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Review

Energy harvesting by implantable abiotically catalyzed glucose fuel cells

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ABSTRACT

Implantable glucose fuel cells are a promising approach to realize an autonomous energy supply for medical implants that solely relies on the electrochemical reaction of oxygen and glucose. Key advantage over conventional batteries is the abundant availability of both reactants in body fluids, rendering the need for regular replacement or external recharging mechanisms obsolete. Implantable glucose fuel cells, based on abiotic catalysts such as noble metals and activated carbon, have already been developed as power supply for cardiac pacemakers in the late-1960s. Whereas, *in vitro* and preliminary *in vivo* studies demonstrated their long-term stability, the performance of these fuel cells is limited to the μW-range. Consequently, no further developments have been reported since high-capacity lithium iodine batteries for cardiac pacemakers became available in the mid-1970s. In recent years research has been focused on enzymatically catalyzed glucose fuel cells. They offer higher power densities than their abiotically catalyzed counterparts, but the limited enzyme stability impedes long-term application. In this context, the trend towards increasingly energy-efficient low power MEMS (micro-electro-mechanical systems) implants has revived the interest in abiotic catalysts as a long-term stable alternative. This review covers the state-of-the-art in implantable abiotically catalyzed glucose fuel cells and their development since the 1960s. Different embodiment concepts are presented and the historical achievements of academic and industrial research groups are critically reviewed. Special regard is given to the applicability of the concept as sustainable micro-power generator for implantable devices.

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1. Introduction

Although today batteries are considered to be the first choice in supplying power to electronic medical implants, there are numerous efforts to develop alternative power-supply systems that are capable of operating independently over prolonged periods of time, without the need of external recharging or refueling [1–4]. Among them are implantable fuel cell systems, which convert endogenous substances and oxygen into electricity by means of a spatially separated electrochemical reaction. Unlike batteries, these systems are constantly replenished with fresh reactants from the body fluids, and are therefore theoretically capable of operating indefinitely, as long as there is a constant supply of reactants. Its ubiquitous availability in body fluids makes glucose the most considered fuel for implantable fuel cell systems.

In general, glucose-consuming fuel cells can be divided into three main types according to the type of catalyst that is used to enable the electrode reactions: enzymatic, microbial, and abiotic glucose fuel cells. *Enzymatic fuel cells* employ enzymes such as glucose oxidase and laccase in their isolated forms, whereas in *microbial fuel cells* the enzymatic system of a whole, electroactive micro-organism is used. In contrast, *abiotically catalyzed fuel cells* make use of non-biological, abiotic catalysts, e.g., noble metals or activated carbon.

Over the last four decades there has been ample research activity both in the development of enzymatic and microbial fuel cells [5–7]. The recent developments in the field have been reviewed extensively [8–13]. Whereas implantable *enzymatic glucose fuel cells* are currently under development [14,15], the limited stability of enzymes renders their application in a long-term implantable fuel cell power supply difficult. Power-supply systems based on microbial fuel cells are not seriously considered for implantation, due to the infective nature of most known micro-organisms and the associated risks therewith.

In past reviews, only minor attention has been given to abiotically catalyzed glucose fuel cells, although these systems were already developed as implant power supplies in the late-1960s, and their feasibility to power cardiac pacemakers has been demonstrated *in vitro* as well as in animal trials. Abiotically catalyzed fuel cells employ mainly noble metal catalysts and are therefore considered to be advantageous regarding their sterilizability, long-term stability, and biocompatibility. However, following the introduction of the lithium iodine battery in 1972 [16–18] and the subsequent improvement of pacemaker battery lifetime no further development of abiotically catalyzed glucose fuel cells has been reported. Instead the research has been refocused towards the application of the concept for glucose sensor technology [19,20].

The current interest in autonomous, self-sufficient MEMS (micro-electro-mechanical systems) implants has revived the research in long-term stable, implantable glucose fuel cells based on abiotic catalysts [21]. This work reviews the development of abiotically catalyzed glucose fuel cells for implantable devices since the early beginnings in the 1960s. Not considered are non-medical applications of abiotically catalyzed glucose fuel cells [22,23], for instance as sensor power supply running on tree sap [24], since their operation conditions differ greatly from physiological environments and the design is not constricted by the vigorous demands on implantable systems in terms of patient safety and system size.

1.1. Operation principle of abiotically catalyzed glucose fuel cells

In a fuel cell electrical energy is generated by the electrochemical reaction of fuel and oxidant at two spatially separated electrodes. Electrons, released upon the electro-oxidation of the fuel, flow from the anode through an external load circuit to the cathode, where the terminal electron acceptor, usually oxygen, is reduced (Fig. 1). The driving force of the electron flow is the difference in electrochemical potential of the anode and cathode redox pairs.

An overview about the tentative oxidation pathways and intermediate reaction products of glucose oxidation is given in Fig. 2 [26]. Theoretically, glucose can be completely oxidized to carbon dioxide and water, releasing 24 electrons per molecule glucose [25]. The corresponding fuel cell reaction and the theoretical cell voltage U^0 would then be given as

$$\text{Anode}: \quad C_6H_{12}O_6 + 24\,OH^- \rightarrow 6\,CO_2 + 18\,H_2O + 24\,e^-$$

$$\text{Cathode}: \quad 6\,O_2 + 12\,H_2O + 24\,e^- \rightarrow 24\,OH^-$$

$$\text{Overall}: \quad C_6H_{12}O_6 + 6\,O_2 \rightarrow 6\,CO_2 + 18\,H_2O$$

$$\Delta G^\circ = -2.870 \times 10^6\,\text{J mol}^{-1}; U^0 = 1.24\,\text{V [25]}$$

In practice, the transfer of 24 electrons per molecule glucose has not yet been achieved. In their early study on glucose electro-oxidation in neutral media (0.5 mol L^{-1} glucose in 1 mol L^{-1} phosphate buffer at pH 7.4, 0.5 mol L^{-1} NaCl) employing platinized platinum electrodes, Rao and Drake reported gluconic acid to be the only reaction product that could be identified by thin layer chromatography [27]. In a later mass spectroscopic study of glucose oxidation products (0.1 mol L^{-1} glucose, in chloride free $NaHCO_3$ buffer at pH 7.4). Ernst et al. identified glucono lactone as the product of glucose oxidation in the potential range of 300–400 mV vs. RHE (reversible hydrogen electrode), which itself undergoes hydrolysis to form gluconic acid [28], a non-toxic metabolite [29]. The oxidation of glucose to gluconic acid only yields two electrons per molecule glucose and the corresponding electrode reactions are thus given as

$$\text{Anode}: \quad C_6H_{12}O_6 + 2\,OH^- \rightarrow C_6H_{12}O_7 + H_2O + 2\,e^-$$

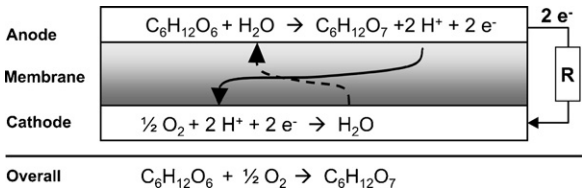

Fig. 1. General electrode reactions of an abiotically catalyzed glucose–oxygen fuel cell, assuming a hydroxyl ion conducting membrane and gluconic acid as the reaction product. According to Ref. [25].

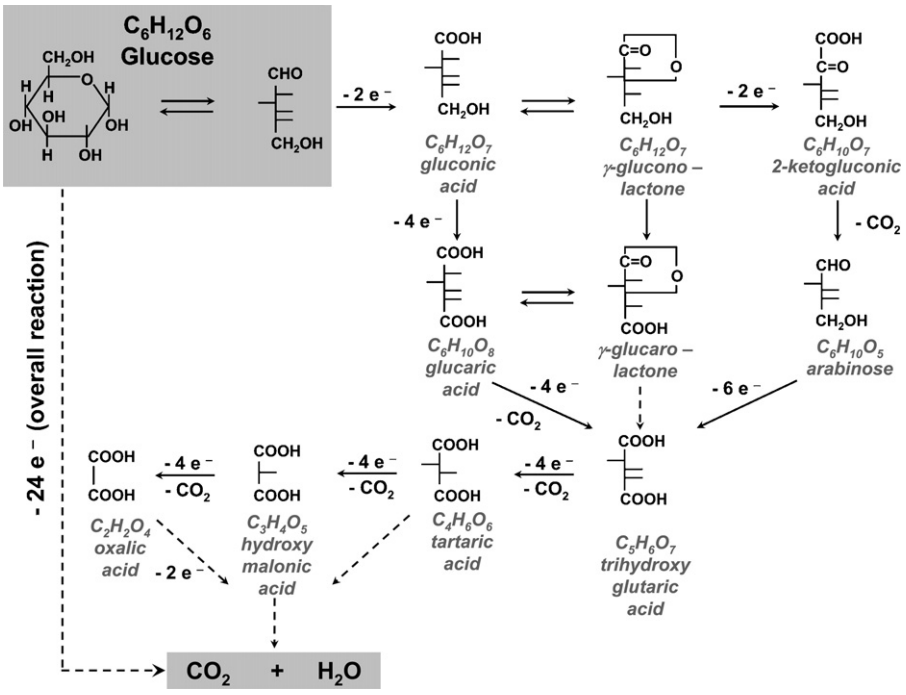

Fig. 2. Tentative oxidation pathways and intermediate reaction products of glucose oxidation, after [26], with corrections from Ref. [41].

Cathode : $0.5\,O_2 + H_2O + 2\,e^- \rightarrow 2\,OH^-$

Overall : $C_6H_{12}O_6 + 0.5\,O_2 \rightarrow C_6H_{12}O_7$

$\Delta G^\circ = -2.51 \times 10^5\,J\,mol^{-1}$ [25]; $U^0 = 1.30\,V$

Several groups demonstrated that gluconic acid can be oxidized in a similar way as glucose, although at lower reaction rate [30–32]. Apart from gluconic acid as the main reaction product Kokoh et al. detected glucuronic, oxalic, glyoxylic, and tartaric acids as well as traces of glycolic and formic acid by means of HPLC (high pressure liquid chromatography) analysis. They used unmodified platinum electrodes and the oxidation was carried out by a continuous triple pulse electrolysis program with the oxidation potential set to 0.62 V vs. RHE (50.6×10^{-3} mol L^{-1} glucose in KH_2PO_4/NaOH buffer at pH 7.3) [33]. This is in agreement with the findings of Lerner and Gebhardt who estimated the number of electrons transferred per glucose molecule. On platinized platinum electrodes (potential range: −200 to 0 mV vs. a saturated calomel electrode, SCE) between 4 and 20 electrons are transferred [34], and for a Raney-type platinum catalyst (at 400 mV vs. RHE) the mean number of electrons was estimated to be 17, from measuring the gradual depletion of 0.1% (5.6×10^{-3} mol L^{-1}) glucose in phosphate buffer over a period of 800 h [32].

The different findings concerning the reaction products might be due to analytical limitations and the fact that not only the catalyst material but also pH and the ionic strength of the electrolyte influence the reaction mechanism of glucose electro-oxidation [35]. A detailed treatise on the mechanisms of glucose electro-oxidation in different media and at different pH can be found in the works of Demele and Vassilyev [35–40].

1.2. Historical development

To our best knowledge, the concept of abiotically catalyzed glucose fuel cells appeared for the first time in a publication by Bockris, who investigated the anodic oxidation of cellulose and lower carbohydrates with respect to its applicability in fuel cells [42]. In 1966, a patent was issued to Union Carbide for a method of using solid organic fuels in a fuel cell, where the performance of a fuel cell oxidizing glucose in alkaline solution was reported [43].

It was not until 1967 that the first abiotically catalyzed glucose fuel cell intended to operate on glucose from body fluids was presented by Warner and Robinson. Their prototype employed an air-breathing cathode, and was suggested as a future power supply for medical implants. They demonstrated fuel cell performance in unbuffered 10% (0.56 mol L^{-1}) glucose solution over a period of 240 h, reaching a plateau performance of 165 μW cm^{-2} within the initial 24 h of operation. First experiments with pleural fluid and plant saps resulted in a lower and more rapidly decreasing cell performance, which has been attributed to the blocking of the electrode by adsorbed proteins [44]. In 1968, Wolfson et al. presented a similar device for pacemaker power supply under the name “Bioautofuel Cell”. Their prototype was a *two chamber* fuel cell (Fig. 3), consisting of two identical platinized fuel cell electrodes immersed in separate beakers. They used phosphate and bicarbonate buffer systems, and an ionic connection between the beakers established by a saturated KCl-agar bridge. The anode compartment contained 5.0×10^{-3} mol L^{-1} glucose and was purged with nitrogen to remove dissolved oxygen from the solution. Although their two chamber prototype was clearly not suitable for operation in a physiological environment where glucose and oxygen are present in the same solution, they carried out a number of experiments regarding the effect of varying glucose concentrations, electrolyte solution buffer capacity, and pH. The detrimental effect of fuel in the cathode or oxygen in the anode compartment has also been demonstrated. The reported fuel cell performance amounted to 3.5 μW cm^{-2}, and the fuel cell’s capability of powering a transistor blocking oscillator circuit over a period of 18 days could be demonstrated [45].

In the following years several academic and corporate activities related to implantable glucose fuel cells are reported. Scientists of the Monsanto Research Corporation developed catalyst materials

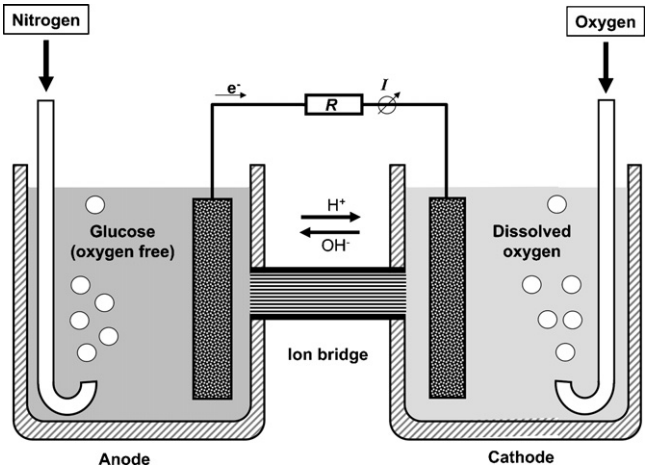

Fig. 3. Two-chamber glucose fuel cell according to Ref. [45] with identical platinum electrodes used as anode and cathode, respectively (schematic outline). See text for explanations.

for glucose oxidation [27,46]. At Union Carbide the performance of oxygen reduction catalysts in physiological solution was investigated [47,48]. Other companies involved were the German Robert Bosch GmbH, who was granted a patent on the application of organo-chemical redox systems for the anodic oxidation of amino acids in an implantable fuel cell [49], and the US-based Leesona Moos Corporation, where electrocatalysts for hydrocarbon oxidation and oxygen reduction from the gold–palladium series were developed [50].

A major development effort has been sponsored by the Artificial Heart Program of the United States National Heart and Lung Institute [51], since it was expected that implantable glucose fuel cells could generate electricity in the range of several watts and therefore supply an artificial heart. However, in a theoretical study, the feasibility of extracting enough oxygen from the blood to operate a 12.5-W implantable fuel cell system was evaluated as only marginally feasible, depending on the effective diffusion coefficient of oxygen in the blood [52]. From a similar study a marginal feasibility of obtaining 4.5 W from an implantable system based on the reaction of glucose to gluconic acid was concluded [53]. To our knowledge the construction of corresponding prototypes has not been reported.

The first truly implantable fuel cell prototypes, intended for the use with cardiac pacemakers, were developed at the American Hospital Supply Corporation [51] and the Michael Reese Hospital in 1970 [54]. Reports of implantable prototypes developed at Siemens and also Tyco followed in 1972 [31,55]. For almost 30 years no further work on implantable abiotically catalyzed glucose has been published, until in 2005 the concept was picked up again in the context of low power medical MEMS implants [21]. The relevant publications and patents related to implantable abiotically catalyzed glucose fuel cells are summarized in Table 1.

2. Design considerations

The following sections describe the constraints a physiological environment imposes on the design of abiotically catalyzed glucose fuel cells. In this context the available abiotic catalysts for glucose oxidation and oxygen reduction play a central role. Their characteristics, in conjunction with the body-defined operation conditions, demand different reactant separation approaches to enable fuel cell operation in a mixture of glucose and oxygen. The site of implantation becomes important when reactant availability, implantation procedure, and patient safety are considered.

The open circuit potentials of several catalyst materials are summarized in Table 2, whereas Fig. 4 compares the reported performance of glucose fuel cell electrodes in a current density–potential plot.

2.1. Catalyst materials for oxygen reduction

Platinum showed the highest oxygen reduction performance in a comparative study comprising also palladium, gold, and silver in isotonic phosphate buffer at neutral pH. Although silver has the advantage to be insensitive towards glucose, its oxygen reduction onset potential is unfortunately 400 mV more negative compared to platinum [47], which directly translates to lower fuel cell voltage and performance. Similar to silver, activated carbon has no affinity for glucose [67] and its oxygen reduction onset potential is only about 100 mV more negative compared to platinum. Activated carbon was therefore favored as a selective oxygen reduction catalyst in fuel cells employing an *oxygen-selective cathode catalyst* [55]. A direct comparison showed that also under working conditions activated carbon exhibits a better oxygen reduction performance than silver, with a 200 mV more positive potential [63].

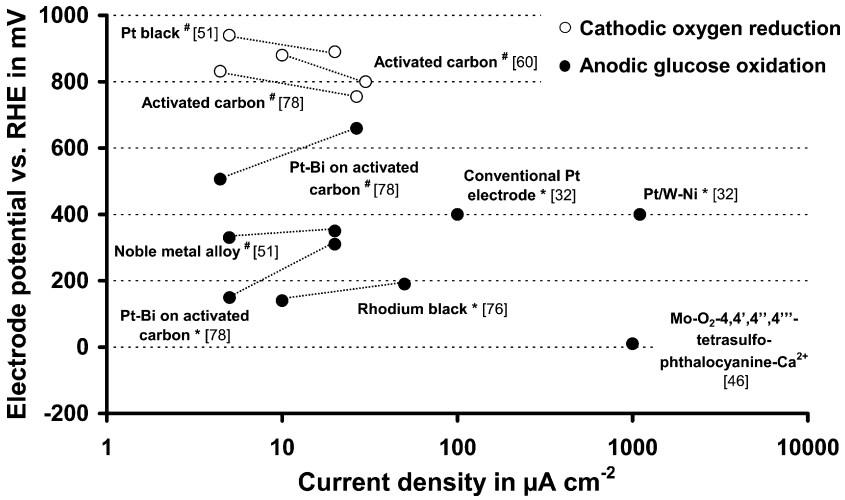

Fig. 4. Current density-potential plot of different electrode materials in neutral buffer containing glucose. Legend: "*": in deaerated solution; "#": electrode part of a complete fuel cell in aerated solution.

Table 1
Publications and patents related to the development of implantable abiotically catalyzed glucose fuel cells

Year, Reference	Affiliation	Comment
1964, Bockris et al. [42]	University of Pennsylvania, Philadelphia (PA)	Anodic oxidation of glucose and other carbohydrates in alkaline/acidic solution
1966, Kordesch and Koehler [43]	Union Carbide Corporation, New York (NY)	US Patent: method of using glucose and other solid organic fuels in a fuel cell
1967, Warner and Robinson [44]	Emory University, Atlanta (GA)	Glucose fuel cell prototype operating on 10 wt% glucose solution and atmospheric oxygen, intended as a power supply of medical implants; use of pleural fluid and plant saps as fuel source
1968, Wolfson et al. [45]	University of Pennsylvania, Philadelphia (PA)	Glucose fuel cell as power source for cardiac pacemakers. Investigation of cell performance under physiological and varying pH and glucose concentration
1969, Colton and Drake [52]	Monsanto Research Corporation, Everett (MA)	Feasibility study for an implantable glucose fuel cell, e.g., as a power supply for the artificial heart.
1969, Rao and Drake [27]	Monsanto Research Corporation, Everett (MA)	Studies into the electrooxidation of glucose; electrode poisoning effect of gluconic acid
1969, Yao et al. [30]	Michael Reese Hospital and Medical Center, and the Institute of Gas Technology, both Chicago (IL)	Investigation of the anodic oxidation of glucose, gluconic acid, glucosamine, and related compounds at neutral pH in a two compartment fuel cell
1969, Arzoumanidis and O'Connell [46]	Monsanto Research Corporation, Everett (MA)	Anodic oxidation of glucose in phosphate buffer saline with electrodes catalyzed by 4,4′,4″,4‴-tetrasulfophthalocyanine-molybdenum dioxide salts
1970, Kozawa et al. [47]	Union Carbide Corporation, Cleveland (OH)	Evaluation of various oxygen reduction catalysts (various noble metals and ferric phathalocyanine) in neutral solution, also containing additons of blood
1970, Kozawa et al. [48]		Oxygen and hydrogen peroxide reduction on ferric phthalocyanine-catalyzed graphite
1970, Fishman and Henry [50]	Leesona Moos Laboratories, Great Neck (NY)	Meeting abstract of the Electrochemical Society Meeting 1970: several alloys in the gold–palladium series are reported to be more active than platinum in simulated body fluids, and selective electrocatalysts for hydrocarbon oxidation and oxygen reduction in an implantable fuel cell
1970, Drake et al. [51]	American Hospital Supply Corporation, Everett (MA), and the University of Vermont, Burlington (VT)	*In vitro* and *in vivo* studies on a tissue implantable glucose fuel cell with permselective membranes
1970, Wolfson et al. [54]	Michael Reese Hospital and Medical Center, Chicago (IL)	*In vitro* studies on an implantable glucose fuel cell with permselective membranes in neutral solution also containing additions of plasma
1971, Appleby [53]	Illinois Institute of Technology, and Institute of Gas Technology, both Chicago (IL)	Feasibility study for an implantable glucose fuel cell to power an artificial heart
1972, Malachesky et al. [31]	Tyco Laboratories, Waltham (MA)	Parametric *in vitro* and *in vivo* studies on glucose fuel cells designed as an artificial heart power source. Demonstrated gluconic acid as fuel with similar performance; a marked decay of anode performance has been observed *in vivo*
1972, Schumann et al. [49]	Robert Bosch GmbH, Stuttgart (Germany)	German patent: anodic oxidation of amino acids in an implantable fuel cell via the application of organo-chemical redox systems
1972, Wolfson and Yao [56]	University of Pittsburgh, and Montefiore Hospital, both Pittsburgh (PA)	Investigation of the effect of creatinine, alanine, urea, uric acid, ammonium chloride, and plasma components on the performance of an implantable fuel cell
1972, Rao et al. [55]	Siemens AG, Erlangen (Germany)	First report on a glucose fuel cell with a special electrode arrangement and activated carbon cathode, presented at the Third International Conference on Medical Physics
1973, Giner et al. [57]	Tyco Laboratories, Waltham (MA)	Overview on the Tyco work on implantable glucose fuel cells, see also [31]
1973, Fishman and Henry [58]	Montefiore Hospital and Medical Center, Bronx (NY)	Meeting abstract of the Electrochemical Society Meeting 1973: report on electrodeposited selective catalysts for glucose oxidation and oxygen reduction in an implantable fuel cell
1973, Henry and Fishman [59]	Montefiore Hospital and Medical Center, Bronx (NY)	Meeting abstract of the Electrochemical Society Meeting 1973: investigation of the transient behavior of the rest potential of an electrodeposited platinum black electrode in aerated glucose saline solution and the effect of lead acetate addition to the plating bath
1973, Henry and Fishman [59]	Montefiore Hospital and Medical Center, Bronx (NY)	Meeting abstract of the Electrochemical Society Meeting 1973: *in vivo* studies with an implantable glucose fuel cell comprising selective Au–Pd electrodes and semipermeable membranes; pulsed cell operation over 5 h without drastic decay
1973, Rao et al. [60]	Siemens AG, Erlangen (Germany)	*In vitro* studies with an implantable glucose fuel cell: concept of a special electrode arrangement in combination with selective oxygen reduction catalysts; fabrication of electrodes and membranes from PVA–PAA hydrogel and results of an 1100 h long-term test
1974, Ng et al. [61]	Institute of Gas Technology, Chicago (IL)	US Patent: air breathing implantable glucose fuel cell intended as power supply for the artificial heart
1974, Wan and Tseung [62]	Royal College of Surgeons of England, and The City University, London (England)	*In vitro* and *in vivo* studies on an implantable fuel cell with selective electrodes; addition of lead acetate to platinum plating solution
1974, Rao et al. [63]	Siemens AG, Erlangen (Germany)	*In vitro* studies with an implantable glucose fuel cell
1974, Rao and Richter [64]	Siemens AG, Erlangen (Germany)	Overview article on implantable bio-electrochemical power sources; 200 h *in vitro* results from animplantable glucose fuel cell

Table 1 (*Continued*)

Year, Reference	Affiliation	Comment
1975, Affrossman et al. [65]	University of Strathclyde, Glasgow (Scotland)	Application of lactic acid, glucose, and glucosamine as fuel in an implantable fuel cell; effect of differently charges membranes on fuel permeability
1975, Rao and Richter [66]	Siemens AG, Erlangen (Germany)	US Patent: implantable glucose fuel cell with special electrode arrangement and selective oxygen reduction catalyst
1976, Sharrock et al. [67]	University of Strathclyde, Gasgow (Scotland)	Implantable fuel cell-based sensor for creatinine, uric acid, and lactic acid, employing an activated carbon anode
1976, Gebhardt et al. [32]	Siemens AG, Erlangen (Germany)	Raney-type electrocatalyst for glucose oxidation in an implantable glucose fuel cell prepared from platinum and ferrous metals
1976, Weidlich et al. [68]	Siemens AG, Erlangen (Germany)	*In vivo* experiments with an implantable glucose fuel cell over a period of 5 months
1976, von Sturm and Richter [69]	Siemens AG, Munich (Germany)	US Patent: integration of a glucose fuel cell as external coating on a cardiac pacemaker
1976, Rao et al. [26]	Siemens AG, Erlangen (Germany)	Summary of the Siemens activities in the field: materials and design, *in vitro* experiments over a period of 600 days, Raney-type electrocatalysts, and the effect of amino acid mixtures on anode performance
1978, Richter et al. [70]	Siemens AG, Berlin and Munich (Germany)	US Patent: fabrication of Raney-type platinum electrodes for implantable glucose fuel cells
1978, Rao et al. [71]	Siemens AG, Erlangen (Germany)	Influence of amino acids on the glucose oxidation on platinum, platinum black and Raney-platinum electrodes in neutral media
1981, Giner et al. [72]	Giner Inc., Waltham (MA)	Influence of amino acids on the glucose oxidation on platinized platinum electrodes in Krebs–Ringer solution, focus on the development of an implantable glucose sensor
1983, Rao [25]	Siemens AG, Erlangen (Germany)	Summary of the Siemens activities in the field: materials and design, *in vitro* and *in vivo* experiments over a period of 600 and 150 days, respectively; Raney-type electrocatalysts and the oxidation of gluconic and glucaric acid on those
2005, Woias et al. [21]	University of Freiburg (Germany)	Energy harvesting concepts for autonomous microsystems, among them abiotically catalyzed glucose fuel cells
2006, von Stetten et al. [73]	University of Freiburg (Germany)	Fabrication and characterization of a prototype based on the Siemens concept
2007, Kerzenmacher et al. [74]	University of Freiburg (Germany)	Fabrication and characterization of a surface-mountable abiotically catalyzed glucose fuel cell

Table 2
Open circuit potentials of abiotic catalyst materials for oxygen reduction and glucose oxidation at neutral pH

Reference	Catalyst material	Open circuit potential mV vs. RHE	Comment
A: Cathodic oxygen reduction			
Kozawa et al. [47]	Platinum	990	Isotonic saline solution at pH 7.22, oxygen saturated (1 atm)
Kozawa et al. [47]	Palladium	940	Isotonic saline solution at pH 7.22, oxygen saturated (1 atm)
Kozawa et al. [47]	Ferric phthalocyanine	890	Isotonic saline solution at pH 7.22, oxygen saturated (1 atm)
Rao et al. [60]	Activated carbon	877	2% (0.11 mol L^{-1}) glucose in phosphate buffer, oxygen saturated
Rao et al. [60]	Activated carbon	794	2% (0.11 mol L^{-1}) glucose in phosphate buffer, air saturated
Kozawa et al. [47]	Gold	710	Isotonic saline solution at pH 7.22, oxygen saturated (1 atm)
Kozawa et al. [47]	Silver	590	Isotonic saline solution at pH 7.22, oxygen saturated (1 atm)
B: Anodic glucose oxidation			
Appleby and Van Drunen [76]	Platinum black	180	Overnight potential in 5×10^{-3} mol L^{-1} glucose in Ringer-solution, deaerated
Appleby and Van Drunen [76]	Rhodium black	120	Overnight potential, 5×10^{-3} mol L^{-1} glucose in Ringer-solution, deaerated
von Stetten et al. [78]	Platinum–bismuth on activated carbon	101	Stable potential, 0.1% (5.6×10^{-3} mol L^{-1}) glucose in phosphate-buffered saline, deaerated
Appleby and Van Drunen [76]	Gold	90	Initial potential, 5×10^{-3} mol L^{-1} glucose in Ringer-solution, deaerated
Appleby and Van Drunen [76]	Iridium	90	Initial potential, 5×10^{-3} mol L^{-1} glucose in Ringer-solution, deaerated
Appleby and Van Drunen [76]	Platinum–ruthenium (8–60 at% Ru)	90	Initial potential, 5×10^{-3} mol L^{-1} glucose in Ringer-solution, deaerated
Arzoumanidis and O'Connell [46]	Mo–O_2-4,4′,4″,4‴-tetrasulfophthalocyanine–Ca^{2+} on carbon black–PTFE	10	In 0.5 mol L^{-1} glucose solution at pH 7.4, room temperature, aeration status not clear

Potentials that were originally given vs. a saturated calomel electrode (SCE) were recalculated to the potential of a reversible hydrogen electrode (RHE) according to the relationship: $RHE_{pH\,7}$ = SCE + 690 mV [76].

Oxygen-selective alloy catalysts from the gold–palladium series were presented by Fishman at two conferences of the Electrochemical Society in 1970 and 1973. Gold–palladium alloys with palladium contents of more than 60 atom percent were reported to be selective towards oxygen reduction, independently of lead acetate additions to the plating solution. *Oxygen-selectivity* was also observed when platinum was electrodeposited from plating solutions containing no lead acetate. However, the information disclosed in the meeting abstracts is scarce and more detailed results have to our knowledge not been published [50,58].

Some efforts have been undertaken to study the oxygen reduction performance of *oxygen-selective* phthalocyanines deposited on carbon supports, but no corresponding fuel cell performance has been reported. The central atom of phthalocyanine has a strong influence on oxygen reduction performance. Catalytic activity increases in the sequence non-metal, copper, cobalt, and iron [75]. For ferric phthalocyanine deposited on pyrolitic graphite the onset potential of the oxygen reduction reaction is approximately only 100 mV more negative compared to platinum [47], and the insensitivity of phthalocyanines towards carbohydrates is advantageous [75].

2.2. Catalyst materials for glucose oxidation

Following the initially reported platinum catalysts [45,60] other noble metals and alloys that are highly active for glucose oxidation have been employed. Among them are platinum–ruthenium alloys, rhodium, and iridium. Smooth platinum electrodes exhibited current densities up to 1 $\mu A\,cm^{-2}$ before rapid irreversible polarization occurred, whereas smooth iridium, platinum–ruthenium (60 at% platinum), and rhodium could sustain current densities three, five, and seven times higher, respectively [76]. More recently a platinum–bismuth alloy on activated carbon support, which has originally been developed for the production of gluconic acid by direct chemical oxidation of glucose [77], has been demonstrated as anode catalyst in a fuel cell. In deaerated phosphate-buffered saline containing 0.1% (5.6×10^{-3} mol L^{-1}) glucose the anode polarization amounted to 210 mV at a current density of 20 $\mu A\,cm^{-2}$ [78].

Rhodium black in connection with a gold fiber felt is disclosed as the preferred glucose electrode in a patent assigned to the Institute of Gas Technology, and reportedly showed a polarization of only 200 mV at a current density of 4 mA cm^{-2} [61].

A special type of Raney-platinum catalyst for implantable glucose fuel cells has been developed at Siemens. Ferrous metals and tungsten have been alloyed with platinum and subsequently removed from the alloy by chemical and electrochemical etching. Platinum–tungsten, fabricated from an alloy containing additions of nickel, exhibited a nine times higher current density compared to a conventional platinum black electrode in deaerated phosphate buffer containing 2% (0.11 mol L^{-1}) glucose (1.1 mA cm^{-2} after 24 h at 400 mV vs. the reversible hydrogen electrode, RHE) [26].

Glucose-selective noble metal alloys that are not influenced by the presence of dissolved oxygen have been presented by Fishman at the Meeting of the Electrochemical Society in 1973. He investigated glucose oxidation on platinum, gold–platinum, and gold–palladium (Pd < 50 at%) alloys and found that the addition of lead acetate to the plating solutions leads to electrocatalytic selectivity for glucose oxidation in neutral media containing dissolved oxygen [58]. However, the information revealed in the meeting abstract is scarce and more detailed results have to our knowledge not been published.

Metal chelates on carbon black–PTFE (poly(tetraflouro ethylene)) supports, hydrophilized by treatment with HNO_3, were investigated by Arzoumanidis. Starting from an open circuit potential of −640 mV vs. SCE (saturated calomel electrode), a Mo–O_2–4,4′,4″,4‴-tetrasulfophthalocyanine–Ca^{2+} catalyzed anode showed virtually no electrode polarization up to a current density of 1 mA cm^{-2}. The electrooxidation was carried out in 0.5 mol L^{-1} phosphate buffer containing 0.5 mol L^{-1} NaCl and 0.5 mol L^{-1} glucose, but it is unclear whether the solution was aerated or not [46].

2.3. Operation conditions

Whereas with non-implantable fuel cell types it is possible to adjust reactant concentration, purity, and temperature to an optimum, the operation conditions of implantable fuel cells are clearly defined by body physiology. Glucose concentration in the human body ranges from approximately 5×10^{-3} mol L^{-1} in blood to 3×10^{-3} and 4×10^{-3} mol L^{-1} in the interstitial fluid of muscle and adipose tissue, respectively [79]. For well-vascularized tissue Gough assumed oxygen partial pressures of 38 torr, corresponding to approximately 5% oxygen saturation [80]. Later studies revealed values between 60 torr in the subcutaneous tissue of the human arm [81], and 24 torr in the femoral muscle of the mouse [82].

Besides glucose and oxygen, the presence of endogenous substances has to be taken into account when *in vivo* operation of the fuel cell is considered. Oxidizable body fluid components can contribute to the fuel cell reaction, whereas other components inhibit or poison the catalyst, resulting in a decreased fuel cell performance. For instance glucosamine [30] and lactic acid [65] can be oxidized in a similar way as glucose, but the amino acid histidine inhibits glucose oxidation on a platinum-based catalyst [71].

The concentration of electrolytes and endogenous substances in blood plasma and serum is known from clinical diagnostics and established as normal range values. The composition of interstitial fluid has not been that well investigated, and often the concentrations found in blood plasma were assumed to be comparable to interstitial fluid [51]. A comparison of interstitial fluid ion concentrations estimated from hemodilution experiments [83] to their diagnostic normal range in blood plasma [84,85] shows that in terms of electrolytes this assumption is valid. For some amino acids, however, significant concentration differences between plasma and the interstitial fluid of muscle and adipose tissue have been found [79]. As compared to plasma, especially the concentration of aspartate is five to seven times higher in the interstitial fluid of muscle and adipose tissue, respectively. Taurine levels in muscle and adipose tissue are three to six times higher than in plasma. In addition, surprisingly high levels of glycerol (approximately 3×10^{-3} to 4×10^{-3} mol L^{-1}) both in the interstitial fluid of muscle and adipose tissue have been found [79].

The plasma amino acid concentrations are therefore only a coarse approximation to the actual levels present in interstitial fluid. From the viewpoint of developing glucose fuel cells for *in vivo* application the actual interstitial fluid concentrations would more precisely reflect the conditions present in body tissue environments.

2.4. Separation of reactants

The availability of glucose and oxygen in body fluids only as a mixture is an important constraint in the design of implantable glucose fuel cells. Since most known noble metal catalysts are active towards glucose oxidation and oxygen reduction, the simultaneous presence of glucose and oxygen at both electrodes would lead to an electrochemical short-circuit. Anode and cathode would assume a similar potential and no electricity could be generated.

Initially, glucose fuel cells have therefore been constructed as *two-chamber cells* where anode and cathode are placed in separate

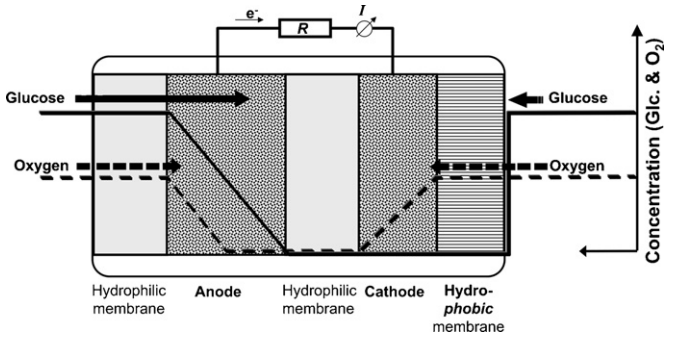

Fig. 5. Glucose fuel cell with hydrophobic cathode membrane (schematic outline) according to Ref. [51]. See text for explanations.

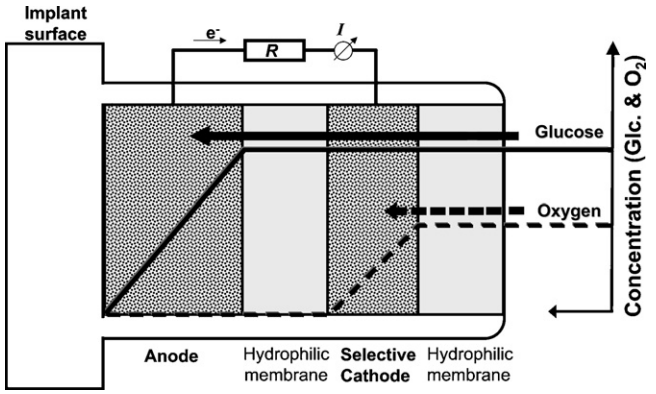

Fig. 6. Fuel cell design with oxygen-selective cathode catalyst and special electrode arrangement (schematic outline) according to Refs. [55,69]. See text for explanations.

compartments, connected by an ion bridge (Fig. 3). The reactants glucose and oxygen were separately added to the individual compartments for anode and cathode, respectively.

To enable fuel cell operation in a physiological solution containing both glucose and oxygen the following three reaction separation concepts are reported.

In the first concept a phase separation of oxygen from body fluid is achieved at the cathode. A *hydrophobic cathode membrane* allows only for the diffusion of gaseous oxygen but hinders glucose from reaching the cathode [52]. The embodiment of this concept is illustrated in Fig. 5. Between cathode and anode a hydrophilic ion conducting separator membrane is placed for electrical insulation. The outer part of the anode serves as sacrificial layer, where oxygen can directly react with glucose on the surface of a noble metal catalyst. This reduces the oxygen concentration in the interior of the anode, where glucose then is electrooxidized under predominantly anoxic conditions and at a potential more negative than the cathode potential. The degree of reactant separation is dependant on the concentration of oxygen: at lower oxygen concentrations the reactant separation becomes more effective and the anode assumes a more negative potential. However, the resulting increase in fuel cell performance is countered by the reduced cathode performance at lower oxygen concentrations [31]. Since some glucose is consumed by the direct reaction with oxygen a surplus of glucose over oxygen is a prerequisite for this embodiment. This is usually the case in body fluids where the glucose concentration amounts to approximately 5×10^{-3} mol L^{-1}, compared to less than 0.2×10^{-3} mol L^{-1} of oxygen. The advantage of the concept is that platinum and other highly active noble metals can be used as catalysts for both the anode and the cathode reaction [51,54].

In the second reactant separation concept an *oxygen-selective cathode catalyst* is used, that is inactive towards glucose oxidation. By arranging the anode sandwiched between the cathode and an impermeable surface (or alternatively between two cathodes) the interior of the fuel cell is depleted from oxygen, and the anodic glucose oxidation takes place under predominantly anoxic conditions [55,60]. A hydrophilic separator membrane electrically insulates anode and cathode while at the same time allowing for the diffusion of glucose and ions. As *oxygen-selective* cathode catalysts activated carbon and silver have been employed. Since body fluid access is required only at the cathode the fuel cell could be constructed as a thin layer directly on the implant surface, as depicted in Fig. 6 [69].

Also with this concept the degree of reactant separation is dependent on oxygen concentration. At higher oxygen partial pressures not all of the oxygen can be depleted at the cathode and the resulting presence of oxygen at the non-selective anode leads to the formation of a more positive anode potential. This results in a decrease of both, cell voltage and power output [60].

With the third concept the need for reactant separation is circumvented by employing *selective electrocatalysts*, that either catalyze glucose oxidation or oxygen reduction. This allows for the construction of a glucose fuel cell from two electrodes exposed to the same solution, as depicted in Fig. 7. Whereas *oxygen-selective* abiotic catalysts are available (e.g., silver, ferric phthalocyanine, and activated carbon), the information on abiotic catalysts selective towards glucose oxidation is scarce (see Sections 2.2 and 4.3). A fuel cell of this type has been constructed from a pair of *selective* platinum-based electrodes. Unfortunately the experimental methods and results are not clearly reported. Also, the authors did not elaborate on the origin of the observed selectivity in their electrodes [62].

2.5. Site of implantation

Theoretically, an implantable fuel cell can either be directly in contact with the blood stream or implanted in tissue.

For *blood stream* implantation fuel cells of the *flow-trough type* have been developed, as depicted in Fig. 8 [31,57,69]. The blood flow promises a steady reactant supply that is not limited by diffusion from blood vessels into the surrounding tissue. However, a blood stream implantable device has to be designed in a way that blood flow is not impaired, and that no areas of reduced flow velocity are formed, which would increase the risk of thrombi formation

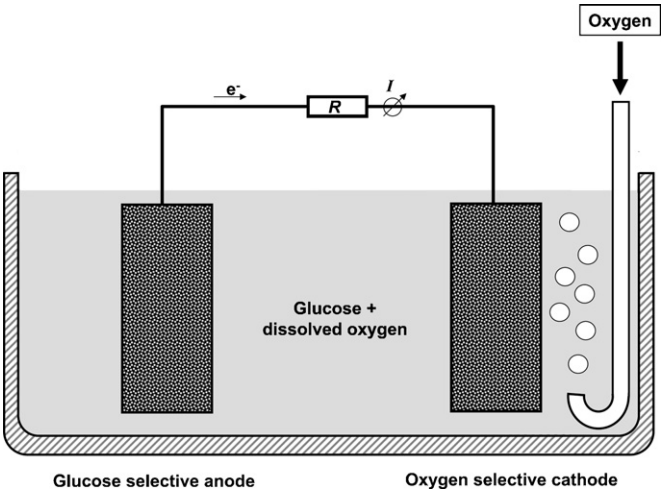

Fig. 7. Glucose fuel cell with selective electrode catalysts (schematic outline) according to Ref. [62]. See text for explanations.

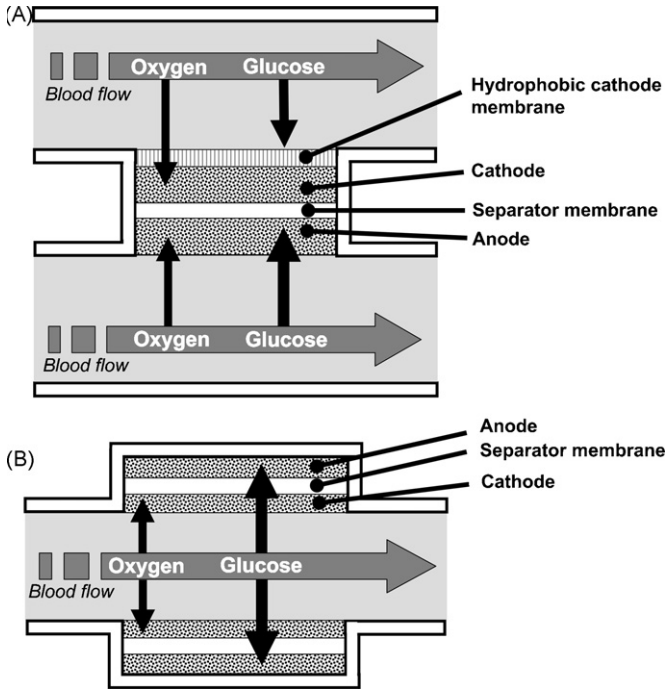

Fig. 8. Simplified schematics of flow-trough type fuel cells intended for blood stream implantation: (A) fuel cell with hydrophobic cathode membrane [31]; (B) concentrically arranged fuel cell with oxygen-selective cathode catalyst [69]. Refer to Section 2.4 for details regarding the reactant separation mechanisms.

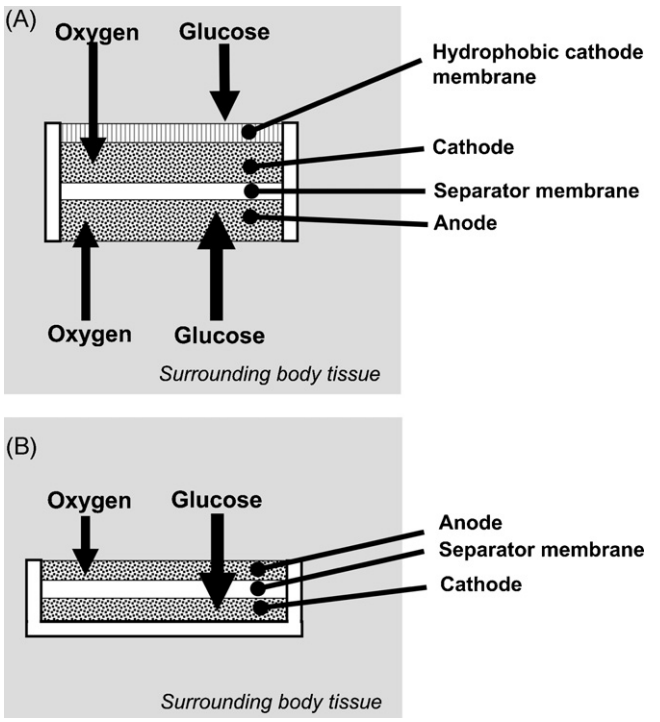

Fig. 9. Simplified schematics of immersible fuel cells intended for tissue implantation: (A) fuel cell with hydrophobic cathode membrane [52]; (B) fuel cell with oxygen-selective cathode catalyst [55]. Refer to Section 2.4 for details regarding the reactant separation mechanisms.

[69]. The employed materials have to be compatible with blood, especially with respect to coagulation [86]. The concept suffers from complications arising when having to surgically introduce the device into a major blood vessel. Implantation in the blood stream has therefore been considered mainly in early studies, where the increased reactant supply posed a major factor to reach the final aim of powering an artificial heart [52].

In contrast, the reactant supply of *immersible* fuel cells developed for *tissue implantation* [51,54,60] relies solely on diffusion (Fig. 9). While the surrounding tissue poses an additional mass transfer resistance, the risk of thrombi formation and blood coagulation is minimized. The fuel cell can be implanted in a similar way as the pacemaker device, enabling fuel cell integration directly on the exterior surface of the pacemaker [30,45]. This would facilitate implantation procedures and eliminate the risk of lead failure, which was a common reason for pacemaker breakdown at that time [87].

A third embodiment where the fuel cell cathode is of the *air-breathing type* and only the anode is in contact with the body fluids was disclosed in a patent assigned to the Institute of Gas Technology [61]. The concept promises an increased performance due to the considerably higher oxygen partial pressure, but the device is fairly complicated and demands a mechanical pumping mechanism to ensure a constant supply of oxygen through a percutaneous airway. Related experimental studies have to our knowledge not been published.

3. Construction of implantable abiotically catalyzed glucose fuel cells

3.1. Electrode fabrication

In the early works of Wolfson commercially available platinum black fuel cell electrodes from American Cyanamid and General Electric, originally developed for hydrogen–oxygen fuel cells, have been used. Electrodes with higher platinum loading exhibited superior performance, but the wettability of the commercial electrodes was not satisfactory, presumably due to the hydrophobic nature of the employed binders [54].

Electrodes specially designed for implantable abiotically catalyzed glucose fuel cells have been fabricated from catalyst particles (e.g., platinum black) using PTFE as a binder [31], sometimes in conjunction with a sintering process at 300 °C [62]. Drake et al. fabricated cathodes from a hydrophobic carbon–PTFE mixture with platinum black being applied as a thin layer on one side only [51]. In the context of PTFE-based electrodes a method to hydrophilize a carbon black–PTFE composite by acid treatment with HNO_3 has been described [46].

Also various hydrophilic polymer hydrogels have been investigated as binding agent. A mixture of activated carbon, poly(vinyl alcohol) and poly(acrylic acid) has been thermally crosslinked to form a hydrogel embedding the catalyst particles. An other hydrogel material reported is glycolmethacrylate [60]. In a corresponding patent the application of phenol sulphonic acid with formaldehyde, polyethylene imine with epichlorhydrine, or the covalent bond between methacrylic acid and di-vinyl benzene has been suggested to fabricate hydrogels for embedding catalyst particles [66].

Polymer hydrogel swelling characteristics proved to be problematic when attempts were made to embed separator membranes and electrodes together in a monolithic hydrogel matrix. Differential swelling in aqueous solution resulted in delamination of the package. By polymerizing 4.9% methacrylic acid in aqueous ethylene glycol a hydrogel could be prepared, that exhibits no dimensional change when brought in contact with physiological solution. Adsorbed oxygen on activated carbon and platinum interfered with polymerization, and the reaction could be carried out successfully only after electrochemical reduction of the catalyst surface [26]. To increase the conductivity of polymer-bound electrodes a noble metal mesh has been commonly used as current collector.

Binder-less electrodes have been fabricated by depositing platinum on graphite sheets. Initially graphite was immersed in chloroplatinic acid and subsequently dried. To form nucleation sites the chloroplatinic acid salts were decomposed at 300 °C. Platinum–ruthenium alloys have then been electrodeposited from chloroplatinic acid and ruthenium chloride solutions [62].

A special type of binder-less electrode for glucose oxidation of the Raney-type has been fabricated from ferrous metals alloyed with platinum. The method yields a dimensionally stable electrode and is suitable to form multi-component alloys. Starting alloys are either obtained by interdiffusion of a ferric metal layer adhering to a platinum support, or by the formation of a fusible regulus from defined mixtures of noble and ferrous metals rolled into thin foils. After alloy formation at temperatures between 800 and 1600 °C, the non-noble component is extracted either by treatment with non-oxidizing acids or electrochemical methods. Potentiostatic activation in H_2SO_4 at a potential of 400–800 mV vs. RHE proved to result in well adhering porous layers. In terms of glucose oxidation activity in an implantable fuel cell electrodes fabricated from platinum–nickel and platinum/tungsten–nickel alloys have exhibited the best results. The latter exhibited a 10 times higher current than conventional platinum electrodes upon potentiostatic load at 400 mV vs. RHE in phosphate buffer containing 0.1% (5.6×10^{-3} mol L^{-1}) glucose [32,70].

3.2. Separator membranes

Separator membranes provide electrical insulation between the electrodes while at the same time they serve as ion conductor to close the electrical circuit of the fuel cell. Given the electrolytic character of body fluids, it would be sufficient to apply a mesh-like hydrophilic spacer as separator membrane, its pores filled with body fluid.

However, the ionic nature of the separator and the corresponding capability to transport either OH^- or H^+ ions influences the electrode reactions. In fuel cells constructed with a *hydrophobic cathode membrane* anion exchange separators are reported to be preferable over cation exchangers. With anion exchangers the reaction water is generated at the anode, and flooding of the cathode and formation of detrimental water pockets inside the fuel cell are prevented [31,54]. In contrast to this the application of strong cation exchangers, nylon fiber mats, asbestos sheets, and cellophane film in fuel cells of essentially the same design has been described [51].

In the case of fuel cells employing an *oxygen-selective cathode catalyst* the separator must not only be an ionic conductor but also allow for the diffusion of fuel and its reaction products to and from the anode. A variety of materials are reported to be suitable, among them weak cation exchange hydrogels of the poly(vinyl alcohol)–poly(acrylic acid) type, glycolmethacrylate, cuprophane, sulfonated PTFE membranes, dialysis and cellulose membranes, the latter also soaked with poly(vinyl alcohol) (PVA) [26,63,64]. Difficulties were encountered with hydrogels based on poly(vinyl alcohol)–poly(acrylic acid) (PVA–PAA) and glycolmethacrylate, that were disconnected after prolonged fuel cell operation, presumably due to hydrolysis or the oxidative effect of electrocatalysts [26].

3.3. Protective membranes

Protective membranes serve as interface between fuel cell and body environment, e.g., tissue or blood. They have to be tissue compatible and permeable to reactants and reaction products. Larger molecules like proteins and enzymes have to be hindered from reaching the electrodes to prevent catalyst deactivation and fouling.

Already in the early *in vitro* studies on two-chamber fuel cells (Fig. 3) it was noted that the deteriorating effect of microorganism growth on performance could be reduced by covering the electrodes with protective membranes made from cellulose [45]. Following this, several materials have been used to cover the electrodes in implantable prototypes.

In the fuel cell design with an *oxygen-selective cathode catalyst* (Fig. 5) materials already employed as separators were used as protective membranes: cellulose, cuprophane, dialysis tube, and cation exchange hydrogels of the poly(vinyl alcohol)–poly(acrylic acid) or glycolmethacrylate type [26,60,64].

Similar materials were employed to cover the anode in fuel cells with *hydrophobic cathode membrane* (Fig. 4). Here supported ionic hydrogels [51] and cuprophane films [31] and more specifically dialysis membranes with 50-nm pore size [54] and 2-nm pore size membranes with 50% porosity [61] are reported. The cathode in this design has been protected by silicone rubber or PTFE membranes that only allow gaseous oxygen and CO_2 to reach to the electrode. This prevents the interference of glucose and other endogenous substances on oxygen reduction [31,51,54].

3.4. Cell housing and system integration

The *cell housing* of the so far reported implantable prototypes has not been fully developed. In stand-alone devices the fuel cell components have been clamped together using a Lucite frame [54], or assembled on porous metal supports with RTV (room temperature vulcanizing) glue [51] and adhesive tape [31]. Membranes and electrodes were also joined with cyanolit glue and applied with an epoxy frame to obtain structural stability [60].

The *system integration* of an abiotically catalyzed glucose fuel into a medical implant as external coating has already been envisioned in the early works of Wolfson et al. [45]. It was, however, not until 1976 that a patent was granted to the German company Siemens for applying the fuel cell directly as external coating on the pacemaker housing. The concept circumvents the need for implanted power leads and uses the fuel cell anode as part of the cardiac stimulation circuit, reportedly improving tissue compatibility of stimulating electrodes [69]. To compensate for the peak power requirements of medical implants a hybrid device, comprising a glucose fuel cell with included storage battery, has been suggested [61].

4. Performance of implantable abiotically catalyzed glucose fuel cells

The operation conditions have a strong influence on the performance of abiotically catalyzed glucose fuel cells. For devices with *hydrophobic cathode membrane* a considerable effect of pH and buffer capacity on performance has been observed [51]. In contrast, the performance of *two-chamber fuel cells* with separate reactant compartments is almost independent of glucose concentrations in the range between 0.05×10^{-3} and 50×10^{-3} mol L^{-1}, indicating that the glucose oxidation rate is only governed by reaction kinetics [45]. The glucose sensitivity of *immersible* and *flow-trough type* fuel cells exposed to glucose and oxygen as a mixture has to our knowledge not been reported.

Since the reported fuel cell performances were mostly obtained under different and often incompletely specified conditions direct comparison of the results is difficult. A summary of the reported construction details and performances is given in Table 3. Operation conditions and sustainability of performance are indicated as reported.

Table 3
Construction details and performance characteristics of implantable abiotically catalyzed glucose fuel cells

Reference	Electrodes	Membranes	Cell housing	Test conditions	Power density ($\mu W\,cm^{-2}$)	Remarks
A: *in vitro*—non-physiological conditions						
Warner and Robinson [44]	Catalyzed conducting electrodes	Cation exchange polymer	Not specified	10% (0.56 mol L^{-1}) glucose in unbuffered solution, air breathing cathode	~165	Stable performance after 72 h
Drake et al. [51]	Cathode: platinum black laminated on one side of a hydrophobic carbon/PTFE matrix. Anode: noble metal alloy black compressed onto platinum screen	Cathode protected by thin silicone rubber membrane Separator and anode protective membrane: dialysis membrane of the supported ionic hydrogel film type	Silicone rubber casing with a porous metal facing on the anode side	0.01 mol L^{-1} glucose in 0.5 mol L^{-1} phosphate-buffered saline, 0.35 mol L^{-1} NaCl, 30–38 °C, pH 7.4	18.6	Over 142 days in solution exposed to air, moderate stirring
Wan and Tseung [62]	Cathode and anode: Pt black mixed with PTFE brushed on Pt screen; both cured at 300 °C in air for 1 h	n/a	Two chamber cell, cathode compartment equilibrated with air, anode compartment purged with nitrogen	5 g L^{-1} (28×10^{-3} mol L^{-1}) glucose, 0.5 mol L^{-1} NaCl	15	Stable performance after 16 h, poorly documented experiment; performance calculated based on the area of front and back of the electrode
Rao et al. [63]	Cathode: activated carbon, anode: Pt black	Separators: cellulose soaked with PVA Protective membranes 20 μm hydrophilic membranes	Not clearly specified	0.1 mol L^{-1} glucose in phosphate-buffered saline, pH 7.2, 37 °C, presumably air saturated	10 (per cathode area)	Long-term performance over 63 days; also reported is a voltage gain of 200 mV with activated carbon as compared to silver cathode Fuel cell with central anode, sandwiched between two cathodes
Rao and Richter [64]	Cathode: activated carbon, anode: platinum deposited on activated carbon	40 μm cellulose membranes, not specified whether as separators or protective membranes	Not specified	0.1 mol L^{-1} glucose in phosphate-buffered saline, pH 7, 37 °C, 0.2 air saturated	8 (per cathode area)	Long-term performance over 83 days; fuel cell with central anode, sandwiched between two cathodes
B: *in vitro*—near physiological conditions						
Wolfson et al. [45]	Platinized platinum	Cellulose protective membranes	Two chamber cell, cathode compartment equilibrated with air, anode compartment purged with nitrogen	pO_2: 90 torr (in cathode chamber)	2.0–3.5	Electrolyte pH and composition not clearly specified, presumably 5×10^{-3} mol L^{-1} Glucose in Ringer solution
Drake et al. [51]	Cathode: platinum black laminated on one side of a hydrophobic carbon/PTFE matrix, anode: noble metal alloy black compressed onto platinum screen	Cathode protected by thin silicone rubber membrane Separator and anode protective membrane: dialysis membrane of the supported ionic hydrogel film type	Silicone rubber casing with a porous metal facing on the anode side	5×10^{-3} mol L^{-1} glucose in Tyrode solution exposed to air, moderate stirring, pH 7.4, 1 g L^{-1} (12×10^{-3} mol L^{-1}) $NaHCO_3$	2.5 (4.4) 6.3 (11.6)	Average performance over 428 and 167 h, respectively, values in parentheses for higher load currents
Wolfson et al. [54]	Cathodes: American Cyanamid AA-40 (40 mg Pt cm^{-2}), General Electric 40 mg Pt cm^{-2}, anodes: AA-40, General Electric Pt-20, Ru, and from Energy Research Corp.	Cathode membranes: hydrophobic General Electric MEM-213, 13 μm; Anode membrane: AHT Cellophane dialysis membrane, 5 nm pores Separator: AMF ion exchange membrane types A100 and A310	Bonded between Silastic spacers	5×10^{-3} mol L^{-1} glucose in Krebs–Ringer, pH 7.4, 37 °C, pO_2 80–90 torr,	26	Stable performance after 20 h

Table 3 (*Continued*)

Reference	Electrodes	Membranes	Cell housing	Test conditions	Power density ($\mu W\,cm^{-2}$)	Remarks
Malachesky et al. [31]	Cathode: Teflon-bonded Pt black (15 mg Pt cm^{-2}) on a gold grid, anode: Pt black 0.7% asbestos paste on gold grid (10 mg Pt cm^{-2})	Cathode membrane: 13 μm GE XD-1, 65–35 dimethylsilicone-polycarbonate copolymer on porous Teflon Separator: AMF A-100 178 μm anion exchange membrane Anode membrane: 13 μm cuprophane	Electrodes and membranes hot pressed to stainless steel frame using double sided adhesive tape; assembly pressed between Lexan plates to form blood channels	5×10^{-3} mol L^{-1} glucose in modified Ringer solution, 0.03 mol L^{-1} $NaHCO_3$, 0.1 mol L^{-1} NaCl pH 7.4, 38 °C, pO_2: 180 torr	~50	Flow through cell with forced reactant flow, performance monitored over a period of 32 h; pO_2 changed between 140 and 180 torr; reported also 100 $\mu W\,cm^{-2}$, time frame not specified
Wolfson and Yao [56]	Cathode: hydrophobic silver or platinum; anode: hydrophilic platinum (construction presumably as in Ref. [54])	Cathode membrane: Silastic film Separator: anion exchange membrane; anode membrane: cellulose (Neprophane)	Not specified, presumably as in Ref. [54]			Performance not clearly specified, focus on the effect off added endogenous substances
Rao et al. [60]	Cathode: Activated Carbon Lurgi LEV 585, anode: platinized carbon (32 mg cm^{-2}), both electrode catalysts embedded in thermally crosslinked, hydrophilic PVA–PAA hydrogel	Separators and protective membrane: 25 μm thick dialysis tube	Membranes bonded with Cyanolit glue, whole assembly embedded in epoxy frame	5×10^{-3} mol L^{-1} glucose in Tyrode solution	4 (per cathode area)	Aeration not specified, fabrication not clearly linked to performance; fuel cell with central anode, sandwiched between two cathodes
Wan and Tseung [62]	Cathode: Pt black mixed with PTFE brushed on Pt screen, anode: Pt black mixed with PTFE brushed on graphite	n/a	Both electrodes in the same air purged solution	1.5 g L^{-1} (8.3×10^{-3} mol L^{-1}) glucose in Krebs–Ringer solution, pH 7.4, 37 °C, equilibrated with air	~10	Stable performance reportedly delivered over night, poorly documented experiment; performance calculated based on the area of front and back of the electrode
Gebhardt et al. [32]	Cathode: silver Anode: Pt–Ni Raney-type catalyst, binders: not specified	Not specified		Physiological, not specified	5	Fuel cell with central anode, sandwiched between two cathodes; Performance over a period of 200 h
Rao et al. [26]	Not specified	Not specified	Not specified	5×10^{-3} mol L^{-1} glucose in Tyrode solution, 37 °C, 5% O_2 saturation ($pO_2 \sim 38$ torr)	~55 in total (see Fig. 9 in reference)	Fuel cell with central anode, sandwiched between two cathodes; presumably activated carbon and platinized carbon, stable performance after 100 days of operation; fuel cell size not specified
Rao et al. [26]	Not specified	Not specified	Not specified	5×10^{-3} mol L^{-1} glucose in Tyrode solution, 37 °C, 5% O_2 saturation ($pO_2 \sim 38$ torr)	~ 0.3 (per cathode area, see Fig. 7 in reference)	Fuel cell with central anode, sandwiched between two cathodes; presumably activated carbon and platinized carbon; stable performance after ~650 days of operation, even with micro-organism growth and catalyst loss; the cell was not operated at maximum performance and exhibited approximately same performance after 300 days

Rao et al. [26]	Not specified	Not specified	Not specified	Conditions of venous blood	8 (per cathode area)	Fuel cell with central anode, sandwiched between two cathodes, presumably activated carbon and platinized carbon, test conditions not further specified
C: *in vivo* experiments						
Drake et al. [51]	Cathode: platinum black laminated on one side of a hydrophobic carbon/PTFE matrix, anode: noble metal alloy black compressed onto platinum screen	Cathode protected by thin silicone rubber membrane; separator and anode protective membrane: dialysis membrane of the supported ionic hydrogel film type	Silicone rubber casing with a porous metal facing on the anode side	Implanted subcutaneously, right flank of adult mongrel dog	2.2	Average performance over a period of 30 days; no evidence of necrosis, hemorrhage, abscess formation, or overt degenerative change upon explantation after 78 days
Henry and Fishman [59]	Selective Au–Pd electrodes	Semipermeable membrane separating the electrodes from blood	Not specified	Operated externally in a dog, pulsed 1 Hz load, duty cycle 2.5–10%	30–70 (per pulse)	Meeting abstract only
Malachesky et al. [31]	Cathode: Teflon-bonded Pt black (15 mg Pt cm^{-2}) on a gold grid, anode: Pt black 0.7% asbestos paste on gold grid (10 mg Pt cm^{-2})	Cathode membrane: 13 μm GE XD-1, 65–35 dimethylsilicone-polycarbonate copolymer on porous PTFE; separator: 178 μm anion exchange membrane; anode membrane: 13 μm Cuprophane	Electrodes and membranes hot pressed to stainless steel frame using double sided adhesive tape, assembly pressed between Lexan plates to form blood channels	As extracorporeal arterio-venous bypass circuit with a sheep	Initially 40, rapid decay	Considerable decay of performance after 1 h of operation, solely due to rise in anode potential to more positive values
Wan and Tseung [62]	Cathodes: Pt black, Pt–Ru black mixed with PTFE brushed on Pt screen, anode: platinized graphite	n/a	n/a	Electrode implanted subcutaneously in rats or rabbits	3.3	Unclear description of experimental methods and results; similar results reported for Pt-Ru cathode
Weidlich et al. [68]	Cathode: activated carbon on metal screen, anode: Pt black on metal screen; binders not specified	Not specified	Silastic encapsulation.	Subcutaneously in dog	0.04 (per cathode area)	Fuel cell with central anode, sandwiched between two cathodes; performance after 3 months, afterwards the cell failed to respond; evidence of infection found at the implantation site, cell severely damaged
Weidlich et al. [68]	Cathode: activated carbon on metal screen; anode: Pt–Ni Raney-type catalyst; binders not specified	Cuprohane membranes as separators, protective membranes not specified	Epoxy frame.	Subcutaneously in dog	1.6 (per cathode area)	Fuel cell with central anode, sandwiched between two cathodes; stable performance after 150 days of operation

Unless otherwise noted the power density is based on the projected electrode area of the fuel cell.

The following sections highlight the achieved power output of implantable fuel cells under *in vitro* conditions. *In vitro* performances are classified into experiments under non- and near-physiological conditions. Non-physiological refers to experiments in unbuffered solutions or at non-physiological levels of glucose, whereas under near-physiological conditions the experiments were performed in neutral buffer containing physiological amounts of glucose ($\sim 5 \times 10^{-3}$ mol L^{-1}). In later sections the effects of endogenous substances on performance and the results of first *in vivo* trials are described.

4.1. In vitro experiments: non-physiological conditions

The highest performance under non-physiological conditions has been reported for a fuel cell operating in unbuffered 10% (0.56 mol L^{-1}) glucose solution. The fuel cell had an air-breathing cathode and delivered approximately 165 $\mu W\,cm^{-2}$ [44].

An *immersible* prototype with *hydrophobic cathode membrane* exhibited 18.6 $\mu W\,cm^{-2}$ over a period of 142 days. For an *immersible* fuel cell with *oxygen-selective cathode catalyst*, operating in physiological solution with 20-fold increased glucose concentration (0.1 mol L^{-1}), a performance of 8 $\mu W\,cm^{-2}$ could be demonstrated over a period of 83 days [64].

4.2. In vitro experiments: near-physiological conditions

For a *flow-through* type fuel cell with *hydrophobic cathode membrane*, designed to be operated directly in the blood stream, approximately 50 $\mu W\,cm^{-2}$ could be reached under physiological conditions in Ringer-solution [31].

Lower performances were achieved with *immersible* prototypes. Devices with a *hydrophobic cathode membrane* exhibited 26 $\mu W\,cm^{-2}$ after 20 h of operation in Krebs–Ringer solution, containing glucose and oxygen in concentrations found in venous blood. Heat sterilization had no negative effect on performance and has routinely been employed to prevent the growth of micro-organisms [54]. Long-term experiments with similarly constructed prototypes have yielded between 11.3 and 4.4 $\mu W\,cm^{-2}$ over periods of 167 and 428 h, respectively [51].

Immersible cells with *oxygen-selective cathode catalysts* exhibited performances between 7 $\mu W\,cm^{-2}$ under the not further specified conditions of venous blood [26], and approximately 4 $\mu W\,cm^{-2}$ in Tyrode solution [60]. Similarly, the performance of an early prototype has been monitored for 650 days in Tyrode solution. Although the oxygen electrode suffered from micro-organism growth and catalyst loss the cell exhibited a performance of approximately 0.3 $\mu W\,cm^{-2}$ after 300 days and also after 650 days [26]. The comparably low performance of this prototype originated from a too high load resistance. A later prototype has thus been operated with lower load resistance and close to its maximum performance. Over a period of 80 days the power output of the fuel cell (operated in modified Ringer-solution, 5.6×10^{-3} mol L^{-1} glucose, 5% oxygen saturation) decreased by 50% from approximately 110 to 55 μW. The active electrode area of the device has unfortunately not been specified [26].

Remarkable is the performance reported for a fuel cell with *selective* electrocatalysts, although experimental procedures and results are not clearly documented. From two uncovered electrodes immersed in the same air-purged glucose solution approximately 10 $\mu W\,cm^{-2}$ have been obtained. Anode and cathode consisted both of a platinum black–PTFE mixture, brushed on platinum mesh and graphite, respectively [62].

4.3. In vitro effect of endogenous substances on fuel cell performance

Oxidizable substances present in body fluids can interfere with the oxygen reduction and induce anodic reactions at the cathode. This leads to a more negative cathode potential and decreased cell voltage [56]. For example activated carbon, which can be employed as an *oxygen-selective* cathode catalyst, is insensitive to glucose, but catalyzes the oxidation of creatinine, lactic acid, and uric acid [67]. Furthermore, some substances can block or poison the electrode surface and thus reduce the reaction rate. For instance chloride ions decrease the glucose oxidation rate on platinum [88,89].

The oxygen reduction performance of bare platinum, silver, and ZTA graphite in oxygen saturated 0.05 mol L^{-1} phosphate buffer (pH 7.22, 0.15 mol L^{-1} NaCl) has been compared upon the addition of 10% of blood. Silver, which is insensitive towards glucose, exhibited a slightly increased peak current and a decrease of approximately 30 mV in the oxygen reduction onset potential. ZTA graphite showed no shift in onset potential and the peak current increased by 30%. For platinum, which is sensitive towards carbohydrates, the addition of blood resulted in an approximately 90 mV more negative onset potential and a 20% reduction in peak current [47].

The effect of creatinine, ethanol, urea, alanine, and ammonium chloride on fuel cell performance in Krebs–Ringer solution (pH 7.4) has been investigated using a *hydrophobically* protected platinum cathode. Remarkably, the *hydrophobic* silastic barrier did not prevent poisoning of the platinum cathodes. The authors presumed that volatile substances like ethanol or gaseous ammonia from substances containing amino nitrogen penetrate the hydrophobic barrier, and interfere with the platinum catalyst. Hydrophobic silver cathodes tested under the same conditions were not affected. Accordingly, fuel cells with hydrophobic silver instead of hydrophobic platinum as the cathode were less affected by the presence of human plasma components. No poisoning effect was observed for *hydrophilic* platinum electrodes operating as anodes when the above-mentioned substances were present in the normal concentration range of human blood [56].

A systematic study of the influence of amino acids on glucose oxidation has been performed employing Raney-type electrodes fabricated from platinum–nickel alloy. As electrolyte deaerated phosphate-buffered saline (PBS) containing 0.1% (5.6×10^{-3} mol L^{-1}) glucose was used. At a potential of 400 mV vs. RHE a current drop of 92% was observed within 6 h when a physiological amino acid mixture was added to the electrolyte, compared to 12% drop when only glucose was present. Despite these drastic effects the current density remained stable at approximately 25 $\mu A\,cm^{-2}$ after 20 h. In experiments where individual amino acids were added a particular drastic effect was observed with basic and unsaturated as well as sulfur-containing amino acids. Especially additions of histidine, phenylalanine, serine and tyrosine resulted in current drops between 65 and 76%. However, the experiments were conducted under non-sterile conditions, and the authors did not exclude potentially deterious effects of bacterial amino acid decomposition [71]. Similar results have been obtained during a cyclic voltammetry study on platinized platinum electrodes in Krebs–Ringer solution, where again basic and sulfur containing amino acids were found to be most inhibitory. The authors related the inhibitory effect to the strength of amino acid adsorption on the platinum electrode [72].

4.4. In vivo experiments

Preliminary *in vivo* studies with implantable fuel cells were quite successful in terms of power output and demonstrated the feasibility of the concept.

Upon testing a first prototype with *hydrophobic cathode membrane*, implanted subcutaneously in the flank of a dog, a low open circuit potential and a rapid decay of cell voltage upon load was encountered. A refined prototype, employing dialysis membranes to protect the electrodes, delivered an average performance of 2.2 $\mu W\,cm^{-2}$ over a period of 30 days. After 78 days of operation no evidence of necrosis, hemorrhage, abscess formation, or overt degenerative change in the tissue surrounding the implanted device was found. The electrodes were not adhering to tissue but covered by a transparent exudate film [51]. A *flow-through* type fuel cell with *hydrophobic cathode membrane* was tested in the blood stream of a sheep. Initially 40 $\mu W\,cm^{-2}$ could be reached, but the performance dropped rapidly within 1 h due to a shift of anode potential to more positive values [31].

Prototypes with *oxygen-selective cathode catalyst* were also subject to subcutaneous implantation in dogs. In first trials a cell with activated carbon cathode and platinum black anode delivered 0.04 $\mu W\,cm^{-2}$ after 3 months of operation. Subsequently the cell failed to respond, and upon explantation the cell was found to be severely damaged. Also, the implantation site showed evidence of infection. A second, more sturdily constructed prototype incorporating an activated carbon cathode and a Raney-type Pt–Ni anode, exhibited a stable performance of 1.6 $\mu W\,cm^{-2}$ even after 150 days of operation [68].

Corresponding to the development of *glucose-selective* electrodes fabricated from gold–palladium alloys, Henry et al. reported the *in vivo* performance of a pair of membrane-covered electrodes at the Electrochemical Society Conference in 1973. Implanted in a dog and subject to a pulsed load profile (1 Hz, duty cycles ranging from 2.5 to 10%) a performance of 30–70 $\mu W\,cm^{-2}$ per pulse was achieved for 5 h [59]. Wan and Tseung implanted a platinum black–PTFE cathode together with a platinized graphite anode subcutaneously in a rat, both electrodes being bare and having a geometric area of 3.5 cm^2. They achieved a performance of 10 μW (2.9 $\mu W\,cm^{-2}$) for periods of at least 4 h, and reported similar results for a platinum–ruthenium cathode. Unfortunately the description of experimental procedures and results is not very clear [62].

5. Conclusions

5.1. State of the art

In *in vitro* experiments under near-physiological conditions several groups demonstrated tissue implantable abiotically catalyzed glucose fuel cells delivering between 2.5 and 8 $\mu W\,cm^{-2}$ for periods up to 100 days. *Flow-through* type fuel cells with *hydrophobic cathode membrane*, intended for operation in the blood stream, exhibited *in vitro* performance of up to 50 $\mu W\,cm^{-2}$, but successful *in vivo* operation has not been demonstrated [31]. Several studies revealed a detrimental influence of amino acids and other endogenous substances on electrode performance, indicating silver cathodes and Raney-type anodes fabricated from platinum–nickel alloys as promising candidates for stable *in vivo* performance. However, a systematic approach comparing the fuel cell performance under physiological *in vitro* conditions, including amino acids and other endogenous substances present in body fluids, has to our knowledge not yet been reported.

First *in vivo* experiments with fuel cells implanted subcutaneously in dogs yielded performances in the range of 2 $\mu W\,cm^{-2}$ for periods up to 150 days. Although no negative tissue response to the implanted fuel cells has been observed, dedicated cytotoxicity and biocompatibility investigations have not been reported.

Whereas these results are encouraging with respect to the application of abiotically catalyzed glucose fuel cells as power supply for low-power medical implants, the majority of publications are imprecise with respect to materials and fabrication of the devices. The performance of different embodiments can therefore hardly be compared, and further effort will be necessary to redevelop the technology and establish an understanding of construction details governing long-term performance and *in vivo* stability.

Based on the so far demonstrated performance an *in vivo* power output of approximately 50 μW can be expected from abiotically catalyzed glucose fuel cells, assuming a reasonably sized device with 25 cm^2 surface area. Potential applications are thus limited to low power medical implants, such as cardiac pacemakers and implantable sensors.

5.2. Performance of abiotically catalyzed glucose fuel cells compared to other energy harvesting devices

In the context of low power medical implants abiotically catalyzed glucose fuel cells compare well to other energy harvesting approaches.

Enzymatically catalyzed glucose fuel cells have exhibited performances of up to 430 $\mu W\,cm^{-2}$ under physiological conditions [15]. Although this is an order of magnitude higher than the highest performance reported for abiotically catalyzed glucose fuel cells [31], the lifetime of their enzymatic catalysts has not yet been demonstrated beyond the order of a month [12]. At present, enzymatic fuel cells appear therefore to be limited to short-term applications.

For *vibrational energy harvesting* systems, subject to the simulated motions of the left ventricular wall of a goat, power outputs between 36 and 58 μW have been demonstrated. These variable-capacitance-type electrostatic (VCES) generators weigh between 0.76 and 1.2 kg, and were therefore too large to be implanted in the thoracic cavity of a goat [90,91]. A much smaller *vibrational energy harvesting* generator intended for biomedical applications has been described recently. For a device of 11 mm by 11 mm in size the authors projected a power output of 80 μW at an operating frequency of 30 Hz [92]. With regard to size the power output of this device is in the range of abiotically catalyzed glucose fuel cells. In contrast, the performance of implantable fuel cells is independent of continuous body motion which makes them superior compared to vibrational systems.

Considerably higher performances have been reported for *thermoelectric generators*. With the aim of supplying a cardiac pacemaker a thermopile system has recently been developed, that delivers 1100 $\mu W\,cm^{-2}$ at a temperature difference of 2 K [93]. However, the performance of encapsulated thermoelectric generators under the relatively low-temperature gradients within the human body has not yet been demonstrated.

5.3. Future prospects

The current trend in developing power efficient medical implants will not only increase battery dependent implant lifetime, but also open a wider area of application for μW-range energy harvesting devices like abiotically catalyzed glucose fuel cells. Recent examples are a low-power mixed-signal integrated circuit (IC) for pacemaker application, consuming on average only 8 μW [94], and a newly developed 211 μW 16-channel bionic ear processor that reportedly cuts the power consumption of state-of-the-art approaches by a factor of 25 [95].

To realize an autonomous implant power supply based on abiotically catalyzed glucose fuel cells, their biocompatibility and functionality in a body environment are of utmost importance. In this context the development of biocompatible catalyst materials

that are poisoning resistant, tolerant toward endogenous substances, and highly active over prolonged periods of time will be essential.

Several of the so far described catalyst materials are prime candidates for further investigation. Silver and Raney-type platinum alloys are especially promising with respect to poisoning resistance and amino acid tolerance. However, their biocompatibility needs to be investigated. Carbon-deposited chelates, rhodium and platinum–ruthenium alloys have shown high activity for glucose oxidation but their response to endogenous substances still has to be assessed.

An important topic of future research will be the application of novel materials and fabrication techniques. Nano-patterned catalysts, carbon nanotubes, and electrically conductive polymers have already found application in biosensors and conventional fuel cells. They are exemplary for a number of promising new technologies that have not yet been explored in the context of implantable abiotically catalyzed glucose fuel cells. A further, largely unexplored field is the development of abiotic catalysts that are selective for glucose oxidation. Such catalysts would render reactant separation obsolete and therefore offer a high degree of freedom in cell construction.

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