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Nano Robots for Continuous Blood Glucose Diagnosis

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ABSTRACT

Diabetes has established itself among the deadliest diseases of the century. Many Leading Fatal diseases are majorly caused or supported by this metabolic disorder. Diabetes has become very common over the years, showing a rapid increase in the number of cases. The increasing trends clearly show that there is a demand to come up with some new efficient methods to support its treatment procedures. Tedious and painful methods for its monitoring on a daily basis has to be carried out by people suffering from it which involves pricking their fingers many times a day, increasing the possibilities of infections and side effects. Nanorobotics can give a potential alternative for its diagnosis which ensures better levels of safety standards as compared to current available methods. In this review, we will present a concept for continuous measuring of blood glucose levels with nano-bots which will stay in the bloodstream and report results to an external system which can be further analysed. The bots will have a structure of a multiwall carbon nanotube. Researchers have been actively working on the development of this field and hence this novel idea will be actively used within the public when it passes its first human trial. The run to construct such nano structures is on and with advancements with each passing day they are expected to hit the markets for public use after the estimated time of 5 years.

KEYWORDS: *Diagnosis of Diabetes, Nanotechnology, Continuous Glucose Monitoring, Biomedical Nanorobotics, Nanosensors*

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INTRODUCTION

Diabetes is a chronic disease which is caused either by malfunctioning of the pancreas or when the body is unable to process blood sugar. The pancreas is responsible for manufacturing insulin in the human body [1]. The improper functioning of the pancreas may arise when they are incapable of producing the required quantity of insulin or if that is not the case then blood sugar levels can rise if our body is unable to use this insulin properly. Insulin is a hormone that modulates blood sugar [2]. Improper management of Diabetes and it getting uncontrolled leads to raised blood sugar levels, which over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

An estimated 3.4 million sufferers of diabetes die from poor management of blood glucose [3]. The number of deaths due to Diabetes is estimated to double between 2005 and 2030, predicts World Health Organisation(WHO). Poor diabetes management is majorly due to irregular monitoring of blood glucose levels on a regular daily basis. Keeping a regular track of one's blood sugar levels can be achieved by Glucose monitors. Traditional methods, to keep a track of the blood sugar levels, include the use of glucometers and lab testing (which provides a comparatively accurate measure of glucose concentrations). But the regular extraction of blood from the body is both physically painful and time-consuming, also increasing the risk of infections [3].

Diabetes has become more common over the years among people. Earlier diabetes was majorly due to hereditary factors or some metabolic imbalances but the vigorous changes in lifestyle, diet and the consumption of artificial products and chemicals have not only increased the cases of diabetes but has also hit the youth. The lethargic routine and the consumption of food lacking proper nutrition makes it no surprise but to hear about increasing cases of diabetes among children.

Some statistics Related to Diabetes

The frequency of people affected by Diabetes, which was about 4.7% in 1980 has increased rapidly on a global level to as high as 8.5% in 2014 among adults [4]. These trends have had an adverse effect which is clearly identifiable by the fact of an estimated 2.2 million deaths in 2012 attributable to high blood glucose and Another 1.6 million being the death toll directly to the name Diabetes in 2016, making it the seventh largest killer of that year [2]. A majority of all deaths attributable to high blood glucose occur before the age of 70 years [2].

Diabetes is a metabolic disorder which leads to the inability of the body to process glucose to its requirements and hence results in high levels of blood glucose [4]. It is of two categories namely Type 1 or Type 2. A person diagnosed with Diabetes is classified as having one of them depending

on the reason for the abnormal levels of glucose. Type 1 diabetes occurs when the pancreas is unable to produce the right amount of insulin (a hormone which sanctions the uptake of glucose by the liver, muscle and fat tissue), whereas Type 2 is a condition where the body's cells are unable to reciprocate to the presence of insulin [5]. However, Type 1 diabetes can be fatal if untreated, most patients today survive into old age – but they have to live a miserable life surviving on insulin syringes to be taken at regular intervals to allow their body to use the glucose from their food [5].

Our understanding and ability to treat these issues have been improving steadily, ever since the first insulin injections were carried out in the early 1920s by Banting and Best. Despite all the advances which have been made, improper manufacturing of insulin cannot be cured altogether, and a good deal of research effort is aimed at improving quality of life for diabetic patients, making their glucose tests and insulin injections as easy and non-invasive as possible, and potentially devising a permanent cure for diabetes [5].

Consequences of Diabetes

Diabetes attacks the circulatory and nervous system of the body, affecting the normal functioning of the heart, blood vessels and nerves. The damage to the blood vessels reduces blood flow which increases the chances of getting foot ulcers, infections and also slows down the healing of an injury [2]. Diabetes also leads to blindness due to long term disruption of retinal nerves and blood vessels (2.6% of global blindness can be attributed to diabetes) [1]. Diabetes is a major contributor to the cause of kidney failure cases [6].

Preventive Measures

Diabetes can be controlled by maintaining a proper lifestyle and following a proper diet. The inclusion of physical activities such as morning walks, jogging, aerobics and yoga can also help. With proper medication and regular screening, the consequences of this fatal disease can be avoided or delayed. [2]

NANOTECHNOLOGY IN MONITORING GLUCOSE LEVELS

Several improved methods for non-invasive, continuous monitoring of blood glucose have been proposed in the last few years. Many of these advances in medical technology are parented by nanotechnology. However, nanoparticles being of the size similar to natural body cells and other harmful infectious organisms may cause the immune system to retaliate against them thinking of them as unwanted foreign particles [5]. There are various methods to overcome the immune responses to the nanoparticles. To ensure their longevity in the blood stream, the biocompatibility of our bots should be taken care of and problems regarding this should be resolved by further researches. Nanorobotics is the technology which deals with robots in the nanometer scale (10^{-9} *m*) used for different purposes across different domains. Its size makes it very advantageous in certain tasks over other existing methods, especially in the medical industry where penetration and physical reach is limited inside the body. It is an emerging field in recent times and is under exploration by researchers all over the world. Nanorobots and their application in the medical field are promising and are currently under development. In alliance with the medical industry, nanorobots can be uniquely programmed to carry out specific biological tasks. When they are injected into the blood, they are capable of performing tasks like the treatment of cells, drug delivery, imaging, diagnosis, etc. as per how they are programmed. Nanorobots merged with biological research will set a new milestone in the development of medical studies and is all set to change the vision of people with discovering new possibilities which are both effective and fast. The shortcomings of the present methods are taken into account to hit upon a better way to measure the glucose levels to keep a check on the alarming disease. Creation of nanobots has been under progress already and may come within the reach of the general public after the estimated time of 5 years.

MOTIVATION

Considering the properties of nanorobots to be able to navigate in the blood stream, they can help in important treatment processes of complex diseases, in their diagnosis and smart drug delivery. Current methods of blood glucose monitoring are painful, infeasible and often lead to the chances of getting the internal body exposed to the external environment. The finger-prick test has been inconvenient for diabetic patients and hence they are not able to properly follow the recommendations for prescribed treatments. Glucometers have very limited accuracy and their results vary from device to device. Also, the currently available methods fall short as there is a proper tedious procedure to be followed and precautions have to be taken. So they cannot be performed while carrying out general day to day activities, including driving and sleeping, and the patchy nature of the time to carry out those tests means that it can overlook important and potentially dangerous spikes and fluctuations in blood glucose levels in between tests [5]. One of the main disadvantages to the finger-prick test is the heightened chances of contaminating a blood sample. There is the obvious issue of eliminating the possibility to monitor night-time variation in the patient's blood glucose levels and so there has been a big demand in the medical industry to introduce methods which are regular and continuous in nature and will not disturb the patient's day to day activities and lifestyle. Nanorobots containing chemicals and nanobiosensors can be instructed to detect levels of blood sugar on a continuous basis and wireless communication can be utilised to report these results for further monitoring.

CONSTRUCTION

The bots to be constructed will have the structure of a Carbon Nanotube (CNT).

Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical structures that are formed by concentric rolled up sheets of carbon atom of unimolecular thickness [7]. They are basically an allotrope of carbon. Having similar properties as of graphene (which is their building block), the carbon atoms in a CNT structure are bonded together by the virtue of *sp2* bonds which happens to be among the strongest form of molecular interaction [7]. This feature about the bonding of atoms in a CNT combined with carbon nanotube's natural tendency to rope together via van der Waals forces, lay the foundation for ultra-high strength, low-weight materials that possess highly conductive electrical and thermal properties.

As the process of diagnosis involves a series of steps, a multi-walled Carbon nanotube (MWCNT) structure will be used which consist of several layers which are concentrically

structured nanotubes and are interconnected with each other. So a structure with diameters more than 100 *nm* has to be constructed where each layer will be designated to perform a specific task. MWCNTs exhibits several traits that ensure the longevity and dependency for accurate diagnosis. MWCNTs are highly conducting in nature and are able to match the levels of metals in conductivity. Due to the strong bonding of carbon atoms, the mechanical tensile strength of MWCNTs can be 400 times that of steel. They are very light weight – their density is approximately one sixth to that of steel [7] (hence will make sure that it doesn't alter the blood density by much and hence not initiating any side effects or toxicity). As far as their thermal conductivity is concerned, it is shown to be better than that of diamond (hence will adapt easily to the surrounding medium – blood). They have an aspect ratio greater than 1000, i.e. in comparison to their length they are extremely thin and light weight [7].

Synthesis of CNT

Production of Carbon Nanotubes have been done through the years by a vast number of different methods. Among them, there are three main methods which have gained popularity due to their feasibility, efficiency, cost effectiveness and a number of advantages over other methods. These methods, namely arc discharge, laser ablation of graphite, and chemical vapour deposition (CVD) are discussed below.

The arc discharge method involves arc-vaporization of the two carbon rods placed end to end in an environment filled with inert gas. It is one of the easiest and most used processes. In laser ablation, the carbon is combusted with the help of laser energy. The most efficient way in which carbon nanotubes can be produced is the chemical vapour deposition process (CVD). The CVD process is carried on by the combination of a metal catalyst (such as iron) and reaction gases containing carbon (such as hydrogen or carbon monoxide) resulting in the formation of carbon nanotubes on the catalyst, all inside a high-temperature furnace. [8]

Purification

The current synthesis techniques have been successful in obtaining high purity carbon nanotubes. But the formation of by-products gives rise to some impurities like carbon nanotubes with their tips blocked with metals, nanoparticles encapsulated with metals, and amorphous carbon. Also, some structural defects may occur during synthesis. The foreign nanoparticle impurities and the defects alter the physio-chemical properties of the carbon nanotubes hence there is a requirement for purification. It can be done by Acid treatment or by use of ultrasound after the production process [7].

Enzyme Carrier

The bot has to carry an enzyme in order to oxidize the blood and hence use the products to generate an electric pulse that has to be measured. The hollow inner cavities of a carbon nanotube can serve as potential containers for a delivery purpose if utilized properly. Keeping their biomedical compatibility in mind, they have to be superficially modified. This can be achieved by a simple technique of doping. It was observed that nitrogen doped CNTs showed better biomedical compatibility. Keeping this fact in mind, Alexander Star, and his team doped CNTs with nitrogen which resulted in the formation of cup-shaped chambers in CNTs uniquely suitable for encapsulation. The nanocups were obtained from fibrous nitrogen-doped CNTs by ultra-sonication. It was later managed to constructively cork the nanocups by gold nanoparticles to create a new type of cup-shaped nano-containers with a corked opening [9].

The potential application of this work is to use the nanocups as nanoscale containers, especially as enzyme delivery vehicles. Star points out that the gold nanoparticle corked nanocups have all the desired properties for biomedical applications, including their hollow, self-confined cup structures, diverse reactivity, and biocompatibility. The gold nanoparticle corks can be designed to be open under certain stimuli, to achieve a controlled release of an enzyme [9].

Sensors/Transducers

Carbon Nanotubes are robust and inert structures but they are also actively responsive as well. Their electrical properties being extremely sensitive to even minute impulsive changes of charge transfer and chemical doping by other molecules, makes them serve as a right fit to be used as a sensor. So, most sensors based on Carbon Nanotubes are field effect transistors (FET). The CNTs will have to be made keeping the analyte in mind to make it specific [7].

Electrodes

The use of Carbon Nanotubes as electrodes for carrying out sensing and conduction purposes in different domains has been really successful. They have unmatched electrical properties and have high materialistic strength, hence are durable. The Uni-molecular nature of its walls provides a large surface area for conduction and makes room for region-specific electron transfer capabilities. [7]

Power Sourcing

The bots have to be in the bloodstream for quite a long time so power sourcing emerges as an important factor to keep in mind. There can be different ways to handle this task. One way is to incorporate the bot with thermal charging batteries which use the high body temperatures to charge the battery. Another way can be to replicate like some of the natural organisms such as bacteria cells or use nuclear technology. The addition of a thin film of radioactive material can make things work out. In that case, it is highly likely that nanobots will be able to fuel themselves on particles released by decaying atoms. [10]

Summing up the construction

The bot will be designed as an MWCNT structure, with each wall performing a specific task. Glucose will be able to easily diffuse through the bot. The outer most wall will have nanocups which contain the enzyme which will oxidise the blood. The next few walls will act as a series of sensors and electrodes that will measure and report the magnitude of the electric pulse generated, which being proportional to the glucose levels will serve the purpose. To design and simulate the structure of the nanorobots, the researchers use open-source software, called Cadnano [11].

WORKING METHODOLOGY

The multiwall structure of our tube gives us different components working together in a synchronous manner to serve the purpose. The carbon nanotube is insulated by a porous layer. The exterior wall will contain an enzyme in its

nanocups, which will be followed by two electrode layers: one working electrode and one counter electrode connected to a transducer which feeds data to an embedded nano chip. The carbon Nanotubes work in a step by step procedure, with each layer having a specific task to perform. An electrochemical method will be used to carry out the diagnosis. The electrochemical method is propelled by a current whose magnitude will be directly proportional to the amount of glucose present in a blood sample. The blood is drawn between two electrodes [3]. The outermost layer of our nanotube is loaded with an enzyme that converts glucose into gluconic acid. So at this level glucose oxidation occurs, and the product on hydrolysis leads to D-gluconic acid [3]. The structure of the tube is porous and hence glucose can diffuse freely through the tube, so when sugar levels are high, the enzyme produces large quantities of gluconic acid. And hence a flow of electrons takes place between the working electrodes and counter electrodes generating an electric current from the reaction. The working electrode has an enzyme to facilitate the generation of current when in contact with glucose. So this leads us to the conclusion that more blood glucose present in a sample, the stronger will be the voltage generated. The electrical current generated is detected by a transducer which records the current in a specific timeframe and calculates a reading of blood glucose concentration [3]. This data could then be supplemented to an embedded nanochip, which could report the data wirelessly to an external device.

PRELIMINARY TRIALS ON NANOBOTS AND THEIR MECHANISM

There has been some great progress which has taken place in the field of nanotechnology in the past decade. New benchmarks were set which laid the foundations for many other ideas and innovations to come up with.

One such successful trial was completed in 2013, where researchers and scientists at David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology along with some of its partner organizations and institutes after years of hard work were able to design an Injectable Nano-Network for Glucose-Mediated Insulin Delivery. Their setup consists of a gel-like substance with a texture similar to toothpaste. The structure of the gel was kept intact by use of oppositely charged nanoparticles, which by the virtue of forces of attraction maintained the structural integrity of the gel. This was the concept behind preventing the particles from drifting away from each other once they are inside the body. Dextran- A modified polysaccharide was used by the researchers to make the gel sensitive to acidity. Every nano-sphere was packed with an enzyme, all encased in a layer of Dextran (which formed the shell of the sphere structure). The gel being porous allowed Glucose to easily diffuse through its walls hence initiating a reaction whenever this happens. So, an increase in glucose levels lead to the production of large quantities of Gluconic Acid in accordance with the reaction of glucose with the enzyme and hence dropping the pH value of the surrounding environment. This acidic environment caused the dextran spheres to disintegrate, releasing insulin. [12]

Also, marking a major advancement in nanomedicine, scientists at Arizona State University, in collaboration with researchers from the National Centre for Nanoscience and Technology (NCNST) of the Chinese Academy of Sciences, have made some successful attempts at programming nanorobots, launching them into the depths of tumours and shrinking them by cutting off their blood supply. [13]

Recently, researchers at the California Institute of Technology have built nanobots using a single DNA strand which is able to sort and deliver the drug. Their bot consists of three parts - a “leg,” a “hand” with an “arm” which carries the drug and delivers it. There are some other additional components which control and direct the delivery of the payload. These bots have potential application in cancer treatment. [14-15]

Scientists have lately used the efficient capacity of a nanobot to carry a drug and hence have evolved a model that delivers thrombin, an enzyme which has the capability to clot blood and hence can be used to obstruct the flow of blood that goes into a tumour by placing a lump in between and thereby making it deficient of blood and eventually destroying the tumour. This trial has cleared many doubts and has possibly given a new ray of hope that nanobots are safe enough for drug delivery inside the human body and can destroy tumours and hence can be used as an effective method for cancer treatment.

So, promising trials have laid a platform and have presented a clear picture regarding their capability and compatibility. Every success achieved takes us a step closer to put nanobots to use in medical sciences, for both diagnosis and treatment of diseases.

ADVANTAGES

The speed and durability of the nanobots are its principal advantages. Use of nanobots can omit human error and readings obtained will be highly precise and accurate. Presence of sensors in the bloodstream itself for an extensive period of time will reduce the degree of invasiveness, hence avoiding the chances of getting an infection. Nanobots will serve as a faster, smarter and a highly sensitive diagnostic tool. Once the nanobots enter the human body, they can be programmed to do other tasks and cure other diseases as well. Therefore, they serve as a complete package for tackling a disease, starting from its diagnosis and regular monitoring to its potential treatment, with the intelligence of a human via its programming and accuracy of a machine. [16-17]

DISADVANTAGES

Nanorobotics is still an upcoming technology and more research needs to be done to make precise predictions of models and to measure its drawbacks and limitations. Designing something at such a small scale is a very laborious task and will require loads of human effort apart from advance tools, resources and large capital. Injecting foreign particles into the bloodstream will trigger a counter response by the body. Hence, the design and functionality of the bot have to be accordingly designed such that it doesn’t affect normal body functioning, hence escaping the body’s immune response. As all the operations will take place inside the body, there is no room for malfunctioning and its actions should be highly accurate. After all, Nanobots are machines which are programmed to perform a specific task and un-ethical use of them by terrorist and hackers make them a potential bioweapon. So, this raises concerned safety issues which pose a serious question to the researchers. Also, if

nanobots start self-replicating inside the body at an uncontrolled rate, a harmful version of the bots could be created. There have been numerous talks regarding the toxicity of the bots and their disposal methods. [16-17]

CONCLUSION

In this paper, we devised a new and effortless method for continuous blood glucose monitoring. Keeping a regular track of Glucose levels has always been a tedious task for people having diabetes. They need to prick their fingers regularly and suffer the pain of those needles and syringes, with the danger of getting an infection back of their mind. These nanobots will ease the process to check for blood glucose level and will provide highly accurate results. All the assumptions made and proposals are based on the previous developments done by researchers in different parts of the world and are subject to further research and trials.

If the trial finds some success, then nanotechnology will be a breakthrough in medical studies. If this technology is used as a replacement for the current treatments, side effects can be prevented. Scientists are also into trying acoustic communication among nanobots so that they coordinate and act on the specific site. Although being still in the research and development phase, their potential is innumerable. Nanorobots should help, through medical target identification, to improve the diagnosis of patients across the globe. In the near future, nanotechnology will play a major part in discovering new and more efficient ways for treatments and cure for not only Diabetes but also for other diseases. While some of the current upcoming technologies are not convincing enough but with regular research and advancement in the medical industry, the trends show that there will soon be some impactful developments in the diagnosis and management of Diabetes.

FUTURE PERSPECTIVES

In the future, medical treatment will expand enormously, reducing the risks and costs because of developments in molecular nanotechnology. The idea described here can be expanded to tackle potential treatment of Diabetes as well. With the evolution of organisms and the continuous changes in the lifestyle of humans over recent times, people are getting prone to a number of diseases. So it's better to check for early symptoms in order to prevent them and in doing so, keeping a track of various measurable parameters related to blood can ensure a normal activity of the body. As the basic mechanism remains the same for the manufacturing of a nanobody, this bot can be further programmed to diagnose not just glucose levels but other parameters as well. Staying in the bloodstream they reduce the pain of maintaining a regular schedule of diagnosis, inspection and treatments so they can help us to get a better and close view of the insight of the body and also prevents the possibility of contamination of blood while drawing it out on a regular basis. With more trials and research, we will see these bots making a huge impact and will surely prove out to be a helpful tool in the medical field.

LIST OF ABBREVIATIONS

1. WHO : World Health Organisation
2. CNT : Carbon Nano Tubes
3. MWCNT : Multi Walled Carbon Nano Tubes
4. CVD : Chemical Vapour Deposition
5. FET : Field Effective Transistors
6. NCNST : National Centre for Nanoscience and Technology

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