



# LUND UNIVERSITY

## Extracting Cardiac Information From the Pressure Sensors of a Dialysis Machine

Holmer, Mattias

2017

*Document Version:*

Publisher's PDF, also known as Version of record

[Link to publication](#)

*Citation for published version (APA):*

Holmer, M. (2017). *Extracting Cardiac Information From the Pressure Sensors of a Dialysis Machine* (1 ed.). [Doctoral Thesis (compilation), Division for Biomedical Engineering]. Department of Biomedical Engineering, Lund university.

*Total number of authors:*

1

### General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

# Extracting Cardiac Information From the Pressure Sensors of a Dialysis Machine

Mattias Holmer



**LUND**  
UNIVERSITY

DOCTORAL DISSERTATION  
Biomedical Engineering  
Lund, June 2017

Dissertation for the degree of Doctor of Philosophy in Biomedical Engineering.

Cover illustration: The screen of an Artis hemodialysis machine, with permission from Baxter International Inc.

Department of Biomedical Engineering  
Lund University  
P.O. Box 118, SE-221 00 LUND, SWEDEN

ISBN: 978-91-7753-313-9 (print)  
ISBN: 978-91-7753-314-6 (pdf)  
ISRN: LUTEDX/TEEM-1111-SE

Report No. 5/17

Printed in May 2017 Sweden by *Tryckeriet i E-huset*, Lund.

© Mattias Holmer 2017

*To my family*

“Nothing is impossible, the word it self says – I’m possible!”  
*Audrey Hepburn*

“The time is out of joint. O cursed spite,  
that ever I was born to set it right!”

*William Shakespeare*

---

# Populärvetenskaplig Sammanfattning

---

**Patienter med njurar som slutat fungera är beroende av dialysmaskiner för sin överlevnad. Men behandlingen är långt ifrån riskfri. Faktum är att en dialysmaskin kan tömma patienten på dess blod inom några få minuter. Forskare från Lund arbetar på att minimera denna säkerhetsrisk.**

Allt fler människor är beroende av dialys för att överleva. Detta beror bland annat på att befolkningen blir allt äldre. En annan orsak är att fler har diabetes, som kan få njurarna att sluta fungera. Njurarna har flera funktioner, bland annat att producera urin. Via urinen blir vi av med överskottsvätska och slaggprodukter. En patient vars njurar har slutat fungera måste antingen få dem transplanterade, eller bli behandlad med dialys resten av livet. Njurarna arbetar kontinuerligt, dygnet runt. För att efterlikna detta borde dialysbehandlingen egentligen utföras så ofta som möjligt. I praktiken utförs behandlingen vanligtvis tre dagar i veckan på en klinik. En sådan dialysbehandling varar i ca 4 timmar. De som väljer att i stället behandla sig själva i hemmet, gör det ofta fler gånger i veckan, men med kortare behandlingstid. Detta för att efterlikna njurens kontinuerliga funktion mer.

## Dialysbehandlingen

När blodet renas med hjälp av dialys, pumpas det ut från kroppen och filtreras över ett filter - en dialysator. Därefter pumpas det tillbaka till patienten. En effektiv behandling kräver ganska höga blodflöden, 300–400 ml/min. För att kunna ta ut så höga flöden har en kirurg skapat en så kallad fistel i patientens arm. Fisteln bildas av att en artär och en ven sammankopplas. Det uppstår en genväg som blodet lätt flödar genom. På

så sätt blir flödet relativt stort. För att få ut blodet ur fisteln sticker man in en kanyl, denna kanyl kallas artärnål. Man lämnar tillbaka blodet via en annan kanyl, som kallas venånål.

### Dialys kan vara livsfarligt

Det är självklart viktigt att nålarna inte faller ur fisteln av misstag. Därför tejpas de omsorgsfullt fast vid patientens arm. Trots detta händer det att nålarna lossnar. Om artärnålen faller ut, suger maskinen in luft via den. Detta upptäcks av en så kallad luftvakt i maskinen. Ett larm genereras och blodpumpen stoppas så att ingen luft riskerar att pumpas in i patienten. Om istället venånålen lossnar förs inte blodet längre tillbaka till patienten, utan kanske hamnar på golvet eller i sängkläderna. Med de höga blodflödena som används kan patienten tömmas på sitt blod inom några få minuter. Om ett venånbortfall inte upptäcks i tid riskerar patienten att dö. Det larmsystem som finns inbyggt i dagens dialysmaskiner bygger på att en statisk tryckförändring uppstår när nålen trillar ut. Det har visat sig att denna tryckförändring i många fall är för liten för att kunna användas. Den kan vara mindre än den tryckändring som uppstår om patienten ändrar läge i sängen. I praktiken kan dagens dialysmaskiner inte upptäcka mer än 50 procent av venånbortfallen.

### Säkrare dialysmaskiner

Det är trots allt ovanligt att venånålen lossnar. Ändå uppskattar man att mer än 200 av världens ca 2 miljoner dialyspatienter dör varje år, medan uppemot tio gånger fler överlever när de drabbas av ett venånbortfall. Forskare på Baxter och i signalbehandlingsgruppen vid institutionen för Biomedicinskt teknik vid Lunds universitet samarbetar för att göra dialysen säkrare för patienterna. Genom att analysera trycksignaler som redan mäts av dagens dialysmaskiner filtreras hjärtpulsen fram. Om pulsen upptäcks i tryckgivaren som sitter i blodslangen kopplad till venånålen, drar maskinen slutsatsen att nålen inte har lossnat från patienten. Skulle däremot hjärtpulsen försvinna, larmar maskinen personalen och stoppar automatiskt blodpumpen så att patienten inte töms på blod.

Andra lösningar på problemet för venånbortfall finns redan på marknaden. Dessa tekniker bygger till exempel på fuktdetektering eller ett slags optiska plåster som känner av blod.

– Fördelen med vår metod är att inga engångsartiklar och inget extra arbete för sjukvårdspersonalen behövs, säger Kristian Solem, forskningsingenjör på Baxter.

Han tillägger:

– Metoden är förmodligen allra viktigast för hemdialyspatienter som ju inte övervakas av någon personal.

## Utmaningen

Lösningen att lyssna efter hjärtpulsen kan tyckas enkel, men är betydligt svårare än den först verkar. Problemet är att det finns en blodpump i dialysmaskinen. Pumpen genererar tryckpulser som är upp till hundra gånger starkare än hjärtpulserna. Dessutom ligger frekvensen som blodpumpen genererar nära hjärtats frekvens, och det förekommer till och med att frekvenserna överlappar varandra. Sammantaget gör detta att det är väldigt svårt att separera hjärtsignalen från pumpsignalen. Här kommer signalbehandlingen in. Etablerade och nyutvecklade metoder har testats för att få fram hjärtsignalen på ett så effektivt sätt som möjligt. Att använda sig av hjärtsignalen öppnar inte bara för säkrare dialys. Metoden innebär också andra fördelar för patienten. Många patienter med njurproblem har också problem med hjärtkärlsjukdomar. Hjärt- och njurfunktion har visat sig hänga intimt ihop. Sambandet gör det extra viktigt att alltid övervaka dialyspatientens hjärta.

– Vår metod att extrahera fram hjärtsignalen ger nya möjligheter till kontinuerlig övervakning av hjärtstatus på dialyspatienter, utan extra mätinstrument som till exempel EKG, säger Leif Sörnmo, professor i signalbehandling.

Att kontinuerligt övervaka hjärtat skulle kunna öka patienternas överlevnad, genom att möjliggöra åtgärder i tid. En aktuell händelse på sjukhuset i Malmö belyser detta. Patienten som var med berättar själv:

”En gång upptäckte personalen att patienten intill mig hade dött. Ingen märkte när det hände. Hjärtat hade bara stannat av någon anledning. Dialysmaskinen körde på som om inget hade hänt. Det kändes kusligt att ha legat där bredvid en död människa.”

– Om dialysmaskinen varit utrustad med vår metod att övervaka hjärtpulsen, så hade maskinen larmat. Då hade personalen förmodligen kunnat återstarta hjärtat och patienten hade kanske överlevt, säger Kristian Solem.



---

# Abstract

---

This doctoral thesis in biomedical engineering deals with cardiac monitoring using the built-in extracorporeal blood pressure sensors of a hemodialysis machine. Patients treated with hemodialysis often suffer from cardiovascular disease. Despite this, cardiac monitoring is not routinely performed during dialysis treatment, since external devices required for such monitoring causes patient discomfort and increased workload for the clinical staff. Extraction of cardiac information from the pressure sensor signals is complicated by the fact that the cardiac pressure pulses are obscured by pressure pulses caused by the peristaltic blood pump of the dialysis machine. The cardiac signal component is of much lower magnitude than the pump pressure component, and the pump and heart rates may coincide.

The thesis comprises an introduction and four papers describing methods for extraction and characterization of cardiac information from the built-in pressure sensors of a dialysis machine. In the first paper, a method is proposed for estimating the cardiac signal by subtracting an iteratively refined blood pump model signal from the signal measured at the extracorporeal venous pressure sensor. The method was developed based on simulated pressure signals, and evaluated on clinical pressure signals acquired during hemodialysis treatment. Heart rate estimated from the clinical pressure signal was compared to heart rate derived from a reference photoplethysmographic (PPG) signal. The results suggest that the accuracy is sufficient for analysis of heart rate and certain arrhythmias.

In the second paper, a method is proposed for improved cardiac signal extraction by combining the arterial and the venous pressure sensor signals of the hemodialysis machine. Using different techniques for combining the arterial and venous pressure signals, the performance is evaluated and compared to that of the method in the first paper. Heart rate and heartbeat occurrence times, estimated from the extracted cardiac signal, are compared to the corresponding quantities estimated from the PPG reference signal in nine hemodialysis treatments. The results show that the proposed

method offers superior estimation at low cardiac signal amplitudes, enabling cardiac monitoring during treatment without the need of extra sensors for more patients.

Ventricular premature beats (VPBs), being abundant in hemodialysis patients, can provide information on cardiovascular instability and electrolyte imbalance. The third paper describes a method for VPB detection in cardiac signals extracted using the method described in the second paper. A set of features characterizing the cardiac pressure pulses is extracted, and linear discriminant analysis is performed to classify beats as normal or VPB. Performance is evaluated on signals from nine hemodialysis treatments, using leave-one-out cross validation. The simultaneously recorded and annotated PPG signal serves as reference. The results show that VPBs can be reliably detected for average cardiac pulse pressures exceeding 1 mmHg.

In the fourth paper, we propose a novel method for detection of venous needle dislodgement. Four features, extracted from the arterial and venous pressure sensors signals, are used as input to a support vector machine which determine whether the venous needle is dislodged. The support vector machine is trained on a set of laboratory data, and tested on an-other set of laboratory data as well as on four clinical recordings. The results show that dislodgement is detected long before the blood loss has caused serious injury to the patient.

In summary, the work in this thesis contributes with novel methods for extraction of cardiac information using the built-in pressure sensors of the dialysis machine. The main benefit of such approach for cardiac monitoring, compared to existing techniques, is that no extra sensors are required. All results are preliminary, and the methods needs to be validated on a larger set of clinical recordings.

---

# List of Publications

---

## Included

The doctoral dissertation is based on four publications. The publications are included in the order listed below.

- [1] Mattias Holmer, Frida Sandberg, Kristian Solem, Eglè Grigonytė, Bo Olde, and Leif Sörnmo, “Extracting a Cardiac Signal From the Extracorporeal Pressure Sensors of a Hemodialysis Machine,” in *IEEE Transactions on Biomedical Engineering*, vol. 62, no. 5, pp. 1305–1315, 2015.
- [2] Mattias Holmer, Frida Sandberg, Kristian Solem, Bo Olde, and Leif Sörnmo, “Cardiac Signal Estimation Based on the Arterial and Venous Pressure Signals of a Hemodialysis machine,” in *Physiological Measurement*, vol. 37, no. 9, pp. 1499–1515, 2016.
- [3] Mattias Holmer, Juan Pablo Martínez, Eduardo Gil, Frida Sandberg, Bo Olde, and Leif Sörnmo, “Detection of Ventricular Premature Beats Based on the Pressure Signals of a Hemodialysis Machine,” submitted to *Medical Engineering & Physics*.
- [4] Mattias Holmer, Bo Olde, Frida Sandberg, and Leif Sörnmo, “Detection of Needle Dislodgement Based on the Presence of a Cardiac Signal in the Pressure Signals of a Hemodialysis Machine,” to be submitted.

## *Author’s contribution*

For all publications, the thesis author was responsible for the development of the computational methods, the simulations, the validation against clinical and experimental data, the analysis of the results, and writing the papers.

## Related

Parts of the work have been presented at conferences. The related conference papers listed below are not included in the thesis.

- [5] Holmer, Mattias; Grigonytė, Eglė; Olde, Bo; Segelmark, Mårten, Leif Sörnmo, Jan Sternby, Kristian Solem “On-line Heart Rate Monitoring Using Pressure Sensors of the Dialysis Machine,” in Abstracts - XXXIX Congress of the European Society for Artificial Organs, Rostock, Germany, *the international Journal of Artificial Organs*, vol. 35, no. 8, p. 569, September 2012.
- [6] Mattias Holmer, Eglė Grigonytė, Bo Olde, Jan Sternby, Mårten Segelmark, Kristian Solem, and Leif Sörnmo, “On-line Heart Rate Monitoring Using the Extra-corporeal Pressure Sensors of a Dialysis Machine,” in *Proceedings of the 16th International Conference on Biomedical Engineering*, Kaunas, Lithuania, pp. 162–165, October, 2012.
- [7] Mattias Holmer, Eglė Grigonytė, Kristian Solem, Bo Olde, Frida Sandberg, and Leif Sörnmo, “Determining Heart Activity Present in the Pressure Sensors of a Dialysis Machine,” in *Computing in Cardiology Conference (CinC)*, 2013, Zaragoza, Spain, vol. 40, pp. 217–220, September, 2013.
- [8] Frida Sandberg, Mattias Holmer, Bo Olde, and Kristian Solem, “Estimation of Respiratory Information from the Built-In Pressure Sensors of a Dialysis Machine,” in *Computing in Cardiology Conference (CinC)*, 2014, Cambridge, USA, vol. 41, pp. 853–856, September 2014.
- [9] Mattias Holmer, Frida Sandberg, Kristian Solem, Bo Olde, and Leif Sörnmo, “Heart Rate Estimation from Dual Pressure Sensors of a Dialysis Machine,” in *Computing in Cardiology Conference (CinC)*, 2015, Nice, France, vol. 42, pp. 29–32, September, 2015.

## Patent

The following patents or patent applications are related to the thesis.

- [10] Bo Olde, Kristian Solem, Mattias Holmer, and Jan Sternby, “Filtering of a Time-Dependent Pressure Signal ,” WO2013000777(A1), granted 2015.
- [11] Mattias Holmer, Bo Olde, and Kristian Solem, “Detecting Blood Path Disruption in Extracorporeal Blood Processing,” WO2012175267(A1), granted 2016.

- [12] Mattias Holmer, Bo Olde, Kristian Solem, and Leif Sörnmo, “Separation of Interference Pulses from Physiological Pulses in a Pressure Signal,” WO2015032948(A1), Application.



---

# Acknowledgments

---

I am grateful to many people, who have in different ways meant a lot to me during my years as PhD student.

First of all, I would like to express my gratitude to my supervisor, Leif Sörnmo, for the enormous amount of time he has spent on trying to turn me into a PhD. Special thanks to my co supervisor Frida Sandberg, for fruitful discussions and good advice. Thanks to always encouraging Kristian Solem, who was my co supervisor at Baxter during the first years. An other essential person for my PhD studies is Bo Olde, whom I would like to thank for all kinds of help and support. I will not forget the effort he put into a clinical study with the purpose of gather more and better clinical data. After over a year of planning, verification and validation of a device intended for the study, etc., the study started but was stopped after a the first included patient.

Thanks also to my colleagues at Kaunas University of Technology, Vaidotas Marozas and Saulius Daukantas, who developed the device that was only used ones. Thanks to my friend Eglė Grigonytė for fruitful cooperation, and for organizing wonderful vacations in Lithuania. Special thanks to Juan Pablo Martínez and Eduardo Gil at University of Zaragoza for excellent cooperation with paper III.

I would like to greatly acknowledge Swedish Research Council and Baxter for funding my PhD studies. I'm especially grateful to my four managers I have had during different periods during my time as a PhD student, namely Jan Sternby, Thomas Hertz, Bo Olde, and Henrik Hall. Thanks for being supportive and understanding of delays. I am also grateful to Per Hansson, Johnny Lien, and Christian Vartia for support at Baxter in different ways, among others for performing tests in the lab.

Special thanks to Mårten Segelmark, Sarok Said, Lena Mattsson at Skånes Universitetssjukhus i Lund, for performing the clinical studies that are an essential part of my thesis.

Thanks to all colleagues at EIT and BME, especially in the signal processing

group, Linnéa Larsson, Eglé Grigonytė, Frida Sandberg, Martin Stridh, Bengt Mandersson, Nedelko Grbic, Hamid Behjat, Mikael Henriksson, Mikael Svartling, Sergey Smirnov, and Leif Sörnmo. A special tank to my faithful lunch company John Albinsson, Maria Evertsson, and Tobias Erlöv. Thanks to my BME neighbour Ingrid Svensson for always being cheerful, and to my BME roommates Sergey Smirnov, Carl Johannesson, and Nebojša Malešević. Thank you Eva Everitt, Désirée Jarnebrant for quick and willing help when needed.

Special thanks to my really good friends and training companions Linnéa Larsson and Oskar Andersson.

At last I would like to thank my parents for all your love and support, especially during the time after I broke my ankle and could not take care of myself.

A handwritten signature in black ink, appearing to read 'Mattias Holmer', with a stylized, flowing script.

Mattias Holmer

---

# List of Acronyms and Abbreviations

---

**AA** Arithmetic averaging

**AK** Artificial kidney

**APD** Automated peritoneal dialysis

**ARMAX** Autoregressive moving average model with exogenous input

**bpm** Beats per minute

**CAPD** Continuous ambulatory peritoneal dialysis

**CKD** Chronic kidney disease

**CRS** Cardioreanal syndrome

**CVP** Central venous pressure

**DBP** Diastolic blood pressure

**EBC** Ectopic beat count

**ECG** Electrocardiography

**EKG** Elektrokardiografi

**EPO** Erythropoietin

**ESRD** End-stage renal disease

|               |                                     |
|---------------|-------------------------------------|
| <b>GFR</b>    | Glomerular filtration rate          |
| <b>HD</b>     | Hemodialysis                        |
| <b>HR</b>     | Heart rate                          |
| <b>HRV</b>    | Heart rate variability              |
| <b>IAP</b>    | intra-access pressure               |
| <b>IPFM</b>   | Integral pulse frequency modulation |
| <b>IR</b>     | Infra red                           |
| <b>LDF</b>    | Linear discriminant function        |
| <b>LSE</b>    | Least squares error                 |
| <b>MAD</b>    | Median absolute deviation           |
| <b>MAP</b>    | Mean arterial pressure              |
| <b>ml/min</b> | Millilitre per minute               |
| <b>mmHg</b>   | Millimetre mercury                  |
| <b>PCA</b>    | Principal component analysis        |
| <b>PD</b>     | Peritoneal dialysis                 |
| <b>PPG</b>    | Photoplethysmography                |
| <b>PVB</b>    | Premature ventricular beats         |
| <b>ROC</b>    | Receiver operating characteristic   |
| <b>RRT</b>    | renal replacement therapy           |
| <b>SBP</b>    | Systolic blood pressure             |
| <b>SNR</b>    | Signal-to-noise ratio               |
| <b>SVM</b>    | Support vector machine              |
| <b>TMP</b>    | Transmembrane pressure              |
| <b>UF</b>     | Ultrafiltration                     |
| <b>VPB</b>    | Ventricular premature beats         |

---

# Contents

---

|                                                          |             |
|----------------------------------------------------------|-------------|
| <b>Populärvetenskaplig sammanfattning</b>                | <b>v</b>    |
| <b>Abstract</b>                                          | <b>ix</b>   |
| <b>List of Publications</b>                              | <b>xi</b>   |
| <b>Acknowledgments</b>                                   | <b>xv</b>   |
| <b>List of Acronyms and Abbreviations</b>                | <b>xvii</b> |
| <br>                                                     |             |
| <b>I Introduction</b>                                    | <b>1</b>    |
| <br>                                                     |             |
| <b>1 Thesis Introduction</b>                             | <b>5</b>    |
| <br>                                                     |             |
| <b>2 Dialysis</b>                                        | <b>7</b>    |
| 2.1 The kidney . . . . .                                 | 7           |
| 2.2 Dialysis . . . . .                                   | 10          |
| 2.3 Cardiovascular diseases in kidney patients . . . . . | 15          |
| <br>                                                     |             |
| <b>3 Characterisation of the Cardiac Component</b>       | <b>17</b>   |
| 3.1 Cardiac Pulse Waves . . . . .                        | 17          |
| 3.2 Photoplethysmography (PPG) . . . . .                 | 24          |
| 3.3 Feature classification . . . . .                     | 27          |
| 3.4 Observed Pressure Signal and Disturbances . . . . .  | 30          |
| 3.5 Signal separation . . . . .                          | 31          |

|           |                                                                                                                           |           |
|-----------|---------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>4</b>  | <b>Summary of the Included Papers</b>                                                                                     | <b>35</b> |
| 4.1       | Paper I: Extracting a cardiac signal from the extracorporeal pressure sensors of a hemodialysis machine . . . . .         | 35        |
| 4.2       | Paper II: Cardiac Signal Estimation Based on the Arterial and Venous Pressure Signals of a Hemodialysis machine . . . . . | 38        |
| 4.3       | Paper III: Detection of Ventricular Premature Beats Based on the Pressure Signals of a Hemodialysis Machine . . . . .     | 40        |
| 4.4       | Paper IV: Detection of Needle Dislodgement Using Information in the Extracorporeal Pressure Signals . . . . .             | 43        |
| 4.5       | Scientific contribution . . . . .                                                                                         | 46        |
|           | <b>References</b>                                                                                                         | <b>47</b> |
| <b>II</b> | <b>Included Papers</b>                                                                                                    | <b>57</b> |
|           | <b>PAPER I – Extracting a Cardiac Signal From the Extracorporeal Pressure Sensors of a Hemodialysis Machine</b>           | <b>61</b> |
| 1         | Introduction . . . . .                                                                                                    | 63        |
| 2         | Alternating, Iterative Estimation of Cardiac Rhythm . . . . .                                                             | 65        |
| 3         | Clinical Data . . . . .                                                                                                   | 74        |
| 4         | Simulation of Pressure Signals . . . . .                                                                                  | 76        |
| 5         | Performance Evaluation . . . . .                                                                                          | 79        |
| 6         | Results . . . . .                                                                                                         | 79        |
| 7         | Discussion . . . . .                                                                                                      | 84        |
| 8         | Conclusions . . . . .                                                                                                     | 87        |
|           | References . . . . .                                                                                                      | 89        |
|           | <b>PAPER II – Cardiac Signal Estimation Based on the Arterial and Venous Pressure Signals of a Hemodialysis machine</b>   | <b>95</b> |
| 1         | Introduction . . . . .                                                                                                    | 97        |
| 2         | Methods . . . . .                                                                                                         | 98        |
| 3         | Experiment and database . . . . .                                                                                         | 106       |
| 4         | Performance evaluation . . . . .                                                                                          | 107       |
| 5         | Results . . . . .                                                                                                         | 107       |
| 6         | Discussion . . . . .                                                                                                      | 113       |
| 7         | Conclusions . . . . .                                                                                                     | 114       |
|           | References . . . . .                                                                                                      | 116       |

**PAPER III – Detection of Ventricular Premature Beats Based on the Pressure**

|                                          |            |
|------------------------------------------|------------|
| <b>Signals of a Hemodialysis Machine</b> | <b>121</b> |
| 1 Introduction . . . . .                 | 123        |
| 2 Background . . . . .                   | 124        |
| 3 Experiment and Database . . . . .      | 126        |
| 4 Methods . . . . .                      | 127        |
| 5 Results . . . . .                      | 131        |
| 6 Discussion . . . . .                   | 136        |
| 7 Conclusions . . . . .                  | 137        |
| References . . . . .                     | 137        |

**PAPER IV – Detection of Needle Dislodgement Using the Extracorporeal**

|                                     |            |
|-------------------------------------|------------|
| <b>Pressure Signals</b>             | <b>143</b> |
| 1 Introduction . . . . .            | 145        |
| 2 Background . . . . .              | 146        |
| 3 Experiment and Database . . . . . | 148        |
| 4 Methods . . . . .                 | 153        |
| 5 Results . . . . .                 | 156        |
| 6 Discussion . . . . .              | 162        |
| 7 Conclusions . . . . .             | 163        |
| 8 Acknowledgements . . . . .        | 163        |
| References . . . . .                | 163        |



## **Part I**

# **Introduction**







## Chapter 1

---

# Thesis Introduction

---

The present thesis deals with novel methods for extracting information from the extracorporeal pressure sensors of a hemodialysis (HD) machine, with the purpose to increase the patient safety during HD treatment.

Patients with kidney failure lack the ability to remove superfluous water, urea and other waste products from the blood, as well as regulating the ionic composition of the blood. If not transplanted or treated with dialysis, disorder will develop in most organs, and eventually lead to death. Despite dialysis treatment, the heart and the blood vessels are often affected, and cardiovascular diseases are common among dialysis patients [1]. A sign of this is that ventricular premature beats (VPBs) are abundant in dialysis patients [2, 3]. VPBs are more common during dialysis than between the treatments, and usually the number of VPBs increase towards the end of the treatment due to changes in the electrolyte balance [4]. For cardiovascular unstable patients, the extra stress caused by the dialysis treatment may provoke cardiac arrest [5]. Despite this, cardiac activity is not continuously monitored during dialysis treatments. Today the only cardiac monitoring that is routinely performed, is measuring heart rate, together with systolic, and diastolic pressure using a sphygmomanometer. These measurements are performed a 3-7 times during a standard 4-hour HD treatment.

Another serious but rarely occurring event during HD is venous needle dislodgement (VND) [6]. During HD, blood is removed from the patient through an arterial needle, pushed through a dialyzer where it is cleared from waste products, and then returned to the patient via the a venous needle. If the venous needle dislodges from the patient, blood is removed from the patient without being returned. If not detected within minutes, so much blood is lost that the patient will suffer from severe injury or even death. According to the standards on medical electrical equipment [7], all HD machines have to be equipped with a venous pressure alarm. The alarm triggers when the venous pressure exceeds an upper or lower pressure limit, that are set by the clinical staff. However, studies have shown that this alarm in practice has low

sensitivity [6, 8].

Continuous cardiac monitoring can be achieved using ECG or pulseoximetry. Humidity sensors or optical sensors can be used for detection of VNDs with increased sensitivity. The use of external devices, however, causes discomfort to the patients and adds extra work load for the clinical staff. In this thesis, it is proposed to use the venous and arterial pressure sensors of the HD machine to address this issue, and thereby eliminate the need for external devices.

During HD, cardiac pressure pulses propagate through the vascular system of the body and enters the extracorporeal blood circuit through the vascular access. The pulses eventually reaches the arterial and venous pressure sensors in the blood circuit of the HD machine. There is, however, another source of pressure pulses; the peristaltic blood pump. The signal measured by the arterial and venous pressure sensors are totally dominated by the pressure pulses from the blood pump. The poor signal to noise ratio constitutes a challenging signals separation problem. In addition, the heart rate and the blood pump rate may overlap, which makes the signals separation even more challenging. In this thesis, methods for separating the cardiac pressure signal from the blood pump signal are presented, together with methods using the extracted cardiac pressure signal to detect VPBs, and VND.

The present thesis is based on four papers, which in different ways deals with extracting cardiac information from the extracorporeal pressure sensors of a HD machine. The central themes of the papers are:

- I. Extraction of the cardiac signal component from the venous pressure signals of a HD machine.
- II. Improved extration of the cardiac signal component using both the arterial and the venous pressure signal of the HD machine.
- III. Detection of VPBs using the cardiac signal extracted from the arterial and venous pressure sensors of the HD machine.
- IV. Detection of VND based on the arterial and venous pressure signals of a HD machine.

The following chapters serves as a background. In Chapter 2 an overview about kidney disease and dialysis is given. In Chapter 4 the characteristics of cardiac pulses are described together with a background on photoplethysmography and related analysis and signal separation methods. Finally, in Chapter 5, the includes papers are summarized.

## Chapter 2

---

# Dialysis

---

### 2.1 The kidney

#### 2.1.1 Functions and anatomy

Most people have probably learned that the kidney is producing urine. Via the urine the kidney purifies blood from metabolic waste products, and removes excess water[9]. Examples of waste products are urea, creatinine, and bilirubin. The yellowish color of urine comes from bilirubin, which is formed when hemoglobin is catabolized. The kidney also regulates the electrolyte levels, e.g., sodium, potassium, calcium, chloride, bicarbonate, as well as the acid-base balance, of the blood in order to ensure homeostasis, i.e. to keep the concentrations and pH within a narrow limit.

In addition to the above-mentioned excretory functions, the kidney has secretory functions as well. Through production of the hormone erythropoietin (EPO), the kidney is stimulating the production of erythrocytes, red blood cells. If not medicated with EPO, most renal patients would suffer from anemia. The kidney also converts vitamin D to its active form, which is important for the uptake of calcium from the food in the intestine. Reduced uptake of calcium will in the long run lead to brittleness of the bone, osteoporosis. The kidney also secretes the enzyme renin, which is important for the regulation of blood pressure. Renal failure might lead to overproduction of renin, which will cause hypertension. A summary of the different functions of the kidney is listed below.

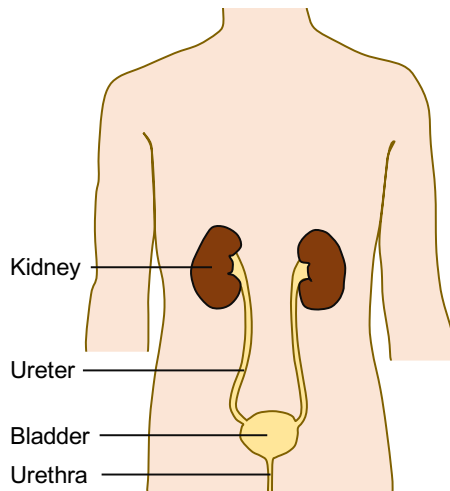
Excretory functions:

- Removal of waste products
- Removal of excess fluid
- Regulation of the acid-base balance
- Regulation of the electrolyte levels

Secretory functions:

- Regulation of the blood pressure (renin)
- Regulation of red blood cell production (EPO)
- Regulation of calcium uptake (active vitamin D)

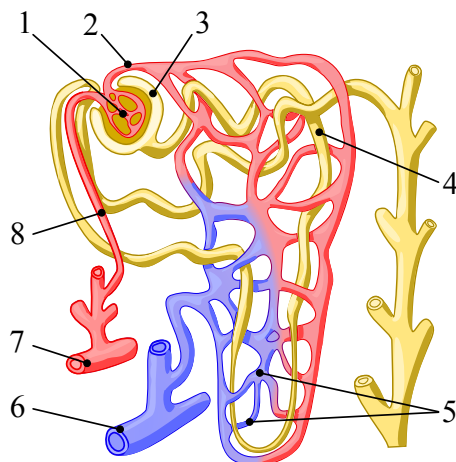
A human has two kidneys, and the capacity of each kidney is more than twice of what is needed in order to purify the blood. It is consequently possible to live a normal life with only one kidney, without any side effects. This makes it possible for living human beings to donate one of its kidneys for transplantation to an end stage renal disease patient.



**Figure 2.1:** The location of the kidneys within the body.

The kidneys are bean-shaped and has the approximate size 6 times 12 cm. They weigh about 160 g each. They are placed one each side of the spine, see Fig. 2.1. About 20 % of the cardiac output is passing through the kidneys. The smallest functional filtering unit producing urine in the kidney is called nephron. A kidney contains approximately 1 million nephrons. A nephron is build up from a network of blood capillaries surrounding a winding tubule, see Fig. 2.2. Within each nephron, the formation of urine can be divided into tree processes: glomerular filtration, tubular reabsorption and tubular secretion [10].

*Glomerular filtration* takes place when blood flows into the capillary network of the glomerulus. A pressure gradient, caused by differences in diameter of the arterioles, filters primary urine into Bowman's capsule. Each day about 180 liters are filtered. The filtration is relatively unspecific, and the primary urine resembles plasma



**Figure 2.2:** A nephron of the kidney [11]. The labeled parts of the nephron are:  
 1. Glomerulus, 2. Efferent arteriole, 3. Bowman's capsule, 4. Tubule, 5. Peritubular capillaries, 6. Vein, 7. Artery, 8. Afferent arteriole.

without proteins.

*Tubular reabsorption* is the process when the primary urine flows to the tubule, where most of the fluid, and certain solutes are reabsorbed into the surrounding peritubular capillaries. The tubular reabsorption is a controlled selective process. Creatinine is not reabsorbed at all, urea is only slightly reabsorbed, whereas glucose, amino acids, vitamins, and bicarbonate in general are completely reabsorbed. Electrolytes are reabsorbed to a controlled varying degree in order to maintain homeostasis.

*Tubular secretion*, active secretion of substances into the tubuli, is the way in which the nephron removes drugs and unwanted substances that have not been removed to a sufficient degree in the glomerular filtration. Acid balance is maintained by secreting hydrogen ions ( $H^+$ ) from the blood into the tubuli. In the same process bicarbonate is regenerated.

The result of the three processes is about 1.5 liters concentrated urine each day.

### 2.1.2 Renal failure

In *acute kidney injury* [12], the kidneys have temporarily stopped working, and the patient may recover after a short period of treatment. Low blood supply to the kidneys or obstruction of the urine flow by kidney stones may cause acute kidney injury. Trauma of the kidneys, caused by e.g. for a car crash, may also decrease the kidney

function. Inflammation in the kidneys may rapidly decrease their functionality.

In *chronic kidney disease* (CKD) [13] the damage is persistent. It may be the result of acute kidney injury, or arise after a slow gradual decrease in the kidney function. Patients with end stage renal disease has a glomerular filtration rate (GFR) below 5 ml/min and require renal replacement therapy such as kidney transplantation or dialysis to survive. Renal failure leads to water and waste product accumulation in the body. It also leads to disorders in most major body systems; a syndrome called uremia. The symptoms are fatigue, anorexia, nausea, skin itching, and café-au-lait-coloured skin. Untreated uremia leads to death. The two main causes of CKD are glomerulonephritis (inflammation in the glomeruli), and diabetes mellitus, which after 15-20 years can cause structural damages in the kidneys. The damage can be prevented by keeping the blood glucose levels under control. Another cause of CKD are urinary tract infections that reach the renal pelvis and cause pyelonephritis. Many further causes for CKD exists, e.g., may hypertension over long time result in stiffening of the small blood vessels in the kidney, nephrosclerosis.

Patients with a GFR below 10% are often prescribed a special diet low in protein, sodium and potassium [14]. This diet results in less waste products and reduced fluid retention. If the strict diet is followed, the start of dialysis treatment can be delayed. When the GFR falls below 5% renal replacement therapy (RRT) has to start, either as dialysis or transplantation.

## 2.2 Dialysis

The original meaning of dialysis is the process in which solutes diffuse through a semi-permeable membrane. In medicine, dialysis is a treatment used to remove waste products, excess water, and maintain acid-base balance, i.e., to replace some of the functions of the kidney in patients with renal failure [15, 16].

### 2.2.1 Dialysis phenomena

Dialysis treatment is based on four phenomena: diffusion, osmosis, ultrafiltration (UF), and convection.

*Diffusion* is the tendency for a compound to spread as evenly as possible within a defined space. In solutions, diffusion describe the process in which solutes move from a space of higher solute concentration to a space with lower concentration, until equilibrium is reached. The diffusion rate depends on the size of the solute. The diffusion rate is slow for large molecules, compared to smaller ones. Equilibrium is obtained rapidly through diffusion over distances in the  $\mu\text{m}$  range, however, it is required days to obtain equilibrium through diffusion over distances of a few centimetres.

*Osmosis* is the movement of water through a semi-permeable membrane from space with high water concentration, i.e. low solute concentration, to a space with low water concentration, i.e. high solute concentration. A semi-permeable membrane constitutes no barrier for small molecules, however slows down middle size molecules, and stops larger molecules. Osmosis occurs when there is a concentration difference of solutes that can't move freely across a semi-permeable membrane. The osmosis continues until equilibrium is reached. The concentrations at which equilibrium is reached can be altered by applying an external pressure. Osmotic pressure is equal to the external pressure needed to prevent the flow of water induced by the concentration difference across the semi-permeable membrane.

*Ultrafiltration* (UF) is the movement of a fluid across a membrane, induced by a pressure gradient across the membrane, called transmembrane pressure (TMP). The fluid is moving from the side of the membrane with high pressure, to the side with low pressure. In dialysis the TMP is used to remove excess fluid from the patient. The TMP can either be obtained mechanically e.g. by a pump, or by the osmotic pressure of large molecules.

*Convection* is the movement of solutes together with the flow of the solvent, for example the movement of permeable solutes together with the UF water. In convection the movement of the solute is directly proportional to the movement of the solvent. During dialysis, convection is the dominating transport principle for large molecules, for which diffusion is extremely slow.

## 2.2.2 Peritoneal dialysis

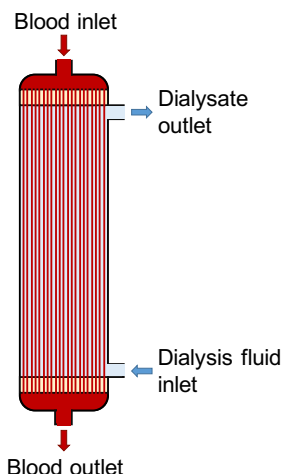
One form of dialysis is peritoneal dialysis (PD) [17]. An advantage with PD is that it doesn't require advanced equipment. During PD, the peritoneal cavity is filled with dialysis fluid through a catheter placed in the lower part of the abdomen. The peritoneum, a thin semi-permeable membrane, forms the wall of the peritoneal cavity, and covers all the adjacent organs. The peritoneum has a surface area of 1–2 m<sup>2</sup>. During PD the peritoneal cavity is filled with 1.5–2.5 l of dialysis fluid, and peritoneum serves as a dialysis membrane. No blood leaves the body of the patient. Excess fluid is removed through osmosis. An osmotic agent, usually glucose, is added to the dialysis fluid. The osmotic agent creates the osmotic pressure needed to achieve UF. Waste products present in the blood vessels perfusing the peritoneum, are removed by diffusion through the capillary wall and peritoneum to the dialysis fluid in the peritoneal cavity. The major barrier for the solute and fluid transport, is the capillary wall. After a dwell period the dialysis fluid contains waste products and excess fluid, and is drained from the peritoneal cavity. After the drain, the peritoneal cavity is filled with fresh dialysis fluid again. In this way PD can be applied continuously, and resembles in this sense the kidney function. Two main forms of PD exist, continuous ambulatory

peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). In CAPD the patient takes care of the fluid exchange manually himself. In APD the fluid exchange is taken care of by a machine. Peritonitis, i.e. inflammation of the of the peritoneal membrane, is the most common complication in PD. Peritonitis is usually caused by bacterial infection, and has to be treated with antibiotics. Repeated episodes of peritonitis, may lead to that the peritoneal membrane degrades, and that the patient has to be transferred to HD.

### 2.2.3 Hemodialysis

Hemodialysis (HD) is another form of dialysis treatment, in which the patients blood is circulated extracorporeally through a dialyzer [15, 16]. The dialyzer contains two compartments separated by a semipermeable membrane. One of the compartments is perfused by blood, and the other is perfused by a dialysis fluid, se Fig. 2.3. The HD machine controls the blood flow and dialysis flow through the dialyzer, and prepares the dialysis fluid. Before treatment, the patients body contains excess waster and waste products. To remove the excess fluid a TMP is applied across the membrane in the dialyzer, using pumps on the dialysis fluid side. This forces the excess water to be removed through UF. At the end of the treatment the removed fluid volume should be equal to the excess fluid volume at the start of the treatment. Small waste products are mainly removed from the blood to the dialysis fluid through diffusion, whereas convection is more important for removal of larger molecule waste products. Increased convective removal of waste products can be achieved by hemodiafiltration (HDF) [18, 19]. In HDF the UF is increased and and the excessive removal of fluid from the blood is replaced by infusion of ultra pure dialysis fluid into the blood. Electrolyte balance and acid base balance is achieved though diffusion between the blood and the dialysing fluid. A patient is usually treated with HD or HDF three times a week. The duration of each treatment is three to five hours. Despite treatment with hemaodialys 3 times a week for 3–5 hours each time, the mortality rate is about 20 % a year [20].

The HD machine controls the extracorporeal blood circuit, see fig 2.4. The blood is pumped from the patient via the arterial needle in the vascular access, through the arterial blood line to the dialyzer, after which it is returned to the vascular access via the venous blood line and the venous needle. A normal blood flow during HD is 250-400 ml/min. A peristaltic roller pump is located upstream from the dialyzer. The pump works as follows: Two rollers, attached on a rotor, compress a soft tube inserted into the pump housing. When rotating, the rollers alternate to compress the tubing and push the blood forwards. A heparin syringe pump is usually also included in the blood circuit, to avoid blood clotting. A drip chamber is located after the dialyzer. The purpose of the drip chamber is to allow air that inadvertently has entered the

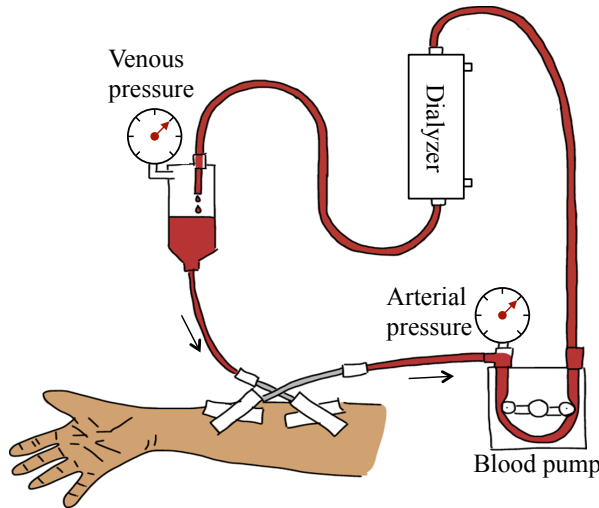


**Figure 2.3:** A hollow fiber dialyzer, also called capillary dialyzer. The blood flows inside thousands of fine capillary formed membranes. The dialysis fluid flows outside the capillaries, counter-current to the blood flow.

blood circuit escape without reaching the patient. An air detector is placed at the lower part of the drip chamber. If air is detected, the blood pump is stopped and an alarm is activated.

Pressure is monitored in the blood circuit for safety reasons. As blood flows through the extracorporeal blood circuit, it is exposed to different pressure levels. The blood is pulled from the vascular access through the narrow arterial needle, causing a negative pressure at the arterial pressure sensor placed upstream from the blood pump. Insufficient blood flow in the vascular access, or an incorrectly placed arterial needle may further lower the pressure and cause an alarm. The venous pressure is measured down stream from the dialyzer, in the venous drip chamber. Here the pressure is positive, since the blood is pushed back to the patient through the narrow venous needle. If upper and lower safety limits are exceeded, the blood pump is stopped and an alarm is given. Reasons for the alarm may be kinked blood lines or VND.

A prerequisite for HD treatments is the possibility to access the blood in the vascular system [21] , and lead part of it through the extracorporeal blood circuit. The most widely used *vascular access* for chronic HD is the *arterio-venous fistula* (AV fistula, or simply "fistula"). A fistula is a "short circuit" between a artery and a vein, made through surgery. After surgery, the fistula needs just over four weeks to mature before it can be used. During the maturation the veins are "arterialised" i.e. the walls are thickened to withstand the high pressure and flow. After maturation, the blood



**Figure 2.4:** The extracorporeal blood circuit of a HD machine.

flow in the fistula can be up to 1000 ml/min, and it should be possible to obtain an extracorporeal blood flow of 400 ml/min. The thick walls of the fistula enables repeated puncturing with large needle. The most common placement of the fistula is the forearm.

Some patients have so fragile blood vessels that it is not possible to create a fistula. Then a synthetic *graft* is used to create the connection between an artery and a vein. The graft can be punctured just like a fistula, but has a shorter life span.

In acute HD a temporary access is made by insertion of a *catheter* into the deep lying veins, for example in the groin or the neck. The tip of the catheter is placed in vena cava, close to the heart. Catheters are sometimes also used in chronic HD when neither a fistula nor a graft can be created.

## 2.2.4 Venous needle dislodgement

Venous needle dislodgement is an adverse but rarely occurring event during HD. If the venous needle is slips out of the patient, the blood that that is removed from the patient through the arterial needle is never returned. Within a few minutes so much blood is removed that the patient is seriously injured and may even die. VND is the most common reason for blood loss during dialysis, causing 65% of the incidents [22]. Other causes for blood loss are needle connector fault, blood line rupture, bleeding at the access, or subcutaneous bleeding. To detect VNDs, all HD machines are equipped with a venous pressure alarm [7]. If the venous pressure exceeds an up-

per or a lower threshold, the blood pump is stopped and alarm is set. To avoid false alarms, the clinical staff usually sets the thresholds so wide apart from the current venous pressure, that the sensitivity for VNDs becomes low [6]. The detection rate has been estimated to 94,1% of patients with grafts, but only in 29.2% of the patients with fistulas [8]. Some clinics therefore use external alarm devices for patients with high risk for VNDs [23]. The detection methods for such devices are for example based on wetness or optical detection of the red color of blood. Moisture monitors have been reported incapable to detect small volumes of blood, which makes them ineffective to detect VND at an early stage [24], whereas an optical device has been reported to issue an alarm at small amounts of blood [25].

## 2.3 Cardiovascular diseases in kidney patients

*Cardioreanal syndrome* is a term for a broad number of diseases where both heart and kidney are involved [1]. There is a strong connection between cardiac and kidney diseases, and depending on the primary cause, they are either recognized as cardiorenal or renocardiac syndromes. Coronary artery disease, congestive heart failure, arrhythmia, myocardial infarction, and sudden cardiac death are main causes of morbidity and mortality in CKD patients [26]. Renal dysfunction is an independent risk factor for cardiovascular disease, with higher mortality rates for myocardial infarction [27], [28]. Major cardiac events cause about 50 % of deaths among CKD patients [29], [30]. The risk of cardiovascular disease is increasing with decreasing remaining kidney function (GFR), as can be observed in Table 2.1.

**Table 2.1:** Cardiovascular risk according to chronic kidney disease stage [31].

| CKD stage | GFR (ml/min/1.73 m <sup>2</sup> ) | Cardiovascular risk (odds ratio) |
|-----------|-----------------------------------|----------------------------------|
| 1         | >90                               | 0.5–0.8                          |
| 2         | 60–89                             | 1.5                              |
| 3         | 30–59                             | 2–4                              |
| 4         | 15–29                             | 4–10                             |
| 5         | <15                               | 10–50                            |
| ESRD      | RRT                               | 20–1 000                         |

CKD chronic kidney disease, GFR estimated glomerular filtration rate, ESRD end-stage renal disease, RRT renal replacement therapy.

In dialysis patients the cardiovascular disease is often manifested as increased number of VPBs [2, 3]. During HD the rate of VPBs usually increases towards the end of

the treatment, as excess potassium is removed [4]. Ventricular arrhythmias have been studied in long-term, ambulatory electrocardiogram (ECG) recordings, showing that VPBs are much more frequent during HD than during the period after the treatment [32]. Hemodialysis is usually performed three times a week, with intervals of 48 h during the week, and 72 h over the weekend. The frequency of arrhythmias is the highest in the period before the first treatment of the week, due to the long time since the previous treatment [33]. Hemodialysis patients with regional wall motion abnormalities, ischemic heart disease, and left ventricular hypertrophy have a higher rate of VPBs during the treatment than the patients without these diseases. Fast changes in VPB rate may be a sign of electrolyte imbalance and cardiovascular instability. The significance of such changes have been investigated for prediction of acute intradialytic hypotension [34].

During HD, the prevalence for cardiac arrest is approximately 7 per 100,000 treatments [35]. The risk of sudden death is approximately six times higher during HD than during the period 12–24 h after the start of the treatment [36]. The highest risk (8 times the 12–24 period after treatment start) is however during the 12 hours before the first treatment after the weekend break, leading to a higher death rate on Mondays and Tuesdays [37].

## Chapter 3

---

# Characterisation of the Cardiac Component

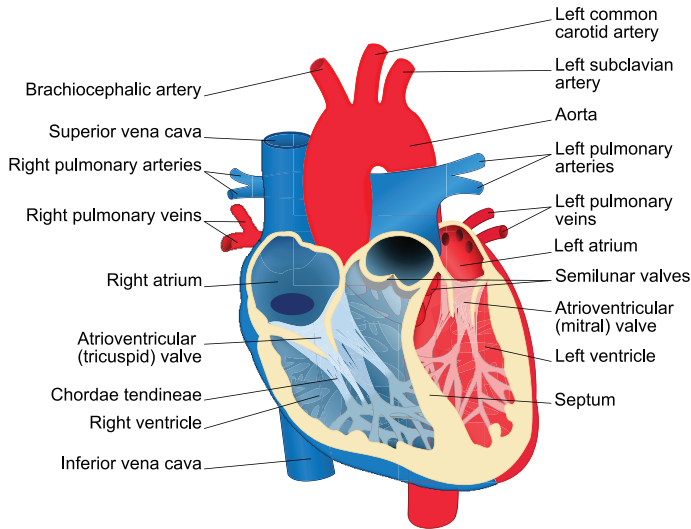
---

### 3.1 Cardiac Pulse Waves

The extracorporeal blood circuit can access the patients vascular system at different locations. The amplitude of the cardiac pressure pulses reaching the arterial and venous pressure sensors is highly dependent on the location and the type of vascular access. The cardiac pulse pressure in the different types of vascular accesses, graft, fistula, and catheter, is however not well described in the literature. In the following a background about cardiac pressure pulses and blood pressures measurements will be given.

The blood pressure in the the arteries is pulsatile, and the ability to interpret the pulsations depends on knowledge of the physiological mechanisms behind the pulses. This section will describe some of the physiological principles behind the pressure pulses in mainly the arteries [38, 39].

A human heart is depicted in Fig. 3.1. Deoxygenated blood is returned from the body in superior and inferior vena cava. The blood is pumped via right atrium and right ventricle to the lungs. Oxygenated blood is returned from the lungs via the right and left pulmonary veins to the left atrium, and pumped out to aorta and the body via the left ventricle. During systole, the phase when the ventricles contract, blood is forced out of the ventricles into the pulmonary arteries and aorta. During diastole, cardiac muscles surrounding the ventricles relax and the ventricles are refilled with blood.



**Figure 3.1:** The human heart anatomy, by ZooFari [40].

### 3.1.1 Blood pressure

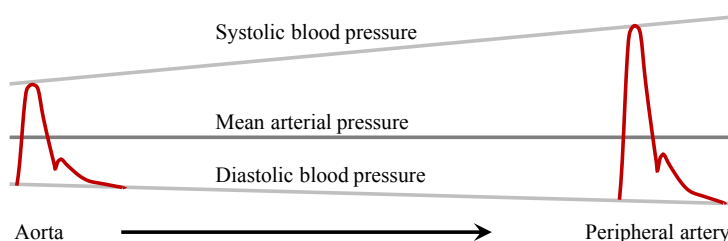
The type of vascular access affects the amplitude of the cardiac pressure pulses that reaches the pressure sensors in the extracorporeal blood circuit. The pressure amplitudes at different positions in the body below should give a hint of the amplitude range of the pressure at the vascular access. In general the amplitude is highest for grafts, somewhat lower for fistulas, and very low for catheters. The low amplitude for catheters is explained by that the amplitude in cardiac pulses in veins are much lower than in arteries. It should be noted that the amplitude in all types of vascular access are much lower than the pulse pressure in the arteries (the difference between systolic and diastolic pressure).

Systolic and diastolic blood pressures are measured in the arteries, usually noninvasively using a sphygmomanometer on the upper arm. *Systolic blood pressure* (SBP) is the peak pressure during one heartbeat. Normal SBP at rest, measured on the upper arm, is 90–129 mmHg [41]. *Diastolic blood pressure* (DBP) is the lowest pressure in between two heartbeats. Normal DBP at rest is 60–84 mmHg at the upper arm. *Mean arterial pressure* (MAP) is the mean pressure in an artery during a cardiac cycle. MAP is often estimated as  $MAP = (SBP - DPB) / 3 + DPB$ , and is normally in the range 70–105 mmHg in the upper arm. *Pulse pressure* is the peak-to-peak amplitude during a cardiac pulse cycle. Normal pulse pressure in the arteries of the upper arm is about 40 mmHg. *Central venous pressure* (CVP) is the pressure measured invasively in vena cava, see Fig. 3.1, where the tip of the dialysis catheter is placed. Normal mean CVP

is 2–8 mmHg [42]. When lying down the mean pressure in peripheral small veins is usually 4–6 mmHg greater than the CVP [10]. Normal central venous pulse pressure in the order of magnitude 5 mmHg [43]. *Intra-access pressure* (IAP) is the pressure measured invasively in the vascular access. For grafts, the mean *intra-access pressure* (IAP) is usually less than half of the MAP. The IAP in fistulas is on average lower than the IAP in grafts [16]. The intra-access pulse pressure, i.e. the amplitude of the pulse that propagates to the extracorporeal pressure sensors, is unfortunately not well described in the literature.

### 3.1.2 The Cardiac Pulse Wave in the Arteries

The MAP practically remains constant throughout the arterial tree, from the ascending aorta to the peripheral arteries. It decreases first at the arterioles, which contribute to the largest part of the systemic vascular resistance. This is in contrast to the SBP and the DBP, that often changes along the aortic tree, see Fig. 3.2.

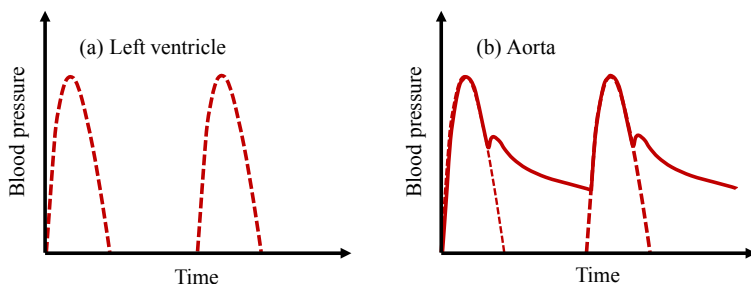


**Figure 3.2:** The mean arterial pressure basically remains constant throughout the arterial tree, whereas the systolic blood pressure and the diastolic blood pressure might change.

The cardiac pulse wave is composed of a forward wave and a reflected wave. The reflected wave mainly arise when the forward wave hits the peripheral vascular resistance, at the arterioles. In the peripheral arteries the peak of the reflected wave is superimposed on the peak of the forward wave, and increases the systolic blood pressure. In aorta, for a person with normal pulse transit time, the peak of the reflected wave is superimposed on the forward wave in the diastolic phase, where it instead increases the diastolic blood pressure. This explains why SBP on average is 15 mmHg less in the aorta than in the peripheral arteries, see Fig. 3.2.

The forward wave depends on interactions between the left ventricular ejection activity, and the mechanical properties of the arterial walls. Thanks to the viscoelastic properties of the large arteries, they store a large quantity of blood during the systolic phase by increasing their diameters. The stored blood is released during the diastolic

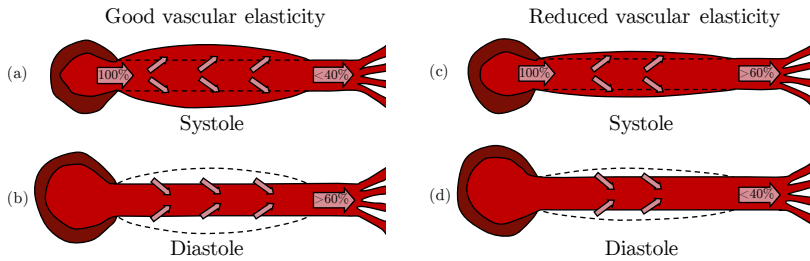
phase, when the diameter of the arteries is decreasing. In this way the intermittent and discontinuous flow out from the left ventricle of the heart, is transformed to a continuous one when reaching the organs. The elastic properties of the arteries are also responsible for that sufficient blood pressure is maintained during diastole, see Fig. 3.3. A sufficient blood pressure during diastole is crucial, especially for the oxygen supply to the heart. During systole, the forceful contractions of the cardiac muscles makes some cardiac vessels to collapse. Thus the myocardium is only supplied with blood during diastole.



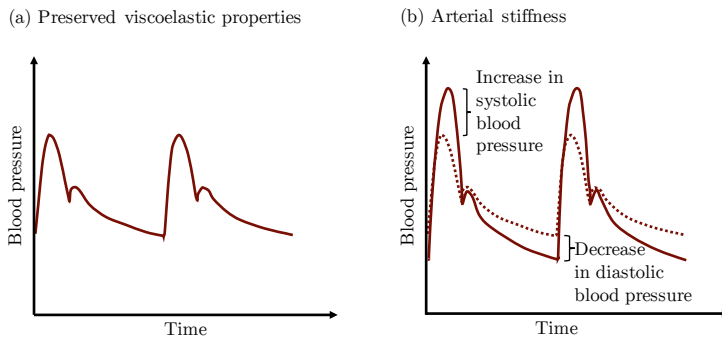
**Figure 3.3:** (a) The pressure in the left ventricle is intermittent. (b) The elastic properties of the large arteries and aorta dampens the pressure pulses.

If the elastic properties of the aorta is undamaged, only a fraction of the stroke volume is forwarded directly to the periphery during systole, see Fig. 3.4(a). The aorta, which has been "inflated" during systole, returns to its normal state during diastole, and the stored blood is pushed forward towards the periphery, see Fig. 3.4(b). Conditions like aging, hypertension, inflammation, and metabolic alterations can alter the properties of the arterial wall, degrading their elasticity. Stiffer arteries decreases the amount of the blood that is stored in the vessels during systole, see Fig. 3.4(c), and thus the peripheral blood flow during diastole, see Fig. 3.4(d). Stiff arteries leads to an increase in SBP, a decrease in DBP, and an increase in pulse pressure, whereas the MAP might not be affected, see Fig. 3.5. Increased systemic resistance, on the other hand, results in both increased SBP and increased DBP.

High SBP puts an extra burden on the heart, since it has to work harder to supply enough blood to the body. High DBP can in the long run lead to arterial stiffness and contribute to damage of vital organs e.g. the kidneys. The acute risk for coronary heart disease is, however, most pronounced if SBP is high and DBP is low. During such conditions the heart has to work hard to contract during systole with a low blood supply during diastole. As shown in Fig. 3.6, the risk for coronary heart disease decreases with increased DBP (for a certain SBP), and the risk increases with pulse pressure. Further more the risk is only dependent on pulse pressure, regardless of



**Figure 3.4:** Illustration of the differences in blood storage and flow between a patient with good vascular elasticity, and a patient with reduced vascular elasticity.



**Figure 3.5:** Arterial stiffness increases the SBP and decreases the DBP.

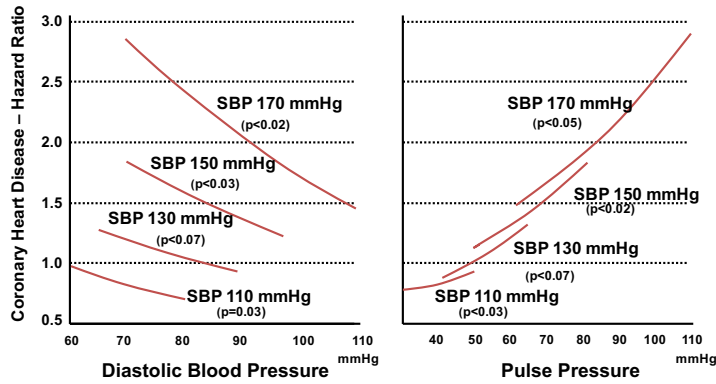
SBP [44].

The simplest way to assess arterial stiffness is to measure pulse wave velocity (PWV). The speed of the cardiac pulse wave that is transmitted through the arteries is related to the viscoelastic properties of the arterial walls [45]. The stiffer the wall, the higher the velocity. Pulse wave velocity is in the range 4-30 m/s. Aortic PWV is regarded as an independent predictor of cardiovascular events, in contrast to PWV in the femoral artery and the brachial artery [46], see Fig. 3.7. Arterial stiffness is frequent among patients with ESRD, and has a dramatic impact on their survival, see Fig. 3.8.

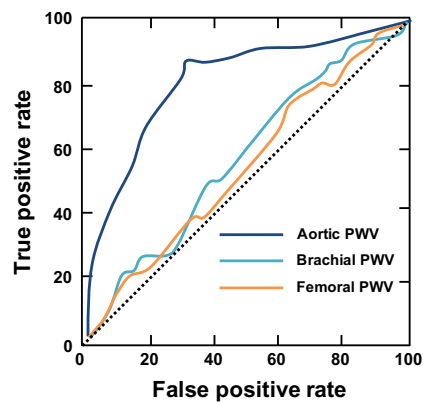
The viscoelastic properties of the arteries depends on structural factors and transient functional factors. Structural alterations depends on changes in the elastin/collagen fiber ratio in the arterial wall. Aging causes degeneration of the elastin fibers, and an increase in collagen fibers [47]. Hypertension tends to increase the synthesis of collagen fibers, and thus the stiffness of the arteries. This stiffness remains after years of antihypertensive treatment. Other causes for structural alterations of the arteries are

inflammation, metabolic diseases, e.g., diabetes, kidney failure, and liver failure.

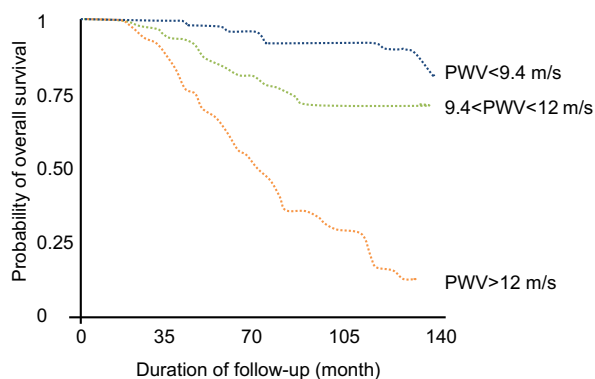
A summary of the factors determining both static and dynamic components of the blood pressure is presented in Fig. 3.9.



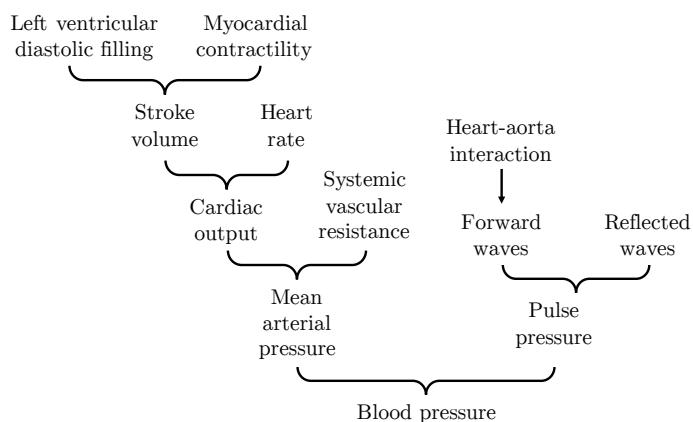
**Figure 3.6:** The risk for coronary heart disease at different SBP, plotted as a function of DBP to the left, and as a function of pulse pressure to the right [44].



**Figure 3.7:** Receiver Operating Characteristic (ROC) for prediction of cardiovascular death using PWV determined at different arterial sites [46].



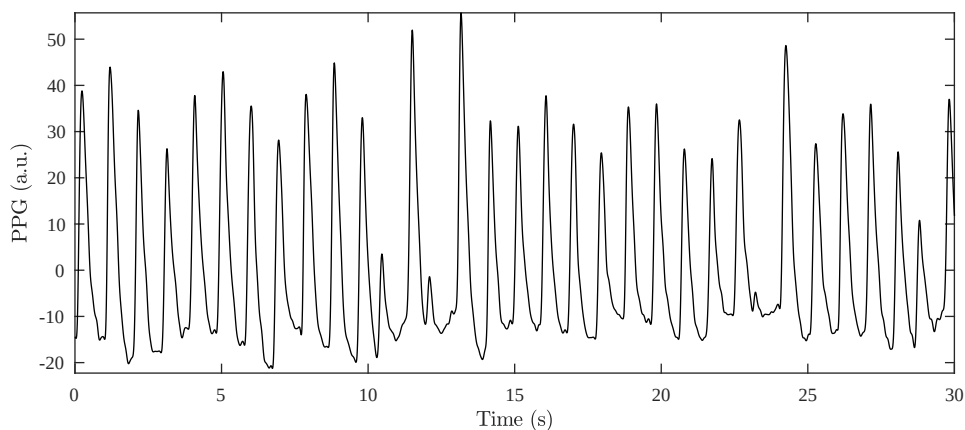
**Figure 3.8:** Impact of aortic stiffness on survival in ESRD. The overall survival rate is plotted versus time for three different ranges of PWV [48].



**Figure 3.9:** The factors that determines the mean arterial blood pressure and the pulse pressure.

## 3.2 Photoplethysmography (PPG)

The photoplethysmographic (PPG) waveform [49], [50], also referred to as the pulse-oximeter waveform, is one of the most frequently displayed waveforms at the intensive care units of the hospital, see Fig. 3.10. The measurement principle of the PPG signal is relatively simple. The sensor basically consists of a light source and a light detector. If the detector is placed on the opposite side of the tissue as the light source, transmittance is measured. If it is placed on the same side, reflectance is measured. Transmittance PPG sensors are often placed on a finger or on an ear, since it requires tissue between the light source and the detector, whereas reflectance sensors can be placed anywhere on the skin of the body. Each heart pulse gives rise to a change in transmittance/reflectance. The PPG signal was first described in 1937 by Alrick Hertzman [51]. The Greek word “plethysmos” means fullness, in this case how full of blood the tissue is. It was Alrick Hertzman who gave the signal its name, photoplethysmography, since his early observations showed that the light absorption was linked to blood volume changes in the tissue. It was first assumed that only arterial blood caused the modulation of the PPG signal. The PPG signal has, however, been shown to also include components originating from the venous blood volume, the respiration, and the autonomic nervous system [52, 53, 54, 55]. The magnitude of the PPG signal varies between patients, and is dependent on e.g. skin color, finger thickness, amount of fat and muscle.



**Figure 3.10:** The PPG with VPBs at 10.5 s, 12 s, and 23.5 s. Note the increase in amplitude of the beat following the VPB.

Clinical pulse oximeters show HR and oxygen saturation. In order to extract the oxygen saturation, PPG measurement is required at two different wavelengths, usually

infrared at 940 nm and red at 660 nm. Light absorption depends on the amount of hemoglobin molecules that are oxygenated. This dependence is different for different wave lengths, and hence the oxygen saturation can be estimated using the infrared and red signals [56].

Many clinical pulseoximeters also show the PPG waveform. The infrared waveform is often displayed, because it is less influenced by oxygen saturation. For a transmittance PPG sensor, the transmittance is low when the pressure is high. The displayed waveform is therefore sign changed in order to resemble the arterial pressure waveform. The PPG amplitude is often auto adjusted, both by amplification of the light detector signal, and by auto adjustment of the intensity of the light source. If changes in amplitude is of interest, it is necessary to turn off the auto-adjustment.

### 3.2.1 PPG analysis

The PPG signal can be used for detecting arrhythmia, e.g. premature ventricular or atrial beats, and atrial fibrillation [57]. Ventricular premature beats can be detected based on timing of detected heart beats, but also the amplitude contains useful information [58, 59]. There are two types of pulse patterns in the PPG at a VPB [60]. The VPB itself may not be visible, instead the VPB can be detected based on the compensatory pause, i.e. the increased time to two subsequent heart pulses. The amplitude of the beat succeeding a VPB is usually also increased. This is explained by the compensatory pause that gives additional time for the ventricle to fill, and the increased stroke volume is reflected in a higher pulse amplitude in the PPG. The VPB may also be visible in the PPG as pulse with low amplitude, followed by a compensatory pause and a pulse with increased amplitude, see Fig 3.10.

Different methods have been suggested for classification of heart pulses in the PPG as either normal or VPB. Gil et al. used linear discriminant analysis and a set of 6 features, based on peak-to-peak intervals, rising amplitudes, and falling amplitudes, for the current and the preceding beat. The features were normalized with their mean of the 5 preceding heartbeats. The method was evaluated on 27 PPG recordings, and the results showed a sensitivity of 90.5%, a specificity of 99.9%, and an accuracy of 99.3% [58]. At a conference Solosenko et al. presented a method using a Naïve Bayes Classifier, and 7 features based on peak-to-peak intervals, pulse duration, pulse width at zero crossing, rising amplitudes, and falling amplitudes to classify the beats. The method was tested on 9 PPG recordings and the results showed a sensitivity of 96.4%, a specificity of 99.9%, and an accuracy of 99.9% [65]. Later, Solosenko et al. suggested a classifier based on artificial neural networks, and features based on peak-to-peak intervals, and pulse power. The method was evaluated on 26 PPG recordings, and the results showed a sensitivity of 92.4%, a specificity of 99.9%, and an accuracy of 99.8% [60]. Suzuki et al. only used the pulse-to-pulse time interval to distinguish

between normal and potential VPBs, and then used the pulse amplitude divided by the pulse-to-pulse time interval to determine if the potential VPB should be classified as noise or a VPB. The method was evaluated on 3 recordings, and the results showed a sensitivity of 91.5%, a specificity of 99.0%, and an accuracy of 98.9% [66].

Photoplethysmography can also be used to estimate heart rate variability (HRV) [61]. Heart rate variability, in turn, may be used for monitoring the autonomic system [62]. Heart beat occurrence time is needed for HRV analysis, heart rate turbulence analysis and detection of VPBs [58]. The pulse onset or the pulse peak can be used for detection of heart beat occurrence time. To give a smaller localization error, the time instant of the mid-amplitude at the rising edge is suggested as a heartbeat occurrence time, since this point is less sensitive to noise [63, 58, 64].

The amplitude of the PPG pulse reflects the interaction between the cardiac stroke volume, local vascular compliance, and tissue congestion [50]. The pulse amplitude of the PPG increases with vaso-dilatation, and decreases with vaso-constriction. At cold temperature the peripheral arteries tend to constrict, and thus the amplitude decreases. Amplitude and pulse shape of the PPG can be used to evaluate functionality of the endothelial cells, the cells lining the interior surface of the entire cardiovascular system, and are involved in vaso-constriction and vaso-dilatation. Tracking of PPG pulse amplitude has also been demonstrated to be able to predict intradialytic hypotension [67, 68]. For amplitude tracking, instruments with possibility to turn off auto-scaling has to be used.

Respiratory rate can be derived from baseline of a PPG signal. Respiration also induces an amplitude modulation of the cardiac pulses in the PPG [69]. An increase in amplitude variability is a sign of hypovolemia, and is used to determine fluid responsiveness in critical care [69]. In a spectrogram, an increase in power in the breathing frequency range, is correlated to hypovolemia [70].

In combination with ECG, the PPG can be used to measure pulse wave velocity through the vascular system of the body. The pulse transit time (PTT) is obtained by measuring the time it takes for a heart pressure pulse to arrive at a distal part of the body (finger or toe). Specifically the QRS of the ECG is used as start time, and the upward deflection of the PPG is used as arrival time [71]. A short PPT is a sign of stiff blood vessels [72], and is associated with aging, high blood pressure, arterial sclerosis, and diabetes [73].

Blood pressure is routinely measured with sphygmomanometers. A lot of research is going on towards continuous unobtrusive blood pressure measurements [74]. PPG in combination with an inflatable finger cuff can be used for continuous beat-to-beat arterial pressure measurement [75]. Blood pressure can also be estimated continuously based on PTT [76]. Currently, there is a lot of interest in estimating blood pressure based on PPG only. Xing et al. have recently proposed a way to extract amplitude and phase features extracted by a fast Fourier transform of the PPG, and use the features

to train a neural network, showing promising results [77].

Since the introduction of smart watches, there has been a growing interest in methods for extracting information from PPG signals. First the PPG signal was only used for HR-monitoring to avoid the chest strap previously needed in sport watches. The first wrist watch measuring blood pressure was introduced 2006 [78], and was based on PPT. Today smart watches based on PPG are estimating HR, blood pressure, oxygen saturation and arrhythmia.

It is well known that PPG measurements are sensitive to patient motion and especially sensor movement. Preferably, the patient and the sensor should be motionless to minimize movement artifacts. HR monitoring based on PPG is today implemented in smart watches, enabling comfortable long term HR monitoring in daily life. Signal processing techniques have been proposed to reduce the influence of motion artifacts in pulse oximetry. In [79] accelerometers and a least mean square adaptive filter is used to suppress motion artifacts, and HR is determined by finding a peak in FFT spectrogram close to previously determined HR. A miniturized battery-free wireless system glued to e.g. a nail is a novell unconventional alternative to avoid introducing motions artifacts [80].

### 3.3 Feature classification

This section contains an overview of the classification techniques used to discriminate between normal and VPBs in paper III and detect VNDs in paper IV.

The goal of *Linear discriminant analysis* (LDA) is to find a direction in space for witch classes of samples are well separated [81]. Here a linear discriminant function (LDF) based on Bayesian decision theory will be derived. Assume we have an observed feature vector  $\mathbf{x}$  of length  $l$ , that we want to classify into the classes  $\omega_i, i = 1 \dots I$ . The posterior probability can be computed from Bayes formula:

$$P(\omega_i|\mathbf{x}) = \frac{P(\mathbf{x}|\omega_i)P(\omega_i)}{P(\mathbf{x})}, \quad (3.1)$$

where  $P(\omega_i|\mathbf{x})$  is the probability that the class is  $\omega_i$  given the observed feature vector  $\mathbf{x}$ ,  $P(\mathbf{x}|\omega_i)$  is the probability of observing  $\mathbf{x}$  given that the sample belongs to  $\omega_i$ , and  $P(\omega_i)$  and  $P(\mathbf{x})$  are the probabilities of  $\omega_i$  and  $\mathbf{x}$ , respectively. Bayes formula implies that we should assign a feature vector  $\mathbf{x}$  to the class  $\omega_i$  corresponding to the highest value of the LDF:

$$g_i(\mathbf{x}) = \ln P(\mathbf{x}|\omega_i) + \ln P(\omega_i) \quad (3.2)$$

Assuming that  $P(\mathbf{x}|\omega_i)$  is multivariate normal distributed, its probability density

function is given by

$$p(\mathbf{x}|\omega_i) = \frac{1}{(2\pi)^{l/2} |\mathbf{C}_i|^{1/2}} \left( -\frac{1}{2} (\mathbf{x} - \mathbf{m}_i)^T \mathbf{C}_i^{-1} (\mathbf{x} - \mathbf{m}_i) \right), \quad (3.3)$$

where  $\mathbf{m}_i$  is the expected value of  $\mathbf{x}$ ,  $\mathbf{C}_i$  is the  $l$ -by- $l$  covariance matrix of  $\mathbf{x}$ , if  $\mathbf{x}$  belongs to  $\omega_i$ . The determinant and inverse of  $\mathbf{C}_i$  are denoted  $|\mathbf{C}_i|$  and  $\mathbf{C}_i^{-1}$ , respectively. Assuming that the covariance matrices are identical for all classes, eq. (3.2) can be rewritten as:

$$g_i(\mathbf{x}) = -\frac{1}{2} (\mathbf{x} - \mathbf{m}_i)^T \mathbf{C}^{-1} (\mathbf{x} - \mathbf{m}_i) - \frac{l}{2} \ln(2\pi) - \frac{1}{2} \ln |\mathbf{C}| + \ln P(\omega_i) \quad (3.4)$$

Since the second and the third term of eq. 3.4 are independent of  $i$ , the LDF can be simplified to

$$g_i(\mathbf{x}) = -\frac{1}{2} (\mathbf{x} - \mathbf{m}_i)^T \mathbf{C}^{-1} (\mathbf{x} - \mathbf{m}_i) + \ln P(\omega_i). \quad (3.5)$$

Assume that we have to classes  $\omega_i \in [n, v]$ . The LDFs for the two classes can be combined to a common LDF:

$$f(\mathbf{x}) = g_v(\mathbf{x}) - g_n(\mathbf{x}), \quad (3.6)$$

where  $\mathbf{x}$  is assigned to  $v$  if  $f(\mathbf{x}) > 0$ , and to  $n$  otherwise. Combining (3.5) with (3.6) gives

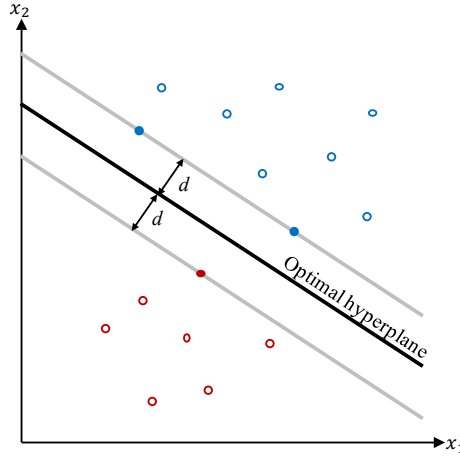
$$\begin{aligned} f(\mathbf{x}) = & (\mathbf{m}_v^T - \mathbf{m}_n^T) \mathbf{C}^{-1} \mathbf{x} \\ & - \frac{1}{2} \mathbf{m}_v^T \mathbf{C}^{-1} \mathbf{m}_v + \frac{1}{2} \mathbf{m}_n^T \mathbf{C}^{-1} \mathbf{m}_n + \ln \left( \frac{P(\omega_v)}{P(\omega_n)} \right), \end{aligned} \quad (3.7)$$

which is used in Paper III to classify normal beats and VPBs.

*Support vector machines* (SVM) is an algorithm for supervised machine learning that can be used for classification [81, 82, 83]. The goal when training an SVM is to find the hyperplane that optimally separates two classes, so that the distance  $d$  to the feature vectors of the training set  $\mathbf{x}_j, j = 1 \dots J$ , closest to the hyperplane is maximized, see Fig. 3.11.

The the distance of a vector  $\mathbf{x}_j$  to the hyperplane is proportional to

$$g(\mathbf{x}_j) = \mathbf{w}^T \mathbf{x}_j + b, \quad (3.8)$$



**Figure 3.11:** Training a SVM the purpose is to find the separating hyperplane, with the largest distance  $d$  to training points. The training points belonging to class I are blue, and the training points for the class II are red. The support vectors are shown as solid dots, the rest of the training points as circles.

where  $\mathbf{w}$  is a column vector of the same size as  $\mathbf{x}_j$ , and  $b$  is a real constant. Let  $y_j = 1$  if  $\mathbf{x}_j$  belongs to class I, and  $y_j = -1$  if  $\mathbf{x}_j$  belongs to class II. Then optimal hyperplane is defined by:

$$\begin{aligned} & \text{minimize} && \frac{1}{2} \|\mathbf{w}\|^2 \\ & \text{subject to} && y_j(\mathbf{w}^T \mathbf{x}_j + b) \geq 1, \end{aligned} \quad (3.9)$$

with respect to  $\mathbf{w}$  and  $b$ . The support vectors are the  $\mathbf{x}_j$  for which  $y_j(\mathbf{w}^T \mathbf{x}_j + b) = 1$ , i.e., the feature vectors nearest the separating hyperplane. The minimization problem in eq. 3.9 can be rewritten using Lagrangian multipliers  $\alpha_j, j = 1 \dots J$ , to enable minimization using e.g. quadratic programming [84], resulting in the following minimization problem:

$$\text{minimize} \quad \frac{1}{2} \|\mathbf{w}\|^2 - \sum_j \alpha_j (y_j(\mathbf{w}^T \mathbf{x}_j + b) - 1), \quad (3.10)$$

with respect to  $\mathbf{w}$ ,  $b$ , and  $\alpha_j$ . The method described above assumes that the data points can be separated by a hyperplane. The method can be modified to find a hyperplane that separate most, but not all data points [83]. To achieve this eq. 3.9 is rewritten by

adding slack variables  $\xi_j$  and a penalty parameter  $C$

$$\begin{aligned} & \text{minimize} && \frac{1}{2} \|\mathbf{w}\|^2 + C \sum_j \xi_j \\ & \text{subject to} && y_j(\mathbf{w}^T \mathbf{x}_j + b) \geq 1 - \xi_j \\ & && \xi_j \geq 0. \end{aligned} \tag{3.11}$$

Using Lagrangian multipliers the problem can be expressed as

$$\text{minimize} \quad \frac{1}{2} \|\mathbf{w}\|^2 + C \sum_j \xi_j - \sum_j \alpha_j (y_j(\mathbf{w}^T \mathbf{x}_j + b) - (1 - \xi_j)) - \sum_j \mu_j \xi_j, \tag{3.12}$$

with respect to the variables  $\mathbf{w}$ ,  $\alpha_j$ ,  $b$ , and  $\mu_j$ , where  $\mu_j, j = 1 \dots J$  are Lagrange multipliers. The minimization problem in eq. 3.12 was used in Paper IV for training the SVM, and was solved using Sequential Minimal Optimization [85].

The optimal solution  $\hat{\mathbf{w}}, \hat{b}$  enables classification of an observed feature vector  $\mathbf{x}_i$  as follows:

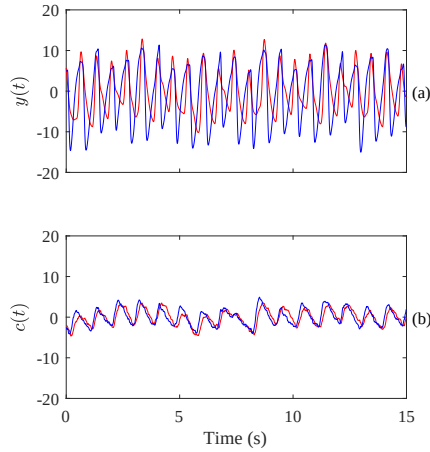
$$y_i = \text{sign}(\hat{\mathbf{w}}^T \mathbf{x}_i + \hat{b}). \tag{3.13}$$

### 3.4 Observed Pressure Signal and Disturbances

Pressure pulses originating from the heart enter the extracorporeal blood circuit via the arterial and venous needles or via a catheter. In the extracorporeal blood circuit the pressure pulses are measured by the arterial and venous pressure sensors. The extracorporeal circuit also contains a blood pump, which generates pressure pulses with an amplitude that can be up to 100 times larger than the amplitude of the pressure pulses of originating heart, see example signals in Fig. 3.12. The signal to noise ratio makes extraction of the cardiac component challenging. Another issue, is that the heart rate and the pump rate may overlap in frequency.

The heart pulsations are not the only signal originating from the patient. In addition a breathing signal may be present, but since it is of much lower frequency it can easily be removed by a high-pass filter. Other sources for disturbances are patient movement, movement of the blood lines. Patient sneezing and coughing may cause large transient disturbances.

Yet another source of disturbances is originating from the dialysate side of the HD machine. Such disturbances pass through the dialyzer, and reach the venous pressure sensor. Disturbances from the dialysate side never reach the arterial pressure sensor, since the peristaltic blood pump effectively obstructs the blood circuit. Changes in



**Figure 3.12:** (a) The observed arterial pressure signal (red) and venous pressure signal (blue). (b) The estimated arterial cardiac pressures signal (red), and the estimated venous cardiac pressure signal (blue).

valve positions inside the dialysis machine may cause transient disturbances, for example at internal calibration procedures. An other source of disturbances originate from the degassing of the dialysis fluid. Some dialysis machines also generate low frequency disturbances. The magnitude of the disturbances on the dialysate side may vary between different machine brands.

Most dialysis machines, like e.g. AK 200 S from Gambro [86], have a dripchamber which contains air and is located downstream from the dialyser. The air compliance in the drip chamber, together with the resistance of the needle, forms a filter which dampens the measured venous pressure signal. The dampening is pressure dependent, and thus also dependent on the blood flow. Some HD machines, like the Artis [87] by Gambro, have an additional volume of air on the arterial side, resulting in that the arterial pressure is also dampened. The difference in damping between arterial and venous sides, together with that blood is pulled on the arterial side and pushed on the venous side, results in very different shape and size of the blood pump pulses in the arterial and venous pressure signals.

### 3.5 Signal separation

Extraction of the cardiac signal from the arterial and venous pressure signals is not described much in the scientific literature. Apart from our methods described in our papers [88, 89], Moissl et al. propose methods to the estimate of heart rate

from the arterial pressure sensor in two conference papers [90, 91]. The heart rate is determined from the location of a spectral peak. In the first conference paper linear filtering is used to reduce the influence of the dominant blood pump signal, and in the second paper the pump signal is removed by first modelling it using truncated Fourier series. Not much detail is offered in the two conference papers, and the performance is only evaluated through examples. The problem of extracting the cardiac signal from the extracorporeal pressure sensors was first described in patents [92, 93], however, without evaluating the performance. Cardiac signal extraction is also indirectly addressed in a conference paper about VND [94].

In the following a brief overview of two signal separation techniques used in the thesis is given.

*Principal component analysis* (PCA) is a classical technique used in statistical data analysis, feature extraction, and data compression [95, 96]. It was introduced by Karl Pearson, and is also known under the names Karhunen-Loève transform and Hotelling transform. Principal component analysis is a linear transform that projects the original multivariate set of variables in to a orthogonal set of variables. No assumption is made about the distribution of the original data. Principal component analysis can be computed based on eigenvalue decomposition of the covariance matrix. The goal is to find a projection matrix  $\mathbf{W}$ , that projects the observed signals in  $\mathbf{X}$  to new signals in  $\mathbf{Y}$ , such that the covariance matrix of  $\mathbf{Y}$  is a diagonal matrix, since then the signals in  $\mathbf{Y}$  are orthogonal. Below is an algorithm describes PCA step by step. Assume that we have  $p$  signals  $\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_p$  of length  $n$ , forming the matrix

$$\mathbf{X} = [\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_p]^T. \quad (3.14)$$

First, each signal is centered around its mean

$$\mathbf{X}_c = \mathbf{X} - [\bar{\mathbf{x}}_1, \bar{\mathbf{x}}_2, \dots, \bar{\mathbf{x}}_p]^T, \quad (3.15)$$

Then the sample covariance matrix is calculated

$$\mathbf{R} = \frac{\mathbf{X}_c \mathbf{X}_c^T}{n - 1}. \quad (3.16)$$

Eigenvalue decomposition is performed on the co variance matrix,

$$\mathbf{U} \mathbf{D} \mathbf{U}^T = \mathbf{R}, \quad (3.17)$$

where  $\mathbf{U}$  is a matrix with the eigenvectors of  $\mathbf{R}$  arranged in columns, and  $\mathbf{D}$  is a diagonal matrix containing the eigenvalues of  $\mathbf{R}$ . The projection matrix  $\mathbf{W}$  is given by

$$\mathbf{W} = \mathbf{U}^T, \quad (3.18)$$

and the orthogonal signals  $\mathbf{Y} = [\mathbf{y}_1, \mathbf{y}_2, \dots, \mathbf{y}_p]^T$  are given by

$$\mathbf{Y} = \mathbf{W}\mathbf{X}. \quad (3.19)$$

Denoising can be achieved by truncating  $\mathbf{W}$ , so that the rows corresponding to the lowest eigenvalues are removed. The denoised signals are obtained by

$$\mathbf{X} = \mathbf{W}_T^{-1}\mathbf{Y}, \quad (3.20)$$

where  $\mathbf{W}_T^{-1}$  is the pseudoinvers of the truncated  $\mathbf{W}$ . In paper II, PCA denoising is used to remove disturbances from the extracted cardiac arterial and venous pressure signals.

*Empirical mode decomposition* (EMD) is a method for dividing non-stationary signals into a sum of intrinsic mode functions (IMF) along with a residual [97]. IMFs are amplitude and frequency modulated signal components with zero mean. In an IMF, the number of maxima, minima, and zero-crossings are not allowed to differ with more than one. The EMD method starts by identifying all local extrema in the given signal  $x(t)$ . Based on the local extrema the signal is divided into a high frequency part, called the detail  $d(t)$  and a low frequency part, the trend  $m(t)$ . The EMD algorithm is summarized in the following steps:

1. Initialize by setting iteration index  $i = 0$ .
2. Set  $y(t) = x(t)$  and increase  $i$  by one.
3. Find all local maxima and minima in  $y(t)$ .
4. Compute upper and lower envelopes,  $e_{\max}$  and  $e_{\min}$ , by interpolating the local maxima and minima in  $y(t)$ , respectively.
5. Compute the trend as  $m(t) = (e_{\max} + e_{\min})/2$ .
6. Compute the detail as  $d(t) = y(t) - m(t)$ . If the mean of  $d(t)$  is sufficiently small,  $d(t)$  is the  $i$ :th IMF, else set  $y(t) = d(t)$  and repeat steps 3-6.
7. Set  $x(t) = x(t) - d(t)$ , then repeat steps 2-7.

For each iteration the number of minima and maxima is decreased. The iteration ends when  $x(t)$  is a monotonic function. The IMF from the first iteration normally contains the highest frequency component, and can often be rejected as noise. In paper III the method was used to remove detrend the cardiac signal estimate, i.e. to remove low frequency disturbances originating from breathing or the dialysate side of the HD machine.



## Chapter 4

---

# Summary of the Included Papers

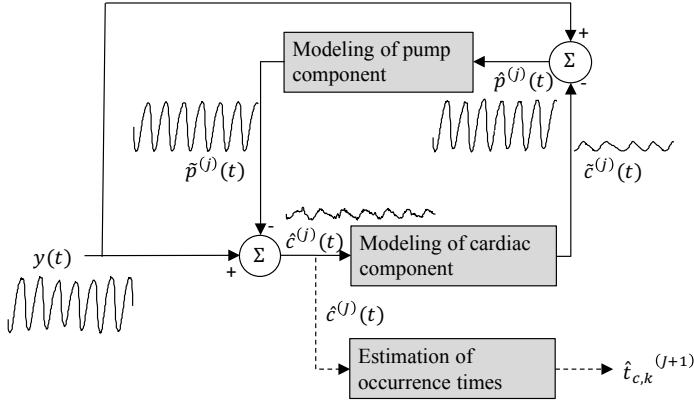
---

This chapter presents summary of the four included papers and their contribution to the research field. The included papers address improved patient monitoring during dialysis. The content of the papers constitutes a framework for how to monitor heart rate, detect heartbeat occurrence times, detect VPBs, and detect VND, all based on information extracted from the extracted from the extracorporeal pressure signals of a HD machine.

### **4.1 Paper I: Extracting a cardiac signal from the extracorporeal pressure sensors of a hemodialysis machine**

In the first paper we present a novel method for extracting the cardiac component from the venous pressure signal of a HD machine. For the first time, HR and heartbeat occurrence time is estimated based on the venous pressure signal. The accuracy of the estimates is evaluated on simulated signals, as well as on clinical data with a PPG as reference.

The recorded venous pressure signal contains two signal components. The component originating from the heart is of much smaller amplitude than the component originating from the blood pump. The proposed method iteratively alternate between estimating the cardiac component and the pump component. The cardiac component is estimated by subtracting a modeled pump signal from the observed pressure signal, and the pump component is estimated by subtracting a modeled cardiac signal from observed signal, see Fig. 3. For each iteration the modeled signals are refined, gradu-

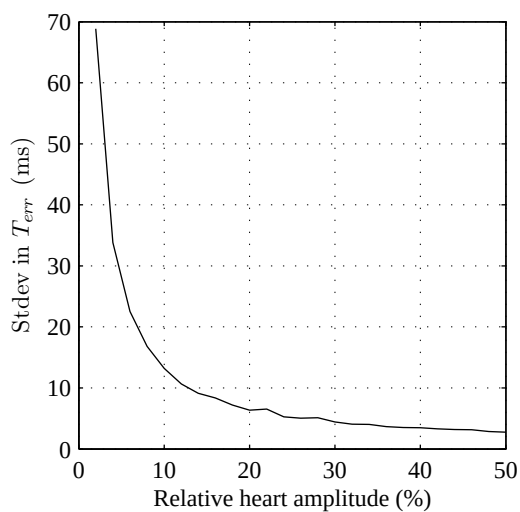


**Figure 4.1:** Overview of the the alternating, iterative pump and heart signal estimation, where  $y(t)$  is the observed venous pressure signal,  $\hat{p}^{(j)}(t)$  is the estimated pump component,  $\tilde{p}^{(j)}(t)$  is the modeled pump signal,  $\hat{c}^{(j)}(t)$  is the estimated cardiac component,  $\tilde{c}^{(j)}(t)$  is the modeled cardiac signal,  $\hat{c}^{(j+1)}(t)$  is the final cardiac signal estimate, after  $J$  iterations, and  $j$  is an index that is increased by 1 for each iteration. The final estimate of the heartbeat occurrence times is denoted  $\hat{t}_{c,k}^{(J+1)}$ .

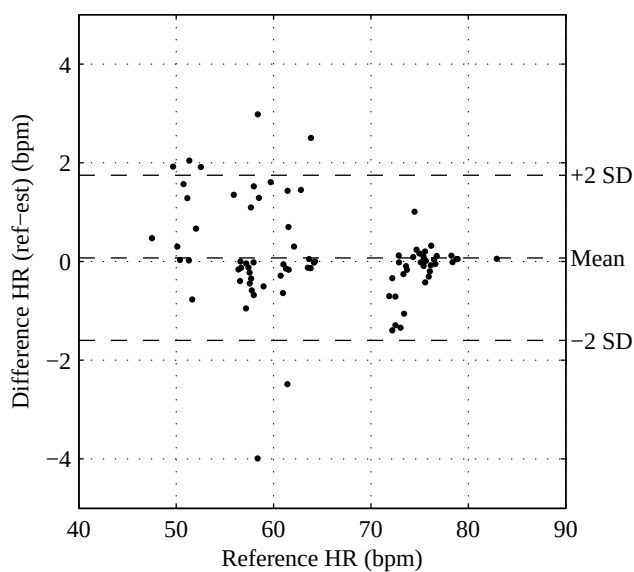
ally increasing the separation of the cardiac component from the pump component. The iteration continues until the difference in successive estimates is sufficiently small.

Clinical and simulated data were used for performance evaluation. The performance was studied on simulated signals with different relative heart amplitudes and heart rates. When the heart amplitude is low the noise dominates, and disturbs the estimated heartbeat occurrence times. For higher amplitudes of the heart component, the accuracy of the timing gradually improves to a standard deviation of about 10 ms at a heart rate of 50 bpm.

The method was also tested on pressure recordings from 9 patients. The average heart rate for each of 20 segments of 1-min duration was calculated using the estimated onset times, and compared with the HR from the reference PPG signal. A comparison between the heart rates can be seen in Fig. 6. The results show that a good agreement between heart rate estimated from extracorporeal venous pressure signal and the PPG signal. The differences are normally within one beat per minute which is sufficient for clinical use.



**Figure 4.2:** The error in the estimates of the heart beat onset times as a function of relative heart amplitude (heart amplitude/pump amplitude) at a heart rate of 67 bpm.



**Figure 4.3:** Bland-Altman plot of the difference between the heart rate extracted from the venous pressure and the reference.

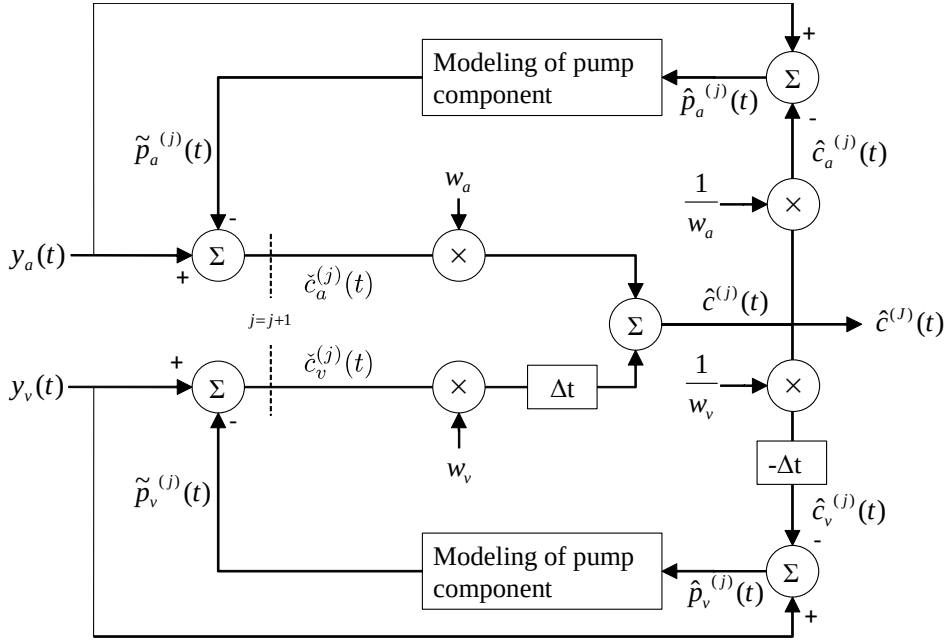
## 4.2 Paper II: Cardiac Signal Estimation Based on the Arterial and Venous Pressure Signals of a Hemodialysis machine

In the second paper, a novel method is proposed for estimating a cardiac pressure signal by combining the arterial and the venous pressure sensor signals of the HD machine. Such a combination should improve the quality of the estimated cardiac pressure signal. The heartbeats are no longer assumed to have identical shape, allowing for better detection of VPBs. Additionally, the modelling of the pump signal is improved by modelling the pulses from the two rollers separately, instead as combined in one pump revolution as in [88].

The proposed method iteratively, for  $j = 0, \dots, J$ , alternate between estimating pump components  $\hat{p}_a^{(j)}(t)$  and  $\hat{p}_v^{(j)}(t)$  for the observed arterial and venous pressure signals  $y_a(t)$  and  $y_v(t)$ , respectively, and estimating a joint cardiac component  $\hat{c}^{(j)}(t)$  common to  $y_a(t)$  and  $y_v(t)$ . The estimate  $\hat{c}^{(j)}(t)$  is computed as the average of an intermediate arterial cardiac estimate  $\check{c}_a^{(j)}(t)$  and a time shifted intermediate venous cardiac estimate  $\check{c}_v^{(j)}(t + \Delta t)$ , where  $\Delta t$  is estimated as the delay with the largest covariance between  $\check{c}_a^{(j)}(t)$  and  $\check{c}_v^{(j)}(t + \Delta t)$ . The intermediate estimates  $\check{c}_a^{(j)}(t)$  and  $\check{c}_v^{(j)}(t)$  are computed by subtracting modeled pump signals  $\tilde{p}_a^{(j)}(t)$  and  $\tilde{p}_v^{(j)}(t)$  from the observed pressure signals  $y_a(t)$  and  $y_v(t)$ , respectively. Arterial and venous cardiac signal estimates,  $\hat{c}_a^{(j)}(t)$  and  $\hat{c}_v^{(j)}(t)$ , respectively, are computed rescaling and realignment of the joint cardiac estimate  $\hat{c}^{(j)}(t)$ . The estimated pump components  $\hat{p}_a^{(j)}(t)$  and  $\hat{p}_v^{(j)}(t)$  are obtained by subtracting  $\hat{c}_a^{(j)}(t)$  and  $\hat{c}_v^{(j)}(t)$  from  $y_a(t)$  and  $y_v(t)$ , respectively. The estimated pump components are in turn used to compute modeled pump signals  $\tilde{p}_a^{(j)}(t)$  and  $\tilde{p}_v^{(j)}(t)$ . The modeled signals are refined for each iteration, which gradually decreases the amount of pump signal disturbances in the cardiac signal estimate. The iteration continues until the difference in successive cardiac estimates is sufficiently small. An overview of the method is shown in Fig. 4.4.

The modeled pump signals  $\tilde{p}_a^{(j)}(t)$  and  $\tilde{p}_v^{(j)}(t)$  are obtained by concatenation of pump profiles. Pump profiles characterizes the pressure changes that occur during one roller period, and one pump profile is determined for each of the two rollers in the blood pump. Before the concatenation the pump profiles are time scaled to fit between the roller period onset times. The pump model signals  $\tilde{p}_a^{(j)}(t)$  and  $\tilde{p}_v^{(j)}(t)$  are then produced by alternating the concatenation of the two pump profiles, i.e., for every other roller period the first pump profile is used, and otherwise the second pump profile.

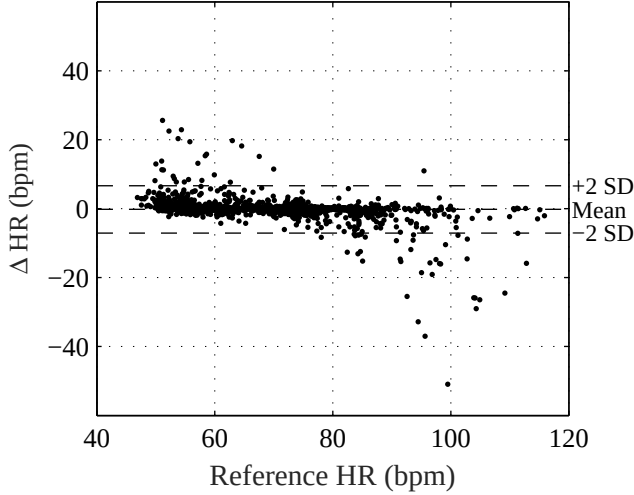
The performance of the new method using both arterial and venous pressure sig-



**Figure 4.4:** Block diagram of the present method for estimating a joint cardiac signal from the input arterial and venous pressure signals [89]. The vertical dashed lines indicate that the iteration index  $j$  is incremented by 1.

nals is evaluated and compared to the earlier method [88], which made use of the venous pressure only. The heart rate and the heartbeat occurrence times, determined from the estimated cardiac pressure signal, are compared to the corresponding quantities determined from the PPG. The performance is evaluated on signals from 9 complete HD treatments. For a cardiac pulse pressure of 0.5 mmHg, the median absolute deviation between estimated and reference heart rate was 1.3 bpm when based on the venous pressure signal only, and dropped to 0.6 bpm when based on both the arterial and venous pressure signals. The results show that the new method offers improved estimation at low heartbeat amplitudes. This enables cardiac monitoring of more patients without the use of extra sensors like ECG and PPG. The results need to be verified on a separate larger dataset.

The method has been improved compared to the method in [88]. The use of both the arterial and the venous pressures signals enables determination of HR also at low cardiac signal amplitudes. The method has been improved to handle all blood flow rates, and to handle flow rate changes automatically. The improved method also handles disturbances automatically. The improvements enable signal extraction



**Figure 4.5:** Plot of the difference in heart rate,  $\Delta\text{HR}$ , the rates being determined from the reference (PPG) signal and the estimated cardiac pressure signal  $\hat{c}_{AA}^{(J)}(t)$ .

throughout entire treatments.

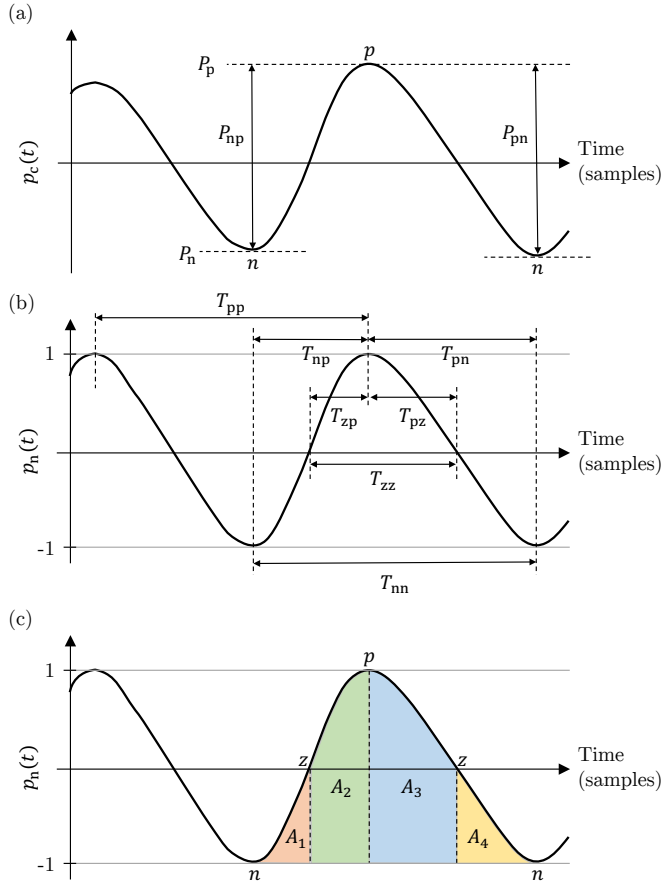
### 4.3 Paper III: Detection of Ventricular Premature Beats Based on the Pressure Signals of a Hemodialysis Machine

Ventricular premature beats are common in dialysis patients, and usually the frequency of VPBs increase during a treatment. Patients with regional wall motion abnormalities, ischemic heart disease, and left ventricular hypertrophy have a higher rate of VPBs during HD than the patients without these diseases. Rapid changes in VPB rate may be a sign of cardiovascular instability and electrolyte imbalance, and may therefore be used for prediction of acute intradialytic hypotension.

In this third paper, we investigate whether the extracorporeal pressure signals of a HD machine can be used for VPB detection. A classification method based on linear discriminant analysis (LDA) is proposed.

Pressure recordings from 9 HD treatments are used to evaluate the proposed method. An annotated PPG signal, where every heartbeat was classified as either a normal beat or a VPB, is used as reference.

The cardiac pressure signal  $p_c(t)$  is extracted from the extracorporeal pressure sig-



**Figure 4.6:** (a) Amplitude features determined from  $p_c(t)$ . (b) Duration and (c) area features determined from  $p_n(t)$ . The following area features are evaluated:  $A = A_1 + A_2 + A_3 + A_4$ ,  $A_{pn} = A_3 + A_4$ ,  $A_{np} = A_1 + A_2$ ,  $A_{zz} = A_2 + A_3$ ,  $A_{zp} = A_2$ ,  $A_{pz} = A_3$ . The vertical axis in (a) has arbitrary units.

nals according to the method described in [89]. Beats are detected in  $p_c(t)$  by identifying local maxima. For each beat, features  $\mathbf{x}$  are extracted based on amplitudes, durations, and areas, from either the estimated cardiac pressures signal  $p_c(t)$  or an amplitude normalized version of the signal  $p_n(t)$ , see Fig. 4.6.

The detected beats are classified as either normal or VPB, using linear discriminant

analysis. A linear discriminant function  $f(\mathbf{x})$  is evaluated for each beat,

$$f(\mathbf{x}) = (\mathbf{m}_v^T - \mathbf{m}_n^T) \mathbf{C}^{-1} \mathbf{x} - \frac{1}{2} \mathbf{m}_v^T \mathbf{C}^{-1} \mathbf{m}_v + \frac{1}{2} \mathbf{m}_n^T \mathbf{C}^{-1} \mathbf{m}_n + \ln \left( \frac{P_v}{P_n} \right), \quad (4.1)$$

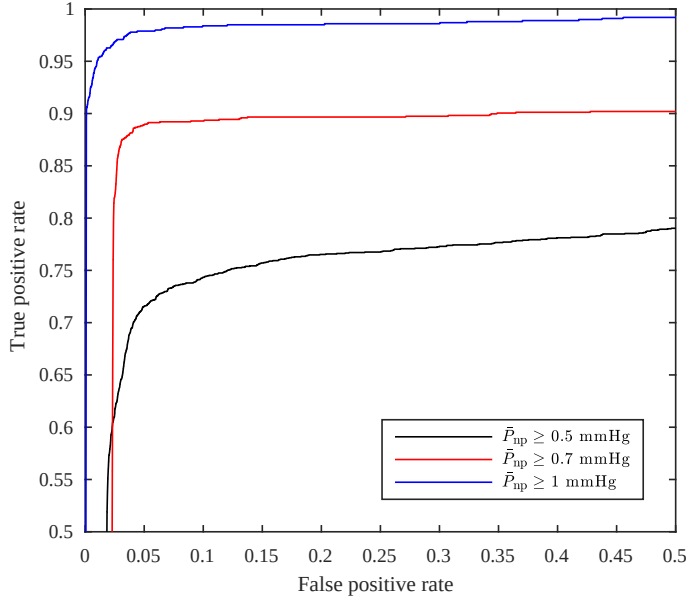
where  $\mathbf{m}_v$  is the average feature vector for all VPBs,  $\mathbf{m}_n$  is the mean for all normal beats,  $\mathbf{C}$  is the estimated covariance matrix of the features based on all beats. For each treatment, the a priori probabilities  $P_v$  and  $P_n$  of VPBs and normal beats, respectively, are determined from the annotations of all other treatments. Leave-one-out crossvalidation is used to evaluate the performance on recordings from 9 HD treatments, i.e., for each treatment, the linear discriminant function  $f(\mathbf{x})$  is determined from all other treatments. If  $f(\mathbf{x}) > 0$ , the beat is classified as VPB, otherwise as normal. The five features giving the highest Youden's  $J$  statistic are used when evaluating the performance of the classification.

$$J = \frac{N_{TP}}{N_{TP} + N_{FN}} + \frac{N_{TN}}{N_{TN} + N_{FP}} - 1, \quad (4.2)$$

where  $N_{TP}$  is the number of annotated VPBs classified as VPBs (true positives),  $N_{FN}$  is the number annotated VPBs classified as normal beats (false negatives),  $N_{TN}$  is the number of annotated normal beats classified as normal beats (true negatives), and  $N_{FP}$  is the number of annotated normal beats classified as VPBs (false positives).

The results show that VPBs can be reliably detected, quantified by a Youden's  $J$  statistic of 0.9, for average cardiac pulse pressures  $\bar{P}_{np}$  exceeding 1 mmHg; when all treatments are included, the  $J$  statistic drops to 0.55. The receiver operating characteristic (ROC) is shown in Fig. 4.7. Again, better performance is achieved when only treatments with  $\bar{P}_{np} \geq 1$  are included. Whether the patient is suitable for VPB detection is determined by the amplitude of the estimate cardiac pressures signal. The two main limitations in the study are: 1. The small data set, 2. That the gold standard for VPB detection, ECG, was not available as reference.

It is concluded that the estimated cardiac pressure signal is suitable for VPB detection, provided that the average cardiac pulse pressure exceeds 1 mmHg. The method has to be verified on an extended data set with ECG available as reference.



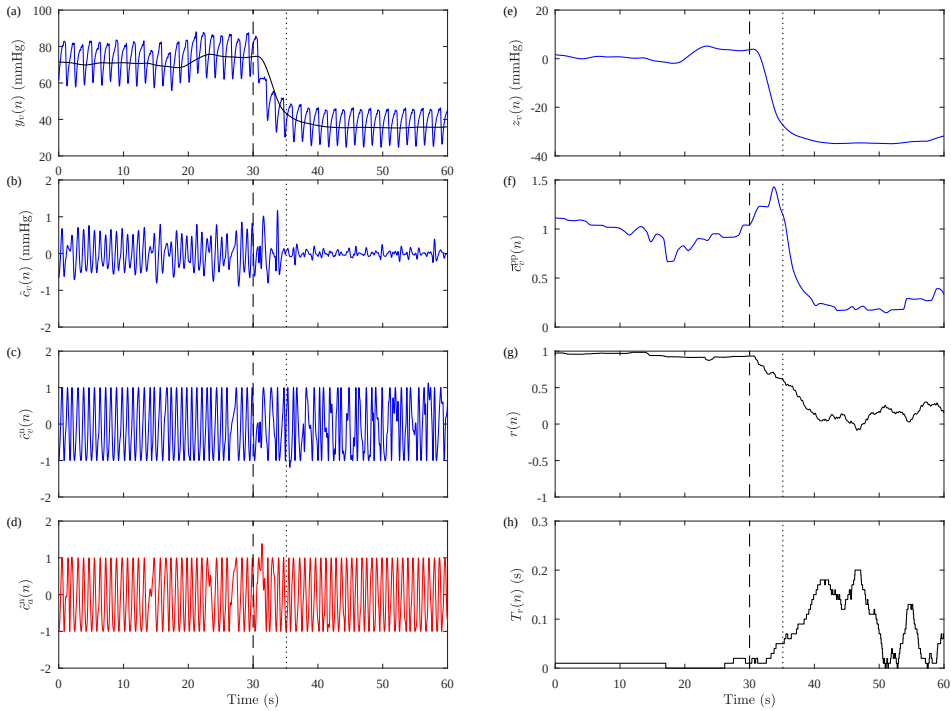
**Figure 4.7:** Receiver operating characteristic for VPB detection using linear discriminant analysis of the five most relevant features, for treatments with different lower limits of  $\bar{P}_{np}$ .

## 4.4 Paper IV: Detection of Needle Dislodgement Using Information in the Extracorporeal Pressure Signals

Venous needle dislodgement is an adverse but rarely occurring event during HD. If not detected in promptly, so much blood is lost that the patient will suffer from severe injury. Hospitalization or acute care may be required. As prevention, HD machines must be equipped with a venous pressure alarm, which stops the blood pump and clamps the blood lines if the venous pressure drops outside the alarm limits. It is, however, difficult for the staff to set the alarm limits such that a high sensitivity is assured without causing numerous false alarms. As result, only about 30% of the VNDs in patients with fistulas are detected.

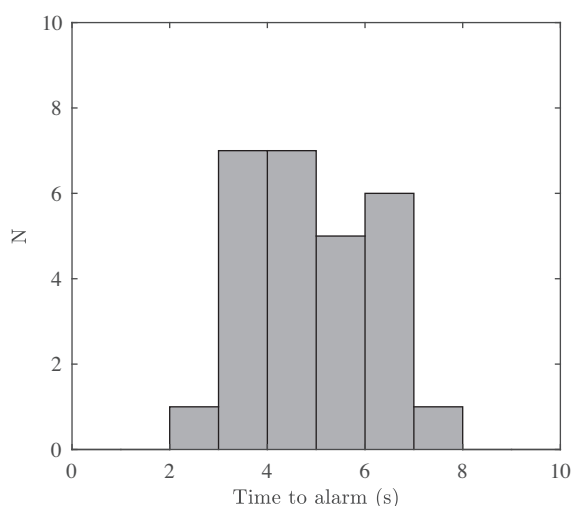
In this paper a novel VND detection method, using the extracted cardiac pressure signal in [89], is proposed and its performance is evaluated. Four features are extracted from the arterial and venous pressure signals in the extracorporeal circuit of the HD machine. The four features are based on, the mean venous pressure, the

venous cardiac pulse pressure, the time delay between the estimated arterial and venous cardiac pressure signals, and the correlation coefficient between the same signals. Fig.4.8 shows how the values of the features change during a VND from a patient. The features are used as input to a support vector machine (SVM), which is trained on simulated VNDs. The VNDs are simulated by combining lab measurements with computer simulated cardiac signals. In this way, the SVM is trained on many combinations of cardiac signal strengths, heart rates, and dislodgement conditions. The performance is evaluated on dislodgements produced in the lab, as well as on a four dislodgements produced under controlled circumstances as part of a clinical study.



**Figure 4.8:** Pressure signals (left column) and related features (right column) at the VND in one of the clinical treatments. The VND occurred at  $t = 30$  s (dashed vertical line), and was detected at the dotted vertical line. (a) Venous pressure  $y_v(n)$  (blue line) and filtered venous pressure  $\bar{y}_v(n)$  (black line), (b) estimated venous cardiac signal  $c_v(n)$ , (c) normalized cardiac venous signal  $c_v^n(n)$ , (d) normalized cardiac arterial signal  $c_a^n(n)$ , (e) centered venous pressure  $z_v(n)$ , (f) normalized venous pulse pressure  $\hat{c}_v^{pp}(n)$ , (g) correlation coefficient  $r(n)$  between  $c_v^n(n)$  and  $c_a^n(n)$ , and (h) time shift  $\Delta T(n)$  between  $c_v^n(n)$  and  $c_a^n(n)$ . Note that (c), (d), (f), and (g) are normalized and thus without unit.

The clinical results show that three out of the four VNDs could be correctly detected. In these three treatments the cardiac signal amplitude was large enough to be detected without causing false alarms. The remaining fourth treatment had however an extremely weak venous cardiac signal amplitude ( $< 0.1$  mmHg), which caused the method to produce false alarms. The lab results show that all 27 VNDs in the test set were correctly detected. The time from VND to detection was between 2.4 s and 7.2 s, with an average of 4.9 s, see the histogram in Fig. 4.9. Assuming that the blood pump is stopped immediately after detection, the corresponding blood loss would become between 7 and 60 ml, with an average of 23 ml.



**Figure 4.9:** Histogram of the time from the annotated VND to the detection.

Provided that the cardiac signal is large enough, the method can detect VND within 7.2 seconds and with a blood loss of less than 60 ml. This is well below 250 ml, which is considered to be a limit for non severe blood loss for HD patients. In addition to VND detection, the method also enables monitoring of cardiac arrest. If the cardiac signal disappears from both the venous and the arterial pressure signals, either both venous and arterial needles are dislodged, or a cardiac arrest has occurred. The number of cardiac arrests during HD is estimated to be even higher than the number of VNDs.

A limitation with the current study is the small data set of clinical VNDs. Such data is extremely difficult to obtain, since only patients with high hemoglobin concentrations are considered ethical to include. The small clinical data set was compensated

by a larger data set recorded in the lab and complemented with simulated data. In the future, the study should be expanded to include a large clinical study investigating false alarm rate.

## 4.5 Scientific contribution

The scientific contribution of this thesis is summarized in the list below.

1. Proposed a novel method for extracting a the cardiac pressure signal from the venous pressure signal of a HD machine.
2. Developed a cardiac pressure signal simulator based on FM modeling.
3. Estimated HR for the first time from venous pressure signal of a HD machine.
4. Estimated heartbeat occurrence time for the first time from the extracorporeal pressure signals of a dialysis machine.
5. Proposed a novel method for improved cardiac pressure signal extraction by combining both the arterial and venous pressure signals.
6. Developed a novel detector for VPBs and based on extracorporeal pressure signals of a HD machine.
7. VPBs were for the first time detected based on the cardiac signal extracted from the extracorporeal pressure sensors of a HD machine.
8. Proposed a novel method for detection of VND based on the extracorporeal pressure signals of a HD machine.
9. Demonstrated improved sensitivity for VND detection compared to the standard venous pressure alarm.

---

## References

---

- [1] L. Di Lullo, A. House, A. Gorini, A. Santoboni, D. Russo, and C. Ronco, “Chronic kidney disease and cardiovascular complications,” *Heart failure reviews*, Oct. 2014.
- [2] O. M. Shapira and Y. Bar-Khayim, “ECG changes and cardiac arrhythmias in chronic renal failure patients on hemodialysis,” *J. Electrocardiol.*, vol. 25, pp. 273–279, 1992.
- [3] S. Abe, M. Yoshizawa, N. Nakanishi, T. Yazawa, K. Yokota, M. Honda, and G. Sloman, “Electrocardiographic abnormalities in patients receiving hemodialysis,” *Am. Heart J.*, vol. 131, pp. 1137–1144, 1996.
- [4] A. Santoro, E. Mancini, R. Gaggi, S. Cavalcanti, S. Severi, L. Cagnoli, F. Badiali, B. Perrone, G. London, H. Fessy, L. Mercadal, and F. Grandi, “Electrophysiological response to dialysis: the role of dialysate potassium content and profiling,” *Contrib. Nephrol.*, vol. 149, pp. 295–305, 2005.
- [5] M. K. Shamseddin and P. S. Parfrey, “Sudden cardiac death in chronic kidney disease: epidemiology and prevention,” *Nat. Rev. Nephrol.*, vol. 7, pp. 145–154, mar 2011.
- [6] H. D. Polaschegg, “Venous needle dislodgement: the pitfalls of venous pressure measurement and possible alternatives, a review,” *J. Ren. Care*, vol. 36, pp. 41–48, 2010.
- [7] “IEC 60601-2-16 Medical electrical equipment part 2-16: Particular requirements for basic safety and essential performance of haemodialysis, haemodiafiltration and haemofiltration equipment (edition 4),” *Int. Electrotechnical Commission*, 2012.

- [8] W. Ribitsch, G. Schilcher, H. Hafner-Giessauf, P. Krisper, J. H. Horina, A. R. Rosenkranz, and D. Schneditz, "Prevalence of detectable venous pressure drops expected with venous needle dislodgement," *Seminars in Dialysis*, vol. 27, no. 5, pp. 507–511, 2014.
- [9] E. Widmaier, H. Raff, and K. Strang, *Vander's Human Physiology - The Mechanisms of Body Function*. Mc Graw Hill, 2006.
- [10] J. E. Hall and A. C. Guyton, *Guyton and Hall textbook of medical physiology*. Elsevier, thirteenth edition ed., 2016.
- [11] B. Radons, "A modern illustration of the basic physiology of a nephron within a kidney." [https://commons.wikimedia.org/wiki/File:Nephron\\_illustration.svg](https://commons.wikimedia.org/wiki/File:Nephron_illustration.svg), June 2012. Creative Commons CC0 1.0 Universal Public Domain Dedication.
- [12] R. Bellomo, J. A. Kellum, and C. Ronco, "Acute kidney injury," *The Lancet*, vol. 380, no. 9843, pp. 756–766, 2012.
- [13] A. S. Levey and J. Coresh, "Chronic kidney disease," *The Lancet*, vol. 379, no. 9811, pp. 165–180, 2012.
- [14] D. Fouque, P. Wang, M. Laville, and J. P. Boissel, "Low protein diets for chronic renal failure in non diabetic adults.," *Cochrane database of systematic reviews (Online)*, no. 2, p. CD001892, 2001.
- [15] W. Hörl, K. Koch, R. Lindsay, C. Ronco, and J. Winchester, *Replacement of Renal Function by Dialysis*. Springer Netherlands, fifth edition ed., 2014.
- [16] J. T. Daugirdas, P. G. Blake, and T. S. Ing, *Handbook of dialysis*. Lippincott Williams & Wilkins, 2012.
- [17] R. Gokal and N. Mallick, "Peritoneal dialysis," *The Lancet*, vol. 353, no. 9155, pp. 823–828, 1999.
- [18] M. J. Nubé, M. P. Grooteman, and P. J. Blankestijn, eds., *Hemodiafiltration: Theory, Technology and Clinical Practice*. Springer, first edition ed., 2016.
- [19] C. Ronco and D. Cruz, "Hemodiafiltration History, Technology, and Clinical Results," *Advances in Chronic Kidney Disease*, vol. 14, no. 3, pp. 231–243, 2007.
- [20] P. W. Eggers, "Mortality rates among dialysis patients in medicare's end-stage renal disease program," *American Journal of Kidney Diseases*, vol. 15, no. 5, pp. 414 – 421, 1990.

- 
- [21] D. Santoro, F. Benedetto, P. Mondello, N. Pipito, D. Barilla, F. Spinelli, C. A. Ricciardi, V. Cernaro, and M. Buemi, "Vascular access for hemodialysis: Current perspectives," *International Journal of Nephrology and Renovascular Disease*, vol. 7, pp. 281–294, 2014.
- [22] T. Bauld and J. Anderson, "Patient safety alert AL 010-13," in *Veterans health administration warning system*, pp. 1–2, V A Central Office, 2010.
- [23] B. Axley, J. Speranza-Reid, and H. Williams, "Venous needle dislodgement in patients on hemodialysis," *Nephrol. Nurs. J.*, vol. 9, pp. 435–445, 2012.
- [24] S. Sandroni, T. Sherockman, and K. Hayes-Leight, "Catastrophic hemorrhage from venous needle dislodgement during hemodialysis: Continued risk of avoidable death and progress toward a solution," in *ASN Renal Week Abstracts, J. Am. Soc. Nephrol.*, vol. 19, p. 891A, 2008.
- [25] J. Ahlmén, K. H. Gydell, H. Hadimeri, I. Hernandez, B. Rogland, and U. Strömbom, "A new safety device for hemodialysis," *Hemodialysis International*, vol. 12, no. 2, pp. 264–267, 2008.
- [26] C. A. Herzog, "Cardiac arrest in dialysis patients: approaches to alter an abysmal outcome," *Kidney Int. Suppl.*, vol. 63, no. 84, pp. S197–S200, 2003.
- [27] N. M. Selby, N. V. Kolhe, C. W. McIntyre, J. Monaghan, N. Lawson, D. Elliott, R. Packington, and R. J. Fluck, "Defining the cause of death in hospitalised patients with acute kidney injury," *PloS one*, vol. 7, p. e48580, Jan. 2012.
- [28] A. Go and G. Chertow, "Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization," *New England Journal ...*, pp. 1296–1305, 2004.
- [29] J. T. Heywood, G. C. Fonarow, M. R. Costanzo, V. S. Mathur, J. R. Wigneswaran, and J. Wynne, "High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database," *Journal of cardiac failure*, vol. 13, pp. 422–30, Aug. 2007.
- [30] S. Shastri and M. J. Sarnak, "Cardiovascular disease and CKD: core curriculum 2010," *American journal of kidney diseases : the official journal of the National Kidney Foundation*, vol. 56, pp. 399–417, Aug. 2010.
- [31] N. C. Edwards, W. E. Moody, C. D. Chue, C. J. Ferro, J. N. Townsend, and R. P. Steeds, "Defining the natural history of uremic cardiomyopathy in chronic

- kidney disease: the role of cardiovascular magnetic resonance.,” *JACC. Cardiovascular imaging*, vol. 7, pp. 703–14, July 2014.
- [32] J. O. Burton, S. Korsheed, B. J. Grundy, and C. W. McIntyre, “Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmia,” *Renal Failure*, vol. 30, pp. 701–709, 2008.
- [33] M. C. G. Wong, J. M. Kalman, E. Pedagogos, N. Toussaint, J. K. Vohra, P. B. Sparks, P. Sanders, P. M. Kistler, K. Halloran, G. Lee, S. A. Joseph, and J. B. Morton, “Temporal distribution of arrhythmic events in chronic kidney disease: Highest incidence in the long interdialytic period,” *Heart Rhythm*, vol. 12, no. 10, pp. 2047–2055, 2015.
- [34] K. Solem, A. Nilsson, and L. Sörnmo, “An ECG-based method for early detection of abrupt changes in blood pressure during hemodialysis,” *ASAIO J.*, vol. 52, pp. 282–290, 2006.
- [35] J. a. Karnik, B. S. Young, N. L. Lew, M. Herget, C. Dubinsky, J. M. Lazarus, and G. M. Chertow, “Cardiac arrest and sudden death in dialysis units,” *Kidney Int.*, vol. 60, pp. 350–357, July 2001.
- [36] A. J. Bleyer, “Characteristics of sudden death in hemodialysis patients,” *Kidney Int.*, vol. 69, pp. 2268–2273, 2006.
- [37] A. J. Bleyer, G. B. Russell, and S. G. Satko, “Sudden and cardiac death rates in hemodialysis patients,” *Kidney International*, vol. 55, no. 4, pp. 1553–1559, 1999.
- [38] W. W. Nichols, M. F. O’Rourke, and C. Vlachopoulos, *McDonald’s Blood Flow in Arteries*. Hodder Arnold, sixth ed., 2011.
- [39] P. Salvi, *Pulse Waves*. Springer, 2012.
- [40] ZooFari2014, “Heart diagram.” [https://commons.wikimedia.org/wiki/File:Heart\\_diagram-en.svg](https://commons.wikimedia.org/wiki/File:Heart_diagram-en.svg), March 2014. Creative Commons Attribution-ShareAlike 3.0 Unported license, via Wikimedia Commons.
- [41] *Guideline for the diagnosis and management of hypertension in adults*. National Heart Foundation of Australia, 2016.
- [42] M. E. Klingensmith, C. Vemuri, O. Fayanju, J. O. Robertson, P. P. Samson, and D. E. Sanford, eds., *The washington manual of surgery*. Lippincott Williams & Wilkins, seventh ed., 2015.

- 
- [43] A. Barbeito and J. B. Mark, "Arterial and central venous pressure monitoring," *Anesthesiology Clinics of North America*, vol. 24, no. 4, pp. 717–735, 2006.
- [44] S. S. Franklin, S. A. Khan, N. D. Wong, M. G. Larson, and D. Levy, "Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study," *Circulation*, vol. 100, no. 4, pp. 354–60, 1999.
- [45] J. C. Bramwell and A. V. Hill, "Velocity of transmission of the pulse-wave, and elasticity of arteries,," *The Lancet*, vol. 199, no. 5149, pp. 891–2, 1922.
- [46] B. Pannier, A. P. Guérin, S. J. Marchais, M. E. Safar, and G. M. London, "Stiffness of capacitive and conduit arteries: Prognostic significance for end-stage renal disease patients," *Hypertension*, vol. 45, no. 4, pp. 592–596, 2005.
- [47] P. Boutouyrie and S. J. Vermeersch, "Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: Establishing normal and reference values," *European Heart Journal*, vol. 31, no. 19, pp. 2338–2350, 2010.
- [48] J. Blacher, A. P. Guerin, B. Pannier, S. J. Marchais, M. E. Safar, and G. M. London, "Impact of aortic stiffness on survival in end-stage renal disease," *Circulation*, vol. 99, no. 18, pp. 2434–2439, 1999.
- [49] J. Allen, "Photoplethysmography and its application in clinical physiological measurement," *Physiol. Meas.*, vol. 28, pp. R1–R39, 2007.
- [50] A. a. Alian and K. H. Shelley, "Photoplethysmography," *Best Practice & Research Clinical Anaesthesiology*, Sept. 2014.
- [51] A. B. Hertzman and C. Spielman, "Observations on the finger volume pulse recorded photoelectrically," *Am. J. Physiol.*, no. 119, pp. 334–335, 1937.
- [52] P. D. Mannheim, "The light-tissue interaction of pulse oximetry,," *Anesthesia and analgesia*, vol. 105, pp. S10–7, Dec. 2007.
- [53] K. H. Shelley, M. Dickstein, and S. M. Shulman, "Case Reports," *J. Clin. Monit.*, vol. 9, no. 4, pp. 283–7, 1993.
- [54] K. H. Shelley, D. Tamai, D. Jablonka, M. Gesquiere, R. G. Stout, and D. G. Silverman, "The effect of venous pulsation on the forehead pulse oximeter wave form as a possible source of error in Spo2 calculation,," *Anesthesia and analgesia*, vol. 100, pp. 743–7, table of contents, Mar. 2005.

- [55] Z. D. Walton, P. a. Kyriacou, D. G. Silverman, and K. H. Shelley, "Measuring venous oxygenation using the photoplethysmograph waveform.," *Journal of clinical monitoring and computing*, vol. 24, pp. 295–303, Aug. 2010.
- [56] P. a. Kyriacou, "Pulse oximetry in the oesophagus.," *Physiological measurement*, vol. 27, no. 1, pp. R1–R35, 2006.
- [57] K. H. Shelley, "Photoplethysmography: beyond the calculation of arterial oxygen saturation and heart rate.," *Anesthesia and analgesia*, vol. 105, pp. S31–6, tables of contents, Dec. 2007.
- [58] E. Gil, P. Laguna, J. P. Martínez, Ó. Barquero-Pérez, A. García-Alberola, and L. Sörnmo, "Heart rate turbulence analysis using photoplethysmography," *IEEE Trans. Biomed. Eng.*, vol. 60, pp. 3149–3155, 2013.
- [59] E. Grigonyte, E. Gil, P. Laguna, and L. Sörnmo, "Relative peripheral blood volume changes induced by premature ectopic beats and their role in hemodialysis," *Biomedical Signal Processing and Control*, vol. 31, pp. 524–528, 2017.
- [60] A. Sološenko, A. Petrėnas, and V. Marozas, "Photoplethysmography-based method for automatic detection of premature ventricular contractions," *IEEE Trans. Biomed. Circuits Syst.*, vol. 9, no. 5, pp. 662–669, 2015.
- [61] S. Lu, H. Zhao, K. Ju, K. Shin, M. Lee, K. Shelley, and K. H. Chon, "Can photoplethysmography variability serve as an alternative approach to obtain heart rate variability information?," *Journal of clinical monitoring and computing*, vol. 22, pp. 23–9, Feb. 2008.
- [62] M. Nitzan, A. Babchenko, B. Khanokh, and D. Landau, "The variability of the photoplethysmographic signal - a potential method for the evaluation of the autonomic nervous system," *Physiol. Meas.*, vol. 19, no. 1, pp. 93–102, 1998.
- [63] J. Lázaro, E. Gil, J. M. Vergara, and P. Laguna, "Pulse rate variability analysis for discrimination of sleep-apnea-related decreases in the amplitude fluctuations of pulse photoplethysmographic signal in children.," *IEEE J. Biomed. Health Inform.*, vol. 18, pp. 240–246, 2014.
- [64] J. Y. A. Foo and S. J. Wilson, "A computational system to optimise noise rejection in photoplethysmography signals during motion or poor perfusion states," *Med. Biol. Eng. & Comput.*, vol. 44, pp. 140–145, 2006.
- [65] A. Solosenko and V. Marozas, *Automatic Extrasystole Detection Using Photoplethysmographic Signals*, pp. 985–988. Cham: Springer International Publishing, 2014.

- 
- [66] T. Suzuki, K. I. Kameyama, and T. Tamura, "Development of the irregular pulse detection method in daily life using wearable photoplethysmographic sensor," *Int. Conf. IEEE EMBS*, pp. 6080–6083, 2009.
- [67] K. Solem, B. Olde, and L. Sörnmo, "Prediction of intradialytic hypotension using photoplethysmography," *IEEE Trans. Biomed. Eng.*, vol. 57, pp. 1611–1619, 2010.
- [68] L. Sörnmo, F. Sandberg, E. Gil, and K. Solem, "Noninvasive techniques for prevention of intradialytic hypotension," *IEEE Rev. Biomed. Eng.*, vol. 5, pp. 45–59, 2012.
- [69] L. M. Nilsson, "Respiration signals from photoplethysmography," *Anesthesia and analgesia*, vol. 117, pp. 859–65, Oct. 2013.
- [70] A. A. Alian, N. J. Galante, N. S. Stachenfeld, D. G. Silverman, and K. H. Shelley, "Impact of central hypovolemia on photoplethysmographic waveform parameters in healthy volunteers part 2: Frequency domain analysis," *Journal of Clinical Monitoring and Computing*, vol. 25, no. 6, pp. 387–396, 2011.
- [71] J. E. Naschitz, S. Bezobchuk, R. Mussafia-Priselac, S. Sundick, D. Dreyfuss, I. Khorshidi, A. Karidis, H. Manor, M. Nagar, E. Rubin Peck, S. Peck, S. Storch, I. Rosner, and L. Gaitini, "Pulse transit time by R-wave-gated infrared photoplethysmography: review of the literature and personal experience," *J. Clin. Monit. Comput.*, vol. 18, no. 5-6, pp. 333–342, 2005.
- [72] M. Nitzan, B. Khanokh, and Y. Slovik, "The difference in pulse transit time to the toe and finger measured by photoplethysmography," *Physiological measurement*, vol. 23, no. 1, pp. 85–93, 2002.
- [73] A. Mitchell, A. Saez, and M. Kos, "Pulse wave velocity predicts mortality in renal transplant patients," *European journal of...*, vol. 15, no. 10, pp. 452–455, 2010.
- [74] X.-R. Ding, N. Zhao, G.-Z. Yang, R. Pettigrew, B. Lo, F. Miao, Y. Li, J. Liu, and Y.-T. Zhang, "Continuous Blood Pressure Measurement from Invasive to Unobtrusive: Celebration of 200th Birth Anniversary of Carl Ludwig," *IEEE Journal of Biomedical and Health Informatics*, vol. 20, no. 6, pp. 1–1, 2016.
- [75] B. P. M. Imholz, W. Wieling, G. A. van Montfrans, and K. H. Wesseling, "Fifteen years experience with finger arterial pressure monitoring: assessment of the technology," *Cardiovascular Res.*, vol. 38, no. 3, pp. 605–616, 1998.

- [76] S.-H. Kim, J.-G. Song, J.-H. Park, J.-W. Kim, Y.-S. Park, and G.-S. Hwang, "Beat-to-beat tracking of systolic blood pressure using noninvasive pulse transit time during anesthesia induction in hypertensive patients.," *Anesthesia and analgesia*, vol. 116, pp. 94–100, Jan. 2013.
- [77] X. Xing and M. Sun, "Optical blood pressure estimation with photoplethysmography and fft-based neural networks," *Biomed. Opt. Express*, vol. 7, pp. 3007–3020, Aug 2016.
- [78] C. C. Y. Poon, Y. M. Wong, and Y. T. Zhang, "M-health: The development of cuff-less and wearable blood pressure meters for use in body sensor networks," *2006 IEEE/NLM Life Science Systems and Applications Workshop, LiSA 2006*, pp. 1–2, 2006.
- [79] Z. Lin, J. Zhang, Y. Chen, and Q. Zhang, "Heart Rate Estimation Using Wrist-acquired Photoplethysmography Under Different Types of Daily Life Motion Artifact," *IEEE International Conference on Communications*, pp. 489–494, 2015.
- [80] J. Kim, P. Gutruf, A. M. Chiarelli, S. Y. Heo, K. Cho, Z. Xie, A. Banks, S. Han, K.-I. Jang, J. W. Lee, K.-T. Lee, X. Feng, Y. Huang, M. Fabiani, G. Gratton, U. Paik, and J. A. Rogers, "Miniaturized Battery-Free Wireless Systems for Wearable Pulse Oximetry," *Advanced Functional Materials*, vol. 201604373, pp. 1–8, 2016.
- [81] R. O. Duda, P. E. Hart, and D. G. Stork, *Pattern Classification*. New York: Wiley–Interscience, 2nd ed., 2001.
- [82] B. E. Boser, I. M. Guyon, and V. N. Vapnik, "A Training Algorithm for Optimal Margin Classifiers," *Proceedings of the fifth annual workshop on Computational learning theory*, pp. 144–152, 1992.
- [83] C. Cortes and V. Vapnik, "Support-Vector Networks," *Machine Learning*, vol. 20, no. 3, pp. 273–297, 1995.
- [84] S. Boyd and L. Vandenberghe, *Convex Optimization*. New York: Cambridge University Press, 2004.
- [85] R.-E. Fan, P.-H. Chen, and C.-J. Lin, "Working set selection using second order information for training support vector machines," *Journal of Machine Learning Research*, vol. 6, pp. 1889–1918, 2005.
- [86] Gambro Lundia AB, Sweden, *AK 200 S dialysis machine operator's manual*, 04.2010 ed., 2010.

- 
- [87] Gambro Lundia AB, Sweden, *Artis operator's manual, base manual for general use*, sw 8.60 ed., 2016.
  - [88] M. Holmer, F. Sandberg, K. Solem, E. Grigonyte, B. Olde, and L. Sörnmo, "Extracting a cardiac signal from the extracorporeal pressure sensors of a hemodialysis machine," *IEEE Trans. Biomed. Eng.*, vol. 62, no. 5, pp. 1305–1315, 2015.
  - [89] M. Holmer, F. Sandberg, K. Solem, B. Olde, and L. Sörnmo, "Cardiac signal estimation based on the arterial and venous pressure signals of a hemodialysis machine," *Physiol. Meas.*, vol. 37, no. 9, pp. 1499–1515, 2016.
  - [90] U. Moissl, P. Wabel, S. Leonhardt, R. Isermann, and M. Krämer, "Continuous observation and analysis of heart rate during hemodialysis treatment," in *Proc. Eur. Med. & Biol. Eng. Conf. (EMBEC)*, vol. 37, pp. S558–S559, 1999.
  - [91] U. Moissl, P. Wabel, S. Leonhardt, R. Isermann, and M. Krämer, "Heart rate monitoring during hemodialysis treatment," in *Proc. Eur. Med. & Biol. Eng. Conf. (EMBEC)*, vol. 3, pp. 584–585, 2002.
  - [92] H.-D. Polaschegg, "Method for measuring and indicating in liquid systems of medical devices, and device for carrying out this method," Eur. Patent 0 330 761, Sept. 8, 1993.
  - [93] T. Hertz, S. Jönsson, and J. Sternby, "Method and arrangement for detecting the condition of a blood vessel access," U.S. Patent 6 090 048, July 18, 2000.
  - [94] M. Segelmark, S. Mattsson, B. Olde, and K. Solem, "Successful detection of venous needle dislodgement using extracted heart pulses obtained from venous pressure monitoring," in *Proc. Am. Soc. Nephrol. Kidney (JASN)*, vol. 21, p. 241A, 2010.
  - [95] A. Hyvärinen, J. Karhunen, and E. Oja, *Independent Component Analysis*. Wiley Interscience, 2001.
  - [96] J. Shlens, "A tutorial on principal component analysis: derivation, discussion and singular value decomposition." [https://www.cs.princeton.edu/picasso/mats/PCA-Tutorial-Intuition\\_jp.pdf](https://www.cs.princeton.edu/picasso/mats/PCA-Tutorial-Intuition_jp.pdf), 2003.
  - [97] G. Rilling, P. Flandrin, P. Gon, and D. Lyon, "On empirical mode decomposition and its algorithms," *IEEE EURASIP Workshop on Nonlin. Signal and Image Process.*, vol. 3, pp. 8–11, 2003.



**Part II**

**Included Papers**



# *Paper I*



# Extracting a Cardiac Signal From the Extracorporeal Pressure Sensors of a Hemodialysis Machine

## Abstract

Although patients undergoing hemodialysis treatment often suffer from cardiovascular disease, monitoring of cardiac rhythm is not performed on a routine basis. Without requiring any extra sensor, this study proposes a method for extracting a cardiac signal from the built-in extracorporeal venous pressure sensor of the hemodialysis machine. The extraction is challenged by the fact that the cardiac component is much weaker than the pressure component caused by the peristaltic blood pump. To further complicate the extraction problem, the cardiac component is difficult to separate when the pump and heart rates coincide. The proposed method estimates a cardiac signal by subtracting an iteratively refined blood pump model signal from the signal measured at the extracorporeal venous pressure sensor. The method was developed based on simulated pressure signals, and evaluated on clinical pressure signals acquired during hemodialysis treatment. The heart rate estimated from the clinical pressure signal was compared to that derived from a photoplethysmographic (PPG) reference signal, resulting in a difference of  $0.07 \pm 0.84$  beats per minute. The accuracy of the heartbeat occurrence times was studied for different strengths of the cardiac component, using both clinical and simulated signals. The results suggest that the accuracy is sufficient for analysis of heart rate and certain arrhythmias.

---

©2015 IEEE. Reprinted, with permission, from  
Mattias Holmer, Frida Sandberg, Kristian Solem, Eglė Grigonytė, Bo Olde, Leif Sörnmo,  
“Extracting a Cardiac Signal From the Extracorporeal Pressure Sensors of a Hemodialysis Machine,”  
in *IEEE Transactions on Biomedical Engineering*, vol. 62, no. 5, pp. 1305–1315, May 2015.



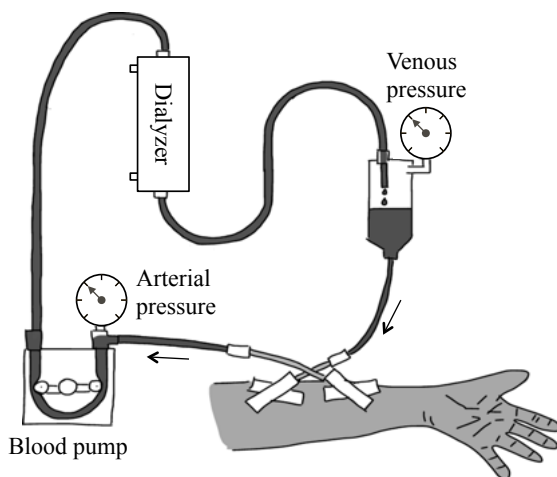
# 1 Introduction

Continuous monitoring of vital physiological information such as heart rate and blood pressure can improve the outcome of hemodialysis treatment. However, monitoring requires the use of additional sensors which increases both patient discomfort and clinical staff workload. As a result, physiological parameters are not monitored on a routine basis during hemodialysis. It is therefore highly desirable to develop novel techniques which take advantage of the built-in extracorporeal pressure sensors so that a cardiac signal can be extracted.

Cardiac monitoring is of special significance since cardiovascular diseases cause about 50% of all deaths in renal patients [1]—a much higher percentage than in the general population. Sudden cardiac death, ischemic heart disease, and heart failure are the most common causes of mortality. It has been established that ectopic beats and certain arrhythmias are more common during hemodialysis treatment than after, especially during the last hour of the treatment [2]. Monitoring of such intradialytic cardiac events is essential for improving patient management and may be used for modifying the treatment to reduce risk and consequences of the cardiac diseases [3, 4]. Although the electrocardiogram (ECG) is sometimes recorded for research purposes during hemodialysis, it has not become part of clinical routine due to the inconvenience of attaching and wearing electrodes. As a result, information on heart rate is not continuously presented to the clinical staff.

The pressure wave initiated by a heartbeat propagates through the vascular system of the body and enters the extracorporeal blood circuit of the hemodialysis machine, where it may be measured by pressure sensors connected to the arterial line (where blood leaves the patient) and the venous line (where blood enters the patient). A peristaltic blood pump, located between the pressure sensors, generates the desired blood flow rate, see Fig. 1. The pump occludes the blood line which effectively breaks the propagation of all pressure waves between the arterial and venous sides of the extracorporeal blood circuit. The pump may thus serve as a definition of the border between the two sides. The blood pump is associated with strong periodic pressure waves in the blood circuit, whose amplitude is considerably larger than that of the waves caused by the heart. The amplitude of the pump pressure waves, being around 30 mmHg peak-to-peak, can be up to 100 times larger than the amplitude of the cardiac waves, see Fig. 2; in fact, the amplitude of the harmonics of the blood pump rate may even exceed the amplitude of the cardiac component.

A major complication when analyzing the pressure signal is that the hemodialysis machine may employ a blood pump rate which coincides with the prevailing heart rate. The rotor of the peristaltic pump contains two rollers and, accordingly, one revolution of the rotor gives rise to two pressure waves, with a fundamental rate which is twice the rotational speed. Due to rotor asymmetry, the resulting two waves are

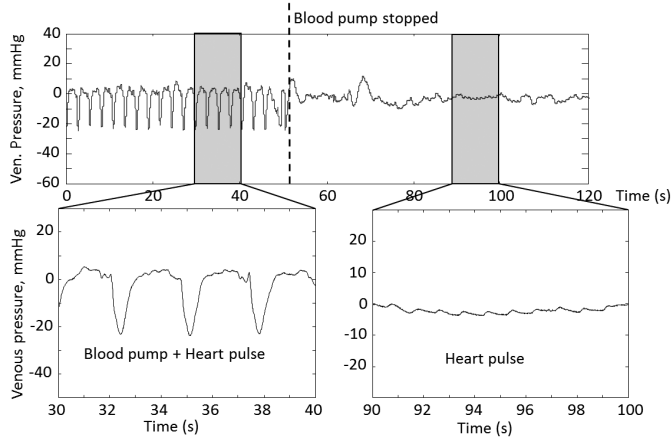


**Figure 1:** The extracorporeal blood circuit of a hemodialysis machine with venous and arterial pressure sensors and a peristaltic blood pump.

not identical in morphology and, consequently, half the fundamental frequency is also present in the blood pump component. A typical blood pump setting is 400 ml/min which corresponds to a rate of 89 beats per minute (bpm)—a pump rate that evidently can coincide with the prevailing heart rate, thus creating a challenging signal separation problem.

The Cardiac signal extracted from the pressure sensors is well-suited for determining heart rate, but it could also be useful for basic arrhythmia analysis including detection of premature ventricular beats (PVBs) and atrial fibrillation [5, 6, 7]. When the aim is to perform more advanced arrhythmia analysis requiring morphologic information on atrial and ventricular waveforms, the pressure signal is no longer well-suited as a surrogate signal for the ECG.

To date, the problem of extracting cardiac signal from the extracorporeal pressure sensors has received very little attention in the scientific literature. In two conference papers, Moissl et al. proposed different approaches to the estimation of heart rate from the arterial pressure sensor [8, 9]. The heart rate was determined from the location of a spectral peak, but the actual heartbeat occurrence times were not determined. After abandoning linear filtering as a means for removing the influence of the dominant blood pump signal, Moissl et al. explored a technique in which the signal for removal was modeled by a truncated Fourier series. None of the two studies offer much detail on methodology, and performance is evaluated through examples only. The problem of extracting a cardiac signal was first addressed within the realm of patents [10, 11] and indirectly when addressing the problem of venous needle dislodgement [12, 13];



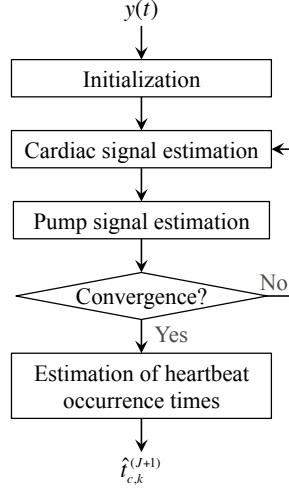
**Figure 2:** The venous blood pressure signal acquired during hemodialysis treatment when the blood pump has been temporarily stopped at time 50 s (upper panel). Prior to stopping, the pump component dominates since the cardiac component has a much lower amplitude (lower left panel). After stopping, the cardiac component is clearly visible (lower right panel).

however, no performance evaluation was part of the patents.

In this paper, we propose a novel method for the extraction of the cardiac component through subtraction of an iteratively refined blood pump signal from the extracorporeal pressure signal (Sec. 2). The venous pressure is analyzed since the venous sensor is the most commonly used in the clinic (the arterial sensor is not always connected), but also since the extraction of a cardiac signal has the potential to improve the monitoring of venous needle dislodgement. The performance of the method is studied for both clinical data recorded during hemodialysis treatment (Sec. 3) and simulated signals (Sec. 4). Estimation of heart rate is the primary application of interest, the accuracy evaluated by comparing the pressure-based estimate to that obtained from the photoplethysmographic (PPG) signal (Sec. 5). The accuracy of the estimated heartbeat occurrence times is also studied, with special emphasis placed on the following two aspects: coinciding pump and heart rates, and low amplitude ratio of the cardiac to blood pump components (Sec. 6).

## 2 Alternating, Iterative Estimation of Cardiac Rhythm

The main idea behind the method is to estimate the cardiac signal by subtracting an iteratively refined blood pump signal from the signal measured at the extracorporeal



**Figure 3:** Flowchart of the proposed method involving iterative estimation of the blood pump signal and the cardiac signal. Please see the text for definition of notations.

venous pressure sensor, i.e., the observed signal  $y(t)$ , see Fig 3. In each iteration, the heartbeat occurrence times are estimated, using a least squares error criterion, so that the interbeat intervals (“RR intervals”) can be determined. The procedure *alternates* between estimation of the pump component and estimation of the cardiac component until the difference in the occurrence time estimates from one iteration to next is sufficiently small.

The *pump profile*  $\bar{p}(t)$  and the *cardiac profile*  $\bar{c}(t)$  are important concepts of the method:  $\bar{p}(t)$  characterizes the pump-induced pressure wave during one complete revolution, i.e.,  $360^\circ$ , of the blood pump, whereas  $\bar{c}(t)$  characterizes the heart-induced pressure wave during one cardiac cycle. The two profiles result from ensemble averaging of successive cycles once subjected to normalization in time with respect to their respective lengths. For both the heart and the blood pump, the *model signals*  $\tilde{c}(t)$  and  $\tilde{p}(t)$  are created by concatenating suitably time-scaled profiles; the model signals have the same length as the observed signal. The resulting model signals are then subtracted from the observed signal to produce *signal estimates* of the cardiac and the blood pump components, denoted  $\hat{c}(t)$  and  $\hat{p}(t)$ , respectively. Thus, each iteration results in updates of the two profiles, the two model signals, and the two signal estimates.

## 2.1 Initialization

Initially, the pump period length  $T_p$  is assumed to be fixed, and thus the occurrence time of the  $k$ :th revolution is given by

$$\hat{t}_{p,k}^{(0)} = kT_p, \quad k = 0, \dots, N_p, \quad (1)$$

where the superscript denotes iteration index and  $N_p$  the number of pump revolutions in a data segment. For simplicity, the first revolution is assumed to occur at  $\hat{t}_{p,0}^{(0)} = 0$ . The number of pump revolutions is determined from the zero crossings of the observed signal  $y(t)$ .

The initial pump profile  $\bar{p}^{(0)}(t)$  is obtained by averaging all  $N_p$  revolutions,

$$\bar{p}^{(0)}(t) = \frac{1}{N_p} \sum_{k=0}^{N_p-1} y(t + kT_p), \quad 0 \leq t < T_p. \quad (2)$$

The period length  $T_p$  in (1) is determined by fitting, in the least squares error (LSE) sense, the pump model signal  $\tilde{p}^{(0)}(t)$  to  $y(t)$  with all  $N_p$  revolutions included in the minimization;  $\tilde{p}^{(0)}(t)$  results from periodic extension of the pump profile  $\bar{p}^{(0)}(t)$ , i.e.,

$$\tilde{p}^{(0)}(t + kT_p) = \bar{p}^{(0)}(t), \quad 0 \leq t < T_p. \quad (3)$$

The initial estimate of the cardiac signal  $\hat{c}^{(0)}(t)$  is obtained by subtracting the pump model signal  $\tilde{p}^{(0)}(t)$ , obtained in (3), from  $y(t)$ ,

$$\hat{c}^{(0)}(t) = y(t) - \tilde{p}^{(0)}(t). \quad (4)$$

The number of cardiac cycles  $N_c^{(0)}$  and the corresponding occurrence times  $t_{c,k}^{(0)}$ ,  $k = 0, \dots, N_c^{(0)}$ , are estimated from the zero crossings of a lowpass filtered version of  $\hat{c}^{(0)}(t)$  (cut-off frequency  $F_{LP}$ ); filtering is introduced since it reduces the influence of pump-related residuals. It should be noted that it is much more challenging to estimate  $N_c$  than  $N_p$  from the zero crossings, not only because the cardiac component is much smaller in amplitude, but also because pump-related residuals are present in  $\hat{c}^{(0)}(t)$ . It should be noted that  $N_p$  is held fixed once estimated during initialization, whereas  $N_c$  is subject to iterative estimation.

The initial cardiac profile  $\bar{c}^{(0)}(t)$  is obtained by normalizing the cardiac cycle length with the scale factor  $a_{c,k}^{(0)}$  prior to ensemble averaging,

$$\bar{c}^{(0)}(t) = \frac{1}{\hat{N}_c^{(0)}} \sum_{k=0}^{\hat{N}_c^{(0)}-1} \hat{c}^{(0)}(\hat{a}_{c,k}^{(0)}t + \hat{t}_{c,k}^{(0)}), \quad 0 \leq t < \bar{T}_c^{(0)}, \quad (5)$$

where the mean cardiac cycle length is given by

$$\bar{T}_c^{(0)} = \frac{\hat{t}_{c,\hat{N}_c^{(0)}}^{(0)} - \hat{t}_{c,0}^{(0)}}{\hat{N}_c^{(0)}}. \quad (6)$$

The series of interbeat intervals is given by the difference of successive estimates of the occurrence times,

$$\hat{T}_{c,k}^{(0)} = \hat{t}_{c,k+1}^{(0)} - \hat{t}_{c,k}^{(0)}. \quad (7)$$

The scale factor is estimated by

$$\hat{a}_{c,k}^{(0)} = \frac{\hat{T}_{c,k}^{(0)}}{\bar{T}_c^{(0)}}, \quad (8)$$

for  $k = 0, \dots, \hat{N}_c^{(0)} - 1$ .

## 2.2 Iterative cardiac signal estimation

The iterative estimation procedure, initiated by setting the iteration index  $j$  to 0, scales the cardiac profile  $\bar{c}^{(j)}(t)$  in time so that it best fits, in the LSE sense, each of the cycles in a lowpass filtered version of the cardiac signal  $\hat{c}^{(j)}(t)$  (cut-off frequency  $F_{LP}$ ). The scaling variable of the  $k$ :th cardiac cycle is denoted  $T_{c,k}^{(j+1)}$ , and represents cycle length. In mathematical terms, the optimization is defined by

$$\hat{T}_{c,k}^{(j+1)} = \arg \min_{\eta_{c,0}\bar{T}_c^{(j)} < T_{c,k}^{(j+1)} < \eta_{c,1}\bar{T}_c^{(j)}} \mathcal{E}_c \left( T_{c,k}^{(j+1)} \right), \quad (9)$$

where

$$\mathcal{E}_c \left( T_{c,k}^{(j+1)} \right) = \frac{1}{T_{c,k}^{(j+1)}} \int_0^{T_{c,k}^{(j+1)}} \left( \hat{c}^{(j)} \left( t + \hat{t}_{c,k}^{(j+1)} \right) - \bar{c}^{(j)} \left( \frac{\bar{T}_c^{(j)}}{T_{c,k}^{(j+1)}} \cdot t \right) \right)^2 dt, \quad (10)$$

and is performed sequentially by incrementing  $k$ , i.e., for successive cardiac cycles. The lower and upper search limits  $\eta_{c,0}$  and  $\eta_{c,1}$  in (9) may be chosen such that both

normal sinus beats and PVBs can be detected. The occurrence time  $\hat{t}_{c,k}^{(j+1)}$  of the  $k$ :th cardiac cycle in  $\hat{c}^{(j)}(t)$  in (10) equals the sum of all preceding cycle lengths,

$$\hat{t}_{c,k}^{(j+1)} = \sum_{l=0}^{k-1} \hat{T}_{c,l}^{(j+1)} + \hat{t}_{c,0}^{(j+1)}, \quad k = 1, \dots, \hat{N}_c^{(j+1)} - 1. \quad (11)$$

Updated versions of the cardiac profile  $\bar{c}^{(j+1)}(t)$  and the mean cardiac cycle length  $\bar{T}_c^{(j+1)}$  are computed analogously to (5) and (6), respectively. From knowledge of  $\bar{c}^{(j+1)}(t)$  and  $\hat{t}_{c,k}^{(j+1)}$ , the cardiac model signal  $\tilde{c}^{(j+1)}(t)$  is produced by concatenation until the entire observation interval has been covered,

$$\tilde{c}^{(j+1)}(\hat{a}_{c,k}^{(j+1)}t + \hat{t}_{c,k}^{(j+1)}) = \bar{c}^{(j+1)}(t), \quad 0 \leq t < \bar{T}_c, \quad (12)$$

for  $k = 0, \dots, \hat{N}_c^{(j+1)} - 1$ . The number of cardiac cycles  $\hat{N}_c^{(j+1)}$  is updated by determining the maximum number of complete cardiac cycles that fits within the observation interval.

An iteration of the cardiac signal estimation finishes by subtracting the cardiac model signal from the observed signal,

$$\hat{p}^{(j+1)}(t) = y(t) - \tilde{c}^{(j+1)}(t), \quad (13)$$

so that a new estimate of the pump signal is obtained.

## 2.3 Iterative pump signal estimation

The initial assumption of a fixed period length  $T_p$ , cf. (1), is relaxed so that each pump revolution has its own individual period length  $T_{p,k}$ , thereby accounting for the fact that the pump speed varies from one revolution to the next. The optimization in (9), producing an estimate of  $T_{c,k}$ , is also employed for estimating  $T_{p,k}$ , except that the search interval is instead defined by  $\bar{T}_p$  and the width parameter  $\eta_p$ , i.e.,

$$\hat{T}_{p,k}^{(j+1)} = \arg \min_{(1-\eta_p)\bar{T}_p^{(j)} < T_{p,k}^{(j+1)} < (1+\eta_p)\bar{T}_p^{(j)}} \mathcal{E}_p \left( T_{p,k}^{(j+1)} \right). \quad (14)$$

The error  $\mathcal{E}_p$  is defined analogously to the error  $\mathcal{E}_c$  in (10), except that the integrand is replaced by its second derivative for the purpose of de-emphasizing rapid changes in the cardiac signal estimate. Another difference is that the error is successively minimized for half revolutions, i.e.,  $180^\circ$ , instead of full revolutions, so that a better fit to the observed signal can be achieved. These two differences were found to decrease the

number of iterations needed as well as to reduce the transient pump signal residuals in the cardiac signal estimate.

In analogy with (5), the pump profile is updated by scaling each pump revolution in time using  $a_{p,k}^{(j+1)}$ , defined analogously to (8), so that its length is normalized prior to averaging. In this case, averaging is performed on the observed signal  $y(t)$  to ensure stability,

$$\bar{p}^{(j+1)}(t) = \frac{1}{N_p} \sum_{k=0}^{N_p-1} y(\hat{a}_{p,k}^{(j+1)}t + \hat{t}_{p,k}^{(j+1)}), \quad 0 \leq t < \hat{T}_p, \quad (15)$$

thereby avoiding that residuals of the cardiac component are gradually intruding into the pump model signal as the iterative procedure progresses. In analogy with (12), the pump model signal  $\tilde{p}^{(j+1)}(t)$  is produced by concatenation until the entire observation interval is covered,

$$\tilde{p}^{(j+1)}(\hat{a}_{p,k}^{(j+1)}t + \hat{t}_{p,k}^{(j+1)}) = \bar{p}^{(j+1)}(t), \quad 0 \leq t < \hat{T}_p, \quad (16)$$

for  $k = 0, \dots, \hat{N}_p - 1$ . Next, the cardiac signal estimate is updated by

$$\hat{c}^{(j+1)}(t) = y(t) - \tilde{p}^{(j+1)}(t), \quad (17)$$

which, in turn, is used to update the cardiac profile as previously described.

The alternating, iterative estimation procedure is considered to have converged when the following criterion is fulfilled:

$$\max_k |\hat{t}_{p,k}^{(j+1)} - \hat{t}_{p,k}^{(j)}| < \delta, \quad (18)$$

where  $\delta$  denotes convergence tolerance. As long as (17) remains unfulfilled, the iteration index  $j$  is incremented and the procedure performs the processing steps described in Sec. 2.2, and so on. However, if convergence is not reached within  $L$  iterations, the procedure is terminated and the estimates of the  $L$ :th iteration are used. It should be noted that convergence is tested on  $\hat{t}_{p,k}$ , rather than on  $\hat{t}_{c,k}$ , since the pump signal is much more dominant.

The computational demands of the alternating, iterative estimation procedure are relatively modest, making it possible to implement the method for operation in real-time.

## 2.4 Lowpass filter cut-off frequency adaptation

The selection of cut-off frequency  $F_{LP}$  for the lowpass filter, introduced to remove high frequency pump residuals in  $\hat{c}(t)$ , was found to be important for reducing the error in heart rate estimation. Preliminary results from simulated data showed that a heart rate dependent  $F_{LP}$  leads to fewer missed and falsely detected beats, and therefore a simple dependence was introduced in which  $F_{LP}$  depends linearly on the heart rate of the preceding 1-min segment.

## 2.5 Final estimation of heartbeat occurrence times

Following convergence, the accuracy of  $\hat{t}_{c,k}^{(J+1)}$  is improved by replacing it with the time instant of the mid-amplitude in each heartbeat of the lowpass filtered cardiac signal  $\hat{c}^{(J)}(t)$ . This definition is identical to the one used in the analysis of PPG signals [14]. The resulting series of occurrence times serves as the basis for the heart rate computation and certain types of rhythm analysis.

The notations used in the method are summarized in Table 1.

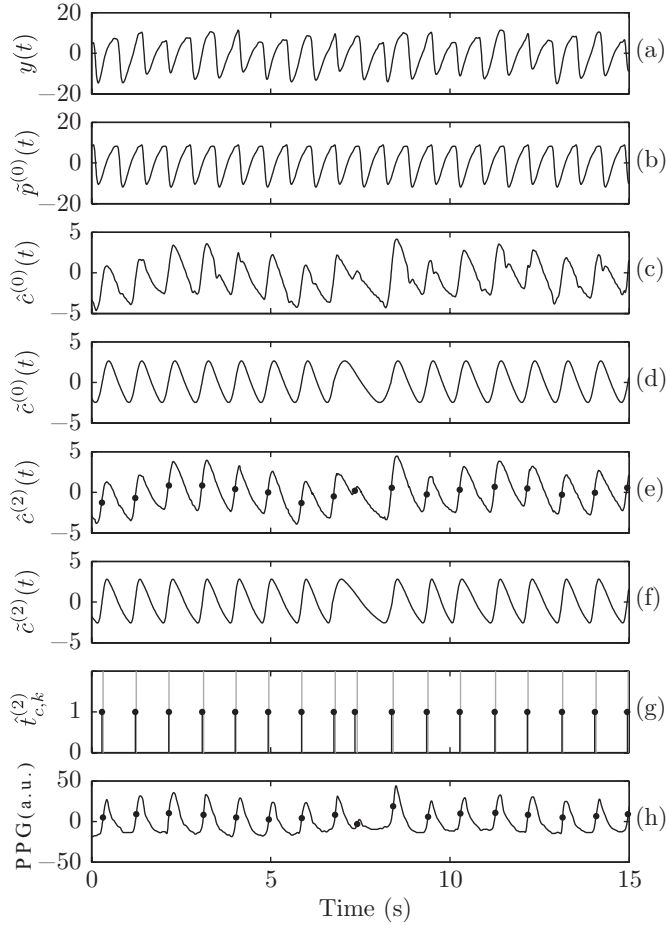
**Table 1:** Frequent Notations in the Present Method.

| Variable name        | Description                                    |
|----------------------|------------------------------------------------|
| $\bar{c}^{(j)}(t)$   | Cardiac profile                                |
| $\tilde{c}^{(j)}(t)$ | Cardiac model signal                           |
| $\hat{c}^{(j)}(t)$   | Cardiac signal estimate                        |
| $F_{LP}$             | Lowpass cut-off frequency                      |
| $j$                  | Iteration index                                |
| $k$                  | Cardiac/pump cycle index                       |
| $\hat{N}_c^{(j)}$    | Estimated No. cardiac cycles in signal segment |
| $N_p$                | No. pump revolutions in signal segment         |
| $\bar{p}^{(j)}(t)$   | Pump profile                                   |
| $\tilde{p}^{(j)}(t)$ | Pump model signal                              |
| $\hat{p}^{(j)}(t)$   | Pump signal estimate                           |
| $\hat{t}_{c,k}$      | Cardiac cycle occurrence time                  |
| $\hat{t}_{p,k}$      | Pump cycle occurrence time                     |
| $\hat{T}_{c,k}$      | Cardiac cycle duration                         |
| $\hat{T}_{p,k}$      | Pump cycle duration                            |
| $y(t)$               | Observed signal segment                        |

## 2.6 Illustration of method

A clinical venous pressure signal illustrates the alternating iterative estimation procedure in Fig. 4. The observed signal  $y(t)$  in Fig. 4(a) contains pressure waves from both the pump and the heart. Figures 4(b) and (c) display the initial pump model signal  $\tilde{p}^{(0)}(t)$  and the initial estimate of the cardiac signal  $\hat{c}^{(0)}(t)$ , respectively, and (d) the initial cardiac model signal  $\tilde{c}^{(0)}(t)$ .

Figures 4(e) and (f) display the signals when the alternating procedure has converged; in this example, convergence is reached after two iterations. It is noted that  $\hat{c}^{(2)}(t)$  is smoother than  $\hat{c}^{(0)}(t)$  thanks to the use of the second derivative for LSE minimization. The estimated occurrence times  $\hat{t}_{c,k}^{(2)}$  are displayed in Fig. 4(g) together with the reference occurrence times determined from the PPG signal in Fig. 4(h). A good agreement between the two series of occurrence times is observed. The PVB occurring at about 8 s from the onset of the signal, which can be identified in the cardiac signal estimate  $\hat{c}^{(2)}(t)$ , cf. Fig. 4(e), is accurately detected.



**Figure 4:** Illustration of the alternating, iterative procedure for estimating the heartbeat occurrence times, using clinical data. (a) The venous pressure signal  $y(t)$ , (b) the initial pump model signal  $\tilde{p}^{(0)}(t)$ , (c) the initial estimate of the cardiac signal  $\hat{c}^{(0)}(t)$ , (d) the initial cardiac model signal  $\tilde{c}^{(0)}(t)$ , (e) the final estimate of the cardiac signal  $\hat{c}^{(2)}(t)$  with dots indicating the estimated occurrence times, (f) the final cardiac model signal  $\tilde{c}^{(2)}(t)$ , (g) the estimated occurrence times (black line) and the reference occurrence times (grey line), and (h) the PPG signal with the reference occurrence times marked with dots. Note that the vertical scales in (a)–(f) all have mmHg as unit.

### 3 Clinical Data

Clinical data were acquired at Skåne University Hospital, Lund, Sweden, in a study approved by the local ethical review board. The data were analyzed for the purpose of comparing the performance of the proposed method to PPG-derived information. The PPG signal is known to be proportional to blood volume changes that result from pressure waves originating from the heart [15]—a property which makes the PPG signal well-suited as a reference when the estimated cardiac pressure signal is assessed.

#### 3.1 Study setup

Eight patients were included in the study, all suffering from chronic renal failure (two of these patients were previously analyzed in [16] using a preliminary version of the present method). Each patient contributed with one hemodialysis treatment, except one patient who contributed with two, and thus a total of nine treatments were included. The patients were treated with hemodialysis at least thrice a week, and at least for three months before the study started. Treatment duration, ranging from 4 to 5 h, complied with the prescriptions given by the responsible physician and followed clinical routine. Patients treated with hemodiafiltration were excluded, as were patients participating in other, interfering studies. Four patients had a history of one or more heart complications. An arteriovenous fistula was used as vascular access in all patients, except in one who had a graft. All patients agreed to participate in the study by signing an informed consent.

The blood pump was stopped for a 1-min period at treatment onset so that the cardiac signal amplitude could be determined, cf. Fig. 2.

#### 3.2 Equipment

All patients were treated with a Gambro AK 200 hemodialysis machine. In order to ensure full compliance with existing safety regulations, as well as to avoid the time-consuming work associated with a software update and accompanying verification and validation, the built-in pressure sensors were not used. Instead, an external device was used with dedicated pressure sensors which were identical to the built-in ones. Hence, the results presented below can still be viewed as deriving from data acquired from the built-in sensors.

Custom-made tubes were used for the external device to access the pressure inside the blood line at the venous side. A transducer protector was connected between the new tube and the venous drip chamber to protect the patient by securing the sterility of the blood line. During treatment the disposable blood circuit was mainly filled

with blood, however, certain parts, like the venous drip chamber, contain air. Since the total air volume affects the damping of the pressure signal, it was kept low by increasing the blood level in the drip chamber, clamping off unused gas tubes, and by selecting small dimensions of the custom made tubes.

A sensor clip of a pulse oximeter (LifeSense®) was attached to a finger of the patient for PPG measurements. Both the resulting PPG signal and the pressure signal were processed at a sampling rate of 100 Hz. The reference occurrence times are given by the time instant for the mid-amplitude point of each heartbeat [14], cf. Sec. 2.5.

### 3.3 Dataset

Twenty consecutive 1-min segments from each treatment were selected for performance evaluation. The segments were located halfway into the treatment at a time when the blood flow rate remained constant during the entire 20-min interval.

Table 2 presents heart rate, pump rate, and blood flow computed as averages over the 20-min interval. The pump rate was given by the harmonic closest to the heart rate, where the harmonic was determined from the pump model signal using the above-described method. Table 2 also presents the ratio between the peak-to-peak amplitudes of the cardiac and pump signals. The cardiac signal amplitude was determined when the pump was stopped, whereas the pump signal amplitude was determined during the 20-min interval from the pump model signal  $\tilde{p}(t)$ . Two treatments (#7 and 8) were excluded from further analysis since the cardiac amplitude was judged as too weak relative the pump amplitude, falling below a ratio of 2%.

**Table 2:** Signal Characteristics.

| Treatment No. | Heart rate bpm | Pump rate bpm | Blood flow ml/min | Amplitude ratio Heart/Pump, % |
|---------------|----------------|---------------|-------------------|-------------------------------|
| 1             | 62.8           | 44.6          | 400               | 41.3                          |
| 2             | 75.9           | 89.1          | 400               | 6.1                           |
| 3             | 51.3           | 41.8          | 370               | 3.6                           |
| 4             | 73.8           | 71.3          | 320               | 20.0                          |
| 5             | 76.8           | 89.1          | 400               | 8.8                           |
| 6             | 59.6           | 44.6          | 400               | 24.7                          |
| (7            | 67.3           | 84.6          | 380               | 0.8)                          |
| (8            | 100.3          | 78.0          | 350               | 1.2)                          |
| 9             | 60.2           | 55.7          | 500               | 2.1                           |
| Average       | 69.8           | —             | 400*              | 12.1                          |

The two treatments in brackets were excluded due to poor signal-to-noise ratio. The asterisk signifies that the median was computed.

## 4 Simulation of Pressure Signals

Simulated data is useful when studying performance since blood flow rate and heart rate can be exactly controlled, as can the amplitude ratio between the pump and cardiac components. In the present study, simulated signals were used for developing the method, whereas clinical and simulated data were used for performance evaluation.

### 4.1 Blood pump pressure signal and noise

The starting point for producing the simulated blood pump pressure signal is a pump profile determined from data acquired in a laboratory setting. Acquisition was accomplished with the above-mentioned equipment, cf. Sec. 3.2, but without any patient involved and thus no pressure caused by the heart or any other physiological activity is present; the resulting signal is denoted  $p_{s,0}(t)$ . Heparinized bovine blood was used as fluid medium in the laboratory setting in order to create conditions of the fluid media similar to the ones during patient treatment, e.g., with respect to viscosity. At a blood flow rate of 400 ml/min, the pump profile  $\bar{p}_s(t)$  was estimated by averaging all periods during the analyzed interval.

Next, modeling of amplitude variability and noise is considered. A pump model signal  $\tilde{p}_s(t)$  was produced by concatenating  $\bar{p}_s(t)$  once its period length had been scaled so that the occurrence times of  $p_{s,0}(t)$  also applied to  $\tilde{p}_s(t)$ , cf. (15). System

identification was performed using an autoregressive moving average model with exogenous input, i.e., ARMAX( $d_a, d_b, d_c$ ), with  $p_{s,0}(t)$  as model input and  $\tilde{p}_s(t)$  as exogenous input [17]. The model order parameters  $d_a, d_b$ , and  $d_c$  were selected to account for typical pressure variations.

Finally, a signal was produced by concatenating  $\bar{p}_s(t)$  using random period lengths for time scaling. The lengths were defined by uncorrelated, Gaussian variables whose mean and standard deviation were determined from the lab measurements. The resulting signal was then filtered with the identified ARMAX model to produce the simulated pressure signal  $p_s(t)$ .

## 4.2 Cardiac pressure signal

The cardiac signal was simulated by employing a model which involves frequency modulation (FM) with the fundamental frequency  $F_0$ , corresponding to heart rate, and  $L - 1$  harmonics,

$$c_s(t) = \sum_{l=1}^L \alpha_l \cos \left( 2\pi l F_0 t + 2\pi l F_\Delta \int_0^t m(\tau) d\tau + \phi_l \right), \quad (19)$$

where  $\alpha_l$  denotes the weight of each sinusoid,  $F_\Delta$  the frequency deviation given by the ratio  $F_0/m_{\max}$ ,  $m(t)$  a function that models heart rate variability, and  $m_{\max}$  the maximum value of the integral of  $m(t)$ . The phase  $\phi_l$  defines, together with  $\alpha_l$ , the shape of  $c_s(t)$ . The model in (19) is inspired by the well-known integral pulse frequency modulation (IPFM) event series model [18], however, the output signal  $c_s(t)$  is instead a sinusoid with harmonics which models the cardiac component of the pressure signal.

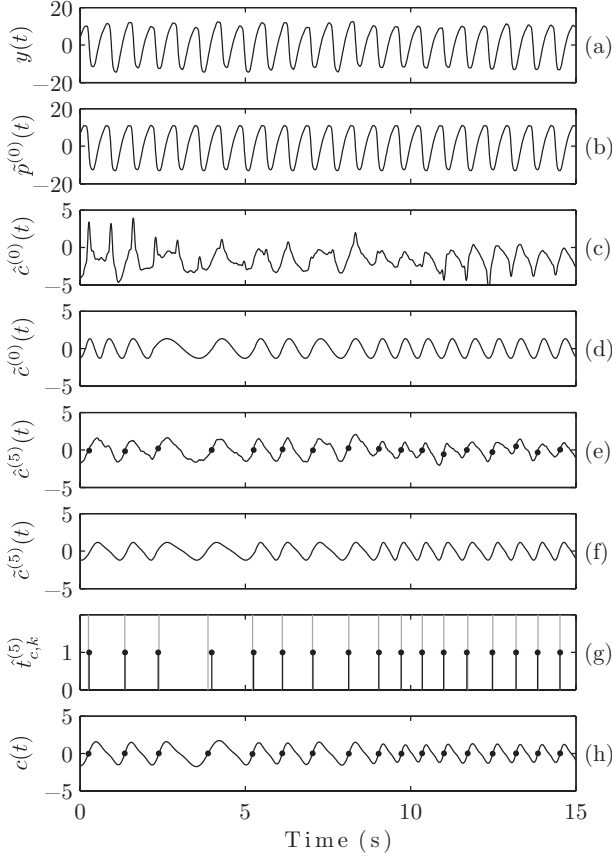
The function  $m(t)$  was modeled by colored Gaussian noise produced by an autoregressive model, whose parameters were originally determined from a subject at rest and used for the IPFM model [19]. Thus, the power spectrum of heart rate variability in the cardiac pressure signal  $c_s(t)$  resembles that produced by the IPFM model.

The observed signal  $y(t)$  is obtained by adding the cardiac signal  $c_s(t)$  and the pressure signal  $p_s(t)$ .

## 4.3 Illustration of the method

The performance is illustrated on simulated data in Fig. 5, containing a rather drastic increase in heart rate. In contrast to Fig. 4, where the PPG served as reference, the simulated (true) cardiac signal here serves as reference. From Fig. 5(c), it is evident that  $\hat{c}^{(0)}(t)$  contains pump-related residuals which obscure the cardiac activity; however,

after five iterations, the agreement between  $c(t)$  and  $\hat{c}^{(5)}(t)$  is much better. It is noted that the model signal  $\tilde{c}^{(5)}(t)$  does not account for the amplitude variation visible in  $c(t)$  and  $\hat{c}^{(5)}(t)$ .



**Figure 5:** Illustration of the alternating, iterative procedure for estimating the heartbeat occurrence times on simulated data. (a) The venous pressure signal  $y(t)$  containing a cardiac component which is 12% of the amplitude of the pump component, (b) the initial pump model signal  $\tilde{p}^{(0)}(t)$ , (c) the initial estimate of the cardiac signal  $\hat{c}^{(0)}(t)$ , (d) the initial cardiac model signal  $\tilde{c}^{(0)}(t)$ , (e) the final estimate of the cardiac signal  $\hat{c}^{(5)}(t)$  with dots indicating the estimated occurrence times, (f) the final cardiac model signal  $\tilde{c}^{(5)}(t)$ , (g) the estimated occurrence times (black lines) and the simulated (true) occurrence times (grey line), and (h) the simulated (true) cardiac signal with the reference occurrence times marked with dots. Note that the vertical scale in (a)–(f) and (h) has mmHg as unit.

## 5 Performance Evaluation

The standard deviation  $\sigma_\epsilon$  of the error between estimated and reference occurrence times, i.e.,

$$\epsilon_{c,k} = \hat{t}_{c,k}^{(J+1)} - t_{c,k}, \quad (20)$$

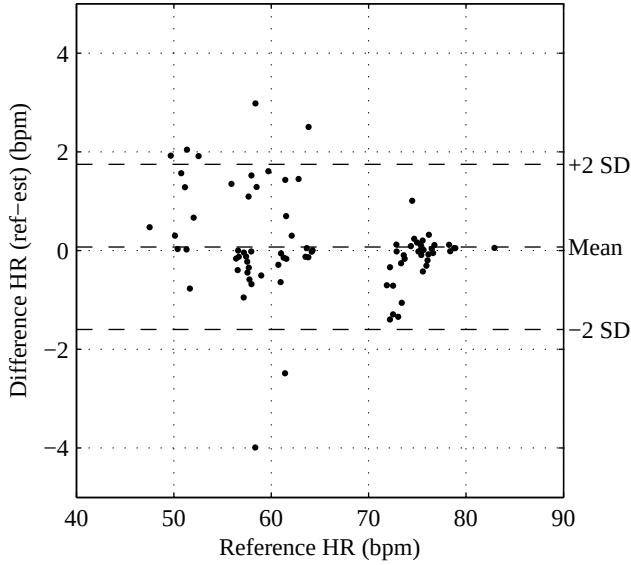
is employed as performance measure. Depending on context, the term “reference” refers either to the occurrence times derived from the PPG or from the simulated data. For the latter type of data, the number of missed beats and the number of falsely detected beats are also considered as performance measures.

The following parameter values are used to produce the simulated signals:  $d_a = 10$ ,  $d_b = 9$ ,  $d_c = 10$ ,  $L = 2$ ,  $\phi_1 = 0$ ,  $\phi_2 = 0.01$ ,  $\alpha_1 = 1$ ,  $\alpha_2 = 0.25$ . The following parameter values are used to process both clinical and simulated data:  $\eta_{c,0} = 0.5$ ,  $\eta_{c,1} = 1.5$ ,  $\eta_p = 0.05$ ,  $\delta = 0.25$  ms,  $L = 50$ .

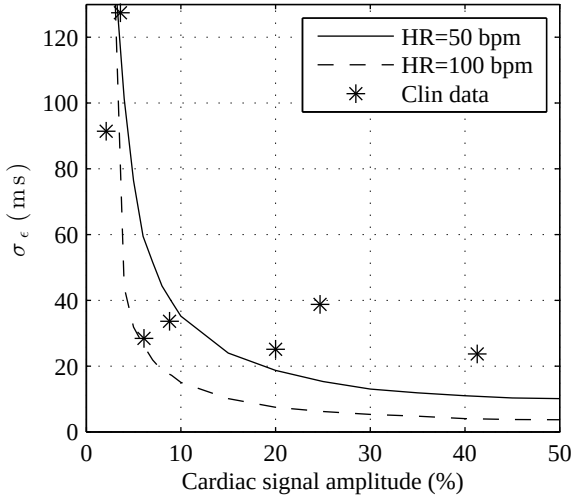
## 6 Results

### 6.1 Clinical Signals

Figure 6 presents the difference between heart rate estimated from the venous pressure signal and from the PPG signal, computed in 1-min segments. The mean difference is 0.07 bpm, with a standard deviation of 0.84 bpm; the clinical significance of this result is further considered in the Discussion. For each of the seven treatments, the standard deviation  $\sigma_\epsilon$  is plotted versus the cardiac signal amplitude determined from the interval when the pump was stopped, see Fig. 7.



**Figure 6:** Plot of the difference in heart rate obtained from the PPG signal and the venous pressure signal.



**Figure 7:** The occurrence time estimation error  $\sigma_\epsilon$  as a function of relative cardiac signal amplitude. The average of  $\sigma_\epsilon$ , computed in 1-min segments, is determined for clinical data, as well as for simulated data. For the latter type of data, the relative cardiac signal amplitude is varied for two different heart rates.

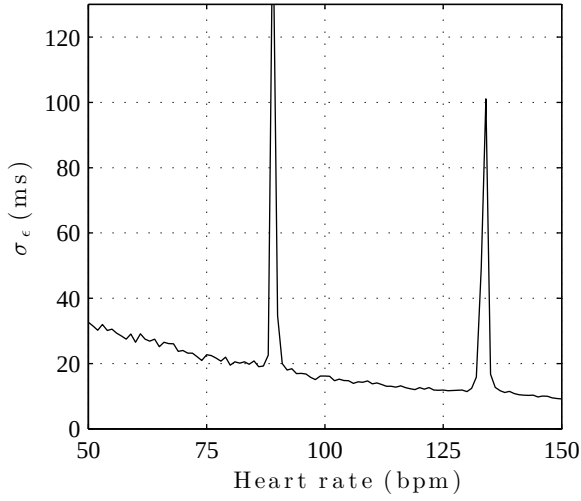
## 6.2 Simulated signals

In addition to the results based on clinical data, Fig. 7 also presents  $\sigma_\epsilon$  as a function of cardiac signal amplitude when the data is simulated. Two different heart rates are studied (50 and 100 bpm). The results show that a higher heart rate is associated with a lower estimation error  $\sigma_\epsilon$ .

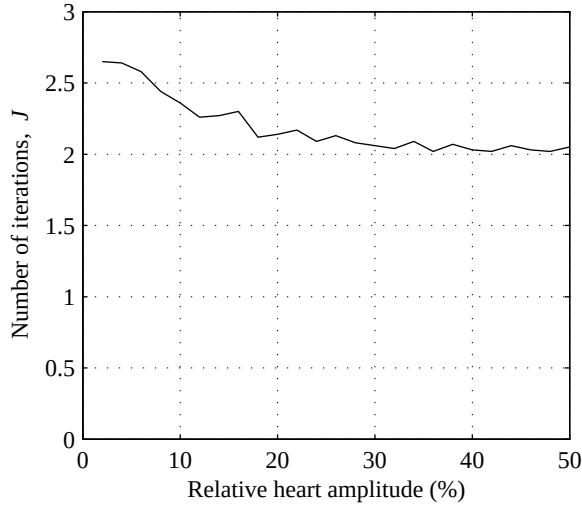
Figure 8 presents  $\sigma_\epsilon$  as a function of heart rate, where the studied heart rates are those typically found in hemodialysis patients. The relative cardiac amplitude is set to 12%, corresponding to the average cardiac amplitude of all treatments given in Table 2. The simulated blood flow was set to 400 ml/min, see Table 2, which corresponds to a pump rate at 44 bpm, a second harmonic at 89 bpm, and a third harmonic at 134 bpm. It is evident from Fig. 8 that performance deteriorates drastically when the heart rate is very close to any of the harmonics of the pump rate; the method is then unable to separate the cardiac and pump components. The better performance observed at higher heart rates is due to that the spectrum of the identified ARMAX model is increasingly attenuated at higher heart rates.

The number of iterations  $J$  required for convergence are presented as a function of relative cardiac signal amplitude, see Fig. 9. For small amplitudes, the number of iterations increases slightly due to that noise is more influential on the initial cardiac signal estimate. The required number of iterations is nonetheless low, and most improvement occurs during the first iteration.

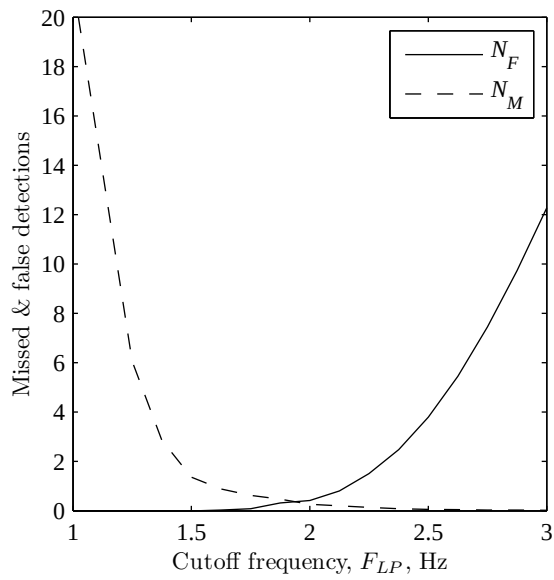
The number of missed beats  $N_M$  and the number of falsely detected beats  $N_F$  are presented as a function of lowpass cut-off frequency, see Fig. 10. The graphs represent the average number of missed and falsely detected beats in 100 1-min intervals. For a heart rate of 80 bpm, the cut-off frequency associated with the lowest number of false and missed beats is about 2 Hz.



**Figure 8:** The occurrence time estimation error  $\sigma_{\epsilon}$  as a function of heart rate. The relative cardiac signal amplitude is set to 12%. The peaks at 89 and 134 bpm are caused by a coinciding pump rate.



**Figure 9:** The average number of iterations  $J$  required to reach convergence, displayed as a function of relative cardiac signal amplitude. The heart rate is set to 60 bpm.



**Figure 10:** The number of missed beats  $N_M$  and falsely detected beats  $N_F$  as a function of lowpass cut-off frequency  $F_{LP}$ . The heart rate is set to 80 bpm and the relative cardiac signal amplitude to 12%.

## 7 Discussion

### 7.1 Clinical relevance

Implementation of cardiac monitoring in a hemodialysis machine may lead to increased patient safety and survival. With the present method, continuous monitoring of cardiac rhythm can be performed during treatment without extra sensors. The primary output of the method is information on heart rate and irregularities in rhythm. The method has also the potential to alarm when the cardiac signal vanishes, probably a sign of cardiac arrest or venous needle dislodgement—this is a topic for future research. When such life-threatening events occur, early detection is crucial so that the clinical staff can make prompt actions to save a patient's life.

The results obtained from clinical data (Fig. 6) show that the heart rate, estimated from the pressure signal in 1-min segments, is close to the heart rate derived from the PPG signal, the difference being  $0.07 \pm 0.84$  bpm. These performance figures suggest that the method is suitable for use in clinical routine.

Table 2 demonstrates that there is considerable patient-to-patient variation in the relative cardiac signal amplitudes, caused by variation in size, shape, and position of the vascular access. We have shown that the amplitude ratio between heart and pump components influences performance, see Fig. 7. All outliers observed in Fig. 6 are from patients with low relative cardiac signal amplitude. In general, the cardiac component amplitude decreases slowly during treatment, due to, e.g., blood pressure, blood viscosity, or sympathetic activity, and thus performance is expected to be slowly reduced during treatment. For the present dataset, the amplitude ratio was essentially constant during the analyzed 20-min segment selected from the second half of the treatments.

When evaluating performance in more precise temporal terms, the occurrence time estimation error  $\sigma_\epsilon$  was found to be 35 ms at a relative cardiac signal amplitude of 10% and a heart rate of 50 bpm (Fig. 7)—an error which becomes increasingly smaller as heart rate increases. For relative cardiac signal amplitudes exceeding 10%, the magnitude of the estimation error suggests that arrhythmia analysis involving the detection of PVBs and atrial fibrillation can be accurately performed, whereas the error is too high to allow spectral analysis of heart rate variability [20]. These results are unfortunately overshadowed by the situation when heart rate is less than  $\pm 2$  bpm from pump rate: a drastic increase in  $\sigma_\epsilon$  is then observed (Fig. 8). To some extent, the situation with similar heart and pump rates can explain the variation in clinical results observed in Fig. 7: since heart rate changes during treatment, it may occasionally coincide with pump rate, with increased  $\sigma_\epsilon$  as a result.

A practical solution to the problem of coinciding pump and heart rates is to automatically adjust the blood flow so that it is as close as possible to the desired flow

rate, but outside a certain margin relative the prevailing heart rate. The rate should also be kept below the access flow rate to avoid recirculation in the blood access, but high enough to ensure that the prescribed dialysis dose can be achieved. The idea to make blood flow dependent on heart rate should be clinically feasible as long as the cardiac signal is strong enough and the selected blood flow does not imply a significant treatment prolongation. If the cardiac signal is lost, the flow rate can be changed or the blood pump can even be stopped temporarily to regain cardiac monitoring.

## 7.2 Methodological aspects

The proposed method bears some resemblance to the well-known Woody method [21, 22], originally developed for latency correction of an ensemble of event-related brain potentials—both methods employ an iterative procedure for parameter estimation. However, to the best of our knowledge, the idea to iteratively estimate time scale parameters from an ensemble of waveforms is novel. Similar to the results reported on the Woody method [18], convergence is typically reached within a few iterations for the pressure signals (Fig. 9).

The assumption of a time-varying pump rate, cf. Sec. 2.3, was founded on data acquired in the laboratory setting, without patient involvement. The data showed that the period length of the pump had a standard deviation of 4.7 ms at a blood flow rate of 400 ml/min. Hence, it was decided that the period length should be subject to estimation as it represents a key factor to achieve good performance. This assumption differs from previous work where the period length was fixed [8, 9]. Indeed, even tiny variations in pump rate can give rise to residuals which worsens the accuracy of heartbeat occurrence times. This property is illustrated by the initial cardiac signal estimate  $\hat{c}^{(0)}(t)$  that rests on the assumption of a fixed period length: it is obvious from Figs. 4(c) and 5(c) that  $\hat{c}^{(0)}(t)$  contains pump-related residuals which are manifested as sharp peaks and edges. These residuals are substantially reduced by the iterative procedure thanks to the estimation of individual period lengths.

Given that PVBs are frequent in hemodialysis patients [23, 24], and occur much more frequently during treatment than after [2], monitoring of PVB rate can have clinical significance [4]. In the present method, PVB detection has not been treated separately, but it is performed in the same way as the detection of any beat, i.e., a beat is detected as long as it is found within the tolerance interval  $[\eta_{c,0}, \eta_{c,1}]$  centered around the expected occurrence times. However, PVB detection probably calls for additional algorithmic structure that builds on the observation that the cardiac profile  $\hat{c}^{(j)}(t)$ , likely to reflect the pressure associated with normal sinus beats, fits less well to a PVB. Consequently, the LSE  $\mathcal{E}_c(\hat{T}_{c,k}^{(j+1)})$  will be considerably larger for PVBs than for sinus beats, suggesting that another tolerance interval should be used or additional

cardiac profiles introduced. The value of additional algorithmic structure remains to be investigated.

The amplitude variation of the blood pump signal was intentionally not taken into account when defining the pump model signal  $\tilde{p}^{(j)}(t)$ . The use of a constant amplitude reduces the risk of a vanishing cardiac component.

### 7.3 Simulation of pressure signals

The error  $\sigma_\epsilon$  was generally lower for simulated data than for clinical data. This finding may be explained by a varying pressure propagation time, either inside the human body or the extracorporeal blood circuit. Since the simulation model was developed for the purpose of testing signal processing algorithms, this property was not taken into account.

Pressure disturbances originating from the fluid side of the hemodialysis machine can occur in the venous pressure measurements. Such disturbances, caused by, e.g., changes in valve positions or the control of the hemodialysis fluid pumps, are transferred from the fluid side to the blood side via the dialyzer. The disturbances have a lower amplitude than the ones originating from the blood pump, and are accounted for by the ARMAX model in the simulator.

### 7.4 Reference signal

It is well-known that heartbeat occurrence times determined from the ECG have better accuracy than those from the PPG, thus making ECG a better choice as reference signal. However, the ECG is less practical for clinical use because of the need to attach many electrodes and the inconvenience with cables that have to be connected throughout treatment. In the present study, the PPG was preferred as reference since just a simple finger clip pulse oximeter is needed which is considered more comfortable to wear. The PPG is known to be proportional to blood volume changes which result from pressure waves originating from the heart [15]. It has a pulse propagation time through the vascular system which is similar to the pressure wave. This property makes the PPG suitable as a reference when assessing the estimated cardiac pressure signal.

Other reasons for using the PPG is that information on blood oxygenation and respiratory rate can be derived, and offers the potential to predict intradialytic hypotension [25]. In some of the studied hemodialysis patients, the finger was less well-perfused which resulted in a weaker PPG signal which, in turn, translated into less accurate heartbeat occurrence times. Hence, the clinical results of the present study are in a few cases influenced by a low signal-to-noise ratio of the reference signal.

## 7.5 Limitations

The small size of the clinical dataset is a limitation of the present study. To fully validate the performance of the proposed method, a larger clinical dataset should be acquired which contains various types of arrhythmia. Performance was studied for only one blood flow rate (400 ml/min), however, other rates should also be studied since the shape of the pump signal is rate-dependent. The assumption that at least one heartbeat is present in the analyzed interval is not always realistic, and therefore additional criteria need to be developed for proper handling of non-cardiac components. The threshold for excluding signals with relative cardiac amplitude below 2%, needs to be further investigated.

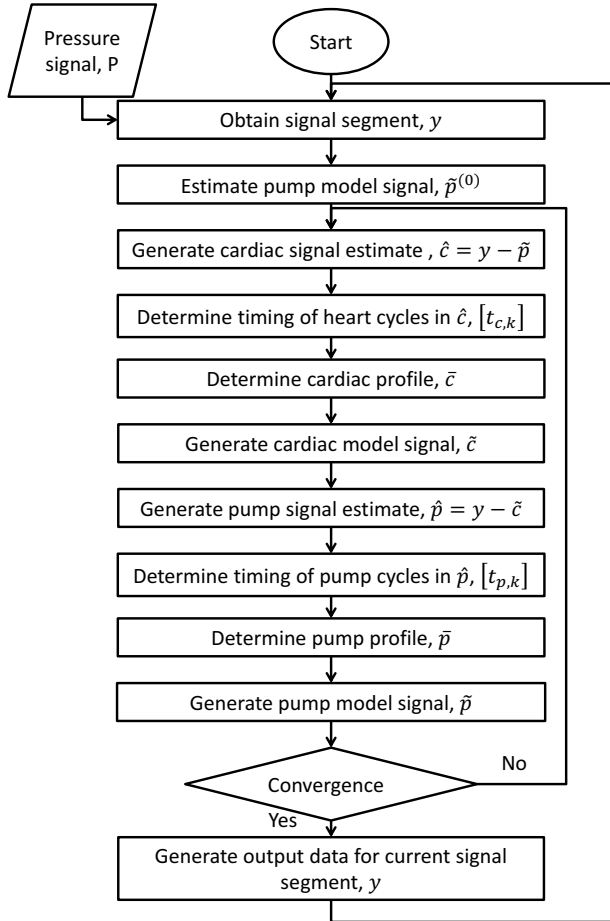
## 8 Conclusions

A novel iterative method has been presented for extraction of the cardiac component from the built-in extracorporeal pressure sensors of the hemodialysis machine. The method is suitable for continuous on-line monitoring of cardiac rhythm, and does not require any external sensor. For both clinical and simulated data, the results show that good agreement can be achieved between heart rates estimated from the pressure signal and from the PPG signal. This study may be viewed as a proof-of-concept for cardiac monitoring during hemodialysis, however, further studies are required before the method can be used in clinical routine.

## Acknowledgments

The authors are grateful to Märten Segelmark, Lena Mattsson, and Sarok Said at “Filialen”, Lund University Hospital, Sweden, and Per Hansson at Gambro Lundia AB, Sweden, for carrying out the clinical investigation. We would also like to thank Johnny Lien for performing laboratory measurements, and Jan Sternby for fruitful discussions, both at Gambro Lundia AB.

## Supplemental Material



**Figure 11:** Flowchart of the method described in Section 2.

## References

- [1] US Renal Data System, "Patient mortality and survival," *Am. J. Kidney Dis.*, vol. 28, pp. 79–92, 1996.
- [2] J. O. Burton, S. Korsheed, B. J. Grundy, and C. W. McIntyre, "Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmia," *Renal Failure*, vol. 30, pp. 701–709, 2008.
- [3] N. M. Selby and C. W. McIntyre, "The acute cardiac effects of dialysis," *Semin. Dial.*, vol. 20, pp. 220–228, 2007.
- [4] L. Sörnmo, F. Sandberg, E. Gil, and K. Solem, "Noninvasive techniques for prevention of intradialytic hypotension," *IEEE Rev. Biomed. Eng.*, vol. 5, pp. 45–59, 2012.
- [5] K. Tateno and L. Glass, "Automatic detection of atrial fibrillation using the coefficient of variation and density histograms of RR and deltaRR intervals," *Med. Biol. Eng. & Comput.*, vol. 39, pp. 664–671, 2001.
- [6] S. Dash, K. Chon, S. Lu, and E. Raeder, "Automatic real time detection of atrial fibrillation," *Ann. Biomed. Eng.*, vol. 37, pp. 1701–1709, 2009.
- [7] C. Huang, S. Ye, H. Chen, D. Li, F. He, and Y. Tu, "A novel method for detection of the transition between atrial fibrillation and sinus rhythm," *IEEE Trans. Biomed. Eng.*, vol. 58, pp. 1113–1119, 2011.
- [8] U. Moissl, P. Wabel, S. Leonhardt, R. Isermann, and M. Krämer, "Continuous observation and analysis of heart rate during hemodialysis treatment," in *Proc. Eur. Med. & Biol. Eng. Conf. (EMBEC)*, vol. 37, pp. S558–S559, 1999.
- [9] U. Moissl, P. Wabel, S. Leonhardt, R. Isermann, and M. Krämer, "Heart rate monitoring during hemodialysis treatment," in *Proc. Eur. Med. & Biol. Eng. Conf. (EMBEC)*, vol. 3, pp. 584–585, 2002.
- [10] H.-D. Polaschegg, "Method for measuring and indicating in liquid systems of medical devices, and device for carrying out this method," Eur. Patent 0 330 761, Sept. 8, 1993.
- [11] T. Hertz, S. Jönsson, and J. Sternby, "Method and arrangement for detecting the condition of a blood vessel access," U.S. Patent 6 090 048, July 18, 2000.

- [12] H. D. Polaschegg, "Venous needle dislodgement: the pitfalls of venous pressure measurement and possible alternatives, a review," *J. Ren. Care*, vol. 36, pp. 41–48, 2010.
- [13] M. Segelmark, S. Mattsson, B. Olde, and K. Solem, "Successful detection of venous needle dislodgement using extracted heart pulses obtained from venous pressure monitoring," in *Proc. Am. Soc. Nephrol. Kidney (JASN)*, vol. 21, p. 241A, 2010.
- [14] J. Lázaro, E. Gil, J. M. Vergara, and P. Laguna, "Pulse rate variability analysis for discrimination of sleep-apnea-related decreases in the amplitude fluctuations of pulse photoplethysmographic signal in children.," *IEEE J. Biomed. Health Inform.*, vol. 18, pp. 240–246, 2014.
- [15] J. Allen, "Photoplethysmography and its application in clinical physiological measurement," *Physiol. Meas.*, vol. 28, pp. R1–R39, 2007.
- [16] M. Holmer, K. Solem, B. Olde, F. Sandberg, and S. Leif, "Determining Heart Activity Present in the Pressure Sensors of a Dialysis Machine," in *Comput. Cardiol.*, vol. 40, pp. 217–220, 2013.
- [17] H. Madsen, *Time Series Analysis*. Chapman & Hall/CRC, 2008.
- [18] L. Sörnmo and P. Laguna, *Bioelectrical Signal Processing in Cardiac and Neurological Applications*. Amsterdam: Elsevier (Academic Press), 2005.
- [19] J. Mateo and P. Laguna, "Improved heart rate variability signal analysis from the beat occurrence times according to the IPFM model," *IEEE Trans. Biomed. Eng.*, vol. 47, pp. 997–1009, 2000.
- [20] M. Merri, D. C. Farden, J. G. Mottley, and E. L. Titlebaum, "Sampling frequency of the electrocardiogram for spectral analysis of the heart rate variability," *IEEE Trans. Biomed. Eng.*, vol. 37, pp. 99–105, 1990.
- [21] C. D. Woody, "Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals," *Med. Biol. Eng.*, vol. 5, pp. 539–553, 1967.
- [22] A. Cabasson and O. Meste, "Time delay estimation: A new insight into the Woody's method," *IEEE Signal Proc. Letters*, vol. 15, pp. 573–576, 2008.
- [23] S. Abe, M. Yoshizawa, N. Nakanishi, T. Yazawa, K. Yokota, M. Honda, and G. Sloman, "Electrocardiographic abnormalities in patients receiving hemodialysis," *Am. Heart J.*, vol. 131, pp. 1137–1144, 1996.

- [24] A. Santoro, E. Mancini, R. Gaggi, S. Cavalcanti, S. Severi, L. Cagnoli, F. Badiali, B. Perrone, G. London, H. Fessy, L. Mercadal, and F. Grandi, "Electrophysiological response to dialysis: the role of dialysate potassium content and profiling," *Contrib. Nephrol.*, vol. 149, pp. 295–305, 2005.
- [25] K. Solem, B. Olde, and L. Sörnmo, "Prediction of intradialytic hypotension using photoplethysmography," *IEEE Trans. Biomed. Eng.*, vol. 57, pp. 1611–1619, 2010.



## *Paper II*



# Cardiac Signal Estimation Based on the Arterial and Venous Pressure Signals of a Hemodialysis machine

## Abstract

Continuous cardiac monitoring is usually not performed during hemodialysis treatment, although a majority of patients with kidney failure suffer from cardiovascular disease. In the present paper, a method is proposed for estimating a cardiac pressure signal by combining the arterial and the venous pressure sensor signals of the hemodialysis machine. The estimation is complicated by the periodic pressure disturbance caused by the peristaltic blood pump, with an amplitude much larger than that of the cardiac pressure signal. Using different techniques for combining the arterial and venous pressure signals, the performance is evaluated and compared to that of an earlier method which made use of the venous pressure only. The heart rate and the heartbeat occurrence times, determined from the estimated cardiac pressure signal, are compared to the corresponding quantities determined from a photoplethysmographic reference signal. Signals from 9 complete hemodialysis treatments were analyzed. For a heartbeat amplitude of 0.5 mmHg, the median absolute deviation between estimated and reference heart rate was 1.3 bpm when using the venous pressure signal only, but dropped to 0.6 bpm when combining the pressure signals. The results show that the proposed method offers superior estimation at low heartbeat amplitudes. Consequently, more patients can be successfully monitored during treatment without the need of extra sensors. The results are preliminary, and need to be verified on a separate dataset.

---

©2016 Institute of Physics and Engineering in Medicine. Reprinted, with permission, from Mattias Holmer, Frida Sandberg, Kristian Solem, Bo Olde, and Leif Sörnmo, "Cardiac Signal Estimation Based on the Arterial and Venous Pressure Signals of a Hemodialysis machine," in *Physiological Measurement*, vol. 37, no. 9, pp. 1499–1515, August 2016.



# 1 Introduction

Most patients with chronic kidney disease also suffer from cardiovascular diseases, causing approximately 45% of all deaths among hemodialysis patients—a much larger proportion than in the general population [1]. The main causes are coronary artery disease, congestive heart failure, and arrhythmias [2]. Premature ventricular beats and complex ventricular arrhythmias occur more often during hemodialysis than after [3]. Continuous cardiac monitoring during hemodialysis improves patient management and helps to reduce the risk of adverse events as it makes manual or automatic modification of the treatment possible [4, 5, 6, 7, 8, 9, 10]. Intradialytic cardiac monitoring is, however, not part of today's clinical routine, one reason being the discomfort caused by wearing electrodes for recording the electrocardiogram (ECG) or a sensor for recording the photoplethysmogram (PPG) during several hours. Another reason is the additional work required by the clinical staff to attach the electrodes or sensors. Hence, it is of vital clinical importance to develop a method for intradialytic cardiac monitoring that does not cause discomfort or add to the workload of the staff.

Pressure waves originating from the heart propagate through the body, enter the extracorporeal blood circuit of the hemodialysis machine, and eventually reach the arterial and venous pressure sensors. Blood from the patient flows through the arterial blood lines of the extracorporeal blood circuit at a flow rate determined by the peristaltic pump. The pump pushes the blood through the venous side, including the dialyzer, back to the patient. Due to the occlusive nature of the peristaltic pump, pressure waves are stopped from propagating between the arterial and venous sides. The pump generates strong periodic pressure waves whose amplitude is considerably higher than that of the pressure waves originating from the heart. Hence, the estimation of a cardiac signal represents a challenging signal separation problem since not only is the signal-to-noise ratio (SNR) poor, but the heart rate and the pump rate may coincide.

The estimated cardiac signal may be analyzed for the purpose of detecting different types of events—cardiac arrest and venous needle dislodgement being two particularly important events to detect as they cause a significant number of deaths among hemodialysis patients [11, 12, 13, 14, 15]. Simultaneous estimation of the cardiac signal using both the venous and arterial pressures would allow event-specific alarms; this is not possible with a method confined to using only the venous pressure sensor. The cardiac signal is likely to disappear in both the venous and arterial pressure signals when cardiac arrest occurs, whereas the cardiac signal is likely to disappear only in the venous signal when venous needle dislodgement occurs. When detecting venous needle dislodgement, it is essential that the blood pump is automatically halted so that the patient's life can be saved. When cardiac arrest is detected, it is essential to elicit an alarm so that the clinical staff can initiate cardiopulmonary resuscitation.

It has earlier been demonstrated that cardiac information can be extracted from the signal produced by the extracorporeal venous pressure sensors of a hemodialysis machine [16]. In that study, however, the venous pressure was analyzed under idealized conditions since only a 20-min data interval was selected in each patient; this interval was excerpted from a part of the treatment where the blood flow remained constant at a normal flow rate. The results showed that the performance deteriorated considerably at lower SNRs, producing an unreliable heart rate estimate.

In the present paper, a novel method for cardiac signal estimation is proposed which rely on information from both the arterial and the venous extracorporeal pressure sensors, hypothesizing that such information improves the quality of the estimated signal. The earlier assumption of all heartbeats having identical morphology is now relaxed so that ventricular ectopic beats can be detected. Rather than modeling the pump pressure wave for a complete pump revolution, separate modeling of the two rollers of the blood pump is introduced so that more accurate characterization can be achieved. The observed signal is processed on a segment-by-segment basis for robust handling of changes in blood flow rate. The performance of the proposed method is evaluated on a set of complete hemodialysis treatments. The main improvements compared to the previous method are: 1. use of signals from both the arterial and venous pressure sensors, enabling the extraction of low cardiac amplitude signals, 2. handling of all possible blood flow rates, even low ones, 3. automatic handling of flow rate changes, and 4. automatic detection and handling of disturbances. Points 2–4 ensure that cardiac signal extraction can be performed throughout the entire treatment session.

## 2 Methods

From the observed arterial and venous pressure signals, the method separates the heart-related arterial and venous pressure signals from the pump-related arterial and venous pressure signals using an iterative estimation procedure. This procedure alternates between estimating the pump-related signals and estimating the cardiac signals, and terminates when the difference between cardiac signal estimates of successive iterations has become sufficiently small.

The pump profile is an important concept which is introduced for characterizing the typical pump-induced pressure wave. A pump profile is computed for each of the the arterial and the venous pressure signals. The two pump profiles are used to create arterial and venous pump model signals by concatenating the profiles once subjected to suitable time scaling, as described below. The resulting arterial and venous pump model signals are, in turn, subtracted from the corresponding observed pressure signal so that improved estimates of the cardiac signals are obtained.

**Table 1:** Notations used in the present method.

| Variable name           | Description                                                                            |
|-------------------------|----------------------------------------------------------------------------------------|
| $j$                     | Iteration index                                                                        |
| $q$                     | Subscript denoting roller 1 or 2 of the pump rotor                                     |
| $x$                     | Subscript denoting either arterial ( $a$ ) or venous ( $v$ ) pressure                  |
| $\hat{a}_{xq,2k}^{(j)}$ | Estimate of time scale factor of the $k$ :th pressure wave                             |
| $\check{c}_x^{(j)}(t)$  | Intermediate cardiac signal estimate                                                   |
| $\hat{c}_x^{(j)}(t)$    | Cardiac signal estimate                                                                |
| $\hat{c}^{(j)}(t)$      | Joint cardiac signal estimate                                                          |
| $\Delta\hat{t}$         | Estimated time delay between $\hat{c}_a^{(j)}(t)$ and $\hat{c}_v^{(j)}(t)$             |
| $N$                     | Number of complete pump revolutions                                                    |
| $\bar{p}_{xq}^{(j)}(t)$ | Pump profile                                                                           |
| $\tilde{p}_x^{(j)}(t)$  | Pump model signal                                                                      |
| $\hat{p}_x^{(j)}(t)$    | Pump signal estimate                                                                   |
| $\hat{t}_{c,k}$         | Occurrence time of the $k$ :th heartbeat                                               |
| $\hat{t}_{x,k}$         | Occurrence time of the $k$ :th pressure wave                                           |
| $\bar{T}_{xq}$          | Mean length of one roller period                                                       |
| $y_x(t)$                | Observed pressure signal                                                               |
| $F_{LP}$                | Low pass cut-off frequency when filtering $\hat{c}^{(j)}(t)$                           |
| $F_{HP}$                | High pass cut-off frequency when filtering $\hat{c}^{(j)}(t)$                          |
| $L$                     | Maximum number of iterations                                                           |
| $\lambda$               | Max time lag between the heart pulses in $\hat{c}_a^{(j)}(t)$ and $\hat{c}_v^{(j)}(t)$ |
| $\alpha$                | Threshold used for initial estimate of roller period                                   |

Table 1 summarizes the notations used in the following to describe the method for cardiac signal estimation.

## 2.1 Iterative cardiac signal estimation

An iterative procedure is proposed in which an intermediate cardiac signal estimate  $\check{c}_x^{(j)}(t)$  is determined by subtracting a pump model signal  $\tilde{p}_x^{(j-1)}(t)$  from the observed pressure signal  $y_x(t)$ , i.e.,

$$\check{c}_x^{(j)}(t) = y_x(t) - \tilde{p}_x^{(j-1)}(t), \quad x \in \{a, v\}. \quad (1)$$

A generic subscript  $x$  is added to indicate that subtraction is performed for both arterial ( $a$ ) and venous ( $v$ ) blood pressure. The procedure is initiated by setting the iteration index  $j = 1$ . The initial pump model signal  $\tilde{p}_x^{(0)}(t)$  is determined by the procedure described in Appendix. Since segment-based processing is employed, the initialization procedure is repeated for each segment. In contrast to [16], the present initialization procedure can handle widely different blood flow rates.

The amplitude and time delay  $\Delta t$  of the cardiac waves in  $y_v^{(j)}(t)$  usually differ from the ones in  $y_a^{(j)}(t)$ . This is explained by differences between the arterial and venous sides of the extracorporeal blood circuit. The main differences are in the length of the tubing, the pressure, and the amount of air (due to the air in the drip chamber that is present only on the venous side). On the other hand, the morphology of the cardiac waves in  $y_v^{(j)}(t)$  and  $y_a^{(j)}(t)$  are similar, rendering it possible to combine the intermediate venous and arterial cardiac signals once subjected to time alignment.

The time delay  $\Delta t$  is estimated by determining the location of the maximum crosscorrelation between  $\check{c}_a^{(j)}(t)$  and  $\check{c}_v^{(j)}(t)$  [17],

$$\Delta \hat{t} = \arg \max_{|\Delta t| < \lambda} \int_0^T \check{c}_a^{(j)}(t) \check{c}_v^{(j)}(t + \Delta t) dt, \quad (2)$$

where  $T$  denotes the segment length (here set to 1 min) and  $\lambda$  the maximum lag between the cardiac waves of the arterial and venous signals. The delay is assumed to be constant within each segment.

A joint cardiac signal estimate  $\hat{c}^{(j)}(t)$  is then computed from the intermediate cardiac signal estimates in (1) as a weighted average of  $\check{c}_a^{(j)}(t)$  and  $\check{c}_v^{(j)}(t)$ ,

$$\hat{c}^{(j)}(t) = w_a \check{c}_a^{(j)}(t) + w_v \check{c}_v^{(j)}(t + \Delta \hat{t}), \quad (3)$$

where two different approaches to determining the weights  $w_a$  and  $w_v$  are investigated: fixed, equal weights given by arithmetic averaging (AA),

$$w_a = w_v = \frac{1}{2}, \quad (4)$$

and data-dependent weights given by principal component analysis (PCA) [18] of the data matrix

$$\check{\mathbf{C}} = \begin{bmatrix} \check{\mathbf{c}}_a \\ \check{\mathbf{c}}_v \end{bmatrix}. \quad (5)$$

The row vectors  $\check{\mathbf{c}}_a$  and  $\check{\mathbf{c}}_v$  result from equidistant sampling of  $\check{c}_a^{(j)}(t)$  and  $\check{c}_v^{(j)}(t + \Delta \hat{t})$ , respectively, using a sufficiently high rate. The two eigenvectors of the correlation

matrix

$$\mathbf{R}_c = \check{\mathbf{C}}\check{\mathbf{C}}^T \quad (6)$$

are then determined and used for defining the orthogonal linear transformation that produces the principal components. In order to ensure that the two pressure components remain in phase, the eigenvector of  $\mathbf{R}_c$  producing the largest absolute value of the scalar product with the direction  $\frac{1}{\sqrt{2}} \begin{bmatrix} 1 & 1 \end{bmatrix}$  is identified; the two elements of the eigenvector determine the weights  $w_a$  and  $w_v$ . Selecting the eigenvector with largest absolute value of the scalar product implies that the eigenvector lies in the 1st or the 3d quadrant. Thus the weights  $w_a$  and  $w_v$  have the same sign, which in turn means that phase between the two signals remains unaltered.

Starting from the joint cardiac signal estimate  $\hat{c}^{(j)}(t)$ , the cardiac signal estimates  $\hat{c}_a^{(j)}(t)$  and  $\hat{c}_v^{(j)}(t)$  related to the arterial and venous pressure, respectively, are determined by suitable rescaling and realignment,

$$\hat{c}_a^{(j)}(t) = \frac{w_a}{w_a^2 + w_v^2} \hat{c}^{(j)}(t), \quad (7)$$

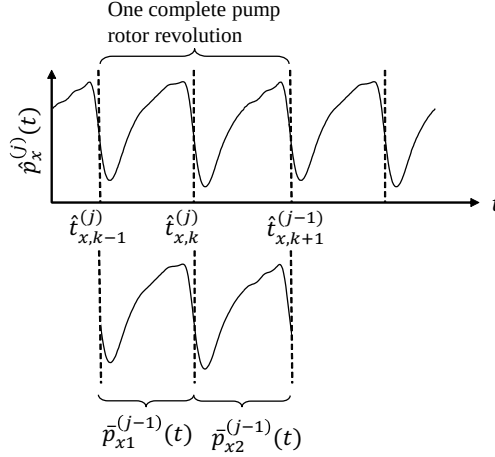
$$\hat{c}_v^{(j)}(t) = \frac{w_v}{w_a^2 + w_v^2} \hat{c}^{(j)}(t - \Delta\hat{t}). \quad (8)$$

These two cardiac signal estimates are used below to compute the pump signal estimates.

## 2.2 Iterative pump signal estimation

The rotor of the peristaltic pump consists of two rollers, and, accordingly, one complete rotor revolution gives rise to two pump pressure waves, one for each roller actuation. As a result, two subsequent pump pressure waves will differ in morphology, whereas every second wave is generated by the same roller and, therefore, has similar morphology. Hence, to achieve better characterization, each of the two pressure waves has its own pump profile, denoted  $\bar{p}_{xq}^{(j)}(t)$ ,  $q = 1, 2$ ,  $x \in \{a, v\}$ , leading to that four different pump profiles have to be computed for one complete rotor revolution, see the illustration in figure 1. It should be noted that the waves of the arterial and the venous pump pressures differ with respect to amplitude and morphology since the sensors are located on opposite sides of the two pump rollers, either pulling the blood through the circuit on the arterial side of the pump or pushing the blood on the venous side of the pump.

The pump profile  $\bar{p}_{xq}^{(j)}(t)$  is determined as the ensemble median resulting from the time-aligned roller periods of the observed signal  $y_x(t)$ . Prior to time alignment, however, the occurrence time  $t_{x,k}^{(j)}$  of each roller period, and the related time scale



**Figure 1:** Occurrence times of roller periods (upper panel) and pump profiles of the two pressure waves of a complete revolution. Every second pressure wave is generated by the same roller and, therefore, has similar morphology. This illustration applies to the arterial as well as to the venous pressure.

factor  $a_{xq,k}^{(j)}$ , need to be estimated; the roller periods are indexed by  $k$ , ranging from 1 to  $2N$  where  $N$  denotes the number of complete pump revolutions.

The estimation of  $t_{x,k}^{(j)}$  takes its starting point in the pump signal estimate  $\hat{p}_x^{(j)}(t)$ , given by

$$\hat{p}_x^{(j)}(t) = y_x(t) - \hat{c}_x^{(j)}(t) \quad (9)$$

which is used for computing the residual

$$\epsilon_x(t; t_{x,k}^{(j)}) = \hat{p}_x^{(j)}(t) - f(\bar{p}_{x1}^{(j-1)}(t), \bar{p}_{x2}^{(j-1)}(t); t_{x,k}^{(j)}). \quad (10)$$

The function  $f(\cdot)$  determines the pump profile of a complete revolution, defined by the concatenation of  $\bar{p}_{x1}^{(j-1)}(t)$  and  $\bar{p}_{x2}^{(j-1)}(t)$  once these two profiles have been time-scaled to fit their respective intervals  $[\hat{t}_{x,k-1}^{(j)}, \hat{t}_{x,k}^{(j)}]$  and  $[\hat{t}_{x,k}^{(j)}, \hat{t}_{x,k+1}^{(j-1)}]$ . Note that  $\hat{t}_{x,k-1}^{(j)}$  is the preceding occurrence time from the current iteration and  $\hat{t}_{x,k+1}^{(j-1)}$  is the succeeding occurrence time that results from the previous iteration. The occurrence time  $t_{x,k}^{(j)}$  of the  $k$ :th roller period is determined by the time instant that minimizes

the least square error

$$\hat{t}_{x,k}^{(j)} = \arg \min_{t_{x,k}^{(j)}} \int \frac{\partial^2 \epsilon_x^2(t; t_{x,k}^{(j)})}{\partial t^2} dt. \quad (11)$$

The reason for minimizing the second derivative of the squared residual, rather than the squared residual itself, is to produce a smoother cardiac signal estimate.

For each roller, the mean period length  $\bar{T}_{xq}^{(j)}$  is determined by

$$\bar{T}_{xq}^{(j)} = \frac{1}{N} \sum_{k=1}^N (\hat{t}_{x,2k+1-q}^{(j)} - \hat{t}_{x,2k-q}^{(j)}), \quad q = 1, 2. \quad (12)$$

The pump profile  $\bar{p}_{xq}^{(j)}(t)$  is computed as the ensemble median at each time instant of all  $N$  revolutions, once the duration of each roller period has been scaled in time, i.e.,

$$\bar{p}_{xq}^{(j)}(t) = \text{median}_k y_x(\hat{a}_{xq,2k}^{(j)} t + \hat{t}_{x,2k}^{(j)}), \quad 0 \leq t < \bar{T}_{xq}^{(j)}, \quad (13)$$

where the time scale factor  $\hat{a}_{xq,k}^{(j)}$  is estimated by

$$\hat{a}_{xq,2k}^{(j)} = \frac{\hat{t}_{x,2k+1-q}^{(j)} - \hat{t}_{x,2k-q}^{(j)}}{\bar{T}_{xq}^{(j)}}. \quad (14)$$

The pump model signal  $\tilde{p}_x^{(j)}(t)$  is then produced by alternating the concatenation of the two pump profiles: for every other roller period, the first pump profile is used,

$$\tilde{p}_x^{(j)}(\hat{a}_{x1,k}^{(j)} t + \hat{t}_{x,2k}^{(j)}) = \bar{p}_{x1}^{(j)}(t), \quad 0 \leq t < \bar{T}_{x1}^{(j)}, \quad (15)$$

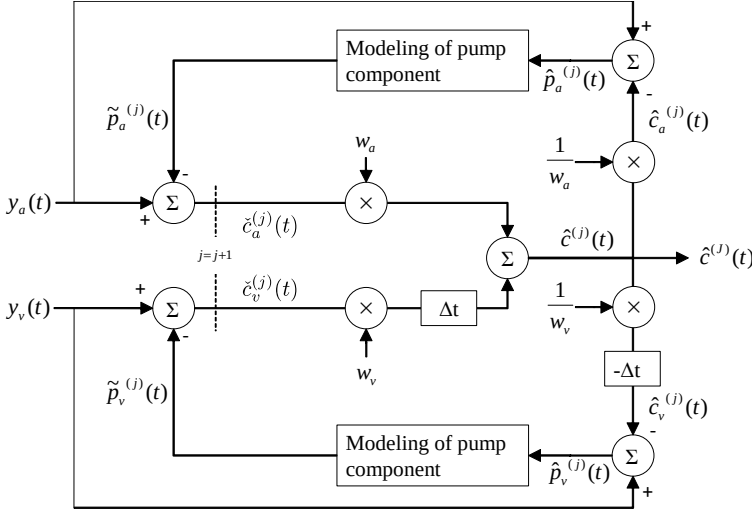
and, otherwise, the second pump profile,

$$\tilde{p}_x^{(j)}(\hat{a}_{x2,k}^{(j)} t + \hat{t}_{x,2k+1}^{(j)}) = \bar{p}_{x2}^{(j)}(t), \quad 0 \leq t < \bar{T}_{x2}^{(j)}. \quad (16)$$

## 2.3 Convergence

The iterative estimation procedure is considered to have converged when the following criterion is fulfilled:

$$\int |\hat{c}^{(j)}(t) - \hat{c}^{(j-1)}(t)| dt > \int |\hat{c}^{(j-1)}(t) - \hat{c}^{(j-2)}(t)| dt. \quad (17)$$



**Figure 2:** Block diagram of the present method for estimating a joint cardiac signal from the input arterial and venous pressure signals. The vertical dashed lines indicate that the iteration index  $j$  is incremented by 1.

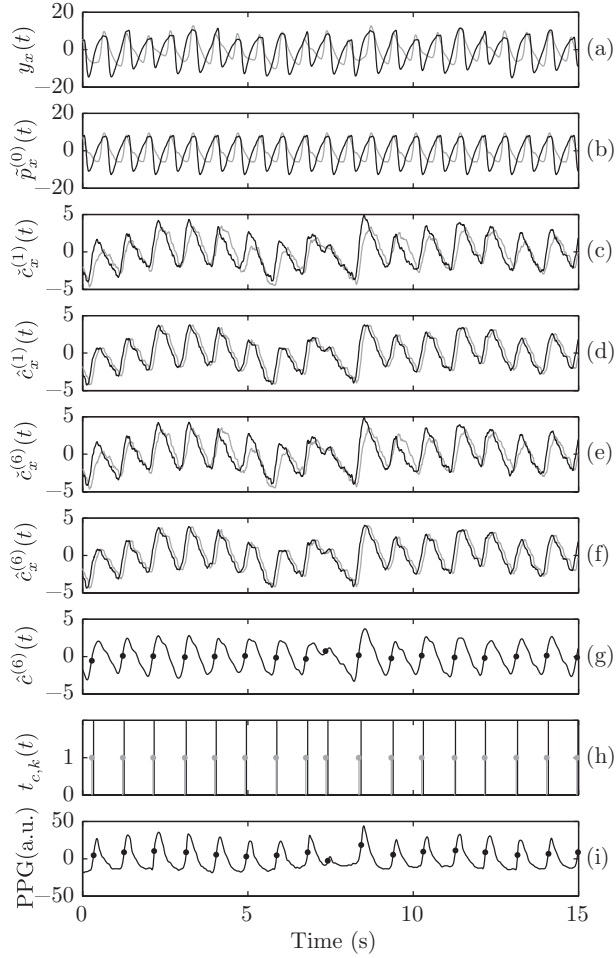
If the procedure has not converged, the iteration index  $j$  is incremented by one and the procedure jumps to section 2.1 and continues processing. If convergence has not been reached within  $L$  iterations, the procedure is terminated and the estimates of the  $L$ :th iteration are used for subsequent analysis.

The block diagram in figure 3 provides an overview of the estimation of a joint cardiac signal from the signals acquired by the arterial and venous pressure sensors.

## 2.4 Estimation of heartbeat occurrence time

Following convergence, the joint cardiac signal estimate  $\hat{c}^{(J)}(t)$  is subjected to band-pass filtering to facilitate the estimation of the heartbeat occurrence times  $\hat{t}_{c,k}$  and to reduce the number of falsely detected beats;  $J$  denotes the number of the iterations required for convergence. The cut-off frequencies of the bandpass filter,  $F_{LP}$  and  $F_{HP}$ , are chosen such that all heart rates can be accommodated in the passband. The occurrence time of a heartbeat is taken as the time of the mid-amplitude of a heartbeat. The mid-amplitude has been successfully used for estimation of the occurrence time in the PPG signal [19].

Figure 2 illustrates the signals produced at different steps of the present method; the final result being a series of heartbeat occurrence times  $\hat{t}_{c,1}, \hat{t}_{c,2}, \dots, \hat{t}_{c,M}$ , where  $M$  denotes the number of estimated heartbeats in the segment.



**Figure 3:** Illustration of the steps involved with cardiac signal estimation based on both arterial and venous pressure (plotted in grey and black respectively). (a) The observed pressure signals  $y_x(t)$ , (b) the initial pump model signals  $\tilde{p}_x^{(0)}(t)$ , (c) the intermediate cardiac signal estimates  $\tilde{c}_x^{(1)}(t)$  that result after one iteration, (d) the cardiac signal estimates  $\hat{c}_x^{(1)}(t)$  based on weighted averaging, (e) the converged intermediate cardiac signal estimate  $\tilde{c}_x^{(6)}(t)$ , (f) the converged cardiac signal estimate  $\hat{c}_x^{(6)}(t)$  based on weighted averaging, (g) the filtered, converged joint cardiac signal estimate based on weighted averaging  $\hat{c}^{(6)}(t)$  with estimated occurrence times  $\hat{t}_{c,k}$  indicated by dots, (h) the estimated occurrence times (grey line with dot) and the reference occurrence times (black line), and (i) the PPG signal with the reference occurrence times indicated by dots. Note that the vertical scales (a)–(g) have mmHg as unit. It should be noted that a ventricular premature beat occurs at about 7 s.

## 2.5 Estimation of heartbeat amplitude

While the clinical significance of heartbeat amplitude is not investigated, this amplitude is still needed since performance is presented as a function of heartbeat amplitude. The amplitude is determined from  $\hat{c}^{(J)}(t)$ , and defined as the difference between the amplitude of the positive peak following the estimated occurrence time and the amplitude of the negative peak preceding the estimated occurrence time, i.e., the peak-to-peak amplitude.

## 3 Experiment and database

A clinical study was conducted at Skåne University Hospital, Lund, Sweden. The study, adhering to the Declaration of Helsinki, was approved by the local ethical review board, and all patients signed an informed consent form before participating. A total of 8 patients were included, all suffering from chronic renal failure and all undergoing hemodialysis treatment for at least 3 months prior to the study onset. A treatment lasted from 4 to 5 hours and was performed according to the ordinary prescription provided by the responsible nephrologist. The blood flow rate varied between 320 and 500 ml/min. Four patients had a history with one or more heart complications. One patient had a graft as vascular access, whereas all others had fistulas. One patient appears twice in the present dataset, and thus a total of 9 treatments were included. Patients undergoing hemodiafiltration treatment and patients participating in other studies were excluded.

All patients were treated with the Gambro AK 200 hemodialysis machine. An external device with pressure sensors identical to the built-in ones was connected to the extracorporeal blood circuit to acquire the arterial and venous pressure signals. The external device was used instead of the built-in pressure sensors in order to avoid the time-consuming work associated with a software update of a commercial machine and subsequent verification and validation. However, the recorded data can still be regarded as derived from the built-in sensors.

A finger pulse oximeter (LifeSense™) was used for acquiring the PPG signal. The pulse oximeter signal is proportional to changes in blood volume, and therefore deemed appropriate for use as reference signal. One-minute signal segments were excluded whenever the dominant spectral peak did not correspond to a heart rate within the interval 30 to 180 beats per minute (bpm); thus, such segments are not part of the results. In addition, PPG segments with motion artifacts were manually excluded, leading to that 4.9% of all 2280 1-min segments were excluded. Recent techniques may be used to lower this percentage, but were not applied in the present study [20, 21].

## 4 Performance evaluation

The performance is evaluated with respect to the accuracy of estimating (i) heart rate and (ii) occurrence time. The following three methods are evaluated:

1. the joint cardiac signal estimate  $\hat{c}_{AA}^{(J)}(t)$  resulting from arithmetic averaging,
2. the joint cardiac signal estimate  $\hat{c}_{PCA}^{(J)}(t)$  resulting from PCA-based weighting, and
3. the cardiac signal estimate  $\hat{c}_V^{(J)}(t)$  resulting from processing of the venous pressure only, i.e., the method described in [16] but here extended to include the procedure described in Appendix so that complete treatments can be analyzed.

The following parameter values are used:  $F_{LP} = 0.5$  Hz,  $F_{HP} = 5.0$  Hz,  $T = 1$  min,  $\lambda = 0.5$  s,  $L = 50$ . Estimation of the cardiac signal is performed in consecutive 1-min segments throughout treatment. All signals are processed at a sampling rate of 100 Hz.

The error between the estimated and the reference heart rate, as well as the error between the estimated and the reference occurrence time, is characterized by the median absolute deviation (MAD). Before the MAD was calculated, the cardiac amplitude range was divided into adjacent intervals of equal length (amplitude bins). The heart rates were, for the complete data set, sorted into the amplitude bins, and the MAD was calculated for each bin; the same was done for the occurrence times.

## 5 Results

The performance is illustrated by the examples in figure 4 where heart rate is presented for two complete hemodialysis treatments. In these examples, the heart rate is determined from  $\hat{c}_{AA}^{(J)}(t)$  and compared to the heart rate determined from the reference signal. The pump rate harmonics are also displayed, being well-separated from the heart rate in figure 4(a), whereas they overlap with the heart rate in figure 4(b). The estimated heart rate agrees well with the reference heart rate most of the time during treatment. Gaps in the estimated heart rate are due to the exclusion of segments with large disturbances in the observed pressure signal, see Appendix. Gaps in the reference heart rate, on the other hand, are due to the exclusion of segments with disturbances in the PPG signal. The exclusion was performed automatically for the estimated heart rate, whereas manually for the reference heart rate.

Figure 5 quantifies the performance by presenting the difference between the estimated and the reference heart rate plotted versus the reference heart rate for all

treatments (i.e., a Bland–Altman type of plot). Each point refers to the heart rate of a 1-min segment.

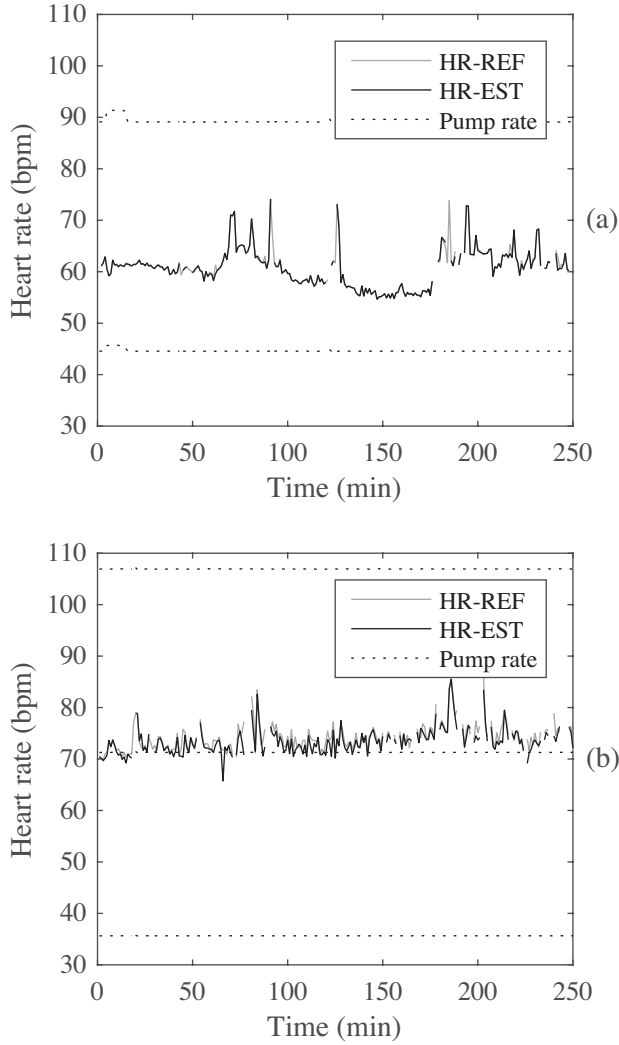
For the dataset, the mean error of the heart rate was  $-0.20$  bpm for AA,  $-0.28$  bpm for PCA and  $-6.49$  bpm for the venous method. The corresponding standard deviation was 3.4, 4.9 and 15 bpm, respectively, whereas the corresponding MAD was 1.2, 1.8 and 10 bpm, respectively. The standard deviation of the occurrence times was 57 ms for AA, 65 ms for PCA and 109 ms for the venous method, whereas the corresponding MAD was 36, 38 and 60 ms, respectively.

The performance of the three methods for extracting heart rate is presented in figure 6(a), where the error between the estimated and the reference heart rate is displayed versus heartbeat amplitude. The MAD is computed for heart rates associated with different amplitudes. The results show that the MAD related to  $\hat{c}_{AA}^{(J)}(t)$  is lower than that related to  $\hat{c}_{PCA}^{(J)}(t)$  when heartbeat amplitudes are below 1 mmHg. For example, at 0.5 mmHg the MAD is 0.6 bpm when using  $\hat{c}_{AA}^{(J)}(t)$ , and 0.7 bpm when using  $\hat{c}_{PCA}^{(J)}(t)$ . Moreover, the results show that the method based on  $\hat{c}_V^{(J)}(t)$ , i.e., the cardiac signal estimated from the venous pressure only, performs much worse at low heartbeat amplitudes, e.g. it has a MAD of 1.3 bpm at 0.5 mmHg, thus demonstrating that the use of both arterial and venous pressure is essential for improving performance.

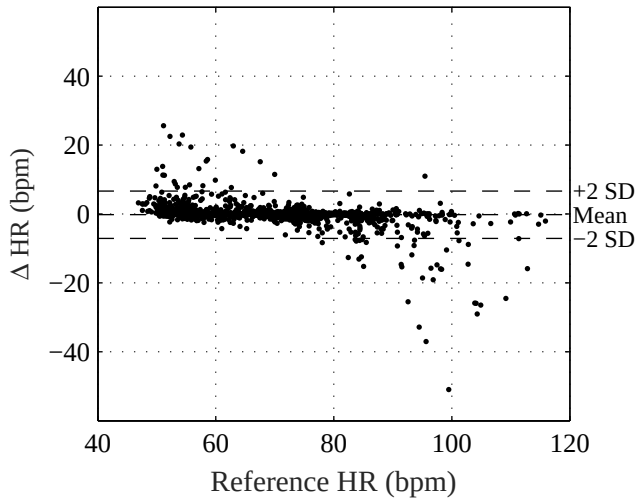
For the three methods, the accuracy of the estimated heartbeat occurrence times is presented versus the heartbeat amplitude in figure 6(b). Similar to the results in figure 6(a), a lower MAD is achieved when both the arterial and the venous pressure are analyzed. The performance is similar when the occurrence times are estimated from either  $\hat{c}_{AA}^{(J)}(t)$  or  $\hat{c}_{PCA}^{(J)}(t)$ , although the former yields a slightly lower MAD at very low heartbeat amplitudes.

Figure 7 illustrates variations in heartbeat amplitude which are representative during hemodialysis treatment. The gradual decrease occurring in heartbeat amplitude is likely due to that the patient's blood pressure is decreasing, which is often observed during hemodialysis. The sudden drop in heartbeat amplitude of the venous pressure, occurring after about 100 min, is ascribed to the PCA technique which is rather sensitive to disturbances: When incorrect principal components are used, the method cannot separate the pump and heart signals. For weak heartbeat amplitudes, the use of PCA tends to emphasize the pump remainders rather than the cardiac activity, leading to that no improvement can be observed from one iteration to the next.

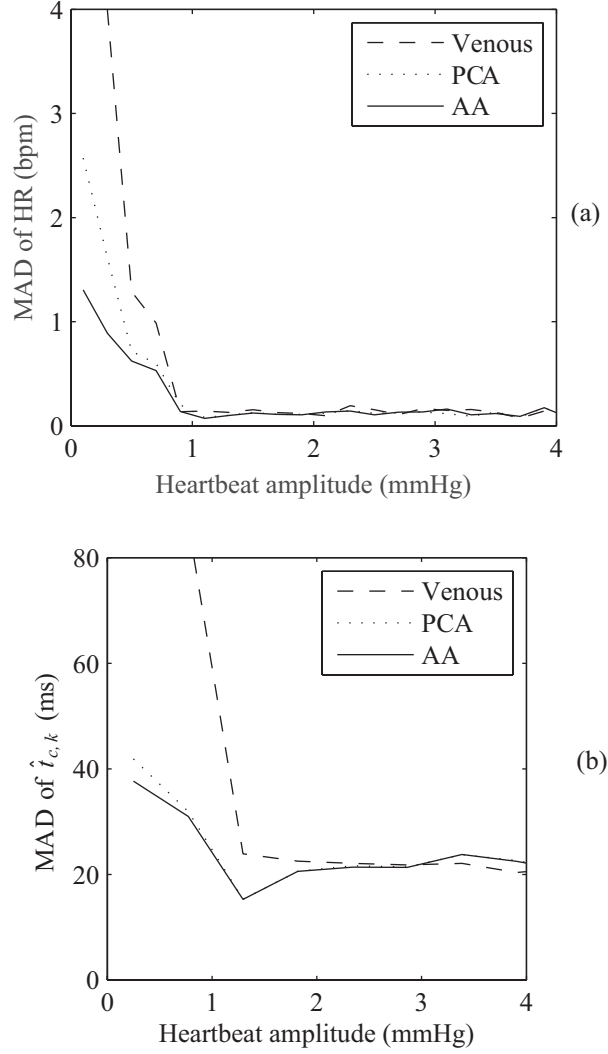
Figure 8 shows a histogram of the heartbeat amplitudes from all treatments, demonstrating the fact that low heartbeat amplitudes are commonly encountered in hemodialysis patients.



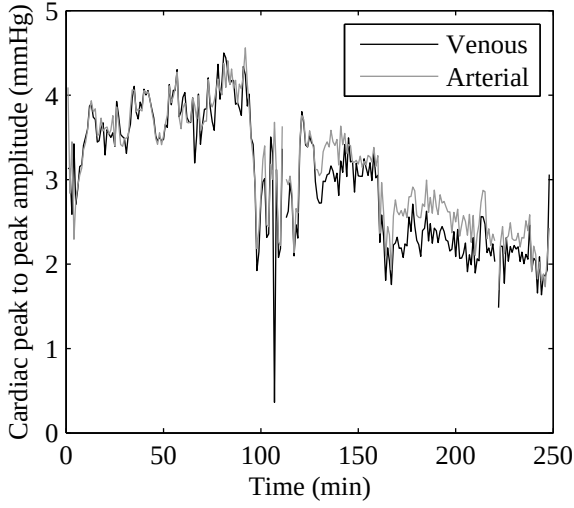
**Figure 4:** Heart rate determined in treatment (a) #1 and (b) #4, displayed together with the pump rate harmonics. The first pump rate harmonic corresponds to the rotor revolutions (rpm) of the blood pump. The reference heart rate determined from the PPG signal is denoted “HR-REF,” and the heart rate estimated from  $\hat{c}_{AA}^{(J)}(t)$  is denoted “HR-EST”. Two pump harmonics are present in (a), whereas three harmonics are present in (b). A gap in the trend indicates that the segment has been discarded from further analysis.



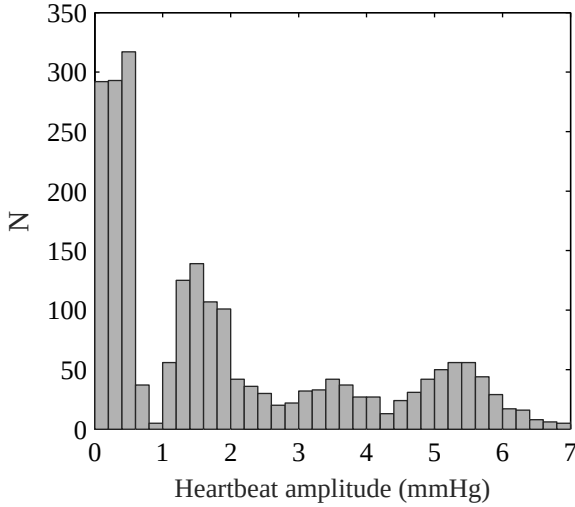
**Figure 5:** Plot of the difference in heart rate,  $\Delta \text{HR}$ , the rates being determined from the reference (PPG) signal and the estimated cardiac pressure signal  $\hat{c}_{AA}^{(J)}(t)$ .



**Figure 6:** (a) Median absolute deviation (MAD) between the heart rate determined from the reference PPG signal and the cardiac signal estimate from the respective methods, and (b) MAD between the heartbeat occurrence times determined from the reference PPG signal and the cardiac signal estimate from the respective methods, as a function of heartbeat amplitude.



**Figure 7:** The heartbeat amplitude estimated from either the arterial or the venous signal estimates  $\hat{c}_a^{(J)}(t)$  and  $\hat{c}_v^{(J)}(t)$  in treatment #6. The PCA-based method was used for heartbeat amplitude estimation.



**Figure 8:** Histogram of the number of 1-min segments as a function of the estimated heartbeat amplitude.

## 6 Discussion

The main novelty of the present study is the use of both arterial and venous pressures for modeling the pump signal and estimating the cardiac signal. Apart from enabling cardiac signal estimation at low heartbeat amplitudes, averaging of the arterial and venous pressure signals makes the present method much more general than the one in [16], since the assumption of identical amplitude and wave morphology of the heartbeats is no longer required. The relaxation of this assumption has particular significance with respect to ectopic beats as their morphology in the pressure signal can be quite different from that of normal beats. Based on annotations of the PPG signal, the data set was found to contain 2000 ectopic beats and 140 000 normal beats.

In contrast to [16], where a 20-min segment with constant flow rate was selected in each patient and subjected to analysis, the present results derive from the analysis of complete hemodialysis treatments. This means that each treatment contains changes in flow rate as well as pressure disturbances, and, consequently, the results reflect performance under clinical conditions.

The heartbeat amplitude histogram in figure 8 shows that weak amplitudes are common, and thus underlines the importance of developing a method which can estimate the cardiac signal at weak amplitudes. Note that the estimated heartbeat amplitudes are much lower than the normal arterial pulse amplitudes (systole–diastole). The fistula, from where the pulsations enter the extracorporeal blood circuit, is a short circuit between an artery and a vein. Depending on how the fistula has matured, the pulsations in it will be more arterial-like (high amplitude) or venous-like (low amplitude). Additionally, the heartbeat amplitude is further weakened on its way through the extracorporeal blood circuit.

The estimated and reference heart rates of the example in figure 4(a) show excellent agreement most of the time during the 4-h treatment. The agreement is slightly less good for the example in figure 4(b) since the heart rate and the blood pump rate coincide.

The error in heart rate exhibits a number of outliers due to a low heartbeat amplitude, cf. Figure 5; all of these outliers originate from 2 of the 9 treatments. Another cause to outliers is the above-mentioned situation with coinciding heart rate and blood pump rate.

Figure 6(a) shows that the error in the estimated heart rate increases rapidly when the heartbeat amplitude drops below 1 mmHg—a property also observed for the estimated heartbeat occurrence times in figure 6(b). If an automatic alert system for sudden cardiac arrest or venous needle dislodgement is implemented, the error rate at low amplitudes may give rise to false alarms. Although it may not be possible to use the proposed method in all patients, it still offers a significant improvement compared

to today's clinical practice, as no cardiac monitoring is employed at all.

When calculating the MAD of the heartbeat occurrence times, cf. figure 6(b), missed and falsely detected beats must first be excluded. On the other hand, such exclusion is not needed when computing the MAD of the heart rate, thus missed and falsely detected beats are included and, accordingly, will influence the result. This observation may explain why, at low heartbeat amplitudes, the difference in MAD between using AA and PCA is less pronounced in figure 6(b) than in figure 6(a). A MAD of 20 mmHg for the heartbeat occurrence times suggest that the accuracy of the timing is not good enough for spectral HRV analysis, but may be good enough for detecting ectopic beats. The pressure signal is obviously not suited for more advanced arrhythmia analysis since it does not convey morphologic information on atrial and ventricular waveforms.

In the present study, the roller period was estimated from the observed pressure signal. When implementing the present method in a hemodialysis machine, it may be preferable to measure the roller period directly from a signal which reflects the rotational speed of the blood pump, possibly replacing the roller period estimation described in Appendix.

A limitation of the present study is that the dataset was used for both development and performance evaluation. Thus, another study should be undertaken which involves a larger dataset, so that performance can be better established. None of the parameters which influence performance, i.e.,  $F_{LP}$ ,  $F_{HP}$ ,  $L$ ,  $\lambda$ , and  $\alpha$ , were, however, subject to optimization, but their values were chosen based on general considerations. For example,  $L$  was set to 50 since a higher value would only lead to increased computation time without leading to estimates with better accuracy, and  $F_{LP}$  and  $F_{HP}$  were related to the frequency content of interest in the cardiac signal.

Another limitation of the study is that the ECG was not recorded when the database was acquired, although the ECG is a gold standard for analyzing the timing of heartbeats. On the other hand, the PPG was recorded for the purpose of monitoring heart rate and therefore used in the present study; Gil et al. have shown that the PPG is a useful surrogate for the ECG when analyzing heart rate variability [22].

## 7 Conclusions

The use of both arterial and venous pressure from the extracorporeal sensors of the hemodialysis machine is found to improve the estimation of heart rate and heartbeat occurrence times at low heartbeat amplitudes, when compared to using the venous pressure only. As a result, cardiac monitoring can be performed in more patients. The new method makes it possible to estimate a cardiac signal also at low blood flow rates, and to automatically handle changes in blood flow, implying that cardiac information

can be reliably extracted throughout complete treatments. The results are preliminary, and need to be verified on a separate dataset.

## Acknowledgments

The authors would like to thank Mårten Segelmark, Lena Mattsson, and Sarok Said at Lund University Hospital for all work with the clinical investigation. This work was partially supported by grants from the Swedish Research Council. M Holmer, B Olde, and K Solem are employees of Baxter International Inc.. A patent application related to the work is pending.

## Appendix

Since the flow rate recorded by the machine has insufficient accuracy for the present application, the rotor period is estimated from the observed signals  $y_x(t)$ . Thus, the procedure for cardiac signal estimation is fully automated.

For each signal segment, initialization starts by determining a rough estimate of the roller period  $\hat{T}_x$  using the entire segment. Then, based on  $\hat{T}_x$ , estimates of each roller period  $\hat{T}_{x,k}$  is determined in order to reflect the fact that the period varies over time.

The rough estimate of the roller period  $\hat{T}_x$  is determined by finding the peak in the autocorrelation function of  $y_x(t)$  which corresponds to the shortest roller period in the interval  $\tau_1 < T_x < \tau_2$ , where  $\tau_1$  and  $\tau_2$  are defined by the flow range of the pump. This interval is chosen such that all adequate blood flow rates are covered. At low flow rates, small peaks may occur in the autocorrelation function at shorter lags than the roller period and, therefore, a threshold  $\alpha$  is used to differentiate such peaks from the peak corresponding to the roller period. If no peak exceeds  $\alpha$ , a blood flow rate change or a large pressure disturbance has likely occurred, and, therefore, the analyzed signal segment is discarded from subsequent analysis.

The estimation of each separate roller period  $\hat{T}_{x,k}$ , starts by estimating the occurrence time of the first roller actuation time,

$$\hat{t}_{x,0}^{(0)} = \arg \max_{0 < t < (1+\delta)T_x} \left| \frac{dy_x(t)}{dt} \right|, \quad (18)$$

where  $\delta$  defines the maximal variation allowed in period time between consecutive roller waves. The absolute value in (18) ensures that maximization can be performed on both arterial and venous signals, since the maximum occurs at positive derivative

for arterial signals, whereas negative for venous signals. Starting from  $\hat{t}_{x,0}^{(0)}$ , the roller period  $\hat{T}_{x,k}^{(0)}$  for all revolutions in the segment are estimated as

$$\hat{T}_{x,k}^{(0)} = \arg \max_{(1-\delta)T_x < T < (1+\delta)T_x} \left| \frac{dy(\hat{t}_{x,k-1}^{(0)} + T)}{dt} \right|, \quad (19)$$

where

$$\hat{t}_{x,k}^{(0)} = \sum_{l=1}^k \hat{T}_{x,l}^{(0)} + \hat{t}_{x,0}^{(0)}, \quad k = 1, \dots, 2N. \quad (20)$$

The pump model signal  $\hat{p}_x^{(0)}(t)$  is then produced by the procedure described in section 2.2, except that the estimated occurrence times described in Appendix should be inserted in Eqs. (13)–(16), using  $j = 0$ .

The following parameter values were used for initialization:  $\tau_1 = 0.5$  s,  $\tau_2 = 1.3$  s,  $\alpha = 0.04$ , and  $\delta = 0.25$ .

## References

- [1] S. Shastri and M. J. Sarnak, “Cardiovascular disease and CKD: core curriculum 2010,” *American journal of kidney diseases : the official journal of the National Kidney Foundation*, vol. 56, pp. 399–417, Aug. 2010.
- [2] L. Di Lullo, A. House, A. Gorini, A. Santoboni, D. Russo, and C. Ronco, “Chronic kidney disease and cardiovascular complications,” *Heart failure reviews*, Oct. 2014.
- [3] J. O. Burton, S. Korsheed, B. J. Grundy, and C. W. McIntyre, “Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmia,” *Renal Failure*, vol. 30, pp. 701–709, 2008.
- [4] M. Shamir, L. A. Eidelman, Y. Floman, L. Kaplan, and R. Pizov, “Pulse oximetry plethysmographic waveform during changes in blood volume,” *Br. J. Anaesth.*, vol. 82, pp. 178–181, 1999.
- [5] N. M. Selby and C. W. McIntyre, “The acute cardiac effects of dialysis,” *Semin. Dial.*, vol. 20, pp. 220–228, 2007.

- 
- [6] E. Mancini, L. Corazza, D. C. Cannarile, M. L. Soverini, S. Cavalcanti, S. Cavani, A. Fiorenzi, and A. Santoro, "Short term variability of oxygen saturation during hemodialysis is a warning parameter for hypotension appearance," in *Proc. Comput. Cardiol.*, vol. 35, pp. 881–883, 2008.
  - [7] B. Yang and K. H. Chon, "A novel approach to monitor nonstationary dynamics in physiological signals: Application to blood pressure, pulse oximeter, and respiratory data," *Ann. Biomed. Eng.*, vol. 38, pp. 3478–3488, 2010.
  - [8] L. Sörnmo, F. Sandberg, E. Gil, and K. Solem, "Noninvasive techniques for prevention of intradialytic hypotension," *IEEE Rev. Biomed. Eng.*, vol. 5, pp. 45–59, 2012.
  - [9] K. Solem, B. Olde, and L. Sörnmo, "Prediction of intradialytic hypotension using photoplethysmography," *IEEE Trans. Biomed. Eng.*, vol. 57, pp. 1611–1619, 2010.
  - [10] F. Javed, P. M. Middleton, P. Malouf, G. S. Chan, A. V. Savkin, N. H. Lovell, E. Steel, and J. Mackie, "Frequency spectrum analysis of finger photoplethysmographic waveform variability during haemodialysis," *Physiol. Meas.*, vol. 31, pp. 1203–1216, 2010.
  - [11] J. a. Karnik, B. S. Young, N. L. Lew, M. Herget, C. Dubinsky, J. M. Lazarus, and G. M. Chertow, "Cardiac arrest and sudden death in dialysis units," *Kidney Int.*, vol. 60, pp. 350–357, July 2001.
  - [12] C. A. Herzog, "Cardiac arrest in dialysis patients: approaches to alter an abysmal outcome.," *Kidney Int. Suppl.*, vol. 63, no. 84, pp. S197–S200, 2003.
  - [13] H. D. Polaschegg, "Venous needle dislodgement: the pitfalls of venous pressure measurement and possible alternatives, a review," *J. Ren. Care*, vol. 36, pp. 41–48, 2010.
  - [14] M. Segelmark, S. Mattsson, B. Olde, and K. Solem, "Successful detection of venous needle dislodgement using extracted heart pulses obtained from venous pressure monitoring," in *Proc. Am. Soc. Nephrol. Kidney (JASN)*, vol. 21, p. 241A, 2010.
  - [15] B. Axley, J. Speranza-Reid, and H. Williams, "Venous needle dislodgement in patients on hemodialysis," *Nephrol. Nurs. J.*, vol. 9, pp. 435–445, 2012.
  - [16] M. Holmer, F. Sandberg, K. Solem, E. Grigonyte, B. Olde, and L. Sörnmo, "Extracting a cardiac signal from the extracorporeal pressure sensors of a hemodialysis machine," *IEEE Trans. Biomed. Eng.*, vol. 62, no. 5, pp. 1305–1315, 2015.

- [17] S. M. Kay, *Fundamentals of Statistical Signal Processing. Estimation Theory*. New Jersey: Prentice-Hall, 1993.
- [18] A. Hyvärinen, J. Karhunen, and E. Oja, *Independent Component Analysis*. John Wiley & Sons, 2001.
- [19] J. Lázaro, E. Gil, J. M. Vergara, and P. Laguna, “Pulse rate variability analysis for discrimination of sleep-apnea-related decreases in the amplitude fluctuations of pulse photoplethysmographic signal in children,” *IEEE J. Biomed. Health Inform.*, vol. 18, pp. 240–246, 2014.
- [20] J. Chong, D. K. Dao, S. M. A. Salehizadeh, D. D. McManus, C. Darling, K. H. Chon, and Y. Mendelson, “Photoplethysmograph signal reconstruction based on a novel hybrid motion artifact detection–reduction approach. Part I: Motion and noise artifact detection,” *Ann. Biomed. Eng.*, vol. 42, pp. 2238–2250, 2014.
- [21] S. M. A. Salehizadeh, D. K. Dao, J. Chong, Y. Mendelson, D. D. McManus, C. Darling, and K. H. Chon, “Photoplethysmograph signal reconstruction based on a novel motion artifact detection–reduction approach. Part II: Motion and noise artifact removal,” *Ann. Biomed. Eng.*, vol. 42, pp. 2251–2263, 2014.
- [22] E. Gil, M. Orini, R. Bailón, J. M. Vergara, L. Mainardi, and P. Laguna, “Photoplethysmography pulse rate variability as a surrogate measurement of heart rate variability during non-stationary conditions,” *Physiol. Meas.*, vol. 31, pp. 1271–1290, 2010.

# *Paper III*



# Detection of Ventricular Premature Beats Based on the Pressure Signals of a Hemodialysis Machine

## Abstract

Monitoring of ventricular premature beats (VPBs), being abundant in hemodialysis patients, can provide information on cardiovascular instability and electrolyte imbalance. In this paper, we describe a method for VPB detection which explores the signals acquired from the arterial and the venous pressure sensors, located in the extracorporeal blood circuit of a hemodialysis machine. The pressure signals are mainly composed of a pump component and a cardiac component. The cardiac component, severely overshadowed by the pump component, is estimated from the pressure signals using an earlier described iterative method. A set of simple features is extracted, and linear discriminant analysis is performed to classify beats as either normal or ventricular premature. Performance is evaluated on signals from nine hemodialysis treatments, using leave-one-out crossvalidation. The simultaneously recorded and annotated photoplethysmographic signal serves as the reference signal, with a total of 149 686 normal beats and 3 574 VPBs. The results show that VPBs can be reliably detected, quantified by a Youden's  $J$  statistic of 0.9, for average cardiac pulse pressures exceeding 1 mmHg; for lower pressures, the  $J$  statistic drops to 0.55. It is concluded that the cardiac pressure signal is suitable for VPB detection, provided that the average cardiac pulse pressure exceeds 1 mmHg.

---

Based on:

Mattias Holmer, Juan Pablo Martínez, Eduardo Gil, Frida Sandberg, Bo Olde, Leif Sörnmo  
"Detection of Ventricular Premature Beats Based on the Pressure Signals of a Hemodialysis Machine,"

Submitted for publication.



# 1 Introduction

It is well-known that ventricular premature beats (VPBs) are frequent in dialysis patients [1, 2], and increase in number when excess potassium is removed [3]. Ventricular arrhythmias in dialysis patients have been studied in long-term, ambulatory electrocardiogram (ECG) recordings, showing that VPBs are much more frequent during hemodialysis than during the postdialysis period [4]. Patients with regional wall motion abnormalities, ischemic heart disease, and left ventricular hypertrophy have a higher rate of VPBs during hemodialysis than have patients without these diseases. Rapid changes in this rate may be a sign of cardiovascular instability and electrolyte imbalance, and the significance of such changes have been investigated for prediction of acute, intradialytic hypotension [5].

Pulse pressure waves propagate from the heart through the arteries to the fistula, where the waves enter the extracorporeal blood circuit of the dialysis machine. In this blood circuit, the waves are measured by the arterial and the venous pressure sensors. A peristaltic blood pump generates a pulsatile blood flow through the extracorporeal circuit. The blood flows from an arterial needle inserted into the fistula, through the dialyzer, purifying the blood, and then back to the fistula through a venous needle. The amplitude of the pressure pulses generated by the blood pump is drastically larger than is the amplitude of the pressure pulses generated by the heart.

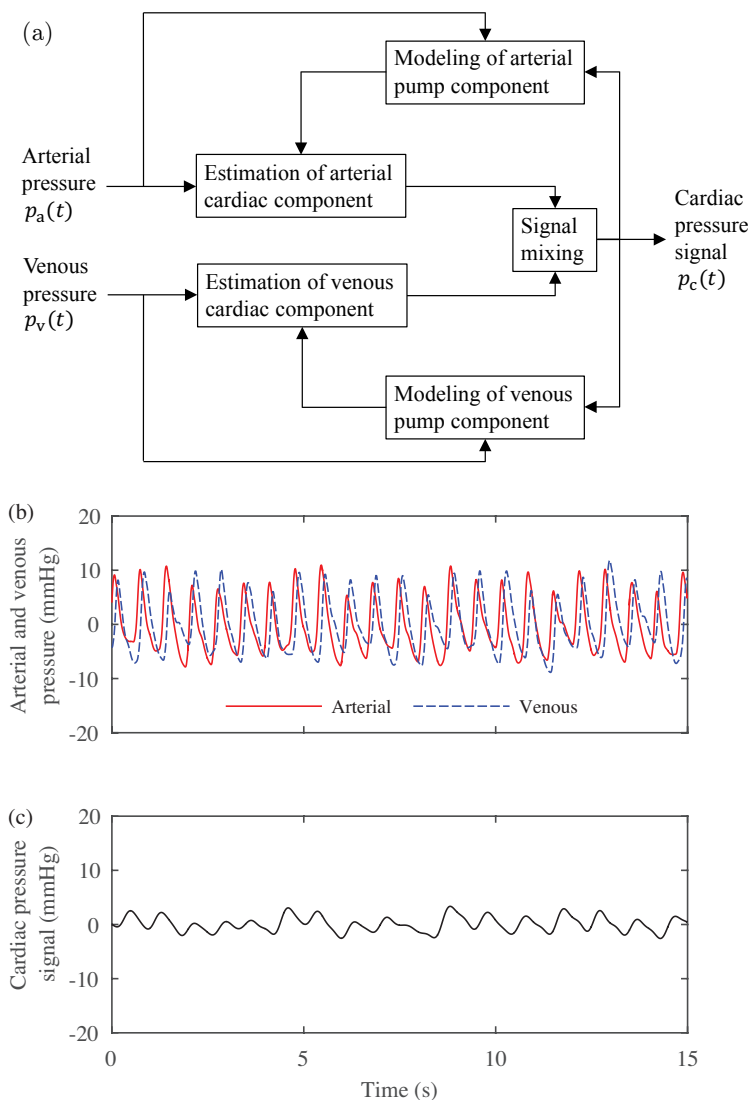
We have previously shown that a cardiac pressure signal can be extracted from the signals produced by the arterial and the venous pressure sensors [6], see also [7]. In these studies, we compared heart rate and heartbeat occurrence time estimated from the extracted cardiac pressure signal to the corresponding quantities obtained from the photoplethysmographic (PPG) signal. The results showed that the proposed method offers excellent accuracy of heart rate and heartbeat occurrence time, also at low signal-to-noise ratios.

In the present paper, we investigate, for the first time, whether the extracted cardiac pressure signal is suitable for VPB detection. A set of features, describing amplitudes, durations, and areas, is proposed and used to classify detected beats as either VPBs or normal based on linear discriminant analysis. Using leave-one-out cross-validation, the performance is evaluated by comparing the results from the proposed classifier to the annotated reference PPG signals.

## 2 Background

### 2.1 Cardiac Pressure Signal Estimation

The cardiac pressure signal is estimated using the iterative method described in [6]. The method alternates between modeling of separate arterial and venous pump components, and estimation of a cardiac pressure signal. The resulting estimate is based on both the arterial and the venous pressure signals, by mixing the arterial cardiac component with the venous cardiac component. The mixing consists of time shifting and averaging, where the time shift is determined by maximizing the correlation between the arterial and venous cardiac components. The arterial and the venous cardiac components are obtained by subtracting the arterial and the venous model pump components from the respective arterial and venous pressure signals. The arterial and the venous pump signal estimates are determined by subtracting the cardiac pressure signal estimate from the respective signals. The pump signal estimates are, in turn, used to iteratively refine the arterial and the venous model pump components, so that the pump component remainders in the cardiac pressure signal estimate are reduced. The iteration continues until the difference in successive cardiac pressure signal estimates no longer improves. The main building blocks of the method are shown in Fig. 1(a), where the input signals and the output signal are illustrated in Figs. 1(b) and (c), respectively.



**Figure 1:** (a) Block diagram of the method for cardiac pressure signal estimation. Note that the output signal is referred to as “cardiac pressure signal”, whereas the intermediate signals are referred to as “components”. (b) The arterial and the venous pressure signals are the input to the method, whereas (c) the cardiac pressure signal is the output. Note the considerable difference in amplitude between the signals in (b) and (c).

## 3 Experiment and Database

### 3.1 Clinical Study

The data originate from a clinical study performed at Skåne University Hospital, Lund, Sweden. The study was approved by the local ethical review board, and all patients signed an informed consent form before participating.

The data set includes 9 treatments from 7 patients with kidney failure who underwent hemodialysis treatment for at least three months prior to the study onset. The treatments were performed according to the regular prescription provided by the nephrologist, and lasted 4 to 5 hours. Four patients had a history of heart complication. One patient had a graft as vascular access, whereas all others had fistulas. The average cardiac pulse pressure  $\bar{P}_{np}$  was determined during a blood pump stop at the treatment onset, see Table 1. Treatments with  $\bar{P}_{np}$  below 0.5 mmHg [6], as well as patients with pacemaker, patients undergoing hemodiafiltration treatment, and patients participating in other studies, were not included.

The patients were treated with AK 200 hemodialysis machines from Gambro. An external device with pressure sensors was connected to the extracorporeal blood circuit to acquire the arterial and the venous pressure signals. The external device was used instead of the built-in pressure sensors to avoid the time-consuming work that comes with a software update of a dialysis machine. However, the recorded data can be regarded as originating from the built-in sensors, since the external and built-in sensors were of identical brand and type.

As reference, a PPG signal was acquired using the LifeSense™ finger pulse oximeter. The PPG signal and the estimated cardiac pressure signal were lowpass filtered, using a cut-off frequency of 5 Hz. All analyzed signals had a time resolution of 10 ms. The use of the PPG signal as a reference is discussed in Section 6.

**Table 1:** Treatment characteristics

| Treatment # | Duration (h:mm) | Discarded (h:mm) | $\bar{P}_{np}$ (mmHg) | $m_{pp} \pm \sigma_{pp}$ (ms) | #VPBs | #normal |
|-------------|-----------------|------------------|-----------------------|-------------------------------|-------|---------|
| 1           | 4:13            | 0:10             | 5.0                   | $993 \pm 109$                 | 158   | 14 526  |
| 2           | 4:10            | 0:03             | 2.9                   | $952 \pm 175$                 | 507   | 15 029  |
| 3           | 4:31            | 0:11             | 1.8                   | $767 \pm 51$                  | 6     | 19 768  |
| 4           | 4:41            | 0:04             | 1.3                   | $785 \pm 107$                 | 336   | 20 852  |
| 5           | 4:40            | 0:26             | 1.3                   | $966 \pm 111$                 | 54    | 15 665  |
| 6           | 4:54            | 1:49             | 0.70                  | $790 \pm 72$                  | 23    | 13 879  |
| 7           | 4:52            | 0:04             | 0.70                  | $756 \pm 134$                 | 773   | 22 060  |
| 8           | 4:37            | 0:02             | 0.55                  | $871 \pm 191$                 | 1382  | 17 586  |
| 9           | 3:42            | 0:51             | 0.54                  | $961 \pm 180$                 | 335   | 10 321  |

The category “Discarded” is the accumulated duration of discarded segments due to motion artifacts in the PPG signal.  $\bar{P}_{np}$  is the average pulse pressure of the cardiac pressure signal determined during blood pump stop.  $m_{pp}$  and  $\sigma_{pp}$  denote the mean and standard deviation, respectively, of the peak-to-peak interval. Note that the number of VPBs and normal beats,  $m_{pp}$ , and  $\sigma_{pp}$  are determined from the annotated PPG signals.

### 3.2 Annotation of the Reference PPG Signal

Firstly, pulse detection was performed on the reference PPG signal, using a lowpass differentiator filter and a time-varying threshold, where the time of the peak amplitude of each heart pulse was used as reference [8, 9]. Secondly, the detected pulses were classified as either normal or VPB using the method in [9]. Next, all VPBs were manually reviewed to avoid incorrect annotations. Segments with motion artifacts were manually excluded, leading to that 9% of the total treatment time were excluded. For each treatment, Table 1 presents its duration, the duration of discarded segments,  $\bar{P}_{np}$ , the mean and standard deviation of the peak-to-peak interval in the PPG signal, and the number of annotated normal and premature beats.

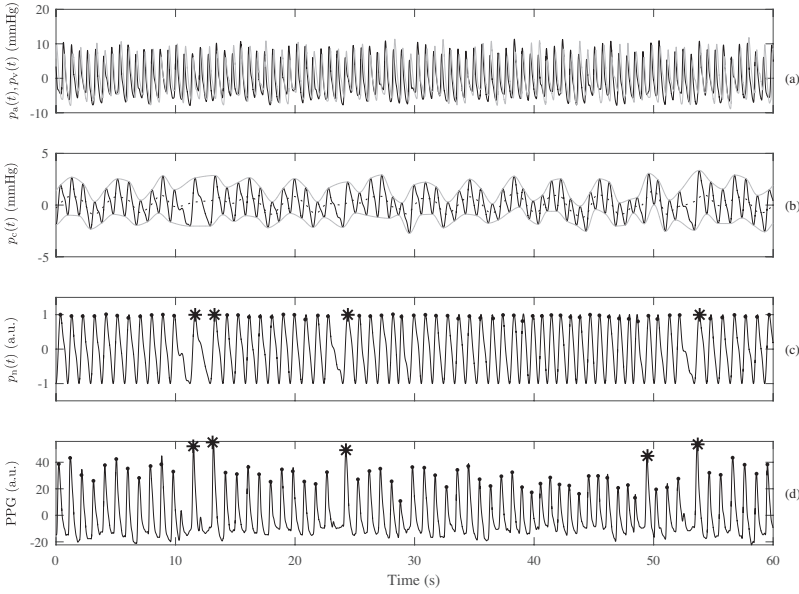
## 4 Methods

### 4.1 Preprocessing

The cardiac pressure signal  $p_c(t)$  is estimated from the observed arterial and venous pressure signals, denoted  $p_a(t)$  and  $p_v(t)$ , respectively, using the iterative method briefly described in Section 2. Segments in  $p_c(t)$  with excessive noise, manifested as sudden changes in energy (at least a factor of 4), or a heart rate lower than 15 or higher

than 180 beats per minute, are excluded. Figures 2(a) and (b) illustrates  $p_a(t)$ ,  $p_v(t)$ , and  $p_c(t)$ , respectively.

Since the amplitude of  $p_c(t)$  varies significantly during treatment,  $p_c(t)$  is detrended and normalized to produce amplitude-independent features, using a method based on empirical mode decomposition [10, 11]. The local extrema are identified in  $p_c(t)$ . If two local extrema with the same polarity are closer than 350 ms to each other, then only the extremum with the largest magnitude is kept. If the peak-to-peak interval  $T_{pp}$  is 1.8–2.2 times larger than the 5-point sliding median of  $T_{pp}$ , denoted  $\tilde{T}_{pp}$ , the previously excluded extremum is recovered, provided that a pulse with the peak-to-peak amplitude larger than 0.4 mmHg exists in the interval  $[0.85, 1.15] \cdot \tilde{T}_{pp}$ . The upper envelope  $e_{\max}(t)$  is obtained by connecting the local maxima using cubic



**Figure 2:** Illustration of signals and VPB detection for treatment #1. (a) Venous pressure signal  $p_v(t)$  (black) and arterial pressure signal  $p_a(t)$  (grey). (b) Cardiac pressure signal  $p_c(t)$  estimated from  $p_v(t)$  and  $p_a(t)$  (black), the envelopes  $e_{\max}(t)$  and  $e_{\min}(t)$  (grey), and the trend  $b(t)$  (dotted line). (c) The normalized cardiac pressure signal  $p_n(t)$ ; VPBs are labeled with “\*” and normal beats with “.”. (d) The reference PPG signal with annotations. Note the large difference in amplitude between  $p_c(t)$  in (b) and  $p_v(t)$  and  $p_a(t)$  in (a).

spline interpolation. The lower envelope  $e_{\min}(t)$  is obtained in the same way, but instead connecting the local minima. The average envelope  $\bar{e}(t)$  and the trend  $b(t)$  are determined by

$$\bar{e}(t) = \frac{1}{2}(e_{\max}(t) + e_{\min}(t)), \quad (1)$$

$$b(t) = \frac{1}{2}(e_{\max}(t) - e_{\min}(t)), \quad (2)$$

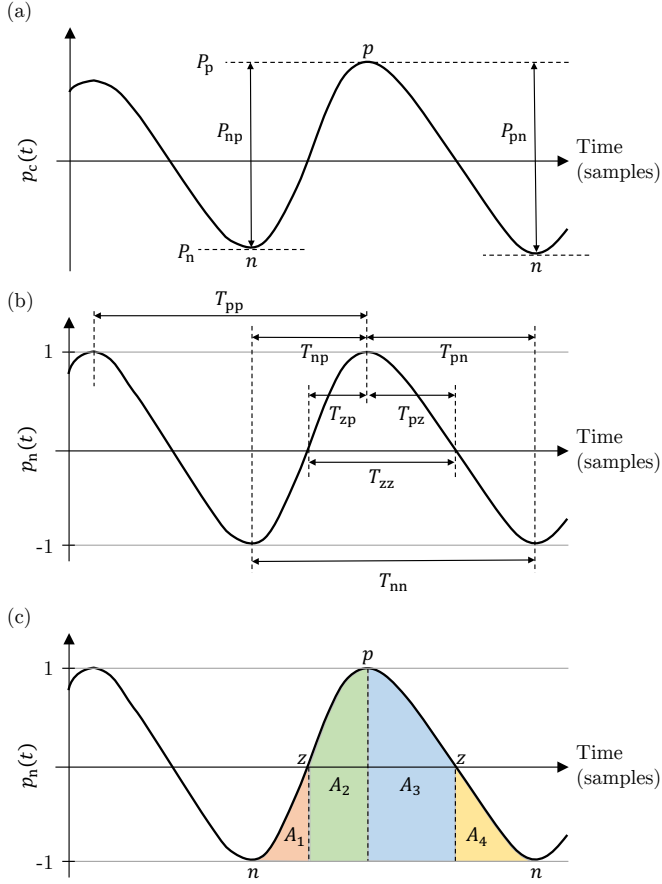
respectively. Figure 2(b) illustrates  $e_{\max}(t)$ ,  $e_{\min}(t)$ , and  $b(t)$ , together with  $p_c(t)$ . The detrended and normalized cardiac pressure signal is obtained by

$$p_n(t) = \frac{p_c(t) - b(t)}{\bar{e}(t)}, \quad (3)$$

illustrated in Fig. 2(c) along with information on beat type as produced by the method described below. Figure 2(d) shows the reference PPG signal and the annotations.

## 4.2 Feature Extraction

Simple features  $X \in \{P, T, A\}$  based on amplitude  $P$ , duration  $T$ , and area  $A$  are used for classification, see Fig. 3. The amplitude features are extracted from  $p_c(t)$ , whereas the features describing areas and durations are extracted from  $p_n(t)$  since this signal is much less influenced by variations in baseline and amplitude. Since a VPB may influence the features of the preceding beat  $X^-$ , as well as the following beat  $X^+$ , the features of the two enclosing beats are also evaluated. Since the feature values may vary considerably within a treatment, the median of the five most recent beats  $\tilde{X}$  is used to center or normalize the features, either with  $X^c = X - \tilde{X}$  or  $X^n = X/\tilde{X}$ , thus leading to additional features based on  $X$ . In addition, the difference between the current beat's peak-to-peak interval and that of the preceding beat, denoted  $\Delta T_{pp}$ , is included as a feature.



**Figure 3:** (a) Amplitude features determined from  $p_c(t)$ . (b) Duration and (c) area features determined from  $p_n(t)$ . The following area features are evaluated:  $A = A_1 + A_2 + A_3 + A_4$ ,  $A_{pn} = A_3 + A_4$ ,  $A_{np} = A_1 + A_2$ ,  $A_{zz} = A_2 + A_3$ ,  $A_{zp} = A_2$ ,  $A_{pz} = A_3$ . The vertical axis in (a) has arbitrary units.

### 4.3 Classification and Training

Beats detected in  $p_c(t)$  are classified as either normal or ventricular premature, using linear discriminant analysis. For each beat, the following linear discriminant function

(LDF) is evaluated [12],

$$f(\mathbf{x}) = (\mathbf{m}_v^T - \mathbf{m}_n^T) \mathbf{C}^{-1} \mathbf{x} - \frac{1}{2} \mathbf{m}_v^T \mathbf{C}^{-1} \mathbf{m}_v + \frac{1}{2} \mathbf{m}_n^T \mathbf{C}^{-1} \mathbf{m}_n + \ln \left( \frac{P_v}{P_n} \right), \quad (4)$$

where  $\mathbf{x}$  is a vector containing the  $K$  features of one beat,  $\mathbf{m}_v$  is the average feature vector for all VPBs,  $\mathbf{m}_n$  is the mean for all normal beats,  $\mathbf{C}$  is the estimated covariance matrix of the features based on all beats. The a priori probabilities  $P_v$  and  $P_n$  of VPBs and normal beats, respectively, are for each treatment determined from the annotations of all other treatments. A different LDF is used for each treatment, determined by leave-one-out cross validation, i.e., for each treatment the LDF is trained using all other treatments. If  $f(\mathbf{x}) > 0$ , the beat is classified as VPB, otherwise as normal.

Youden's  $J$  statistic [13] is used as performance index to determine the  $K$  most relevant features,

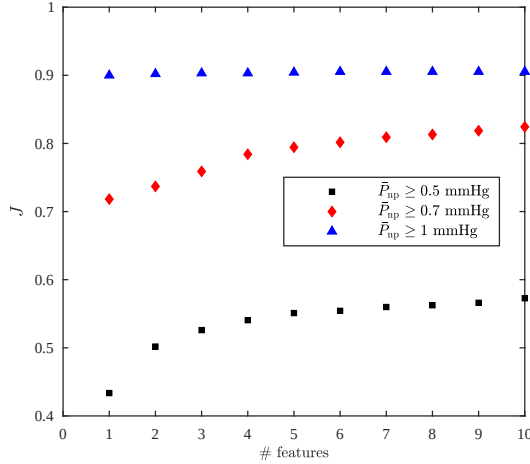
$$J = \frac{N_{TP}}{N_{TP} + N_{FN}} + \frac{N_{TN}}{N_{TN} + N_{FP}} - 1, \quad (5)$$

where  $N_{TP}$  is the number of annotated VPBs classified as VPBs (true positives),  $N_{FN}$  is the number annotated VPBs classified as normal beats (false negatives),  $N_{TN}$  is the number of annotated normal beats classified as normal beats (true negatives), and  $N_{FP}$  is the number of annotated normal beats classified as VPBs (false positives). Note that perfect performance, i.e.,  $J = 1$ , is achieved for  $N_{FN} = 0$  and  $N_{FP} = 0$ . The  $J$  statistic was chosen as performance index since the data set is highly unbalanced, with many more normal beats than VPBs.

To determine the most relevant feature, LDFs with feature vector length of  $K = 1$  are first determined for all features separately. The feature whose LDFs (one for each treatment) yields the largest  $J$  for the evaluated set of treatments, is judged as the most relevant. Then, the second most relevant feature is determined for LDFs when  $\mathbf{x}$  contains two features, i.e.,  $K = 2$ . The feature which, together with the most relevant feature, results in the largest  $J$  is judged as the second most relevant. The third most relevant feature is determined in the same way, and so on.

## 5 Results

Figure 4 presents the performance index  $J$  as a function of the number of features. For the complete data set the following five features were found to be the most relevant— $T_{pp}^n$ ,  $T_{zp}^c$ ,  $T_{np}^{c-}$ ,  $\Delta T_{pp}$ , and  $P_{np}^{c-}$ —and therefore used for classification. When the data set is reduced to only include treatments with  $\bar{P}_{np} \geq 1$  mmHg,  $T_{pp}^n$  remains the most



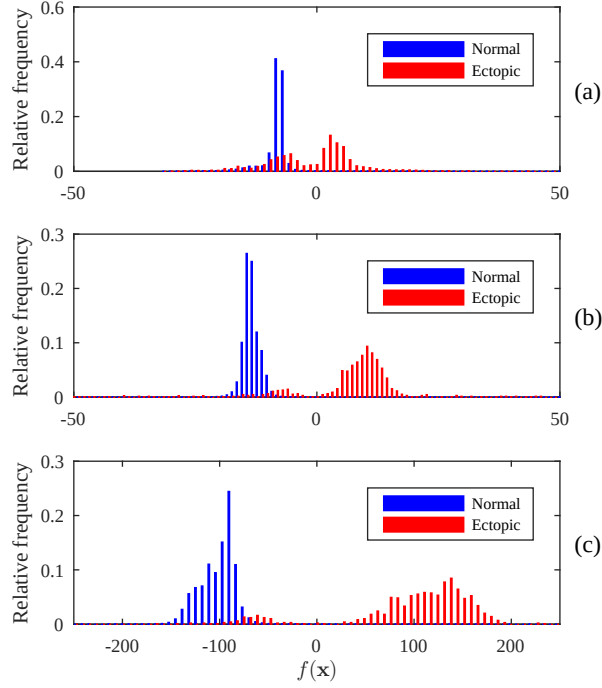
**Figure 4:** The performance index  $J$  versus the number of features used for linear discriminant analysis when based on (a) all nine treatments, (b) seven treatments with  $\bar{P}_{np} \geq 0.7$  mmHg, and (c) five treatments with  $\bar{P}_{np} \geq 1$  mmHg.

relevant feature, whereas the order of relevance changes for the other features; the same observation applies to  $\bar{P}_{np} \geq 0.7$  mmHg. From Fig. 4 it is noted that  $J$  equals 0.9 when requiring that  $\bar{P}_{np} \geq 1$  mmHg, while it drops to 0.55 when all treatments are analyzed.

Histograms of  $f(\mathbf{x})$  for normal and VPBs are shown in Fig. 5. Since the total number of normal beats is much larger than the total number of VPBs, the histograms have been normalized with respect to the total number of beats in each class. As expected, the two beat classes becomes more well-separated as the lower limit of  $\bar{P}_{np}$  increases.

The receiver operating characteristic (ROC) is shown in Fig. 6 when the five most significant features are used for classification. As expected, better performance is achieved as the lower limit of  $\bar{P}_{np}$  increases.

The ectopic beat count (EBC), defined as the relative number of VPBs in a 10-min sliding window [5], is shown for treatment #1 in Fig. 7. The agreement between the EBC derived from the estimated cardiac pressure signal and the EBC derived from the annotations is satisfactory. The number of VPBs increases towards the end of the treatment—a behavior often observed in hemodialysis patients. The EBC for treatment #2 fluctuates more over time, see Fig. 8, but the agreement is still satisfactory. For both these treatments,  $\bar{P}_{np}$  exceeds 1 mmHg. On the other hand, the agreement is much worse for treatment #8 due to that  $\bar{P}_{np}$  is very low (0.55 mmHg), see Fig. 9. Table 2 presents the mean difference and standard deviation of EBC for all treatments.

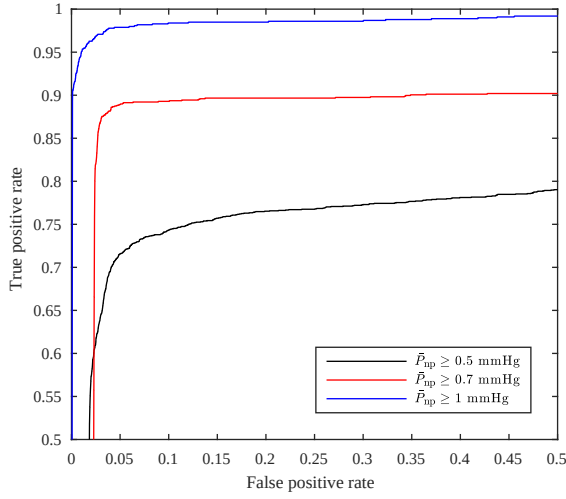


**Figure 5:** Normalized histograms of normal beats and VPBs as a function of the linear discriminant function  $f(\mathbf{x})$ , involving (a) all nine treatments, (b) seven treatments with  $\bar{P}_{np} \geq 0.7$  mmHg, and (c) five treatments with  $\bar{P}_{np} \geq 1$  mmHg.

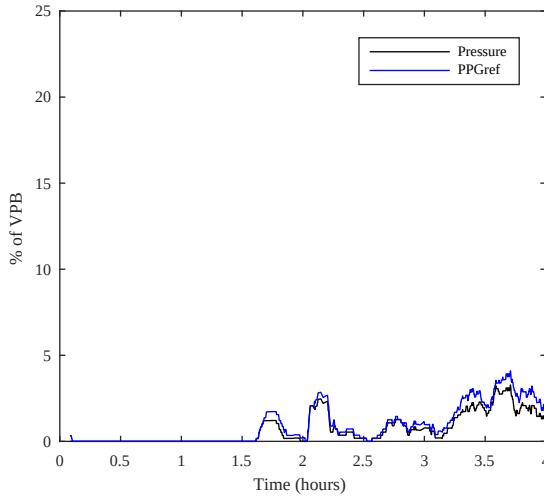
**Table 2:** Ectopic beat count

| Treatment # | $\bar{P}_{np}$ | Mean $\Delta\text{EBC}$ , % | Std $\Delta\text{EBC}$ , % |
|-------------|----------------|-----------------------------|----------------------------|
| 1           | 5.0            | -1.46                       | 1.89                       |
| 2           | 2.9            | -0.40                       | 1.18                       |
| 3           | 1.8            | 0.32                        | 1.01                       |
| 4           | 1.3            | -0.52                       | 2.41                       |
| 5           | 1.3            | 0.15                        | 0.74                       |
| 6           | 0.70           | 0.49                        | 2.39                       |
| 7           | 0.70           | 32.99                       | 12.67                      |
| 8           | 0.55           | 23.63                       | 11.91                      |
| 9           | 0.54           | -4.56                       | 13.76                      |

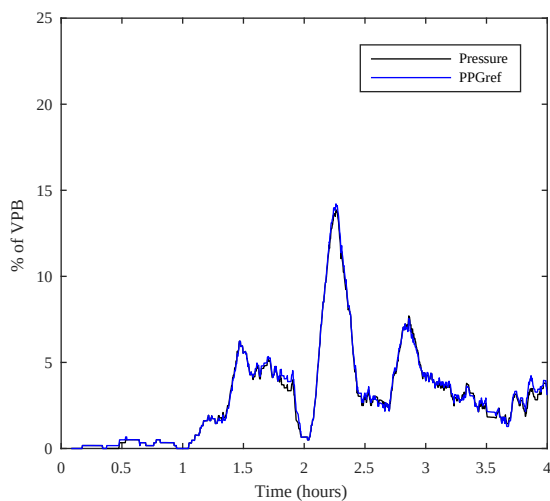
$\bar{P}_{np}$  is the average pulse pressure of the cardiac pressure signal determined during blood pump stop.  $\Delta\text{EBC}$  denotes the difference between classified and annotated EBC.



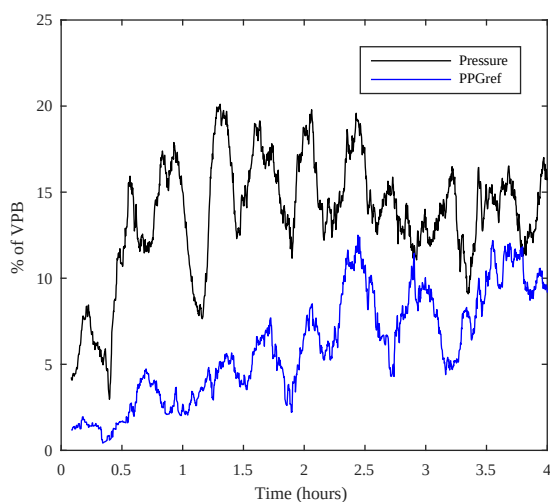
**Figure 6:** Receiver operating characteristic for VPB detection using linear discriminant analysis of the five most relevant features, for treatments with different lower limits of  $\hat{P}_{np}$ .



**Figure 7:** Percentage of VPBs during a 10-min sliding window in treatment #1. “PPGref” denotes the percentage of VPBs according to the annotations, and “Pressure” denotes the percentage of VPBs from detection.



**Figure 8:** Percentage of VPBs during a 10-min sliding window in treatment #2. “PPGref” denotes the percentage of VPBs according to the annotations, and “Pressure” denotes the percentage of VPBs from detection.



**Figure 9:** Percentage of VPBs during a 10-min sliding window in treatment #8. “PPGref” denotes the percentage of VPBs according to the annotations, and “Pressure” denotes the percentage of VPBs from detection.

## 6 Discussion

We have demonstrated that the information provided by the extracorporeal arterial and venous pressure sensors can be used for detecting VPBs when the average cardiac pulse pressure  $\bar{P}_{np}$  exceeds 1 mmHg, previously suggested in [6]. When exceeding, the detection performance is similar to that achieved by analyzing the PPG. However, for  $\bar{P}_{np} < 1$  mmHg, the performance drops due to reduced separation between normal beats and VPBs, see Fig. 5. Another manifestation of a low  $\bar{P}_{np}$  is that the number of VPBs is overestimated, see Fig. 9, which is related to inaccurate estimation of the peak-to-peak interval  $T_{pp}$  in treatments with  $\bar{P}_{np} < 1$  mmHg. For the particular treatment in Fig. 9 the considerable variation in heart rate ( $\sigma_{pp} = 191$  ms, see Table 1) may have contributed to overestimation of VPBs.

In our experience, the properties of the fistula largely determines the amplitude of the cardiac pressure signal, and, accordingly, whether the patient is suitable for VPB detection. In addition, this amplitude may vary between different designs of hemodialysis machine. Unfortunately, the present data set is much too small to provide insight on the percentage of the hemodialysis population which is suitable for VPB detection with the present method.

For treatments with  $\bar{P}_{np} \geq 1$  mmHg, the performance index  $J$  does not improve when more than one feature are analyzed, see Fig. 4. On the other hand, for  $\bar{P}_{np} < 1$  mmHg,  $J$  improves with at least four additional features. Irrespective of  $\bar{P}_{np}$ ,  $T_{pp}^n$  remains the most relevant feature on the present data set.

Given that the data set is unbalanced, the number of false positives will surpass the number of true positives for  $\bar{P}_{np} < 1$  mmHg, see Fig. 6. As a result, the classifier overestimates the number of VPBs for virtually any point on the ROC. On the other hand, for  $\bar{P}_{np} \geq 1$  mmHg, a true positive rate of 0.9 is achieved with very few false positives.

Heartbeat classification is a well-studied problem in ECG signal processing, and many sophisticated techniques have emerged for this purpose, see, e.g., [14, 15, 16, 17]. While those studies rest on solid knowledge on the properties of the ECG signal, the present study explores heartbeat classification in relation to a novel type of signal whose properties have never before been explored for VPB detection. As a result, the present focus is more on feasibility than on methodological advances, and, therefore, well-known techniques are embraced such as empirical mode decomposition and linear discriminant analysis.

When collecting the present database, it was unfortunately not practically feasible to record the ECG. However, we have previously shown that VPBs can be classified from the PPG signal, and that the PPG signal can be used as a surrogate for the ECG signal when analyzing heart rate turbulence [9], see also related work on automated VPB detection in the PPG signal [18, 19]. Although the ECG signal offers better

temporal accuracy than does the PPG signal, we consider the accuracy of PPG-based classification to be sufficient when the goal is to evaluate detection performance for a method analyzing the cardiac pressure signal.

A major limitation of the present study is that the data set is much too small for a meaningful division into training and test sets. Therefore, the results of the present study should be viewed as a proof-of-concept that VPBs can be detected from the cardiac pressure signal.

## 7 Conclusions

The results show that VPB detection based on the cardiac pressure signal, estimated from the arterial and the venous pressure signals, is feasible. Satisfactory detection performance can be achieved when the average cardiac pulse pressure exceeds 1 mmHg. Another study is required on a much larger data set.

## Acknowledgments

The authors are grateful to Mårten Segelmark, Lena Mattsson, and Sarok Said at Skåne University Hospital, Lund, Sweden, for carrying out the clinical investigation.

Bo Olde and Mattias Holmer are employed by Baxter International Inc. Bo Olde has a registered patent, WO2011080189(A1), related to the present paper.

This work was supported by the Swedish Research Council (00923/2011), the Crafoord Foundation, MINECO (Spain) through projects TIN2014-53567-R and DPI2016-75458-R, and by European Social Fund and Aragón Government through consolidated group T96.

Ethical approval was given by the Regional Ethical Review Board in Lund, Dnr 314/2008.

## References

- [1] O. M. Shapira and Y. Bar-Khayim, “ECG changes and cardiac arrhythmias in chronic renal failure patients on hemodialysis,” *J. Electrocardiol.*, vol. 25, pp. 273–279, 1992.
- [2] S. Abe, M. Yoshizawa, N. Nakanishi, T. Yazawa, K. Yokota, M. Honda, and G. Sloman, “Electrocardiographic abnormalities in patients receiving hemodialysis,” *Am. Heart J.*, vol. 131, pp. 1137–1144, 1996.

- [3] A. Santoro, E. Mancini, R. Gaggi, S. Cavalcanti, S. Severi, L. Cagnoli, F. Badiali, B. Perrone, G. London, H. Fessy, L. Mercadal, and F. Grandi, "Electrophysiological response to dialysis: the role of dialysate potassium content and profiling," *Contrib. Nephrol.*, vol. 149, pp. 295–305, 2005.
- [4] J. O. Burton, S. Korsheed, B. J. Grundy, and C. W. McIntyre, "Hemodialysis-induced left ventricular dysfunction is associated with an increase in ventricular arrhythmia," *Renal Failure*, vol. 30, pp. 701–709, 2008.
- [5] K. Solem, A. Nilsson, and L. Sörnmo, "An ECG-based method for early detection of abrupt changes in blood pressure during hemodialysis," *ASAIO J.*, vol. 52, pp. 282–290, 2006.
- [6] M. Holmer, F. Sandberg, K. Solem, B. Olde, and L. Sörnmo, "Cardiac signal estimation based on the arterial and venous pressure signals of a hemodialysis machine," *Physiol. Meas.*, vol. 37, no. 9, pp. 1499–1515, 2016.
- [7] M. Holmer, F. Sandberg, K. Solem, E. Grigonyte, B. Olde, and L. Sörnmo, "Extracting a cardiac signal from the extracorporeal pressure sensors of a hemodialysis machine," *IEEE Trans. Biomed. Eng.*, vol. 62, no. 5, pp. 1305–1315, 2015.
- [8] J. Lázaro, E. Gil, J. M. Vergara, and P. Laguna, "Pulse rate variability analysis for discrimination of sleep-apnea-related decreases in the amplitude fluctuations of pulse photoplethysmographic signal in children.," *IEEE J. Biomed. Health Inform.*, vol. 18, pp. 240–246, 2014.
- [9] E. Gil, P. Laguna, J. P. Martínez, Ó. Barquero-Pérez, A. García-Alberola, and L. Sörnmo, "Heart rate turbulence analysis using photoplethysmography," *IEEE Trans. Biomed. Eng.*, vol. 60, pp. 3149–3155, 2013.
- [10] N. E. Huang, Z. Shen, S. R. Long, M. C. Wu, H. H. Shih, Q. Zheng, N.-C. Yen, C. C. Tung, and H. H. Liu, "The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis," *Proc. Royal Soc. London A: Math. Phys. Eng. Sci.*, vol. 454, no. 1971, pp. 903–995, 1998.
- [11] G. Rilling, P. Flandrin, P. Gon, and D. Lyon, "On empirical mode decomposition and its algorithms," *IEEE EURASIP Workshop on Nonlin. Signal and Image Process.*, vol. 3, pp. 8–11, 2003.
- [12] R. O. Duda, P. E. Hart, and D. G. Stork, *Pattern Classification*. New York: Wiley–Interscience, 2nd ed., 2001.

- 
- [13] W. J. Youden, "Index for rating diagnostic tests," *Cancer*, vol. 3, no. 1, pp. 32–35, 1950.
  - [14] M. Lagerholm, C. Peterson, G. Braccini, L. Edenbrandt, and L. Sörnmo, "Clustering ECG complexes using Hermite functions and self-organizing maps," *IEEE Trans. Biomed. Eng.*, vol. 47, pp. 838–848, 2000.
  - [15] I. Christov, G. Gómez-Herrero, V. Krasteva, I. Jekova, A. Gotchev, and K. Egiazarian, "Comparative study of morphological and time-frequency ECG descriptors for heartbeat classification," *Med. Eng. & Physics*, vol. 28, no. 9, pp. 876–887, 2006.
  - [16] I. Jekova, G. Bortolan, and I. Christov, "Assessment and comparison of different methods for heartbeat classification," *Med. Eng. & Physics*, vol. 30, pp. 248–257, 2008.
  - [17] M. Llamedo and J. P. Martínez, "An automatic patient-adapted ECG heartbeat classifier allowing expert assistance," *IEEE Trans. Biomed. Eng.*, vol. 59, no. 8, pp. 2312–2320, 2012.
  - [18] T. Suzuki, K. I. Kameyama, and T. Tamura, "Development of the irregular pulse detection method in daily life using wearable photoplethysmographic sensor," *Int. Conf. IEEE EMBS*, pp. 6080–6083, 2009.
  - [19] A. Sološenko, A. Petrénas, and V. Marozas, "Photoplethysmography-based method for automatic detection of premature ventricular contractions," *IEEE Trans. Biomed. Circuits Syst.*, vol. 9, no. 5, pp. 662–669, 2015.



## *Paper IV*



# Detection of Needle Dislodgement Using the Extracorporeal Pressure Signals

## Abstract

Venous needle dislodgement during dialysis is a rarely occurring adverse event which becomes life-threatening if not handled promptly. Since the standard venous pressure alarm, implemented in most dialysis machines, has low sensitivity, we propose a novel approach to the detection of needle dislodgement. Four features are extracted from the arterial and venous pressure signals of the dialysis machine, describing the mean venous pressure, the venous cardiac pulse pressure, and the time delay and the correlation between the arterial and the venous pressure. The features serve as input to a support vector machine determining whether a dislodgement has occurred. The support vector machine is trained on a set of laboratory data, and then tested on another set of laboratory data as well as on data from four hemodialysis clinical sessions. The results show that dislodgement can be detected already after 2–8 s, corresponding to 7–60 ml blood loss. The results are promising, however, the method should be tested on a larger set of clinical data to better establish its performance.

---

Based on:

Mattias Holmer, Bo Olde, Frida Sandberg, Leif Sörnmo

“Detection of Needle Dislodgement Using the Extracorporeal Pressure Signals,”

To be submitted.



# 1 Introduction

Venous needle dislodgement (VND) is an adverse, but rare, event occurring during hemodialysis. After a few minutes, so much blood is lost that the patient will suffer from severe injury. Patients with a normal blood volume of 3–5 liters, subjected to a normal extracorporeal blood flow rate of 200–500 ml/min not returned to the body, will likely suffer from fatal blood loss within 2–5 min. Blood loss during dialysis has several causes, including VND, needle connector fault, blood line rupture, bleeding at the access, and subcutaneous bleeding. According to a survey by Veterans Health Administration, as many as 65% of all blood loss incidents are caused by VND, whereas 20% by needle connector fault [1].

The VND incidence rate depends on several factors such as the material and technique used for needle fixation, the position of the blood access, and the mental condition of the patient [2]. The reported number of VNDs falls within a wide range. The number has been estimated to more than 200 per day worldwide [3]. In Germany, the number of accidental VNDs per treatment has been reported to be 0.028% [4]. In a patient questionnaire by US Renal Physician Association [5], about 5% of all patients claimed that, during the last 3 months, the needle had dropped out of its access before the end of treatment. Sardoni et al. have estimated the VND incident rate to 1 in 125 000 treatments, of which 10–33% led to death [6]. Veterans Health Administration analyzed VNDs in their clinics during 2002–2008 [7], reporting on a rate of 1 in 62 000 treatments. Of all VNDs, 75% occurred in patients characterized as restless, confused, agitated, or uncooperative; about 25% of all patients belong to this group.

According to the standards of medical electrical equipment [8], a dialysis machine must be equipped with a venous pressure alarm which stops the blood pump and clamps the blood lines in case of a venous pressure outside the alarm limits. It is, however, often difficult for the staff to set the alarm limits such that a high sensitivity is assured without also causing numerous false alarms [9]. Moreover, the location of the leakage may have vital importance for detection. For example, if a dislodged needle is trapped in the bed under the clothes of the patient, the venous pressure may remain within the acceptable interval, and large amounts of lost blood may go undetected. Ribitsch et al. determined the number of patients in which venous pressure monitoring is expected to detect VND, by measuring the mean intra-access pressure in 99 patients (34 with grafts and 65 with fistulas) [10]. The results showed that VND was detected in 32 of the patients with grafts, but only in 19 of the patients with fistulas. In another study, based on a questionnaire answered by dialysis nurses, a VND alarm was issued immediately in 50% of all patients, after a delay in 30%, and not at all in 20% [11]. The length of the delay was unfortunately not specified.

In the present paper, we propose a novel method for VND detection and evaluate

its performance. The method makes use of the arterial and venous pressure sensors in the extracorporeal circuit of the dialysis machine by monitoring the presence of cardiac pulses in the venous pressure sensor. If the cardiac signal disappears from the venous pressure signal a VND is assumed to have occurred, the blood pump is then stopped, and an alarm is issued. The method involves nonlinear filtering [12, 13] to separate the pressure pulses originating from the heart from the much larger pressure pulses originating from the peristaltic blood pump. This pump is responsible for creating the blood flow in the extracorporeal blood circuit of the dialysis machine. The performance of the method is evaluated on VNDs produced in the lab, as well as on a number of VNDs produced under controlled circumstances as part of a clinical study.

## 2 Background

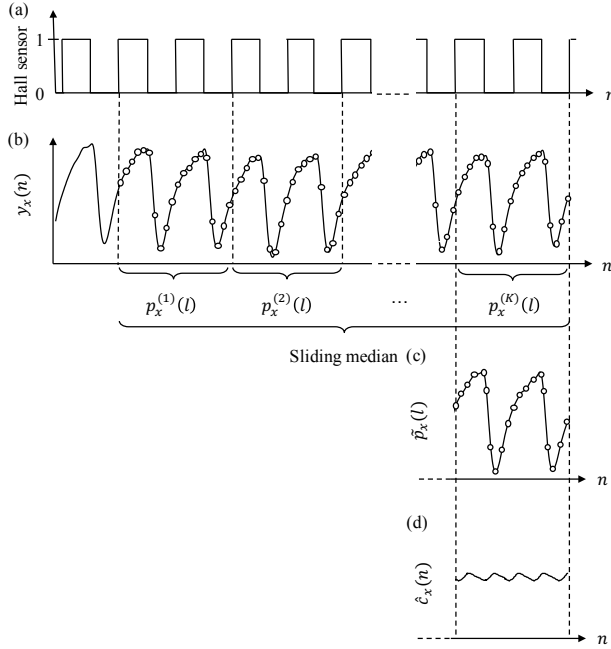
The arterial and venous cardiac pressure signals, denoted  $c_a(n)$  and  $c_v(n)$ , respectively, are estimated from the arterial and venous pressure signals, denoted  $y_a(n)$  and  $y_v(n)$ , respectively; the latter signals are measured at the inlet and outlet of the extracorporeal blood circuit of the dialysis machine, respectively. The signals  $y_a(n)$  and  $y_v(n)$  are dominated by the pump pressure signals, denoted  $p_a(n)$  and  $p_v(n)$ , respectively, but also contain  $c_a(n)$  and  $c_v(n)$  which have much lower amplitudes. When processing clinical data (instead of lab data), the cardiac pressure signals are estimated using the method previously described in [13], but with the difference that two separate cardiac signal estimates are produced, i.e.,  $\hat{c}_a(n)$  and  $\hat{c}_v(n)$ .

The lab data was recorded with a dialysis machine different from the one used in the clinical study. Since the angular position of the blood pump rotor was provided by a Hall sensor in the lab machine, the original extraction method was modified to also take this information into account. The Hall sensor samples the angular position four times per pump revolution, see below.

The pressure signals are resampled  $L$  times per pump revolution (the samples being evenly distributed between the four angular positions provided by the Hall sensor), resulting in the local signals  $p_x^{(k)}(l)$ ,  $x \in \{a, v\}$ , where  $l$  ( $= 1, \dots, L$ ) indexes the angular samples of one revolution, and  $k$  ( $= 1, \dots, K$ ) indexes the revolutions, see Figs. 1(a) and (b). The samples at the same local angular position  $l$  in different revolutions are subjected to median filtering,

$$\tilde{p}_x(l) = \text{median}(p_x^{(1)}(l), \dots, p_x^{(K)}(l)), \quad l = 1, \dots, L, \quad (1)$$

which removes outliers that sometimes are present, see Fig. 1(c). The signal  $\tilde{p}_x(l)$  represents an estimate of the pressure pulses due to the blood pump, observed at the



**Figure 1:** Overview of the signal extraction method used to process lab data. (a) Hall signal for identifying complete pump revolutions (dashed, vertical line). (b) Pressure signal  $y_x(n)$  (solid line). The circles denotes  $y_x(n)$  at the angular equidistant positions, together constituting the local functions  $p_x^{(k)}(l)$ . (c) Median pump signal  $\tilde{p}_x(l)$ . (d) Desired estimate of the cardiac signal  $\hat{c}_x(n)$  at revolution  $K$ .

$K$ :th revolution. A local cardiac pressure estimate of the same revolution is obtained by

$$\hat{c}_x(l) = p_x^{(K)}(l) - \tilde{p}_x(l). \quad (2)$$

The local cardiac estimate  $\hat{c}_x(l)$  is evenly resampled to produce the desired cardiac estimate  $\hat{c}_x(n)$  with the original sampling rate, see Fig. 1(d). Then, the estimation procedure is repeated for the subsequent pump revolution, and so on.

## 3 Experiment and Database

### 3.1 Clinical Data

A clinical investigation of VND was performed on patients with kidney failure at Lund University Hospital, Sweden. The study was approved by the local ethical review board, and all patients agreed to participate in the study by signing an informed consent. The patients were treated using the AK 200 dialysis machine from Gambro, Lund, and the venous and arterial pressures were recorded with an external device connected to the blood circuit. Only patients withstanding a blood loss of 100 ml at 200 ml/min were included in the study. The patients had a predialysis haemoglobin concentration of at least 135 g/L, and a predialysis blood pressure of at least 130 mmHg. The blood pressure was not allowed to fall below 120 mmHg before the VND, and not fall more than 15 mmHg from start of treatment to VND. A physician was present during the test to make the final decision whether the patient's condition was adequate for pursuing the VND.

The patients were given saline and plasma expanders in advance to compensate for the blood loss due to the VND. A few seconds before the VND, the patient was placed in the Trendelenburg position (i.e. feet tilted up and head down) to avoid hypotension. To prevent bleeding from the venous access site after dislodgement, the staff applied pressure onto a sterile gauze placed at the access site immediately before the needle was dislodged. After dislodgement, the venous needle was held steadily and the blood was pumped into a waste container for 30 s. The treatment was terminated immediately afterwards by feeding back the blood in the dialyzer and the blood line via the arterial needle to the patient. Four patients were scheduled to undergo six treatments, however, one patient suffered from cardiovascular complications during two treatments, thereby preventing the staff from completing the protocol. The remaining three patients went through the VND procedure without any adverse symptoms.

The arterial and venous pressure signals were recorded at 1000 Hz, and then decimated to 100 Hz before extraction of the cardiac signals.

The blood pressure and the hemoglobin concentration are presented for the patients in Table 1.

**Table 1:** Treatment data

| Treatment number | $p_{\text{SBP1}}$<br>mmHg | $p_{\text{SBP2}}$<br>mmHg | $c_{\text{HGB}}$<br>g/L | $\bar{c}_a^{\text{PP}}$<br>mmHg | $\bar{c}_v^{\text{PP}}$<br>mmHg |
|------------------|---------------------------|---------------------------|-------------------------|---------------------------------|---------------------------------|
| 1                | 192                       | 184                       | 127*                    | 0.95                            | 0.97                            |
| 2                | 150                       | 150                       | 119*                    | 0.80                            | 0.77                            |
| 3                | 164                       | 164                       | 135                     | 0.42                            | 0.40                            |
| 4                | 165                       | 122**                     | 135                     | 0.17                            | 0.08                            |

Treatment data before VND. The systolic blood pressure  $p_{\text{SBP1}}$  was measured before treatment and  $p_{\text{SBP2}}$  immediately before VND. The hemoglobin concentration before treatment, and the mean arterial and mean venous cardiac signal pulse pressure measured during blood pump stop are denoted  $c_{\text{HGB}}$ ,  $\bar{c}_a^{\text{PP}}$ , and  $\bar{c}_v^{\text{PP}}$ , respectively. In two cases (marked with \*), the predialysis value was lower than that of the predefined selection criteria, however, the physician still judged the patients to withstand VND. In one case (\*\*), the systolic blood pressure dropped more than 15 mmHg, but the patient was still judged to withstand VND.

### 3.2 Laboratory Data with Artificial Cardiac Pulses

In order to get more data, as well as to investigate VND detection under less restrictive conditions than those in the clinic, lab tests were conducted in a series of treatments on a vascular access simulator, using an Artis dialysis machine from Gambro, Medolla, Italy. The vascular access simulator is a lab set-up for dialysis of bovine blood, providing a “vascular access” with blood flow and pressure pulses which mimic the ones in the vascular access of a patient. The temperature of the bovine blood was kept constant at 37° C. Access to the vascular access simulator was established by inserting the dialysis needles via two blood ports into the vascular access, being a plastic tube with 8 mm inner diameter. In all treatments utilizing the vascular access simulator, several VNDs were performed at different blood flows, with different needle sizes, heart pulsation magnitudes, and rates. The time of the VND was annotated manually. The arterial and venous pressure signals were recorded at 200 Hz, and decimated to 100 Hz before extracting the cardiac signals.

A Hall sensor was used to indicate the angular position of the blood pump rotor. The resulting Hall signal, sampled at a rate of 400 Hz, produced two pulses per revolution, where the time of the positive and negative flanks corresponded to four different angular positions of the rotor.

Two different methods for generating the arterial and venous signals with heart pulsations were employed when creating the training and test sets. The training set was created by first recording arterial and venous pressure signals without any cardiac pressure pulses. A simulated cardiac pressure signal  $c_s(n)$  was then added to the entire arterial pressure signal, whereas, to simulate a VND,  $c_s(n)$  was added to the venous pressure signal only until the annotated time for VND. By adding simulated cardiac signals, it is possible to test various treatment settings and dislodgement scenarios, using different cardiac signal characteristics. The conditions for creating the training set are summarized in Table 2—conditions which are combined with heart rates and cardiac signal amplitudes in the intervals given in Sec. 3.3. The training set was defined by a total of 1782 dislodgement combinations.

The test set was based on recordings with physically generated cardiac pressure pulses, i.e., with the heart pulsations of the vascular access simulator enabled. For the test set, access flow, access pressure, heart pulsation magnitude, and heart pulse rate were selected according to Table 3.

**Table 2:** Conditions at dislodgements without cardiac pulses

| Dislodgement # | Needle mode    | Needle size | Blood pump flow<br>ml/min |
|----------------|----------------|-------------|---------------------------|
| 1              | Into sponge    | 16G         | 100                       |
| 2              | Into sponge    | 16G         | 400                       |
| 3              | Into sponge    | 14G         | 300                       |
| 4              | Into sponge    | 14G         | 500                       |
| 5              | At fixed level | 16G         | 100                       |
| 6              | At fixed level | 16G         | 300                       |
| 7              | At fixed level | 16G         | 430                       |
| 8              | At fixed level | 16G         | 400                       |
| 9              | At fixed level | 14G         | 100                       |
| 10             | At fixed level | 14G         | 300                       |
| 11             | At fixed level | 14G         | 450                       |
| 12             | Moving         | 16G         | 100                       |
| 13             | Moving         | 16G         | 300                       |
| 14             | Moving         | 16G         | 400                       |
| 15             | Moving         | 14G         | 100                       |
| 16             | Moving         | 14G         | 300                       |
| 17             | Moving         | 14G         | 400                       |

Summary of VND experiments performed on the vascular access simulator without physical heart pulsation enabled. “Into sponge” simulates a venous needle stuck in the patient’s bedding. “At fixed level” means that the needle has first dropped 20 cm, and is then remaining in a fixed position. “Moving” means that the needle has first dropped 20 cm, and then allowed to move freely. The access flow in the simulated fistula is set to 600 ml/min, the access pressure is set to 20 mmHg, and the hematocrit is set to 34%. The dialyzer is a PolyFlux 170H by Gambro.

**Table 3:** Conditions at dislodgements on the vascular access simulator

| Dislodgement # | Needle mode    | Blood pump flow<br>ml/min | Heart rate<br>bpm |
|----------------|----------------|---------------------------|-------------------|
| 1–3            | Moving         | 100                       | 59.4              |
| 4–6            | Moving         | 300                       | 59.4              |
| 7–9            | Moving         | 500                       | 98.9              |
| 10–12          | At fixed level | 100                       | 59.4              |
| 13–15          | At fixed level | 300                       | 59.4              |
| 16–18          | At fixed level | 500                       | 98.9              |
| 19–21          | Into sponge    | 100                       | 59.4              |
| 22–24          | Into sponge    | 300                       | 59.4              |
| 25–27          | Into sponge    | 500                       | 98.9              |

Summary of the conditions at the dislodgements performed with physical generation of cardiac signal with the vascular access simulator. The venous cardiac peak-to-peak amplitude is approximately 1.2 mmHg, the access flow in the simulated fistula is set to 750ml/min, the access pressure is set to 25mmHg, hematocrit is set to 34%, the dialyzer type is Polyflux 170H by Gambro, and the needle size is 15G.

### 3.3 Simulated cardiac signal

The cardiac signal  $c_s(n)$  is simulated using the model previously described in [12], involving frequency modulation of sinusoids with the fundamental frequency  $f_0$  and  $L - 1$  harmonics:

$$c_s(n) = a(n) \sum_{l=1}^L \alpha_l \cos \left( 2\pi l f_0 \left( n + \frac{g(n)}{g_{\max}} \right) + \phi_l \right), \quad (3)$$

where  $a(n)$  is a amplitude modulating function, the weights  $\alpha_l$  and the phases  $\phi_l$  together define the shape of the heart pulses, and  $g_{\max}$  is the maximum of the frequency modulating function  $g(n)$  defined by

$$g(n) = \sum_{j=0}^n m(j). \quad (4)$$

The function  $m(n)$  models heart rate variability as an autoregressive model with Gaussian input; the parameter values are given in [14]. The amplitude modulation is de-

scribed by

$$a(n) = A - \frac{\sigma_c}{\sigma_m} m(n), \quad (5)$$

where the mean amplitude  $A$  has the (preset) standard deviation  $\sigma_c$ , whereas the standard deviation  $\sigma_m$  is determined for each realization of  $m(n)$ .

## 4 Methods

### 4.1 Feature extraction

Four features serve as input to the classifier, namely,

1. the mean venous pressure,
2. the venous cardiac pulse pressure,
3. the time delay between  $\hat{c}_a(n)$  and  $\hat{c}_v(n)$ , and
4. the correlation coefficient between  $\hat{c}_a(n)$  and  $\hat{c}_v(n)$ .

The mean venous pressure  $z_v(n)$  reflects the fact that a VND is typically accompanied with a change in the "static" venous pressure level, denoted  $\bar{y}_v(n)$ . This signal is determined as a sliding mean,

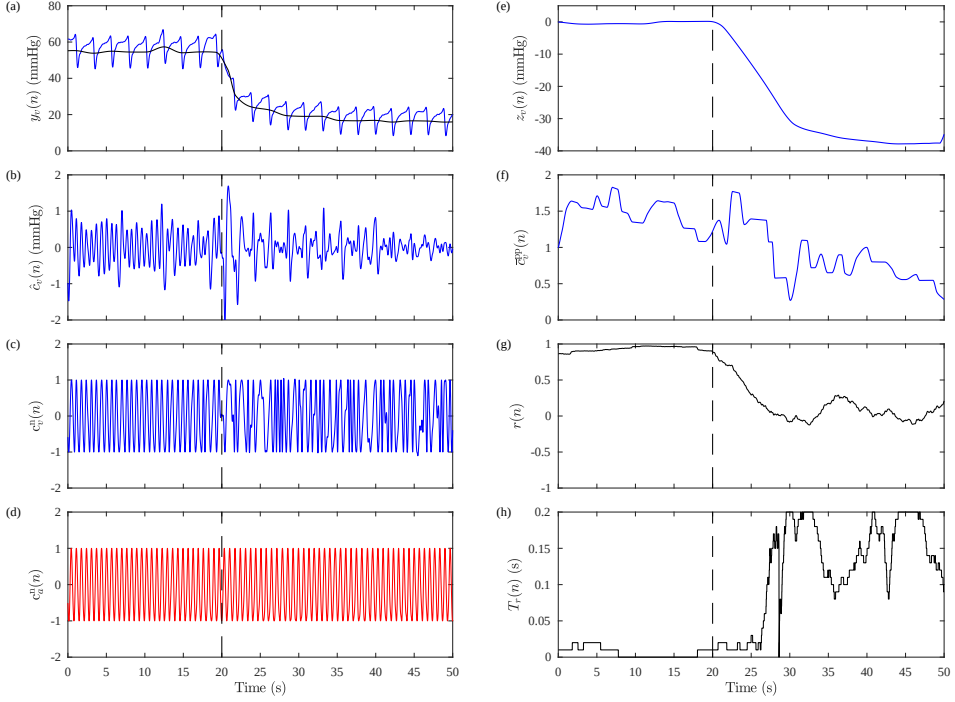
$$\bar{y}_v(n) = \frac{1}{N_p} \sum_{j=n-N_p+1}^n y_v(j), \quad (6)$$

where the window length  $N_p$  is set equal to the length of one blood pump revolution, see Fig. 2(a). The resulting signal  $\bar{y}_v(n)$  is centered by subtracting the sliding median,

$$z_v(n) = \bar{y}_v(n) - \text{median}(\bar{y}_v(n), \dots, \bar{y}_v(n - N_m + 1)), \quad (7)$$

where  $N_m$  is the window length, see Fig. 2(e). The sliding median represents a robust estimate of the dominating static venous pressure level.

The venous pulse pressure  $\bar{c}_v^{\text{PP}}(n)$  is selected as a feature since the venous cardiac signal will vanish at a VND. The pulse pressure of each heartbeat  $c_v^{\text{PP}}(k)$  is determined from  $\hat{c}_v(n)$  by subtracting, for the  $k$ :th pulse, the amplitude of the local maxima with the amplitude of the preceding local minima. To equidistantly sample  $c_v^{\text{PP}}(k)$ ,



**Figure 2:** Pressure signals (left column) and related features (right column) for the VND, occurring after 20 s (vertical dashed line). (a) Venous pressure  $y_v(n)$  (blue line) and filtered venous pressure  $\bar{y}_v(n)$  (black line), (b) estimated venous cardiac signal  $\hat{c}_v(n)$ , (c) normalized cardiac venous signal  $\hat{c}_v^n(n)$ , (d) normalized cardiac arterial signal  $\hat{c}_a^n(n)$ , (e) centered venous pressure  $z_v(n)$ , (f) normalized venous pulse pressure  $\bar{c}_v^{pp}(n)$ , (g) correlation coefficient  $r(n; \theta = 0)$ , and (h) time shift  $T_r(n)$ . Note that (c), (d), (f), and (g) are normalized and thus without unit.

the pulse pressures are interpolated using cubic splines, followed by normalization of  $\bar{c}_v^{pp}(n)$  with its sliding mean,

$$\bar{c}_v^{pp}(n) = \frac{\bar{c}_v^{pp}(n)}{\frac{1}{N_m} \sum_{j=n-N_m+1}^n \bar{c}_v^{pp}(j)}, \quad (8)$$

see Fig. 2(f).

The time delay between  $\hat{c}_a(n)$  and  $\hat{c}_v(n)$  is explored as a feature since the time delay resulting in the highest correlation between these two signals is expected to be zero when cardiac pulses are present in both signals. The absolute time delay  $T_r(n)$ ,

shown in Fig. 2(h), is determined by,

$$T_r(n) = \left\lfloor \frac{1}{F_s} N_r(n) \right\rfloor, \quad (9)$$

where

$$N_r(n) = \arg \max_{|\theta| < \lambda} r(n; \theta), \quad (10)$$

where  $\lambda$  defines the length of the search interval for the delay  $\theta$ . The correlation coefficient  $r(n; \theta)$  at a certain delay  $\theta$ , is computed in a sliding window of length  $N_c$ ,

$$r(n; \theta) = \frac{1}{\sigma_a(n)\sigma_v(n+\theta)} \sum_{j=n-N_c+1}^n \hat{c}_a^n(j) \hat{c}_v^n(j+\theta), \quad (11)$$

where  $\hat{c}_a^n(n)$  and  $\hat{c}_v^n(n)$  are amplitude normalized versions of  $\hat{c}_a(n)$  and  $\hat{c}_v(n)$ , respectively, and  $\sigma_a(n)$  and  $\sigma_v(n)$  are defined as the root sum square of the signals in the moving window,

$$\sigma_x(n) = \sqrt{\sum_{j=n-N_c+1}^n \hat{c}_x^n(j) \hat{c}_x^n(j)}, \quad x \in [a, v]. \quad (12)$$

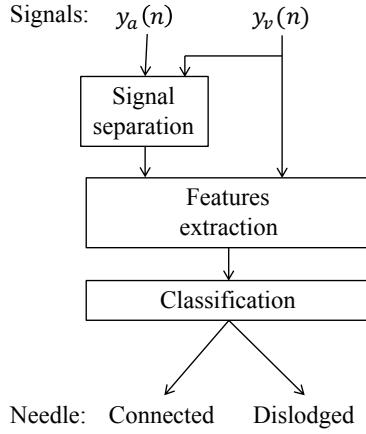
The signals  $\hat{c}_a^n(n)$  and  $\hat{c}_v^n(n)$  are computed by

$$\hat{c}_x^n(n) = \frac{\hat{c}_x(n) - \frac{1}{2}(e_x^{\max}(n) + e_x^{\min}(n))}{\frac{1}{2}(e_x^{\max}(n) - e_x^{\min}(n))}, \quad x \in [a, v], \quad (13)$$

where  $e_x^{\max}(n)$  and  $e_x^{\min}(n)$  are the upper and lower envelopes, respectively, of  $\hat{c}_x(n)$ , see Figs. 2(c) and (d). The upper envelope is computed by connecting the local maxima in  $\hat{c}_x(n)$  using cubic splines, whereas the lower envelope is computed by connecting the local minima in a similar manner.

The correlation coefficient  $r(n; \theta = 0)$  between  $\hat{c}_a^n(n)$  and  $\hat{c}_v^n(n)$  is the fourth feature, expected to be close to one when a cardiac signal is present in both the arterial and the venous pressure signals, see Fig. 2(g).

An overview of the method is shown in Fig. 3.



**Figure 3:** Overview of the VND detection method.

## 4.2 Training and testing

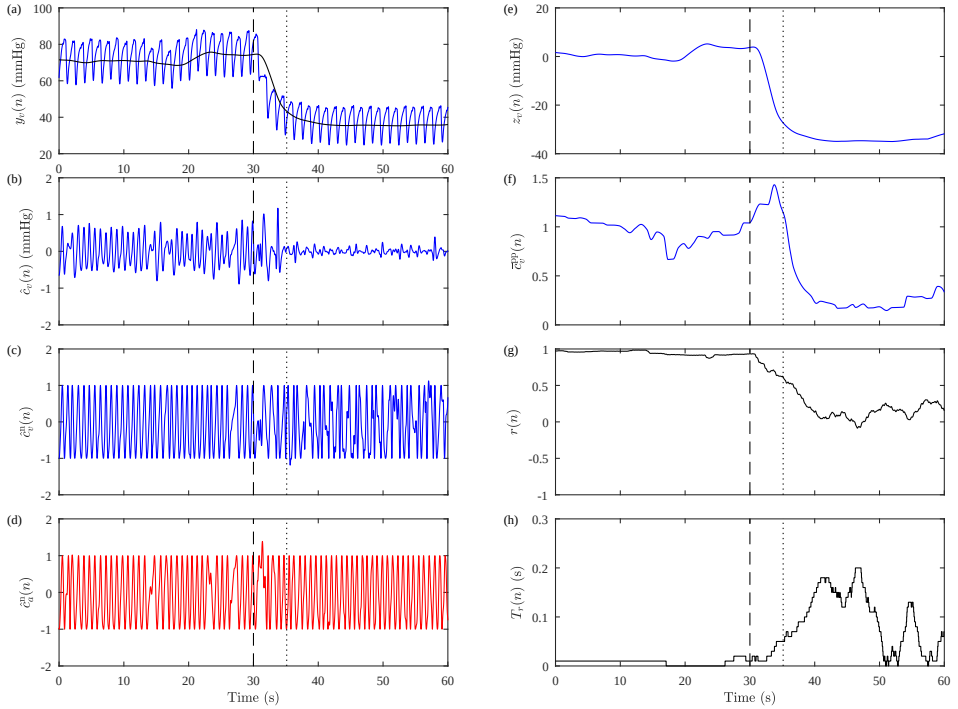
The above-mentioned four features serve as input to a support vector machine (SVM) learning model [15]. The signals are trained on the lab data, described in Sec. 3.2, to which a simulated heart signal is added, described in Sec. 3.3. The time period 3–14 s before the annotated time of VND was classified as needle connected, whereas the period 3–14 s after the VND was classified as dislodged; these two periods were used for training. The trained SVM classifier was then used on the test set, i.e., the lab data with a heart signal generated by the vascular access simulator.

## 4.3 Parameter settings

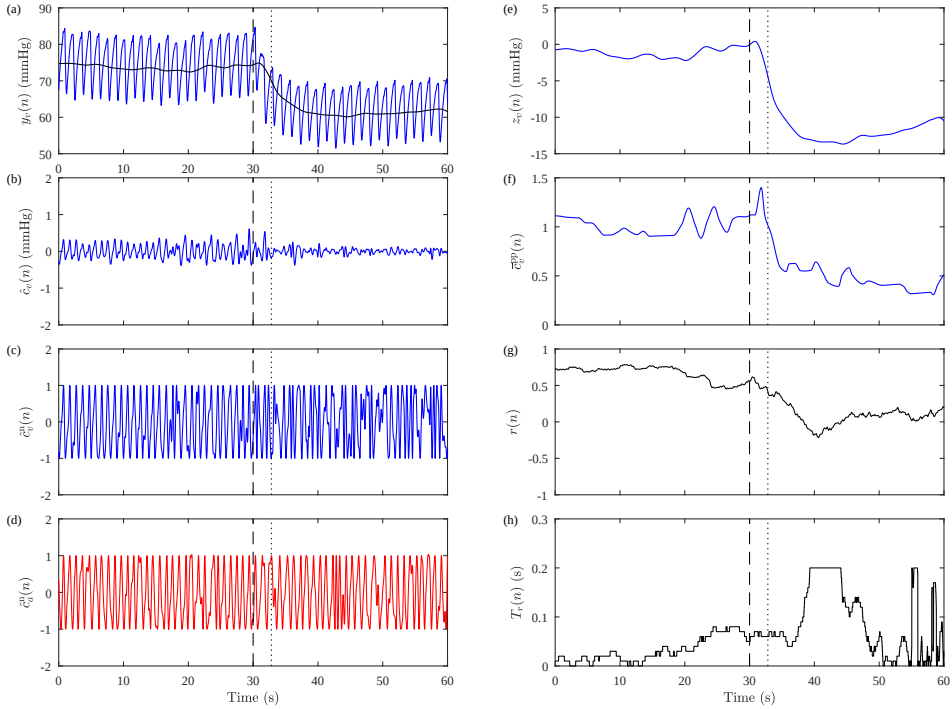
The following parameter values were used:  $L = 2$ ,  $\phi_1 = 0$ ,  $\phi_2 = 0.01$ ,  $\alpha_1 = 0.908$ ,  $\alpha_2 = 0.227$ ,  $\sigma_s = 0.05$ .  $K = 10$ ,  $N_m = 6000$  (corresponding to 60 s),  $\lambda = 200$  (corresponding to 0.2 s),  $N_c = 1000$  (corresponding to 10 s),  $F_s = 100$  Hz.

## 5 Results

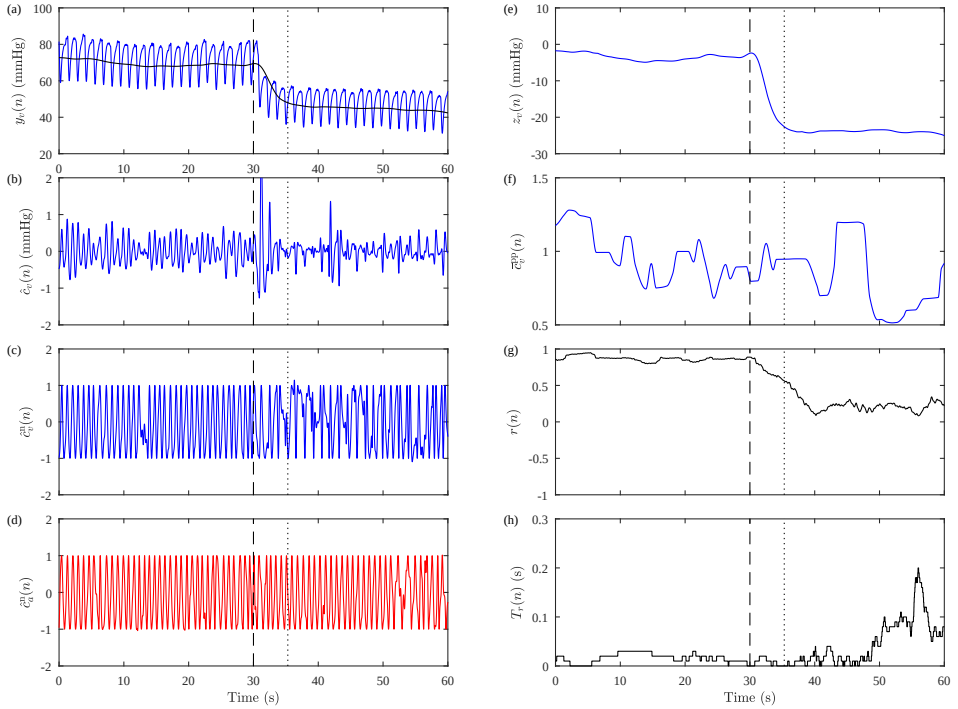
The VNDs in three out of the four patient treatments were correctly detected, even though their cardiac signal amplitudes were all below 1 mmHg, the limit below which the error in the estimated HR rapidly decreases [13], see Figs. 4–6. The remaining treatment had an extremely weak venous cardiac signal amplitude ( $< 0.1$  mmHg) which caused false alarms, see Fig. 7.



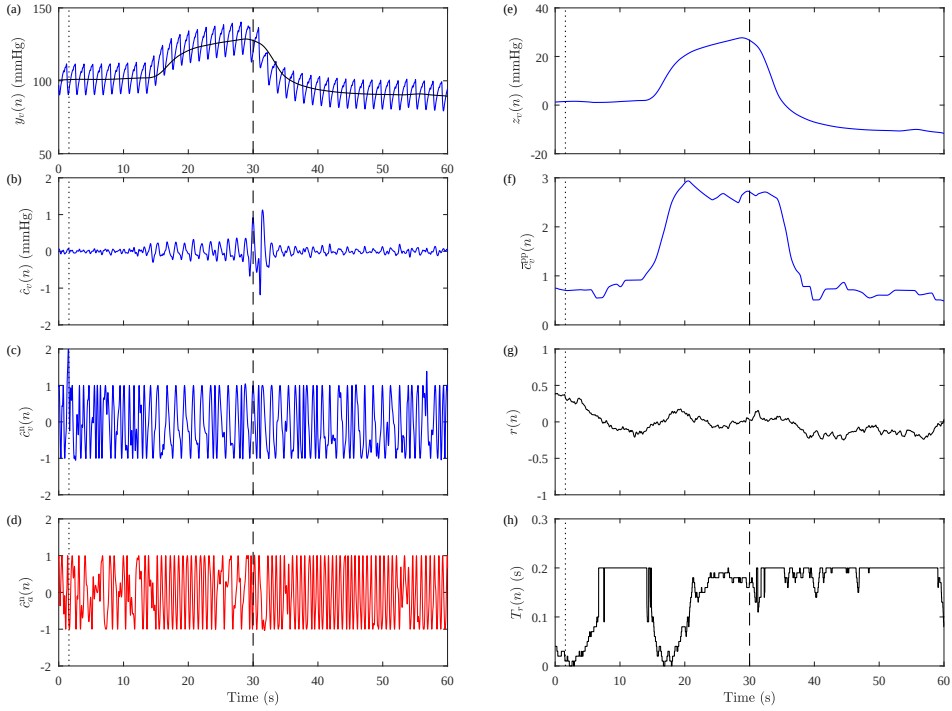
**Figure 4:** Pressure signals (left column) and related features (right column) for the VND in treatment #1, occurring after  $t = 30$  s (dashed vertical line). The detected time of the VND is indicated by the dotted vertical line. (a) Venous pressure  $y_v(n)$  (blue line) and filtered venous pressure  $\bar{y}_v(n)$  (black line), (b) estimated venous cardiac signal  $\hat{c}_v(n)$ , (c) normalized cardiac venous signal  $\hat{c}_v^n(n)$ , (d) normalized cardiac arterial signal  $\hat{c}_a^n(n)$ , (e) centered venous pressure  $z_v(n)$ , (f) normalized venous pulse pressure  $\hat{c}_v^{PP}(n)$ , (g) correlation coefficient  $r(n; \theta = 0)$ , and (h) time shift  $T_r(n)$ . Note that (c), (d), (f), and (g) are normalized and thus without unit.



**Figure 5:** Pressure signals (left column) and related features (right column) for the VND in treatment #2, occurring after  $t = 30$  s (dashed vertical line). The detected time of the VND is indicated by the dotted vertical line. (a) Venous pressure  $y_v(n)$  (blue line) and filtered venous pressure  $\bar{y}_v(n)$  (black line), (b) estimated venous cardiac signal  $\hat{c}_v(n)$ , (c) normalized cardiac venous signal  $\hat{c}_v^n(n)$ , (d) normalized cardiac arterial signal  $\hat{c}_a^n(n)$ , (e) centered venous pressure  $z_v(n)$ , (f) normalized venous pulse pressure  $\hat{p}_v^{pp}(n)$ , (g) correlation coefficient  $r(n; \theta = 0)$ , and (h) time shift  $T_r(n)$ . Note that (c), (d), (f), and (g) are normalized and thus without unit.

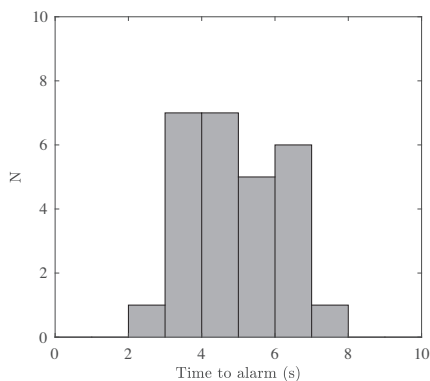


**Figure 6:** Pressure signals (left column) and related features (right column) for the VND in treatment #3, occurring after  $t = 30$  s (dashed vertical line). The detected time of the VND is indicated by the dotted vertical line. (a) Venous pressure  $y_v(n)$  (blue line) and filtered venous pressure  $\bar{y}_v(n)$  (black line), (b) estimated venous cardiac signal  $\hat{c}_v(n)$ , (c) normalized cardiac venous signal  $\hat{c}_v^n(n)$ , (d) normalized cardiac arterial signal  $\hat{c}_a^n(n)$ , (e) centered venous pressure  $z_v(n)$ , (f) normalized venous pulse pressure  $\hat{c}_v^{PP}(n)$ , (g) correlation coefficient  $r(n; \theta = 0)$ , and (h) time shift  $T_r(n)$ . Note that (c), (d), (f), and (g) are normalized and thus without unit.

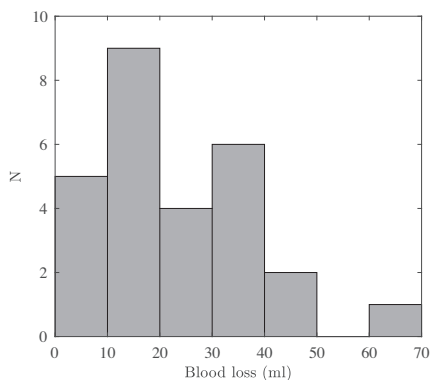


**Figure 7:** Pressure signals (left column) and related features (right column) for the VND in treatment #4, occurring after  $t = 30$  s (dashed vertical line). The detected time of the VND is indicated by the dotted vertical line. (a) Venous pressure  $y_v(n)$  (blue line) and filtered venous pressure  $\bar{y}_v(n)$  (black line), (b) estimated venous cardiac signal  $\hat{c}_v(n)$ , (c) normalized cardiac venous signal  $c_v^n(n)$ , (d) normalized cardiac arterial signal  $\hat{c}_a^n(n)$ , (e) centered venous pressure  $z_v(n)$ , (f) normalized venous pulse pressure  $\hat{c}_v^{pp}(n)$ , (g) correlation coefficient  $r(n; \theta = 0)$ , and (h) time shift  $T_r(n)$ . Note that (c), (d), (f), and (g) are normalized and thus without unit.

All 27 VNDs of the test set were correctly detected. The time from the actual VND to its detection was between 2.4 s and 7.2 s, with an average delay of 4.9 s. The distribution of the detection delay is shown in Fig. 8. Assuming that the blood pump is stopped immediately after detection, the blood loss would be between 7 and 60 ml, with an average of 23 ml. The distribution of the blood loss is shown in Fig. 9.



**Figure 8:** Histogram of the delay between the annotated VND and the detection, based on the 27 VNDs in the test set.



**Figure 9:** Histogram of blood loss occurring between the annotated VND and the detection, based on the 27 VNDs in the test set.

## 6 Discussion

We have demonstrated that the proposed method can detect VND within 7.2 s or less, implying a blood loss of less than 60 ml. These results are based on the assumption that the amplitude of the cardiac signal is sufficiently large. The blood loss is well below the 250 ml which is considered to be an upper bound on non-severe blood loss for dialysis patients. The resulting blood loss is also well below the 30 s which corresponds to 250 ml at the highest blood flow (500 ml/min). Since the method extracts a new cardiac signal segment each time a new blood pump revolution has been completed, an additional delay should be added to the detection time, ranging from 0–4.6 s, where 4.6 s corresponds to the duration of one pump revolution at 100 ml/min. This corresponds to an additional blood loss of 0–7.6 ml.

For the clinical dataset, three of four dislodgements were correctly detected. One of the patients had an extremely weak cardiac signal amplitude ( $< 0.1$  mmHg), leading to a false detection before the VND. This should be compared to the performance of the prevailing clinical VND method, where the alarm limit is set to 30–40 mmHg below the actual venous pressure [10]. An alarm limit of 40 mmHg below the venous pressure would only detect 7 of the 27 VNDs in the test set, and none of the 4 VNDs in the clinical dataset, see the drop in (a) at the VNDs in Figures 4 to 7.

When implementing the method in a dialysis machine, the blood pump should be stopped as soon as the VND is detected. At a pump stop, with the dialyzer in bypass, the signal-to-noise ratio is favorable, and a cardiac signal is easy to detect. An alarm is issued only when no heart signal is present in the venous pressure signal during blood pump stop. If a cardiac signal is present, the treatment may be resumed without any alarm issued. In this way the number of false alarms due to transient disturbances can be reduced. During a blood pump stop, or at treatment start-up, the cardiac signal amplitude can be accurately determined. Thus, the suitability of the present method can be determined with respect to each patient's cardiac signal amplitude. If too low, VND detection will have to rely on the standard monitoring of the venous pressure only. If, during a blood pump stop, the cardiac signal amplitude is judged to be too weak, an alarm should be issued so that the staff can determine whether the treatment should be resumed with VND monitoring based on the venous pressure only.

Although the SVM was trained on data from one of the dialysis machines, it worked well also on the other dialysis machine using a different cardiac signal extraction method. It is, however, preferable to train the SVM on the target machine, since the machine components may differ.

In the present paper, four features are used to determine a VND. Figures 4 to 7 suggest that the correlation coefficient  $r(n; \theta = 0)$  and the centralized venous pressure  $z_v(n)$  convey the most important information for detection: both trends exhibit distinct changes when the VND occurs. The feature  $c_v^{pp}(n)$  may be useful during

partial needle dislodgement, when blood is leaking but the needle tip remains in limited contact with the fistula, resulting in reduced cardiac signal amplitudes. The effect of a partial dislodgement remains to be investigated in future studies, as well as the significance of each feature.

An advantage with the present method is that it enables monitoring of cardiac arrest during dialysis. If the cardiac signal disappears from both the venous and the arterial pressure signals, this signifies either that the venous and the arterial needles have been dislodged or cardiac arrest has occurred. The latter event is not uncommon: The number of cardiac arrests during dialysis is estimated to be about 20 000 worldwide every year [16], being even higher than the corresponding number of VNDs.

A limitation of the present study is the small data set with clinical VNDs. Unfortunately, such data is extremely difficult to obtain, since only a few patients fulfill the strict inclusion criteria; only patients with high hemoglobin concentrations are considered ethical to include. To compensate for the small clinical data set, a larger data set is obtained from the lab and complemented with simulated data. In the future, the study should be expanded to include a large clinical data set so that the false alarm rate, e.g., due to movement artifacts in the pressure signals, can be better investigated.

## 7 Conclusions

Detection of VND has been successfully demonstrated both on clinical data, following a strict study protocol, and lab data acquired under varying conditions simulating realistic VND scenarios. The time delay of detection was shown to be less than 7.2 s, and the maximum blood loss was less than 60 ml. The method needs to be verified on a large set of clinical data to better establish the false alarm rate.

## 8 Acknowledgements

The authors would like to thank Mårten Segelmark, Lena Mattsson, and Sarok Said at “Filialen”, Skåne University Hospital, Lund, Sweden, for carrying out the clinical investigation.

## References

- [1] T. Bauld and J. Anderson, “Patient safety alert AL 010-13,” in *Veterans health administration warning system*, pp. 1–2, V A Central Office, 2010.
- [2] B. Axley, J. Speranza-Reid, and H. Williams, “Venous needle dislodgement in patients on hemodialysis,” *Nephrol. Nurs. J.*, vol. 9, pp. 435–445, 2012.

- [3] J. A. Hurst, "Venous needle dislodgement — a universal concern," *Eur. Nephrol.*, vol. 5, no. 2, pp. 148–151, 2011.
- [4] F. Dellanna, D. Stippel, W. Schmitz, and C. Baldamus, "Safety on hemodialysis machines; surveillance of the venous blood return," in *Am. Soc. Nephrol. 28th Ann. Meeting Abstracts*, vol. 6, p. 486, J Am Soc Nephrol, 1995.
- [5] "Health and safety survey to improve patient safety in end stage renal disease – report of findings from the esrd patient survey," tech. rep., Renal Physicians Association, March 2007.
- [6] S. Sandroni, T. Sherockman, and K. Hayes-Leight, "Catastrophic hemorrhage from venous needle dislodgement during hemodialysis: Continued risk of avoidable death and progress toward a solution," in *ASN Renal Week Abstracts, J. Am. Soc. Nephrol.*, vol. 19, p. 891A, 2008.
- [7] J. Anderson, "Bleeding episodes during dialysis, patient safety advisory AD09-02," in *Veterans Health Administration Warning System*, pp. 1–7, V A Central Office, 2008.
- [8] "IEC 60601-2-16 Medical electrical equipment part 2-16: Particular requirements for basic safety and essential performance of haemodialysis, haemodiafiltration and haemofiltration equipment (edition 4)," *Int. Electrotechnical Commission*, 2012.
- [9] H. D. Polaschegg, "Venous needle dislodgement: the pitfalls of venous pressure measurement and possible alternatives, a review," *J. Ren. Care*, vol. 36, pp. 41–48, 2010.
- [10] W. Ribitsch, G. Schilcher, H. Hafner-Giessauf, P. Krisper, J. H. Horina, A. R. Rosenkranz, and D. Schneditz, "Prevalence of detectable venous pressure drops expected with venous needle dislodgement," *Seminars in Dialysis*, vol. 27, no. 5, pp. 507–511, 2014.
- [11] E. Lindley, M. Chamney, S. Olausson, J. Pancirova, M. Sundström, J. Tattersall, and J. Van Waeleghem, "Venous needle dislodgement survey Dublin 2010. Part 2: Risk factors and outcomes," (Dublin, Ireland), p. 66, EDTNA/ERCA, 2010.
- [12] M. Holmer, F. Sandberg, K. Solem, E. Grigonyte, B. Olde, and L. Sörnmo, "Extracting a cardiac signal from the extracorporeal pressure sensors of a hemodialysis machine," *IEEE Trans. Biomed. Eng.*, vol. 62, no. 5, pp. 1305–1315, 2015.

- [13] M. Holmer, F. Sandberg, K. Solem, B. Olde, and L. Sörnmo, "Cardiac signal estimation based on the arterial and venous pressure signals of a hemodialysis machine," *Physiol. Meas.*, vol. 37, no. 9, pp. 1499–1515, 2016.
- [14] J. Mateo and P. Laguna, "Improved heart rate variability signal analysis from the beat occurrence times according to the IPFM model," *IEEE Trans. Biomed. Eng.*, vol. 47, pp. 997–1009, 2000.
- [15] R. O. Duda, P. E. Hart, and D. G. Stork, *Pattern Classification*. New York: Wiley–Interscience, 2nd ed., 2001.
- [16] M. K. Shamseddin and P. S. Parfrey, "Sudden cardiac death in chronic kidney disease: epidemiology and prevention," *Nat. Rev. Nephrol.*, vol. 7, pp. 145–154, mar 2011.