Remote Accessibility to Diabetes Management and Therapy in Operational Healthcare Networks

REACTION (FP7 248590)

D2-2 Clinical watch report

Date 2012-07-31

Version 2.0

Dissemination Level: Public

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Document control page

Code	D2-2_2012-31-07_Clinical-watch-report_V20_UBRUN.docx
Version	2.0
Date	2012-07-31
Dissemination level	P
Category	R
Participant Partner(s)	UBRUN
Author(s)	Malcolm Clarke
Verified and approved by	
Work Package	WP2
Fragment	No
Distribution List	All
Abstract	This document provides a review of state of the art of clinical research and work that pertains to clinical pilot activity and clinical service design within the REACTION project.
Comments and modifications	
Status	☐ Draft ☒ Task leader accepted ☒ WP leader accepted ☐ Technical supervisor accepted ☐ Medical Engineering supervisor accepted ☐ Medical supervisor accepted ☐ Quality manager checked ☒ Project Coordinator accepted
Action requested	☐ to be revised by partners involved in the preparation of the deliverable ☐ for approval of the task leader ☐ for approval of the WP leader ☐ for approval of the Technical Manager ☐ for approval of the Medical Engineering Manager ☐ for approval of the Medical Manager ☐ for approval of the Quality Manager ☐ for approval of the Project Coordinator **Deadline for action**: N/A
Keywords	
References	
Previous Versions	

Version Notes

Version	Author(s)	Date	Changes made
1.0	M Clarke	2012-02-24	
1.1	M Clarke	2012-02-28	Response to internal reviewers' comments
1.2	M Clarke	2012-03-01	Final revision with new template
2.0	M. Clarke, H. Udsen	2012-07-31	Final version, resubmitted to the European Commission, addressing external reviewers' comments.

Internal review history

Reviewed by	Date	Comments made
R.W. Jones, CHC	2012-02-27	Approved with comments
L. Schaupp, MUG	2012-02-28	Approved with comments

1. Executive summary

This document provides a review of state of the art of clinical research and work that pertains to clinical pilot activity and clinical service design within the REACTION project. The document covers areas: using health information technology to manage diabetes; in hospital glucose management; self-monitoring of blood glucose (SMBG); continuous glucose monitoring (CGM); insulin pumps; closing the loop; and insulin delivery; The document is written as a systematic review of each area, and covers up to February 2012.

2. Terms and Definitions

2.1 Abbreviations and Acronyms

CGM	continuous glucose monitoring
ConA	concanavalin A
CSII	Continuous subcutaneous insulin infusion
FRET	Förster resonance energy transfer
GOx	glucose oxidase
ISF	interstitial fluid
MDI	Multiple daily injections
NAD	nicotinamide adenine dinucleotide
NIR	near infrared
PBP	published best practice
SC	subcutaneous
SMBG	self-monitoring of blood glucose
SSI	sliding scale regular insulin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TRM	tissue response modifier
VA	Veterans Health Administration

3. Using Health Information Technology to Manage Diabetes

The growing number of patients with increasingly complex co-morbidities has resulted in a larger number of projects. These use health information technology to assist the clinician to manage the disease and support patient self-management.

3.1 Web technologies

There is increasing interest in how web technology can help patient self-management; there are many new ways of exploiting the web being explored.. A review of web-based interventions [1] identified twenty articles representing 13 different studies. None of the studies were ranked as low in their methodological quality. Goal-setting, personalised coaching, interactive feedback and online peer support groups were some of the successful approaches which were applied in e-interventions to manage type 2 diabetes mellitus. Strong theoretical background, use of other technologies and longer duration of intervention were proven to be successful strategies as well. The conclusion is that when enhanced by proper e-research strategies, t web-based interventions have achieved successful outcomes

A Cochrane review of self-management interventions [2] identified a number of strategies for intervention and provides informative insight in Figure 1. As the interventions were intended to impose behaviour change, the most powerful approach that was to employ the strategy of short concentrated interventions (along the lines of cognitive therapy).

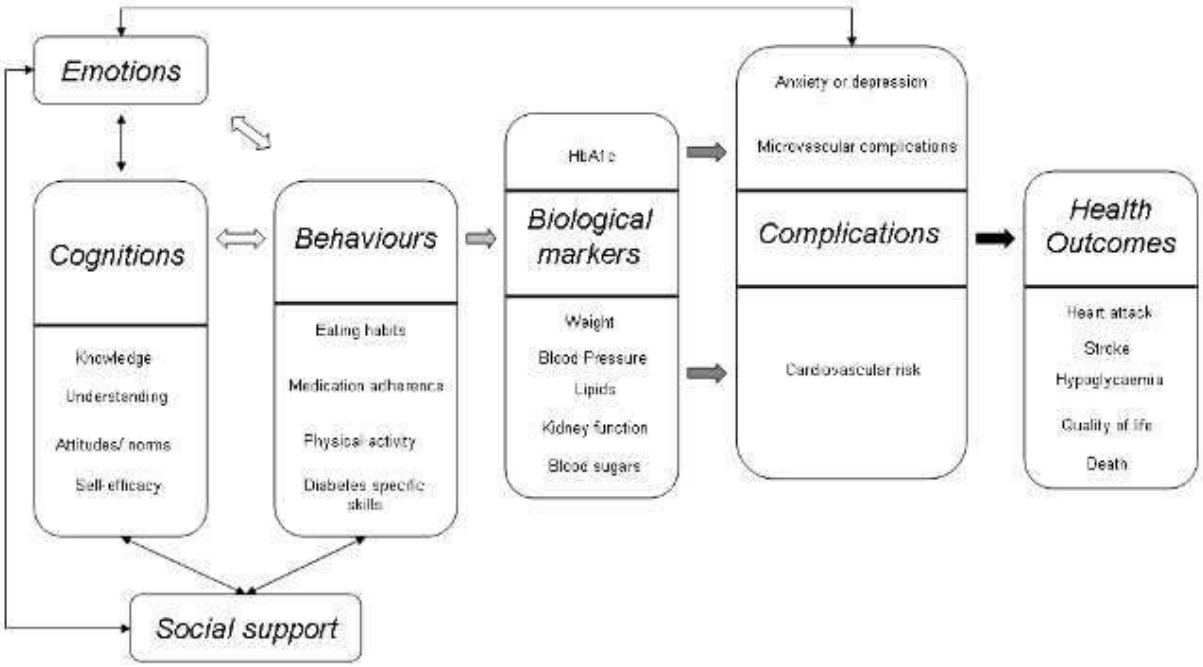

Figure 1: A model to demonstrate how self management interventions might affect outcomes in type 2 (from [2])

Randomised controlled trials further support this finding. [3]

There is little evidence on employing and evaluating use of health IT technology with users not familiar with technology, as will be the case in Reaction.

3.2 Primary care management technologies

New reports on the use of health IT for management of chronic disease in primary care remain limited. A review of the use of telemedicine within the Veterans Health Administration (VA) demonstrates that it can become widespread and mainstream. [4] However the VA can call upon large resources and has the advantage that it covers the complete provision of services, so that savings in one area can be

used to fund in another. Moreover, where the primary care elements of the VA have exploited case management with the telehealth monitoring, significant improvement in long term management of diabetes is achieved. [5] Similar results are demonstrated where UK primary care is used. [27]

3.3 Mobile technologies

Studies continue into the use of mobile technologies to support diabetes patients. Specific areas of interest are to identify the best target groups to use the technology, the approach used in the technology and how it is integrated into a larger platform.

Many groups continue to assess impact on the use of mobile technology for adolescent diabetes management and generally report that technology is well received in this group. [6] Results were less conclusive in a general population. [7] Participants that used the technology appreciate its value. , There are though many patients who refuse to use mobile technology and there is no clear explanation or solution for this finding.

3.4 Conclusions

Structured research on the use of web-based technology and self-management interventions clearly identifies that the approach based on short focused strategy has greatest overall impact. This supports the approach in the primary care pilot in Reaction to deploy technology with patients for short periods.

Good outcomes for management of diabetes are achieved in primary care when case management is used in addition to the technology.

4. In hospital glucose management

4.1 Status of in hospital glucose management

Hyperglycaemia in hospitalised patients with diabetes type 2 is a common and costly health care problem with profound medical consequences. Increasing evidence indicates that the development of hyperglycaemia during acute medical or surgical illness is not a physiologic or benign condition but is a marker of poor clinical outcome and increased mortality [8][9][19][11]. Observational studies in diabetic subjects admitted to general medical and surgical areas have shown that poor glycaemic control is associated with prolonged hospital stay, infection, disability after hospital discharge and death [8][12][13].

In the critical care setting, a variety of continuous insulin infusion protocols have been shown to be effective in achieving glycaemic control, with low rate of hypoglycaemic events [14][15]. Prospective randomized trials in postsurgical patients have shown that improved glycaemic control reduces short- and long-term mortality, rates of multi-organ failure and systemic infections, and length of hospitalization [16]. These results could not be confirmed in a study of mixed surgical and medical intensive care patients [17].

Hyperglycaemic patients on general medicine wards are not well managed [8][9][18][19]. Although several treatment guidelines for outpatient management of type 2 diabetes have been defined [14][20], there is no clearly defined treatment regimen to establishing the glycaemic control of hospitalised patients [21][22].

The consensus panel of the American Diabetes Association reviewed research together with the original investigators to formulate standards for diabetes management in the hospital. The panel concluded that hospitalised patients should have a target glycaemic pre-meal/fasting level of <140 mg/dL (7.8 mmol/L and that insulin, whether administered intravenously or subcutaneously is the primary means of effective glycaemic control in the hospital setting [22].

Reports from academic institutions have shown that most patients are treated with sliding scale regular insulin (SSI) and that basal insulin is prescribed in less than half of the patients [18]. A recent audit of glycaemic control in two general wards of the University Hospital of Graz has shown that hospitalised patients with type 2 diabetes mellitus have a mean blood glucose level above the recommended target range. The analysis of 50 consecutive patients, who were treated with insulin on the endocrinology and cardiology wards, revealed a mean blood glucose level of 167 mg/dL. No difference between admission and discharge blood glucose values was observed, indicating an insufficient insulin titration process throughout the hospital stay[1].

4.2 Status of in hospital glucose management algorithms

In contrast, use of a basal bolus insulin treatment protocol in a multi-centre randomized trial has shown that, in general, medical patients with non-insulin treated type 2 diabetes had improved glycaemic control without an increase in their risk of severe hypoglycaemia when compared with an SSI regimen [11]. In another study, type 2 patients under previous treatment with diet, oral agents and/or insulin the same basal bolus insulin titration protocol was equivalent with NPH and regular twice daily insulin [23]. In a recent randomised controlled study, this protocol not only improved glycaemic control, but also reduced the incidence of postoperative complications (wound infections, pneumonia, bacteraemia, respiratory and acute renal failure) [24]. Thus, this protocol represents the currently published best practice (PBP) to manage type 2 diabetic patients in non-intensive care beds on general wards.

[1] One possible explanation for these results is that many hospitals are having difficulty in maintaining the necessary number and quality of nurses to monitor general ward diabetic patients, understand the observations and arrange appropriate interventions despite improved monitoring tools.

5. Self-Monitoring of Blood Glucose (SMBG)

5.1 Status of SMBG

The technique of self-monitoring blood glucose is well established and the technology is mature. Although development continues to improve accuracy, repeatability and discomfort, the performance of commercial technology falls well within international standards.

5.2 Outcomes from SMBG

Studies continue to determine the most effective application of SMBG in the management of type I and type II diabetes patients. Studies targeting the poorly controlled [8] demonstrate significant improvements in clinical outcomes, including significant reduction of HbA1C, with many more medication changes in the active control group compared to the usual care group. Further studies on the cost effectiveness of use of SMBG can show significant benefit of cost compared to the benefit from increased life expectancy and quality adjusted life year over a 30 year time horizon, given the likelihood to avert complications through reduction of Hb1Ac and associated risk of clinical event. [26]

5.3 Conclusions

Studies on the outcome of targeted use of SMBG and its cost-effectiveness indicate that a targeted approach is advocated.

6. Continuous Glucose Monitoring (CGM)

Continuous Glucose Monitoring (CGM) is an area that is becoming increasingly mature, with existing devices becoming more accurate, and new technologies to increase accuracy and ease of use becoming available. Studies continue to assess the impact on control of diabetes with use of CGM devices. The reader is directed to the excellent recent review for further detail [1].

6.1 Evolving Technology

6.1.1 Categorization of Technologies

Continuous glucose monitoring systems are categorized by the level of invasiveness required to make the measurement. They are categorized in broad terms as invasive, minimally invasive and non-invasive. Subcutaneous and most current sensors are invasive.

The intent is to develop sensors that are non-invasive.

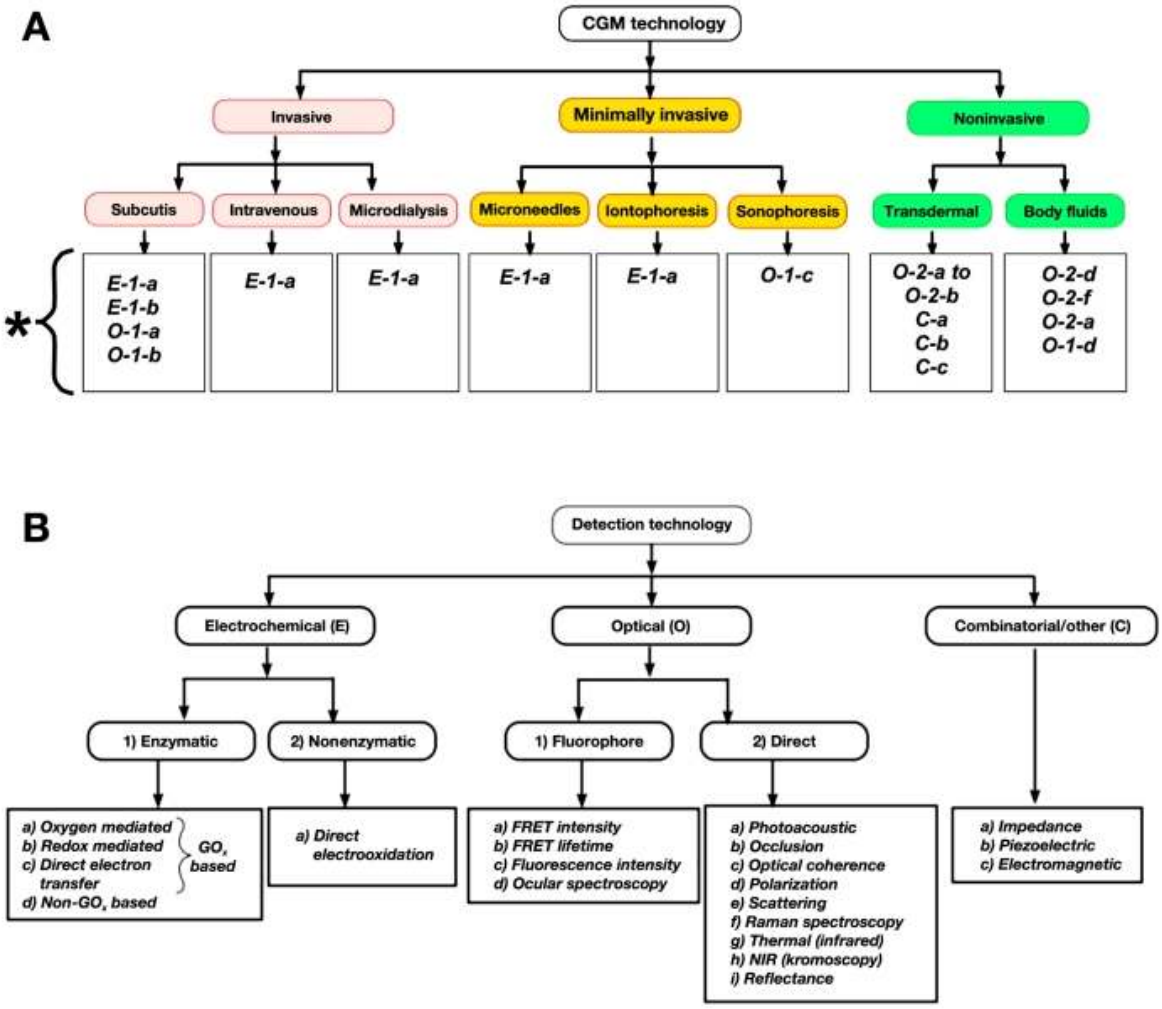

Figure 2: Classification of various CGM technologies according to their (a) invasiveness and (b) transduction mechanism of the sensor

Code definitions in Figure 2A correspond to the respective transduction mechanisms shown in Figure 2B. The asterisk in Figure 2A displays code definitions corresponding to the detection technologies shown in Figure 2B. For example, code E-1-a corresponds to electrochemical (E) detection based on enzymatic (1) reaction that is oxygen mediated (a) (from [1]).

6.1.2 Subcutaneous Continuous Glucose Monitoring

Subcutaneous continuous glucose monitoring, an invasive technique, remains the single solution in widespread use in clinical practice. Studies continue to assess its accuracy, and recent studies demonstrate that current devices are reliable and safe for decisions on insulin therapy in intensive care settings [29], [58]. Manufacturers continue to refine devices to increase absolute accuracy and long term stability.

6.1.3 Enzymatic Electrochemical Sensors

The majority of current sensor technology is based on electrochemical-based methods which can be broadly categorized under enzymatic and non-enzymatic approaches, as Figure 2.

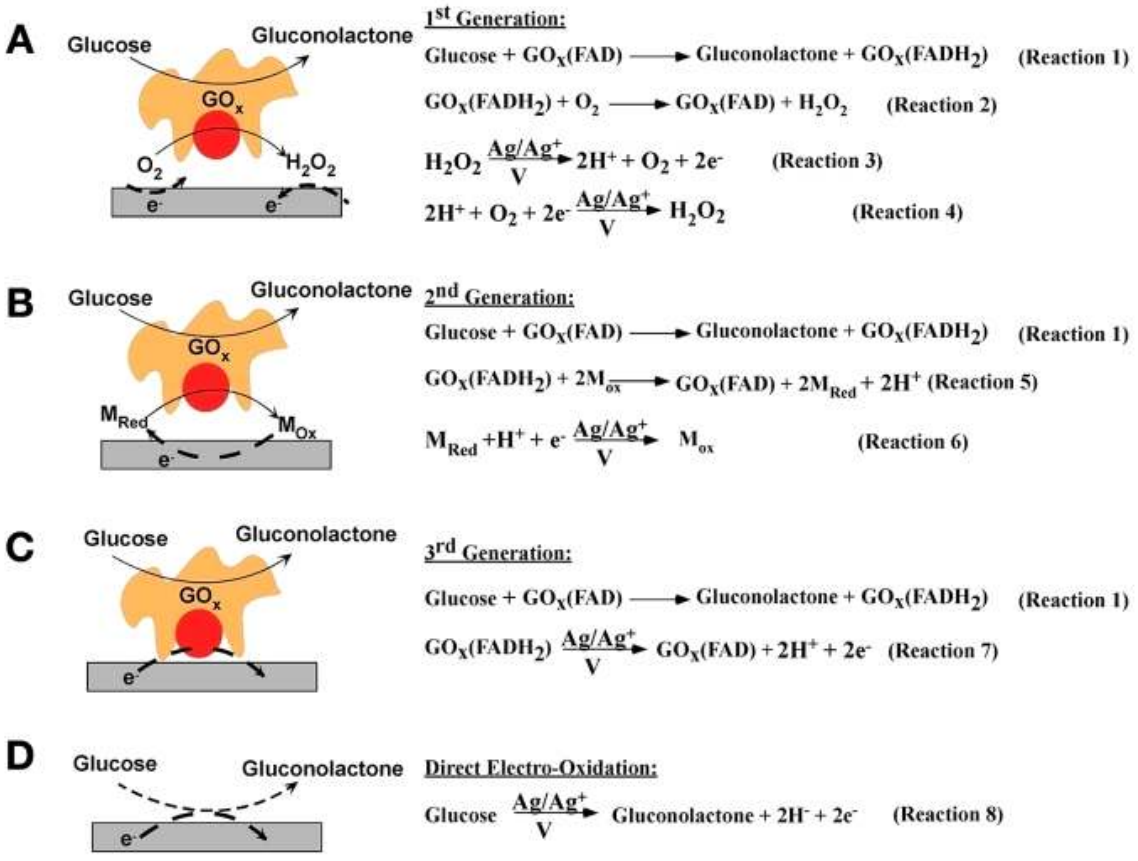

Figure 3: Various modes of electrochemical detection of glucose, detailed below

(A) first-generation biosensors based on the use of natural oxygen cofactor, (B) second-generation biosensors based on artificial redox mediators, (C) third-generation biosensors based on direct electron transfer between GO_x and the electrode, and **(D)** direct electro-oxidation of glucose (from [1])

6.1.4 Optical Approaches (from 1)

Optical measurement of glucose can be broadly classified as (1) fluorophore-based and (2) direct (nonfluorophore)-based techniques.

The fluorophore-based approaches use an affinity sensor principle in which glucose and a fluorophore bind competitively with a receptor that is site specific to both ligands. For example, concanavalin A (ConA) can be used as the receptor molecule as it has four glucose- binding sites and its competitive binding can be assessed against other binders such as fluorescein-labeled dextran, α-methyl mannoside and glycated protein. Various spectroscopic techniques have been utilized to measure glucose concentration. Some of these are listed here:

1. The binding of fluorescein-labeled dextran to ConA results in charge transfer and subsequent quenching in the fluorescence intensity of fluorescein-labeled dextran. Glucose preferentially binds to ConA compared to fluorescein-labeled dextran, thereby the presence of glucose causes an increase in the amount of free (unbound) fluorescein-labeled dextran. This results in an increase in the intensity of the fluorescence emission (Figure 3A). Thus the intensity of the fluorescence emission from the binder molecule (fluorescein-labeled dextran) is used as a measure of glucose concentration. The higher the glucose concentration, the higher the fluorescence intensity of fluorescein-labeled dextran.

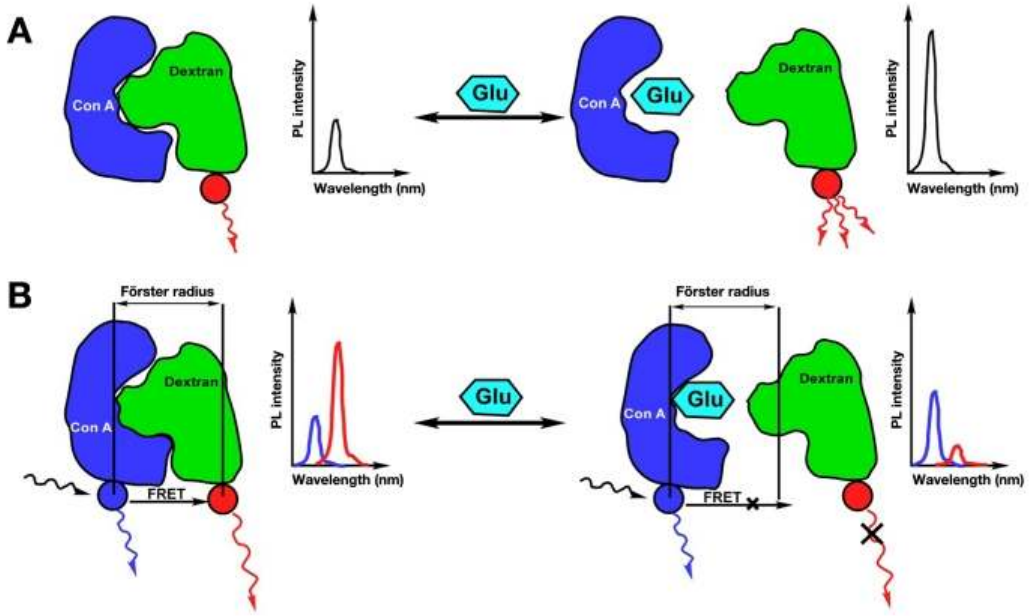

Figure 4: Optical detection of glucose based on (A) fluorescence intensity decrease as a result of affinity binding and (B) decrease in FRET-induced fluorescence intensity (from [1])

2. Fluorescence emission that occurs as a result of the Förster resonance energy transfer (FRET) between the allophycocyanin labeled ConA (donor) and fluorescein labeled dextran (acceptor) when they are within atomic distances (Förster radius) of each other. [30] Any glucose molecule present binds to ConA, thereby increasing the distance between the two (greater than the Förster radius), leading to a decrease in FRET-induced fluorescence emission (Figure 3B). Thus glucose concentration can be evaluated by monitoring changes in the FRET-induced fluorescence emission intensity of fluorescein-labelled dextran.[31]-[58]
3. The occurrence of FRET between the donor and acceptor molecules is also accompanied by a decrease in the lifetime of the donor. Based on this and the fact that the presence of glucose decreases the possibility of FRET (Figure 4B), an increase in the lifetime of the donor can be seen with increasing glucose concentration. Thus glucose concentration can be evaluated by monitoring changes in the lifetime of the donor molecule that is in close proximity to an acceptor molecule.[35]
4. Fluorescence intensity of human tissue, using glucose itself as the fluorophore. When human tissue is excited with light at 308 nm, the glucose molecules become excited and there is claim [36] that fluorescence emission can be detected at any of following wavelengths, 340, 380 and 400 nm, although this remains to be scientifically validated.[36] Thus glucose concentrations can be evaluated by direct tissue excitation at 308 nm and monitoring the emission intensity at 380 nm, the wavelength at which glucose has the strongest emission.
5. Ocular spectroscopy utilizes synthetic boronic acid derivatives (loaded within a polymer matrix) that specifically, yet reversibly, binds to glucose. In addition, these molecules are coupled to fluorescent moieties that allow their spectroscopic analysis. The boronic acid group, which is in its sp2 hybridized trigonal form, turns into a more electron-rich sp3 hybridized and tetrahedral geometry upon interaction with glucose, thereby leading to changes in the spectra of the fluorescent moiety.

Non-fluorophore-based optical detection of glucose utilizes light of variable frequencies to investigate changes in the absorbance, reflection, or refraction (scattering) of tissue containing various concentrations of glucose.[38] In particular, light with wavelengths in the near-infrared (NIR) range has been found to pass through the human stratum corneum with minimal tissue absorption. Moreover, the fact that the absorption of water creates a window in the NIR (0.8–1.4 μm) region, where tissue components do not absorb, allows light to pass deep into the epidermis and subcutaneous (SC) space, independent of skin pigmentation. This renders NIR light as a possible means to investigate glucose-induced changes in the optical properties of the SC tissue. For example, variations in glucose concentration alter the dielectric strength, polarizability, and permittivity of the SC tissue, thereby registering changes in the absorbance, reflection, and refraction of NIR radiation, respectively. Based on these changes, a number of optical techniques that involve no fluorophores are listed here:

1. Optical coherence tomography and chromoscopy quantify glucose via assessment of the intensity of the reflected/scattered and transmitted light upon interaction with the SC tissue glucose concentration.[39],[40]
2. Polarimetric technique utilizes the ability of glucose to rotate linearly polarized light to subsequently quantify glucose concentration, based in the degree of optical rotation.[41],[42]
3. Thermal infrared spectroscopy utilizes changes in the refractive index of the tissue upon illumination with a time-modulated light that creates change in the temperature of the local tissue. Such local heat changes create microcirculation that induces change in the refractive index of the tissue. These refractive index changes are dependent on the amount of glucose present in the SC tissue.[43]
4. Photoacoustic spectroscopy that is based on the principle of adsorption of light by tissue-localized heating and subsequent generation of ultrasonic waves as a result of volumetric expansion. For glucose detection using photoacoustic spectroscopy, the tissue is illuminated with NIR wavelength light and the velocity of the generated ultrasonic wave is recorded. Since the velocity of the generated ultrasonic wave is dependent on the specific heat of the irradiated tissue (which, in turn, is dependent on the glucose concentration), a quantitative assess-ment of glucose concentration can be made.[44],[45]
5. Raman Spectroscopy that is based on inelastic scattering of photons. When monochromatic light interacts with glucose, owing to the Raman Effect, there will be a shift in the energy of the photons proportional to the vibrational or rotational energy of glucose.[46],[47] Since the Raman Spectrum is characteristic of a specific intramolecular motion (vibrational or rotational) of the molecular bonds of glucose, it can provide selective information about the concentration of glucose. For example, Raman Spectroscopy can be utilized to differentiate between galactose and glucose, two epimers with the same chemical composition but structurally different in the position of one atom.
6. Photonic crystal-based glucose sensors work on the principle of shift in the wavelength of diffracted light from a hydrogel-based crystalline colloidal array. The sensor consists of a polyacrylamide-polyethylene glycol polymer network with an embedded crystalline colloidal array and a recognition element (such as a boronic acid derivative) that specifically binds to glucose. Interaction of glucose with the recognition element results in the formation of cross links (such as bis-bidentate) that shrinks the hydrogel volume. This volume shrinkage causes a blue shift in the diffraction from the crystalline colloidal array that is proportional to the bound glucose. Such colour changes can be perceived visually (without instrumentation) across the visible spectral region, from red to blue over physiologically relevant glucose concentrations.[48] Because this scheme involves chemically-induced swelling (i.e., corresponding to mechanical deformation) to the optical properties of the photonic crystal, this technology can also be considered as chemo-mechano-optical transduction.

6.1.5 Other Approaches

Apart from electrochemical and optical approaches, glucose detection based on electric or electromagnetic transduction has also been reported. Some of these include the following:

1. Impedance spectroscopy. An increase in the local glucose concentration results in a decrease in the sodium levels and an increase in the potassium levels of the plasma, changing the dielectric strength, permittivity, and conductivity of the plasma.[49] This forms the principle of glucose detection using impedance spectroscopy, which utilizes the transport of alternating

current through the tissue to measure changes in plasma conductivity and subsequently relates this to glucose concentrations.[50]-[54]

2. Electromagnetic spectroscopy utilizes changes in the electromagnetic coupling between two inductors to measure glucose concentration. Because electro-magnetic coupling is dependent on the permittivity of the media, which, in turn, is dependent on the local glucose concentration, quantitative assessment of glucose levels can be achieved.[55],[56]

6.1.6 Sensor Lifetime

CGM will only be acceptable to the patient if it is convenient. For this, the sensor is required to be comfortable in use and to be in place for as long as possible without pain. Efforts are in place to extend the time devices may be left in place. Lifetime is restricted as a result of enzyme degradation, electrode degradation, biofouling, membrane delamination, battery discharge, component failure of telemetry packs, and electronic package failures. Advances in electronic design have reduced some of these sources of failure, but biocompatibility remains an issue.

6.2 Outcomes in the use of CGM

Clinical use of CGM remains a subject of investigation. Although the ability to obtain CGM with a certain degree of accuracy and stability has been demonstrated, the most effective clinical use of CGM and its impact in managing the disease is not well understood. Randomised controlled trials to determine outcome on control of diabetes outcomes such as Hb1Ac do not demonstrate equal ability to have impact across all patient groups.

Systematic review and meta-analysis can demonstrate statistically significant benefit from the use of CGM over self monitoring of blood glucose (SMBG), with lowering of Hb1Ac by 0.3% [90]. However such a change may be of limited clinical importance. Analysis of stratified initial value shows significant reduction in those with high starting value; 0.9% reduction over SMBG was found in those with initial Hb1Ac of 10%. However significant lowering of Hb1Ac could lead to greater likelihood of episodes of hypoglycaemia. A further meta-analysis showed similar results, with a greater change being observed in adults [91]. However other studies showed reduction in episodes of hypoglycaemia [92].

Furthermore, as with all trials in the use of technology, the importance of other factors is essential. Details of the clinical service and clinical protocol to act on the information are needed.

Compliance was a major barrier to some users, especially younger age groups [92]. Such results may indicate that prolonged continuous use may not be indicated, rather a regime based on shorter periods of monitoring to establish control.

6.3 Non-glucose based hypoglycaemic detection

6.3.1 Review

This section reviews past and current research in the field of hypoglycaemic detection and focuses on hypoglycaemic detection based on non-glucose based parameters such as heart rate, heart rate variability and QT intervals, galvanic skin response or skin temperature.

Investigation of an executive hypoglycaemic study group indicates the importance of hypoglycaemic detection and the state of the art in this field. [59] They conclude that “To date, no reliable hypoglycaemia detection system is available, even frequent conventional spot blood glucose measurements fail in this regard”.

The demand from diabetic patients, the scientific challenge, and a potentially attractive market is thus in place. Several studies have addressed the chances of physiological parameters suitable for non-invasive measurements in response to hypoglycaemia.

The most suitable parameters beyond glucose to detect hypoglycaemic events are investigated in [60]. They found: heart rate, skin temperature, and EEG. They furthermore conclude that the specificity to hypoglycaemia is low in single use of each of these parameters (except EEG); they should therefore be used in combination.

The hypoglycaemic response of heart rate, and blood pressure in healthy subjects and in diabetic patients was investigated in [61]. They did only to some extent observe a statistically significant increase in heart rate and blood pressure during hypoglycaemia.

The length of the QT interval in the ECG and an association between the length of the QT interval and hypoglycaemia was investigated in [83], however, with a larger inter-individual variability. Furthermore the glucose-QT interval associations were analysed for periods excluding daily activities and physical exercise since these themselves have an impact on the QT.

The prolongation in the QT interval of the ECG was investigated in [84]. They conclude that a prolongation is observed; however, they were unable to demonstrate if this was due to hyper-insulinaemia or hyperglycaemia.

Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes were investigated in [85]. They found that QT intervals of the ECG were longer during nocturnal hypoglycaemia compared with normoglycaemic control periods but with a high inter-individual variability. Cardiac rate and rhythm disturbances were seen in 62% of hypoglycaemic events. The results may be used to demonstrate QT prolongation and cardiac rate/rhythm disturbances in response to episodes of nocturnal hypoglycaemia in ambulant patients with type 1 diabetes. This may support an arrhythmic basis for the 'dead in bed' syndrome but it does not support a hypoglycaemia measurement/detection system.

The review “Hypoglycaemia, Diabetes, and Cardiovascular Events” [86] concludes that it has been shown in several studies that hypoglycaemia is associated with a change in the QT interval of the ECG in subjects with and without diabetes. Other electrocardiographic abnormalities observed during hypoglycaemia include a decrease in PR interval and moderate ST segment depressions. However there is no strict causal link between hypoglycaemia and alterations in the electrocardiographic parameters.

Ngyuyen et al (2009) report about HypoMon which is a real-time non-invasive monitor that measures relevant physiological parameters continuously to provide detection of hypoglycaemic episodes in type 1 diabetes mellitus patients. Based on heart rate and corrected QT interval of the ECG signal, they continued to develop effective algorithms for early detection of nocturnal hypoglycaemia. From a clinical study of 24 children with Type 1 diabetes, associated with natural occurrence of hypoglycaemic episodes at night, their heart rates increased and their corrected QT intervals increased also. It is interesting to note that QT interval and heart rate are less correlated when the patients experienced hypoglycaemic episodes through natural occurrence compared to when clamp studies were performed. This also reflects the difficulty to detect hypoglycaemia reliably under “real life conditions”.

Electrocardiographic (ECG) parameters for artificially induced hypoglycaemia detection are described in [87]. A hybrid technique of swarm-based support vector machine (SVM) is introduced for hypoglycaemia detection using the ECG parameters as inputs. In an experiment using medical data of patients with Type 1 diabetes, the introduced ECG parameters show significant contributions to the performance of the hypoglycaemia detection which results in the best performance with a sensitivity of 70.68% and specificity of 81.45%. Although these data were derived under optimal conditions they are rather poor: one in three hypoglycaemic events would not be detected.

6.3.2 Conclusions of the literature review

Whereas the literature provides indications that there is a link between hypoglycaemia and cardiovascular parameters there is no proof of the principle that hypoglycaemia can be detected from electrocardiographic data (no causal dependency), nor does the literature provide solid proof of the actual usability of these parameters in terms of sensitivity and specificity. It is thus not just a question of developing a device that is convenient to use, to the best of our knowledge, an acknowledged working principle for non-invasive hypoglycaemic detection has not been reported so far.

6.3.3 Non-glucose hypoglycaemic detection devices in development

A few devices for detection of hypoglycaemia based on non-glucose measurements are currently in development. The development of a hypoglycaemic detection technology in REACTION should go beyond the efforts undertaken by others. It is therefore important to measure the impact REACTION could have in this field. Furthermore, it could be considered to adapt and integrate hypoglycaemic detection technologies developed by others in REACTION.

HypoSafe develops an EEG monitoring device for subcutaneous implantation. The device monitors the EEG and applies algorithms to detect changes in the EEG due to hypoglycaemia. The device and technology is currently being investigated in several clinical studies in Denmark. The plans for a commercial CE marked device are unclear from the company website. However, given the time frame usually associated with development and CE marking, it is unlikely that this device will reach the market before the end of the REACTION project. Since the concept is currently under investigation it is difficult to see how a REACTION device and solution could benefit from it. However, from a scientific point of view it is relevant to interact with this company, if possible, and the scientists they have employed.

AIMEDICS develops a system, HypoMon, for detection of hypoglycaemic events in children and young adults during sleep. The system contains a monitor that is wrapped around the chest of the subject and a wireless receiving station close to the bed. The monitor measures ECG, skin impedance and heart rate. By analysing the signals the monitor is able to detect hypoglycaemic events and transmit a signal to the receiving station to set off an alarm to wake the subject.

The sensing technology of HypoMon is quite similar to the approach suggested by the reviewers in relation to the ePatch with a combination of ECG analysis and skin impedance. However, due to the adhesive properties of the ePatch and the ePatch user model, the ePatch would be suitable for 24/7 use and not only during sleep. It could be interesting to use the ePatch in a similar manner. However, as described in the literature review the scientific findings with this technique are mixed, and several studies question the approach. HypoMon is currently being studied in clinical studies in Australia, but so far no breakthrough results have been published.

Novo Nordisk has also been involved in the development of hypoglycaemic detection technologies. Patent applications US 2006/0281980 A1 and US 2010/0030092 A1 by Novo Nordisk suggest that such a device would be based on a combination of ECG measurement, skin impedance, and possibly glucose measurements, most likely non-continuous. From the material which is publicly accessible, the dominant parameter in their work is the QT segment of the ECG.

6.3.4 Conclusions on non-glucose based devices in development

Devices for detection of hypoglycaemia based on the ECG are currently under development. However, it is unclear to which extent these devices actually can detect hypoglycaemia. Besides the lack of break through with this technology, several indications suggest that this approach could be a key component in non-glucose detection of hypoglycaemia.

It is clear from the above review that it would take considerable resources to engage in this non-glucose hypoglycaemic detection.

6.4 Conclusions

The field of CGM continues to develop, however pace is not as rapid as would be preferred. Manufacturers of existing sensors continue to make improvements in accuracy, stability and life time of sensors. Development of new technologies, especially non-invasive, continues to be slow.

7. Insulin Pumps

7.1 Status of insulin pumps

The debate of the merit of the use of the insulin pump (Continuous subcutaneous insulin infusion - CSII) over multiple daily injections (MDI) continues. There is, however, growing consensus that CSII generally provides improved clinical outcome, including lowering HbA1c and reducing the incidence of hypoglycaemia. [62]

Research therefore concentrates on improving delivery method, regime for insulin delivery, the effect of the type of insulin, and the effect of type of patient.

7.2 Insulin pump delivery method

Although well established, the insulin pump remains bulky and can be painful in use. Technical research is directed towards reducing size and increasing convenience.[63] Current efforts are directed towards development of the patch pump.

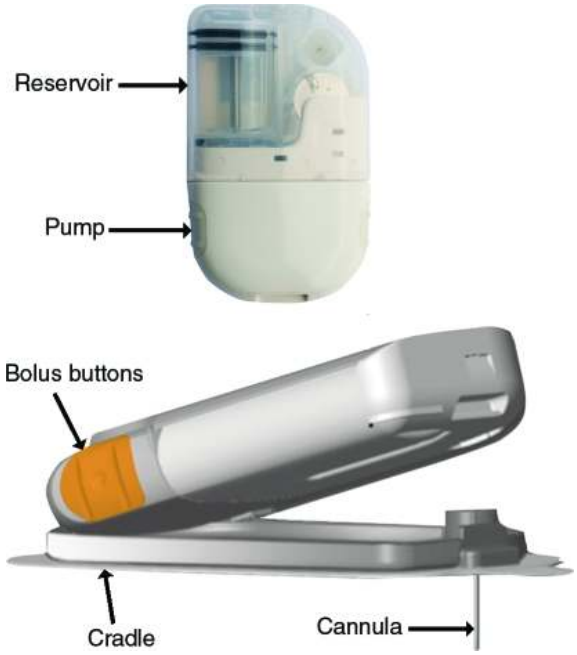

Figure 5: Insulin patch pump (from [63])

The patch pump differs from current technology in having a cradle attached semi-permanently to the patient through an adhesive pad, and a miniaturized pump is then attached to the cradle, as in Figure 5. The reservoir is refillable (or a cartridge) and the body containing the pump is usually exchanged with a second body that has been on charge. The patch pump has the advantage that the cannula has to be changed less frequently (reducing pain and inconvenience), the design is smaller, it is held to the body of the patient and so conforms to body shape and is less obtrusive, waterproof design makes it more convenient. The patch pump retains basal and bolus delivery of insulin. The miniature design often includes a separate control device. Experience to date has been good, and several manufacturers are bringing products to market. This includes:

The Cellnovo Pump (Cellnovo Ltd., formerly Starbridge Systems, London, UK) is a low-power, basal-bolus pump with an integrated power supply coupled with a reservoir containing a 3-day supply of insulin and a cannula for drug delivery. Two pump sizes are to be available: the reservoir in a pump for children is 0.5 mL, and that for adults is 1.5 mL. The empty reservoir and cannula are replaced after 3 days; the entire pump case is retained. This pump will utilize proprietary technology to control mechanical energy. It was projected to be available throughout Europe at the start of 2010.

The Freehand™ system (MedSolve Technologies, Inc., Manhattan Beach, CA) for basal and bolus insulin delivery will consist of an electronically controlled pump usable for 3 months, a disposable

insulin reservoir, a tubeless patch with contained cannula, and a remote control. The system will contain seven basal profiles. Basal delivery will be able to be temporarily suspended, and boluses can be delivered remotely or manually.

The Nanopump™ (Debiotech SA [Lausanne, Switzerland] and STMicroelectronics [Geneva, Switzerland]) for continuous subcutaneous insulin infusion will be equipped with a reusable aspect, containing the electronics, vibration alarm, buzzer, and capabilities for programming and remote control, and a disposable aspect, containing an insulin reservoir, pump, and batteries. The device's adhesive patch containing an auto-inserted infusion cannula is to be changed every 3 days. Several sizes of insulin reservoir will be available. The pump will be based on micro-electromechanical systems technology.

The NiliPatch Disposable Insulin Pump system (NiliMEDIX Ltd., Tirat-Carmel, Israel) consists of a disposable insulin pump that delivers basal and bolus insulin. The pump uses a patented pressure-triggered release mechanism and is controlled by a system of valves and sensors. The NiliPatch has been certified for marketing in the European Union and Israel.

The PassPort® system (Altea Therapeutics Corp., Atlanta, GA) for delivery of basal insulin will comprise an applicator and PassPort Patch, which contains a drug reservoir under which there is a small screen (porator) containing metallic filaments. The applicator delivers an electric charge to the porator, galvanizing the filaments and vaporizing the closest skin cells, creating micropores through which insulin passes transdermally. Drug delivery will be initiated by folding the patch after attaching it to the skin. The micropores created by controlled bursts of thermal energy permit the flow of not only insulin but also other proteins, peptides, and CHOs into the body without needles or pumps. Phase 1 clinical data indicate that the PassPort system provides sustained, therapeutic insulin levels.

V-Go™ (Valeritas, Inc., Bridgewater, NJ) is a basal-bolus pump that uses a transdermal h-Patch™ (hydraulic) that needs to be replaced daily. The pump has no electronics, batteries, or programming. The original h-Patch product received Food and Drug Administration (FDA) 510(k) premarket approval in 2005. After product refinements, a new 510(k) for the V-Go and its filling device was submitted and is under FDA review at this writing.

The CeQur™ (Montreux, Switzerland) insulin infuser, a disposable basal-bolus patch pump intended for type 2 patients, will be available in one of seven basal rates and offer bolus insulin by pressing two buttons simultaneously. It alerts when the device is activated and when it should be replaced.

The following are developmental patch pumps for which there is little available information: the Medipacs patch pump (Medipacs, Inc., San Diego, CA); the Medtronic, Inc. Patch Delivery system (Medtronic, Inc., Minneapolis, MN); and the SteadyMed patch pump (SteadyMed Ltd., Tel-Aviv, Israel), which is based on an electrochemical battery that expands, propelling a bolus, when a button is pressed.

7.3 Regime for delivery of insulin

The purpose for the insulin pump is to deliver the correct dose of insulin at the correct time in order to maintain blood glucose within specified levels. There are two excursions of blood glucose that receive most attention; postprandial and hypoglycaemia.

7.3.1 Postprandial glycaemic excursion

The normal response to food intake is an increase in blood glucose. The body normally compensates through release of insulin which both reduces the rate of food digestion to lower the peak, and by acting on the glucose released to the blood.

In type 1 diabetes, the insulin pump is used to mimic by injecting a bolus of insulin with food intake. There is a delay in absorption of insulin when infused subcutaneously, and this can result in a peak of blood glucose immediately postprandial. Therefore strategies to reduce this peak and maintain blood glucose in range are examined. [64] Best results are obtained for bolus injection 15 minutes before the meal.

7.4 Single port devices

The next natural development is to incorporate glucose measurement and insulin infusion in close proximity or co-located, leading to a single device. There are preliminary developments but remain some years away.

8. Closing the Loop

8.1 Control algorithms and mathematical modelling

Two major pump-controlling algorithms are currently under investigation in closed-loop systems; the proportional integrative derivative (PID) algorithm [66],[67] and the model predictive control (MPC) algorithm. [67]-[69]

8.1.1 PID algorithm

The PID algorithm calculates the amount of insulin to be delivered based on a model of multi-phasic insulin responses to hyperglycemia within pancreatic β-cells. [70] The model's three components, which correspond to the phases of β-cell insulin response, are proportional (P), integral (I), and derivative (D). Total insulin delivery by the β-cell, and hence the amount to be delivered by an insulin pump according to the PID algorithm, represents the sum of insulin delivery corresponding to each of the three secretory components.

As indicated in the following equations (in which n denotes the most recent 1-min sensor glucose [SG] value and n – 1 denotes the previous 1-min value), the P component controls insulin delivery, increasing it when glucose is above a pre-specified target value and reducing it when it is below target. Because no insulin is delivered when glucose is at target, it does not contribute to the basal insulin requirement [70]. The I-component mimics the β-cell's slow second-phase insulin excursion, adjusting insulin upward when glucose is above target (and downward when below) but exerting no effect when glucose is at target. The D component corresponds to the β-cell's rapid first-phase insulin rise, increasing insulin delivery when glucose levels are rising and decreasing it when declining. The constants KP, TI, and TD in the equations below balance the amount of insulin delivered by each component:

$$P(n) = K_p[SG(n) - \text{target}]$$
$$I(n) = I(n-1) + K_p/T_I \cdot [SG(n) - \text{target}]$$
$$D(n) = K_p \cdot T_D \cdot dSG/dt(n)$$
$$PID(n) = P(n) + I(n) + D(n)$$

The PID equation may also be written in the following form, in which the insulin infusion rate at any time [u(t)] is equal to the basal insulin rate (u0) plus three functions of the error [e, the difference between the measured glucose value and the target value, i.e., SG(n) − target]: P is directly proportional to the error e(t), I is proportional to the integral of the error [$\int$ e(t)dt], and D is proportional to the derivative of the error [de(t)/dt]:

$$u(t) = u_0 + k_C\left[e(t) + \frac{1}{\tau_1}\int e(t)dt + \tau_D\frac{de(t)}{dt}\right]$$

8.1.2 MPC algorithm

The MPC algorithm, which is a composite of multiple algorithms, determines the level and timing of insulin infusion rates based on predictions of the ways in which insulin will affect future glucose concentrations. These algorithms have been developed after taking into account many glucose regulatory sub-models. One of these, developed by Dalla Man et al [71] and evaluated by Magni et al.[68] in an in silico trial, relates to intestinal glucose absorption:

$$Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t)$$
$$\dot{Q}_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t) + D \cdot d(t)$$
$$\dot{Q}_{sto2}(t) = -k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) + k_{gri} \cdot Q_{sto1}(t)$$
$$\dot{Q}_{gut} = -k_{abs} \cdot Q_{gut}(t) + k_{empt}(Q_{sto}) \cdot Q_{sto2}(t)$$
$$Ra(t) = \frac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW}$$

where Q_{sto} (in mg) denotes the amount of glucose in the stomach (solid phase, Q_{sto1}; liquid phase, Q_{sto2}), Q_{gut} (in mg) is the glucose mass in the intestine, k_{gri} signifies the rate of grinding, k_{abs} is the rate constant of intestinal absorption, f indicates the proportion of intestinally absorbed glucose that appears in plasma, D (in mg) is the amount of ingested glucose, BW represents body weight (in kg), and R_a (in mg/kg/min) is the rate of glucose appearance in plasma.[71]

Algorithms have been developed for glucose regulatory sub-models in addition to the multi-phasic β-cell insulin response to hyperglycaemia. These take into account renal excretion, endogenous production, and utilization of glucose, as well as subcutaneous insulin and glucose kinetics. Each model and sub-model has its own mathematical expression and corresponding equations.[68]

Algorithms other than the PID and MPC include a linear quadratic Gaussian algorithm for subcutaneous blood glucose regulation [82] and Lehmann and Deutsch model and Elashoff model algorithms for glucose absorption by the intestine.[73]

Algorithms now include an optimizer function that enables them to find the best set of current and future changes in insulin delivery to maintain desired glucose levels over a pre-specified prediction time horizon.[74] Algorithms can decrease postprandial insulin infusion to avoid hypoglycaemia by projecting a time-limited postprandial glucose excursion.[74]

8.1.3 In silico models

In January 2008, the FDA approved an in silico simulation environment as a substitute for animal trials in preclinical closed-loop control experiments. In April 2008, the agency allowed this investigational device to be used in preclinical experiments. The algorithm system used in a follow-up in silico trial included a cohort of 300 simulated subjects based on real data and was reflective of a T1DM patient population. The system included a simulator of errors of marketed CGM sensors and of insulin delivery via marketed insulin pumps. It represented glucose fluctuations observed during prandial challenges in patients with T1DM.[75]

Buckingham [76] demonstrated the ability of algorithms to prevent nocturnal hypoglycaemia or to sound an alarm at the approach of hypoglycaemia. This system could suspend pump operation to avoid hypoglycaemia using a “voting” system for triggering a predictive alarm when two of five algorithms predicted future hypoglycaemia. Marchetti et al. [66] developed and validated a closed-loop strategy in silico that was based on the physiologic compartment model of Hovorka et al.[69] The system enables PID-based postprandial insulin delivery control and filters to reduce sensitivity to CGM sensor noise.

In initial human trials using the FDA-approved paradigm, closed-loop fasting glucose control was excellent, with a fivefold reduction in nocturnal hypoglycaemia. Overnight, closed-loop subjects spent significantly more time at glucose targets of 70–140 mg/dL (vs. open-loop systems).[77] In silico evaluations of closed-loop control algorithms are likely to be prerequisites to clinical trials of the artificial pancreas.

8.1.4 The way forward

Although intravenous or intra-peritoneal devices may deliver insulin more physiologically than subcutaneous devices, they entail risks associated with invasive procedures (e.g., infection). Use of conventional pump and patch pump subcutaneous systems in combination with CGM cannot effectively “close the loop” because of inherent delays in glucose sensing and insulin delivery, rendering these conventional systems unable to accommodate the effects of large or rapidly absorbed meals or exercise. Until improved software and hardware become available, near-term iterations of the artificial pancreas will likely be open- or modified-loop types where the patient will need to direct the pump to deliver insulin at certain times (i.e., meals).

8.2 Suspended insulin delivery

Hypoglycaemia can be an especial problem at night. Suspended insulin delivery is being investigated as an interim solution. [78] In this approach, if detected blood glucose is falling towards a specified threshold, all insulin delivery, including basal, is suspended, either for a fixed period, or until blood glucose rises above threshold. The approach has been found successful in reducing hypoglycaemia without significant incidence of hyperglycaemia.Outcome from trials

Limited closely supervised clinical based studies have been undertaken.[79] Most studies have concentrated on evaluating the ability of algorithms to achieve better control of blood glucose during sleep. Some studies include evaluating performance when challenged by meals and exercise. In general results are good, with increased periods spent within given range, decreased incidence of hypoglycaemia, and low incidence of hyperglycaemia.

The general conclusion is that current approaches are limited by the time lag experienced in the subcutaneous measurement of glucose and subcutaneous infusion of insulin and that alternative fast measurement and fast delivery techniques are essential if high performance algorithms able to respond closely to meals and exercise are to be developed.

8.3 Sensor augmented pump therapy

The next development in technology is to combine sensor technology with the insulin pump, either by having sites in close proximity and mounted on the same housing, or ideally co-located. Sometimes called sensor-augmented pump therapy, initial approaches have been to use supervised pump settings determined by external (internet) mechanisms rather than automatic feedback (closed loop). Early results show good reduction in HbA1c for the therapy group compared to control group. [80]

9. Insulin Delivery

No new insulin delivery methods are reported recently. Oral intake, injection and CSII remain delivery methods in clinical practice.

9.1 Insulin pens

There are no developments on the basic technology of the insulin pen, and no manufacturers have reported pens capable of sending information.

9.2 Intraperitoneal insulin infusion

Roche have introduced the Accu-Chek DiaPort system, which enables continuous intraperitoneal insulin infusion (CIPII): that is, infusion of insulin into the peritoneal cavity using an Accu-Chek insulin pump and an infusion set. The Accu-Chek DiaPort consists of a metal body with a catheter that is placed in the abdomen. The opening of the port is raised above the surface of the skin about 5 mm, while a flower-shaped plate is placed under the skin, providing stability for the port. The port has been designed for those diabetics who cannot benefit fully from subcutaneous insulin infusion. This is currently undergoing clinical trials.

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