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Amperometric enzyme-based biosensors:

Refined bioanalytical tools for *in vivo* biomonitoring

Carlos Alberto de Lima Braga Lopes Cordeiro

The research presented in this thesis was performed partially at Brains On-Line BV and partially in the University of Groningen. First at the Biomonitoring and Sensoring Department and later at Pharmaceutical Analysis department, member of the Groningen Research Institute of Pharmacy. The work was financially supported by Brains On-Line BV.

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- Front Cover- Surface of a W-Au microelectrode, magnified 10000x.
- Back Cover- Detail of the surface of a Pt microelectrode functionalized with OPPy, magnified 10000x.

Both pictures taken by Jeroen Kuipers (RuG): to whom the author would like to thank for his excellent work on the SEM images.

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Amperometric enzyme-based biosensors:Refined bioanalytical tools for *in vivo* biomonitoring

PhD thesis

to obtain the degree of PhD at the
University of Groningen on the authority of the
Rector Magnificus Prof. E. Sterken
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Friday 12 January 2018 at 14.30 hours

by

Carlos Alberto De Lima Braga Lopes Cordeiro

born on 26 April 1982
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Para a Raquel, a Carolina, a Maria Tereza e o Alberto.
Obrigado por não me deixarem desistir.

"Dos fracos não reza a história, é preciso ter força para ser forte!"
- Alberto Lopes Cordeiro, 2001

Aim and scope of the thesis

Diabetes is a disease that affects millions of people around the globe, and whose prevalence is estimated to double (at least) within the next decades. Unfortunately, despite the innumerous efforts by the scientific community, no cure was found yet. Therefore, the life quality of diabetes patients is closely related to their ability to closely monitor glucose levels, by means of Continuous Glucose Monitoring (CGM).

The need for reliable glucose monitoring tools led, in 1962, to the inception of the biosensor field, with the "invention" of the first biosensor by Clarke and Lyons. Since then, the continuous pursuit for better biosensors for CGM has been the main drive behind exponential growth of the field.

Despite a large amount of proof-of-concept biosensors described, with numerous biorecognition liable to be coupled multiple types of transducers, state of the art glucose biomonitoring still relies point-of-care enzyme-based biosensors. Although significant advances in the last decades in electrochemical enzyme-based biosensors technology enabled CGM, innumerous challenges still hamper the reliability of these devices.

The aim of this thesis is to better understand the fundamentals of state-of-the art electrochemical enzyme-based biosensors. Additionally, I aim to use the newly acquired knowledge to develop and characterize biosensors that may enable better continuous *in vivo* biomonitoring of glucose and related biomarkers.

I start to explain (**Chapter 1**) the prevailing need for improvements on state-of-art CGM biosensors. Also I briefly describe how biosensors, especially electrochemical enzyme-based ones work and the challenges for we need to face towards a "truly" CGM.

Chapters 2 and **3** are devoted to better understand the mechanisms underlying the major breakthrough in electrochemical enzyme-based biosensors for *in vivo* biomonitoring, permselective membranes. I will study the impact of membrane assembly on surface availability and its impact on membrane induced selectivity, and how this impact influences biosensor performance.

In **Chapter 4** I describe the development and characterization of an implantable microbiosensor device (*i*MBD) for CGM in freely moving animals. In **Chapter 5** I try to go beyond fundamental biosensor research, towards a widespread utilization of amperometric enzyme-based biosensors as bioanalytical tools. In order to be regarded as tools for *in vivo* biomonitoring, all biomedical devices should assure a minimum sterility level. Therefore, in this chapter, I evaluate the effect of several sterilization methods on the performance of

implantable electrochemical enzyme-based biosensors for *in vivo* biomonitoring.

As glucose homeostasis is closely related to brain glucose regulation and diabetes has been linked to abnormalities in brain energy metabolism. Therefore, in **Chapter 6**, I develop and characterize a multiplex biosensor device for *in vivo* continuous and simultaneous monitoring of brain energy biomarkers; glucose, lactate and pyruvate.

The last experimental chapter (**Chapter 7**) is dedicated to the first step towards enhanced spatial resolution of electrochemical enzyme-based biosensors. I describe the development and characterize electrochemical enzyme-based biosensors based on "miniaturizable" W-Au microelectrodes.

Finally in **Chapter 8**, I summarize and discuss the most striking findings of the thesis. Furthermore I speculate on what would be the logical next steps in development of electrochemical enzyme-based biosensors for *in vivo* biomonitoring.