Using Off-the-Shelf Biosensors to Implement Gateways for Alarm-System Nanonetworks

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Abstract

DNA-based nanonetworks hold great promise for future biomedical applications, especially in the areas of early disease detection and targeted therapy. However, reliably transmitting information from the nanoscale to external monitoring systems remains a major challenge. This paper explores using commercially available continuous glucose monitoring (CGM) sensors as gateways between in vivo nanonetworks and external devices. We propose a novel architecture in which DNA-based nanosensors release glucose as a signaling molecule when disease-relevant biomarkers are detected. CGM systems can detect these glucose surges, enabling real-time external communication. After analyzing various biosensor types, we found that CGM sensors are the most viable option due to their widespread availability, biocompatibility, and ability to measure biochemical signals. We present several architectural alternatives, calculate the required signal strength for reliable detection, and discuss potential experimental validation strategies. Our findings highlight a feasible and practical pathway toward integrating nanoscale diagnostics with existing biosensing technologies.

Keywords: Biosensors, nanonetwork, continuous glucose monitoring, nanobots, nanonetworks, DNA-based nanonetworks, keyword

1. Introduction

Advancements in medical technology have led to the development of increasingly sophisticated bio-sensing systems capable of monitoring physiological parameters in real time [1, 2]. *Continuous Glucose Monitoring* (CGM) sensors, for example, have revolutionized diabetes management by providing non-invasive, real-time glucose level monitoring [3]. Similarly, nanotechnology and specifically molecular nanonetworks—microscopic systems composed of engineered biomolecules—–hold great promise for next-generation medical applications. These systems operate at the nanoscale, offering potential breakthroughs in disease detection, targeted drug delivery, and personalized healthcare [4, 5].

Among the most promising forms of nanonetworks are DNA-based molecular communication systems, which leverage the computational and self-assembly properties of DNA to detect biomarkers and process biochemical signals within the human body. They are among the few technologies already implementable on the nanoscale today [6, 7, 8].

In [9], we developed a powerful DNA-based nanonetwork architecture. The overarching paradigm is shown in Figure 1. A number of nanosensors constantly monitor their environment for the presence of predefined biomarkers or other information. Once detected, the sensors release a so-called DNA-tile (the little squares in the figure) to signal their detection to their surroundings. Once sufficiently many nanosensors have released their tiles, the latter may assemble into message molecules, representing a certain combined finding due to the presence of several biomarkers. These messages may then be detected by other nanodecives or gateways for further consideration. For more details on this process, the interested reader is encouraged to check [9].

However, a critical challenge remains: how to reliably transmit information from these nanoscale networks to the outside world, i.e., how to implement Phase 3 in the figure with the "gateway" being a device which emits the out-of-body signals when detecting message molecules. Unlike traditional electronic biosensors, today's nanonetworks lack standardized communication mechanisms that bridge the microscopic biological domain with macroscopic devices.

This paper explores the potential of off-the-shelf biosensors, specifically the popular and widely used CGM sensors, as an interface between in-vivo DNA-based nanonetworks and external medical monitoring systems. By re-

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Article published in Elsevier Nano Communication Networks 45 (2025) 10-26. (10.1016/j.nancom.2025.100584)

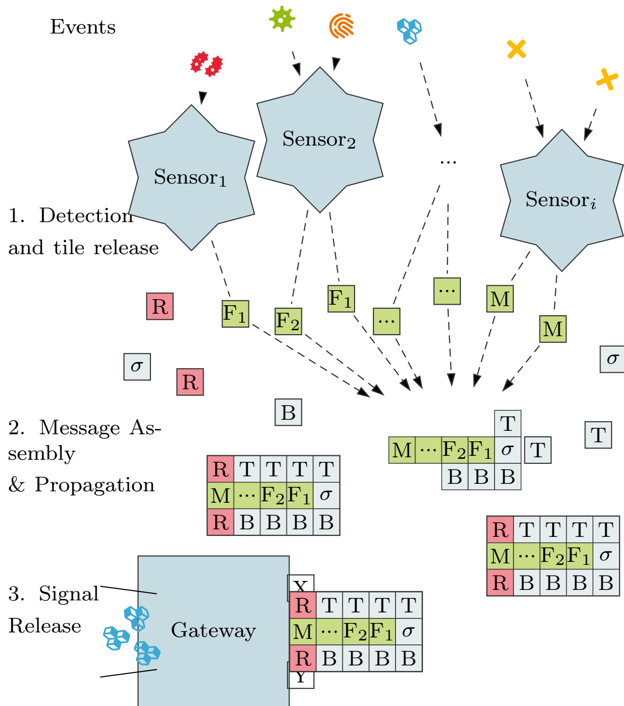

Figure 1: Detection of Biomarkers using DNA-based nanonetworks. The nanonetworks observes its environment for predefined biomarkers or messages from other devices and releases tiles that signify the bodily location (F_1...F_n) as well as tiles that signal a specific disease (M) once it detects a noteworthy event. All other tiles that are requires for a message molecule to form (σ (seed-tile), R (receptor parts), T/B (top and bottom framework tiles)) are always present in the environment. A message with a fully functional receptor can only form once all tile types are present in sufficient quantities.

purposing existing biosensing technology, we propose a novel approach in which nanonetworks encode diagnostic signals into detectable biochemical markers that can be sensed and transmitted by CGM devices. This could enable a real-time, bio-integrated alarm system for early disease detection, significantly enhancing the applicability of nanonetworks in clinical settings.

The remainder of this paper is structured as follows: Section 2 provides an overview of current biosensor technologies, emphasizing their potential as gateways for nanonetwork communication. Section 3 details the mechanisms by which CGM sensors can be integrated as a gateway into DNA-based nanonetwork architectures. It presents a holistic system architecture, exploring potential implementations and challenges. Section 4 presents several experimental setups to verify the principle as a proof-of-concept and highlights the practical difficulties. Finally, Section 5 summarizes the key findings.

2. Analysis of Available Biosensors

The continuous and long-term monitoring of target analytes, such as a chemical or biomolecules, can be achieved using *in vivo* biosensors. Biosensors are sensors that combine biological sensing elements with a physical transducer to detect specific substance or biomarkers. Chemical-based sensors employed in a biological environment are also considered biosensors in a broader sense. Nevertheless, *in vivo* applications remain challenging due to the harsher *in vivo* environment and other limiting factors [10].

In [11] biosensors are categorized as wearable, ingestible, and implantable devices. In the following sections, we provide further explanations of wearable and implantable biosensors. We exclude ingestible biosensors because their area of application does not align with the context of nanonetworks that are envisioned to operate in the bloodstream. In addition to being categorized based on their location, biosensors can also be classified according to the type of signal they detect or the components used in their construction. Ultimately, we compare the various types of sensors and select the most suitable candidate for implementing a gateway.

2.1. Wearable Sensors

Wearable sensors are non-invasive and in close contact with the skin. We can integrate wearable sensors into clothing or shoe insoles. Additional sensing methods include electronic skin, electronic tattoos, and smartwatches. Consequently, flexible, lightweight, and stable materials are required. However, these materials must not interfere with immune compatibility; for example, a biosensor should not induce skin inflammation. Different detection modes include electrical, physical, and biochemical ways. In the context of nanonetworks, the biochemical detection of molecules in sweat or the interstitial fluid is particularly interesting. Sweat contains measurable molecules, such as glucose and electrolytes. Furthermore, measuring targets in sweat is a non-invasive process. Electronic skin and tattoos also have great potential in the field of wearable biosensors [11].

Another well-known example are smartwatches. Users may utilize them to detect oxygen saturation and blood pressure. The underlying mechanism of sensing is *photoplethysmography* (PPG). PPG operates by measuring light transmission or reflection to gauge the volumetric change in the heart [12]. This method leverages the different light absorption rates of tissue and blood cells. Tissues have a low absorption rate for red light and near-infrared light, whereas red blood cells have a high absorption rate for near-infrared light. We can derive the oxygen concentration of red blood cells from these differences. Furthermore, to estimate the blood pressure, we can utilize the PPG waveform [13]. This raises the question of whether we can use near-infrared or infrared light to detect other targets that may prove helpful as a gateway for nanobots.

2.2. Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIR) is a powerful tool for examining the optical properties of tissues non-invasively at the microvessel level. NIR operates by absorbing electromagnetic radiation in the near-infrared region, with wavelengths ranging from 650 to 950 nm. Due to the relatively low absorption rates of tissue, this radiation can penetrate thick and deep layers. Molecules absorb radiation at specific frequencies, which depend on factors such as atomic masses, bond strength, and the surrounding environment. Consequently, different types of chemical bonds exhibit distinct frequencies. We can utilize NIR to identify and quantify various molecular species within a sample. It enables the detection of tissue absorption, scattering, and concentrations of oxygen, water, and lipids. In addition, NIR can measure the levels of various metabolites, hormones, and other small molecules in biological samples *in vivo*. While NIR can assess tumor blood flow and oxygen metabolism in cancer detection, it can detect and monitor glucose levels in urine and blood [14]. Furthermore, it can detect glucose *in vivo*; however, much improvement is required [15]. Advanced glycation end products in type 2 diabetes patients can also be detected by using a table top NIR apparatus [16]. NIR technology can be integrated into portable devices, making it a versatile tool for real-time, on-site analysis [14].

2.3. Implantable Sensors

Another closely-related type of biosensor are implantable sensors. Implantable sensors come into direct contact with blood and tissue, enabling them to detect and target complex signals. We can categorize these measured parameters as physiological, mechanical, or biochemical.

Physiological signals include respiratory rate and temperature. Biochemical signals encompass ions, glucose, dopamine, and pH. Detecting biochemicals is a promising application for nanonetworks. However, there are challenges associated with implantable sensors. Biocompatibility is crucial, as sensor implantation can lead to inflammation or other immune system reactions. Additionally, proteins or fats attaching to the sensor can reduce sensitivity and signal stability [11, 17].

2.4. DNA Sensors

DNA biosensors utilize built-in DNA as a sensing element. These sensors can detect nucleic acids, such as DNA or RNA, as well as other analytes like proteins, small biological molecules, and metal ions. The advantages of DNA biosensors include high thermal stability, structural programmability, high sensitivity, and specificity. However, DNA is susceptible to pollution and degradation, requiring strict storage conditions [18]. Further, the immobilized DNA on the sensor could overstimulate the immune response [19].

We can classify DNA biosensors in various ways; here, the focus is on the DNA structure of the detection element. The following presents six types of DNA biosensors: aptamers, DNAzymes, i-motifs, G-quadruplexes, DNA hybridization, and DNA tiles.

- Aptasensors. Aptamers are single-stranded oligonucleotides that can be immobilized onto nanoparticles. These sensors have specific three-dimensional structures, resulting in high affinity and specificity for their target. They can recognize cells, proteins, antigens, nucleic acids, and metal ions. Aptamers can also be immobilized onto nanomaterials and integrated into various biosensors. Using Aptasensors for *in vivo* detection is possible [18]. A sensor for dopamine in living rat cells [20] and a wearable cortisol sensor [21] are two examples.

- DNAzymes. DNAzymes are DNA oligonucleotides that can catalyze specific biochemical reactions. They consist of a catalytic core and two substrate-binding arms, requiring a metal ion to function. DNAzymes detect metal ions, nucleic acids, and bacteria [18]. They can also detect *in vivo*, such as for tracing miRNA localization [18].

- i-Motif. i-Motifs are cytosine-rich, four-stranded intercalated structures found under acidic conditions. Their conformation changes with pH, making them suitable for detecting pH changes [18].

- G-Quadruplexes. They can detect metal ions and interact with organic dyes, insulin, and miRNA. Live detection in cells is also possible. For example, NO and SO_2 can be detected in the microenvironment of cellular membranes [22, 18].

- DNA Hybridization. We can construct Sensors based on DNA hybridization amplification. For instance, a single-stranded DNA can form a DNA hairpin with a self-complementary sequence, providing high specificity for detecting nucleic acid fragments. Telomerase activity can also be detected *in situ* [19].

- DNA Tiles. DNA tiles are two-dimensional nanostructures, such as DNA lattices with four-arm junctions, multi-arm junctions, or crossover tiles. DNA tiles can construct three-dimensional nanostructures and be used in electrochemical sensing, optical sensing, and intracellular imaging [19]. For example, breast cancer biomarkers can be targeted *in vivo* [23].

2.5. Glucose Sensors

Glucose monitoring sensors are essential for treating diabetes mellitus by tightly controlling blood sugar levels to reduce complications. It is achieved through minimally invasive sensors that are implanted or inserted into the skin, known as CGM systems. These systems automatically and continuously measure glucose concentration in the interstitial fluid. CGM systems can connect to various devices, such as smartphones or cloud databases, enabling real-time and automatic data transfer. Furthermore, the

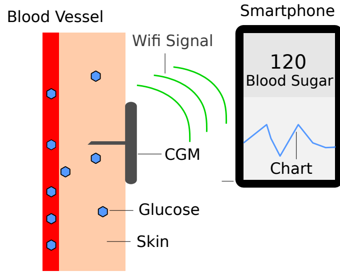

Figure 2: Continuous Glucose Monitoring System (CGM) which enzymatically measures the glucose in the interstitial fluid. The measuring electrode is inside the body while the rest is outside of the body. The sensor sends the detected glucose concentration wirelessly (e.g. via Bluetooth) to a smartphone.

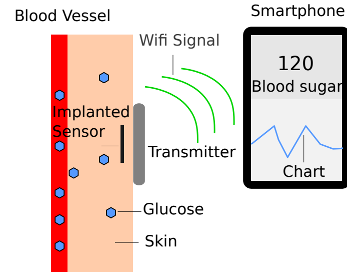

Figure 3: GCM-System which measures the glucose in the interstitial fluid using fluorescence. Unlike in Figure 2 where a needle pierces the skin every time the sensor is applied, this type of sensor is (partially) implanted into the body. A detachable transmitter may read out the measured values and sends the glucose concentration wirelessly (e.g. via Bluetooth) to a smartphone.

sensors can process data using various filtering techniques, such as the Kalman filter and Wiener filter. Additionally, they can predict future glucose levels and alert the patient in the event of a medical emergency [24]. In [25] the advantages and disadvantages of CGM-based wearable technologies were highlighted, including non-invasive body fluid-based techniques and invasive electrode implantations. The implantable CGM systems primarily detect single indicators, but advancements in nanomaterials and functional modifications enable multi-parameter monitoring for better disease detection. The limited sensing area and penetration depth of microneedle-based CGM devices constrain their electrochemical sensitivity and accuracy in glucose detection.

There are various types of electrodes used in CGMs. The most commonly employed are electrochemical sensors, which operate via an oxidation-reduction reaction facilitated by glucose oxidase, an enzyme that reacts with glucose. Figure 2 shows an example of this type of sensor. This type of sensor typically features a small needle that must be inserted into the skin and operates at body temperature. Users can typically wear these sensors for up to 14 days.

In addition to electrochemical sensors, some sensors utilize fluorescence as a detection method [26]. Specific molecules, known as fluorophores, can absorb light at specific wavelengths (see Figure 3). This leads to the excitation of an electronic transition and the subsequent re-emission of light at a different wavelength as the electron decays from the excited state to the ground state [27]. CGMs using fluorescence detect signals from a fluorophore that reversibly interacts with glucose and is surgically implanted into the skin. Fluorescent sensors have a longer lifespan, as Users can wear them for up to 90 days. In [28] a non-invasive, wearable biosensor was introduced for in situ monitoring of sweat glucose. The fluorescent nanosensor probe incorporates boric acid-functionalized *carbon quantum dots* (CQDs) and a hydrophilic cotton thread-based microfluidic channel. It enables real-time monitoring of sweat glucose concentrations using a smartphone, providing a biodegradable and non-invasive approach to glucose sensing. However, most of these CGMs using fluorescence are still in their early stages of research [26].

In addition to fluorescence-based sensors, recent advancements include *Surface-Enhanced Raman Spectroscopy* (SERS)-based glucose sensors [29]. Unlike fluorescence, SERS leverages nanostructured metallic surfaces, typically silver or gold nanoparticles, to enhance Raman scattering signals, enabling highly sensitive, label-free glucose detection. This approach could significantly improve measurement accuracy even at low glucose concentrations in small volumes of body fluids such as sweat, tears, or interstitial fluid. Thus, integrating SERS into next-generation wearable gateway systems could substantially enhance their sensitivity and specificity.

2.6. Comparison

Based on the various types of nanosensors analyzed thus far, we compare them and provide a rationale for selecting CGM sensors for the remainder of this paper. We compare the sensors by their detection target, their *in vivo* availability, and their (medical) use on patients. We also examine the requirements of signal molecules that sensors would detect, as well as scenarios in which they find application. Finally, we provide their suitability based on the aforementioned parameters.

2.6.1. Requirements for Signal Molecules

We can use chemical signals to communicate within a living organism [30]. Regarding nanonetworks, we can utilize the release of molecules by gateways to communicate a detected event to the outside, illustrated in Figure 1 (3.signal release). There are special requirements for such a molecule: interference with homeostasis, lipophilicity/hydrophilicity, toxicity, and half-life. The following will further elucidate these concepts.

Homeostasis refers to the state of stability within the body, which allows it to self-regulate. It ensures that the concentrations of molecules within a body stay at a healthy

Sensor	Measurand	In Vivo	Off-The-Shelf	Suitability
wearable sensors [11]	glucose, lactase, Na+, Cl-, K+	yes	no	low
smart watches [12]	heart rate	yes	yes	low
NIR	blood flow, oxygenational glucose	?	no	low
implantable sensors [11]	Glucose, Ka+, Na+, Ca2+	yes	no	low
CGM [24]	glucose	yes	yes	high
Aptasensor [18]	dopamine, cortisol			
DNAzymes [18]	miRNA imaging	yes	no	low
i-motif [18]	ph changes	?	no	low
G-quadruplex [18, 22]	metal ions, NO, SO2, miRNA, Insulin	no	no	low
DNA hybridiztaion [19]	nucleic acid fragments telomerase activity	?	no	low
DNA tiles [19, 23]	Cancer biomarkers	no	no	low

Table 1: comparison of the different biosensors presented prior. For each sensor the measurand (*in vivo* and *in vitro*) as well as the ability for *in vivo* measurements, the off-the-shelf availibility and the suitabilityas a gateway in our nanonetwork is given. The suitability is high if the measurand can be used as a signal molecule and the sensor is available off-the-shelf. Otherwise it is set as low.

level. Feedback loops and hierarchical control regulate the homeostatic system. A disturbance of the homeostatic state leads to medical problems [31].

The term lipophilicity refers to a compound's likelihood to distribute into a nonpolar, lipid environment rather than an aqueous environment. Additionally, we can utilize it to assess the possibility of a compound to cross a cell membrane. If a compound is lipophilic, it can diffuse a membrane passively. However, if it is too lipophilic, the compound could be trapped in the membrane [32].

Toxicity describes the harmful effects that a substance can have on an organism. Several factors, such as the mechanism of action, exposure, dose, age, and underlying diseases, determine the toxic effect [33].

The biological half-life of a chemical refers to the time required for a biological system to eliminate half of the substance. [34]. A signal should stay long enough in the body for the target sensor to detect it. However, it should also not remain in the body for an extended period, as this would interfere with the detection of new signals.

Furthermore, the release frequency of such signaling molecules is a critical factor when determining which molecule we should integrate into a nanobot communication architecture.

Of the available signal molecules that the presented technologies may detect, glucose fulfills most of the desired requirements. Glucose is hydrophilic [34], and intravenously infused glucose has an approximate half-life of 14.3 minutes [34]. This is a fitting period from signal release to sensor detection. However, a chronic excess of glucose causes toxic effects on cells and organs [34]. Thus, we should avoid the frequent release of glucose as it would disturb homeostasis. However, if the signal molecule is only released rarely, then the benefits of the disturbance outweigh the short-lived disturbance of the homeostasis.

2.6.2. Scenarios

Two scenarios must be considered to evaluate and prioritize the aforementioned requirements for detectable molecules:

1. frequent signal detection and
2. rare signal detection.

We must assess frequent signal detection with significantly higher stringency compared to rare signal detection. For example, using the proposed architecture to measure glucose and administer insulin in a patient with diabetes is a case of frequent signal detection. This signal would be released several times a day. If, for example, homeostatic disturbances can cause diseases, it would be detrimental to disrupt the body's balance multiple times a day. However, in some scenarios, a signal would only be released rarely, e.g., when the system detects cancer or infectious diseases such as HIV, tuberculosis, or Ebola. In such a case, the risk or disturbances caused by the signal molecule are negligible because a) such an event does not occur very often, and b) the advantages of early detection of such diseases outweigh the risks caused by the signal molecule.

2.6.3. CGM as a Most Promising Biosensor

Based on the information gathered thus far, we can now determine the most suitable biosensor technology that may find application in gateway construction for in-body nanonetworks. As Table 1 displays, only smartwatches and CGM are widely used and commercially available. Only the CGM has high suitability as a gateway in the nanonetwork, as it can to measure a molecule, whereas the smartwatches measure physiological parameters that are difficult to modify. Thus, CGM are the most suitable off-shelf sensors that we can use for nanonetworks gateways.

3. Using CGM as Alarm Gateway Technology

In this section, we conceptualize a system in which glucose molecules serve as signaling agents for external communication, utilizing CGM sensors as a gateway technology. To achieve this, we first present several possible architectures that could produce this effect and subsequently calculate the appropriate constraints and conditions that must be met to recover a signal successfully.

3.1. Architecture

This section describes the architecture we used for an in-body nanonetwork based on DNA, which serves as an alarm system for detecting rare diseases. To achieve this, we analyze three different alternative methods that utilize glucose for signal transmission to the CGM sensor. Furthermore, we advocate for an optimized placement of the CGM sensor within the human body to maximize its effectiveness as a gateway technology.

We now provide an overview of the various scenario alternatives, as depicted in Figure 4. Disease-specific biomarkers can either bind to a nanosensor or a storage unit containing signal molecules. Such a storage unit can either be a single reservoir (*Method A*) or multiple DNA boxes (*Method C*) [35, 18]. While DNA-boxes of roughly 40 nm^3 size are usually suggested as drug carriers, it may be too difficult to fit the necessary amount glucose inside of them or to release a sufficient amount at once. As such, it might be better to use a macroscopic implant/"reservoir" that can store higher amounts of glucose. Such a device might be much easier to create and control.

The binding of the biomarker to the nanosensor triggers the release of DNA tiles, which may then assemble into a message molecule (*Method B*) [18]. The message molecule or the biomarker can either bind to the DNA boxes or the reservoir. This binding event triggers the opening of the DNA box or reservoir, leading to the release of the stored glucose. A CGM sensor may detect the released glucose, which transmits the detection of the biomarker to an external device. Thus, a CGM sensor could serve as a medium for transmitting detected events from within the body to the external environment.

In the following, the direct binding of the biomarker to the storage unit (Method A or C) is compared with the use of the intermediate step using DNA-based message molecules (Method B). If biomarkers bind directly to the storage unit, the system would be limited to detecting only a single type of biomarker. However, using the extra step of the nanosensor and DNA tile release in method B, more than one biomarker may be detected, thus opening the possibility of a more fine-tuned and complex detection. The additional formation of a message molecule would slow down the entire system and introduce additional complexity, but at the same time, it allows for complex computations. Those computations may be used to correct errors, form a distributed consensus among nanodevices, or to compute near arbitrary additional operations that might come in handy.

The disadvantage of DNA boxes (Method C) over a reservoir (Method A) is that there is a possibility that not all DNA boxes are reached or that the signal release is consecutive because not all boxes are approached at the same time. This could lead to an insufficient amount of released glucose molecules, which would not be high enough to exceed the threshold of the physiological concentration (background noise). Thus, no detectable signal can be reliably distinguished from background glucose levels with certainty. However, the release through a reservoir is an "all-or-nothing situation". If the biomarker or the message molecule binds to the reservoir, the amount of glucose released is sufficient to have a detectable signal. As a result, all proposed solutions have their advantages and disadvantages, and one must decide based on the requirements of the intended application. In general, the use of message molecules as an intermediate step (Method B) is necessary for most diseases, as a single biomarker is typically insufficient to ensure a definitive diagnosis for most diseases.

3.2. Glucose Levels for Useful Signal Transmission

All the above scenarios use glucose molecules to encode information about the detection of a disease (as seen in the final step in Figure 4). In this section, we calculate the concentration of glucose molecules necessary to distinguish the signal from the background levels with near certainty. For this, the naturally occurring blood glucose concentration range needs to be taken into account. The difference between a low blood glucose level and a high value provides a lower threshold of the amount of glucose that must be released to generate a signal.

The average blood glucose concentration is 99 mg/dl [36]. With an average of 5.5 l or 55 dl of blood in a human body [37], the total calculated amount of glucose in the circulatory system is $5,445$ mg. A study carried out with healthy, non-obese, non-diabetic participants using CGM showed that 96 % of the time, the blood glucose levels range between 70–140 mg/dl [36]. The study further demonstrated in a 24-hour period, that the median time when the glucose sensor values where < 70 mg/dl is 1.1 %, > 140 mg/dl is 2.1 %, > 160 mg/dl is 0.3 % and > 180 mg/dl is 0.0 %. To minimize a false positive signal and use 180 mg/dl as the upper limit, the amount of glucose in the blood is calculated to be $9,900$ mg. To distinguish a signal from the background glucose levels, the amount of released molecules must surpass the physiological upper limit of 180 mg/dl. Taking into account the possible value of 70 mg/dl as a lower limit, the difference between the lower and the upper value is 110 mg/dl, which equals $6,050$ mg of glucose. However, the measuring error of the CGM needs to be taken into consideration. For this, the *mean absolute relative deviation* (MARD) can be used. The MARD of the different commercially available CGM systems can be assumed to be 10 % [24]. Considering the MARD the difference between the lower and upper values

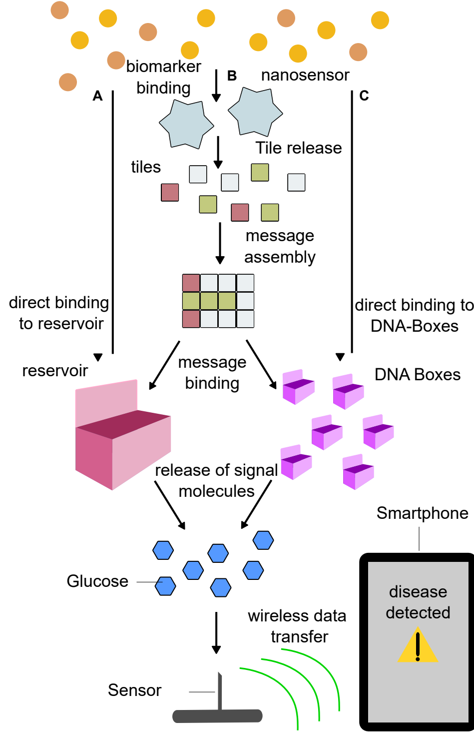

Figure 4: Proposed architecture with three possible methods. In method A the biomarkers bind directly to the reservoir which contains the signal molecules. In method B the biomolecules bind to a nanosensor which triggers the release of DNA tiles. They can be used for various computational tasks. The DNA tiles can then either bind to a reservoir or DNA boxes. In method C the biomarkers directly bind to the previously mentioned DNA boxes. The binding event leads to the release of the stored signal molecules. In all three methods the signal molecules bind to a gateway sensor which communicates the detected event to the outside to a smartphone or similar device via wireless data transfer.

is $6,655$ mg, which is used in the following as the amount required for a glucose signal.

While this amount is clearly too high for regular signal transmission and would likely adversely affect the human body, the benefits may outweigh the risks if detection is sufficiently rare in alarm systems. $6,655$ mg of glucose is just "slightly more" than the expected maximum glucose levels after a large meal. If a more regular signal transmission is necessary, alternative techniques to encode the information in the glucose level may be required to ensure biocompatibility.

3.2.1. Storage of Glucose Molecules

There are different means of storing glucose molecules, e.g., DNA boxes (as in Method C depicted in Figure 4) or a single large reservoir that functions similar to e.g. an insulin pump (as in Method A also depicted in Figure 4). Details of the various architectural methods were discussed in previous sections. We also demonstrated that the DNA boxes must be capable of containing at least $6,655$ mg. One DNA box has the dimensions of 34 nm x 33 nm x 48 nm [35] and thus a volume of $53,856$ nm^3. To determine the number of boxes required to release the above-calculated $6,655$ mg of glucose, the volume of a glucose molecule is needed. Based on the data of crystallography measurements for beta-D-glucose [38], the volume of glucose in a solid state is 0.19 nm^3. To determine the number of glucose molecules that can fit into a single DNA box, the volume of the DNA box can be divided by the volume of a single glucose molecule. This calculation yields $2,835,578$ molecules of glucose in one box. Using the molecular weight of glucose of 180.16 g/mol [34] and the Avogadro constant of 6.02×10^{23} 1/mol [39] the weight of one glucose molecule is 2.99×10^{-22} g. Thus, there are 8.48×10^{-17} g glucose in one DNA box. The threshold value divided by the weight of glucose per box yields 7.84×10^{16} boxes to harbor the necessary $6,655$ mg.

This calculation is based on data on glucose in a solid state. However, in the context of *in vivo* systems, the hydration needs to be taken into account. Using a hydrodynamic radius for glucose of 0.40 nm [40] and assuming a glucose molecule is a sphere, the volume of one glucose molecule in the solution can be calculated. The volume is 0.2681 nm^3. By doing the same calculations as above, 1.11×10^{17} boxes are required to store $6,655$ mg of glucose. This calculation is only an approximation, as the hydrodynamic radius depends on temperature and concentration [40].

Alternatively, a single reservoir or implant (Method A) might be used to detect a message molecule and release a predefined amount of glucose in reaction. In $6,655$ mg of glucose there are 2.22×10^{22} glucose molecules. Using the volume of a single glucose molecule in the solution, the total volume of $6,655$ mg glucose is 5.96×10^{21} nm^3. This volume equals the minimal volume of such a box. Assuming the box is cubic, the dimensions would be 18.10 mm x 18.10 mm x 18.10 mm.

3.2.2. Errors

After collecting these numbers, we can calculate the probability of an error at the glucose sensor (the last step of each method in Figure 4). Based on the given concentration of a signal and the threshold, we calculate the probability of a false positive signal. Assuming a normal distribution of the glucose level in the blood, inferred by the data of the study [36] with a mean μ of 5575 mg and a standard deviation σ of 650 mg, we can create a distribution function $\varphi(x, \mu, \sigma, 0)$, defined in Equation 1, for the base level of glucose in the bloodstream. γ represents the amount of glucose added to the bloodstream by an emitted signal, so it takes the value 0 for the calculation of the base level, as no signal is emitted in this case.

$$\varphi(x, \mu, \sigma, \gamma) = \frac{1}{\sqrt{2\pi\sigma^2}} \cdot e^{-\frac{1}{2}(\frac{x-\mu}{\sigma})^2} + \gamma \quad (1)$$

With a threshold ϑ of 9.900 mg, which is equivalent to 180 mg/dl, we can calculate the error probability of a false positive signal as in Equation 2.

$$p_\beta = \int_{\frac{10}{11}\vartheta}^{\infty} \varphi(x, \mu, \sigma, 0)dx \tag{2}$$

Furthermore, a false negative signal could occur in the cases of extremly low physiological blood sugar levels. Assuming the same normal distribution as for the base level of glucose but shifted by a value γ of glucose that is used as a signal, we obtain a distribution function of $\varphi(x, \mu, \sigma, \gamma)$, defined in Equation 1, for the glucose level in the bloodstream as a combination of the signal and the base level. Using the same threshold ϑ, we calculate the error probability of a false negative signal with Equation 3. However, based on the data presented in the study [36] and considering the MARD of the sensor, the possibility of a false positive or false negative signal should be minimal and could be fine-tuned by adjusting ϑ or γ. Furthermore, the already used CGM could be utilized to take the previously measured data of the physiological glucose concentration into account when it detects a sudden surge of glucose due to the release of the signal molecules.

$$p_\alpha = \int_{0}^{\frac{10}{9}\vartheta} \varphi(x, \mu, \sigma, \gamma)dx \tag{3}$$

3.3. Characteristics of the Glucose Signals

Finally, we examine the properties of the glucose signal, utilized in the final step of each method shown in Figure 4. The sampling rate of commercially available CGM is 5 minutes [24], and the half-life of glucose is 14.3 minutes [34]. Thus, a detection of the signal can be ensured. The sensors can be worn between seven and 90 days and have a warm-up time of 2–24 hours depending on the device and the commercial supplier [24]. There is no signal detection during the warm-up time. The release of glucose molecules from a reservoir and the following blood glucose levels could exhibit a rough similarity to blood glucose levels after a meal. Typically, blood glucose levels do not exceed 140 mg/dl after a meal and return to baseline within two to three hours post-meal in healthy individuals. The glucose curves of healthy individuals have a tendency to be biphasic, which means that there is a peak in the curve around 30–60 minutes after a meal, which is followed by a decrease and another peak 90–120 minutes after a meal [41]. However, the release of glucose from an internal reservoir may exhibit a slower or more rapid return to baseline or follow a different curve profile as the absorption step from the intestine into the bloodstream is bypassed.

4. Evaluation & Experimental Setup

There are some demands for a CGM that could be tested in wet lab experiments, including a short warm-up time and the possibility of performing calibrations. We suggest using Dexcom G7 sensors, which have a 30-minute warm-up time, and it is possible to calibrate but not mandatory [42, 43]. As such CGM sensors are commercially available, experiments that verify the principle in isolation are possible but more challenging to perform than most would initially assume. In this section, we present three experimental setups that verify CGM sensors as a means for retrieving information from in-body nanonetworks in ascending order of realism. Although simulation is theoretically possible as a means of verification, it seems out of place because of the general availability of the biosensors in question, even if there are technical hurdles.

4.1. Experiment 1: in vitro Petri Dish

The simplest way to measure the functionality of a CGM would be to place the CGM electrode in a Petri dish with a glucose-containing solution. Glucose could be gradually added to increase glucose concentration. The range of glucose concentration should be within the measuring range of the CGM.

Although this setup appears simple, as shown in Figure 5, it presents a few challenges. Most commercially available CGMs use glucose oxidase as the sensing molecule. Glucose oxidase uses oxygen as an electron acceptor for glucose oxidation [24]. Thus, the oxygen concentration of the glucose solution should be measured beforehand to ensure that enough oxygen is present. A further issue is the warm-up time, which ranges from 2 to 24 hours, depending on the commercial supplier. Some CGMs require calibrations [24]. Thus, it would be best to use CGMs for these experiments, as they do not require calibration and have a short warm-up time. Furthermore, the solution should also model the interstitial fluid as this is where the sensor measures in application [24]. The interstitial fluid is composed similarly to blood [44].

That said, as CGM-sensors are medical products and thus heavily regulated, each CGM sensor had to undergo extensive testing in the lab, on animals, and on humans before commercial release. Such simple tests have been performed many times by the corporations in question, even though testing protocols are usually barely obtainable. Such experiments would not provide additional insights into the workings of such a sensor and are, therefore, not part of this theoretical proposal.

A step further would be not just to inject the glucose into the solution but to have a reservoir that stores glucose. With this setup, it could be determined whether the reservoir is triggered correctly and whether the sensor detects the sudden surge of glucose molecules. However, this would require an elaborate design of a reservoir triggered by the binding of a specific biomarker.

4.2. Experiment 2: in vitro Petri Dish with Tissue Samples

In the following steps, the initially proposed experiment will be gradually adjusted to reflect real-world conditions better. To achieve this, it is first advisable to adapt

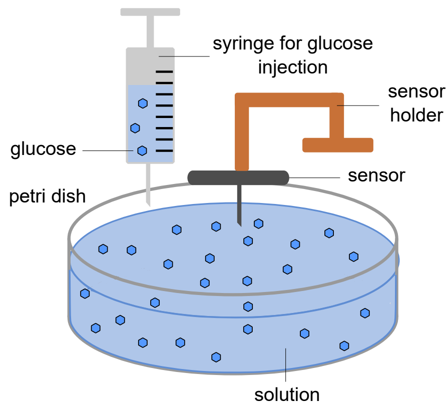

Figure 5: Example set up for experiment 1. A Petri dish contains a glucose solution. Additional glucose can be injected. A sensor measures the glucose concentration. A contraption holds the sensor in place.

the chemical environment of the sensor as closely as possible to the actual sensor environment. Since CGM sensors typically measure certain chemicals, such as hydrogen peroxide, as a byproduct of glucose metabolism in the interstitial fluid under the skin, it makes sense to use a real sample. However, from this step onward, an ethics application is required, as human samples will be used.

Nevertheless, it is expected that the CGM sensor may perform even better than in the simplified experimental setup simply because it operates closer to its intended functional environment. If it does not work effectively in the first step, it is likely to do so at this stage. However, an ethical application is required to obtain tissue samples.

4.3. Experiment 3: in vivo Murine Experiment

The next refinement of the experimental setup involves testing on a living organism and moving away from the artificial replication of the chemical environment in a petri dish. Although no human samples are used in this case, making the experiment less realistic in that regard, this limitation is potentially offset by many other parameters that are "more realistic".

In this scenario, the CGM sensor would be applied to a suitable animal. Once the sensor reaches its operating temperature, a precisely dosed glucose injection could be used to assess whether the sensor provides meaningful readings regarding our proposed nanonetwork. A step further would be to implant a reservoir that can be triggered by a prior specified biomarker, leading to the release of the signal molecule glucose, which is subsequently detected by the CGM. This biomarker may be naturally present in the animal or introduced, for example, as a pathogen through an infection. In this scenario, an uninfected control group is necessary, which increases the number of animals required.

However, it is important to note that an ethics application is also required for these steps, which makes experiments of this kind lengthy and sometimes challenging. The animal studies have to follow the 3Rs principle – replacement, reduction, refinement and undergo approval by an *institutional animal care and use committee* (IACUC – or an equivalent).

4.4. Experiment 4: in vivo On-Human Use With Glucose Solution Injection

The fourth and likely most realistic test involves using a CGM sensor on a healthy person.

The individual equipped with a CGM sensor would receive an injection of a glucose solution (either subcutaneously or intravenously) to simulate the sudden release of glucose from a reservoir while the sensor monitors blood sugar levels in the tissue. Although the setup is surprisingly simple, such an experiment is not without risks and requires ethical approval, suitable test subjects, and medical personnel for both injection and monitoring.

Additionally, volunteers under various conditions would be needed to ensure that the CGM functions properly across different individuals with different lifestyles. The experiment should be repeated multiple times to obtain meaningful statistical insights into the sensor's performance under diverse conditions. We refer back to the law of large numbers and hope that, even in a system as complex as the human body, after several hundred or thousand tests, all possible contingencies and potential complications will have emerged. If the CGM sensor successfully passes this stage of experimentation, its viability as a gateway technology would be conclusively demonstrated.

Human studies would follow the Declaration of Helsinki and applicable national and institutional ethical review processes. Full IRB/ethics board approval would be obtained prior to any human testing.

5. Summary & Conclusion

One of the major remaining challenges in the nanonetworking community is extracting molecular communication signals from within the human body to external devices. This work explored the use of common CGM sensors for diabetes glucose monitoring in molecular nanonetworks.

To avoid the potential cost of developing a new type of technology, we first analyzed various, sometimes commercially available, biosensors, including wearable sensors, those utilizing near-infrared spectroscopy, implantable sensors, and DNA sensors. Ultimately, only the CGM sensor technology was sufficiently advanced and biocompatible to serve as a gateway for nanonetworks.

We then conceptualized a system in which glucose molecules serve as signaling agents for external communication, utilizing continuous CGM sensors as a gateway technology. To achieve this, we first compared four possible scenarios that could produce this effect and subsequently calculated the necessary amounts of glucose to ensure a successful signal detection by the CGM sensor, given an arbitrary error rate.

Finally, we proposed ideas for various experiments using the CGM sensor. Overall, real-world applications are much more complex than initially expected. While laboratory-scale glucose sensors exhibit high precision and sensitivity in the context of diabetes, the off-label use as a gateway technology inside a laboratory remains challenging.

As the experiments become more realistic when using tissue or incorporating it into a real circulatory system, the ethical requirements increase. Empirical tests require detailed protocols outlining the risks, benefits, and informed consent procedures for human trials. Animal models are often used for preliminary safety assessments before progressing to clinical studies, but they also require clear reasoning about the necessity of such experiments and the expected benefits.

Acknowledgments

This work has been supported in part by the German Research Foundation (DFG): Project 419981515, NaBoCom II and the BMBF-financed Project 16KIS1991, IoBNT.

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