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RESEARCH ARTICLE

NANOTECHNOLOGY ADVANCEMENT IN PID ALGORITHM BASED BLOOD GLUCOSE CONTROL

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ABSTRACT

Nano-in-Medicine is a complex field of exploration with far-reaching technological and medical possibilities. Nanotechnology in diabetes research has facilitated the evolution of novel glucose measurement and insulin delivery systems. Not only is detecting glucose in the food and pharmaceutical industries very important. In addition, glucose monitoring is particularly critical for diabetes supervision. The objective of any kind of diabetes therapy is to reach nearly physiological glucose levels. The current view points toward a continuous insulin infusion by means of insulin pumps. A PID algorithm for blood glucose control is outlined, and the importance of sensor development emphasized. In addition to nanotechnology, the modern information technology has entered the field. Worldwide diabetes research activities at its interface with nanotechnology have created devices at the micro- or nanoscale by which the experimental approach toward an artificial pancreas is already put in practice. In the present paper, some aspects of a three-term control algorithm for glucose are treated, as well as few glucose sensors are set as examples, based on concepts and developments of nanotechnology in the field of diabetes research.

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INTRODUCTION

Diabetes mellitus is one of the most prevalent and pressing ailments in the world. As a metabolic disease the body either fails to produce or fails to respond to the glucose regulatory hormone insulin, characterized by chronically elevated blood glucose levels (BGL's) and an inability to maintain BGL homeostasis (Etheridge *et al.,* 2013; Kerner *et al.,* 2014). Insulin is required in order for cells to take up glucose from the blood, and in diabetics, a defect in insulin signaling can give rise to large fluctuations in blood glucose levels unless proper management techniques are employed. Glucose itself is the most important energy source for the body's cells. Disruptions in this energy loop therefore represent a serious disease.

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Type 2 diabetes is characterized by the fact that insulin resistance and beta cell dysfunction is caused by various pathological factors, so that the glucose level can no longer be controlled in the desired glucose range. Diabetes has grown to become one of the largest public health challenges globally, affecting over 380 million individuals worldwide with the tendency of steep growth in number during the upcoming years. Therefore, systems that improve blood glucose monitoring and efficient treatment are highly desirable. Blood-salivary glucose level and salivary-lacrimal flow rate have been studied in order to detect the diabetes mellitus at an early stage by establishing a positive correlation between blood- and salivary glucose levels. Saliva is a complex fluid containing many analytes that permeate from blood, thereby in principle providing a useful insight into a person's metabolic and nutritional state. As a result, saliva has been investigated as an alternative fluid for non-invasive glucose sensing (Bruen *et al.,* 2017; Dr.Swati *et al.,* 2018). Wide-reaching research activities are under way in order to develop insulin-delivery systems that could act as an artificial pancreas, automatically detecting

glucose levels and secreting insulin. Hereby nanotechnology is playing a pivotal role and carries the promise of attractive and viable solutions. It has profoundly influenced the area of biosensors, particularly through their high sensitivity and selectivity, as well as the miniaturization of sensor devices. Yet, it cannot clearly be foreseen whether technical solutions in the sense of an artificial pancreas, or biological solutions by growing insulin-producing cells will be a valid answer. Both are technologically connected with principles and methods of nanotechnology. In the first case a technical product would result, in the second case a biological material. Notable progress is made in both directions. To mention only few: The implementation of nanostructured materials in glucose sensors as compared to currently used GOx sensors of the first generation was proposed by Cash *et al.,* (2010). An optical nano sensor based on single walled nanotubes has been used as glucose sensor. It modulates fluorescence emission in response to the adsorption of specific biomolecules (Agrawal *et al.,* 2012).

Nanotube transistors have been explored as glucose sensors, polymer encapsulation devices were considered to treat diabetes by thin-film micro- and nanoporous cell-encapsulation devices (Nyitray et al.,2015), magnetic nano emulsion is studied for non-enzymatic blood glucose detection, whereby optical properties and intermolecular interactions in magnetically responsive nanoemulsions in the presence of glucose are probed (Mahendran *et al.,* 2014), the development of a plasmonic gold chip for near-infrared fluorescence-enhanced detection of islet cell-targeting autoantibodies with high sensitivity and specificity for the diagnosis of type1 diabetes has been described by BoZhang *et al.,* (2014), biosensors are implanted for continuous glucose monitoring (Bandokar *et al.,* 2015), grapheneoxide–multiwall carbon nanotube nanocomposites were fabricated as electrochemical platform for direct electrochemistry and electrocatalysis measurements (Benchirouf *et al.,* 2016). Several optical sensor approaches utilizing metal nanoparticles have been developed. As one example, a novel photoluminescent glucose nanosensor was presented at (Shao-wei *et al.,* 2016), characterized by coupling glucose oxidase (GOx) with poly-l-lysine coated oxygen nanosensors via a glutaraldehyde-mediated Schiff-base reaction. A bihormonal closed-loop artificial pancreas for type 1 diabetes was described (El-Khatib *et al.,* 2010), and an overview is given of stem cells, the purpose of nanotechnology and various surface modifications of nanoparticles for enhanced drug delivery, as well as of how stem cell therapy is used to treat type 1 and type 2 diabetes mellitus (Shahidadpury *et al.,* 2016). In order for an "artificial pancreas" to become a reality for ambulatory use, a practical closed-loop control strategy must be developed in such a system. The control algorithm is the key technique of precise insulin infusion.

Algorithm for the control of insulin administration in an artificial pancreas: Daily subcutaneous insulin injections are the current standard of care for type 1 and advanced type 2 diabetics. The best way of diabetes therapy is the continuous insulin infusion with the help of an insulin pump (Ly *et al.,* 2013). However, as an insulin pump works only manually, it is desirable, that a glucose sensor would automatically control the insulin supply. A common mechanism of glucose detection involves using hydrogen peroxide (H_2O_2) or a similar reduced species as a chemical intermediary, which drives the reduction of another species. Advantages of hydrogen peroxide-based detection systems include relatively straightforward sensor

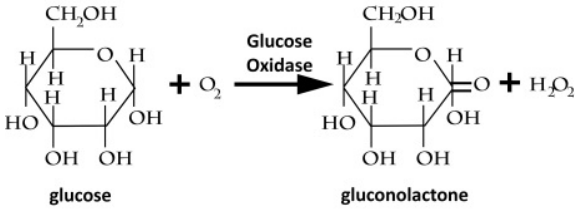


Fig. 1. The oxidation of glucose by glucose oxidase. Glucose and di-atomic oxygen are consumed to form a gluconolactone and hydrogen peroxide

operation and characterization via amperometric techniques (Mukhopadhyay *et al.,* 2018), but fluorescence measurements have also proven useful (Samsulida *et al.,* 2017). Glucose oxidase (GOD) is capable of enzymatically catalyzing the oxidation of glucose to gluconic acid with high specificity (Fig. 1):

$$\text{Glucose} + O_2 + H_2O \quad \text{Gluconic acid} + H_2O_2 \qquad (1)$$

$$H_2O_2 \quad 2\,H^+ + O_2 + 2\,e^- \qquad (2)$$

From the reaction products formed during the GOD reaction, hydrogen peroxide (H_2O_2) is oxidized electrochemically in a second reaction downstream at a platinum electrode with a voltage of 600 … 900 mV. The resulting electrons generate a current flow, which is directly proportional to the amount of converted glucose. At glucose concentrations of 40-400 mg/dl (2.2 to 22.2 mmol/l) such a current is typically in the nano ampere range. The electrochemical measurement requires direct access to the glucose-containing unit. This implies that the glucose sensor (the electrochemical enzyme electrode wrapped with an oxygen permeable membrane) has to be inserted through the skin into the subcutaneous adipose tissue in order to obtain access to interstitial fluid. Yet, only in the case of glucose stability would the glucose sensor measure the same glucose concentration as present in the blood. In the case of a glucose increase or decrease, a temporal shift from 5 to 25 minutes between the measured values in the blood and the interstitium will happen. Consequently, the importance of measured data is of little use unless the postponement in time is observed.

Algorithms for the control of the insulin delivery in an artificial pancreas consider this fact, which not only realize the insulin delivery based on the existing glucose value, but also predict the glucose concentration over the subsequent period of 2-3 hours. It must be ensured that in addition to the glucose concentration C_{Gluc} the insulin concentration C_{INS} is regulated in accordance to physiology. In principle, the glucose homeostasis is maintained through a system of networked negative-feedback loops. Beta cells and alpha cells represent the controller, and the secreted insulin or glucagon denote the manipulated variables. The latter should adjust the controlled variable "glucose" at a set point (3.9 to 7.8 mmol/l) which ideally is situated between 70-140 mg/dl. All of the processes within the controlled system operate with a time lag, as different factors enter the glycemic regulation, being it the time-dependent absorption of carbohydrates and insulin, physical activity, stress, etcetera. The physiological insulin secretion can be simulated as *PID* control, where *P* is the proportional control, *I* the integral control, and *D* represents the differential control. These three phases correspond to the feedback behavior of the beta cells (Fig. 2).

The proportional phase (*P*) considers the difference between the current value of the glucose and the glucose target value (C_{Sensor} - C_{Target}); the insulin delivery is proportional to the glucose levels

$$P(t) = K_p \cdot [C_{Sensor} - C_{Target}], \quad (3)$$

C_{Sensor} – glucose concentration sensor,
C_{Target} - target value of glucose concentration, t - time.

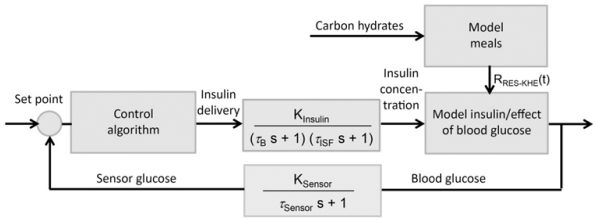


Fig. 2. Control circuit for an AP considering a subcutaneous glucose monitoring and subcutaneous insulin dose ($R_{RES-KHE}$ - absorption of carbohydrates)

In the escalation phase (Increment phase I) is the insulin delivery proportional to the difference between the current value of the glucose and the glucose target value (C_{Sensor} – C_{target}),

$$dI(t)/dt = K_p \cdot [C_{Sensor} - C_{Target}] / T_I \quad (4)$$

Response phase (Derivative phase) means that the insulin delivery is proportional to the rate of glucose change (D),

$$D(t) = K_p \cdot T_D \cdot dC(t)/dt \quad (5)$$

dC/dt - change of glucose concentration/time.

The parameters K_p, T_I, T_D have to be adjusted. The factor K_p determines the insulin secretion rate as response to the basal glucose levels, the parameter T_I (in minutes) determines the proportion of the growth phase, and the parameter T_D the proportion of the derivatives phase. The total control algorithm results then as the sum (Eq.6) of three components (Fig. 3):

$$PID(t) = P(t) + I(t) + D(t) \quad (6)$$

Thus, the necessary insulin dosage is calculated from the knowledge of the current glucose concentration, the glucose target value and the parameters K_p, T_I, T_D. When the glucose sensor is placed subcutaneously and the glucose concentration is variable, the measured value of the glucose concentration C_{ISF} (ISF - interstitial flow) is different from the blood glucose concentration C_B (B - blood).

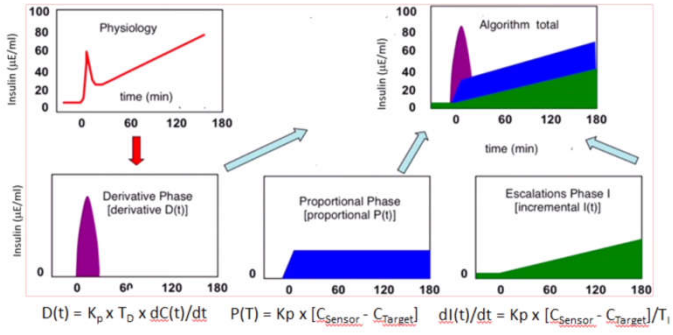


Fig. 3. Insulin infusion using the PID - algorithm for imitation of the physiological insulin release

The change in time of the glucose concentration in subcutaneous tissue depends on the glucose transfer between blood and interstitial fluid, represented by the flow rates of glucose k_{BISF}, k_{ISFB} and the flow of the glucose in the body cells k_{ISFZ} (glucose consumption). An increase in the insulin concentration increases glucose consumption of the peripheral cells. The result is:

$$dC_{ISF}/dt = -(k_{ISFZ} + k_{BISF}) \cdot C_{ISF} + k_{ISFB} \cdot V_B/V_{ISF} \cdot C_B \quad (7)$$

C_B - glucose concentration in the blood
C_{ISF} - glucose concentration in interstitial
$k_{B\rightarrow ISF}$ - flow rate of blood → interstitial
$k_{ISF\rightarrow B}$ -flow rate interstitial → blood
V_B - volume in the blood
V_{ISF} - volume in the interstitium
$k_{ISF\rightarrow Z}$ - glucose consumption in peripheral cells

The concentrations ratio of glucose in the interstitial flow and in the blood is (C_{ISF}/C_B) the concentration gradient. After reaching the glucose homeostasis, the glucose concentration in the interstitial space is given by:

$$C_{ISF} = C_B \text{ x } [k_{ISFB} \cdot V_B/V_{ISF}]/ (k_{ISFZ} + k_{BISF}) \quad (8)$$

The time delay of the glucose concentration in the interstitial space compared to the blood ('time-lag') is:

$$\tau_{Sensor} = (k_{BISF} + k_{ISFZ})^{-1} \quad (9)$$

This time constant refers to the time needed to reach a 63% of the balance. When using an enzymatic electrochemical glucose sensor, a sensor current is created in the interstitial space proportional to the glucose concentration I_{sig}:

$$I_{sig} = \alpha \cdot C_{ISF} \quad (10)$$

Here α is a parameter expressing the sensitivity of the sensor (in nA/mg /dl). This is not a constant in time during the entire application. Because the glucose sensor must be calibrated, the measured glucose concentration with the calibration factor F_{cal} is provided finally by:

$$C_{Sensor\ glucose} = F_{cal} \cdot I_{sig}\ . \quad (11)$$

In the PID model follows the necessary insulin dosage per unit time as

$$I_{Dosis} = K_p \cdot F_{Err} + 1/T_I \int F_{Err}\, dt + TD_s \quad (12)$$

F_{Err} is the resulting error due to a deviation of the blood glucose, K_p, T_I, T_D are individually tailored parameters from the PID model. Eq. 12 does not take into account that insulin delivery is subcutaneous. In that case of subcutaneous delivery, the ratio of sensor glucose $C_{Sensor\ glucose}$ to blood glucose C_B results in:

$$C_{Sensor\ glucose}/C_B = F_{cal} \cdot K_{Sensor} /(\tau_{Sensor}\, s + 1) \quad (13)$$

It finally follows the ratio of blood insulin levels I_{Blood} and insulin dosage I_{Dose}:

$$I_{Blood}/ I_{Dose} = K_{Ins} / [(\tau_{Blood}\, s + 1) \cdot (\tau_{ISF}\, s + 1)]. \quad (14)$$

The formalism aims to predict the expected glucose concentration, thus a complex model of glucose metabolism has to be applied.

Diverse models have been adapted (Kropff *et al.,* 2016) including fuzzy logic or neural networks (Perez-Gandia *et al.,* 2010).

Glucose measuring based on nanotechnology

Presently, devices at the micro- or nanoscale enter the field of diabetes research at its interface with nanotechnology. Micro- and nano electronic technologies offer the possibility of a cost-effective mass production. As the costs of such sensors depend on their widespread usage, diabetes therapy might be revolutionized if low-cost glucose sensors based on nanotechnology become available. When the geometrical dimension of condensed matter is reduced to nanoscale, their physical and chemical properties change drastically. Because of its tiny size, the laws of quantum mechanics govern the electron behavior. Nanotechnology opens up a wealth of new opportunities for the development of new materials, nanostructures, nanoscale electronic devices in general. It involves almost all applications in the diverse medical fields. At the nanoscale, physical, chemical, and biological properties of materials differ in fundamental and valuable ways from the properties of individual atoms and molecules or bulk matter. Most outstanding are quantum effects, as e.g. quantum mechanical tunneling of electrons, electron transport in quantum dots, quantum dot fluorescence, absorption and emission of radiation in a wide frequency range. The surface-to-volume ratio of nanoparticles becomes very large and leads to a number of unexpected physical and chemical effects, such as interfacial phenomena, altered chemical reactivity, charge carrier effects and enhanced optical properties, as for example quantum dot fluorescence (Thomas *et al.,* 2015).

Nanoparticles are synonymous of a sub-genre in the wide field of nanotechnology. They include any type of natural or artificial particles whose spatial confinement is less than 100 nanometers. Nanoparticles may contain a few hundred atoms or molecules in one-dimensional (nanowires, quantum wires), two-dimensional (ultrathin layers), or three-dimensional (nano powders, functional supramolecular nanotubes, quantum dots) array. Exploitation of nanoparticles in the dermis may allow transdermal monitoring of glucose changes in interstitial fluid. Nanoscale carbon as fullerene, nanotube or graphene exhibits excellent mechanical, electrical and optical properties. Nanofabrication techniques permit to generate glucose sensors with very small geometric dimensions. Small sensors can easily be implanted. The implantation of reversible optical sensors has led to the concept of a 'smart tattoo' that continuously measures the blood glucose level by modulating the tattoo's optical color in response to the glucose concentration (Benchirouf *et al.,* 2016). Nanotechnology of coated colloids and microcapsules allows precision control over optical, mechanical and catalytic properties to achieve sensitive response. Indeed, there are two steps by which nanoscale building blocks are incorporated in nanosensors: those that improve the glucose sensor function, and those that directly measure glucose concentrations. Nanoscale electronics offers new solutions for glucose sensors, providing a high signal-to-noise ratio. One of the best studied nano-materials beside graphene are carbon nanotubes, both in their single-wall and multiwall structure (single-walled carbon nanotubes, SWCNT, and multi-walled carbon nanotubes, MWCNT). Typically, the diameter of a nanotube is between 0.6 and 6 nanometers, the tube wall reaches a thickness up to 0.3 nanometers.

During the production process at very high temperatures, specific substances can be introduced into and onto the nanotubes that react with glucose (for example: glucose oxidase bound to a fluorescent dye). Here, the nanotube works as a light amplifier. The fluorescence signal is proportional to the glucose concentration. SWNT fluorescence control can be reached with high selectivity (Fig. 4).

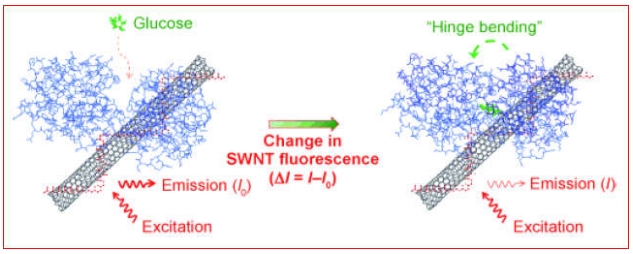
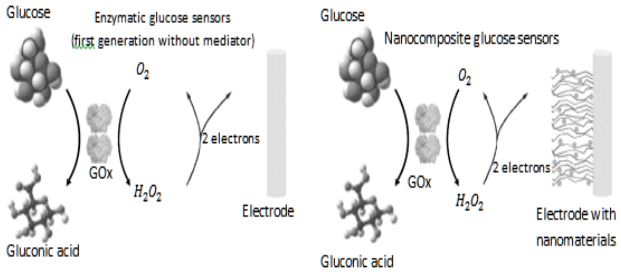


Fig. 4. Glucose-binding protein covalently conjugated to a fluorescent SWNT is shown to act as an optical switch. Hinge bending response to glucose causes a reversible exciton quenching of the SWNT fluorescence with high selectivity. Reproduced from (Yoon *et al.,* 2011).



It is under study, that such nanotubes are wrapped in a dialysis fiber and transplanted under the skin. The glucose measurement is performed by irradiating the skin area with a laser and measuring the induced fluorescence light as amount of the glucose concentration. From quantum mechanical reasons have thinner nanotubes a larger energy band gap and consequently a stronger energy absorption and fluorescence signal. By use of single-wall nanotubes (SWNT), enzyme-based optical glucose sensors were reported in (Chen *et al.,* 2018).

Graphene, a sheet of carbon just one atom thick, shows much promise for use in wearable electronics since it is flexible, soft, conducts electricity very well, and can be transparent. A graphene-based wireless patch that can detect glucose in sweat has already been reported (Bandokar *et al.,* 2015; Hyunjae *et al.,* 2016). Carbon nanotubes exhibit properties, which make them ideal for fluorescent biosensing, such as emission at a near-infrared wavelengths, which is a wavelength at which skin is particularly transparent. Owing to its small size, high electrochemical activity, excellent physical properties, low density and biocompatibility, the CNT fibre has huge potential for implantable applications for continuous monitoring of clinically relevant analytes, including glucose. He and co-workers (He *et al.,* 2012) reported a highly sensitive glucose sensor made by immobilizing GOx on Ag/Au nanoshells *via* poly(L-histidine). Bundles of carbon nanotubes (CNT), were designed for electrochemical biosensor applications, which efficiently worked as an enzymatic glucose biosensor (Cash *et al.,* 2010; Zhu *et al.,* 2010). The bundles of CNTs were concentrically compacted into multiple layers, forming a nano-porous network structure.

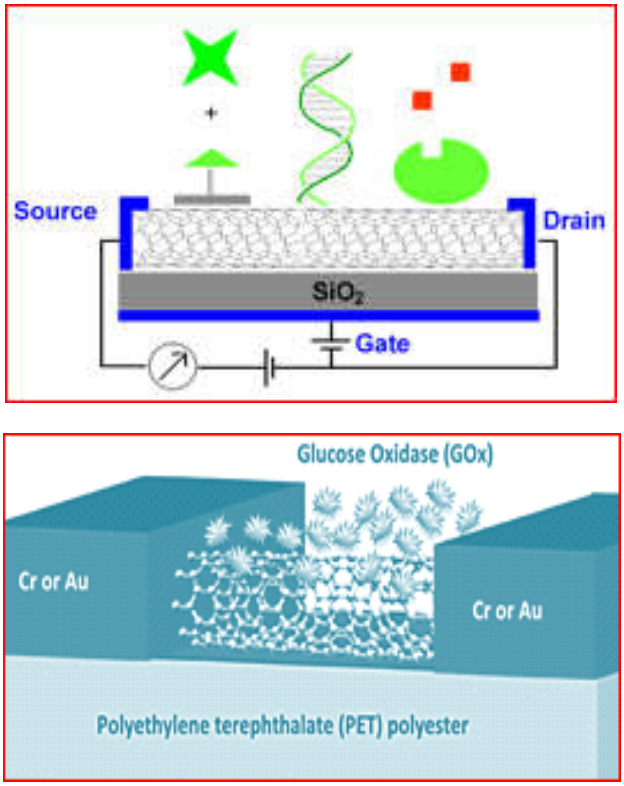


Fig. 6. Key components of a Field-Effect Transistor with CNT's between source and drain (izqu.), and glucose biosensor using Carbon nanotubes (SWCNT) with polyethylene terephthalate (PET) polyester as a back gate, and chromium (Cr) or gold (Au) as the source and drain, respectively (Pourasl *et al.,* 2014; Allen *et al.,* 2007; Taguchi *et al.,* 2014)

The electrode end tip of the CNT fiber was freeze-fractured to obtain a unique brush-like nano-structure resembling a scale-down electrical 'flex', where glucose oxidase (GOx) enzyme was immobilized using glutaraldehyde crosslinking in the presence of bovine serum albumin. Superior efficiency of CNT fiber for glucose biosensing was demonstrated compared to a traditional Pt-Ir sensor (Fig. 5). Fig.5: Nanostructured materials used in glucose sensors. Left: Presently applied electrochemical glucose sensors use glucose oxidase (GOx) for the chemical process and generation of an electrochemical signal. This signal is transferred through O_2 reduction to H_2O_2. Nanomaterials are incorporated in order to increase surface area, improve catalytic action, modify operating parameters, and improve electron transfer from the enzyme to the electrode. This can be accomplished using nanomaterials, such as carbon nanotubes, or nanocomposites consisting of multiple nanomaterials working together (right), (adapted from (Cash *et al.,* 2010). Because of the high surface area-to-volume ratio, CNT's demonstrate good device performance when they are used as a semiconducting channel in FET-biosensors (Fig. 6).

Fig. 6. Key components of a Field-Effect Transistor with CNT's between source and drain (izqu.), and glucose biosensor using Carbon nanotubes (SWCNT) with polyethylene terephthalate (PET) polyester as a back gate, and chromium (Cr) or gold (Au) as the source and drain, respectively (Pourasl *et al.,* 2014; Allen *et al.,* 2007; Taguchi *et al.,* 2014). Similar to ordinary glucose sensors, based on GOx, the electron transfer between the enzyme and the electrode can be enhanced by use of an electrochemical mediator. Improvement in sensor performance is made possible by the combination of CNT's with various nanoparticles, as e.g. noble metals (silver, gold, platinum) or silica, by which the catalytic activity and in consequence the sensitivity of measurement is enhanced.

Conclusion

Nanomaterials are unique in many of their physical and chemical properties, and make it suitable for applications in several key technologies, such as down scaled sensors and imaging devices, nanoelectronics and nanophotonics, energy conversion and nanobiomedicine. Intense research in the field of diabetes is driven by the worldwide high and continuously growing number of diabetes cases, particularly of type 2. Different approaches to improve conventional methods of glucose measuring and control have yet too little contributed to overcome painful daily finger pricking. In a closed-loop system, the control algorithm is the key technique of precise insulin infusion. Nanosensor technology is highly beneficial then to be part of a PID algorithm for blood glucose control. Nanotechnology allows novel materials to be prepared and integrated in reduced dimensions at the nanoscale, forming nanostructures for high-throughput by integration of microfluidics devices. The connection of the advanced medicine to micro- and nanoelctronic technologies enables cost-effective mass fabrication of devices. As the cost of sensor production determines its distribution, the treatment of diabetes might be transformed, particularly in terms of the control of an artificial pancreas.

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Abbreviations

AP-	Artificial Pancreas
BGL-	Blood Glucose Level
CGM-	Continuous Glucose Monitoring
CNT-	Carbon Nanotube
CT-	Conventional Insulin Therapy
GDH-	Glucose Dehydrogenase
GOD; Gox-	Glucose Oxidase
H_2O_2-	Hydrogen Peroxide
ICT-	Conventional Intensified Insulin Therapy
MWNT-	Multi-Wall Nanotube
PID -	Proportional Integral Differential
SWCNT-	Single-Wall Carbon Nanotube

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