-10 cpm) [17]. Analysis of the EGG signal can give an insight into different stomach functionality processes and assist the examiner in making valid conclusions. EGG could benefit the clinicians as an additional diagnostic tool due to its safety and relative simplicity. Feature extraction from the EGG recording can be very challenging, and educated observation of an expert could be required. An example of an EGG signal recorded from surface electrodes placed on the abdomen is presented in Figure 1.1. As it can be observed, it is required to have an adequate EGG device that will provide initial processing of raw electrical signal acquired by the surface electrode in order to have reliable EGG timeseries.

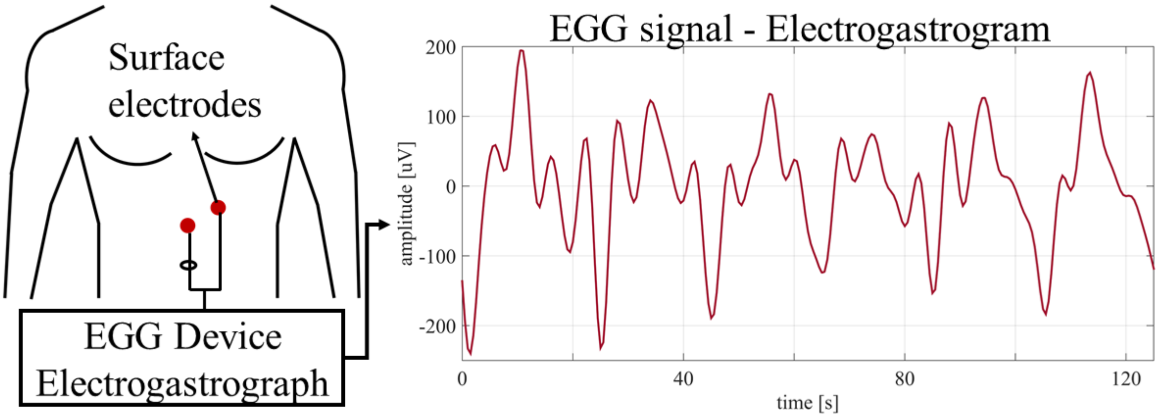


Figure 1.1. Diagram of the recording process with the example of the signal. EGG timeseries used in this Figure is retained from the open-source EGG database (subject ID9 postprandial) [18].

1.2. Historical Overview of Electrogastrography

After the initial introduction of electrogastrography by Alvarez [1] in 1922 for the following six decades, EGG was measured mainly from the mucosal or serosal membrane due to the inadequate equipment for the recording of low amplitude signals from the non-invasive electrodes placed on the skin [16]. It was reported in [19] that up until the 1960`s it was unclear if the signal acquired by EGG actual representation of GEA or an artifact produced by stomach motility. However, now it is clear that EGG provides a reliable recording of slow wave activity. Since then, advancements in signal acquisition and signal processing methods are continuously led to the further introduction of EGG in research and clinical practice.

In one of the first review articles by Stern et al. in 1987 [20], authors provided four important conclusions: 1) 3 cpm EGG activity correlates with the one recorded from the mucosal and serosal surface, 2) enhanced stomach contractility is represented as an increase in EGG amplitude, 3) tachygastric EGG activity also correlates with mucosal recordings, and 4) low EGG frequency (~1cpm) remain unexplained from the physiological point of view. In 1989 Pezzola and colleagues reported that EGG could be a useful tool for investigating unexplained nausea and vomiting [14].

During the 1990`s interest in EGG increased [19]. In 1996 Lindberg et al. [21] presented results of the study conducted in 30 healthy volunteers using a 24-hours ambulatory recording. Although some interesting findings regarding an increase in DF in the postprandial state were found, the main conclusion was that further improvement of recording equipment is needed. Similar insights were presented by Bortolotti in terms that “the future of EGG rests in the hands of the electronic engineers“ [22]. Mintchev, with his associates during the late 1990`s investigated the impact of external factors [23], the thickness of the abdominal wall [24], as well as effects of internal tachygastria [25] on EGG, and in the review article [26] concluded that cutaneous EGG recording highly correlates with internal Gastric Electrical Activity (GEA) and that it can be used for Gastric Motility Assessment (GMA). The introduction of Multichannel Electrogastrography (M-EGG) opened a possibility for investigating slow wave propagation by detecting a time lag between channels [27].

In 1993 Chen and McCallum [28] reviewed the potential of EGG application in clinical practice. It was suggested that EGG could be used as an effective additional diagnostic tool for many gastrointestinal disorders. Gastric dyspepsia, non-ulcer dyspepsia, chronic idiopathic intestinal pseudo-obstruction, cyclic vomiting syndrome, idiopathic gastroparesis, nausea in pregnancy, *helicobacter pylori*, irritable bowel syndrome, and central nervous system disorders in children, are some of the conditions evaluated by EGG [29]–[36]. It was reported that these pathologies can affect EGG signal in the following manners: 1) occurrence of tachygastria, 2) occurrence of bradygastria, 3) inability to determine gastric rhythm, 3) absence of the dominant peak in the spectrum of the signal, and 5) absence of postprandial increase in EGG signal power [35].

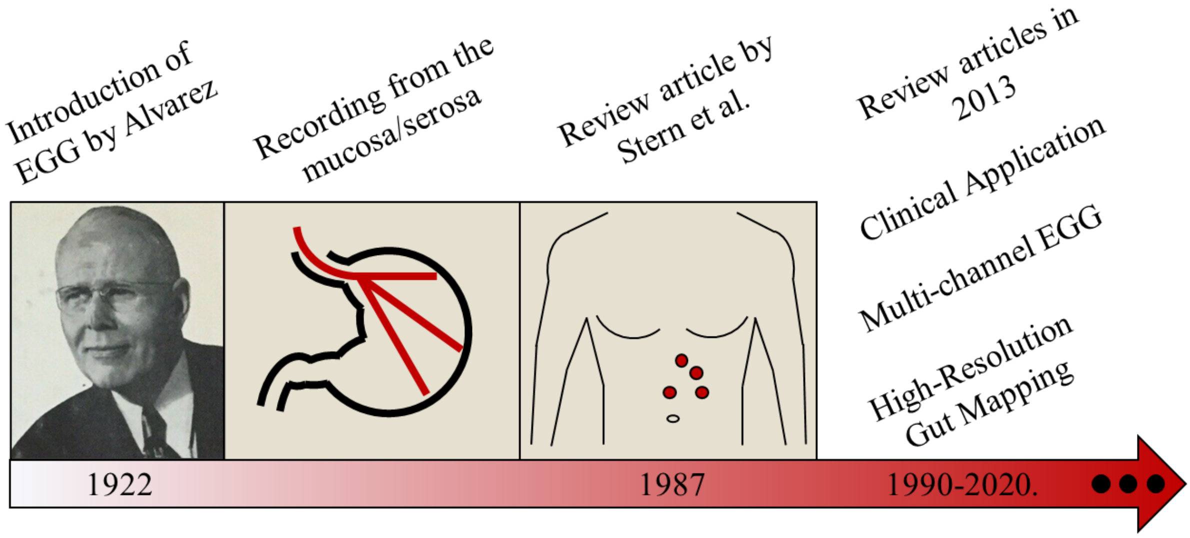


Figure 1.2. Graphical representation of the historical development of EGG. Portrait image of dr Walter C. Alwarez, public domain.

A multicenter study published by Simonian et al. in 2004. explored effects of gender, age, Body-Mass Index (BMI), and study location on EGG-based parameters [37]. While the Authors concluded that gender and age did not affect EGG, it was reported that subjects with BMI > 25 had a decrease in absolute Dominant Frequency (DF) and postprandial decrease in Percentage of Slow Wave Coupling (%SWC). Also, compared to American, in

European/Asian volunteers decrease in %SWC was reported. Reproducibility of EGG was investigated in [38], and it showed that parameters describing frequency content have better reproducibility than the ones regarding the power of the signal. It was also reported that gender, test meal, and GI disorders do not affect the reproducibility of the parameters [39].

1.3. Current Status of EGG

Today, EGG is accepted as a reliable gastric electrical activity assessment technique, but it still remains mainly experimental methodology, without wide clinical application. The main reason for this is the lack of standardization regarding recording equipment, protocol, and signal analysis and interpretation. As one of the main aims of this Dissertation was to provide Author`s insights related to this issue, in this subchapter, a brief introduction into the current status of EGG will be discussed.

From the document prepared by the gastric section of the American Motility Society Clinical GI Motility Testing Task Force [40] and review articles prepared by Murakami et al. [16] and Riezzo et al. [17], the following conclusions on the status of EGG can be listed:

1. There are many issues that need to be addressed prior to the implementation of a surface EGG in standard clinical practice.

2. There are no standard recommendations for EGG recording protocol. Resolving of this issue could result in a much wider application of the technique in the future.

3. When appropriately recorded, EGG is a valid measure of gastric electrical activity, and it can be a powerful diagnostic tool.

To present a more detailed insight into the current status of the EGG, answers to the following questions should be provided:

1. What is the most commonly used methodology for the recording and processing of EGG?

2. What features are used to describe EGG signal?

3. In what clinical applications is EGG used?

Although EGG signals are commonly acquired with low sampling rates (< 4 Hz), some researchers are suggesting that it could be beneficial to record EGG signal with higher rates (> 100 Hz) in order to have additional information regarding heart rate variability, breathing, or even a possibility to reconstruct spike potentials [41]–[43]. While many researchers recommend the usage of a long-term protocol (> 1 hour) [37], [40], the latest trends go towards a shorter duration of recording (20 minutes) [16], [2]. It has been suggested that the subject should be in a supine position to 45° inclination during the recording session [16], [17], [40], [44]. In the study designed to investigate the effects of posture on EGG acquisition, it is concluded that recording can be obtained suitably in a sitting position if the guidelines are carefully followed [45]. Several different approaches for surface electrode placement were introduced, including our 3-channel setup [2], [26], [44], [46], [47]. The general principle is to use more than one bipolar channel due to the increased robustness of the protocol and the possibility to compare recordings from different channels. While artifacts with frequencies higher than EGG range are relatively simple for cancelation, one of the main setbacks for wider implementation of the method are movement artifacts that can have similar frequency content as EGG [16]–[17], [26], [44], [48], [49]. So far, the most reliable way for cancelation of motion artifact is manual extraction of compromised samples detected by educated visual observation [50].

Dominantly used parameter for the description of EGG is dominant frequency – position of the highest amplitude peak in the frequency spectrum [51]. Percentage of time, while DF is in each of the three frequency sub-bands (bradygastric, tachygastric, and normogastric), is also a frequently used feature [16]. Differences between the definition of three characteristic EGG ranges have a negative influence on the reproducibility of EGG analysis. This is why in subchapter 1.3.1. a detailed discussion of that issue is provided. Power of the signal can be used both independently and as a value used for the calculation of Power Ratio (PR) between the postprandial and fasting EGG [17]. Percentage of slow wave coupling can be calculated only for multichannel EGG, and it presents percentage of time during which dominant frequencies are similar between different channels [16]. The Instability Coefficient (IC) estimates level of DF variation – it is a ratio between standard deviation and mean value of DF [17].

Today, despite the fact the EGG is not widely used in clinical practice, its medical application is not insignificant [35]. It is proven that many conditions and disorders can be evaluated using slow wave assessment: nausea and vomiting at pregnancy, motion sickness, central nervous system disorders in children, gastroparesis, diabetic gastropathy, Irritable Bowel Syndrome (IBS), gastric dyspepsia, etc. [14], [16], [29], [30], [32], [40], [33]–[53].

The new trend in the assessment of gastric electrical response is High-Resolution (HR) mapping of the gastrointestinal tract [54]. This concept is inspired by cardiac electrophysiology, and it is based on the application of dense array electrodes placed on the tissue in order to track fine spatial electrical activations of cells [50]. There are some controversial findings suggesting that the effects of movement artifacts are much severe than it was thought [49], but the latest results had proven the validity of the method [50], [55]–[57]. Despite the fact that by using HR mapping, more detailed insight into electrical activity of GI system could be obtained, the development of non-invasive methods such as cutaneous EGG is still “a key need“ in this field [50]. Application of active electrodes, which can be described as a minimally invasive procedure, was described and investigated in [58].

1.3.1. EGG Frequency Ranges – Different Approaches

As EGG field evolved, different frequency ranges for the calculation of corresponding parameters were used. In the middle 1980s, Abell and his colleagues stated that the normal frequency of EGG ranges from 1 cpm to 6 cpm and that everything above and below those limits can be classified as tachygastria and bradygastria, respectively [59], [60]. Over the course of time, investigators tended to use the narrower band for normogastria. Thus, in 1998. Sanmiguel et al. proposed the following frequency bands: 1) 1.0-2.5 cpm – bradygastria, 2) 2.5 – 3.7 cpm – normogastria, and 3) 3.7-10.0 cpm – tachygastria [26]. These standards were accepted with slight changes by Stern et al. – the upper limits for normogastria and tachygastria were changed to 3.75 cpm and 9.00 cpm [12]. In a more recent work following values were proposed for bradygastria, normogastria, and tachygastria, respectively:

1. Murakami et al. 2013 [16] – 1.00 cpm to 2.25 cpm, 2.25 cpm to 3.75 cpm, 3.75 cpm to 9,.0 cpm;

2. Yin et al. 2013 [19] – 0.50 cpm to 2.00 cpm, 2.00 cpm to 4.00 cpm, 4.00 cpm to 9.00 cpm;

3. Riezzo et al. 2013 [17] – 1.00 cpm to 2.00 cpm, 2.00 cpm to 4.00 cpm, 4.00 cpm to 10.00 cpm

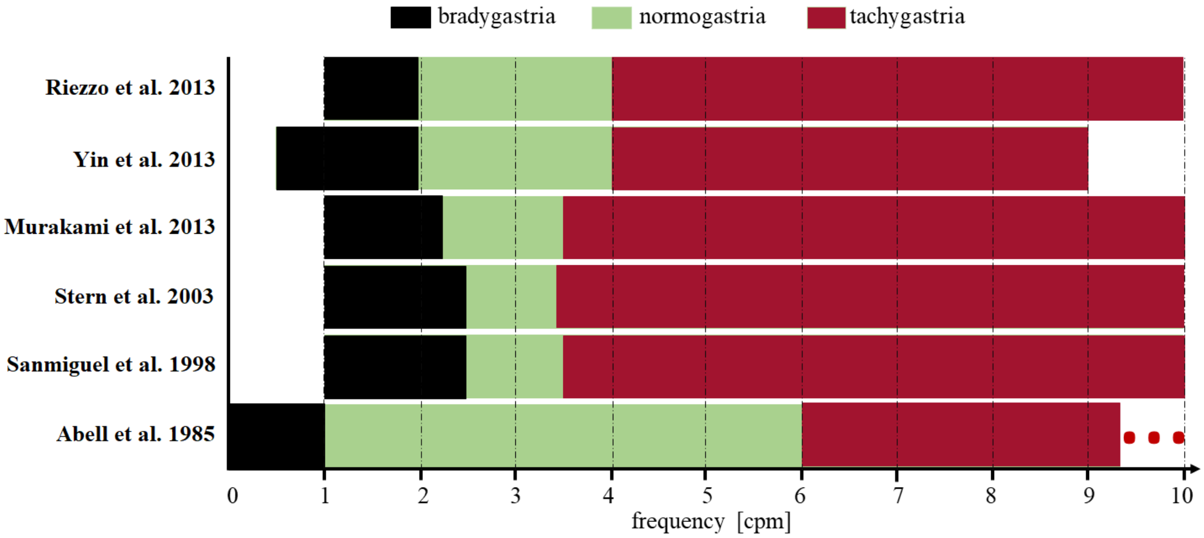


Figure 1.3. Proposal for EGG frequency ranges derived from literature and graphically represented.

In this research, approach from Riezzo et al. was adopted [17]. Rationale behind that was to have the widest range of both normogastric and overall EGG range since there is no enough data that supports narrowing of corresponding bands. Our attitude was to be careful when determining something as abnormal gastric rhythm without clear evidence for that.

1.4. Further Improvement of EGG

Although crucial steps in EGG development have been made, there is still a lot of potential for further improvement. Additional efforts regarding different segments of the recording and processing techniques could be enhanced in order to enrich application of EGG in both clinical and research domains. The main aspects that should be revised include: 1) instrumentation, 2) protocol, 3) signal processing, 4) feature extraction, and 3) spectrum of application.

Devices for EGG recording nowadays offer relatively good signal quality and reliability, confirming that the first and the most important step in its development is finished.

The secondary goal should be to establish correspondence with today's sophisticated technological trends to make these devices easy-to-use and, by that, receptive to a broader range of consumers.

The recent trend in that area is the wireless transmission of the signal, and the first prototypes are already tested with satisfactory results [41], [61]. It should be mentioned that Poscente and colleagues published their research regarding an ingestible capsule that contains an electrical circuit for the recording of gastric electrical activity in the method called Enhanced Electrogastrography (EEGG) [62]. Optical mapping of gastric slow wave propagation presented in [63] is an exciting approach that uses different sensors but should deliver a similar signal. Software solutions for the visualization and analysis of the signal are available, but without a clear response from the end-users. Evaluation of the developed EGG interfaces by the clinicians and researchers in the corresponding area could be crucial for further improvement. As an increasing tendency in biomedical engineering worldwide, open-source hardware and software could attract many innovators to contribute [3].

Without the standardization of the EGG recording protocol, EGG will remain limited to the research and relatively unapplicable in the clinical practice. Time consumption combined with the complex recording setup for someone without engineering background results in a lack of interest in the method. Its simplification by minimizing session time duration and delivering clear guidelines for electrode placement and device manipulation could increase the end-users' attention. Results published in [2] suggested that for some relevant parameters, only one recording channel for 20 minutes protocol could be a suitable solution. Additional protocol considerations related to the body posture, test meal, different stressors that could induce alterations in EGG signal should be thoroughly examined.

Electrogastrogram is still challenging to process properly in order to extract artifacts and preserve all useful components. Specifically, the low frequency spectrum of EGG is the main reason why traditional digital filtering gives promising results since there is a minimal overlapping with other electrophysiological signals. Despite that, there are still many problems related to the detection and cancellation of movement artifacts in EGG recordings in a dynamic environment. Besides, there are also breathing artifacts, electrical signals from skeletal muscles and hearth, and activity from other parts of the GI system that could interfere with the signal of interest. While it is considered that educated visual inspection is the most reliable way to discriminate between slow waves and noise [50], there are still expectations that automatic algorithms could substantially advance EGG signal preprocessing. Some of the proposals include the application of neural networks, adaptive filtering, Independent Component Analysis (ICA), and Empirical Mode Decomposition (EMD) [64]–[67]. In [5], video-based artifact cancelation was proposed by synchronously recording video and EGG and by rejecting erroneous parts of the signal. Results regarding the application of fractional order calculus for extraction of Electrocardiographic (ECG) artifacts from electrogastrographic recordings were presented in [4].

Commonly used parameters for the description of EGG listed in subchapter 1.4.3. could be supported by the addition of novel features. Especially when the analyzed signal is recorded in non-standard conditions, alternative approaches for quantification of frequency content could be beneficial. Crest factor and median frequency were suggested in [3], [6] as the possible alternatives. While the spectrum remains the first step in the analysis of EGG, some signal power estimators, such as RMS, derived from the time domain, showed to be useful parameters for the determination of EGG alterations [3].

As for any diagnostic technique, clinical application is imperative. The path to that goal could be through the research studies obtained in healthy subjects. In that journey, EGG could become a useful tool for many other fields. There are many ideas on how recording stomach electrical activity could help researchers evaluate the effects of different stressors on the human organism. Driving Simulators (DS), both with and without motion feedback, can induce stomach distress [68]. Virtual Reality (VR) application is limited by the occasional onset of nausea reported by the users [69]. Also, various types of emotional stress affect the gut [70], [70]–[74]. These are all examples in which the application of EGG can offer additional insight and help the developers with the improvement of existing systems.

2. Instrumentation for EGG Recording

The main prerequisite for a successful recording of the electrophysiological signals is suitable and reliable equipment. Essential parts of the EGG recording system include: 1) surface electrodes, 2) amplification and filtering circuit (i.e., EGG device), 3) Analog-to-Digital (A/D) converter, and 4) acquisition software (see Figure 2.1.). The device should be dedicated for EGG due to the specific requirements for signal amplification and filtering, while A/D conversion and software could be commercially available ones.

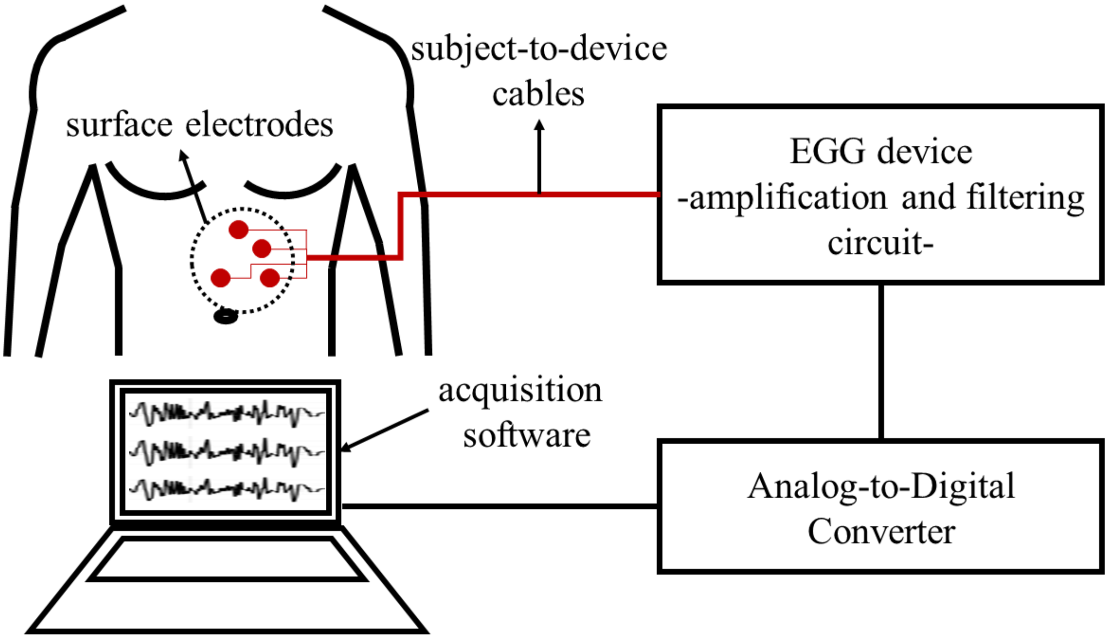


Figure 2.1. Schematic presentation of the EGG recording equipment.

2.1. Key Considerations

Among the variety of considerations that should be considered when developing an EGG device, the key ones are: 1) properties of the signal, 2) artifact presence, and 3) amplification and filtering.

2.1.1. Properties of the Signal

Characteristics of the electrophysiological signal are an important aspect to consider when choosing or designing a recording device. The nature of the slow wave activity makes EGG highly challenging in the means of signal acquisition. Namely, as discussed in Chapter 1, amplitude of the signal is varying from 0.1 mV to 0.5 mV, and frequency range is from 1 cpm to 10 cpm. Compared to the most commonly recorded electrophysiological signals, amplitude is lower than in the electromyography (EMG) – 0.00 mV to 10.00 mV and electrocardiography (ECG) – 0.01 mV to 4.00 mV, while it is comparable with electroencephalography (EEG) – 0.01 mV to 0.10 mV [75]–[77]. This dictates a relatively high gain of amplification circuit or alternatively high-resolution analog-to-digital (A/D) conversion [47]. Additionally, hardware filtering is essential in order to avoid high frequency signals that are not informative in terms of gastric electrical activity, as well as baseline drift that may lead to saturation. Properties of EGG timeseries are illustrated on the example of the signal recorded in healthy volunteer presented in Figure 2.2.

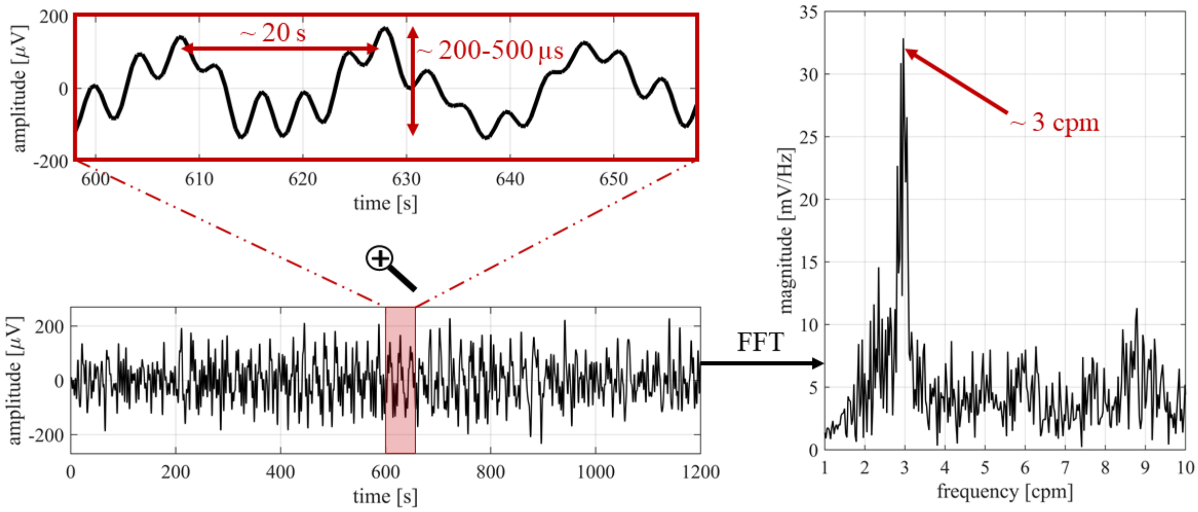


Figure 2.2. Properties of EGG clear signal marked on the signal recorded in a healthy subject. Lower left panel – EGG timeseries, upper left panel – zoomed EGG, right panel – frequency characteristic of EGG. Signal was retained from the open-source EGG signal database [18].

2.1.2. Artifact Presence

The presence of various artifacts in the EGG signal can also lead to unreliable recordings. Base on its origin, noise can be classified as physiological or non-physiological.

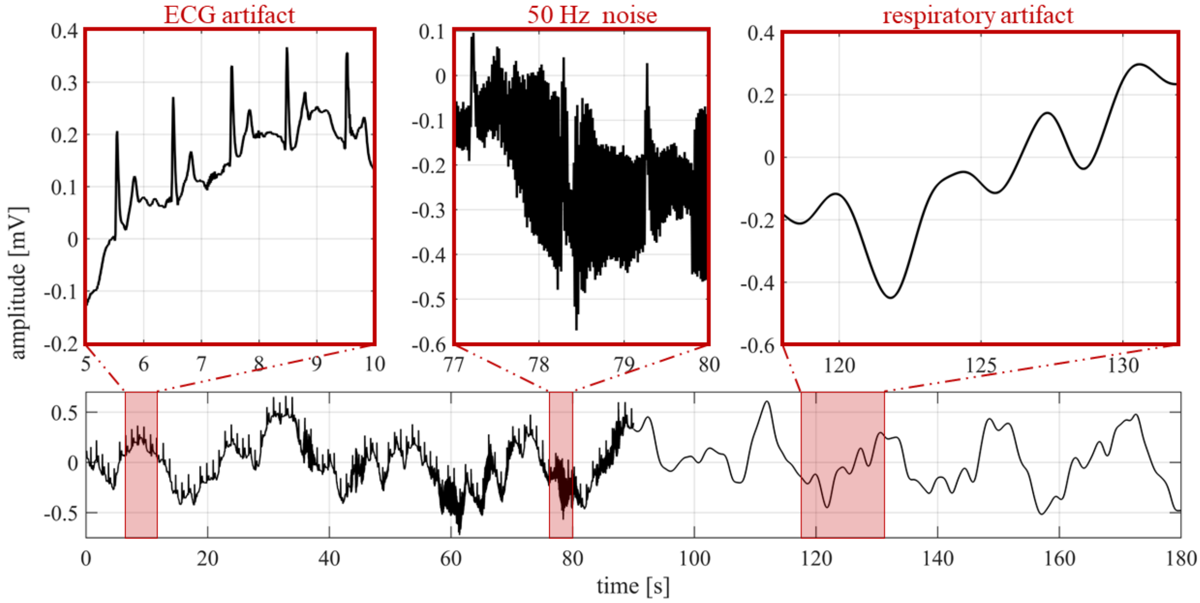


Figure 2.3. Illustration of EGG artifact presented signal recorded with a sampling rate of 100 Hz.

The physiological ones include interfering electrical activity from the hearth – electrocardiography, skeletal muscles – electromyography (EMG), and distal parts of the GI system relative to the stomach. Respiration signal can also be superimposed to slow waves. The non-physiological ones are electromagnetic interference (EMI) from the power grid with 50 Hz or 60 Hz frequency and the ones coming from the movement of the subject and cables. While most artifacts could be extracted from the signal by applying digital filtering techniques with appropriate cut-off frequencies, the ones with frequency range overlapping with EGG one (most commonly movement artifacts) could be much more challenging for cancelation. Although there are some proposals for automatic extraction of those motion induced signal disturbances, the most reliable method for their detection and extraction is a visual inspection performed by an educated observer. In Figure 2.3. simulated EGG signal compromised with various artifacts is presented. [12], [40], [48], [49], [53], [55], [64]–[66], [5], [78], [79]

2.1.3. Amplification and Filtering

Delivering the suitably filtered and amplified analog signal to the A/D converter is one of the prerequisites for reliable EGG recording. Therefore, it is crucial to carefully evaluate a selection of hardware amplifiers and filters that should be implemented in EGG device. Considering the nature of the signal (amplitude from 0.1 mV to 0.5 mV), a relatively high gain is required (~1000), which can amplify the DC component, resulting in a saturated output signal is presented in Figure 2.4.

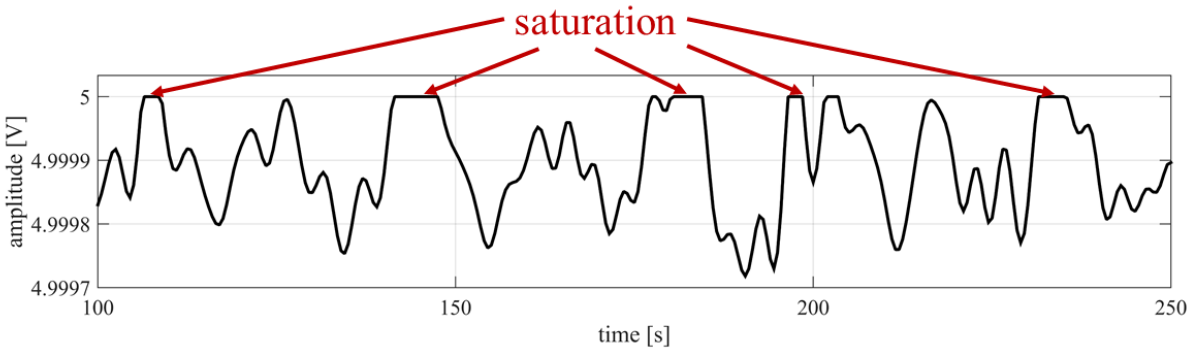


Figure 2.4. Example of saturated output signal if DC component is not canceled out from the signal using hardware HP filter.

Cancelation of DC component from the slow wave signal can resolve the saturation problem. That can be done using a high-pass (HP) filter with the careful selection of filter design and cut-off frequency in order to preserve the EGG range of interest. Higher quality factor (Q) in active filters, compared to the passive ones, suggests that they are more suitable. Cut-off frequency should be equal to or less than 1 cpm (0.0167 Hz), which is the lower limit of EGG frequency range [17]. A low-pass filter should also be included in the EGG recording device to extract the higher frequencies artifacts, as described in subchapter 2.1.1.

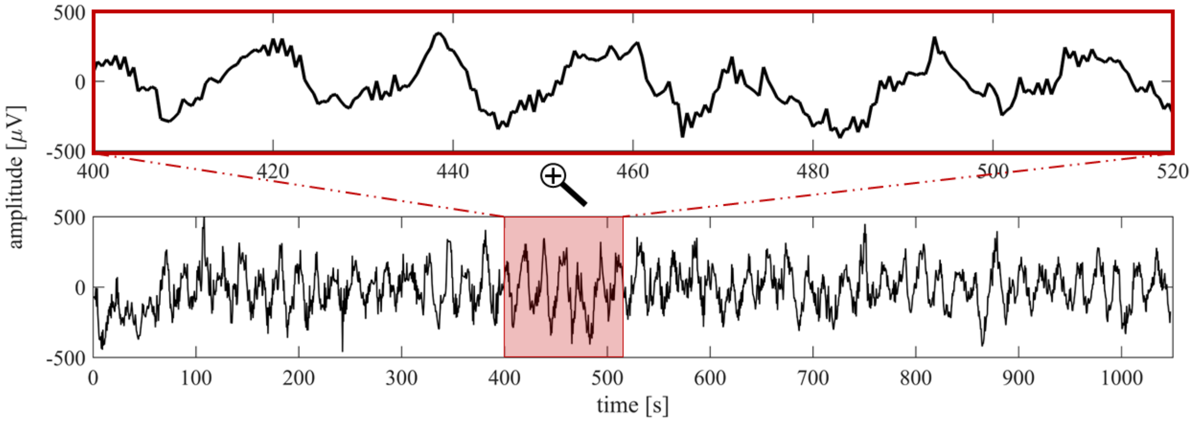


Figure 2.5. Example of the suitable EGG signal after hardware amplification and filtering, prior to the A/D conversion and software preprocessing.

An illustrative example of what is expected as an output signal from an EGG device resulting from a static recording obtained in a healthy subject is presented in Figure 2.5. Timeseries should have a clear sinusoidal shape with amplitude in the expected range, without saturation in any part of the signal.

2.2. EGG Recording with Non-dedicated Devices

In this context, non-dedicated devices are the ones used for all other electrophysiological measurements except EGG. It is customary that measurement equipment includes ECG, EMG, and EEG recording devices in many laboratories for biomedical research. Usage of those devices for gastric electrical activity acquisition could expand interest in EGG research, but the question arises: Are they suitable for EGG measurement?

It is not uncommon for the biosignals to present with baseline drift during recording because of subject and cable movements, breathing, or another external artifact. This could be resolved with the implementation of HP filters in order to cancel out components of the signal with frequencies lower than the ones of interest. For EMG and ECG, frequency range is from 20 Hz to 1000 Hz and from 0.05 Hz to 100 Hz, respectively [76], [80]. Consequently, devices for its acquisition have HP cut-off limit higher or equal to 0.05 Hz, which discards both EMG and ECG amplifiers as potential apparatuses for slow wave recording. On the contrary, EEG frequencies range from 0.01 Hz to several hundred Hz [81], and the corresponding devices should be able to acquire signals in that range suitably. Technical specification of those devices should be checked prior to the recording and confirmed that the frequency range is suitable for the EGG recording. Amplitude range of EEG and EGG is comparable, so the amplification should be appropriate.

It was reported that EGG could be recorded using EEG dedicated DC amplifiers [47]. The authors in those papers stated that it is possible to measure EGG signals with EEG devices constructed out of DC filters combined with a large analog-to-digital conversion range. Devices that were used are BioSemi (BioSemi B.V., Amsterdam, Netherlands) and BioMag (BioMag Laboratory, Helsinki, Finland) systems [47]. Comparable amplitudes between the EEG and EGG signals suggest that this is possible, but only if lack of HP filter does not result in high amplitude baseline drift that could lead to signal saturation, and consequently, distortion of the signal. An interesting approach was described in the Doctoral dissertation entitled “Feasibility of incorporating electrogastrography into an undergraduate physiology laboratory curriculum” by Lauren Foropoulos [82]. Electrooculography (EOG) device ML317 (ADInstruments Ltd., Dunedin, New Zealand) was used for EGG recordings. Considering the fact that this device has a frequency range from DC to 500 Hz and an amplification gain of 1000 is comparable with EEG devices, in terms of EGG application, used in previously discussed research [47].

2.3. Commercially Available Devices

As the need for a reliable EGG recording system increased, various companies producing medical devices worked on its development. During the last few decades, different commercially available solutions were released. In this subchapter, the most commonly used instruments will be presented.

One of the companies dedicated to the research and development in EGG is 3CPM Company (Sparks, Maryland, USA). Their solution offers a comprehensive system including the amplifier, connector cables, A/D converter, and software. It is designed to record signals with a frequency range from 1 cpm to 15 cpm. Two recording channels are incorporated, one for EGG recording and one for respiration signal, in order to detect breathing artifacts in EGG. After the acquisition, the signal is stored, and Fourier transformation is performed. Produced report includes a Running Spectrum Analysis (RSA) plot and distribution of the power in the four frequency ranges (bradygastric, normogastric, tachygastric, and respiratory-duodenal). In many publications [31], [83]–[85], signals acquired via described device were used. [86]

Biopac Systems, Inc. (Goleta, California, USA) offers EGG recording module EGG100C as a compatible part of their complete research system solution, with corresponding cables, A/D converters, and analysis software. It is a single channel module, with the possibility of recording more than one channel using multiple modules. This device incorporates filters with adjustable cut-off frequencies: High-pass (DC, 0.005 Hz or 0.05 Hz) and Low-pass (0.1 Hz or 1 Hz). Gain can also be set to 500, 1000, 2000, or 5000. [87]

One of the solutions is BioSignalPlux EGG Sensor from the PLUX – Wireless Biosignals, S.A. (Lisbon, Portugal). It is a wearable device for the user-friendly acquisition of gastric electrical activity. Since it gives analog output, it should be connected to the BioSignalPlux hub in order to digitalize signal. It has a gain of 6114 and bandwidth from 0.01591 Hz to 0.1591 Hz. The possibility of multichannel recording is available by connecting more than one EGG sensor to 4-channel or 8-channel hub. [88]

Although it is still not commercially available, it is worth mentioning the EGGDWPack system [41]. This is a novel Matlab (Mathworks Inc., Natick, MA, USA) based software compatible with the wireless 4-channel EGG recording device described in [89]. It incorporates preprocessing methods for artifact cancelation and digital filtering of the raw signal. The main innovation includes in this tool is the possibility to analyze heart-rate-variability (HRV) from EGG signal if it was acquired with appropriately high sampling frequency.

It should be mentioned that one of the first commercially available, FDA approved solution was provided by Medtronic Inc. (Dublin, Ireland). However, publicly available technical data regarding that device is scarce.

2.4. Device Development

The research covered in this Doctoral dissertation was based on the analysis of the signals recorded using a custom-made EGG sensing system [3]. This device can be described as a 3-channel EGG recording amplifier with appropriate hardware filters for the extraction of non-EGG components of the signal. It receives input from the cables connected to the surface electrodes attached to the subject`s body and delivers an analog output signal that should be further digitalized.

2.4.1. Motivation for Device Developement

Lack of standardization in the area of a non-invasive recording of gastric myoelectrical activity includes instrumentation related issues. Namely, there are no clear guidelines regarding the requirements that need to be fulfilled to declare EGG device reliable for the acquisition of slow wave activity from the abdominal surface. Common problems with EGG recording, already discussed in subchapter 2.1., demand a relatively high level of engineering knowledge in order to design a suitable acquisition circuit. Unlike other diagnostic techniques (electromyography, electrocardiography, or electroencephalography) for electrogastrography, there is limited literature regarding the technical details of the recording apparatus. Thus, documented experience concerning the process of EGG device production could be a significant contribution to this area. Every additional resource could be beneficial for further improvement in the field. Also, the aim was to introduce an open-source EGG device available for researchers and encourage all of them to participate in the further development of the designed device. It is our belief that this is the most appropriate direction towards overall advancement in EGG equipment by sharing knowledge and interactively work with the scientific community on common issues.

2.4.2. Signal Acquisition Circuit

In this context, a signal acquisition circuit is defined as a hardware part of the EGG device that performs initial processing of the EGG signal from the surface electrodes and delivers suitable output to the A/D converter. Considering the nature of the signal, its three main tasks are: 1) amplification, 2) filtering of the baseline drift, and 3) cancelation of artifacts with frequencies higher than EGG range.

An instrumentational amplifier was used for the amplification due to its proven performance in the measurement equipment for biomedical applications. As for any differential amplifier, it is expected to extract common potentials that could be a problem when recording from the abdominal area of the body abundant with different biosignals. The device of choice was INA114BP with a common-mode rejection ratio (CMRR) of 115 dB and settable gain from 1 to 10000. Additional features beneficial for the specific use are: 1) low-cost, 2) operability on low power supply ±2.25 V that allows usage of battery supply, and 3) low offset voltage of 50µV maximum. The gain was set to 1000 using a 50 Ω resistor.

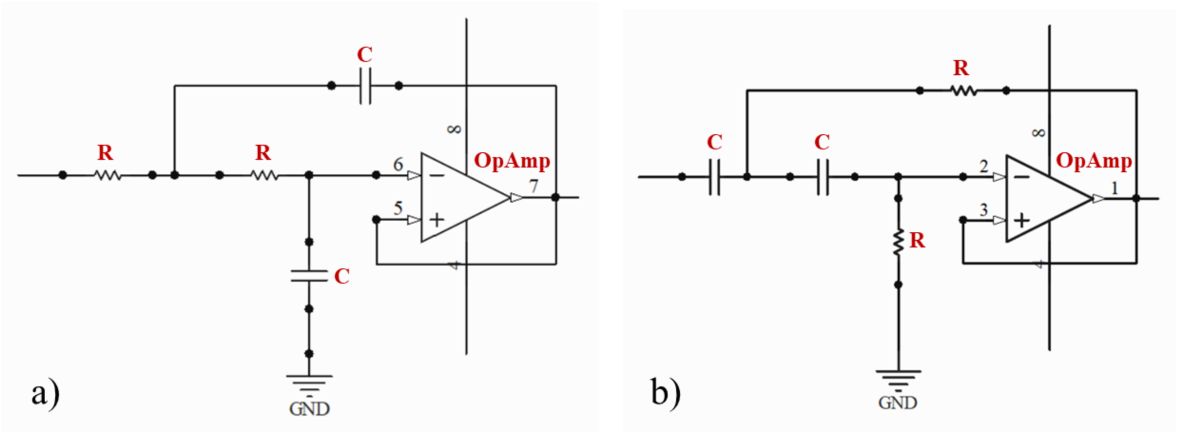


Figure 2.6. Sallen-Key topology for a) low-pass (left-hand panel) and b) high-pass (right-hand panel) filter. C stands for a capacitor, R for a resistor, and OpAmp for an operational amplifier.

For the filtering part of the circuit, both low-pass (LP) and high-pass (HP) filters were realized as active 2nd order filters in Sallen-Key topology (see Figure 2.6.). To minimize the number of components, the most suitable option was dual operational amplifier TL072CP since one chip was sufficient for both HP and LP filter. Values of capacitors and resistors in Sallen-Key topology are determining cut-off frequency. For the LP filter, 2.2 µF capacitors and 15 kΩ resistors were used in order to have a 4.820 Hz cut-off frequency. In the same manner, 1 µF capacitors and 10 MΩ resistors gave 0.014 Hz HP cut-off frequency. Schematic for one channel of the device is presented in Figure 2.7. a), while values of the components are declared in Table 2.1. The complete device consisted out of three separate channels. [rreferenca1]

Table 2.1. Components of the designed EGG device.

Amplification		**LP filtering**			**HP filtering**		
Instrumentational amplifier	R_g	Operational amplifier	R_{lp}	C_{lp}	Operational amplifier	R_{hp}	C_{hp}
INA114BP	50 Ω	TL072CP	15 kΩ	2.2 µF	TL072CP	10 MΩ	1 µF

In Figure 2.7. b) frequency characteristic of the device is presented. It was calculated using an automatic system for frequency response analysis designed in a free software environment. The system included the following: 1) waveform generator - 33220A (Keysight Technologies, Inc. Santa Rosa, CA, USA), 2) digital oscilloscope - TBS 1052B-EDU (Tektronix, Inc. Beaverton, OR, USA), 3) personal computer - Ubuntu 16.04 LTS operating system, and 4) DC power supply - E3630A (Keysight Technologies previous Agilent). In total, 41 points were used to determine frequency characteristics in the range from 0.010 Hz to 100 Hz. The software that was used was designed in Python (Python Software Foundation, Wilmington, DE, USA). All three recording channels were tested, and the difference between their characteristics was less than 2%. In Figure 2.7. characteristic for channel 1 was plotted. [27]

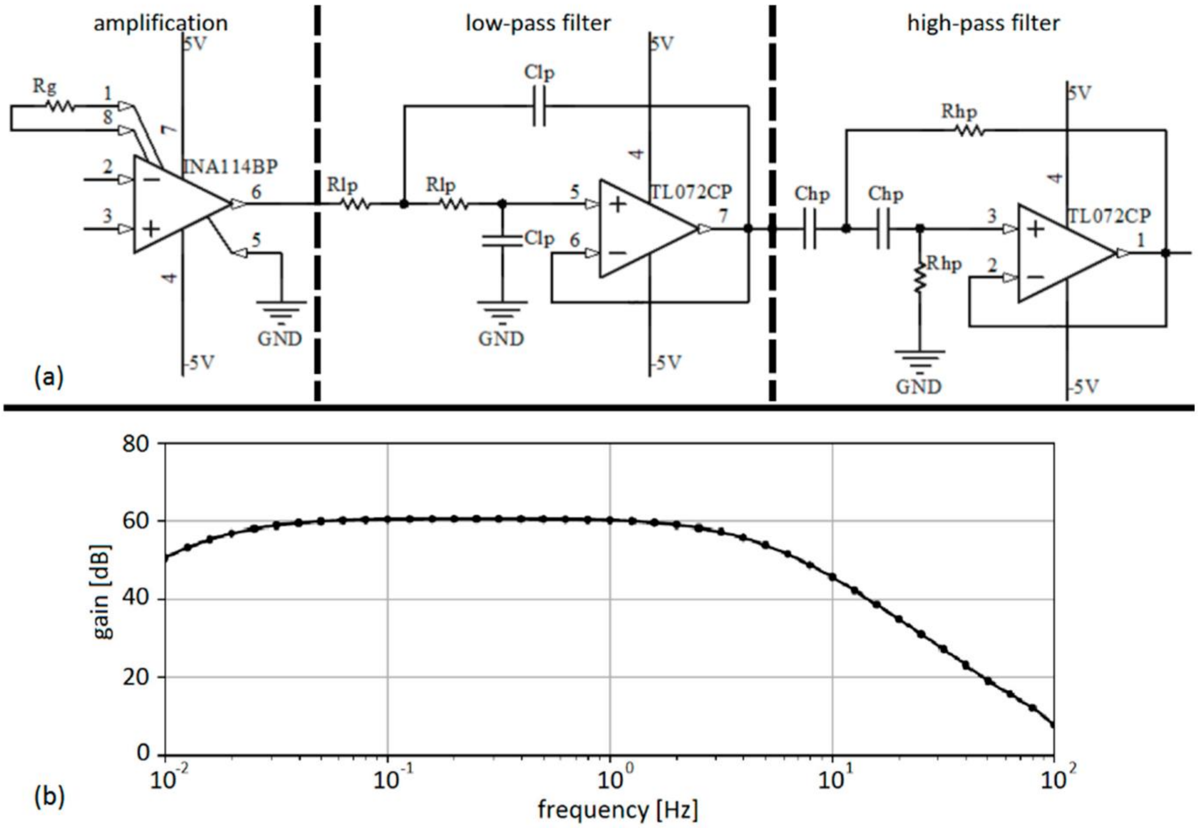


Figure 2.7. a) Schematics for one channel of the EGG device. b) Frequency characteristic of the EGG device. Image is taken from [3]. (License: CC BY 4.0)

The device was assembled on the protoboard, and power supply (±15 V) was obtained from NI ELVIS II (National Instruments Inc., Austin, TX, USA) workstation, as well as A/D conversion [77].

2.4.3. Acquisition Software

An essential part of the EGG recording apparatus is acquisition software. Acq16ch program developed by N. Miljković, J. Jakić, and J. Jović, as a part of N. Miljković`s Master Thesis [90], and it was used for the acquisition in investigations published in [2], [3], [5]–[6]. The main properties that qualify this tool for the application as a part of the EGG recording are the following:

1. It can record up to 16 channels, which is vital for multichannel EGG application.

2. Option for manual sampling frequency setup allows investigators to record EGG with various sampling rates.

3. Data storage to .txt file makes obtained signals open for further processing in various programming tools.

A screenshot of the Acq16ch interface is presented in Figure 2.8.

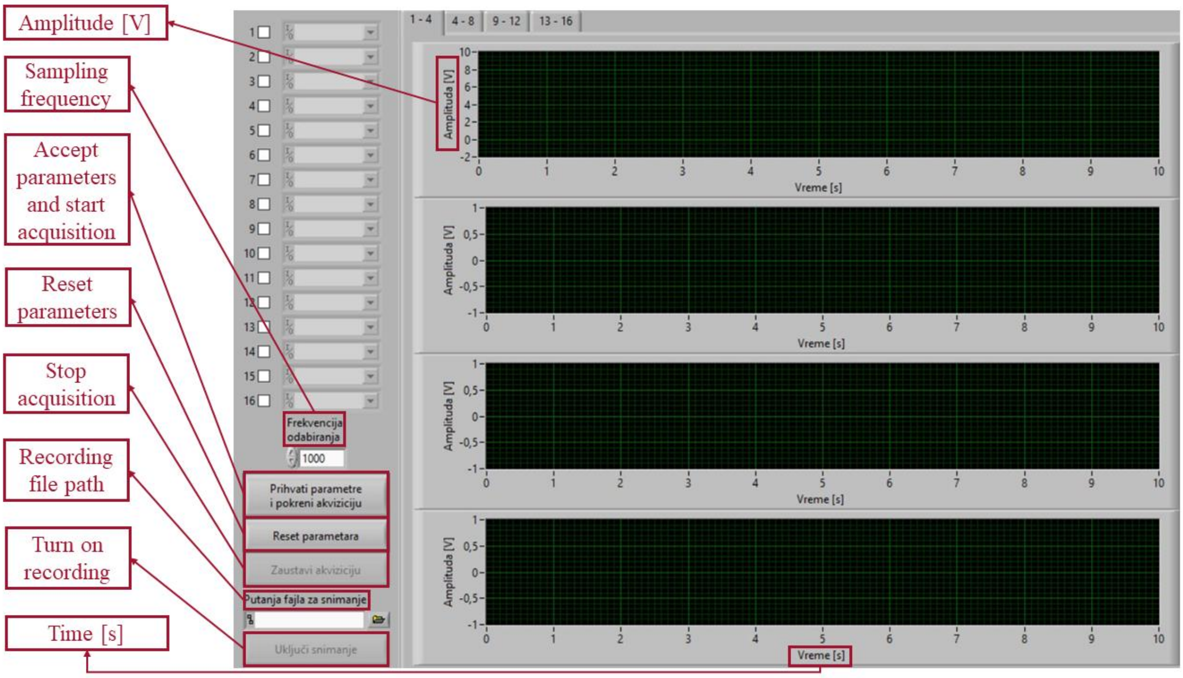


Figure 2.8. The interface of Acq16ch acquisition software.

2.4.4. Discussion of Scientific Contribution of the Designed EGG Device and Its Application

As it was discussed in subchapter 2.1.3. the main challenge in the development of the custom-made EGG device was the design of HP filter with the cut-off frequency low enough not to interfere with frequency range of interest, and at the same time high enough to cancel out DC component and baseline drift.

The proposed methodology for analogue realization of the instrument with active filter provided appropriate frequency response of the system. In order to evaluate the frequency characteristic of the EGG device with very low frequencies, we applied a modified version of the automated system for frequency characteristic measurement, initially described in [91]. The modifications include modification of the synchronization method for the oscilloscope, as required by the low frequency of measured signals. Internal synchronization algorithms of the oscilloscope fail in this case, since they are designed for signals with the frequency above 10 Hz. Also, it was required to modify the voltage scale auto-range algorithm in order to minimize the number of frames needed to be taken. It should be noted here that one period of the 1 mHz signal lasts 1000 s, which is almost 17 minutes, while at modest frequency of 1 kHz it takes 1 ms, which is a million times shorter time span. This quantitative difference rescaled importance of certain algorithm parts and required significant algorithm modifications in order to record the frequency response within a reasonable time. The analogue realization was selected over digital as the EGG signals are of relatively small amplitude, as we strived to avoid electro-magnetic interference, and as there was no need for mass production.

After preliminary in-lab testing, the system was applied for the recordings in 20 healthy subjects for the investigation published in [2]. In total, the 800 minutes of EGG signal (20 subjects, 2 sessions, 20 minutes per session) were recorded (data are openly available on Zenodo [18]). Additional testing of the device was obtained in dynamic environment in 14 healthy subjects during driving simulation and published in journal with impact factor [3]. Overall, including other tests, the device was examined in more than 50 subjects.

The performance of the device was tested in [2] in comparison to the results from the literature. Recently, a study from another research group from Slovenia showed that similar analogue realization gives results that are comparable with the commercially available Biopac EGG device (BIOPAC Systems, Inc., Goleta, USA) [92]. For the comparison of two devices, authors in [92] used protocol from this Doctoral dissertation published in study [2].

2.5. Improvement of the EGG Device

The main goal for further improving the device included the realization of signal acquisition circuit, described in subchapter 2.3.2., on a printed circuit board (PCB). This leads to the minimization of device volume and its packaging in a suitable plastic case, making it less sensitive to external artifacts. Testing of the improved device is still undergoing, so only a brief explanation of its design will be provided in this Doctoral dissertation

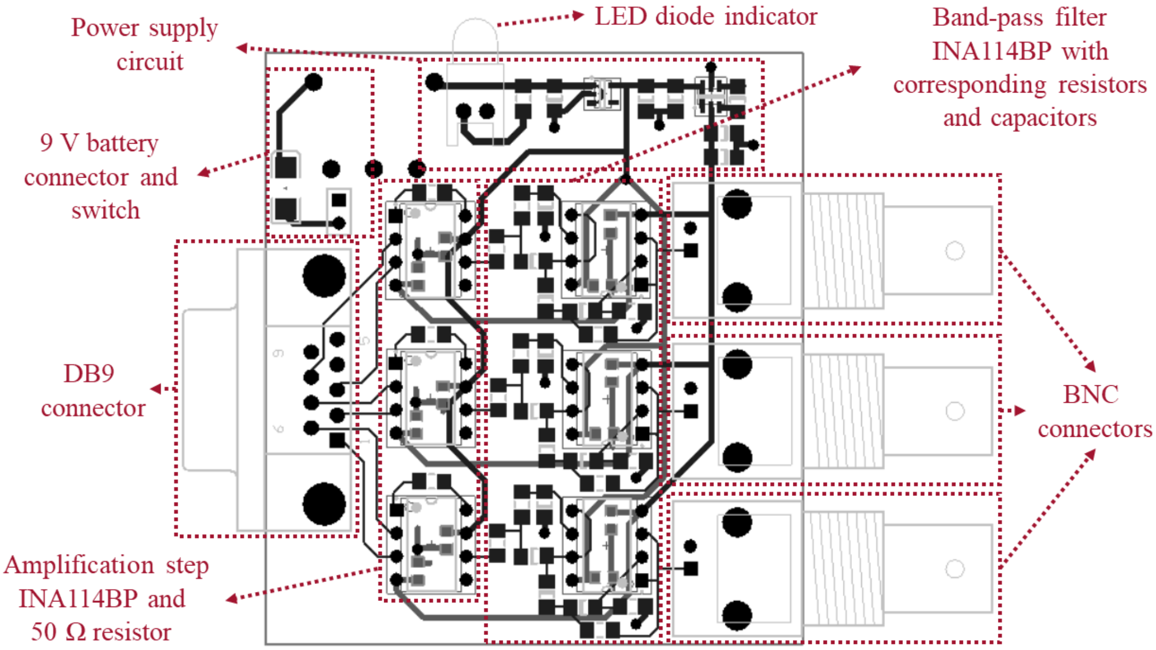


Figure 2.9. PCB design for improved EGG device with marked parts.

PCB design and initial simulated testing were done using Altium Designer (Altium Ltd., California, USA). For the resistors, and capacitors surface-mount devices (SMD) were used. Resistance and capacitance of the components were the same as described in subchapter

2.3.2. For instrumentational amplifiers (INA114BP) and operational amplifiers (TL072CP), through-hole devices were utilized. Additional parts included through-hole connectors (DB9 for input and three BNC connectors for output) and a power supply circuit. In order to provide ±5 V voltage supply, 9 V battery was used in combination with low-dropout (LDO) voltage regulator to deliver 5 V, and subsequently, switching-voltage regulator to deliver -5 V. LE (Light Emitting) diode as an indicator of device status (On/Off), as well as switch were included. In Figure 2.9. PCB design with marked parts is presented.

The image of the improved current version of the EGG device with the PCB prototype is presented in Figure 2.10.

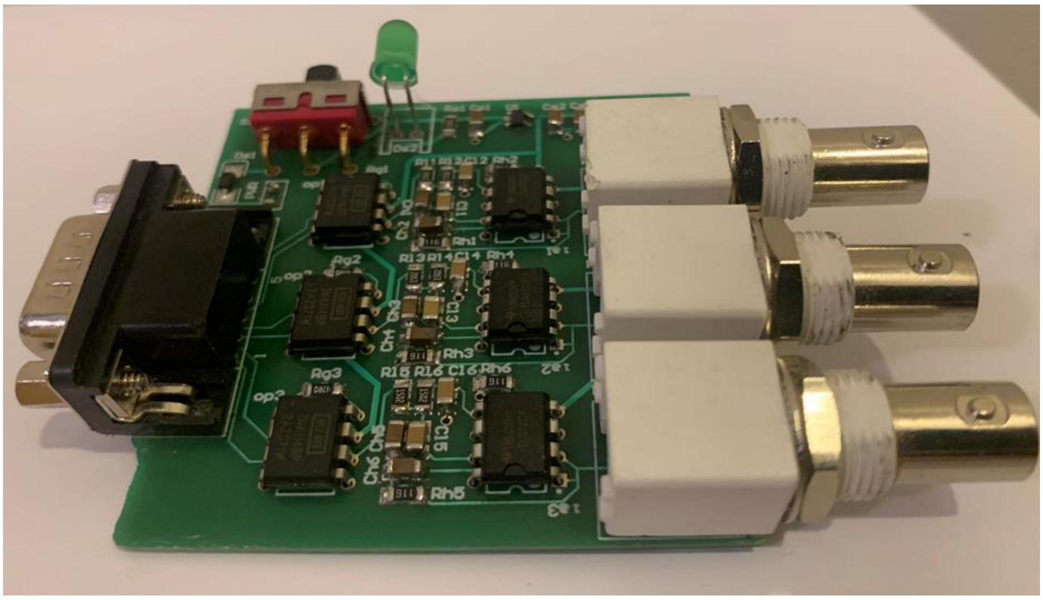


Figure 2.10. The prototype of improved EGG device on PCB.

The image of the improved EGG device prototype in black plastic housing is presented in Figure 2.11.

Figure 2.11. The prototype of improved EGG device in the plastic housing.

The corresponding subject to the device and device to A/D converter cables were also designed.

3. Recording Protocol

Well defined recording protocol is one of the prerequisites for reliable and reproducible EGG analysis. As for any experiment, variables that can affect results should be minimized in order for the conclusions to be significant. While for more commonly used diagnostic procedures, standard protocols exist, there is a lack of such guidelines for recording gastric myoelectrical activity. For ECG, there is a Clinical Guidelines by Consensus document for the Recording a Standard 12-Lead Electrocardiogram, approved method by the Society for Cardiological Science & Technology (SCST) [93]. For EMG, there is a SENIAM (Surface EMG for a Non-Invasive Assessment of Muscles) protocol that provides clear recommendations regarding the sensors and their placement for the recording [94]. For example, [94] contains the description of the commonly used electrodes, their size, shape, construction material, and inter-electrode distance. Additionally, there is a step-by-step procedure for electrode positioning that includes: 1) selection of the electrode type, 2) skin preparation, 3) subject`s posture, 4) determination of the electrode location, 5) fixation and positioning of the electrodes, and 6) connection testing. The document also includes practical guidelines for adequate application of the EMG. The technical and practical aspects of the document were evaluated by all the members of the SENIAM club (>100). A similar initiative is required for the standardization of the EGG. The first step towards that initiative is a public scientific discussion among the researchers in this field. In the self-published Letter to Editor [95], we pointed out to the overlooked elements regarding the characteristics of used instrumentation in [47]. Precise explanations regarding the EGG procedure in the published investigations are crucial. Unlike in standardized methods, in EGG it is not possible to state that the measurements were done in accordance with the recommendations. The response to imprecise methodologies in the published references related to the EGG research could increase awareness of EGG research reproducibility and promote EGG standardization efforts.

Lack of a document analogous to SENIAM protocol [94] for EGG implicates that for EGG recordings, researchers need to implement one of the published approaches or develop a new one, which results in limited comparability with reported results obtained by applying the different protocol.

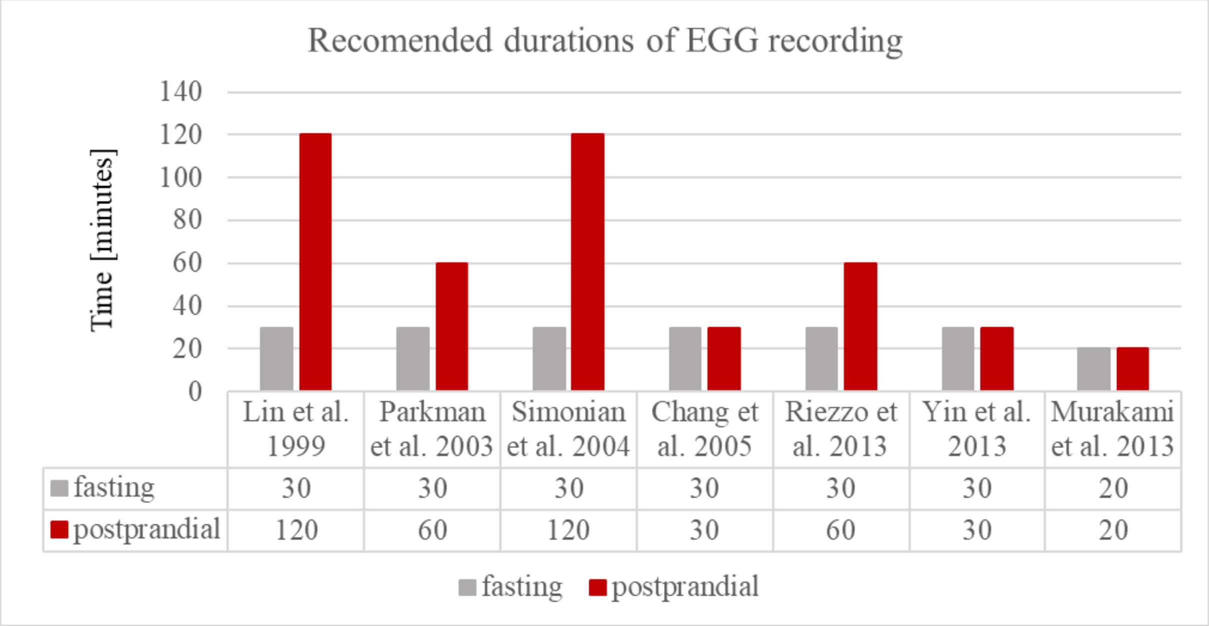
This challenge is even more significant if it is considered that EGG is highly sensitive to artifacts. The main aspects of the protocol that can influence recording quality will be discussed in this chapter. They include: 1) the duration of the recording session, 2) the subject posture, 3) the electrode placement, and 4) the meal intake effect.

3.1. Duration of the Recording Session

The motility of the smooth stomach muscles and its corresponding electrical signal with frequency around 3 cpm (slow waves) are much slower than the other commonly measured muscle contractions. Heart muscle is evoked approximately 60 to 100 times in one minute, while skeletal muscle contraction, both voluntary and involuntary, can be detected almost immediately upon its activation using EMG. Consequently, to have an opportunity to evaluate the gastric electrical activity, it is crucial to utilize an appropriate recording duration that is relatively long compared to the ECG or EMG protocols. There is a clear benefit with the long-term protocol since many different processes in the stomach cycle can be monitored. Thus, signals obtained by those protocols are more informative than the short-term ones. On the contrary, the longevity of the session is affecting subject`s comfort and potentially induces unwanted disturbances in the functionality of the GI tract. Reduction of the protocol duration can result in improved quality of signal, since there is higher chance that subject will avoid movement and subsequently minimize possibility of motion artifacts. Recording protocol should also be designed in relation to concrete application. Namely, when there is a need for continuous monitoring of several phases of gastric electrical activity increased duration is justified. However, when the aim is to detect potential slow wave disturbances triggered by specific stimulus, it is rational to use short-term protocol. In conclusion, there is a need for the compromised duration of the recording session to enable assessment of at least one phase of the gastric cycle while being as short as possible.

3.1.1. Existing Recommendations

In the literature, there are various recommendations for the EGG recording duration. To the best of the Author`s knowledge, the longest continuous EGG recording analysis was published in 1996. by Lindberg et al., and it was 24-hours ambulatory EGG [21]. While this research provided significant results regarding the GI system functionality and EGG reliability during a more extended period of time, it is only suitable for in-hospital patients already limited with movement and monitored for additional physiological parameters. The first publication that offered a review of existing protocols and suggested minimal values for the EGG session duration was [40] by Parkman et al. They stated that fasting signal is usually recorded for 15-30 while postprandial signal acquisition lasts from 30-120 minutes. Based on that consensus, the opinion arises that 30 and 60 minutes for fasting and postprandial protocols, respectively, should be used. Chang et al. in [48] stated that the most optimal recording time for both fasting and postprandial recording is 30-60 minutes. Many publications supported 30 minutes or more for the acquisition duration [17], [19]. In 2004. a research group led by Hrair P. Simonian published results from one multicenter study in normal subjects [37] and one single-center study in symptomatic patients [96]. The same protocol duration was suggested and used in both patients and healthy subjects: 60 minutes fasting and two 60 minutes sessions for postprandial. In his review paper [16], Murakami and his colleagues stated that 20-minutes for both fasting and postprandial recording could be sufficient. The main reason for this shortening was the potential lack of cooperativity from the subject. Thus, they suggested recording protocol that could be finished in 1 hour, including both fasting and postprandial recording, test meal intake, and procedure-related explanation. In Figure 3.1. bar graph with suggested durations of EGG signal acquisition from different authors is presented. From the bar chart, it can be observed that there is a tendency of shortening the duration of EGG recording, which is precisely what was followed in this Dissertation [2], [3], [6].



	Lin et al. 1999	Parkman et al. 2003	Simonian et al. 2004	Chang et al. 2005	Riezzo et al. 2013	Yin et al. 2013	Murakami et al. 2013
fasting	30	30	30	30	30	30	20
postprandial	120	60	120	30	60	30	20

Figure 3.1. Graphical overview of the existing suggestions for the duration of the EGG recording protocol.

3.1.2. Simple Short-term Recording

Based on the recommendations from Murakami et al. [16], simple short-term EGG recordings were obtained, and the results of the analysis were published in [2]. This investigation provided one of the main results presented in this Dissertation. The idea was to test the hypothesis that it is possible to acquire reliable and informative EGG recordings with the protocol that will last up to 60 minutes, including two recordings and test meal intake. The study group consisted of 20 healthy volunteers who were asked not to eat for 6 hours and drink for 2 hours before the session. A fasting signal was obtained for 20 minutes, after which a meal was provided to the subject, followed by another 20 minutes recording. A graphical representation of the protocol is presented in Figure 3.2. Subjects were asked to limit movements and not to talk or laugh during the recording sessions.

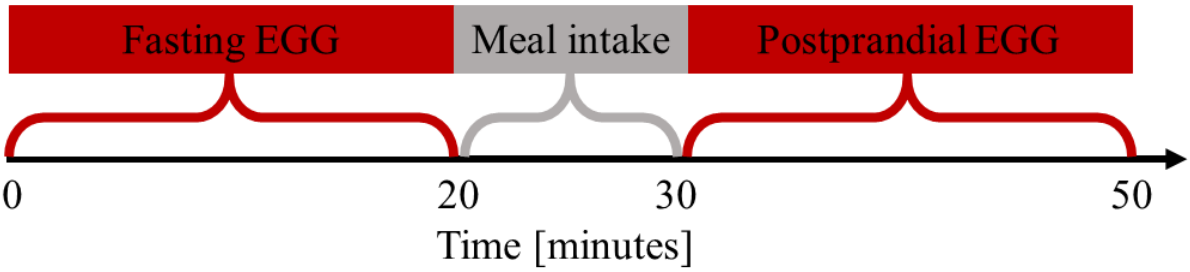


Figure 3.2. Short-term EGG recording protocol. Duration is limited to 1 hour, during which two 20-minutes recordings should be acquired (fasting and postprandial), including the time for test meal intake.

3.1.3. *Discussion of the Recording Duration*

Signals from all 20 participants were suitably obtained, showing satisfactory reliability. There was a statistically significant increase in dominant frequency for postprandial signals compared to the fasting ones. This was in accordance with previously published results [14], speaking in favor of the possibility of recording a useful 20-minutes EGG signal.

The experience that was obtained from the recording sessions conducted in [2] showed that even this reduced duration protocol was uncomfortable for the subjects. That served as motivation to introduce even shorter baseline sessions for the EGG acquisition in subsequent investigations.

In [3], [6], it was stated that baseline EGG, for the calculation of resting parameters, can be recorded by using an even shorter protocol (5-15 minutes) but with the condition that during the recording, an educated observer should confirm the quality of the signal.

For the EGG signals recorded during some external stimuli, that are expected to produce changes in the signal parameters, it could be justified to limit the acquisition duration. In references [3], [6], such cases were reported, and a detailed description will be provided in Chapter 5.

3.2. Subject`s Posture

While in the majority of published articles in the EGG area, a suggestion is to record in a supine position or mild inclination, in some applications, it is necessary for the subject to be in a sitting or even standing position. Data regarding the effects of body posture on the quality of EGG signal is scarce.

The intensity of motion-induced artifacts can be different if the recording is obtained in different subject posture. That can also affect position of the stomach relative to the surface electrodes [97]. Also, the influence of breathing artifacts can differ with various inclinations of the upper body. Wrinkling of the skin, dependable on the posture, at the contact area between self-adhesive electrodes and skin can induce additional artifacts [64].

3.2.1. *Sitting, Supine or Standing Position?*

The majority of EGG studies were performed in a supine position. The question is: Is there a possibility to record EGG in a sitting or standing position?

A partial answer to that question was offered via the research by Jondarenko et al. [45], in which 17 healthy participants were included. They underwent 30 minutes fasting and 90 minutes postprandial EGG recording in both recumbent and sitting positions. Following parameters were calculated: 1) dominant frequency, 2) dominant frequency instability coefficient – DFIC, 3) dominant power – DP, 4) overall postprandial increment in the dominant power – ΔDP, 5) maximum instantaneous postprandial increment in the dominant power - Max_ΔDP, and 6) percentage of normogastria. There were no significant changes in parameters between supine and sitting positions, with the exception of DP in the postprandial recording, which was significantly decreased in the sitting position compared to the recumbent. Based on the results, the Authors stated that EGG could be obtained in sitting posture, but it is required to follow recommendations regarding the procedure strictly. By doing so, it is possible to have EGG with comparable quality with the ones recorded in a supine position.

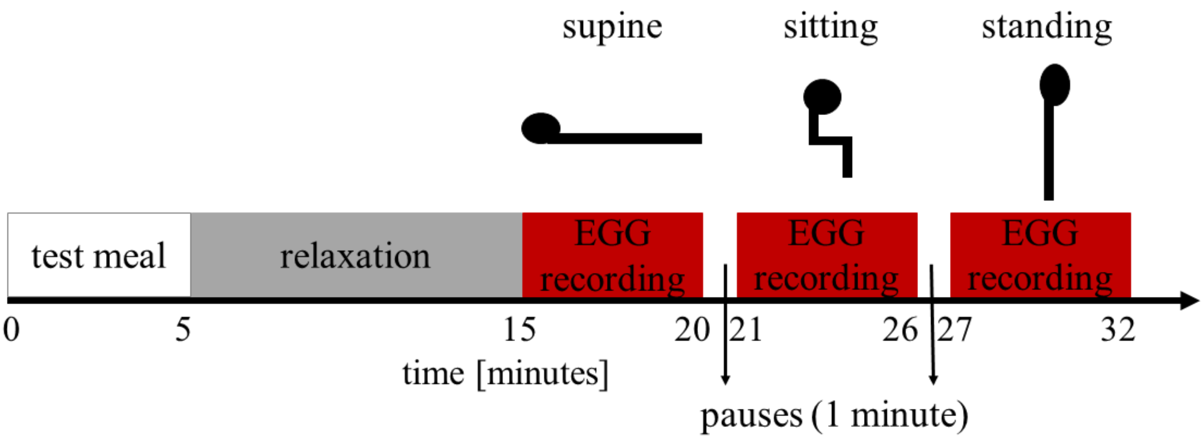


Figure 3.3. Illustration of protocol for the EGG recording in supine, sitting, and standing posture, published in [7].

Some level of extension to previously described research was provided in a published case study [7] performed in a healthy 24-year-old female subject. Postprandial EGG signals were recorded in supine, sitting, and standing positions. Protocol started with 10 minutes of relaxation after the meal consumption, followed by three short-term (5 minutes) recordings in each out of three body postures. Breaks between recordings lasted for 1 minute. The protocol is presented in Figure 3.3. Dominant frequency and percentage of normogastric power share (% normogastria) were calculated. Following results were obtained for supine, sitting, and standing posture, respectively: 1) DF -2.93 cpm, 3.10 cpm, and 2.75 cpm, 2) the percentage of normogastria share – 74.4 %, 30.0 %, and 45.2 %. Although larger study samples are needed for more significant conclusions, calculated normogastria percentage values speak in favor of more reliable recordings in supine, especially compared to the sitting position.

3.2.2. Discussion of Subject`s Posture

Although, preliminary research presented in Dissertation showed that EGG signal changes when subject`s posture changes, additional measurements on larger sample are needed to confirm these findings. The majority of EGG studies are performed with subject in a supine posture, therefore the supine position should be the first choice if there is no specific reason to record EGG signals from subjects while sitting and standing. Once determined, subject`s position should be kept constant across trials and subjects in order to warrant the reproducibility.

3.3. Electrode Placement

The actual position of self-adhesive surface electrodes on the skin over the portion of the abdomen around the stomach is referred to as electrode placement. This is one of the crucial aspects of EGG protocol because the recorded signal characteristics correlate to a high degree with applied electrode placement. In 1987. Stern and colleagues stated that electrode placement "will not affect the frequency of the EGG, but will affect the amplitude and waveform of the EGG" [20]. Consequently, the lack of standard protocol influences the reproducibility of the method and comparability between results acquired with various setups. In parallel, ECG, EMG, and EEG have clear guidelines regarding the placement of surface electrodes [93], [94], [98].

The majority of the proposed solutions include more than one channel for the acquisition of EGG [37], [96], [99]–[102]. Two main benefits from using more than one recording channel are: 1) increased robustness of the system – there is a possibility that one channel is affected by artifacts while others are still suitable for the analysis, and 2) there is a possibility for comparison between different channels and calculation of parameters that require signals from more than one channel. On the contrary, a simplicity that arises from the application of only one channel could increase interest in this method, especially for researchers and clinicians without advanced engineering knowledge.

3.3.1. Overview of Existing Electrode Placement Setups

Bipolar electrode configuration is preferable due to the increased Signal-to-Noise Ratio (SNR) and decrease of artifacts from the sources nearby. Due to that, in this overview, only bipolar solutions will be described. The positioning of the electrodes over the ribs should be avoided due to the possibility of extensive breathing artifacts [2]. In Figure 3.4. terms that will be used as markers for the explanation of electrode placement are presented. While some of the terms are self-explanatory (sternum, border of the rib cage, umbilicus), others are defined as following: 1) midline – the imaginary line that divides the body into left and right part, 2) midclavicular line – the imaginary vertical line that passes through the middle of the clavicle, 3) midaxillary line – the imaginary vertical line that divides posterior and anterior parts of the body, 4) xiphoid process - a small cartilaginous extension on the bottom of the sternum [103].

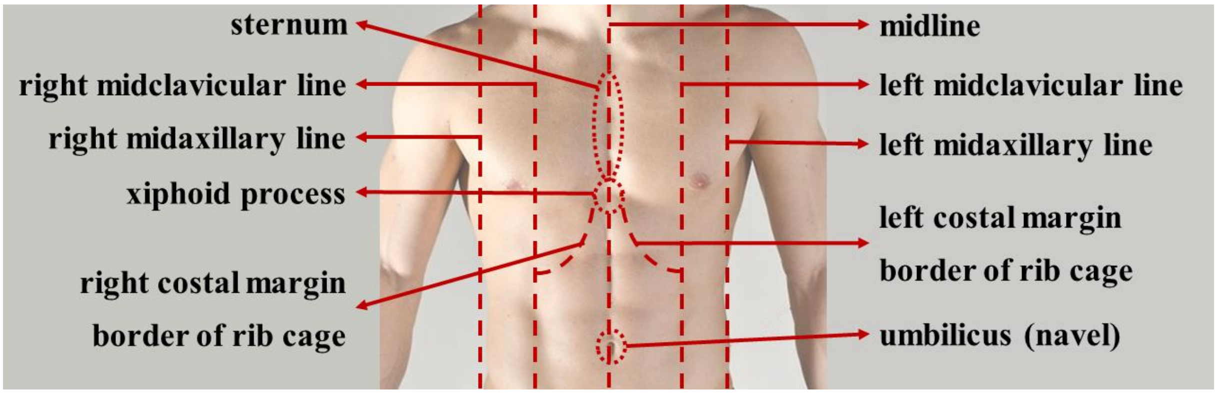


Figure 3.4. Image of the human abdomen with anatomical landmarks that will be used for the description of electrode placement. Image of the body taken and adapted from "wait, active, activity, aerobics, attractive, body, caucasian, class, club, coaches, equipment, exercise, fit, fitness, gym, gymnastics, health, healthy, lifestyle, male, man, microphone" by www.audio-luci-store.it. Accessed in November 2020. (License: CC BY 2.0)

Stern et al. [20] suggested that one active electrode should be placed on the midline, above, and close to the umbilicus for single-channel acquisition. At the same time, the position of the second one should be around 6 cm to the left of the midline and just below the lowest rib (see Figure 3.5. a)). Similar to the setup recommended in [20], in the "Handbook of Electrogastrography" by Kenneth L. Koch and Robert M. Stern [12], it is suggested following: 1) one active electrode should be attached around 10 cm above the umbilicus and around 6 cm to the left from the midline, with percussion to avoid rib cage in order to minimize breathing artifacts, 2) other active electrodes should be attached roughly 4 cm above the umbilicus on the midline in the near to the point that is in the middle between the xiphoid and navel, and 3) reference electrode should be placed on the right side of the abdomen around 10 to 15 cm from the midline, on the midclavicular line around 3 cm from the lo border of the rib cage (see Figure 3.5.a)). In "Electrogastrography: a document prepared by the gastric section of the American Motility Society Clinical GI Motility Testing Task Force" by Parkman et al. [40], it is stated that common electrode setup includes two active electrodes, one at the midline around the point that divides distance from navel and xiphoid process into equal segments, and another one 5 cm to the left of the midline, 2 cm below lowest rib, and in such manner that angle between the horizontal line and line that connects to active electrodes is around 30° (see Figure 3.5. b)). In article [23] by Mintchev et al., five active electrodes were used and placed equidistantly between two points: 1) 5 cm to the left from the sternum, just below the costal margin, and 2) on the mid-clavicular line just below the right costal margin (see Figure 3.5. c)). One of the most commonly used electrode placements was described in 1999 by Chen et al. [27]. It consists of six Ag/AgCl electrodes primarily designed for ECG recording (DNM, Dayton, OH). Four of those are active, one is common, and one is a reference. Active electrodes should be placed according to the following guidelines: 1) first one 2 cm cephalad the point that divides in half distance between the xiphoid process and the navel, 2) the second one in the same horizontal direction as the first one, 4 cm right from the midline, 3) the third one should be placed left from the midline, around 4-6 cm from the first electrode, on the line that makes 45° angle with the horizontal line, 4) the fourth one should be placed at the same line as the third one, 4-6 cm from it. The common electrode should be positioned at the point of a cross-section between the horizontal line connecting the fourth active electrode and midline. This setup provides a recording of four bipolar channels, each of them consisted of one active electrode and the common one (see Figure 3.5. d)). In order to calculate the vector of EGG, in [46], Tokumaru et al. proposed a setup where two bipolar channels were used. The first pair of electrodes were positioned horizontally, on the one fourth of the distance between the xiphoid process and umbilicus, closer to the xiphoid - one electrode at the right and the other at the left midclavicular line. The second pair was placed along the left midclavicular line with the same distance between two electrodes as it is in the first pair (see Figure 3.5. e)). The most recent setup was proposed by Wolpert et al. in [47], where they state that coverage of the stomach area can be suitable by placing eight electrodes, which is much simplified than the 17 that they initially used. Finally, they implemented the placement presented in Figure 3.5. f), which includes four pairs of electrodes (four bipolar channels) with a distance of around 4 cm between paired electrodes. Positions of three pairs were in the area below the left rib cage, while one pair was placed near the midline. The ground electrode was attached to the electrically neutral area near the iliac crest. A detailed explanation of the setup is provided in [47].

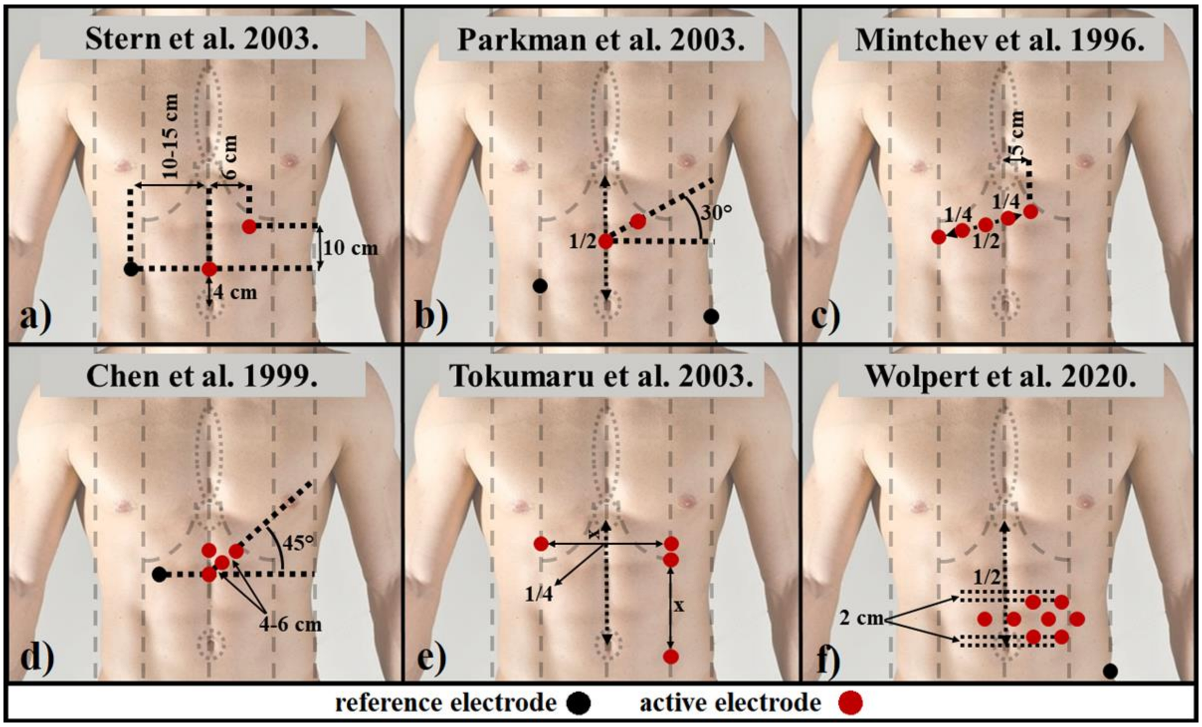


Figure 3.5. Proposed electrode placement from 6 selected publications that were used as guiding principles for electrode placement in this Dissertation. Image of the body taken and adapted from "wait, active, activity, aerobics, attractive, body, caucasian, class, club, coaches, equipment, exercise, fit, fitness, gym, gymnastics, health, healthy, lifestyle, male, man, microphone" by www.audio-luci-store.it. Accessed in November 2020. (License: CC BY 2.0)

It should be mentioned that some researchers suggest an individualized approach – electrode placement corresponding to the determined position of the stomach in each subject. In order to implement that methodology, a suitable imaging technique is required prior to the setup. It is reported that X-ray imaging [104] and sonography [12] could be used for this purpose.

3.3.2. Simple Setup with One Channel

The robustness of the method, the possibility of signal propagation tracking as well as the calculation of parameters that include analysis of the signals from multiple channels are clear advantages of multichannel electrogastrography. Despite that, the chances are that the path towards standardization of EGG includes simplifying the recording setup – a process that favors the single-channel approach. Reproducibility of the results and the possibility of comparing data from various publications could increase if only one channel is applied. This could lead to significant advancements in the field. Consequently, greater interest in the method, from the side of both clinicians and researchers, could be achieved. Subject`s conformity during recording protocol could be increased as well. Also, there are many unanswered questions regarding the best position of the electrodes, vulnerability to the artifacts, and reliability of the recording using only one pair of electrodes. These are the main reasons and motivation why it was decided to investigate this simplistic approach to EGG recording and publish results in [2]. The idea was to compare results from three different bipolar EGG channels in terms of reproducibility of previously published results in order to answer the following questions:

1. Is it possible to reliably record EGG using one channel?

2. What is the most suitable surface electrodes position for single-channel EGG recording?

Answers to the listed questions were one of the main contributions of this Doctoral Dissertation.

3.3.2.1. Methodology for Simple Single-channel Setup

In [2], three-channel electrogastrography signals were recorded in 20 healthy subjects, including 8 females and 12 males, from 20 to 31 years old (average 25.0 ± 2.7). Recording protocol explained in subchapter 3.1.2. included two 20 minutes recording, fasting and postprandial. The body posture in which signals were recorded was supine. To be included in this protocol, participants needed to fulfill the following criteria: 1) no history of gastrointestinal tract disorders, including unexplained nausea, stomach pain, and vomiting, and 2) not on any prescribed pharmacological therapy in the last six months. Informative consent written according to the Declaration of Helsinki and approved by the Local Ethics Committee was signed by all study volunteers. Custom made acquisition apparatus (see subchapter 2.3.) was used, with 16-bits resolution and sampling frequency of 2 Hz. Signals were preprocessed in software package Matlab ver. R2013a (Mathworks Inc., Natick, MA, USA) – zero-phase Butterworth 3rd order band-pass filter (0,03-0,25 Hz) was applied to remove baseline drift and higher frequency artifacts such as breathing and ECG.

Novel electrode placement, illustrated in Figure 3.6., was implemented. Prior to the attachment of electrodes, careful skin preparation, including shaving of the hair and abrasive gel, was performed. The setup consisted of five electrodes – reference, common, and one for each of the three recording channels. The reference electrode was placed on the electrically neutral area over the iliac bone (left midaxillary line), while the common one was positioned on the midline 8 cm above the umbilicus. Each of the three additional electrodes was placed to form one bipolar channel with the common one. Channel positions were not chosen to follow the pattern of wavefront propagation as it was common for multichannel setups. They were placed on the different anatomical landmarks of the stomach since this research aimed to determine from which site the most reliable signal can be obtained. Thus, the channel 1 (CH1) electrode was placed above the lesser curvature of the stomach and channel 3 (CH3) above the greater curvature. Channel 2 (CH2) electrode was positioned in a way that the line connecting common electrode and CH2 electrodes cuts in half angle between the horizontal line and line connecting common and CH1 electrode (~ 70°). Distances between channel electrodes and common were approximately 8-9 cm.

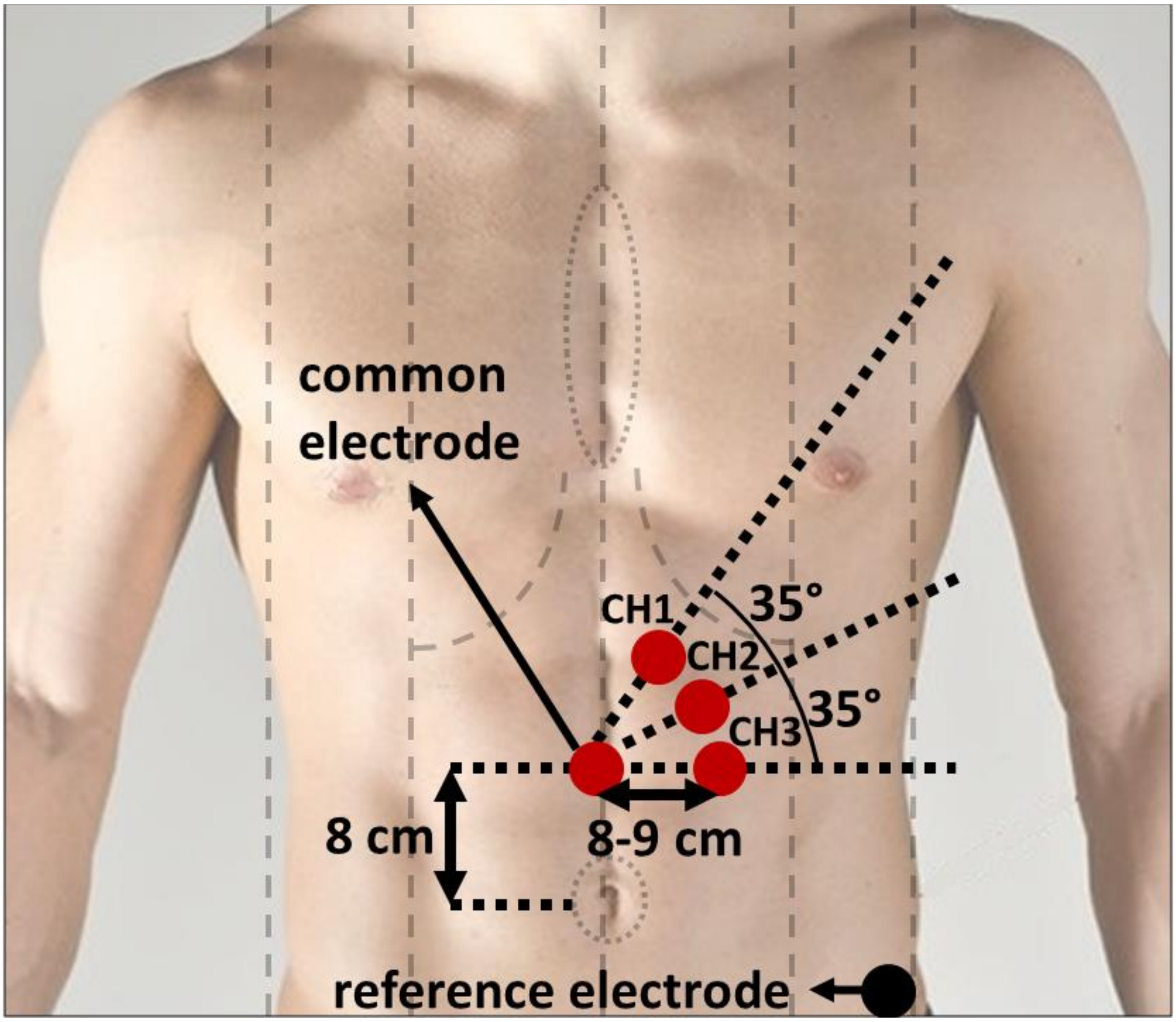


Figure 3.6. Presentation of electrode placement used in [2]. Image of the body taken and adapted from "wait, active, activity, aerobics, attractive, body, caucasian, class, club, coaches, equipment, exercise, fit, fitness, gym, gymnastics, health, healthy, lifestyle, male, man, microphone" by www.audio-luci-store.it. Accessed in November 2020. (Licensed CC BY 2.0)

As the most commonly used parameter to describe the frequency content of EGG, dominance frequency was calculated to determine in which channel the most significant increase in frequency is present. It was defined as a maximum peak position in the signal spectrum determined using Fast Fourier Transform (FFT). Paired-sample t-test was used to compare DF data between fasting and postprandial signal in the entire study group to establish the statistical significance (p-value less than 0.05).

3.3.2.2. Results for Simple Single-channel Setup

Average dominant frequencies for all 20 subjects for fasting and postprandial EGG signals, respectively, were: 1) channel 1 – 2.78 ± 0.36 cpm and 3.00 ± 0.40 cpm, 2) channel 2 – 2.76 ± 0.37 cpm and 3.00 ± 0.36 cpm, and 3) channel 3 – 2.79 ± 0.36 cpm and 3.01 ± 0.36 cpm. An increase in DF was statistically significant in all three channels, with $p < 0.05$ for

CH1 and CH3, and $p < 0.001$ for CH2. Bar graphs representing average DFs are presented in Figure 3.7.

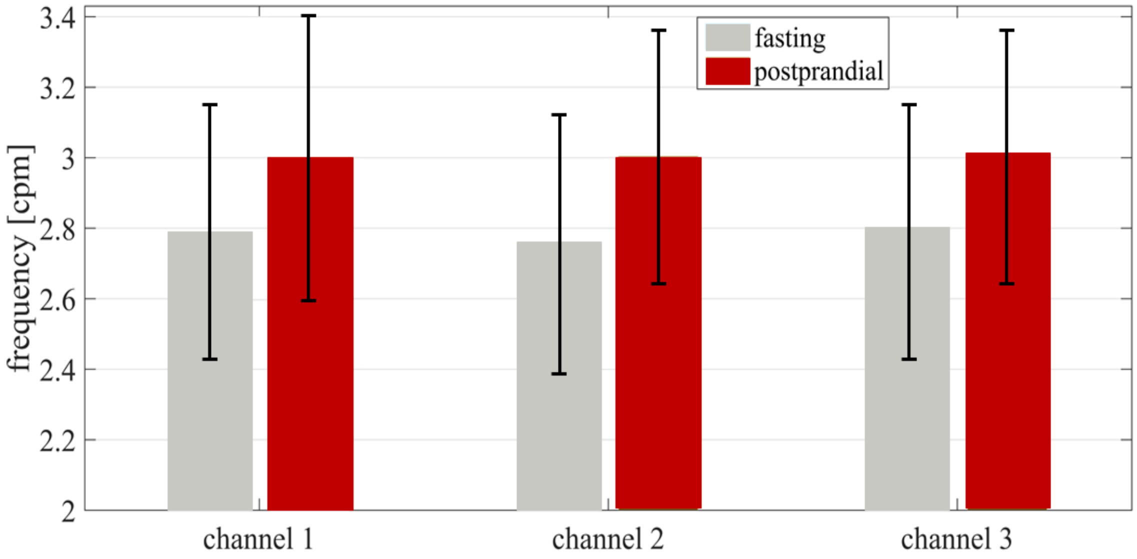


Figure 3.7. Average DF for fasting and postprandial recordings obtained in 20 subjects for the research published in [2].

3.3.2.3. Discussion for Simple Single-channel Setup

As expected, there was an overall increase in the frequency of recorded EGGs after meal intake in each channel, speaking in favor of the possibility to acquire reliable signals with the usage of only one channel. If any of the proposed channels were used, without the other two, results that correlate with previously published ones [17], [21] would be acquired. In Table 3.1. overview of the selected publications demonstrating postprandial increase in DF is presented. The study performed on the larger study group would be beneficial to confirm these results. However, this research strongly suggests that a single-channel technique is suitable for static EGG recording when multichannel parameters are not required.

It should be noticed that signals acquired from CH2 gave a stronger level of statistical significance. Thus, based on these results, bipolar EGG recording from correspondingly placed surface electrodes should give the most reliable signals. It is known that electrical activity of the stomach is most prominent in the region of greater curvature (rich with Interstitial Cells of Cajal) [11]. From that, it would be expected that CH3 is the most promising channel. What should be taken into account is the proximity of the lower GI part that could induce severe artifacts. Like that, breathing and ECG artifact could be influencing CH1 to a higher degree than the other two channels. In conclusion, the compromise between proximity to the greater curvature and distance from interfering noise sources, both incorporated into the placement of electrodes for CH2, could be the reason for its preferability.

Table 3.1. Overview of selected papers demonstrating postprandial DF increase.

Reference	**Number of subjects**	**Fasting DF [rcpm]**	**Postprandial DF [rcpm]**	**p-value**
Chen et al. 1991 [15]	10	2.95	3.29	$p < 0.020$
Levanon et al. 1998 [105]	14	2.89 ± 0.05	3.17 ± 0.07	$p < 0.007$
Simonian et al. 2004 [37]	61	2.89 ± 0.62	3.08 ± 0.27	$p < 0.010$
Vargas-Luna et al. 2019 [106]	14	2.72 ± 0.16	2.83 ± 0.14	$p < 0.003$
Popovic et al. 2019 [2]	20	2.76 ± 0.37	3.00 ± 0.36	$p < 0.001$

3.4. Fasting or Postprandial?

One of the leading and often proposed questions is – What is the difference between fasting and postprandial EGG recording? Due to the fact that the primary purpose of the stomach is storage, mixing, and digestion of the food, this question is reasonable. Many different variables could affect EGG recording (some of them – subject posture, electrode placement, already discussed in this chapter). However, meal intake is something that affects the functionality of the GI tract, and as such, needs to be carefully examined. Depending on the length of the gastric cycle in each individual, different latencies for EGG changes after meal intake are expected. Itoh et al. in [107] stated that the approximate duration of the digestive cycle after meal intake is 4-5 hours. Based on that, the definition of fasting signal is any EGG recorded after 6 hours of food abstinence [19].

In order to have a comprehensive overview of this topic, the following questions will be discussed in the next chapters:

1. In what manner meal intake affects EGG signal?

2. Is there a different EGG response to various types of a meal?

3. For what EGG application is more suitable to record in fasting, and for what in a postprandial phase of the gastric cycle?

3.4.1. Effects of Meal Intake on EGG Signal

The first effects of meal intake were reported over five decades ago, in the article published by Nelsen and Kohatsu in 1968. [108]. They stated that there is an increase in the frequency content of EGG after food consumption. This observation was subsequently confirmed in many articles [15], [17], [19]. From research conducted in 10 healthy subjects [15], Chen et al. reported an increase in dominant frequency after solid mean intake from 3.0 cpm to 3.3 cpm. This speaks in favor of faster contractility, connected to the enhanced mechanical response of smooth muscles required to mix the food in the stomach after food ingestion.

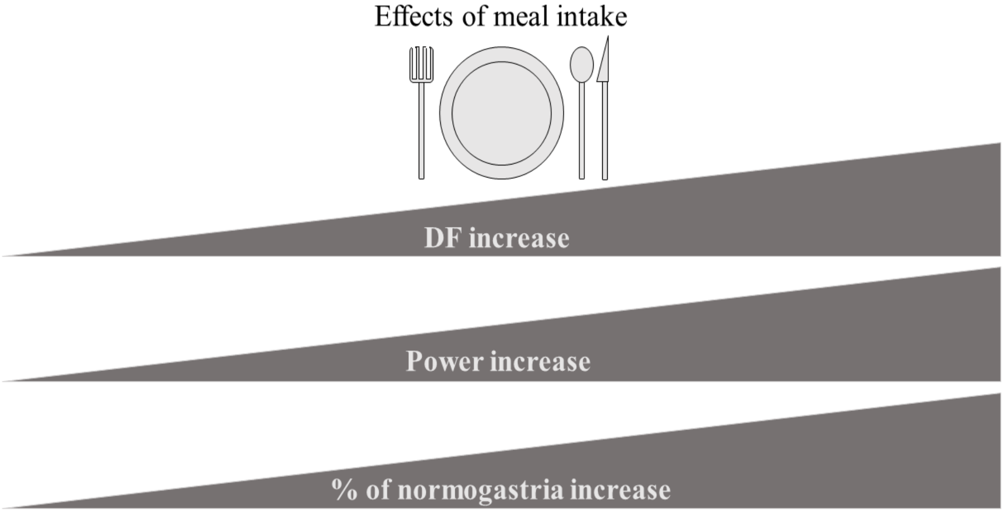


Figure 3.8. Graphical representation of meal intake effect on EGG parameters.

In addition to the heightened frequency, there is a reported increase in the amplitude and power of EGG signal postprandially [12], [19], [40]. Chen et al. in 1991 [15] reported that the power of EGG signal raised after both water and solid meal intake. A power increase of the gastric slow wave after drinking water was observed in 8 out of 10 subjects. Average increase was 3 dB ($p < 0.01$) and 6 dB ($p < 0.01$), for water and solid food intake, respectively. Postprandial amplitude was in average two times higher for the postprandial state compared to fasting. Explanation of this phenomenon could lie in a more prominent occurrence of spike potentials during the postprandial period. Namely, as explained in subchapter 1.3. spike potentials are related to the contractions of the stomach smooth muscle. Thus, it is expected that they occur more frequently after meal intake. Considering the fact that they are superimposed to slow-wave activity, it is plausible that they increase the value of EGG amplitude, and consequently, power.

Simonian et al. in [37], during research conducted in 61 healthy subjects observed a postprandial increase in the percentage of time during which DF was within the normogastric range (2-4 cpm). This parameter raised from 76.9 ± 20.2 % to 80.7 ± 15.1 % as a result of meal intake.

Results, presented in [2], confirmed the postprandial increase in DF. From many investigations that were not dedicated to the examination of meal intake, it was suggested that these changes in power and increase in normogastria percentage are consistent among healthy subjects.

Based on the literature review, the expected increase of the three discussed parameters is presented in Figure 3.8.

3.4.2. Gastric Response to Different Type of Meal

Extension to the research regarding the effect of meal intake on EGG signal characteristics is provided by investigating corresponding changes relative to the meal structure. Standardization of the EGG recording procedure should include recommendations for test meal, which implies that research in this area can substantially contribute to the field. Test meals that are used for examinations published in several articles are listed in Table 3.1.

Table 3.2. Overview of used meals in several different research articles. Information regarding meal description or characteristics is not available in each reference, which is why description and/or characteristics are presented.

Reference	Meal description and/or characteristics
Chen et al. 1991	The meal consisted out of turkey breast sandwich, banana, and oatmeal-raisin cookies.
Cucchiara et al. 1992	The solid-liquid meal consisted out of bread, butter, ham, and fruit juice – 300 kcal.
Ferdinandis et al. 2002	The meal with high carbohydrate level, low fat - 165-170 kcal. Varying consistency of meals - solid, semisolid, and liquid.
Geldof et al. 1986	The meal included 250 ml of yoghurt with 20 g of sugar - 990 kJ, 8-75 g of protein, 8.75 g of fat, and 30 g of carbohydrate.
Holmvall et al. 2002	The liquid nutritional drink - Fresubin (Fresenius Kabi, Stockholm, Sweden) or Nutridrink (Nutricia Nordica AB, Stockholm, Sweden) - 1.0 to 1.5 kcal/ml (35% from fat, 49% from carbohydrates, and 16% from protein. Several different flavors were available.
Jednak et al. 1999	The meal included soda crackers – 400 kcal (one nutrient predominant – protein, carbohydrate, or fat).
Jondarenko et al. 2005	The meal included slice of bread (50 g) scrambled egg fried on butter (10 g), and a glass of milk (250 ml, 1.5% fat).
Lin et al. 1999	The meal consisted out of Sunny Fresh Free Cholesterol (120 g) and Fat Free Egg Product (Sunny Fresh Foods, Inc., Monticello, USA) (60 kcal), two slices of whole bread (120 kcal), jelly (30 g, 75 kcal), and water (120ml).
Parkman et al. 2003	The meal included an egg sandwich and water - 32% protein, 46% carbohydrate, and 22% fat.
Popović et al. 2019	**The commercially available oatmeal – 274 kcal (14.15% protein, 61.6% carbohydrates, 8.42% lipids, 5.94% fibers) and 100 ml of squeezed orange juice - 30 kcal.**
Vargas-Luna et al. 2019	The solid meal included two scrambled eggs and 120 mL of water. Liquid meal - milk (240 mL, 2% fat).

In 1998. Levanon et al. published an article entitled “Effects of meal volume and composition on gastric myoelectrical activity” [105], in which they aimed to “investigate the effect of meal volume and composition on postprandial myoelectrical activity”. In the study, 14 healthy participants from 22 to 41 years old (average 30.7 ± 1.8, 7 female and 7 male) were included. They underwent EGG recording, fasting and postprandial, with four different test meals: 1) reference - turkey sandwich, chips (potato), chocolate cookie, and 1/2 cup of orange juice, 2) reduced-calory meal, 3) high-fiber meal, and 4) low-volume meal. While meals with reduced volume and increased fiber content did not produce any significant changes compared to the reference meal, reduced-calory meal failed to induce frequency, power, and normogastiric percentage increase. It was suggested that meals with lower calory content than usual are not suitable for the EGG recording protocol.

Effects of meal temperature on the characteristics of EGG were also examined in [119]. Concretely, a shift in dominant frequency after meal intake was observed regarding the same liquid meal (36 kcal, 300 mL) served at three different temperatures – 4°C, 27°C, and 55°C. The study group was consisted out of 10 healthy volunteers ranging from 20 to 27 years old. Results suggested that longer duration and higher magnitude of frequency change is connected to the coldest meal (4°C). It is suggested that the temperature of the meal should be taken into account when recording and analyzing EGG signals.

The study published by Ferdinandis et al. [110] aimed to explore the effects of meal consistency variation on EGG signal. It was obtained in 18 healthy participants, 21 to 35 years old, including 6 males and 12 females. On three separate days, subjects were asked to eat an isocaloric meal (165-170 kcal) with different consistency (solid, semisolid, and liquid). While solid and semisolid meals induced a statistically significant increase in signal power, liquid meal failed to do the same. Additionally, intake of these meals did not result in an increase in frequency content, which is consistent with results published in [105], where it is stated that reduced-calory meals do not induce frequency shift.

Patients with functional dyspepsia did not show an increase in the power or frequency of the EGG after a meal, compared to the fasting state [106]. This was observed in the study, which included two subject groups: 1) healthy control group – 14 subjects and 2) functional dyspepsia group – 12 subjects. On the contrary, in research published in [111], there was no significant difference in EGG parameters between 20 healthy subjects and 10 patients with functional dyspepsia. Those controversial findings suggest that the study group should be much higher in order to deliver reliable conclusions.

Exciting results were provided by Jendak et al. [32] considering EGG performance in pregnancy. This research was obtained in 14 pregnant women (20-35 years old) who reported nausea during the first trimester. Effects of six 400 kcal meals with different compositions (distribution of protein, carbohydrates, and lipids) and two non-caloric meals (water and sugar-free gelatin) were examined. Based on the findings, meals with a higher percentage of protein statistically significantly ($p < 0.05$) decreased both reported nausea occurrence and the percentage of gastric dysrhythmias detected by EGG. This result also supports the fact that gastric dysrhythmias assessed by EGG correlate with nausea occurrence.

3.4.3. Application of Fasting and Postprandial EGG

Following the previous subchapter, an issue that needs to be addressed is in what applications fasting and in what postprandial EGG should be used. Although the most suitable way to get an insight into the gastrointestinal tract functionality is to record both before and after a test meal, sometimes that protocol is not convenient. Thus, discussion regarding the appropriate phase of the gastric cycle for EGG recording could be highly beneficial.

After a meal, slow waves are presented with higher amplitude [19]. Therefore clearer signal with easier detection of cycles speaks in favor of using postprandial signals in the majority of applications. Additionally, if the aim is to study digestive processes, it is reasonable to acquire the signal when the stomach is more active. Increased percentage of normogastria postprandially [37] implicates that there are higher chances to obtain an unusable signal (without slow wave activity) if the recording is done during fasting. This resulted in many specific examinations that used only EGGs after the test meal for the analysis. One more issue that should not be overlooked is the reproducibility of the recording protocol. While for postprandial recordings, uniformity of the meal and the latency between meal intake and recording onset are easily achievable, the period of fasting before subject arrives for the recording is subjective and depends on the confidence between the researcher and study participant.

In examinations where an additional stimulus is presented to the subject (drum rotation, virtual reality, driving simulation, etc. [6], [112]–[114]), a previously ingested meal can induce severe symptoms of nausea as reported in [3]. In those circumstances, recording in a fasting state can be much more convenient. As already stated in subchapter 3.4.1. postprandial increase in EGG amplitude could be induced by the incidence of peak potentials superimposed to slow wave activity. Although the occurrence of peak potentials correlates with the gastric contractions, the main aim of EGG remains solely detection and analysis of slow waves. It should also be stated that in 1992. Riezzo et al. studied the reproducibility of the EGG recording prior to the meal and, based on the signals acquired in three consecutive days and concluded that there are no significant changes in parameters extracted from EGG signal [53]. Thus, EGG recorded in fasting state could be a reliable method for the slow wave assessment technique.

4. Analysis and Interpretation of EGG Signal

Reliable recording of EGG should be followed by suitable analysis and interpretation of the signal in order to obtain relevant conclusions. Over the course of years, many researchers made their efforts to make significant advantages in the processing and interpreting of EGG signal. It should be stated that the first stage in the analysis of the signal is its evaluation. The reliability of the results is highly dependent on the signal quality. Thus, assessment of EGG usability is a crucial step towards suitable extraction of features. Evaluation of the signal does include not only a decision regarding its fitness for further analysis but also the determination of noise presence and the ability for its cancelation . Only after a signal is evaluated and prepared for the analysis, it is suitable to obtain parameter calculation, i.e., feature extraction. Considering that, in this chapter, the following challenges will be addressed:

1. evaluation and noise detection in EGG signal;

2. preprocessing, including methods for artifact cancelation;

3. quantification of EGG signal.

These steps are prerequisites to acquire reliable parameters that can give the researcher opportunity to deliver significant conclusions based on the comparison of numerical values and statistical analysis.

Quantification of the commonly used electrophysiological signal is essential, but it has even higher significance in the case of EGG. Exemplified, from ECG signal timeseries, even without quantification, a skilled interpreter can determine many valuable conclusions – heart rate, conduction disturbances, presence of arrhythmias, etc. On the other hand, EGG signal in time is highly challenging for interpretation, and it requires quantification to deliver valuable and useful information.

4.1. EGG Signal Evaluation

As already stated, assessment of signal quality should be the first step towards suitable analysis and interpretation. That process could be divided into two subprocesses: 1) determination of signal usability and 2) recognition of artifacts. A signal can be defined as adequate for further analysis if it is not contaminated with severe artifacts or if the artifacts can be extracted using established methods. Due to the lack of standard techniques to quantify the quality of the signal, the primary approach is visual observation [50]. Different computational methods had been introduced, but results regarding their performance are still scarce.

4.1.1. Visual Observation

In 2019 O`Grady et al. in [50] stated that since many physiological or external artifacts can mimic slow wave activity, it is still necessary to introduce educated visual observation to discriminate between artifacts and gastric myoelectrical activity. This statement clearly describes the current status in the field of EGG evaluation. Namely, there is still a need for insight from an expert in order to proceed with EGG analysis. Visual assessment of EGG signal can be performed from both timeseries and frequency spectrum.

In the majority of applications, EGG is recorded for a relatively long time (over 20 minutes), so observation of the whole signal cannot provide many conclusions. As presented in Figure 4.1. it is suggested that separate parts of the signals should be zoomed and evaluated. The first thing that could be determined from the signal in the time domain is its amplitude. It should be within the determined range – from 100 µV to 500 µV [2]. While slight variations out of the range do not mean that signal is unusable if the amplitude is much lower than expected, it could indicate problems with recording equipment or physiological absence of slow waves. On the contrary, values significantly higher than 500 µV could imply that there is probably a severe motion artifact that affects the signal. It is expected that EGG in healthy subjects has a sinusoidal shape of the signal, with a period around 20 s, detectable visually. Lack of this periodicity in the parts of timeseries does not discard signal from further analysis. Still, if there is a lack of it in the whole recording, probably, interpretation of the signal would not give valuable information.

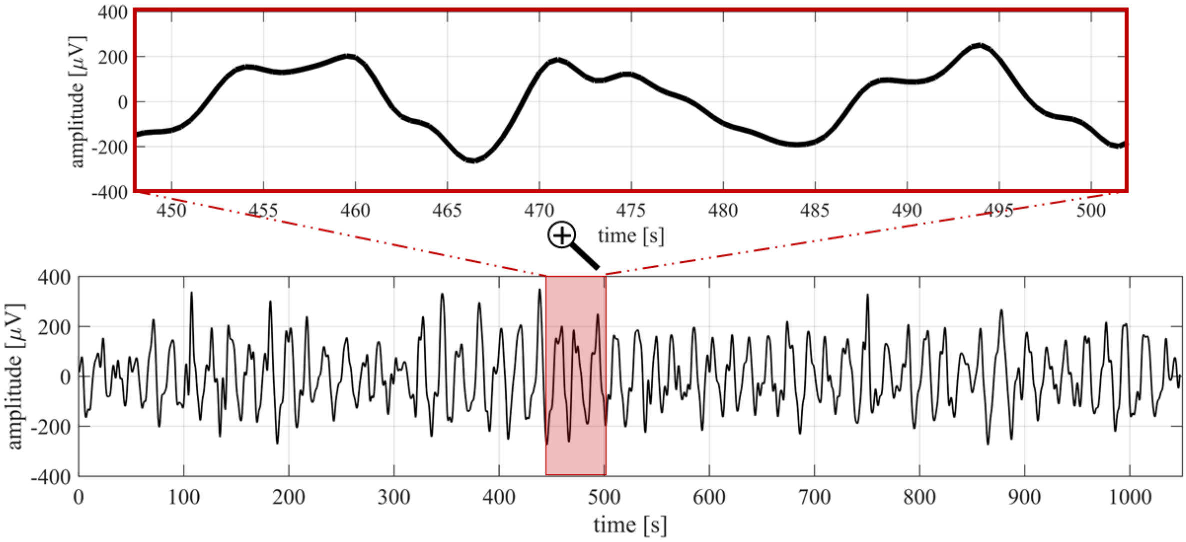


Figure 4.1. Illustration of the principle of zooming signal in order to obtain suitable visual observation. The EGG signal used is from a free, open-source EGG database (subject ID9 postprandial) [18].

A spectrum of the suitable recorded EGG signal from a healthy subject should contain a strong dominant peak at the frequency around 3 cpm (0.05 Hz) [40]. In specific cases, when recording is obtained in patients with gastrointestinal disturbances, or when they report symptoms of nausea, there can be more than one peak in the frequency characteristic. That phenomenon does not mean that the signal should be rejected from further processing since many more parameters could be calculated for a description of frequency content. If there is a "flat" spectrum of EGG signal, meaning that there is no variability in the magnitude on the whole frequency range, that signal is not suitable for further analysis. The main question that can be answered from the visual observation of frequency spectrum is: Is it possible to easily extract existing artifacts? If there are apparent artifacts superimposed on the slow wave activity in timeseries, but their frequency content is in a separate range from the EGG (<1 cpm and >10 cpm), digital filtering can resolve that problem. Examples of the acceptable and unacceptable spectrum are presented in Figure 4.2.

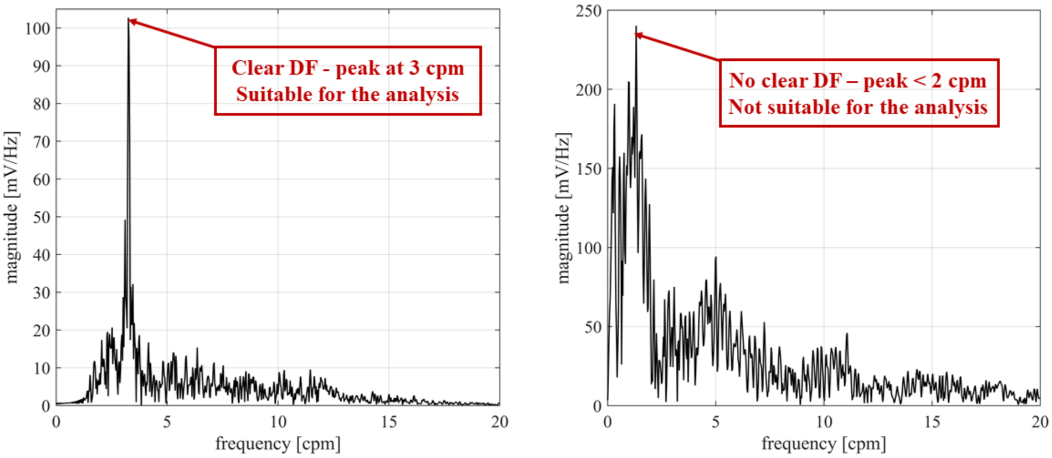


Figure 4.2. Presentation of frequency spectrums of suitable (left panel) and unsuitable – severely nauseated (right panel) EGG signals. The appropriate EGG signal that was used is from the free, open-source EGG database (subject ID9 postprandial) [18]. In contrast, the unsuitable signal was obtained during the testing of the device described in Chapter 2.

4.1.2. Quantification Methods

In our article [3] entitled "Lessons Learned: Gastric Motility Assessment During Driving Simulation" an algorithm for the evaluation of EGG signal is presented. This method aimed to determine which signal, from the three recorded via different channels, is the most suitable for the analysis. Initial assumptions were: 1) abrupt changes in the signal can correspond to movement artifact and 2) from the suitable recorded signals, free of severe noise presence, most adequate for the analysis is the one with the lowest power. To incorporate those hypotheses in the evaluation algorithm, maximum peak-to-peak amplitude and power of the signals were calculated. In the first step, out of the three signals, the ones with maximum peak-to-peak amplitude 100 % higher than any of the other two were excluded. Out of the remaining signals, the one with the lowest power was selected. The diagram of the algorithm is presented in Figure 4.3. To the best of the Author`s knowledge, this is the first automated algorithm for choosing the most appropriate recording channel. Compared to the visual observation, it delivered satisfactory results, mainly in terms of avoiding channels with substantial artifact power that could result in the false calculation of the features. In the corresponding protocol, electrode placement suggested in [2] and designed in order to cover the pacemaker region of the stomach, was used. Therefore, it is hypothesized that EGG signals from all recorded channels will deliver similar or the same amount of information regarding slow wave activity as long as there are no severe artifacts [2]. Subsequently, this algorithm provided channel selection by discarding compromised signals with excessive power originating from noise. This promising automated method should be further tested in different recording conditions and in a larger study group. Future research might be directed towards developing an estimator of usefulness of the signal, which could be used for the evaluation of automated algorithms.

A fractal dimension approach to EGG signal assessment is proposed in [115] for the examination of electrode surface area impact on electrogastrogram. Although this paper was not aiming to evaluate EGG signal quality, the principle can be transferred to it. Considering the nature of signal acquired by EGG devices, which is before the preprocessing often presented as breathing artifact and ECG artifact superimposed on slow wave activity, calculation of its fractal dimension could be an exciting approach.

Matsuura et al. reported in [116] the application of the Wayland algorithm to evaluate EGGs recorded in a supine and sitting position. This method, described as determinism evaluation of timeseries, could be a promising tool for assessing EGG usability in specific applications.

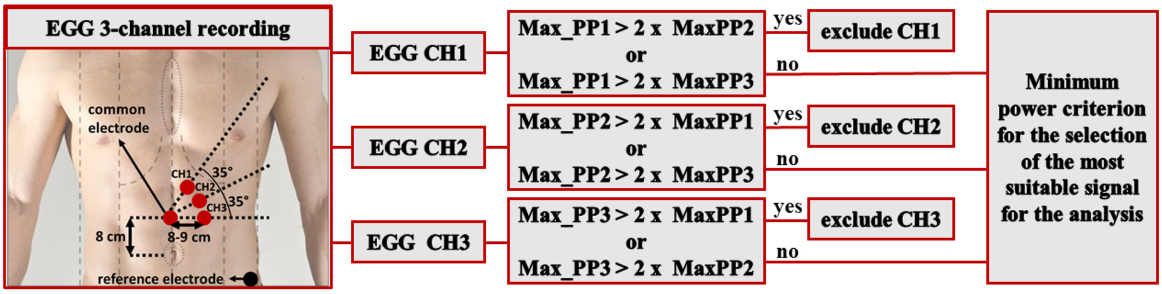


Figure 4.3. Schematic presentation of the evaluation algorithm for the selection of the most suitable out of the three EGG signals recorded with a 3-channel device [3]. EGG CH1, EGG CH2, and EGG CH3 are signals recorded using channels 1, 2, and 3, respectively. Max_PP1, Max_PP2, and Max_PP3 are calculated maximum peak-to-peak amplitudes from corresponding signals.

4.1.3. Artifact Recognition

For the suitable evaluation of the signal, an experienced examiner needs to be able to recognize the most commonly detected artifacts in the EGG recording. They include the following: 1) ECG (pulse rate) artifact, 2) breathing (respiratory) artifact, and 3) motion artifact. Suitable detection of its presence and severity is a crucial step towards deciding should the corresponding EGG be included in the analysis. There are two approaches for artifact identification, but the best practice is to use both timeseries and frequency spectrum of the signal.

Artifacts, especially ones with frequencies higher than the EGG range, are more prominent when a signal is recorded with a higher sampling rate. Therefore, it was decided to use the example of EGG recorded with the device described in Chapter 2. and a sampling frequency of 100 Hz. The corresponding signal was acquired in a healthy 23-year-old female (57 kg, 168 cm) in static conditions, supine posture after meal ingestion.

4.1.3.1. Timeseries Approach

Interfering artifacts coming from the heart muscle will be presented as superimposed, relatively sharp (depending on the hardware filters cut-off rates) peaks that occur periodically. Considering that the heart rate in healthy subjects varies from 60 bps (beats per minute) to 100 bps [117], it is expected that period between peaks is approximately 0.6 to 1.0 seconds.

Assuming that subject does not have any cardiac rhythm disorders and if no physical or psychological stress has been induced, this period should not change abruptly. In Figure 4.4. the example of ECG artifact (R and T waves) in timeseries of EGG signal is presented. It should be stated that based on our experience, T waves are not commonly present as a part of ECG artifacts in EGG timeseries.

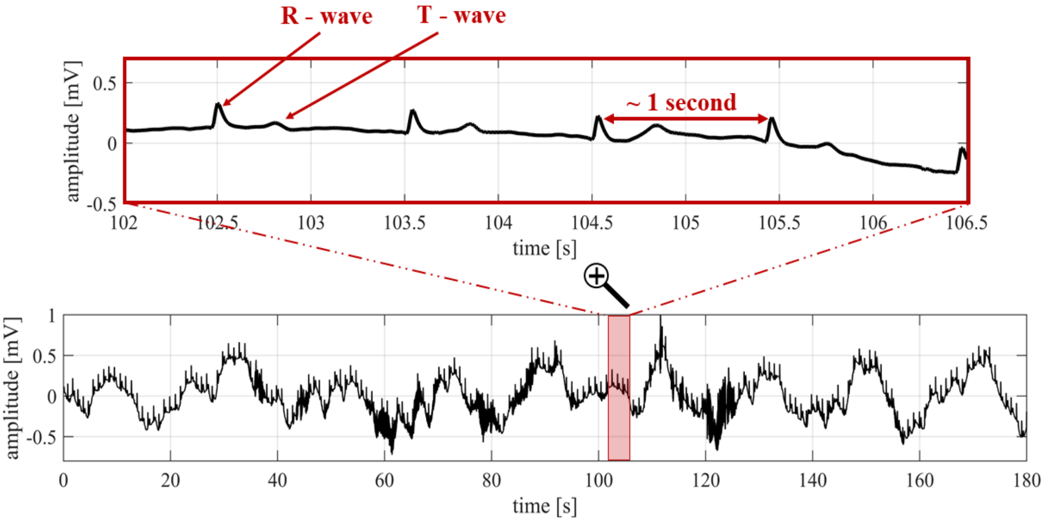


Figure 4.4. Example of ECG artifact presented in the signal recorded using device described in Chapter 2, with sampling frequency 100 Hz.

Similar to ECG, a respiratory artifact is a superimposed periodical signal with a period ranging from 0.86 s to 15 s [118]. Those deflections tend to be smoother than the ECG peaks, and the period can change suddenly (if the subject takes a deep breath). The illustration of breathing artifact is presented in Figure 4.5.

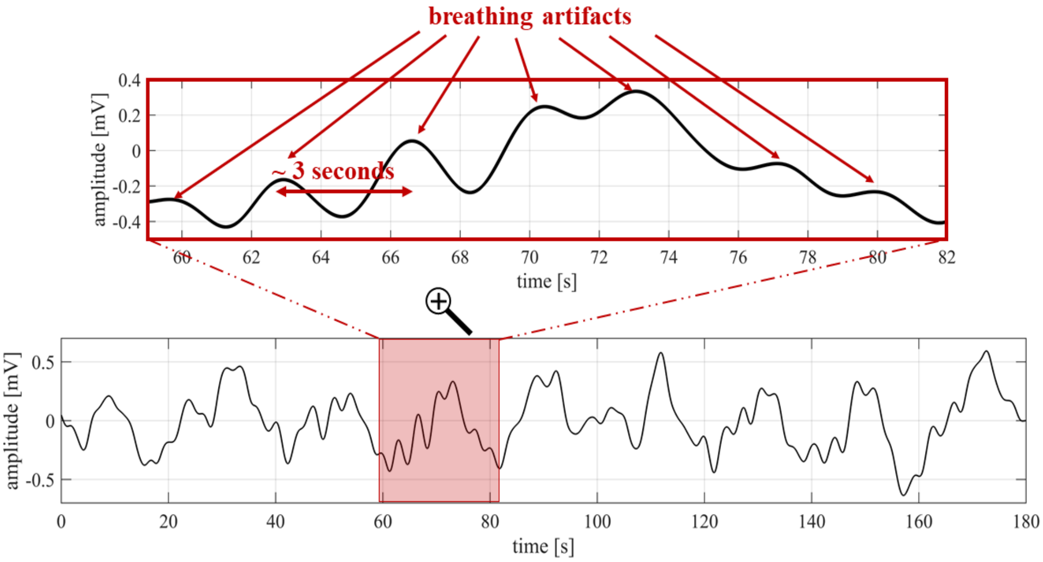


Figure 4.5. Example of EGG signal compromised with respiratory artifacts. Signal was recorded using the device described in Chapter 2, with a sampling frequency of 100 Hz.

Motion artifacts are arguably the most challenging issue in the EGG preprocessing. This is due to the fact that their frequency is often overlapping the EGG frequency content. Their identification is usually commonly done by the observation of timeseries. Motion artifacts are presented with abrupt changes in the amplitude given with the values higher than the rest of the slow wave activity. In Figure 4.6. apparent motion artifact in EGG signal is presented. In [3], motion artifacts were visually identified, and compromised samples were extracted from the timeseries manually. During the research described in this Dissertation, the gained experience revealed that this type of noise is often present in EGGs acquired by using a dynamic protocol.

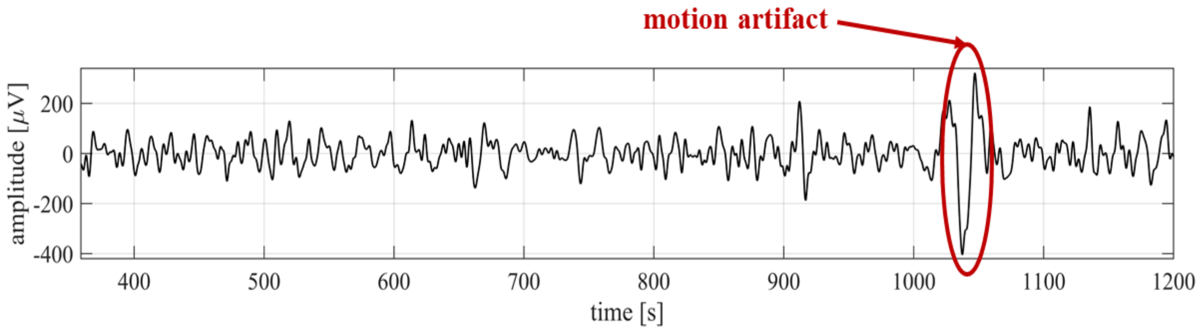


Figure 4.6. Example of motion artifact presence in EGG timeseries. The signal that was used is from the free, open-source EGG database (subject ID4 postprandial) [18].

It should be mentioned that a 50 Hz (or 60 Hz) common power grid artifact can also be observed in EGG signals, mostly if a recording is obtained with a high sampling frequency. One example is provided in Figure 4.7.

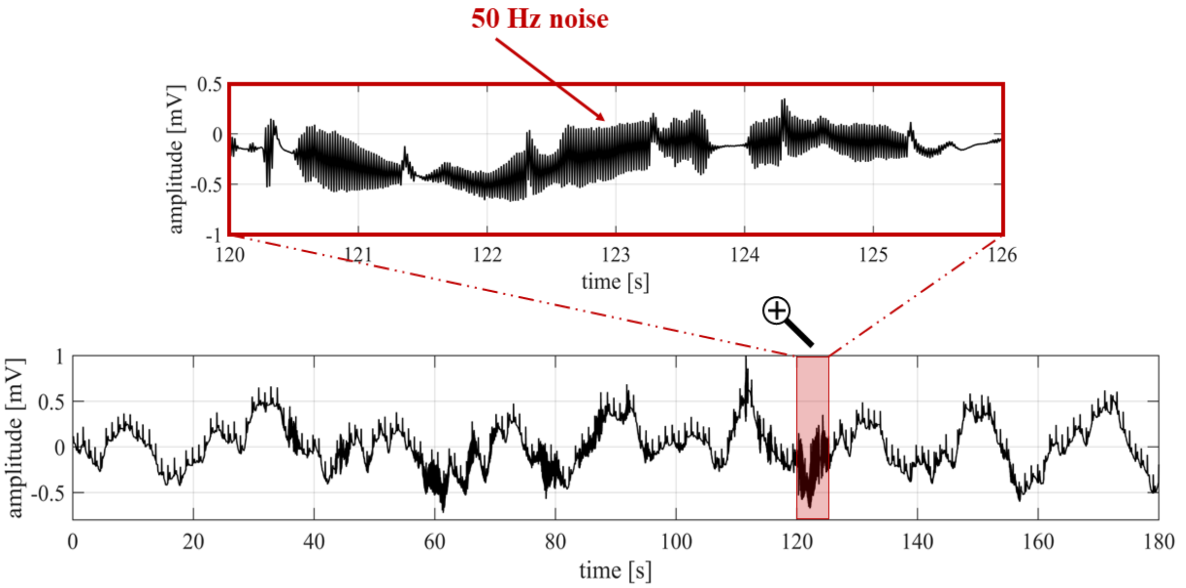


Figure 4.7. Example of noise visually detected 50 Hz artifact in EGG signal. Signal was recorded using the device described in Chapter 2, with a sampling frequency of 100 Hz.

4.1.3.2. Frequency Domain Approach

Observation of signal spectrum can reveal frequencies of the ECG and breathing artifact. Depending on the individual characteristics of each subject, it is expected that ECG artifact should be represented with frequency component from 1.0 Hz to 1.67 Hz (60 bpm to 100 bpm) [117], while breathing artifact should be around 0.08 Hz to 0.7 Hz (from 4.8 to 43 breaths-per-minute) [119]. In the recording that can be denoised from these two artifacts using digital filtering, its frequency content should be easily identified and separated from the EGG content, as presented in Figure 4.8.

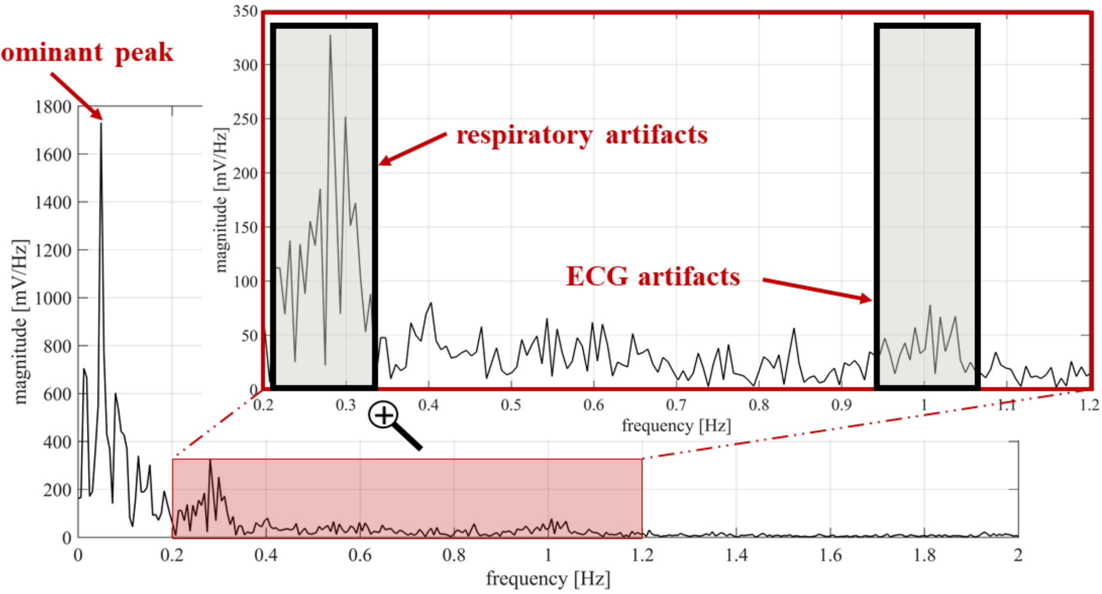


Figure 4.8. Illustration of the identification of ECG and respiratory artifact from EGG frequency characteristics. Signal was recorded using the device described in Chapter 2, with 100 Hz sampling frequency.

Unlike ECG and respiration, motion artifacts could be unidentifiable from frequency characteristic due to the overlapping with EGG content. Depending on the severity of the artifact, it is expected that there is a low-frequency component that almost completely covers EGG dominant frequency.

4.1.4. Discussion on EGG Quality Assessment

Ideally, method for EGG signal evaluation in terms of noise contamination should be automated since it would reduce time for the analysis and improve reproducibility and comparability of the results from various investigations. This subchapter provided the groundwork for further research on assessment of EGG quality. To this day visual observation remains the method of choice for the assessment of signal quality [50]. The empirical method for determination of the best recording channel in three-channel EGG recording presented in subchapter 4.1.2. [3] showed promising results for automatic discrimination among signals recorded in the same subject simultaneously, from different channels. While neural networks were already used for EGG artifact detection [61], to the best of the Autor`s knowledge they were not applied for signal evaluation. This could be one of the directions for future improvements of EGG signal quality assessment techniques. Also, fractal analysis, used in [115], could be applied due to the fractal nature of the raw EGG signal (periodical artifacts superimposed on slow wave activity).

4.2. Artifact Cancelation

It was already stated that artifact presence is one of the main pitfalls in the recording and analyzing EGG signals. That was a motivation for many investigators to design suitable methodology for artifact extraction. The majority of artifacts are in the frequency range that does not include the EGG range. Consequently, those noises can be extracted from the signal by applying digital filters with appropriate cut-off rates. On the contrary, disturbances in EGG with the frequency content that overlaps EGG requires different techniques. There are two approaches for addressing this issue: 1) manual extraction of artifacts and 2) automatic algorithms. While manual extraction offers confidence based on an educated EGG observer`s decision, automated methods are more convenient and suitable for large data bases.

4.2.1. Digital Filtering

Even though EGG recording devices usually have a band-pass filter implemented, it is still beneficial to do additional preprocessing with a relatively narrow band digital filter [47]. This will extract the possible artifacts with corresponding frequency content outside of the band defined by cut-off frequencies. Thus, the major decision to consider is related to the determination of the cut-off values. Some recommendations from the relevant literature are presented in Table 4.1.

Table 4.1. Recommendations for cut-off frequencies values from the literature. DF stands for the dominant frequency of EGG signal.

Reference	**Lower cut-off frequency range [rHz]**	**Higher cut-off frequency range [rHz]**
Mintchev et al. 1996 [23]	0.020	0.100
Sanmiguel et al. 1998 [26]	0.020	0.150
Amaris et al. 2002 [79]	0.000	0.300
Komorowski et al. 2015 [43]	0.015	0.150
Wolpert et al. 2020 [47]	DF – 0.015	DF + 0.015
Popovic et al. 2019 [2]	**0.030**	**0.250**

It should be mentioned that in [47] suggestion was to determine cut-off frequencies relative to the dominant frequency of the EGG, as specified in Table 4.1.

In our research [2] relatively wider band, compared to the values in Table 4.1., was used – 0.03 Hz to 0.25 Hz. The rationale behind it was to ensure the saving of all EGG components. When establishing cut-off frequencies for digital filters, the adopted frequency range (see subchapter 1.3.1.) needs to be considered. For example, we use EGG frequency range from 1 cpm to 10 cpm, which corresponds to 0.017 Hz to 0.17 Hz. Because this range is wider than some other commonly used ones, it is reasonable to apply a wider band-pass filter range. If the recording is more prone to breathing artifacts, as could be the case in sitting posture recordings, the upper cut-off limit should be decreased. In [6], we applied Butterworth 3rd order band-pass filter with frequency band 0.03-0.2 Hz.

4.2.2. Manual Extraction of Artifacts

Extraction of the samples compromised with severe artifacts is sometimes the only option to perform suitable EGG signal preprocessing [3]. This is mainly the case when noise induced by the subject`s motion during the recording session is present. The main reason for removing the noisy part of the signal is its effect on frequency content. Namely, while it is possible to disregard that part in the timeseries, its contribution to the corresponding spectrum cannot be overlooked. It can lead to a false conclusion about the lack of dominant frequency or its shift. In Figure 4.9. the example of misleading effect of motion artifact is presented.

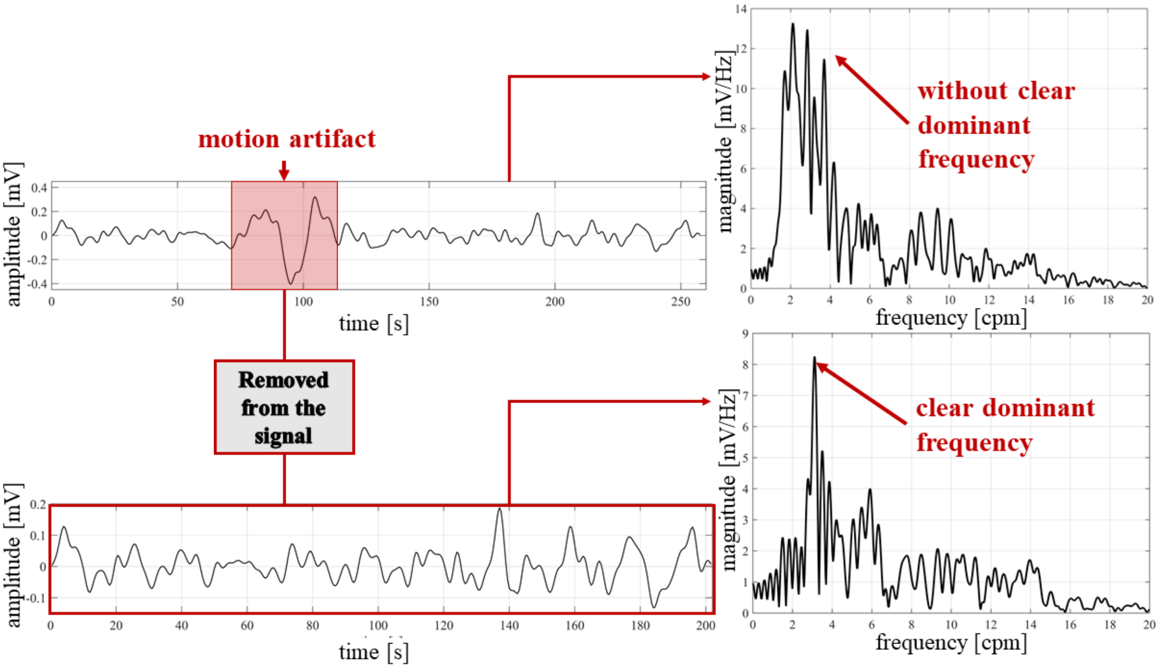


Figure 4.9. Benefits of manual extraction of movement artifacts exemplified. The signal that was used is from the free, open-source EGG database (subject ID4 postprandial) [18].

The severity of motion artifacts could be increased when EGG signal is recorded in a dynamic environment, since complete limitation of subject`s body movements is not attainable. That was the case in the EGG recordings obtained during driving simulation presented in [3]. In accordance with the recommendations from [50] educated visual observation of the signals was performed to detect and cancel motion artifact. Corresponding procedure included following steps [3]:

1. Experienced EGG researcher visually observed signals and detected the ones with motion artifacts.

2. The compromised samples of the signals with detected artifacts were marked.

3. Corresponding samples were deleted from the timeseries.

The examples of EGG signals recorded during driving simulation [3] that underwent previously described manual artifact cancelation are presented in Figure 2.10.

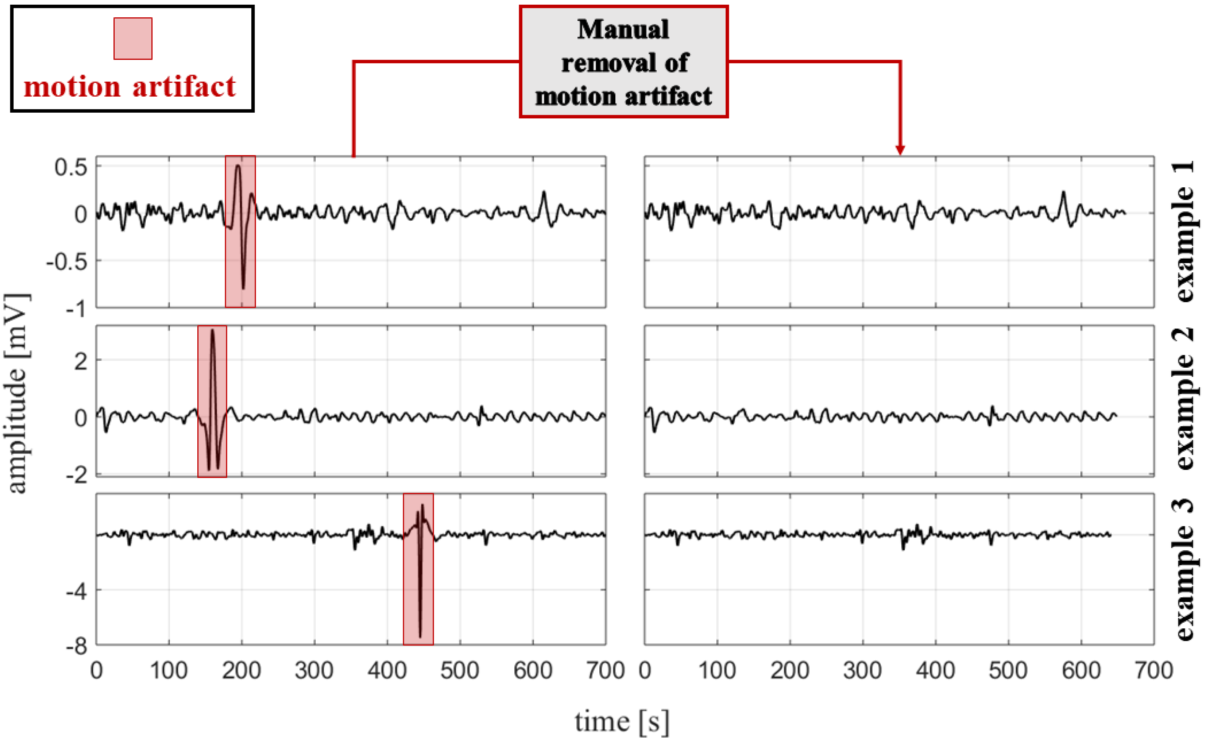


Figure 4.10. Sample EGG signals recorded for the study published in [3], that underwent manual extraction of movement artifacts.

4.2.3. Video-based Artifact Cancelation

One of the techniques that can be used to detect subject movements is the analysis of video signal obtained during EGG session. In [5], the method for motion artifacts cancelation via camera recording analysis was introduced. Additionally, it was tested through the case report.

In many electrophysiological recording protocols, there is a need for a camera that synchronously records the subject. The rationale behind that is to make a correlation between changes in signal parameters and physical activity of the corresponding subject or to provide any additional input to the measurement notebook. In EGG, there is a substantial need for an algorithm that offers the opportunity to link parts of the signal compromised by noise with movements from the subject in order to confirm the presence of the movement artifact. This can be done by including a recording of the video in the protocol. Analysis of that two-dimensional signal could be used as an automatic method for artifact cancelation.

4.2.3.1. Method for Video-based Artifact Elimination

Video recorded in grayscale was used for the analysis since the proposed algorithm does not require color frames. Analysis of video recording was performed in the following steps:

1. Mean value of all frames was calculated. The original video was used to generate a new sequence of images by subtracting the mean frame from other frames.

Rationale: As this video recording should be stationary (the subject is still asked to limit movements), the mean frame will represent the subject`s image while not moving. Considering that, after subtraction of it from other frames, most of the resulting ones will have pixels with values close to zero, except the ones in which there was a change originating from the subject`s movement.

2. Sequence of two-dimensional images was converted into the one-dimensional signal by summing absolute pixel values from each frame and assigning obtained values to the corresponding sample of the new signal.

Rationale: Analysis of 1D signal is more convenient, takes less memory, and could increase algorithm performance.

3. Samples that exceeded the empirically determined threshold - 15 % of the maximum signal amplitude was declared as the one that corresponds to the presence of movement in the video.

Rationale: By following the previous step, it can be deduced that samples of 1D signal with higher values have a greater chance to correlate to the actual movement of the subject in the video.

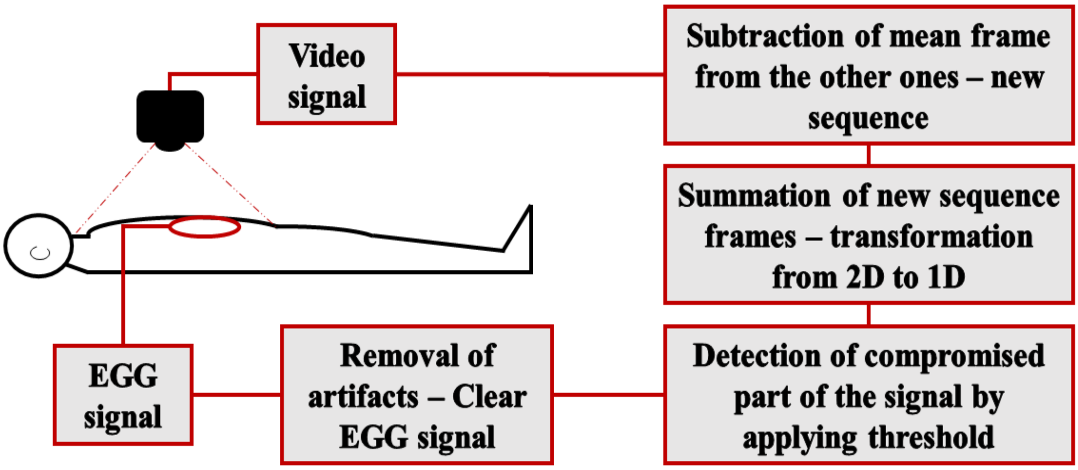


Figure 4.11. Scheme of video-based motion artifact cancelation introduced in [5].

Explained analysis of video recording results in points in time that correlate with the movement. Samples of synchronously recorded EGG signal that correspond with these points in time were extracted from the timeseries. The diagram of the algorithm is presented in Figure 4.10.

The algorithm was tested on EGG recording acquired in the healthy male subject (25 years old, 93 kg, 180 cm). The session lasted for 90 minutes, and it was obtained in a postprandial state while the volunteer was in a supine position. Power shares of spectrum in normogastric range (2-4 cpm) were calculated for the signal before and after video-based artifact cancelation.

4.2.3.2. Results for Video-based Artifact Elimination

Normogastric power shares were 33 % and 40 % for the EGG signal prior and after removal of possibly affected samples, respectively. The algorithm resulted in 247 removed samples (123.5 s) from the original signal.

4.2.3.3. Discussion of Video-based Artifact Elimination

Performance of the algorithm was beneficial in terms of an increase in normogastric content that was expected in this subject (postprandially, without any digestive disturbances) as a consequence of noise removal. While the percentage increase was not substantial, it should be stated that only 0.02 % of the samples were excluded. This implies that parts of the signal with no explicit slow wave activity were deleted, which speaks in favor of suitable detection of compromised samples by video-based artifact cancelation algorithm. In order to determine the effect of discarded artifact duration, intensity, and occurrence frequency on the resulting EGG signal quality, further investigation on a larger sample is required.

Due to the fact that this method was tested in only one subject (case study), an empirically set threshold of 15 % of the maximum amplitude should be considered preliminary and further examined.

As the direction for future work, besides testing in a larger study group, tendency should be to examine the influence of different video-recording techniques on the algorithm performance. Namely, different frame area or angle could have substantial effects on the method. The ultimate goal would be to develop a video-based movement artifact recognition algorithm that would work in real-time and give both subject and examiner feedback that there is a potential problem with the recording procedure.

Ultimately, approach that uses strategically positioned accelerometers with the purpose to detect movement should be designed. This could lead to an alternative approach or ideally combined approach that would incorporate benefits from both methods.

4.2.4. Fractional Approach for Noise Cancelation

Application of Fractional Calculus (FC) in combination with commonly used averaging filters for the extraction of ECG artifact from EMG signal recorded on pectoralis major muscle was presented in [120], [121]. Extension of that research was directed towards the opposite approach – cancelation of EMG artifact from ECG [122], [123]. The reported multipolarity of FC as an additional tool for noise cancelation was the motivation for the algorithm presented in [4], where the combination of FC and Savitzky-Golay filter (SG) was applied for processing of high-sampled semi-synthetic EGG signal contaminated with artifacts originating from the heart muscle.

Although EGG is the most commonly recorded with sampling frequencies above or equal to 4 Hz [41], more frequent acquisition of samples can be beneficial and increase the amount of useful information derived from the signal. Expectations are that with a higher sampling rate, there is a possibility of detecting electrical response activity, which correlates with smooth muscles contractions. Investigators in [43] proposed 200 Hz, while in [124], it was even higher (250 Hz). The main challenge with high sampling rate acquisition is the interference of ECG signal. Due to the relatively high amplitude (up to 10 mV) compared to EGG, ECG presents a significant disruption of EGG signal quality [76]. While smoothing filter, like SG, provides satisfactory results, this approach will also extract spike potential. The idea behind the research presented in [4] was to test non-inferiority of SG and FC combination, compared to the SG only, which can be the foundation for further improvement of FC based algorithms for artifact cancelation in EGG signals. The proposed approach was tested on the semi-synthetic signal.

4.2.4.1. Fractional Order Calculus (FC)

Calculation of derivatives with non-integer order can be referred to as fractional order calculus. It can also be described as expanded ordinary differential calculus. Its application is widespread and includes biomedical signal analysis, as well as modeling of biological systems and medical image processing [125], [126]. Form of FC that was used in [4] is defined in its general manner [127], [128] by the equation:

$$aD_t^{\alpha} f(t) = \lim_{n\to\infty} \left\{ \frac{\left(\frac{t-a}{n}\right)^{-\alpha}}{\Gamma(-\alpha)} \sum_{j=0}^{n-1} \frac{\Gamma(j-\alpha)}{\Gamma(j+1)} f(t - j\left(\frac{t-a}{n}\right)) \right\} \tag{1}$$

in which *Γ()* stands for gamma function, a for upper limit, α is the order of fractional derivative of function $f(t)$, while $n = [(t-a)/T]$, $t > a$, and T is sampling period for fractional order derivative numerical calculation.

4.2.4.2. Savitzky-Golay (SG) Filter

This Finite Impulse Response (FIR) digital filter, most commonly used for signal smoothing, was introduced by Abraham Savitzky and Marcel J. E. Golay in 1964. [129]. It is applied in many areas, including image and signal processing, chemistry, and spectroscopy [130]. The main advantage of SG over other averaging filters is its ability to preserve some amount of useful high-frequency content while performing low-pass filtering [131]. It uses a polynomial function of defined order for fitting a set of points in an odd sample size window. This fitting is done in the least square manner. Equations that were used in [4] for the implementation of the SG filter are following:

$$\varepsilon_n = \sum_{n=-M}^{M} \left(p(n) - x(n)\right)^2 \tag{2}$$

$$p(n) = \sum_{k=0}^{N} a_k n^k \tag{3}$$

where ε_n stands for mean squared error (window size is $2M + 1$, centered at $n = 0$) which was minimized. Coefficients of fitting polynomial $p(n)$ are a_k, while N was its order. In order to obtain output, calculations were done for each sample.

4.2.4.3. Method for Application of SG Filter and FC for Signal Separation

The semi-synthetic signal was made as a combination of EGG signal recorded with the device described in Chapter 2. in the healthy female subject (28 years old, 167 cm, 53 kg) after test meal ingestion (postprandial recording). The sampling rate for recording was set at 2 Hz, but afterward, the signal was upsampled to 1 kHz and preprocessed with Butterworth 3rd order band-pass filter (with cut-off frequencies of 0.03 Hz and 0.20 Hz). An artificial pulse rate signal was designed with a 60 bpm heart rate and the sampling rate of 1 kHz in order to be compatible with the previously described EGG signal. Adjacent waves of ECG (P and T) were extracted due to the low possibility of its prominence in EGG. Signal was additionally normalized to its maximum amplitude and superimposed to EGG. Gaussian white noise was also added to simulate more realistically in vivo conditions. The process of semi-synthetic signal production is graphically described in Figure 4.11.

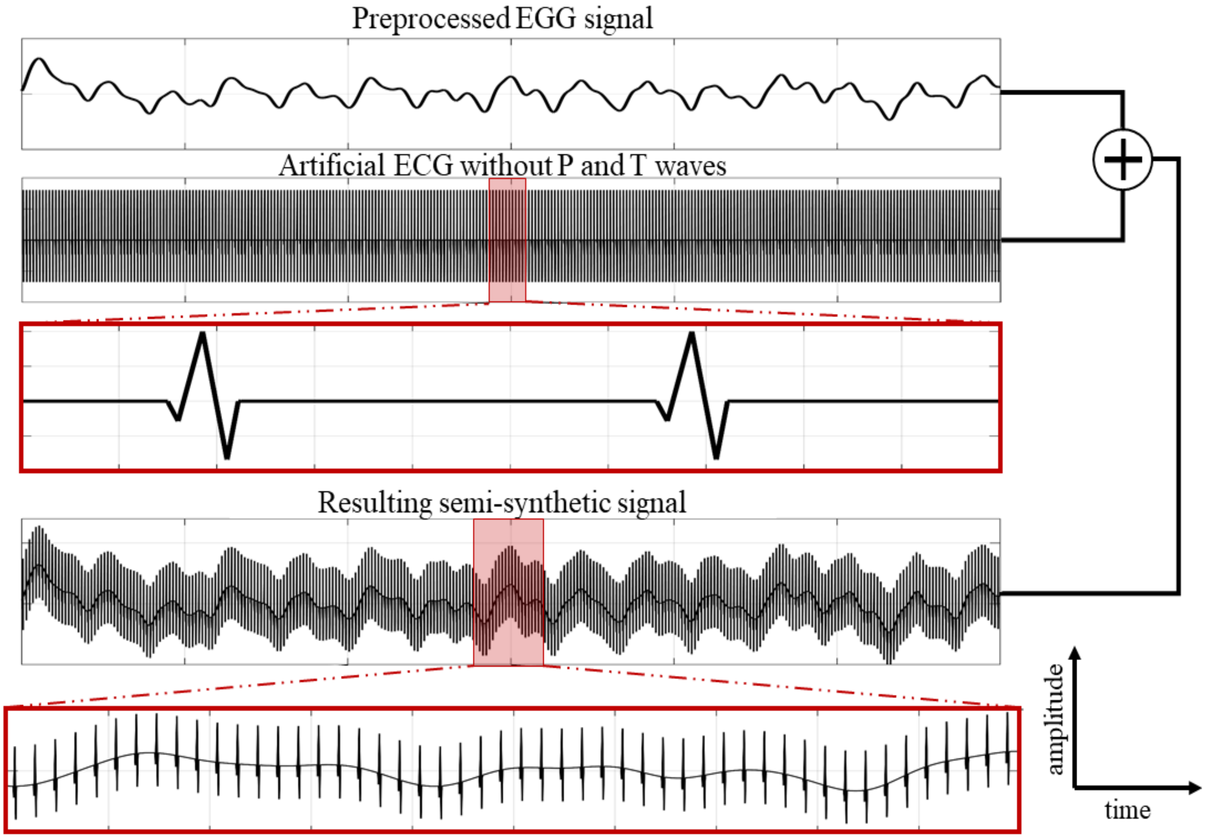


Figure 4.12. Production of semi-synthetic EGG signal contaminated with severe ECG artifact.

A two-step procedure was obtained to extract pulse rate signal from semi-synthetic timeseries:

1. FC with order from 0 to 1.2 with the step of 0.1, including the shorter step size (0.02) from 0.9 to 1, was applied to semi-synthetic signal;

2. SG filter with window size ranging from 99 ms to 999 ms (step 100 ms) was applied to semi-synthetic signal after FC.

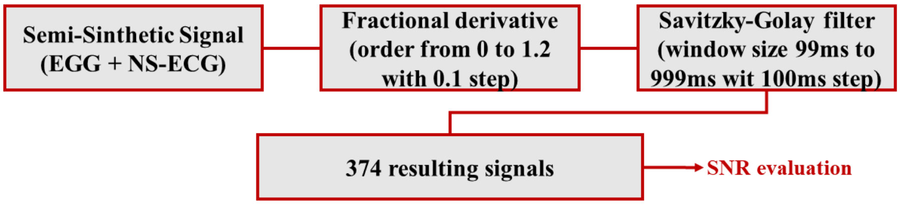


Figure 4.13. Scheme of testing protocol for performance evaluation of FC and SG combination applied on the semi-synthetic signal.

By applying combinations of different FC orders and SG window widths on both signal with and without Gaussian white noise, 374 different output signals were acquired and subsequently evaluated using signal-to-noise ratio (SNR) – where the signal was the semi-synthetic timeseries after FC and SG application, and the noise was synthetic NS-ECG signal. Described protocol is schematically presented in Figure 4.12.

4.2.4.4. Results of Application of SG Filter and FC for Signal Separation

For the signal without Gaussian white noise, SNR had its highest value (25.2 dB) for SG window size 999 ms and FC order from 0 to 0.9 and from 1.1 to 1.2. With Gaussian white noise, SNR was 8.3 dB for SG window size 999 ms and FC order from 0 to 0.94 and from 1.1 to 1.2. Results are graphically presented in Figure 4.13.

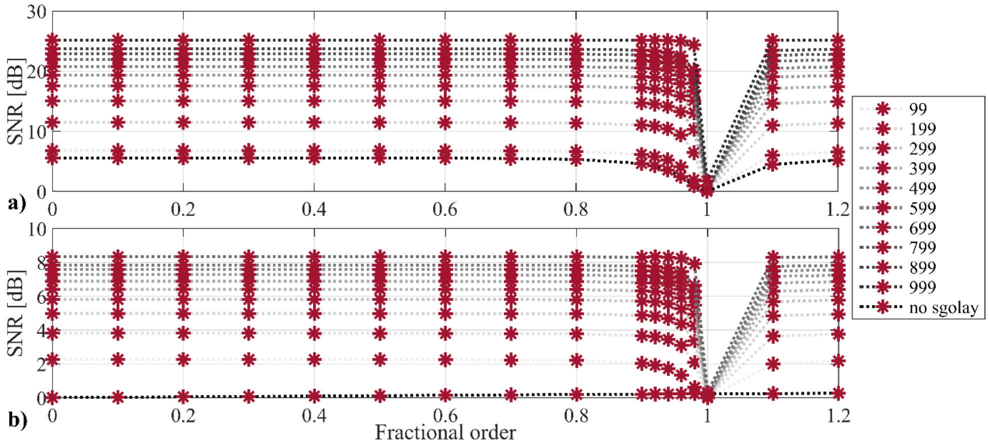


Figure 4.14. SNR values for the outputs of the algorithm with different combinations of FC order and SG window width, when the input was: a) without Gaussian white noise, and b) with Gaussian white noise. The figure is taken and modified from [120] with permission from the publisher.

4.2.4.5. Discussion of Application of SG Filter and FC for Signal Separation

Although there were no clear benefits from the addition of fractional calculus to Savitzky-Golay filter, these results suggest that there is no inferiority when fractional order is not close to 1. From the actual example presented in Figure 4.14. it can be observed that pulse rate peaks are entirely extracted from the signal and that now clear slow waves are present.

For more relevant conclusions regarding the suitability of fractional calculus as an additional tool for artifact cancelation from EGG timeseries, it is necessary to evaluate its performance on an actual high sampled large EGG signal database.

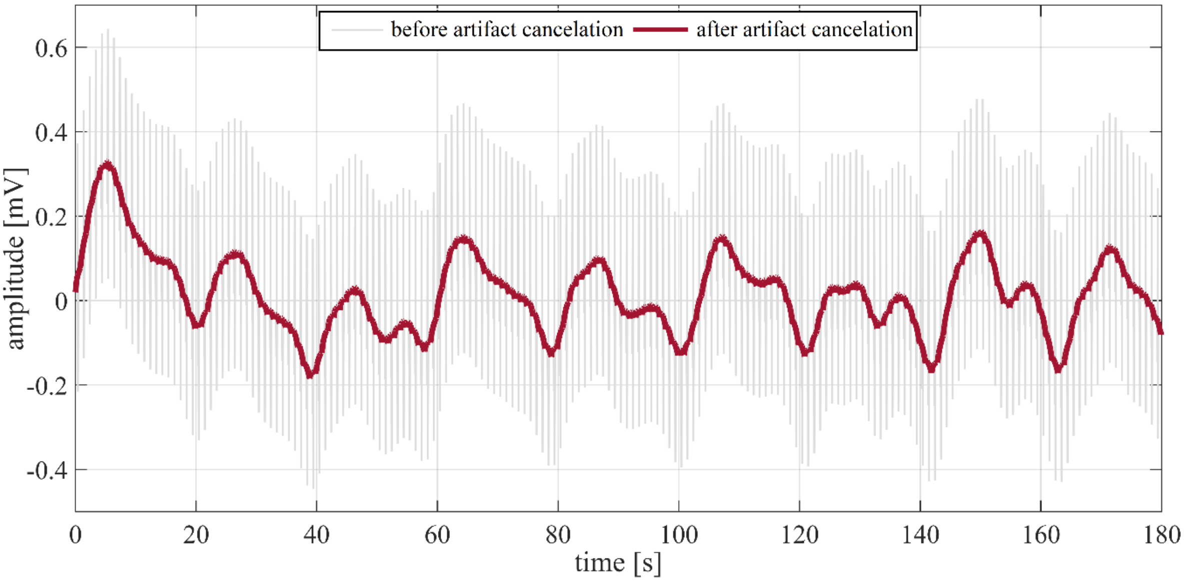


Figure 4.15. Exemplified illustration of combined SG and FC algorithm performance on the semi-synthetic signal. The image was taken and adapted from [4] with permission from the publisher.

4.2.5. Effect of Pathologies and Physiological State on EGG Artifact

As any other electrophysiological procedure, EGG can be affected by the individual characteristics of both healthy subjects and patients. One of the conditions that can influence EGG recording is obesity [132]. Namely, thickness of the tissue between surface electrode and smooth stomach muscles is correlated with the decrease in signal power [132]. This could potentially lead to inability to record EGG signal, but to the best of the Author`s knowledge, the limitations for EGG recording in relation to the obesity are still undetermined. Pathologies related to the myocardial muscle could influence amplitude and shape of ECG signal (mainly R-peaks) [133], [134] and subsequently influence manifestation of ECG noise in EGG signal. Additionally, cardiac arrhythmias influence ECG in the terms of intervals between two R-peaks [135], which could also be visible on EGG signal compromised with ECG interference. It should be mentioned that artifacts originating from the heart muscle, in majority of the cases, can be canceled from the EGG signal by the application of digital filters. In Table 4.2.

an overview of specific pathologies and physiological states that can interfere EGG signal are presented.

Table 4.2. Overview of pathologies that could influence artifact manifestation in EGG signals.

Individual Characteristics	**Influence**	**Reference**
Obesity	Thickness of the tissue at the site of surface electrodes could decrease the power of the slow wave signal and subsequently affect SNR.	Riezzo et al. 1991 [132]
Dilated Cardiomyopathy	Due to the increased size of the heart left ventricle amplitude of R waves could be increased. Subsequently it can be expected that ECG artifacts in EGG would be more prominent.	Feldman et al. 1985 [133]
Hypertrophic Cardiomyopathy	Increased thickness of the myocardial wall can influence amplitude of R waves, and subsequently affect ECG artifacts in EGG signal.	Madias 2013 [134]
Cardiac arrhythmias	Irregular heart rhythm which is present in various cardiac arrhythmias can influence manifestation of ECG artifact in EGG signal.	Antzelevich et al. 2011 [135]

4.2.6. Discussion of Artifact Cancelation

Advancements in EGG signal processing are going in the direction of entirely automatic extraction of noise from the timeseries. Several novel approaches were proposed in the last few decades for computerized artifact cancelation from EGG.

In 1993. one of the first articles regarding adaptive filtering was published by Chen et al. [78]. They were mainly focused on the cancelation of motion and respiratory artifacts. The main aim was to compare time-domain, frequency-domain, and transform-domain of adaptive filtering. Based on the results, it was stated that frequency-domain adaptive filtering offers the best performance, especially for the breathing artifacts extraction. The extension of this work was presented in the following investigations [43], [136]. Komorowski and his colleagues described an interesting approach for denoising high-sampled EGG signal that included adaptive filtering based on the ECG derived respiratory signal [43]. The principle was to calculate respiratory signal by using the fact that R-wave amplitude depends on the breathing rate. Subsequently, they used the estimation of respiratory signal to determine adequate filtering parameters. Additionally, in 2018, the same authors (Komorowski et al.) introduced a method that combined Noise-Assisted Empirical Mode Decomposition (NI-MEMD) and adaptive filtering [136]. NI-MEMD was used to extract reference signal that was later used for adaptive filtering.

Empirical Mode Decomposition (EMD), as a technique for disintegration of the signal in its basic components, is often used for biosignal processing [137]–[141]. It was introduced to EGG field in 2000. by Liang et al. [66], where promising results regarding its performance were reported. Similarly, in 2007. Peng et al. investigated the possibility of Independent Component Analysis (ICA) application to separate smooth muscle electrical activity from artifacts [65]. They concluded that this approach could be used for the reliable extraction of gastric slow wave activity. Consequently, in 2018. Sengottuvel et al. proposed a method incorporating both EMD and ICA and obtained promising results [64].

It should be mentioned that several investigators proposed a neural networks approach for denoising and analysis of EGG signal [61], [142], [143]. In the paper by Haddab et al. [61], a three-layer neural network was used to detect motion artifacts.

Although many different solutions were offered over the course of time, none of them has proven their efficacy. That suggests that in the future, researchers in this area should be focused on the evaluation of different algorithms on large databases of various EGG signal. Only by obtaining that kind of analysis, there is a chance to conclude which methodology is most suitable to be standard EGG preprocessing technique.

4.3. EGG Signal Feature Extraction

A prerequisite for the suitable analysis of EGG signal is to quantify its characteristics, which can be done by performing feature extraction. Resulting parameters are medium toward acquisition of scientific discoveries and expansion of knowledge in the corresponding area. Thus, one of the main challenges in every field, including electrogastrography, is the definition of standard parameters.

4.3.1. Standard Features

Lack of standardization in EGG research did not bypass the parametrization of signals. There are still no recommendations regarding which parameters should be used. Despite that, it can be stated that there is a variety of commonly accepted quantifications of EGG signals that are widely used. They can be divided into two groups based on the domain from which they are calculated: 1) time-domain parameters and 2) frequency domain parameters. Additionally, to incorporate both time and frequency domain benefits, Running Spectrum Analysis was introduced [17].

4.3.1.1. Time-domain

Two main parameters that can be calculated from EGG signal in time are its amplitude and power.

Amplitude of the signal is calculated in µV or mV, and it can change during the recording. Those changes can be an indicator of alterations in the contractility of smooth muscles. It is believed that spike potentials that occur during stomach contractions could increase amplitude of the signal [144]. From the work of Chen et al. [15], it is suggested that changes in amplitude do not correlate between mucosal and cutaneous recording. This is because the different abdominal anatomy of each subject can influence amplitude of EGG signal. Consequently, analysis of EGG amplitude should be taken with caution.

Power of the signal calculated from timeseries can also be used. It should be utilized as a comparator between two recordings in the same subject. In [19], it is reported that it is generally accepted that if a ratio between power of the signal recorded after some event and the power of the signal recorded prior to it is higher than one, that event resulted in increased contractility of stomach muscles. On the contrary, ratio values less than one suggests that there was inhibition in contractility.

4.3.1.2. Frequency Domain

One of the milestones in electrogastrography was the introduction of spectral analysis by Stevens et al. in 1974. [145]. After that, most parameters for the description of non-invasively recorded gastric electrical activity were derived from the frequency domain. In this chapter, the most commonly used features will be described.

Dominant frequency can be defined as the position of maximum magnitude peak in the spectrum of the EGG signal [17]. From the recordings performed in healthy subjects, this peak should be easily identifiable around 3 cpm (0.05 Hz). Its magnitude is also used as it correlates with a predominance of frequency content in a corresponding frequency range.

As it was stated in Chapter 1. three frequency ranges are defined: 1) normogastric – 2 cpm to 4 cpm, 2) bradygastric – 1 cpm to 2 cpm, and 3) tahygastric – 4 cpm to 10 cpm [17]. Based on this division, many parameters can be calculated. Namely, spectral power of the signal in the mentioned limits (with slight alterations explained in subchapter 1.3.1.) is widely used [16], [37], [5], [96]. It describes frequency content in terms of ranges of interest for the interpretation of EGG. Overall power is also used, mainly as a factor in power ratio defined as a ratio between postprandial and fasting power. It is suggested that if value of PR is less than one, it indicates that there is prolonged GI emptying [17].

Instability coefficient can be determined by calculating mean value and standard deviation of DF from different recordings acquired in the same subject and dividing standard deviation with mean value. Lesser variation in DF will result in lower IC, and subsequently in more stable DF in related subjects [17].

4.3.1.3. Running Spectral Analysis

Running Spectral Analysis (RSA) was introduced by van der Schee et al. in 1982 [146] to overcome the inability to perform observation of frequency domain EGG parameters variability over time. This method offers the possibility to analyze spectrums of the equally long portions of the signal. It is used for both visual observation and calculation of parameters.

RSA is obtained by dividing EGG timeseries into a uniformly long part, calculating Fast Fourier Transformation for each, and plotting them to form a pseudo-3D chart, as presented in Figure 4.15.

The signal used for the example of RSA was recorded in a healthy 28-year-old male (205 cm, 112 kg) postprandially while resting for 40 minutes. The subject was asked to limit movements and not to speak or laugh. From the visual analysis of RSA, it can be concluded that there was a clear dominant peak around 3 cpm during the whole session. A slight increase in DF is also observable, which is consistent with the reported postprandial increase in EGG frequency [2].

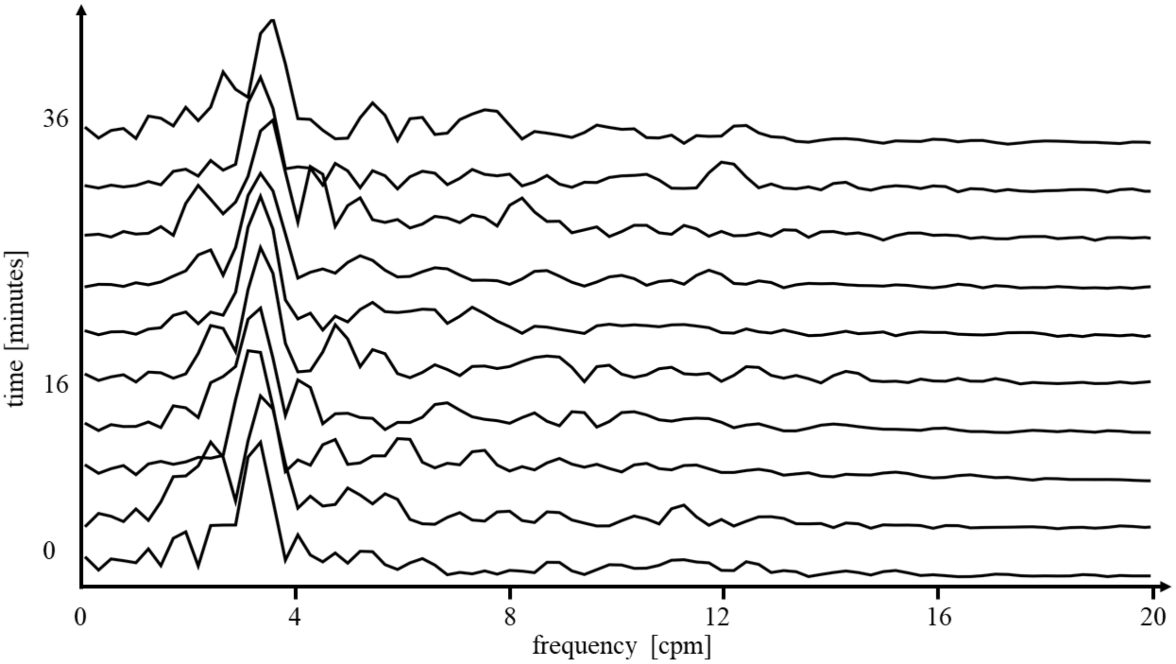


Figure 4.16. Example of Running Spectral Analysis of EGG signal recorded in healthy volunteer for 40 minutes.

The most commonly used parameters that can be derived from RSA are following:

1. % of time in which DF was in each out of three EGG ranges [19];

2. % of slow wave coupling (% SWC) – the percentage of time during which DF is similar among different recording channels in multichannel EGG [16];

3. instability coefficient (IC) for one EGG recording [40].

4.3.2. Novel Parameters

One of the directions in EGG methodology improvement is the development of new parameters for the quantification of signal characteristics that will improve the assessment of the GI tract. For the purposes of research published in [3], [6], three novel parameters were introduced. They include: 1) Root-Mean-Square (RMS) value of EGG signal in time, 2) Median Frequency (MF) of EGG spectrum, and 3) Crest Factor (CF) of EGG spectrum. Each of these parameters was tested in the corresponding investigation and gave promising results for assessing the gut state in a variety of recording conditions. Their usability was examined mainly for dynamic EGG recordings described in Chapter 5. Those preliminary results revealed that there are many benefits in using these novel features for the description of altered EGG signals.

4.3.2.1. Root Mean Square

Root Mean Square (RMS) value is widely used in signal processing, but prior to the results published in [3], to the best of the Authors` knowledge, it was not used for the analysis of EGG signal. It provides an estimation of mean amplitude and power value. Thus, it can be used as an alternative for mentioned parameters. The equation that defines it and provides guidance for its calculation is following:

$$RMS = \sqrt{\frac{1}{N}\sum_{i=1}^{N} sig(i)^2}$$

(4)

where $sig(i)$ are samples of EGG signal and N is its length in samples.

The example of RMS value of the EGG signal is presented in Figure 4.16.

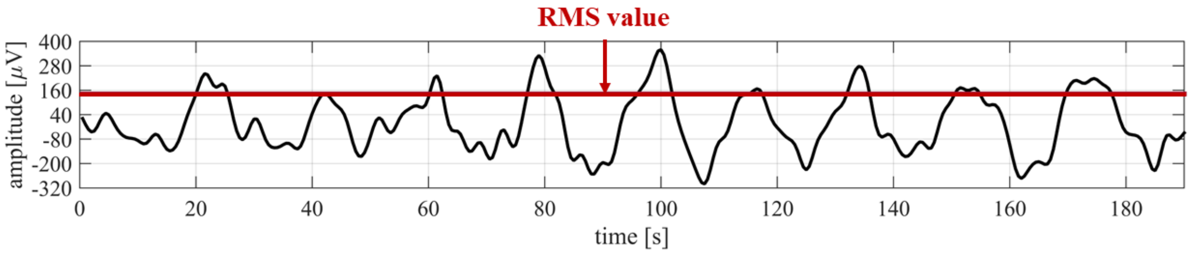


Figure 4.17. Example of calculated RMS value calculated on EGG signal from open-source database [18] (subject ID7 postprandial).

Based on the fact that amplitude and power of the signal rise postprandially, it can be expected that RMS will have the same response to the ingestion of test meal. In [3], it was suggested that there is an increase in RMS value during and after subject was experiencing driving simulation. Additionally, as reported in [147], violent video stimulus can also result in EGG RMS increase.

4.3.2.2. Median Frequency

Although dominant frequency is the most commonly used EGG parameter, it has its limitations. Namely, it is highly dependent on the presence of one dominant peak in the signal spectrum. This can lead to an inability to calculate DF or even error in determining its value when EGG frequency characteristic has more than one peak in the normogastric area. This is not often the case for the signals acquired in healthy subjects while resting, but for patients with gastrointestinal disorders or healthy volunteers exposed to some kind of stimulus that can provide gastric disturbances. Therefore, it is relatively common that the spectrum of EGG does not have a clear dominant peak. Considering the fact that it is crucial to have a suitable quantification method for these signals, there is a need for an adequate parameter.

Median frequency is mainly used for the analysis of EMG signals in frequency domain [148], [149]. It can be described as an indicator of a shift in frequency of spectral power density, making it suitable for evaluating changes in frequency content of EGG signal. By definition, MF divides power spectrum into two parts with equal areas under the curve, as presented in Figure 4.17.

For the recording acquired in a healthy subject while resting, MF is expected to correlate with DF. For the EGGs with altered spectral characteristics, it follows the trend of the frequency shift. Namely, if there is an increase in the tachygastric frequency range, it will be expected for MF to have higher values.

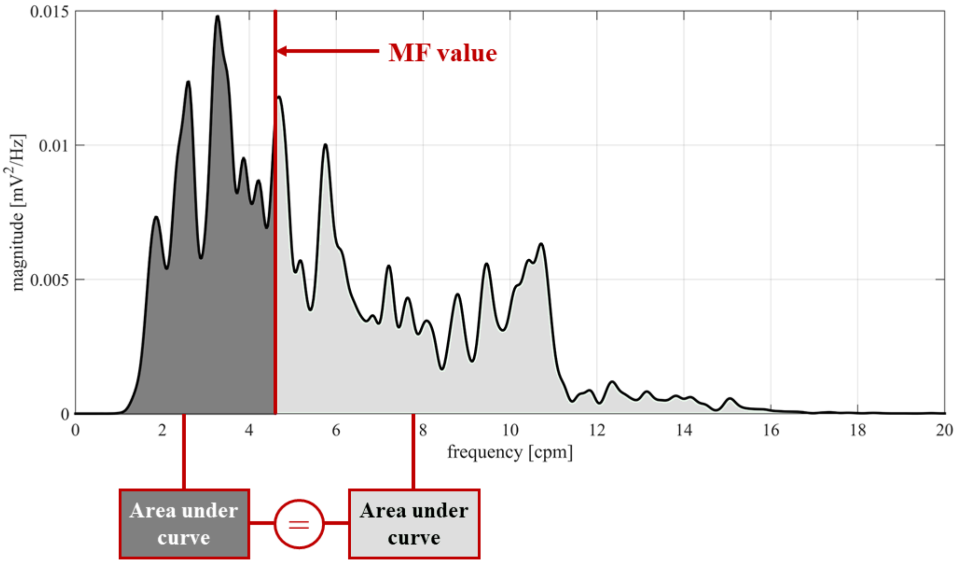


Figure 4.18. Example of signal with illustrated method form median frequency calculation. EGG signal is taken from the free, open-source EGG database [18] (subject ID6 postprandial).

4.3.2.3. Crest Factor

Many parameters are used to describe EGG frequency content, but there was a lack of the one that will describe its shape. As there is an expectation that the usual shape of EGG is characterized with a clear dominant peak, it was decided that crest factor, as the measurement of peak prevalence, could be a suitable choice for the assessment of EGG spectrum morphology.

CF is defined as the ratio between peak amplitude and RMS value. The principle of its calculation is presented in Figure 4.18.

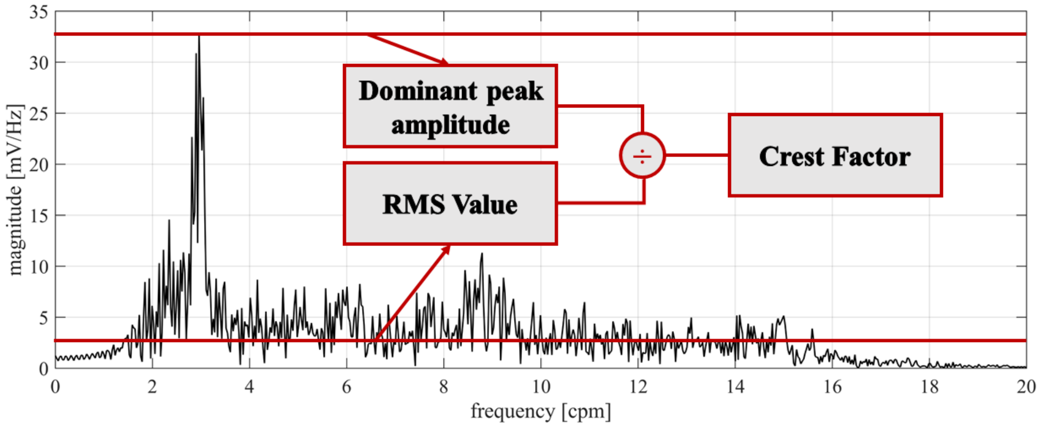


Figure 4.19. Calculation of crest factor presented graphically with the example of EGG frequency characteristic. Used EGG signal is from the free, open-source EGG database [18] (subject ID1 postprandially).

Based on its nature, it is expected that CF has higher values for clean EGG signals with a spectrum characterized by a majority of frequency content in the dominant peak. On the contrary, signals with variations in frequency content throughout the recording should have decreased CF values. The first application of crest factors published in [3], [6] showed encouraging results. It is suggested that it can quantify alterations of a frequency spectrum in a highly efficient manner.

4.3.2.4. Novel Parameters – Discussion

Novel parameters were proposed with the aim to describe spectrum alterations induced by different states of gastrointestinal tract caused by the virtual reality experiences and application of driving simulator.

RMS is commonly used for EMG signal analysis, mainly for the estimation of signal power and contraction intensity of skeletal muscles [150]. Consequently, it was rational to introduce this parameter into the area of smooth muscle electrical activity assessment, especially due to the fact that EGG amplitude can be changed in response to external stimuli [151]. Scientific studies published in [3], [6] and in detail explained in Chapter 5, aimed to examine influence of motion sickness during virtual reality and driving simulation on EGG. It was expected that amplitude of the signal will increase as an effect of induced sickness symptoms. Therefore, having the parameter that can be used for the estimation of signal amplitude, such as RMS, was required.

MF is commonly used as a descriptor of EMG signal in studies of muscle fatigue as its changes are correlated with the frequency shifts of signal spectrum [152], [153]. MF was introduced for EGG assessment in this Dissertation as it was hypothesized that MF would be more sensitive to the frequency spectrum alterations than DF, which depends only on the position of the most dominant peak in the spectrum [40]. As MF divides the spectrum into the two parts with same areas under the curve, it was hypothesized that it would be affected by even slight changes i.e., shifts in the frequency content. Finally, the results presented in Dissertation showed that MF was essential for an adequate comparison between the frequency characteristic of the baseline EGG and the one recorded during driving simulation or virtual reality application [3], [6].

In order to assess the shape of EGG spectrum in terms of peak prominence, we used CF. Previously, this parameter was used in order to determine the level of ECG noise in the EMG signal by assessing the prominence of ECG artifact [120]. CF parameter was used in order to assess the prevalence of the dominant peak over the rest of EGG spectrum. CF, unlike MF or DF, describes frequency characteristics of the dominant peak amplitude of EGG signal in relation to the power of the rest of the signal. Thus, CF can reveal alterations in the signal characteristics not being related to the frequency shift, but still being sensitive to the presence of frequency components that are not part of dominant peak. In conclusion, CF is an ultimate parameter for the description of spectrum shape, and it can be of crucial importance for quantification of changes EGG frequency changes caused by the measurements in dynamic environment [3], [6].

Due to their above mentioned characteristics, RMS, MF, and CF can vary independently. This speaks in favor of using all three parameters for parameterization of EGG signal.

4.4. EGG Interpretation

In the terms of its application, it is important to have in mind two EGG approaches – clinical and non-clinical. While instrumentation and the basis of its analysis remains the same in both, there are differences in the protocol and interpretation that should be pointed out. The aim of this Dissertation was to provide insights in common challenges and recommendations for further improvement of EGG, which could enhance both diagnostic and research application. However, corresponding studies [2]–[7] were non-clinical, meaning that only healthy participants were included in the protocols.

Clinical application of EGG as a diagnostic procedure remains limited due to the lack of the standardization [35]. Despite that, there were many clinical studies reporting promising results regarding different patient conditions (gastric and non-ulcer dyspepsia, chronic idiopathic intestinal pseudo-obstruction, cyclic vomiting syndrome, idiopathic gastroparesis, nausea in pregnancy, *helicobacter pylori*, irritable bowel syndrome, and central nervous system disorders in children) [29], [32], [34]–[36], [38], [83]. One of the challenges in the EGG-based diagnostics is scarce benchmark data obtained in healthy subjects. As a result of the investigation published in [2], recordings obtained in 20 healthy subjects with calculated parameters are published in an open access repository with CC license [18].

5. Assessment of Gastric Myoelectrical Activity in Dynamic Environment

Electrogastrography is often described as an additional diagnostic tool, which implies that its main application should be in clinical conditions for the assessment of the gastrointestinal tract in patients with various digestive disorders. Although this is the primary role of EGG, there is still no wide clinical application. On the contrary, many researchers are still proposing diverse EGG based techniques for the evaluation of smooth muscle electrical activity in healthy subjects. The rationale for that is in the fact that even healthy subjects can experience symptoms of GI disorders (nausea, vomiting, stomach pain, etc.) when they are exposed to various external stimuli. EGG signal parameters` response could be an exciting marker of these symptoms and subsequently provide relevant information for understanding corresponding phenomena. The main challenge in this area is to acquire a reliable EGG signal, in a dynamic environment, synchronously with a stimulus that could induce symptom and subsequently perform adequate analysis and interpretation.

In this Chapter, published results regarding the application of EGG in non-standard conditions during Virtual Reality (VR) and Driving Simulation (DS) will be presented with a comprehensive discussion regarding its relevance and usefulness.

5.1. Introduction to EGG Recording in Dynamic Environment

The phenomenon with a major, mainly negative, effect on the traveling, virtual reality, or simulation experience is motion sickness (MS). It can be defined as an expected response from a healthy subject to unusual motion perception, real or simulated (virtual). The occurrence of MS is often described as unpleasant, and as such, it has a negative influence on the modern technology that can induce it. One of the challenges in addressing this issue is an assessment of corresponding physiological responses. [154]–[156]

Since any modality of sickness is correlated with a gut feeling, thus - gastrointestinal system, it was sensible to approach this task using techniques for GI evaluation. The non-invasiveness of EGG recommends itself as the first choice. Implementation of EGG as an assessment method for MS requires modifications in its methodology. Namely, while EGG is most commonly recorded in static conditions for a long-lasting period of time, this novel application dictates dynamicity and a decrease in recording time. Thus, the recording protocol will be different from the one commonly used in static conditions. Additionally, an alternate approach toward analysis and interpretation was also needed.

Nausea as an symptom was evaluated by electrogastrography and EGG showed promising results [30], [32], [36], [59], [157]–[160]. In the paper published by Bob Cheung and Peter Vaitkus in 1998. [161], an overview of EGG applications related to motion sickness in the previous ten years was presented. It was suggested that there were some controversial results. Many investigations reported promising findings regarding the correlation of EGG parameters and visually, simulator and flight induced sickness [112]–[114], [161]. There were also some promising results regarding the evaluation of pharmaceuticals usage for MS.

However, some attempts to confirm these findings failed [161]. This suggests that there is a need for careful discussion and assessment of EGG technique as an MS evaluation tool, which is the focus of this research.

5.2. Protocol for EGG Recordings in Dynamic Environment

The importance of recording protocol to the reliability of EGG signal is substantial. Even slight variances in the setup could induce changes in the timeseries that subsequently reflects on the EGG parameters values. While recommendations for the recording in static conditions are discussed in many articles [48], [97], [105], [162], information regarding acquisition of EGG in a dynamic condition is scarce. Many investigators in their research considered some parts of a dynamic protocol, like subject posture [113] or limited duration of recording [163]. Still, overall assessment, to the best of the Author`s knowledge, was not reported. This was a motivation for providing a comprehensive analysis regarding important segments of recording protocol by following the questions defined in Chapter 3:

1. How long should dynamic EGG recording last?

2. In what posture should it be obtained?

3. What are the recommendations regarding electrode placement?

4. Should it be done in a fasting or postprandial state?

While it is common for EGG to be recorded for more than 30 minutes [40], in some circumstances, for the sake of subjects comfortability, it is preferable to have short term recording (5-15 minutes) [163]. In one of the first articles that addressed MS [114] by Stern et al., baseline EGG was recorded for 15 minutes in resting state, 15 minutes during circular vection drum rotation, and additional 15 minutes afterward. Tokumaru et al. in [46] proposed slightly decreased longevity of acquisition – 8 minutes prior, 16 minutes during, and 16 minutes after the rotational stimulus. Benson et al. used 5 minutes of baseline for the same application followed with 4 minutes sequences during drum rotation [164]. Kim et al. [165] addressed biofeedback in a VR environment, 5 minutes before, 9.5 minutes during, and 1 minute post VR experience. Five minutes of baseline recording in a healthy subject corresponds to approximately 15 slow waves of EGG, which could be enough to determine the resting parameters. Undeniably, a longer duration (~15 minutes) for baseline recording is beneficial in terms of decreased chances to have an unusable recording. On the contrary, shortening of it increases subject`s comfortability and procedure efficiency. Duration of EGG acquisition, while a stimulus is ongoing, depends on its stimulus longevity, but post stimulus recording can be useful to determine time for which EGG parameters will return to the resting values. In [147], during and after EGG recordings were analyzed as one continuous signal. This could be the most optimal practice as it provides an overall assessment of stimulus-induced EGG alterations.

Investigations related to the body posture effects on EGG reported that supine position is the most reliable for its acquisition [45], [116], [166]. For various dynamic protocols such as EGG recording during driving simulation where subject should hold the wheel and control the vehicle, that is not an option. Therefore, the results suggesting that adequate EGG in sitting position are viable were substantial [166]. Investigations published in [113], [114], [164], [165] confirmed that suggestion because each EGG was recorded while subject was in a sitting position. While for driving simulation, there is no possibility to perform recordings in a supine position, for VR, that is an option. However, in [6], it was decided to use a sitting position with minimal inclination since subjects usually experience VR while sitting.

Regarding electrode placement, in the majority of researches oriented towards a dynamic environment, one of the commonly used approaches, described in subchapter 3.3.1., was applied [112]–[114]. Based on the fact that there is a higher chance of artifact presence in the dynamic recording setup compared to the static one, it is beneficial to use more than one channel to increase robustness and in parallel to decrease chances that recording is not suitable for the analysis. Sub-analysis performed in [3] suggested that CH1 is the least suitable for acquisition, while CH2 and CH3 outperformed it. Precisely, out of 9 EGGs recorded with the 3-channel EGG device, CH1 signal was used only in one case, while CH2 and CH3 were more suitable in the remaining 8 (4 recordings each).

In Figure 5.1. Tendencies related to protocol changes from static to dynamic environment, derived as a takeaway from our research presented in [3], [6].

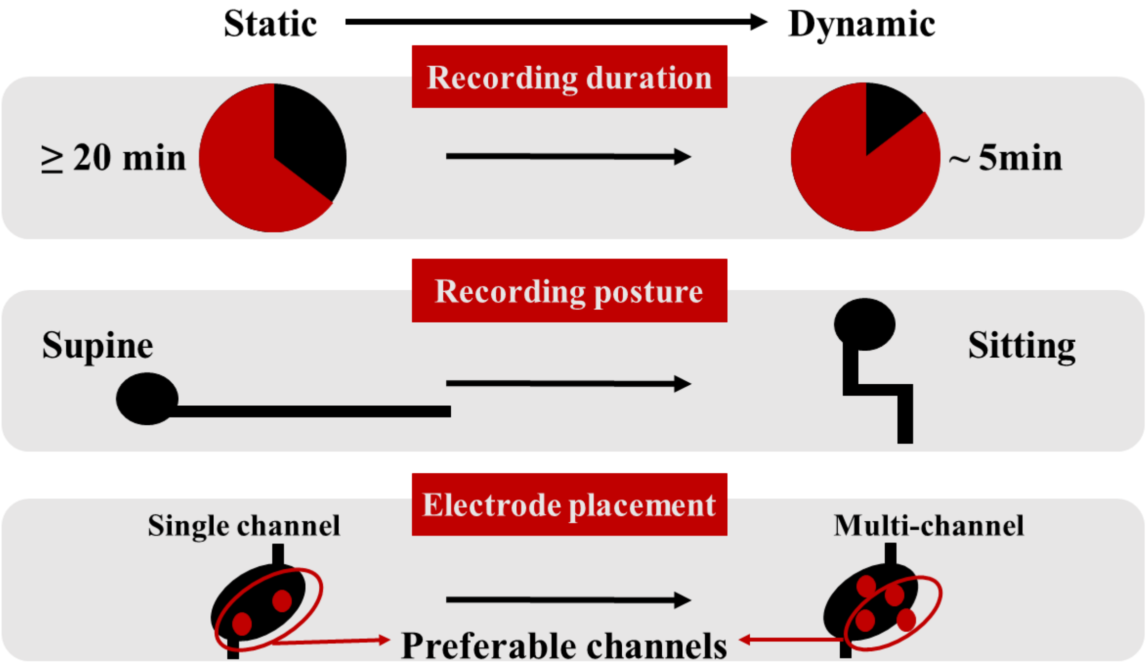


Figure 5.1. Shift from static to dynamic EGG protocol in terms of recording duration, posture, and electrode placement.

It is a known fact that amplitude of the signal and percentage of normogastry increases after a meal, which is why it is more suitable to evaluate slow wave activity from the signal recorded postprandially [2]. Despite that, it has been reported that EGG protocol, which included stimuli that could induce sickness, was recorded in a fasting phase of the gastric cycle [113]. In [114], participants were asked not to consume any food four hours prior to the measurement, while in [168] and [165], that time was decreased to two hours. It should be said that protocols used in investigations [114], [165], [168] cannot be stated as fasting due to the fact that 6 hours of food abstention is required for fasting protocol [19]. In [6], the compromise between fasting and postprandial was made by asking subjects not to eat one hour before the protocol to prevent the occurrence of severe nausea. The limitation of this approach is the lack of information about the phase of the gastric cycle. Standard fasting protocol (6 hours of fasting prior to the recording session) was applied for the DS assessment using EGG [3].

5.2.1. Virtual and Augmented Reality

The terms virtual and augmented reality are parts of the so-called "virtuality continuum", defined in [169] as a continuum ranging from the reality itself to computer-generated virtual reality. While VR can be defined as an environment in which subject experience telepresence, augmented reality is described as a technique that expands real-world experience [169]. Their application is still mainly in the video games industry, but there are clear tendencies that they could be beneficial in medicine, the transportation industry, education, and science [169]–[173]. To achieve their full potential, these technologies must be improved. One of the main pitfalls of these technologies that should be resolved is the occurrence of sickness symptoms while using virtual and augmented reality products [154]. EGG technology as a promising technique for assessment of gastric motility and consequently for assessment of sickness was applied in order to evaluate the electrical potentials of the stomach during virtual and augmented reality experiences.

The potential occurrence of sickness in virtual and augmented reality was assessed by EGG measurements in two studies. In the first study, VR experience was delivered with the Oculus Rift. Namely, different VR videos were played to subjects and EGG signals were recorded and used to assess sickness [6]. This investigation is further described in detail in subchapter 5.3. EGG During Virtual Reality Experience. The other study presented in the subchapter 5.4. and published in [3] was focused on EGG recording during a driving simulation.

Driving simulation with included motion feedback platform introduces additional and real sensation to the virtual reality provided by software simulation, i.e., the computer-generated environment and can be classified as augmented rather than virtual reality [169].

5.3. EGG During Virtual Reality Experience

In this subchapter the introductory considerations regarding the application of EGG for assessment of GI system during VR experience are presented. Results of the research published in [6] are presented with comprehensive discussion. Finally, recommendations for the future work illustrated with the results of unpublished case-study are given.

5.3.1. What is Cybersickness?

The introduction of virtual reality environment into the various fields of technology presents substantial advancement. In the time when online content is available worldwide, including shopping, museum, interactive video games, driving, and flying simulators, VR provides enhanced and similar to real-life experiences. While its application is commonly related to the entertainment industry, it has a much wider application. Its usability in training and education is significant. Namely, driving and flying simulators provide an option for the basic training of future drivers and pilots, as well as the possibility to test and enhance their preparedness in a critical situation in a completely safe manner. The introduction of VR in those simulators can increase the potential of mimicking real-life situations and consequently give an advancement of related training activities. [174]–[171]

One of the main challenges in the VR industry is the occurrence of sickness that can include various unpleasant symptoms (e.g., nausea, vomiting, dizziness, general discomfort, sweating). Cybersickness (CS) is the most suitable term for this phenomenon. In general, cybersickness can be defined as any form of sickness related to the application of virtual reality, driving or flight simulators. Its underlying cause remains unrevealed, but there are some insights suggesting that conflict between gut and brain sensory input can play a major role. This is why appropriate technology for the evaluation of physiological response in VR users should be applied to address this issue. Literature in this area is scarce, and there is a substantial need for further improvement. [69], [177]–[182]

5.3.2. Importance of Biofeedback in VR Environment

Virtual reality provides an enhanced digital content experience, and as such, it has an important impact on information technologies. As stated in [183], it is a path to the revolutionary new era of entertainment, education, social interactions, and many other essential aspects that substantially affect the quality of life. To expand to its full potential, it needs to fulfill one of the main conditions – comfortability for the consumer. Number one obstacle towards this could be physical discomfort that is reported, mainly in terms of cybersickness. The path towards the solution could be through answering the questions: 1) What are the triggers for the reported symptoms? and 2) What should be changed in the technology to suppress these triggers? Implementation of biofeedback that applies non-invasive techniques for the assessment of the human body could be beneficial for both finding the reasons for discomfort and resolving them. Alternatively, it could be used to notify users that they could expect the occurrence of unwonted symptoms and provide them the opportunity to prevent it.

5.3.3. Overview of Related Work - Biofeedback in VR Environment

Chardonnet et al. in [184] reported a method for evaluation of visually induced motion sickness in virtual reality using postural sway signal. This signal estimates variations in the body`s center of gravity (CoG), and it could provide promising results regarding sickness assessment. Subjects were asked to navigate in three-dimensional VR, and frequency-domain analysis of postural sway signal was performed. The authors concluded that this technique could be used for acquiring an insight into the motion sickness occurrence in virtual reality.

Heart rate variability (HRV) as a signal usually derived from ECG offers an insight into the variability of heart inter-beat intervals. In [185], it was used to assess cybersickness induced by applying a head mount VR device - Oculus Rift DK2 (Oculus VR, Facebook Technologies, LLC.). HRV signal was acquired by recording 2-lead ECG. Results showed that four out of 13 subjects that reported severe nausea symptoms had a statistically significant change in HRV signal compared to the other 9 study participants. It should be noted that in the two participants, ECG signals were not usable due to the electrode detachment, which illustrates the complexity of recording electrophysiological signals in a dynamic environment. The same group of authors provided some extension to this research in [186] by developing a classifier for the determination of CS occurrence. They used ECG, electrooculographic (EOG), respiratory, and skin conductivity signals for the classification. The methodology was tested in 66 subjects. Binary approach (no CS/ yes CS) showed 82% while tertiary classifier (no/mild/severe CS) showed 56 % classification accuracy.

Lin et al. in [187] studied the effects of motion sickness on electroencephalographic (EEG) signal. Following protocol was used: “three-stage experimental protocol is designed for this study. Before each experiment, a 10-minute practice session was held to ensure the subjects are used to the environment. After the practice session, subjects were asked to wear an EEG electrode cap and then begin the first stage of the experimental protocol, a 10-minute straight road called “the Baseline Stage”. Next, “the Motion Sickness Stage”, which consists of a 40-minute consecutive-curve road, is aimed to induce motion sickness, and the final stage is a 15-minute straight road for rest.”. Power increase in the frequency range from 8 Hz to 10 Hz was observed in most of the subjects, while in some, there was a power increase in the 18 Hz to 20 Hz range. The authors stated that the effects of cybersickness are detectable on EEG tracings. The investigation described in [188] included ECG signal in addition to EEG for the assessment.

The most comprehensive study was performed by Dennison et al. [178] in which various physiological assessment techniques were used (electrocardiography, electrogastrography, electrooculography, pulse oximetry, breathing rate, and galvanic skin response - GSR) for the assessment of cybersickness while using a display monitor and head mount display (HMD). ECG recordings suggested that there is a significant increase in heart rate during HMD application. Frequency of blinking according to the EOG was also increased as well as skin conductance and breathe rest. Pulse oximetry signal did not present any significant alterations. The results derived from EGG signals suggested that there is a frequency shift towards higher frequencies (% tachygastric power increase, % bradygastric power decrease) during the HMD phase, compared to the resting.

5.3.4. Methodology for EGG-based Assessment of Cybersickness

In [6] procedure for EGG based assessment of cybersickness in a virtual environment is described, and outcome measures were discussed. In the following subchapters overview of that work will be presented.

5.3.4.1. Measurement Setup for EGG-based Assessment of Cybersickness

Experience of VR was delivered to the subject by using head-mounted device Oculus Rift Consumer Ver 1. (Oculus VR, Facebook Technologies, LLC.) with the following characteristics [189]: 1) resolution – 1080x1200 per eye (two OLED displays), 2) refresh rate – 90 Hz, 3) field of view - 110°, 4) 360° positional tracking, 5) ergonomic design, and 6) integrated headphones for 3D audio (see Figure 5.2. a)). Required desktop computer (operating system - Windows 10, CPU - Intel(R) Core(TM) i7-3770K, 3.50 GHz RAM - 24.0 GB, graphic card - GeForce GTX TITAN) was placed around 50 cm from the subject. EGG was recorded with the device described in Chapter 2. Subject posture was supine, and electrode placement was 3-channel one described in [2] as suggested in subchapter 5.2. Two roller coaster experience VR videos were used – Rock Falls VR (RF VR) and T-Rex Kingdom VR (TRK VR) [190]. The illustration of the recording setup is presented in Figure 5.2.b).

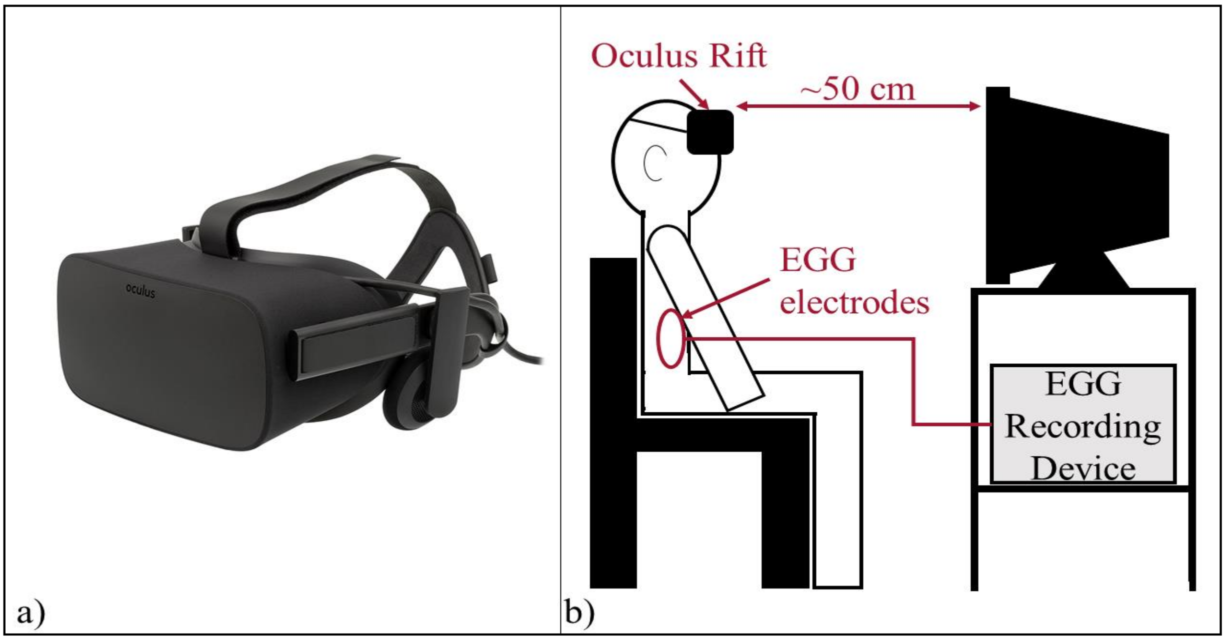


Figure 5.2. a) Oculus Rift Consumer Version 1 (Oculus VR, Facebook Inc., Menlo Park, California, USA), and b) recording setup used for virtual reality experience in [6]. Image from the public domain [189].

5.3.4.2. Measurement Procedure for EGG-based Assessment of Cybersickness

The study was obtained in three healthy female subjects (29.0±2.6 years old, 172.7±2.9 cm, and 68.0±7.0 kg) that signed, Local Ethics Committee approved, Informed Consent created in accordance with the Declaration of Helsinki. Participants stated that they are not pregnant and did not take any medications 4 months prior to the study.

The procedure was done in the following phases:

1. Skin preparation and electrode placement followed by 10-15 minutes to establish satisfactory electrode-skin contact [17].

2. Acquisition of 5 minutes baseline EGG signal while subjects were asked to rest with open eyes.

3. EGG signal acquisition during VR experience (RF VR) for 4 minutes followed by 10 minutes of the continuous recording after the end of the video.

4. Four days of pause between recordings for the subject to completely recover for possibly induced cybersickness.

5. Recording of new baseline EGG in same conditions as in Phase 2. for 5 minutes.

6. Acquisition of EGG during VR experience with different video than in Phase 3. (TRK RF) for 6 minutes and 20 seconds, followed by 10 minutes after-video recording.

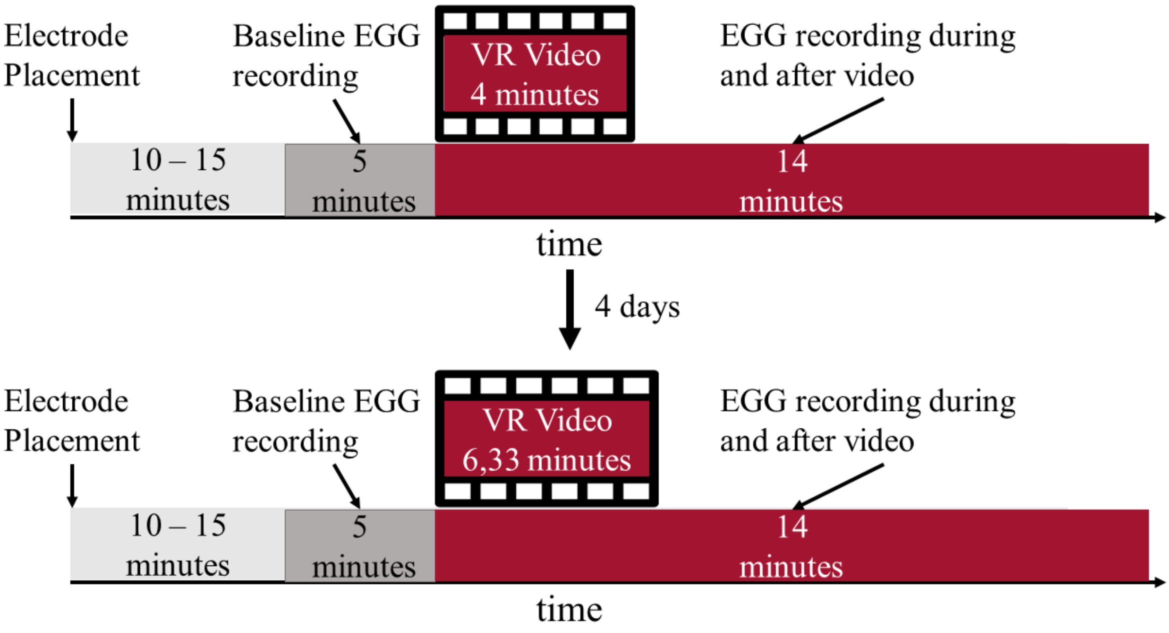


Figure 5.3. Graphical representation of the recording procedure applied in [6]

The described measurement procedure is graphically presented in Figure 5.3.

5.3.4.3. Calculated Parameters for EGG-based Assessment of Cybersickness

Prior to the feature extraction, a signal was preprocessed by applying Butterworth 5th order band-pass filter (0.0167 Hz – 0.3333 Hz). To quantify recorded EGG signals following parameters were calculated: 1) total spectral power, 2) spectral power in three specific EGG ranges (bradygastric – 1 cpm to 2 cpm, normogastric – 2 cpm to 4 cpm, and tachygastric - 4 cpm to 10 cpm), 3) median frequency, and 4) crest factor of power spectrum density. While the first two parameters are commonly used, MF and CF are novel parameters (see subchapter 4.3.2.) designed for numerical description of non-standard EGG spectrums and were for the first time presented in this research. These parameters were derived from Power Spectrum Density, calculated by the function that implements Hamming windowing (50 % overlap). Additionally, subjects were asked to describe the subjective feeling of cybersickness on the scale from 0 – no nausea to 10 – almost vomiting. Since commonly used statistical tests were not suitable for the study group of three participants, interpretation of the results was done based on the corresponding trends (increase/decrease) in the feature values.

5.3.5. EGG Parameters Variation Induced by VR

Total power, median frequency, and crest factor values are presented in Table 5.1.

Table 5.1. Total power, median frequency, and crest factor values calculated for the signals recorded for research published in [6].

Subject	**Recording no. 1 - RF VR**								
	Resting sequence			**VR sequence**			**Post VR sequence**		
	TP [rmV/Hz]	**MF [rHz]**	**CF**	**TP [rmV/Hz]**	**MF [rHz]**	**CF**	**TP [rmV/Hz]**	**MF [rHz]**	**CF**
ID1	2.21	3.75	7.60	57.35	2.81	6.04	1.85	3.75	6.05
ID2	3.20	3.75	5.21	5.26	3.75	5.19	7.70	3.28	7.63
ID3	1.30	3.28	5.90	101.39	2.81	6.17	30.17	3.75	5.55
	Recording no. 2 - TRK VR								
ID1	1.21	2.81	5.48	249.28	2.34	7.33	10.03	2.48	8.47
ID2	0.91	3.75	7.26	103.84	3.75	5.61	72.81	3.75	9.15
ID3	5.35	3.28	6.04	56.38	2.81	7.18	20.83	3.75	8.31

Graphical representation of spectral power percentage in three EGG ranges is presented graphically in Figure 5.4.

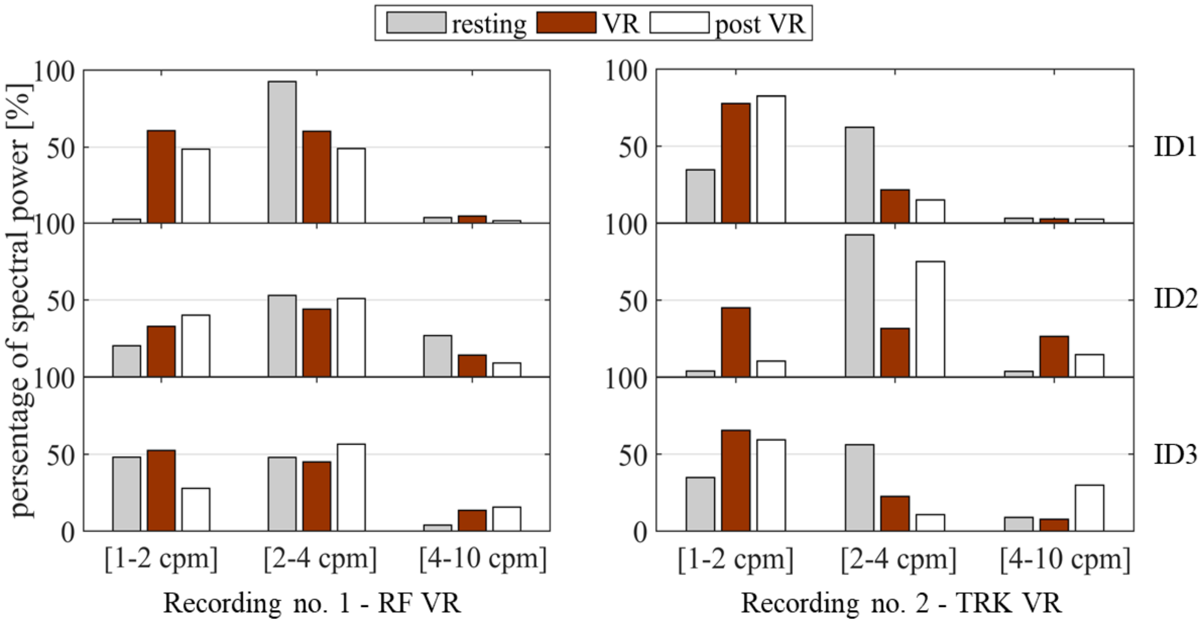


Figure 5.4. Percentages of power chares in characteristic EGG frequency ranges calculated for each subject, in resting, VR, and post VR EGG recording, for both recording sessions (RF VR and TRK VR). Taken and adapted from [6] with permission from the publisher.

Bar graphs of CF values are presented in Figure 5.5.

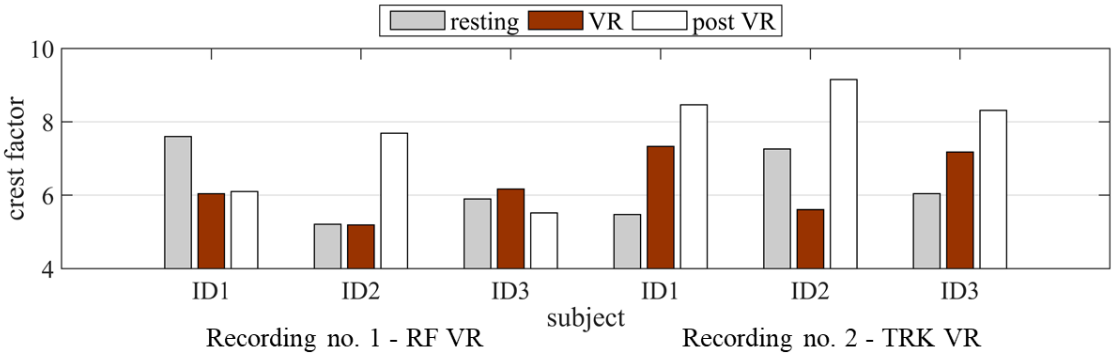


Figure 5.5. Crest factor values for each subject, in resting, VR, and post VR EGG recording, for both recording sessions (RF VR and TRK VR).

Subjective feelings of nausea reported by subjects for the first recording were 0, 7, and 3, and for the second 2, 5, and 2, for subject ID1, ID2, and ID3, respectively.

5.3.6. Relation Between Virtual Reality Experience and EGG Parameters

While MF did not reveal any substantial shift between baseline values and the ones calculated for VR and post-VR EGG, TP showed an increase from baseline to VR in each subject for both recordings. Lack of expected MF alterations could be the consequence of low-frequency noise presence induced by more extensive movement from the subject during VR. An increase in TP is consistent with the results presented in [163], and it can be an indicator of more frequent smooth muscle contractility during VR. As an estimator of peak prominence, Crest factor was expected to have lower values during the VR experience. This trend was not confirmed in the corresponding study group. Still, a promising result is that in subject ID2, which experienced the most severe nausea symptoms, it was decreased from baseline to VR.

From the spectral power shares, it can be observed that there was a decrease in normogastria, which is in agreement with the results presented in [161]. Additionally, this portion of power was transferred to both bradygastric and tachygastric range. While it was expected to have a higher share of tachygastria, considering the findings from [178], bradygastria increase was not. This can be explained by the presence of motion artifacts since manual extraction of possibly contaminated parts of the signal (described in subchapter 4.2.2.) was not performed.

It should be stated that this preliminary protocol was not designed to induce severe cybersickness, which was in accordance with relatively low sickness self-assessed values, except in ID2. Results obtained in subject ID2, especially regarding the decrease in normogastric power share between baseline and VR sequence, suggest that there could be a correlation between EGG and SSQs.

5.3.7. Can EGG Provide Valuable Insight into VR Induced Cybersickness?

Research presented in [6] was aiming to provide preliminary insight into the assessment of VR induced cybersickness and to address main issues regarding methodology. Considering that, it can be concluded that EGG signal is susceptible to alterations induced by VR experience. Feature extraction using common methods could fail to give an adequate representation of those changes. Thus, the development of reliable quantification methods for the description of corresponding variations is the first step towards broader usage of EGG signal as biofeedback medium in VR environment. Inconclusive results based on the median frequency suggested that there could still be a problem with motion artifacts and that progress in the noise cancelation area is required for further advancement. Description of PSD shape by CF showed the most promising results. It could be a critical factor in introducing EGG as a standard for assessing user`s physiological status during VR experiences.

5.3.8. Limitations and Introduction to Future Work on Assessment of VR experience using EGG

To deliver more significant conclusions, research needs to be done in a larger study group. That would enable investigators to perform valid statistical analysis, leading to clearance of different parameter variations trends. The possibility of misleading results as a consequence of individuality that could be present in the anatomical, physiological, or psychological characteristics of study participants would be minimized.

Insight into the information regarding the time of subject`s most recent meal intake could be beneficial in order to analyze the influence of the gastric cycle phase on EGG signal. Additionally, in a larger study group, the physical characteristics of subjects could be included in the sub-analysis. Level of experience in VR environment should be obtained from each volunteer as it could be an important factor for different gastric response in any individual. In [6], obtained, simplified sickness evaluation was mainly done in order to have an idea of possible VR effects on the subject. To acquire reproducible results, some of the widely used sickness questionnaires should be used, such as Pensacola Motion Sickness Questionnaire, Pensacola Diagnostic Index, Kennedy`s Simulator Sickness Questionnaire, Nausea Profile, Virtual Reality Symptom Questionnaire [177], [191].

In addition to resolving limitations, there are many proposals that can improve the significance of the extended research. Based on the case study that served as motivation, ideas for future work will be described in the following subchapter.

5.3.8.1. Case Study – Groundwork for Research Extension

This case study was realized to obtain an insight into the possibilities for the extension of the research presented in [6]. The same equipment was used as well as the setup for the recording including the position of the subject relative to the desktop computer, its posture, electrode placement, preparation, and inclusion criteria. Following differences were added: 1) instead of recording over two separate days, both VR videos were played to the subject on the same day, with 10 minutes pause between them, 2) continuous EGG signal was acquired during the complete protocol, including 8 minutes prior to the first VR video (baseline EGG), 10 minutes between two VR video, and 8 minutes after the second one, and 3) subject (female

28 years old, 162 cm, 54 kg) reported severe sickness symptoms during prior VR experiences. Due to the onset of nausea, the second VR video was stopped after approximately 2 minutes.

In Figure 5.6. recorded EGG signal was presented, with zoomed baseline and first VR segments of the signal, and corresponding PSDs.

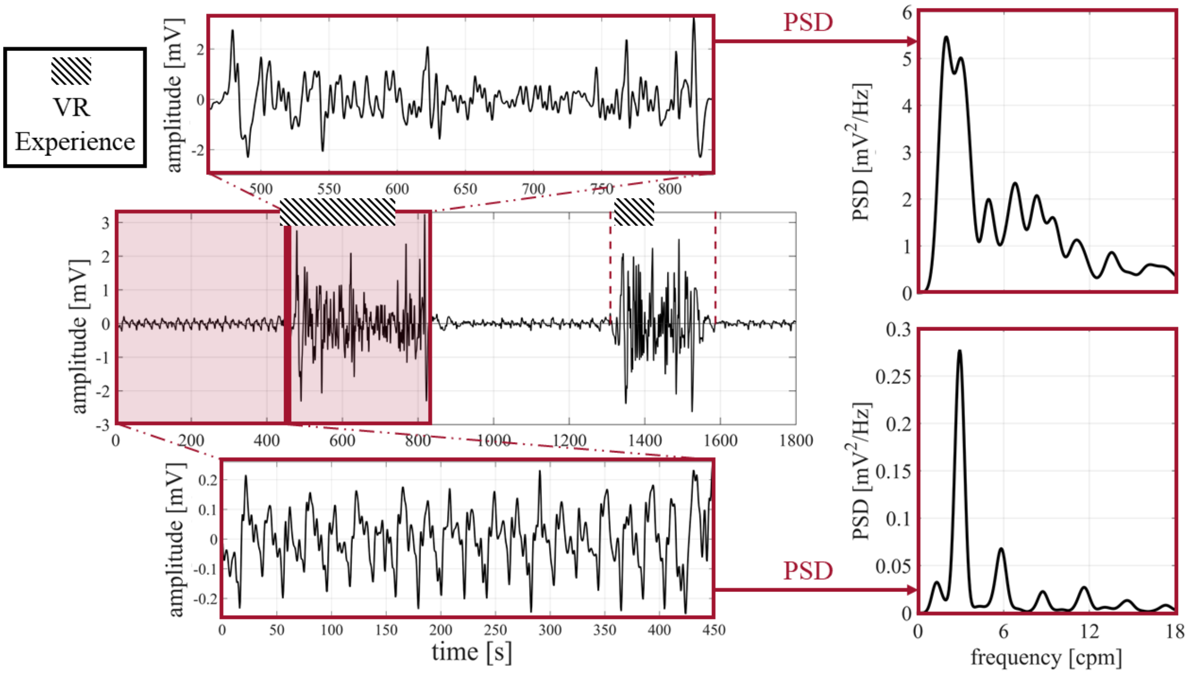


Figure 5.6. EGG signal from the case study during VR experience with zoomed segments of the signal (baseline and first VR video) and corresponding PSDs.

From the visual observation of the entire signal, it is possible to detect abrupt changes in amplitude of the signal, which correlate with the beginning of the first and the second VR videos. These amplitude changes will affect power of the signal. Thus, RMS value, as well as signal power calculated both from time and frequency domain, would suitably describe observed changes. There is a clear visual difference in the characteristic of the zoomed signals. In addition to the amplitude, it is also noticeable that the oscillatory pattern present in the baseline signal is missing in the VR part. This is reflected in PSD graphs where for the baseline, there is a dominant peak around 3 cpm with its harmonics, while for the VR, PSD is disturbed, there is a lack of a single dominant peak, and frequency content is shifted towards higher values. Values of CF and MF confirm this. It should be noticed that in timeseries like this, the onset of amplitude increase could be determined and even automatically detected. That would open a possibility to calculate time latencies between the onset of symptoms, amplitude change, and beginning of VR experience. Additionally, time from the end of the video to the return of amplitude to the baseline values could also be of interest.

Based on the previous discussion, the following guidelines for future work can be proposed:

1. Inclusion of subjects with the reported occurrence of cybersickness in prior VR experiences. **Rationale:** To investigate phenomena of VR induced symptoms, it is beneficial to cause its occurrence. Frequent consumers of VR products can develop resistance to cybersickness, and consequently, its gastric myoelectrical activity could remain in baseline form during the VR video. The focus should be on the users that feel discomfort associated with the VR application. On the other side, this can provide ethical issues as subjects can have these unpleasant symptoms during the study conduction.

2. Parameters from the time domain should be included. **Rationale:** While frequency domain parameters are more reliable in the typical long-term EGGs, for the description of abrupt changes in short dynamic recording, the ones derived from the timeseries could be beneficial.

3. Calculation of latencies between critical events. **Rationale:** As already stated, the possibility of detecting the point in time when EGG variation happens should be used for this. Determination of timewise correlation between the onset of symptoms and changes in signal could improve understanding of the underlying process, which is the first step towards a solution.

5.4. EGG During Driving Simulation

Transportation industry went through many positive changes since the middle of the 20th century. Today, the number of people that frequently travel via different means of transportation is multiplied. While that had a substantial beneficial influence on the various areas of life, including business, education, culture, entertainment, and overall quality of life, it also increased safety concerns. Following technological advancement, different tools for transportation safety improvement had been designed. Driving Simulator (DS) could be considered as one of those since it is mainly used for training and on-road testing in a safe manner. [68], [192], [193]

Since DS was first introduced during World War II [194], it was improved in many aspects. Despite that, there are still many challenges that need to be addressed. The focus of this subchapter will be the possibility of an EGG-based assessment of sickness symptoms induced during a driving simulation.

5.4.1. Driving Simulation – Benefits and Challenges

Driving simulation is an alternate technique to the traditional on-road assessment of driving skills. Its clear advantages are: 1) complete safety of the user, 2) simple application, 3) cost efficiency, 4) possibility to easily change driving conditions, and 5) induction of specific situations and evaluation of driver`s response to them. [68], [195]

On the contrary, simulated conditions can never be identical to the real ones. As much as this technology advanced over time, there are many factors that will probably never be as realistic as in the real on-road experience. This leads to the problem of transferability of driver evaluation obtained via DS to its actual capabilities. Besides, there are also many issues regarding DS reliability. [68]

One of the main pitfalls in the DS field is the occurrence of sickness symptoms in subjects during a simulation. It includes, but is not restricted to, nausea, dizziness, extensive sweating, headache, and vomiting. The occurrence of such physical sensations during driving simulation is called simulator sickness (SS). This phenomenon has a significant negative influence on the usability of DS. General discomfort suffered by the user can influence driving performance and lead to ambiguous conclusions. It can limit the simulation duration if the user feels severe symptoms and increase the number of dropouts. The overall quality of the experience can also be compromised with the consequence of decreased future interest in DS. Thus, this issue needs to be addressed. The pathway towards the reduction and possible elimination of SS could lead to reliable assessment procedures. [154], [196]–[198]

5.4.1.1. Assessment of Simulator Sickness

Simulator Sickness Questionnaires (SSQ) were designed to determine if there was an occurrence of sickness and, if yes, to provide a quantified estimation of its severity [199]. They can reveal what the most common symptoms of SS are and how they manifest in different conditions or user population. Keshavartz et al. in [200] compared the performance of the simplified approach using the Fast Motion Sickness Scale (FMS), which uses values from 0 to 20 to describe the severity of nausea with SSQ. Results showed a high level of correlation, but the authors stated that FMS still has many limitations. The main downside of self-reporting methods for SS evaluation is that they are not designed to provide relevant information regarding the underlying cause of SS. [201]

In [202], Min et al. reported a study conducted in 20 healthy adult participants (10 female and 10 male, 20 to 28 years, the average age of 23.4 ± 1.8 years) regarding physiological measurements evaluation of cybersickness. Following techniques were used: 1) electrocardiography, 2) electroencephalography, 3) galvanic skin response (GSR), and 4) skin temperature. The protocol consisted out of the 5 minutes baseline recording followed by 60 minutes of simulation. Graphic DS was used, and participants were asked to drive in a four-lane street at 60±10 km/h speed. Before the protocol, all subjects did 10 minutes of practice on DS. ECG signal presented with a significant increase in heart rate during the simulation compared to the resting. Regarding brain activity, results showed a significant increase in δ wave activity in 5 minutes, while θ, α, and β wave activity decreased in 5 to 35 minutes, compared to the baseline. Skin temperature decreased significantly after the beginning of the DS, while the GSR signal increased, but without statistical significance. This research confirmed a measurable physiological response to DS experience, suggesting that there is a potential of using biofeedback as a tool for the improvement of future simulators regarding subject conformity.

One of the physiological signals that could provide additional information regarding the gastrointestinal tract functionality during driving simulation is EGG. The advantage of signal originating from stomach smooth muscles could be in the possibility to provide an insight into the gut response that is commonly related to the occurrence of sickness symptoms. To the best of Authors` knowledge, the introduction of EGG based assessment of simulator sickness was published in our paper [3].

5.4.2. Methodology for EGG-based Assessment of Simulator Sickness

The investigation published in [3] was preliminary research that primarily aimed to define the appropriate methodology for the recording and analyzing EGG signals in the DS environment. Due to that, it was entitled “Lessons Learned: Gastric Motility Assessment During Driving Simulation”. The scope of the paper was to provide a detailed description of measurement equipment, protocol, signal analysis, and feature extraction, as well as to present suitable discussion. The secondary goal was to report variability of the results and their correlation with different driving simulation phases. The importance of motion feedback in DS environment is substantial. In addition to enhancement in terms of more realistic experience, it can also decrease the incidence of sickness symptoms. This is most possibly a consequence of reduced sensory conflict in the human organism. [155] In this research we primarily wanted to test the influence of motion feedback on signal quality, but also its impact on the EGG features. Due to that we created the protocol in which we have phase without and phase with motion. Ultimately, the following research questions were defined:

1. Could EGG signal be reliably measured in a driving simulation environment using an open-source EGG device presented in Chapter 2?

2. What are the most promising parameters for the description of slow wave activity signal acquired during driving simulation?

3. Can the signals acquired during different modalities of DS and baseline period be discriminated by EGG signal analysis?

4. In what manner motion feedback influence quality of the signal and its corresponding features?

The following subchapters will be dedicated to answering these questions.

5.4.2.1. Measurement Setup for EGG-based Assessment of Simulator Sickness

The driving simulation was obtained using the Nervtech 4DOF motion car driving simulator. It includes a racing car seat with a set of three pedals and a steering wheel, all manufactured by Fanatec (Endor, Landshut, Germany). Image reproduction was done using three 49“ curved displays and SCANeR software (AVSimulation, Bouligne-Billancourt, France). The driving simulator includes 4DOF motion platform that mimic car movements and improves realistic feeling of the experience. This system incorporates four electro motors that allows platform to move in the X, Y and Z directions. Besides, it can also slide horizontally in order to simulate movement of the rear part of the car. Overall, the simulator have 4 degrees of freedom. These features enable the simulator to realistically mimic real-life driving conditions including sudden turns, breaking, and rough terrain. In Figure 5.7. used Nervtech driving simulator is presented. [203]

Figure 5.7. Nervtech 4DOF motion car driving simulator during a driving simulation. The image was taken and modified from [3]. (License: CC BY 4.0)

For the recording of EGG signal, the device described in Chapter 2 was used, with a sampling frequency set to 2 Hz. Electrode placement was the same as proposed in subchapter 3.3.2. An additional part of the equipment was Force Sensing Resistor (FSR). It was introduced as a tool for synchronization between EGG and DS. It was used in the form of a push button that was pressed at the beginning and the end of each phase of driving simulation described in the following subchapter.

5.4.2.2. Measurement Procedure for EGG-based Assessment of Simulator Sickness

The study group consisted out of 13 healthy participants, 4 females and 9 males (29 ± 8 years old, 73 ± 19 kg, 177 ± 8 cm), which signed informed consent compliant with the Code of Ethics of the University of Ljubljana and in accordance with the Declaration of Helsinki. Table 5.2. shows detailed demographic data of the subjects. Inclusion criteria were following: 1) no known history of gastrointestinal or vestibular disorders, 2) not pregnant, 3) no chronic or acute diagnosed pathologies, 4) not on any pharmaceutical therapy in the past 6 months, and 5) abstinence from eating for 6 hours and drinking for 2 hours prior to the start of the recording session.

Table 5.2. Demographic data of subjects included in the study published in [3]. (License: CC BY 4.0)

Subject	**Age [ryears]**	**Sex**	**Height [rcm]**	**Weight [rkg]**	**Driving experience [ryears]**	**Driving simulator experience [rYes/No]**
ID1	23	F	173	60	5	Yes
ID2	23	M	172	60	5	No
ID3	26	F	169	56	8	No
ID4	23	M	180	88	4	No
ID5	32	M	192	115	14	Yes
ID6	47	M	182	87	29	No
ID7	23	M	173	65	5	Yes
ID8	40	F	160	49	15	Yes
ID9	25	F	169	59	6	Yes
IDN1	26	M	183	97	6	Yes
IDN2	27	M	181	75	9	Yes
IDN3	33	M	177	60	15	Yes
IDN4	35	M	186	78	17	No

EGG recording was obtained continuously through four different stages:

1. Initial 5 minutes of a test drive in order for subjects to become familiar with the operation.

2. Baseline EGG recording for additional 5 minutes.

3. Recording during operation of the driving simulator with included motion feedback for 5 minutes.

4. Recording during operation of driving simulator without motion feedback for 5 minutes.

Phases 3. and 4. were altered for each subject. Prior to the test drive and during the pauses between different sequences, subjects were asked to fill simulator sickness questionnaire proposed in [201]. Used SSQ could give a sickness score ranging from 0 to 235.62, and a nausea sub-score from 0 to 200.34. The timeline of the described protocol with the example of EGG timeseries and signals from FSR is presented in Figure 5.8.

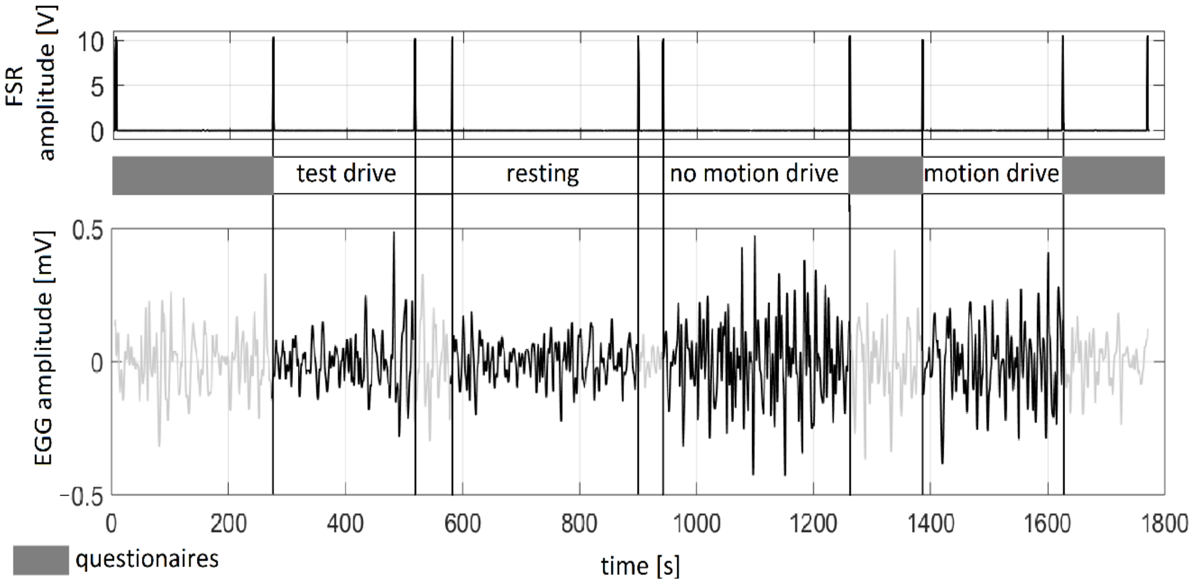


Figure 5.8. Illustration of recording protocol timeframes with the example of the recorded EGG and FSR signal for synchronization. Image is taken from [3]. (License: CC BY 4.0)

5.4.2.3. Calculated Parameters for EGG-based Assessment of Simulator Sickness

Preprocessing of the signal was done by applying Butterworth 3rd order band-pass filter (0.03-0.25 Hz). Manual motion artifact cancelation was done as described in subchapter 4.2.2. Out of the three recording channels, EGG from only one of them was analyzed. The channel selection was made by using the algorithm described in subchapter 4.1.2.

After the most suitable channel was determined, the following EGG parameters were calculated: 1) dominant frequency, 2) median frequency, 3) crest factor, and 4) root mean square value of the timeseries. Parameters were obtained for each phase of the measurement and each subject. Also, SSQ values were calculated. Additionally, from calculated PSD, the percentage of normogastric spectral power share was derived from each signal segment.

Statistical analysis was done to determine the significance of variation between calculated parameters for baseline, driving without, and driving with motion feedback included. A paired-sampled t-test was applied and results characterized by a p-value less than 0.05 were considered significant.

5.4.3. Results for EGG-based Assessment of Simulator Sickness

One of the subjects experienced severe sickness and nausea, which resulted in the recording interruption. Due to the artifact presence that could not be resolved with commonly used methods (see subchapter 4.2.) EGG signals recorded in three subjects were excluded from the analysis. Summarized, in 9 out of 13 subjects (69%), suitable EGGs were acquired.

For the analyzed signals, MF, DF, RMS, and CF values are presented in Figure 5.9. for resting, drive with motion, and drive without motion.

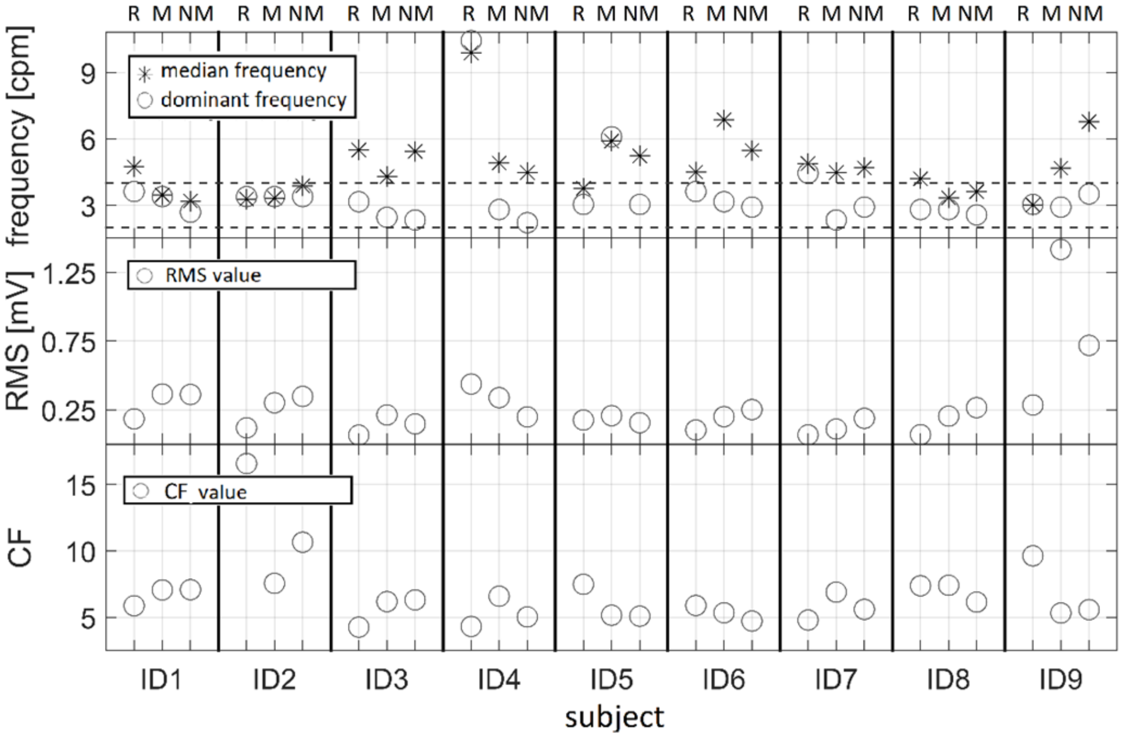


Figure 5.9. Dominant and median frequencies (upper panel), root mean square (middle panel), and crest factor (bottom panel) values for resting (R), motion (M), and no motion (NM) driving simulation. Parameters calculated for subjects ID1-ID9 and initially presented in [3]. (License: CC BY 4.0)

Variations in parameters for different protocol phases were statistically significant only for RMS values between resting and drive with motion – p = 0.03. Between resting and motion with motion, there was no statistical significance – p = 0.10. For RMS values, box plots are presented in Figure 5.10.

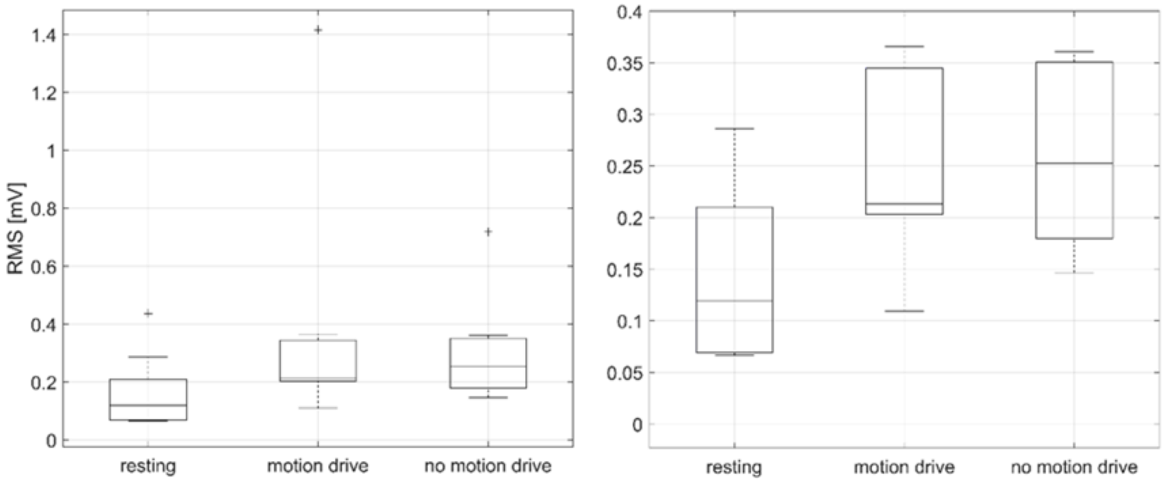


Figure 5.10. RMS values for three phases of the protocol (resting, motion drive, no motion drive) presented using box plots. The difference between the left and right panel is in the range of y-axes, which is zoomed in the right one for better visualization. Results originally presented in [3]. (License: CC BY 4.0)

The relation between RMS values and spectral power percentage in normogastric range is presented via scatter plot in Figure 5.11. For the four signal segments that underwent manual artifact cancelation (ID2 and ID5 resting, ID3 drive with motion, and ID4 drive without motion), both values prior to and after noise extraction are presented and connected with arrows.

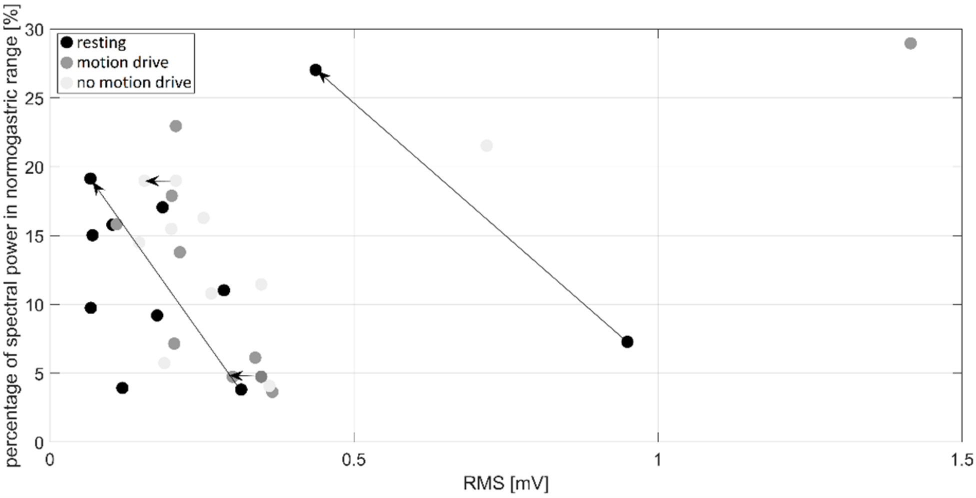


Figure 5.11. Scatter plot presenting the relation between RMS value and % of normogastric power share for resting, driving with and without motion. Four segments that underwent manual artifact cancelation are presented with both values prior and after it – connected with arrows. Results originally presented in [3]. (License: CC BY 4.0)

Results of SSQs are presented in Table 5.3. Considering the fact that Total SSQ scores of 0, 78.54, 157.08, and 235.65, and Nausea SSQ scores of 0, 66.78, 133.56, and 200.34 correspond to none, mild, moderate, and severe symptoms, respectively, almost all of the subjects reported non to mild symptoms.

Table 5.3. Nausea and Total SSQ scores reported by the subjects included in the research published in [3]. (License: CC BY 4.0)

Subject	**Resting**		**No motion drive**		**Motion drive**	
	Nausea	**Total**	**Nausea**	**Total**	**Nausea**	**Total**
ID1	28.6	49.2	0.0	19.0	0.0	34.2
ID2	28.6	30.0	28.6	18.8	/	/
ID3	9.5	15.0	9.5	31.5	19.1	22.7
ID4	19.1	11.3	28.6	37.6	38.2	68.0
ID5	38.2	18.7	38.2	15.1	57.2	68.1
ID6	0.0	7.6	19.1	15.0	19.1	7.5
ID7	28.6	22.6	28.6	7.5	9.5	7.5
ID8	0.0	11.2	9.5	11	0.0	0.0
ID9	9.5	26.4	76.3	117.4	47.7	71.8
IDN1	47.7	68.1	57.2	83.2	57.2	56.5
IDN2	0.0	0.0	19.0	18.9	0.0	0.0
IDN3	9.5	7.5	38.2	49.2	/	/
IDN4	0.0	0.0	0.0	0.0	9.5	3.7

5.4.4. Key Takeaways Regarding EGG-based Assessment of Simulator Sickness

As the main aim of the research conducted as part of this Doctoral dissertation and published in [3] was to acquire and document first experiences regarding EGG application during driving application, in this subchapter, we will present key takeaways obtained from the corresponding investigation. They include conclusions related to the: 1) recording setup and protocol, 2) preprocessing of the signal, 3) influence of motion, and 4) quantification of the signal.

5.4.4.1. Recording Setup and Protocol

A detailed discussion of the main considerations regarding recording protocol and setup for EGG acquisition in dynamic conditions was presented in subchapter 5.2. Hear, a brief point-by-point summary of derived conclusions will be stated. It includes the following:

1. Although it was suggested to record EGG in a supine position, it is possible to obtain a suitable signal in sitting posture.

2. Short-term baseline EGG recording and EGG recorded during driving experience are more comfortable for the subject, and they can provide reliable information. Continuous EGG recording during different phases of the protocol should be considered with a suitable synchronization tool.

3. Electrode placement with multiple channels should be used to enhance the robustness of the technique. The setup described in [2] showed promising results, especially for channels 1 and 3.

5.4.4.2. Preprocessing of EGG Signal

In addition to digital software filtering, signals recorded in [3] underwent manual artifact cancelation, which provided promising results. Namely, by observing Figure 5. it can be concluded that in two out of four signal segments, in which manual noise cancelation was performed, there was a substantial increase in the normogastric spectral power share. Furthermore, RMS values that were included in the statistical analysis were also altered. These results suggest a considerable influence of manual noise cancelation and that it can increase the reliability of calculated parameter. In conclusion, driving simulator EGG recording should be carefully visually examined by an educated observer and cleared from motion artifacts.

5.4.4.3. Influence of Motion Feedback

It was expected that motion feedback, as a mechanical feature, could increase noise presence and even be a contraindication for EGG acquisition. Based on the presented findings, there was no significant difference in any parameter between drive with and without it. This is a promising result which suggests that motion feedback could be included in EGG assessed driving simulations. This opens the possibility for evaluation of the theory that it could reduce the occurrence of SS. Although in this research results that support that theory were not acquired, it should be additionally tested in high-fidelity driving simulator with improved motion feedback, on a larger study group.

5.4.4.4. Feature Extraction

While both MF and DF failed to provide statistically significant discrimination between baseline and driving simulator EGG sequences, results from [3] were significant for the evaluation of mentioned parameters suitability for the description of EGG. Out of the 18 analyzed driving EGG segments, DF was in normogastric range (2-4 cpm) in 17 (95 %), while MF was in that range on only 6 (33 %). These results are in agreement with the suggestion from subchapter 4.3.2.2. that MF is more sensitive and that it could replace DF for the quantification of EGGs with altered PSD. This is exemplified in Figure 5.12. where the spectrum of one resting EGG and one recorded while driving simulation are presented with marked values of MF and DF. While DF failed to describe frequency shift towards higher values from baseline to driving, MF did it in a suitable manner.

RMS value was the only parameter with a statistically significant change from baseline to driving without motion. Although the same trend towards drive with motion was not significant, RMS showed promising results as an estimator of the amplitude and power increase in driving simulator EGG signals.

Since baseline EGGs were not recorded in ideal conditions, their dominant peaks were not drastically higher than the rest of the spectrum. This could be the reason why crest factor was not successful in quantifying alterations in spectrum between resting and driving sequences. Despite that, based on the results from [6], CF remains one of the features that should be evaluated in future studies cause it could prove reliable results in discriminating EGGs recorded in dynamic conditions.

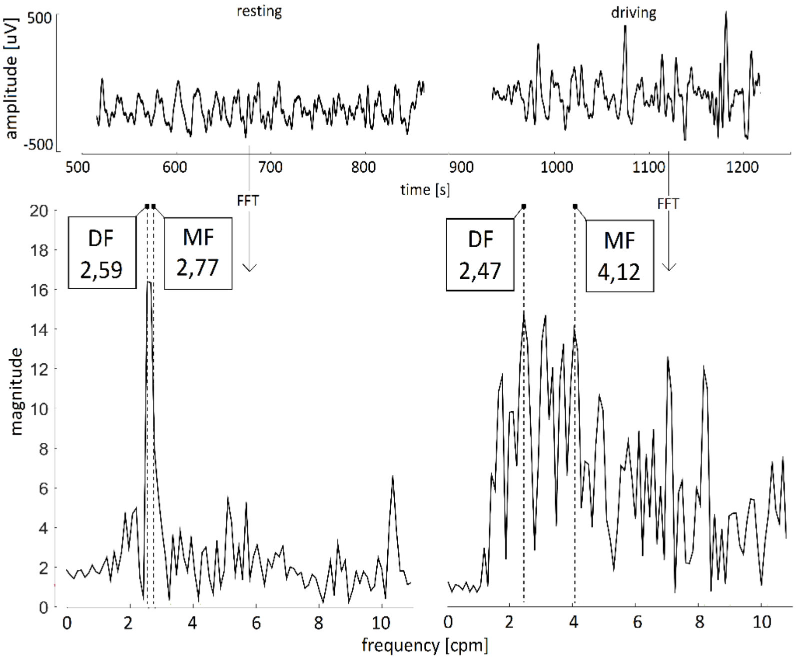


Figure 5.12. Examples of resting and driving EGGs with calculated spectrums and marked DF and MF values. The figure is taken from [3]. (License: CC BY 4.0)

5.4.5. Preliminary Results with Application of Suggested Guidelines

In [204], results regarding EGG based assessment of simulator sickness was presented. The methodology was designed in accordance with the guidelines suggested in [3]. Modifications were following: 1) timeframes for the EGG recordings were prolonged for baseline and driving simulation sequences to approximately 15 minutes, 2) additional 15 minutes of EGG was recorded after the end of DS, 3) one parameter to describe alterations in power of the signal (RMS) and one for variation in frequency spectrum (CF) were calculated, and 4) simulation was performed as driving in autonomous vehicle – no need for extensive movement from the subject. The study group consisted out of 30 healthy volunteers.

These preliminary results showed a non-significant increase in RMS and a significant CF increase ($p < 0.05$). The main takeaway from this initial research is confirmation that CF could be a beneficial parameter for quantifying PSD shape.

5.4.6. Conclusion Regarding EGG-based Assessment of Simulator Sickness

In conclusion, answers to three research question defined in subchapter 5.4.1.1 are following:

1. EGG could be recorded in a driving simulator environment by following guidelines for recording protocol. More research should be obtained for a precise evaluation of its application for the assessment of simulator sickness. Since EGG recording during driving simulation is possible, it could be assumed that slow wave activity can also be suitably obtained during autonomous driving simulation. Since autonomous driving is one of the growing areas in the transportation industry, extension of this research can be focused on it [176].

2. Based on acquired results, RMS and CF are the most promising parameters for describing variation in EGG signal during a driving simulation. The usefulness of MF and DF is yet to be determined. However, results from published research give an advantage to MF for the description of altered EGG spectrums.

3. Results regarding EGG based discrimination between driving and baseline sequences, obtained in two preliminary studies, are not sufficient for the firm conclusion. Despite that, assessment of smooth muscle electrical activity showed promising results in this area, and it should be the focus of future research.

4. Based on the acquired results, motion feedback did not influence EGG signal quality, which is promising for future investigations. However, in this research differences between EGG parameters calculated for motion and no motion drives were not found. Next step in examining effects of motion feedback on EGG features should be testing on larger study group with high-fidelity simulator (improved motion feedback).

6. Conclusion

In this Doctoral dissertation, an overall approach toward electrogastrography as a method for the assessment of smooth muscles electrical activity, was presented. After the initial introduction into the anatomical and physiological concepts, as well as EGG as a method, a detailed explanation of the design process for custom-made open-source EGG device was provided. For the future of electrogastrography, it is of substantial importance to improve equipment availability, which is why the described device could increase interest in this area. Our aspirations towards open-source hardware resulted in the device that could be replicated by any investigator attracted to EGG methodology. Consequently, it could lead to many significant conclusions from different researchers` experiences regarding protocol, preprocessing, and analysis. Insights presented in Chapter 3. speak in favor of recording with simplistic protocol by using only one channel for a limited time duration. Introduction of this relatively easy-to-use method aimed to motivate the wider scientific community to contribute to the field. This approach could be useful in clinical practice due to the limited time resources for medical staff training and education. While educated visual observation remains the golden standard for evaluating and processing EGG, presented automated methods showed promising results. Our algorithm for the selection of the most suitable EGG channel is, to the best of our knowledge, the first method for that purpose. For the described protocol, it delivered beneficial outcomes. Additional testing and development of a video-based and fractional approach for artifact cancelation should be performed. Still, even at this moment, they could be applied as a useful tool in specific EGG protocols. Delivery of adequately preprocessed signal is one of the main prerequisites for suitable feature extraction. Having that in mind, this Dissertation provided valuable conclusions and laid the foundation for future work. While standardization of EGG and its wide application in clinical practice remains the future goal, results presented in Chapter 5. imply that EGG in virtual reality and driving simulation could already give valuable insights. Namely, provided results suggest that it can be used as a tool for the evaluation of sickness symptoms. While this application could improve the design of DS and VR systems, it could also substantially increase interest in the EGG recording in the long run. Subsequently, that could lead to resolving the majority of current issues in the field.

Main conclusions derived from this research will be provided in the form of answers to the research questions stated in the Preface.

Is it possible to acquire a reliable EGG signal via a custom-made open-source device by employing a simplistically designed short-term recording protocol with one recording channel?

Yes, it is. Based on the results presented in subchapter 3.1.2. in static recording conditions, while a subject is resting, one channel should be sufficient to obtain a reliable EGG signal. Protocol duration of 20 minutes was suitable to provide a postprandial increase in DF.

What are the perspectives of completely automated processing algorithms for artifact cancelation?

In terms of ECG and ECG artifacts, the method that included fractional calculus and Savitzky-Golay filter showed promising results. Considering the fact that this evaluation was done by using semi-synthetic signals, more significant conclusions should be derived from the in vivo acquired data. The video-based approach is one of the directions toward resolving the artifact issue. Results from the described case study were encouraging, and further investigation in a larger study group should confirm that.

Is it possible to record EGG in the dynamic environment, and what are the main guidelines that need to be followed?

Results showed that EGG-based assessment in a dynamic environment is possible with the careful application of protocol and analysis related recommendations presented in subchapter 5.2. motion While subject could be in a sitting position and recording can be obtained in a short-term time window, motion artifacts could still be present. This is why educated visual observation of timeseries and manual cancelation of movement noise should be performed.

What novel parameters should be used to quantify EGG signal recorded in a dynamic environment?

Crest factor and median frequency were more suitable in describing non-standard EGG frequency characteristics than the commonly used DF. CF provides an estimation of spectrum shape and peak prominence, while MF follows the shift in frequency content regardless of the dominant peak presence, which is not the case when DF is used. RMS could be a useful approach for the estimation of power and amplitude of EGG timeseries.

What are first the results regarding the correlation between EGG alterations and occurrence of nausea symptoms in a dynamic environment?

Preliminary results showed that there are noticeable alterations in EGG timeseries and spectrum related to the VR and DS environment and the occurrence of nausea. The most promising results regarding the quantification of observed changes were obtained by applying CF and RMS. More reliable conclusions should be derived from the investigations on a larger study group.

The research described in this Doctoral dissertation confirmed the initial hypotheses:

1. *With the appropriate instrumentation and clearly defined post-processing and signal analysis methods, it is possible to reduce and simplify the protocol for EGG recording for appropriate adaptation of the EGG method to wider clinical and research application. In addition, such protocol should enable high-quality EGG acquisition with decreased noise presence.*

2. *Electrogastrography as a non-invasive method can provide useful information regarding gastric electrical activity alterations in healthy subjects during driving simulation and virtual reality.*

6.1. The Most Important Scientific Contributions

In summary, the following scientific contributions should be stated as the most important ones:

1. Custom-made open-source EGG device was designed and realized. In addition, important experiences derived from that process were described in this Dissertation.

2. Short-term (20 minutes) single-channel EGG protocol was developed and evaluated in 20 healthy subjects.

3. Video-based and fractional order calculus approaches were used for the design of novel automated algorithms for noise cancelation from EGG signal.

4. Comprehensive evaluation of EGG measurement in dynamic environment was performed, and corresponding recommendations regarding recording protocol, signal processing and analysis were delivered.

5. Three novel, promising EGG features (median frequency, crests factor, and root-mean-square) were proposed and their application was evaluated.

6. EGG-based assessment of sickness induced by driving simulation and virtual reality in healthy subjects was introduced and investigated.

6.2. Further Improvement

While this Dissertation provided a valuable contribution, many approaches could be useful for further improvement in the field. Besides the extensions of presented ideas, novel ones include the following:

1. Testing and verification of improved EGG device presented in Chapter 2. Investigation of differences between the performance of circuit realized on protoboard and PCB. Testing of different types of passive components implemented in the device. ***Rationale:*** This technical investigation will provide final conclusions regarding the most appropriate methods for the design of EGG equipment. Following that, further improvement of the device could lead to the introduction of an EGG holter-monitor, able to record continuously slow wave activity while a subject is performing usual daily activities.

2. Development of algorithms for the evaluation of EGG signal based on the fractal dimension calculation. **Rationale:** Considering the nature of raw EGG signal that could present with periodical artifacts (ECG and respiratory), it is sensible to quantify the level of noise contamination using fractal dimension. This estimation could be beneficial for the classification of the signal prior to preprocessing in terms of its feasibility to provide information regarding both gastric slow waves and additionally heart or breathing rate.

3. Application of EGG based assessment of gastrointestinal disturbances triggered by different psychological stressors. **Rationale:** In [147], the aim was to induce alterations in EGG features by playing violent video content to subjects during EGG acquisition.

Preliminary results were promising and suggested that, especially with novel parameters presented in this Doctoral dissertation, it could be possible to evaluate physiological effects on the gastrointestinal system via EGG.

4. Assessment of sickness symptoms induced by long-term exposure to online video conferences, learning, or meeting platforms. **Rationale:** In this challenging period when, due to the SARS-CoV-2 virus crisis, in-person contacts are restricted, recent tendencies are to replace the majority of educational, business, and scientific meetings in the virtual world. This will increase the number of people that are using this type of communication, and consequently, increase the number of subjects that have sickness symptoms while using it. Similarly, as for the simulator sickness and cybersickness, EGG could be a valuable tool for the assessment of related symptoms.

Appendix A – Anatomy and Physiology of Gastrointestinal System

The main purpose of the gastrointestinal system, alternatively called the alimentary tract or the gut, is to support the nutritional needs of the human organism. For large molecules to be decomposed into the smaller ones that can be further absorbed via adequate structures, as food for metabolism, the functionality of this system is essential. Intake of carbohydrates, fats, proteins, vitamins, minerals, and fibers is required to keep the body energized, as well as for the growth and repair of tissues. General health of the organism is also dependent on all the processes that take place in the GI system. [r1, 2]

7.1. Anatomical Overview of GI System

There are two parts of the gastrointestinal system: 1) luminal GI and 2) hepato-biliary-pancreatic GI [205]. The scheme of its structure is presented in Figure 7.1.

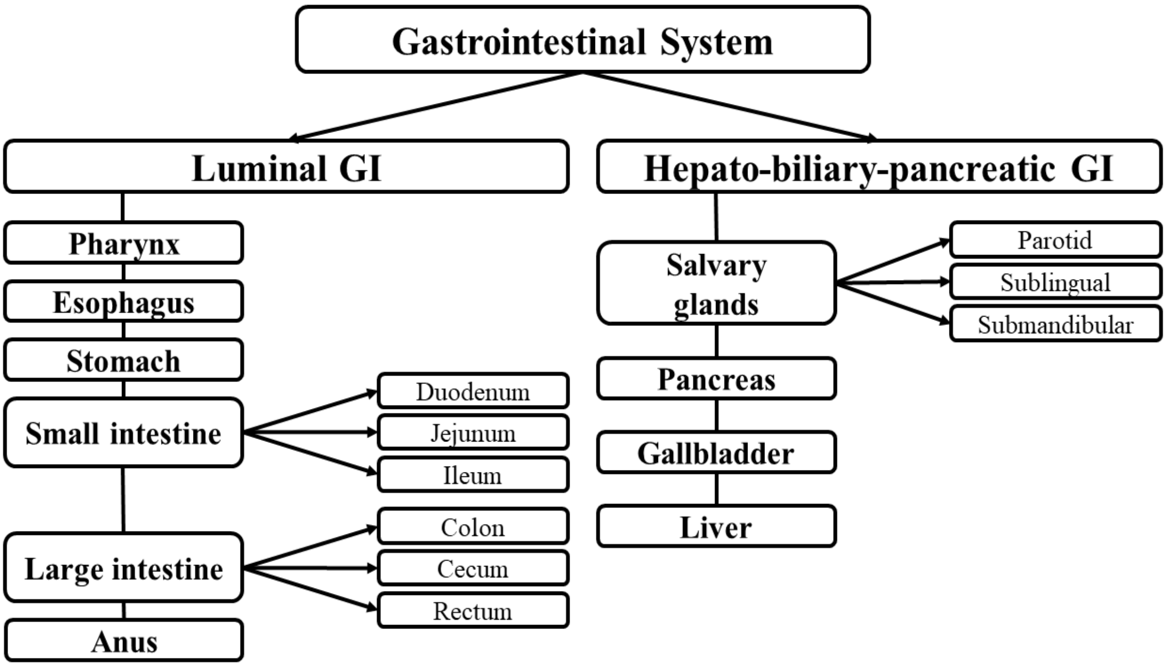


Figure 7.1. Schematic presentation of gastrointestinal (GI) system. Image is designed based on the information from [205].

Luminal (or tubular) GI can be described as a structure consisting of hollow organs with specific functions. It includes the following: 1) pharynx, 2) esophagus, 3) stomach, 4) small intestine, 5) large intestine, and 6) anus. Additionally, the small intestine can be structurally divided into duodenum, jejunum, and ileum, while the large intestine consists of the colon, cecum, and rectum. Essential parts of luminal GI are sphincters, structures that can be described as separators between different GI organs. From the pharynx to the anus, there are: 1) upper esophageal, 2) lower esophageal, 3) pyloric, 4) sphincter of Oddi, 5) ileocecal,

6) internal anal, and 7) external anal sphincter. Hepato-biliary-pancreatic GI includes: 1) salivary glands (parotid, sublingual, and submandibular), 2) pancreas, 3) gallbladder, and 4) liver. The anatomical position and shape of the GI system structures are presented in Figure 7.2. [r1, 2, 4, 5]

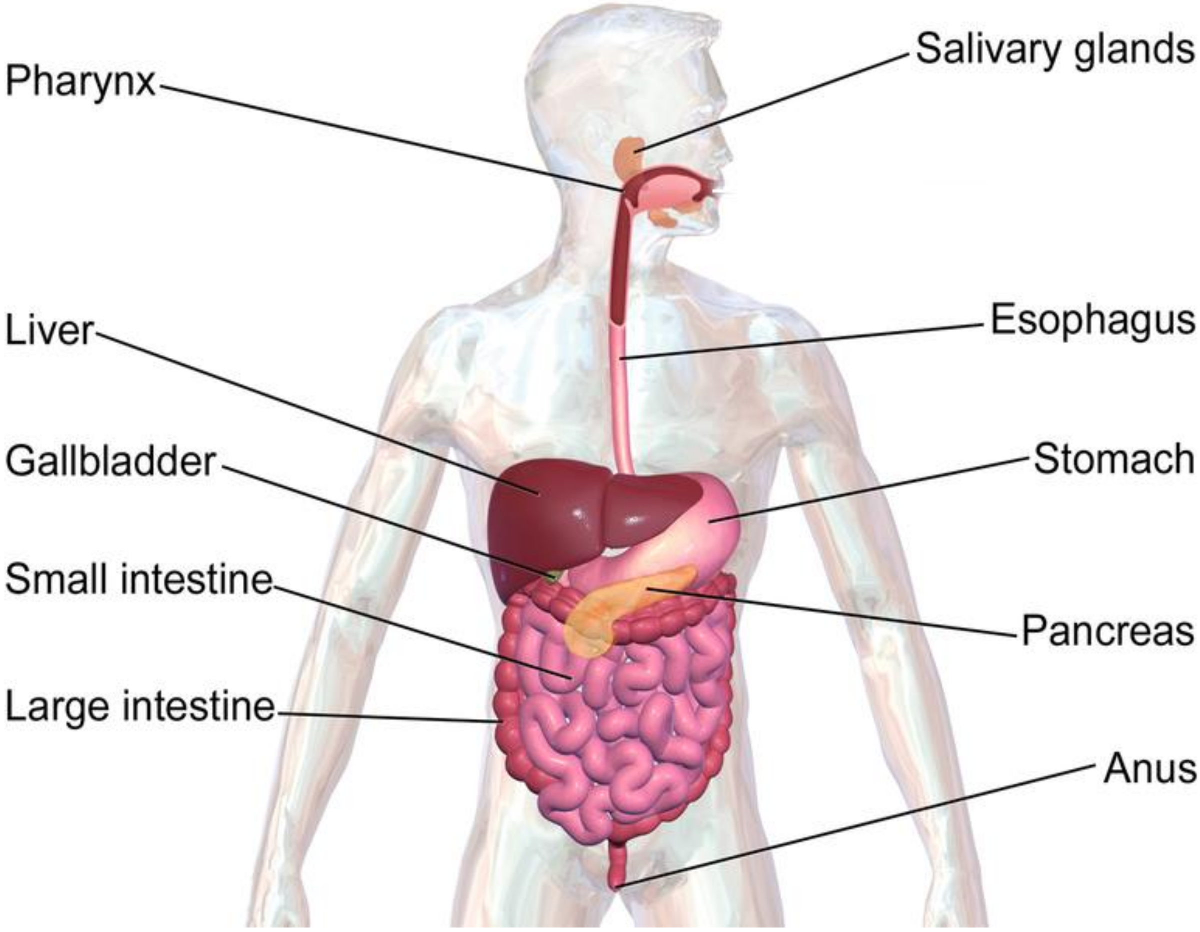


Figure 7.2. Illustration of the GI system organs. Image taken and adapted from: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI: 10.15347/wjm/2014.010. ISSN 2002-4436. Accessed in May 2020. (License: CC BY 4.0)

Cross-section of the luminal GI is similar through its full length with some changes in structure and function of layers in different organs. From the inside to outside, there are five major gut layers: 1) mucosa, 2) submucosa, 3) circular smooth muscle layer, 4) longitudinal smooth muscle layer, and 5) serosa. The mucosa can be divided into three sublayers: 1) epithelium, 2) lamia propria, and 3) muscularis mucosa. Two clusters of parasympathetic ganglions that are creating the enteric nervous system of the GI tract can be found in the submucosal layer – Meissner`s plexus, and between the two muscle layers – myenteric plexus (see Figure 7.3.). [r1, 2, 6, 7]

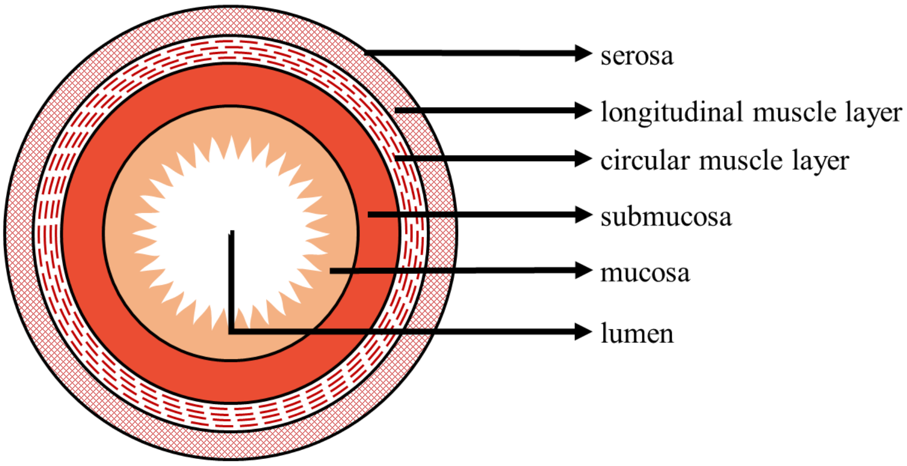


Figure 7.3. Cross-section of luminal GI with corresponding layers marked.

7.2. Functionality of the GI System

Gastrointestinal system functionality is a complex process that includes four main subprocesses: 1) digestion, 2) absorption, 3) secretion, and 4) motility. In order for food to be processed and adequately delivered to the cells of the human organism, all of these subprocesses need to be perfectly synchronized. Secretion can be described as the activation of secretory glands that release substances essential for digestion and absorption. Decomposition of the ingested food into the smaller parts suitable for the absorption is referred to as digestion. A vital part of the GI function is its motility that is taking place during the whole gastric cycle and, with the help of gravity, pushes and mixes nutrients through luminal GI. It should be stated that some of the subprocesses are dominantly related to distinct parts of the GI. Digestion and mixing of food are occurring mainly in the stomach, while absorption in the small intestine. [r2, 4, 8–10]

Control of releasing and holding gastric content, defined as gut tone, is regulated by the sphincters. These structures are made from the smooth muscles. Their contractility gives sphincters valvular nature capable of opening and closing at the appropriate moment, based on the needs determined by the gastric cycle phase. [8], [213]

Other processes that are simultaneously taking place in the GI system are:

- storage and excretion of waste material;

- hepato-biliary-pancreatic GI secretion, which helps lubrication, absorption, and digestion of different structures;

- secretion of GI hormones. [9], [209], [214]

Since the gastrointestinal environment is open to various external influences, its protective role is critical. Warning for the body that the food is not suitable for the ingestion is provided via the senses of smell and taste, followed by the vomit reflex, which helps the organism to remove dangerous substances. Also, stomach acid and natural bacterial flora are capable of killing or preventing the reproduction of unwanted bacteria in the GI tract. Finally, in the wall of the gut part of the immune system, called Peyer`s patches, provides the first response to possible antigens found in the nutrients. [9]

7.3. Focus on the Anatomy and Physiology of the Stomach

The organ with the largest lumen in the tubular GI is the stomach. It is J shaped, and according to the Gray`s Anatomy of the human body [10], its position can be described by the following statements: “It lies in the epigastric, umbilical, and left hypochondriac regions of the abdomen, and occupies a recess bounded by the upper abdominal viscera, and completed in front and on the left side by the anterior abdominal wall and the diaphragm.” It is separated from the esophagus by the lower esophageal sphincter and from the small intestine by pyloric sphincter (see Figure 7.4.) [214]. The stomach lies in the stomach bed, comprised of the diaphragm, left adrenal gland, kidney, pancreas, and transverse colon [207]. Precise size, shape, and position of the stomach are challenging to determine because they can diverge depending on the body posture and amount of the ingested food. The stomach can be anatomically divided into five main parts (see Figure 7.4.), from the esophagus to the small intestine: 1) cardia, 2) fundus, 3) body, 4) antrum, and 5) pylorus. Lesser curvature on the right lateral wall and greater curvature on the left lateral wall are connecting anterior and posterior surfaces of the stomach [206], [215]. The blood supply for the stomach comes from the four main arterial branches: 1) the left gastric artery – along the lesser curvature, 2) the splenic artery – across a posterior abdominal wall, 3) the common hepatic artery that supplies the right gastric artery - along the lesser curvature, and 4) gastroduodenal artery (towards pylorus and duodenum) [8]. Regarding innervations, the stomach has both sympathetic (from autonomic coeliac plexus) and parasympathetic (from the vagal nerve) supply. As already explained in subchapter 7.1. the stomach has its two intrinsic plexuses – Meissner`s and myenteric [211].

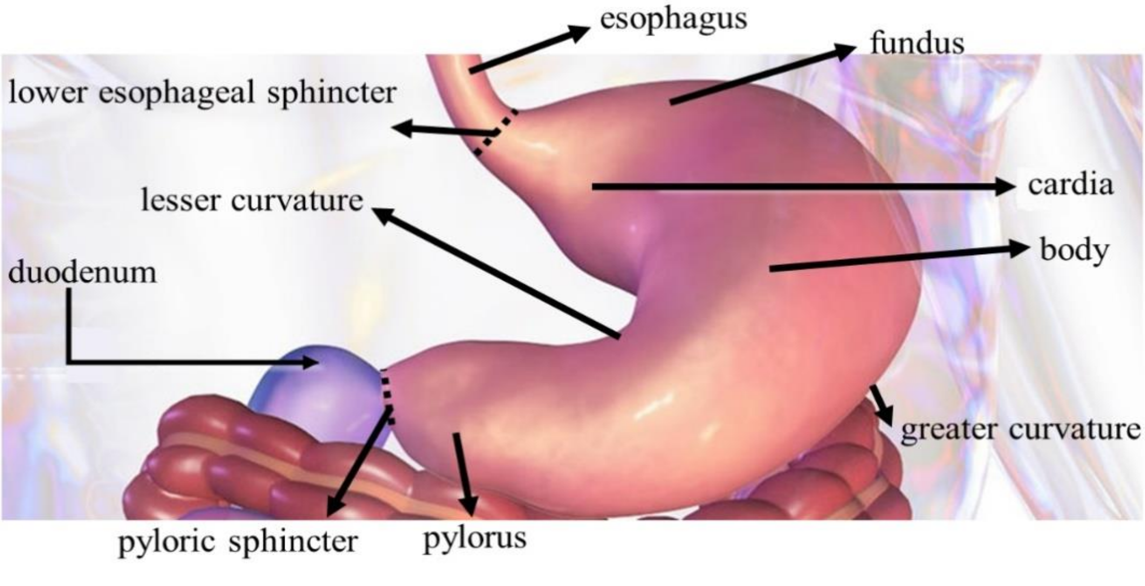


Figure 7.4. Illustration of stomach anatomy with specific parts marked. Image taken and adapted from: "Digestive System for labeling" by Rambling Professor. Accessed in October 2020. (License: CC BY SA 2.0)

Three core processes that are happening in the stomach are motility, digestion, and secretion, while absorption can only take place in it for some liquids. Its main role is to receive food from the esophagus through the lower esophageal sphincter and deliver it to the small intestine through the pyloric sphincter [9]. While the food is in the stomach, few fundamental processes occur. First, nutrients are mixing with the digestive juices forming a substance called chyme. The proximal part of the stomach, body and fundus are dilating in order to store whole content. The stomach volume is approximately 2-3 L. Contractions are happening mainly in the distal part of the stomach, near to the pylorus, forming a motion that mixes the chyme. After each contraction, smaller parts of the chyme, suitable for the next phase of digestion, pass through the pylorus into the duodenum. On the contrary, larger parts are being pushed back into the body of the stomach for further processing. By performing this procedure, illustrated in Figure 7.5., the stomach ensures proper transport of the suitably processed food towards the distal end of the luminal GI for further digestion and absorption. The contractility of the stomach is mainly determined by its electrical activity that will be explained in the following subchapter. [8], [209], [212], [215]

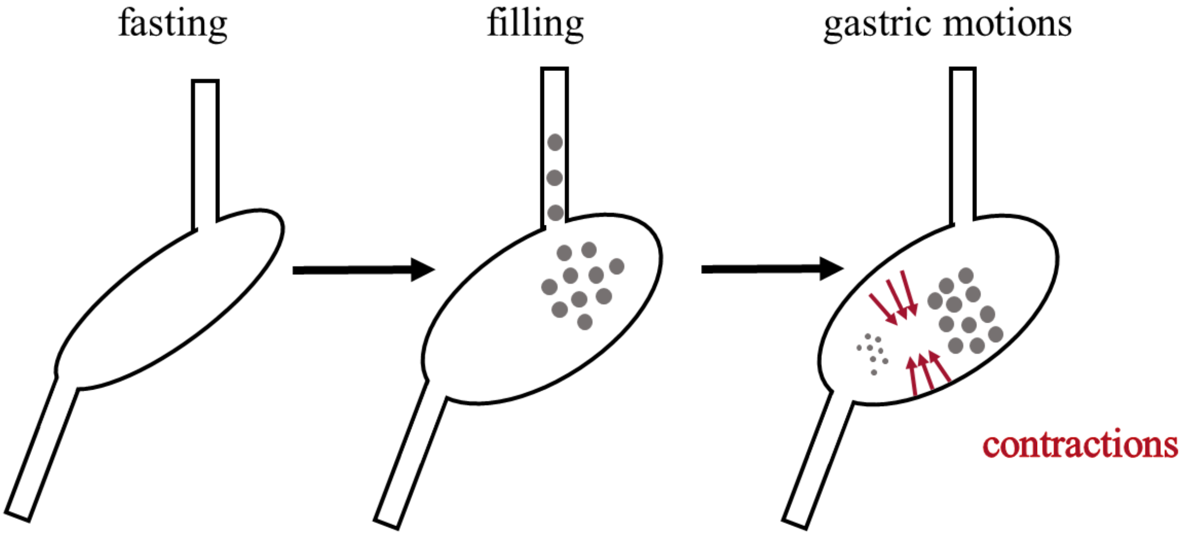


Figure 7.5. Illustration of gastric motility. The first phase is fasting, followed by the food intake, and the last part is active mixing with stomach contractions.

7.4. Electrical Activity of the Stomach

As an organ with periodical motility, the stomach is also presenting with electrical activity - control mechanism for its contractions. Electrical signals that can be recorded both invasively and non-invasively are definite proof that there is an organized flow of ions that dictates mechanical activity of the stomach. There are both sympathetic and parasympathetic nervous systems behind this phenomenon, combined with stomach intrinsic nervous plexuses, described in subchapter 7.3. To understand functionality and processes that are taking place in the GI tract, it is essential to have an insight into its electrical activity.

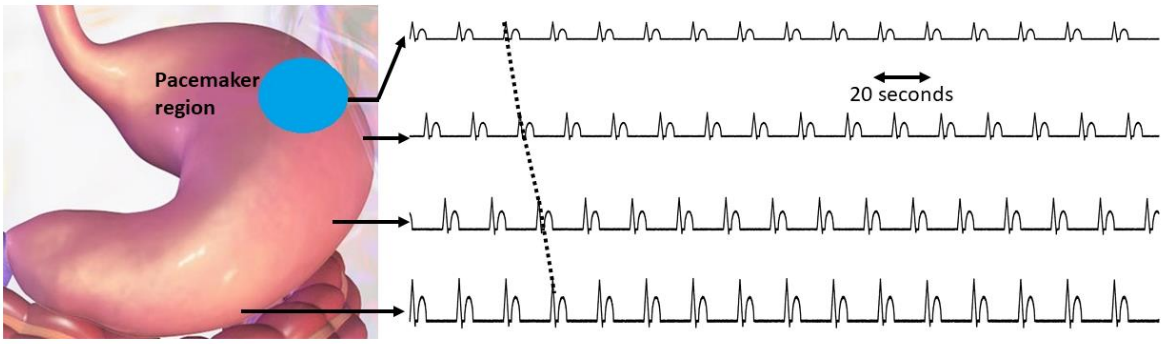


Figure 7.6. Graphical presentation of stomach electrical activity and its propagation. Image of the stomach anatomy taken and adapted from: "Digestive System for labeling" by Rambling Professor. Accessed in October 2020. (License: CC BY-SA 2.0)

The pacemaker region of the stomach is placed near the fundus at the greater curvature. Electrical signals originate from the stomach pacemaker region. They are propagating through the body of the stomach, towards the distal portion of the stomach, i.e., pylorus (Figure 7.6.). In that zone, electrical signal has the highest amplitude as a consequence of its thick layer. Electrical signal originating from the stomach pacemaker region is periodical with a period of around 20 seconds. [12], [216]–[219]

7.5. Interstitial Cells of Cajal

The pacemaker region of the stomach is populated with Interstitial Cells of Cajal (ICC) – cells capable of spontaneous generation of electrical current that are coupled with smooth muscle cells of the stomach [12]. They are located in the inner muscular layer and innervated by the myenteric plexus [11], [13]. Light microscopy of the single ICC provided evidence regarding its "firing" ability. Sanders et al. stated that "The initiation of pacemaker activity in the ICC is caused by a release of Ca2+ from inositol 1,4,5-trisphosphate (IP3) receptor-operated stores, uptake of Ca2+ into mitochondria, and the development of unitary currents. Summation of unitary currents causes depolarization and activation of a dihydropyridine-resistant Ca2+ conductance that entrains pacemaker activity in a network of ICC, resulting in the active propagation of slow waves." [11]. This localized microscopically approach delivered significant findings that supported previously derived conclusions based on the macroscopic investigation regarding electrical activity of the stomach [144], [145].

7.6. Electrical Control and Electrical Response Activity

Invasive recording of the stomach electrical activity from the serosal surface revealed that it could be divided into two main components: 1) electrical control and 2) electrical response activity [26]. Electrical Control Activity (ECA), alternatively called Basic Electrical Rhythm (BER), represents slow variation of resting potential between -60 mV to -75 mV and from -20 mV to -40 mV [12], [220]. These variations are a consequence of the shifting between depolarization and repolarization of the electrically active cells in the stomach approximately three times a minute, which is why ECA is often called slow waves. As discussed in subchapter 7.5. ECA originates from Interstitial cells of Cajal (pacemaker region) and propagates very rapidly towards the distal portion of the stomach. Described electrical activity, except in rare cases, cannot provoke contraction of the stomach smooth muscle. In order for that to happen, more intense alterations in membrane potential differences need to take place. Those abrupt variations are called Electrical Control Activity (ECA) or spike potentials. ECA can happen only during the depolarization phase of slow waves if the threshold potential is achieved. The operating principle is illustrated in Figure 7.7. A high degree of correlation between the spike potentials and stomach contraction was demonstrated. Based on this, it can be stated that ECA dictates the maximal frequency of gastric motions, while ERA is responsible for actual contractions. [14], [20], [22], [26], [51], [99], [216]

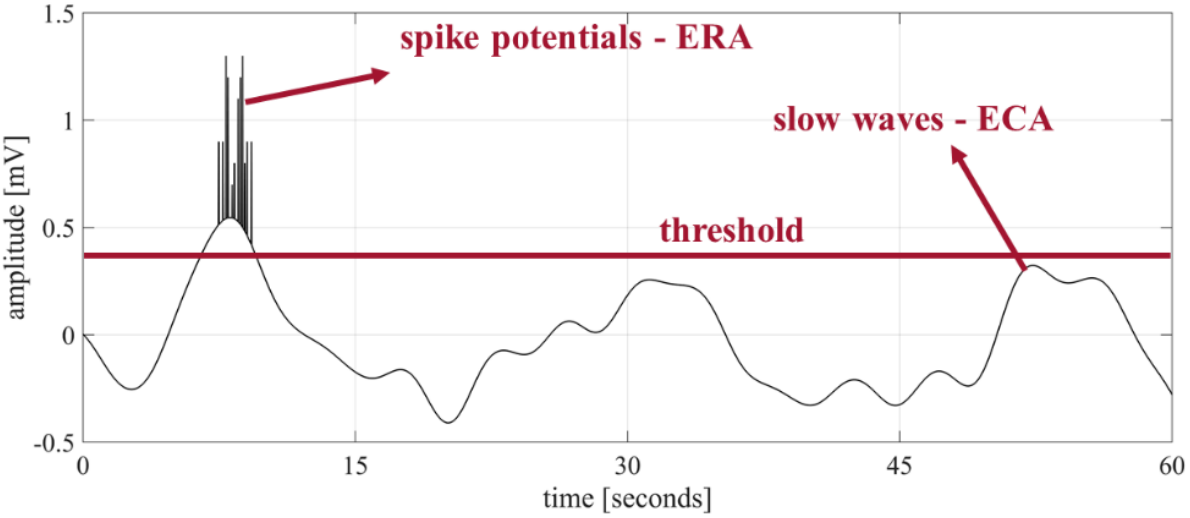


Figure 7.7. Representation of slow waves and spike potentials. The figure presents the semi-synthetic signal synthesized from recorded slow waves and artificial spike potentials.

Appendix B – Methods for the Assessment of Gastrointestinal System

Although in approximately 80 % of the cases, the GI system diagnosis comes from the patient's history and symptoms [9], it is crucial to have suitable diagnostic tools to confirm or exclude initial assumptions. Additionally, to design a research protocol that examines the effects of different stressors on the GI tract, it is crucial to have at hand evaluation techniques that will deliver quantified results. Based on the information from [9], [206], [210], [221], [222], following clinical and diagnostic procedures are described:

- blood tests;
- swab or stool samples for microbiological assessment;
- biopsy for histological or cytological approach;
- breath test;
- esophageal manometry;
- endoscopic procedures;
- imaging procedures.

Blood tests provide an insight into hematological and biochemical balance and can be used to evaluate the functionality of GI organs. If further investigation is needed, commonly it includes a swab or a stool sample in which different types of parasites, fungi, bacteria, or viruses can be found that can explain disturbances in GI performance. Sometimes inspection of actual tissue (histological approach) or cell (cytological approach) is needed. This method is called a biopsy, and it requires a sample of corresponding tissue or cells examined by light or electron microscopy.

The breath test method is based on the assumption that some enzymes can trigger a reaction that subsequently can produce gas like hydrogen or carbohydrate in the gut lumen. If a suitable substance that will react with the corresponding enzyme is given to the subject, then the resulting gas will be detectable in the breath.

Measurement of the pressure changes using the probe placed through the nasal cavity into the esophagus is called esophageal manometry. It is expected that the pressure wave will propagate through the esophagus to the lower esophageal sphincter, which should then open to allow the substance to pass into the stomach while releasing the pressure. Disturbances from the expected measurements can be correlated to gastric motility disorders.

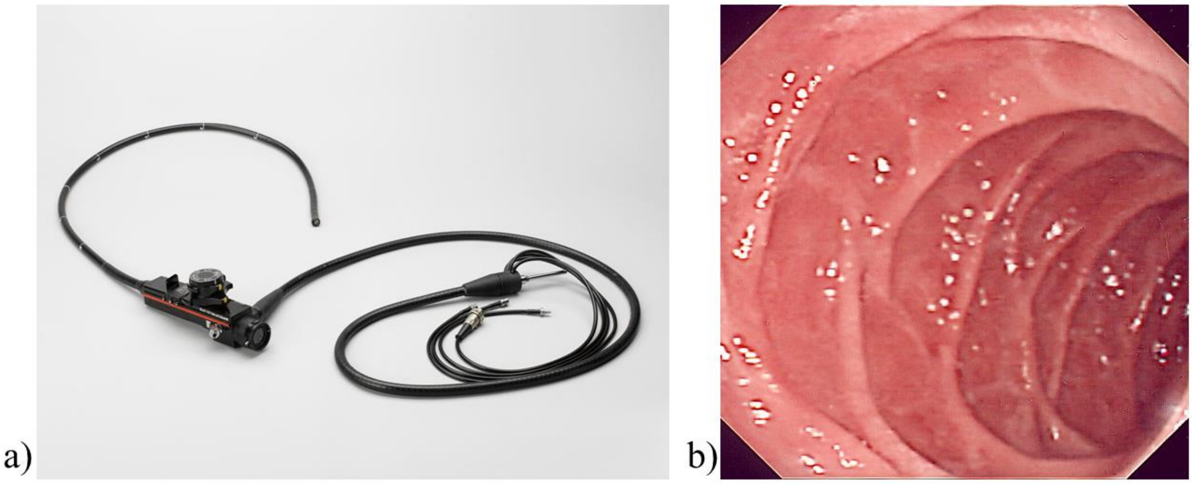


Figure 8.1. a) Photograph of fiber optic gastroscope ("PFS -F III fiber optic gastroscope with accessories (gastroscopes)" Accessed in July 2020. (License: CC BY-NC-SA 4.0). b) Example of the image taken during a gastroscopy ("My Duodenum" by MindSpigot), Accessed in July 2020. (License: CC BY-NC-SA 2.0.)

An endoscope can be described as the probe with the camera on the distal end, which allows an examiner to get an insight into the inner lumen of the GI system (see Figure 8.1.). The two most commonly applied endoscopic procedures are gastroscopy and colonoscopy. Gastroscopy, alternatively called OesophagoGastroDuodenoscopy – OGD, is used to assess the upper gastrointestinal tract up to the duodenum. The probe is placed through the mouth and esophagus while a subject is laid on the left side. Prior to OGD, overnight fasting is mandatory. Mild sedation could be performed in order to increase patient comfort. Colonoscopy is a similar procedure, with the difference is that an endoscope is inserted through the rectum and anal canal to examine the lower part of GI, mainly the large intestine. It is more uncomfortable for the subject, so stronger sedation may be applied. Besides the camera, some probes have an ultrasonic transducer at the distal end to record ultrasonographic images – the corresponding procedure is called an endoscopic ultrasound. With an endoscope application, selected therapeutic procedures could be performed (lesion or polyp removal, bleeding control, gallstones removal, etc.).

Non-invasive visualization is frequently used in diagnostic tools, and gastroenterology is not an exception. The most commonly used imaging techniques for assessment of GI system are: 1) radiography (with and without contrast), 2) angiography, 3) Computerized Tomography – CT, 4) Magnetic Resonance Imaging – MRI, 5) radioisotope scanning, and 6) ultrasonography. A different absorption rate of X-rays from various structures allows visualization of the borderlines between the GI organs. By additional insertion of contrast media into the luminal GI (most commonly barium), visualization quality can be enhanced. This can provide better insight into potential shape and position abnormalities. Angiography can be described as radiography with a contrast of blood vessels. It is useful to evaluate the blood supply to the GI organs. Computerized tomography and magnetic resonance imaging can give a detailed 3D overview of GI structures (see Figure 8.2.b)) being ideal for the detection of tumorous tissue. Radioisotope imaging working principle is the detection of radioisotope accumulation (most commonly Iridium-99) near so-called hot and cold lesions on the parts of hepato-biliary-pancreatic GI that can be correlated with organ abnormalities. Ultrasonography is based on the reflection of high-frequency sound waves. It is less precise and detailed than other imaging techniques, but it is entirely non-invasive and safe to use in pregnancy.

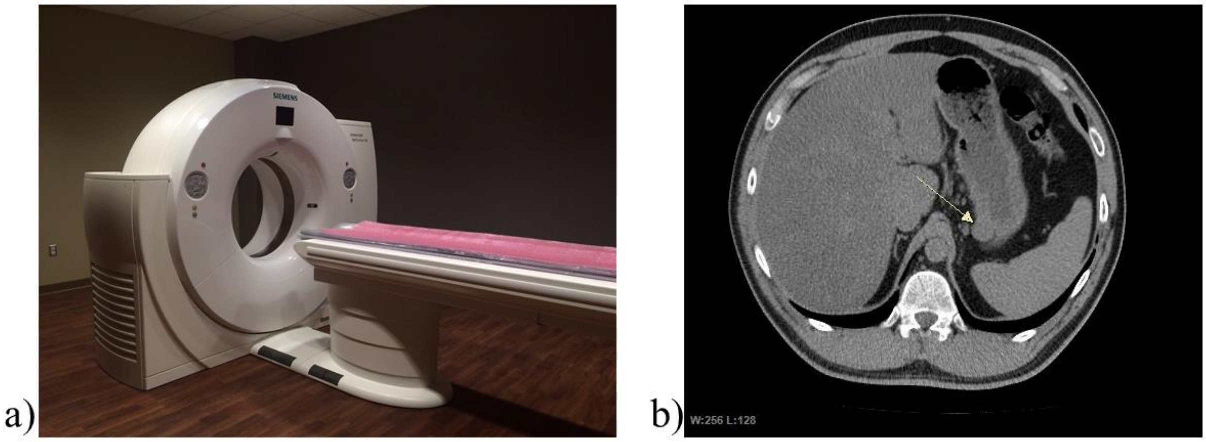


Figure 8.2. a) CT scanner photograph ("64F56219-4C85-459F-B2B3-4BD0E6FDA219-735" by J.G. Accessed in July 2020. (License: CC BY-NC-SA 2.0). b) Example of one slice image of GI System from CT scanner ("File:GIST CT image.jpg" by Inversitus). Accessed in July 2020. (License: CC BY-SA 3.0.)

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Nenad B. Popović - Biography

Nenad B. Popovic was born on September 3, 1992 in Ivanjica. In the same city he finished primary school "Kirilo Savic" and high school "Gimanzija Ivanjica", both as holder of diploma "Vuk Karadzic" and the best student in the class.

After graduating from high school, in 2011 he enrolled at the School of Electrical Engineering, University of Belgrade. He graduated in 2015 with the topic "Design of a device for measurement and frequency analysis of electrogastrography signals" with mentor prof. dr Mirjana Popovic and co-mentor prof. dr. Nadica Miljković. For his thesis he received the second prize at the ETFA BAFA U.S.A. competition for the best graduate thesis during 2015. He completed his undergraduate studies with grade point average of 9.74 and as the best student in the class at Biomedical and Eco Engineering module.

He enrolled in master studies, also at the School of Electrical Engineering, Module of Biomedical and Eco Engineering, immediately after undergraduate studies and graduated in 2016. The master's thesis on "Design of methods for signal analysis and user interface for multi-channel electrogastrogram" was defended under the mentorship of prof. dr. Nadice Miljković.

In the same year, at the same faculty, he started his PhD studies at the study module Systems Management and Signal Processing (The Department of Signals and Systems). He passed all the exams and is currently working on his Doctoral dissertation. His area of scientific interest is recording, processing and application of electrophysiological signals, with the focus on non-invasive recording of electrical activity of gastric smooth muscles – electrogastrography. The aim of his research is realization of the instrumentation for recording as well as the proposal and evaluation of innovative methods for acquisition, processing and analysis of electrogastrographic signals.

From January 1, 2016 until May 13, 2018, he worked as a technical consultant for implantation and follow-up of implantable pacemakers and cardioverter defibrillators, at Biotronik LLC (Biotronik SE & Co. KG, Berlin, Germany). After that, he continued his career in the company Abbott Medical Balkan LLC (Abbott Laboratories, Illinois, USA), at the same position, where he works to this day. He supported over 750 implantations and provided significant number of consultations, as well as educations of health care professionals in the region of Eastern Europe. During 2020, he held many online lectures aimed to educate newly hired engineers in EMEA region (Europe, Middle East, and Africa).

He is the author or co-author of three papers in scientific journals from the SCI list (two as the first author), and 11 papers at international and national conferences (7 as the first author). He gave one invited lecture at conference of national significance.

образац изјаве о ауторству

Изјава о ауторству

Име и презиме аутора Ненад Б. Поповић

Број индекса 2016 / 5026

Изјављујем

да је докторска дисертација под насловом

Методе за оцену електричне активности глатких мишића (наслов на енглеском: Methods for assessment of electrical activity of smooth muscles)

- резултат сопственог истраживачког рада;
- да дисертација у целини ни у деловима није била предложена за стицање друге дипломе према студијским програмима других високошколских установа;
- да су резултати коректно наведени и
- да нисам кршио/ла ауторска права и користио/ла интелектуалну својину других лица.

Потпис аутора

У Београду, 10.12.2020.

Поповић

образац изјаве о истоветности штампане и електронске верзије докторског рада

Изјава о истоветности штампане и електронске верзије докторског рада

Име и презиме аутора Ненад Б. Поповић

Број индекса 2016 / 5026

Студијски програм Електротехника и рачунарство, Управљање системима и обрада сигнала

Наслов рада Методе за оцену електричне активности глатких мишића наслов на енглеском: Methods for assessment of electrical activity of smooth muscles

Ментор др Надица Миљковић, ванредни професор

Изјављујем да је штампана верзија мог докторског рада истоветна електронској верзији коју сам предао/ла ради похрањивања у **Дигиталном репозиторијуму Универзитета у Београду.**

Дозвољавам да се објаве моји лични подаци везани за добијање академског назива доктора наука, као што су име и презиме, година и место рођења и датум одбране рада.

Ови лични подаци могу се објавити на мрежним страницама дигиталне библиотеке, у електронском каталогу и у публикацијама Универзитета у Београду.

Потпис аутора

У Београду, 10.12.2020.

образац изјаве о коришћењу

Изјава о коришћењу

Овлашћујем Универзитетску библиотеку „Светозар Марковић" да у Дигитални репозиторијум Универзитета у Београду унесе моју докторску дисертацију под насловом:

Методе за оцену електричне активности глатких мишића
(наслов на енглеском: Methods for assessment of electrical activity of smooth muscles)

која је моје ауторско дело.

Дисертацију са свим прилозима предао/ла сам у електронском формату погодном за трајно архивирање.

Моју докторску дисертацију похрањену у Дигиталном репозиторијуму Универзитета у Београду и доступну у отвореном приступу могу да користе сви који поштују одредбе садржане у одабраном типу лиценце Креативне заједнице (Creative Commons) за коју сам се одлучио/ла.

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