A final word

The central theme in this thesis is the development of a glucose measurement system for diabetic patients. Diabetics must frequently measure their blood glucose levels using a self-monitor device and adjusting their insulin dosage, food intake and physical activity to keep these levels as close to “normal” as possible. The best way to avoid hyperglycaemic and hypoglycaemic events is to frequently monitor the blood glucose levels. However, even the most diligent patients who perform blood glucose measurements many times a day achieve only a poor approximation of continuous monitoring. As described in the first chapter of this thesis, a continuous glucose measurement system or glucose sensor could be of likely benefit for diabetic patients in the management of their blood glucose concentration. Most implantable glucose sensors are amperometric enzymatic glucose sensors. Although progress is made during the years of development of this type of directly implantable sensors, they still suffer from a poor in vivo performance. A major problem of hydrogen peroxide based sensors is that the oxidation of hydrogen peroxide requires an applied potential at which many other species commonly found in the body are electro-oxidisable, creating possible interference. It is therefore important that the detector part of a glucose sensor contains some barrier to prevent the transport of substances not to be measured. A potential danger is that these sensor designs allow hydrogen peroxide to enter the body causing inflammation reactions. Directly implantable glucose sensors which detection scheme measures the oxygen consumption suffer in vivo from the “oxygen deficit” problem, the low ratio of oxygen to glucose that exists in the body. In addition, these glucose sensors can not be miniaturised to the same extent as hydrogen peroxide based glucose sensors. Microdialysis is a technique that might be use to separate the site of sampling and the site of reaction. After diffusion of glucose from
the tissue into the system, an enzyme reactor might be applied so the amount hydrogen peroxide produced or the amount of oxygen used can be measured. This configuration is a combination between an amperometric enzymatic biosensor and the in vivo sampling/transportation technique that microdialysis is. The single circulation glucose-measurement system presented in this thesis is a good example of such a “hybrid system”. The sensor has evolved from the glucose sensing system designed by Schoonen and Schmidt. Several adaptations have been made to the flow system to minimise the leakage of enzyme into the body. Furthermore, the electronics of the sensor have been miniaturised to a great extent. This makes it possible to wear the sensor and a read-out device outside the body in a belt pack where only the microdialysis probe is implanted subcutaneously. With the newly designed system we were able to perform ambulatory studies on human subjects during daily life conditions. A problem remains the robustness of the system during these ambulatory studies. Our initial goal to measure glucose continuously in vivo for at least two weeks could therefore not be accomplished yet. The results show that it is very well possible to measure a number of days reliable in vivo. However, further improvements to the flow system have to be made in order to reach our goal of continuous in vivo measurement for two weeks. At this moment our sensor system is merely a “functional model”, providing a “proof of principle” instead of a finished product ready for the market. Future developments must be directed both towards the improvement of the robustness and further miniaturisation of the system. Although a number of companies are in the process of bringing commercial glucose sensors to the market, including Roche Diagnostics GmbH who are developing a glucose sensor system based on one of our patents, there remain some problems for each invasive method, including microdialysis. The device, or a part of the device, has to be inserted percutaneously. Insertion is causing some damage to the microstructure of the tissue and the body reacts to the implant as an insult and produces a specialised biochemical and cellular response. For glucose we have shown that the concentration of glucose measured by the system increases in time until a plateau value is reached. In fact the capillary glucose concentration is the driving force for diffusion of glucose into the system. Disruption of the capillary bed results in a lower density of capillaries and
thus in a lower supply of blood around the device. Often a short inflammation period of a few hours may be seen. This inflammation process itself consumes glucose, also lowering the glucose concentration recovered by the device. For microdialysis, very low flow rates, combined with the use of long membrane probes are minimizing the effect of a low capillary density, but not the short time inflammation effect. If higher flow rates are used, like in our sensor system, the question remains if this change in glucose recovery can be predicted for every individual subject every time a sensor is applied. If so, than a correction factor can be used. If not, you have to wait until the recovery has reached the plateau value. The long-term membrane permeability in adipose tissue is not a problem. We have measured for three weeks and did not find a decrease of permeability of the microdialysis membrane in time.

Where to go from here?
The ultimate goal, an automated feedback controlled insulin dosage system, requires a reliable glucose measurement system. Looking back from the time that the concept of a glucose sensor was introduced in the 1960s, a lot of progress has been made. The fact that there is not a commercial glucose sensor available at this moment doesn’t mean that the industry has lost their interest in the subject. Companies like Minimed Inc. and Roche Diagnostics GmbH. are both working hard to bring a glucose sensor to the market. The marketing and commercialisation of these sensors means more clinical testing which inevitably raises some new questions. However, problems of robustness and miniaturisation of sensor systems are for these companies with their financial resources not a major obstacle. With the introduction of a reliable glucose sensor and a better understanding of problems related to biocompatibility and biophysics, the development of an artificial pancreas will be accelerated. In the mean time, the patient can improve his glycaemic control using a glucose sensor. Especially an appropriate first goal is a hypoglycaemic alarm that alerts patients when their glucose levels drops below a threshold value. The best solution for a sensor would ultimately be a total implantable glucose measurement system (“out of sight, out of mind”). A total implantable system requires much more from a technical point of view. Implanted sensors have to be engineered to last longer than
the percutaneous sensors (months to years opposed to days). This means that to use of fluids like enzymes, electrolytes etc. and moving parts like pumps (relative high energy consumption) are not appropriate. For future developments, a glucose sensor based on Fourier-Transform-Infrared (FTIR) combined with fiber-optics may provide a solution (see illustration below). The discovery of insulin in the 1922 by Banting and Best together with the introduction of the self-monitoring of blood glucose are regarded as milestones in the treatment of diabetes. A glucose sensor in combination with an insulin delivery device may well be the next major improvement.

Impression of (pacemaker like) future type of implantable glucose sensor based on FTIR-detection of glucose using an optical fiber.