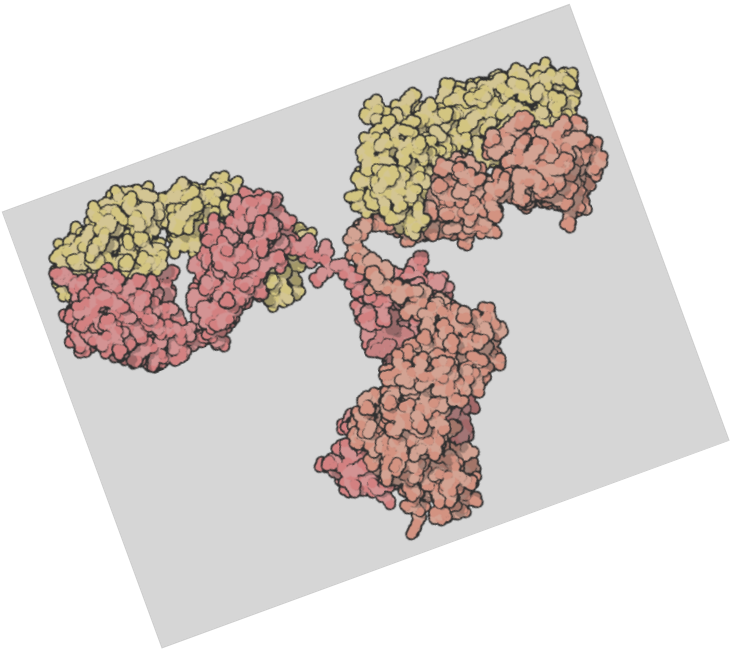
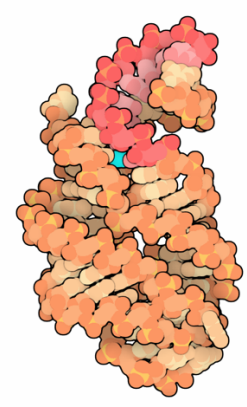


BIOSENSORS:
CURRENT STATE & FUTURE DIRECTIONS



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ABSTRACT

Interest in biosensors has spiked in recent years and their potential applications in healthcare, analytical chemistry, and life sciences have broadened. This essay examines how biosensors work and what their strengths are, what can lead to their commercial success based on experiences drawn from glucose biosensors, how DNA and semisynthetic biorecognition allow for circumvention of inherent drawbacks of biological molecules, and finally whether biosensors live up to the “hype” and what future trends the authors believes to be of significance for the field.

INTRODUCTION

What are biosensors?

The term “biosensor” was first used by Cammannn referring to electrode-based enzymatic biosensors.[1] The current definition by the International Union of Pure and Applied Chemistry (IUPAC) defines a biosensor in its most fundamental form as a two-component system based on a biochemical reaction of a molecular receptor and a signal transducer.[2] The purpose of a sensor is to assay an analyte with a high degree of sensitivity and selectivity and produce a detectable signal. The construction of the first biosensor is accredited to Clark et al. for their development of a blood glucose sensor using immobilized glucose oxidase.[3]

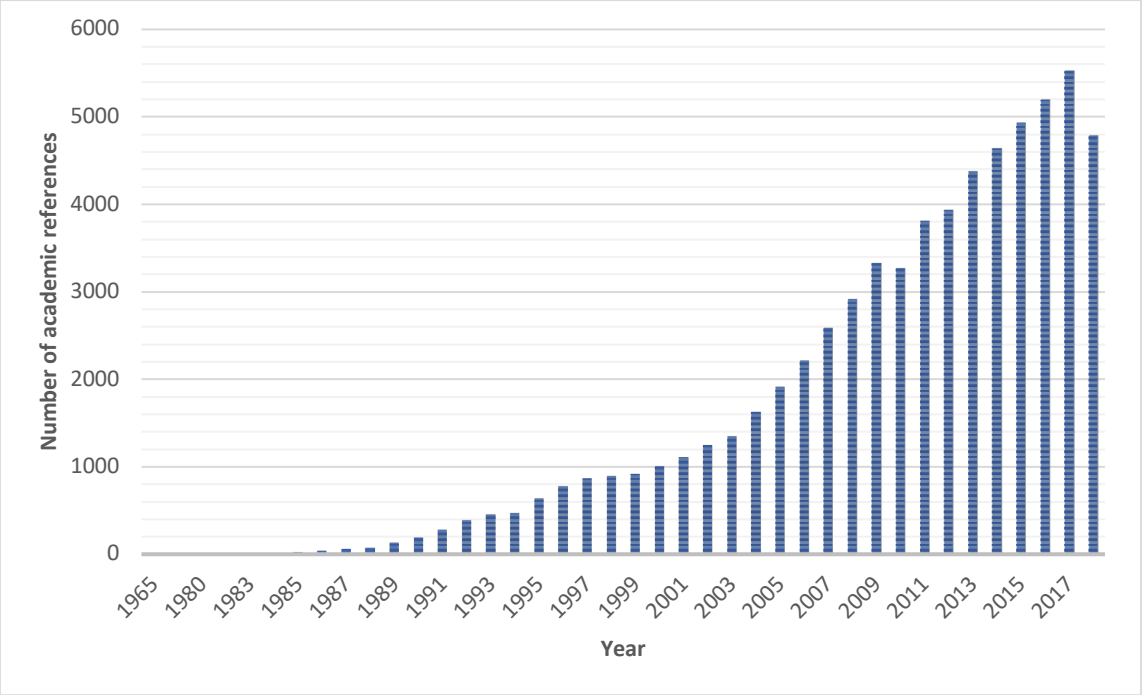

Figure 1 – use of “biosensor” in academic context from 1965-2018, web of science

Since then, interest (Figure 1) and progress in biosensors has dramatically increased along with enabling technologies such as machine manufacturing, nanotechnology, liquid handling and better interaction between life scientists, physical scientist and engineers.[4] Originally, biosensors were found in instruments but since then miniaturization and advances in manufacturing such as printing electronics have led to cheaper and disposable biosensors allowing for on-site detection.[5]

The general structure of a biosensor can be subdivided into two modules: input or biorecognition of the analyte, and signal transduction producing a measurable output signal. Analyte scope is only limited by biochemistry and different classes of biomolecules allow for an extensive range of analytic tasks. The analyte-bio-detector interaction leads to a physiochemical change and results in a discrete or continuous signal, ideally proportionate to the analyte concentration. Often, an amplification step is introduced to increase sensitivity. Broadly speaking, biosensors can be divided into two subtypes: high-throughput, expensive, accurate laboratory machines and cheap, portable, single-use biosensors. They can either offer continues monitoring or are designed to be used once.

Why biosensors?

The immense diversity of biological molecules allows for a vast amount of analytes to be detected, antibodies alone can make more than 10^{12} different antibody molecules even in the absence of antigen stimulation.[6] They offer the potential detection of trace amount of chemicals and especially biological molecules, for example for cancer biomarkers in the pg/ml range.[7] As our knowledge about biology and gene regulation grows, so does our capacity to manipulate organisms and produce recombinant proteins and compounds diversifying the tools available to detect analytes. The suitability of biosensors in comparison to more conventional manners of detection, such as HPLC and GSMS, is dependent on the application. Emerging techniques leading to the generation of semi-synthetic/synthetic biomolecules, such as aptamers, allow for an even wider range of detectable analytes and circumvent some of the issues associated with biological systems (stability, reliability).[8]

Biosensor structure

Performance criteria [4,9]

How is performance of a (bio)-sensor assessed and what are the general characteristics required for a biosensor in order to detect an analyte?

First and foremost a biosensor has to be able to selectively detect the analyte of interest, often in a complex sample (such as blood). A good example of this selectivity is the antigen-antibody interaction being able to selectively bind to the epitope of the antigen. Sensitivity is the minimum amount of analyte which the biosensor can reliably detect. Oftentimes low concentrations in the ng/ml or fg/ml range have to be detected depending on the application. Especially in healthcare, for example cancer biomarkers, limit of detection (LOD) is required to be very low (picogram/ml range).[7]

Resolution and linearity are two important criteria when assessing biosensor capabilities, especially when a detection range of different concentration and not only the presence of an analyte is required. Resolution of a biosensor refers to the minimal change in analyte concentration that produces a detectable signal. Linearity refers to the range of analyte concentration producing a linear signal response.

Lastly, a critical characteristic of a biosensor is its reproducibility and stability. For commercial applications biosensors are required to have a shelf-life of at least several months and are required to function under a variety of ambient disturbances. In order to be accurate and precise, assays need to be able to function reliably and reproducible after storage. Unfortunately, biological systems tend to not exert long-term stable and reproducible behavior, even under laboratory conditions.[5]

Biorecognition

Generally, the type of analyte that can be detected is highly dependent on the type of material employed. Broadly speaking, biosensor mechanisms can be divided into three subcategories: biocatalytic, microbe/tissue-based and bio-affinity.[10]

Biocatalytic: The first biosensor by Clark et al. relied on an immobilized enzyme oxidizing the analyte (glucose) and detecting the resulting oxygen concentration change. Enzymatic detection is the most popular recognition element and either relies on the binding of the substrate or inhibition of the enzyme and is often used to detect metabolites, such as glucose, lactate, urea, creatinine etc. Common enzymes include oxidoreductases, dehydrogenases, and polyphenol oxidases.[9]

Microbe and tissue-based biosensors are complex systems and able to respond to a number of analytes and conditions. They can be engineered to block/induce metabolic pathways upon detection of the target molecule resulting in products leading to changes in optical or electrochemical properties. One of the greatest challenge facing these type of biosensors is the immobilization of the microbes.[11]

Bio-affinity biosensors, such as antibodies and nucleic acids, rely on the natural high affinities of these molecules. Antibodies bind to the epitope of their respective antigens and single strand nucleic acids are able to selectively bind to the complementary strand via hydrogen bonds.[12,13]

Signal transduction

The first biosensor by Clark et al. relied on electrochemical transduction but several other mechanisms have been elucidated since then, most notably: optical, piezoelectric, pyroelectric, magnetic, Förster/fluorescence resonance energy transfer (FRET), and surface plasmon resonance (SPR).[5]

Electrochemical transduction can be subdivided into amperometry, potentiometry, conductometry, and voltammetry. Amperometry relies on detecting the change in current at an applied potential between two electrodes and correlates the change with the concentration of the electroactive analyte (or oxygen). The analyte is reduced or oxidized at the working electrode. This allows for very sensitive measurements down picoamperes. Potentiometry relies on the use of ion-selective electrodes or gas-sensing electrodes to measure the potential when no voltage is applied, for example due to ion accumulation in the presence of the analyte. Conductometry measures the change in conductance of a solution due to consumption/production of ionic species. Voltammetry measures both the current as well as the potential and correlates peak current to the analyte and peak current density to the concentration. The advantage lies in its ability to distinguish several analytes in one assay as well as a low noise proportion.[11,14]

Optical assays rely on the measurement of fluorescence, luminescence and colorimetry. Fluorescence assays are especially prominent in microbial biosensors and in R&D, most notably the green fluorescent protein GFP. Analytes lead to a change of fluorescent molecules (e.g. via promoters regulating gene expression).[15] Luminescence transduction relies on the production/destruction of luminescent molecules (e.g. luciferase).[16] Colorimetric transduction relies on the change of color due to the presence or absence of an analyte.[7]

Piezoelectric/ gravimetric biosensors detect changes due to mass bound on a crystal surface. Piezoelectricity refers to the phenomenon when a voltage is produced upon mechanical stress and vice versa of a material such as anisotropic crystals. Analytes bound on the surface cause differences

in mechanical oscillation, which are a result of alternating voltages or acoustic waves being applied to the crystal. The decay in frequency of these oscillations is proportional to mass bound and can therefore be used to specifically detect an analyte or a change in the mass of the bound recognition molecule (binding of antibody to antigen, pairing of ssDNA to its complementary strand…).[17]

Pyroelectric materials generate voltage when heated or cooled due to a change in polarization caused by temperature corresponding shift of atom positions within the material. Presence or absence of the analyte leads to changes in temperature and is detected electrically.[18]

Magnetic biosensors usually involve magnetic nanoparticles bound to biorecognition elements interacting with the analyte of interest. Alternatively, the analyte can also be labelled magnetically and interaction with biorecognition module is recorded. As a result, corresponding changes in the magnetic field are detecting.[19]

Fluorescence resonance energy transfer (FRET) involves the local (1-10nm distance) transfer of energy between two chromophores. Excited "donor" fluorophores transfer energy to an "acceptor" fluorophore and as a result causing the detectable release of a photon. Biosensors utilizing FRET either have the analyte labeled with one fluorophore and the biorecognition molecule with another or an analyte causes a conformational change in the biorecognition module leading to a proximity between the fluorophores resulting in FRET.[20]

Surface plasmon resonance (SPR) works by detecting the angle of reflection of a light beam passing through a prism onto a metal sensor. At the resonance angle, light energy is absorbed by electrons (surface plasmons) causing them to resonate. Bound analytes cause a shift in the reflectivity curve due to their interaction with the plasmon, allowing for a label-less detection.[8]

Applications

Overview

Biosensors have applications in the food and agriculture industry, in environmental monitoring, in defense, in research and development, and most notably in healthcare.

The main application in the food and agricultural industry is in quality control and process monitoring. They offer inexpensive and reliable quality control to detect pathogen contamination (E. coli, Salmonella), monitor nutrients (short chain fatty acids, vitamins, sulfites, sugars, etc.) and fermentation parameters (biomass, product formation, saccharification), food quality (taste, texture, aging), toxins (heavy metals) and identify pesticide pollution.[8,10,21]

Environmental monitoring can comprise a wide array of applications ranging from ozone monitoring, eutrophication monitoring, antibiotic and pesticide contamination, heavy metal detection, genotoxic compound detection to endocrine disruptor detection. The clear advantage of biosensors is the cost-effective and simple implementation compared to traditional analytic technologies such as HPLC and GCMS. Portability and on-site detection are critical parameters for environmental monitoring that can be satisfied by biosensors. Efforts to continuously screen for the toxins by implementing sensitive species can also offer means of analyte detection that traditional detection methods cannot.[11,22–25] Environmental detection of antibiotic resistance genes, monitoring of gene drives or invasive species could be envisioned. Combining continuous monitoring systems with i*n vivo* genetic memory could

allow for long-term monitoring of analytes, such as environmental toxins or diagnostically relevant biomarkers.[26]

Military interest in biosensors is mainly directed towards the detection of chemical and biological warfare agents, such as nerve gases (sarin), toxic proteins (ricin) and pathogenic organisms (anthrax). Efforts of developing biosensors to detect various explosives and narcotics have also yielded promising results and widespread implementation. Besides these obvious interests, military funding has also been directed towards the development of biosensors allowing for continues monitoring of key physiological parameters to assess stress levels and improve combat effectiveness of soldiers.[27,28]

Research and development tend to be fields that see early adaptation of innovative technologies. Life science, clinical and industrial research have greatly benefitted from advances in biosensors. Common laboratory techniques are taking advantage of the specific binding of biorecognition molecules (e.g. immunoassays, q-PCR, microarrays…), as well as labeling and recognition of tissues, organelles and molecules, drug discovery, screening of suitable phenotypes in metabolic engineering (FACS), DNA sequencing (Nanopore), and SNP detection all of which have profited from biosensors advances.[8,29–31] Research and development constitute a somewhat special case since the requirements for a biosensor in a lab setting tend to be different from healthcare or on-site detection of pollution. Cost is also less of an influential factor in the adaptation of technologies.[32]

The greatest potential for widespread application of biosensors is in the healthcare industry. Monitoring of key physiological parameters (single-use, cost-effective, home use glucose biosensors) and diagnostics are the most visible areas of biosensor application. Innovative diagnostics of infectious diseases allow for detection in resource-limited settings (Dengue virus, tuberculosis, HIV, Ebola, Avian Influenza virus).[17,33–35] Early stage cancer and other disease diagnosis can be facilitated through the use of biosensors to detect biomarkers characteristic to these illnesses. [7,10,36] The trend towards continuous monitoring represents a significant advantage over traditional means of detection, for example, by using a microbial biosensors engineered for gut long-term detection of inflammation.[37] Currently, the most significant commercial success is the widespread application of glucose biosensors and pregnancy tests. Glucose biosensors alone make up 85% of the global biosensor market and the extraordinary success story allows for a good case study to highlight the challenges and potential of deploying biosensors at scale.[5]

Glucose biosensors

The astonishing success of biosensors for glucose monitoring cannot be explained by scientific innovation alone. Economic factors, converging technologies and the lack of a better alternative have all contributed significantly.

Diabetes mellitus is a major health problem: According to the WHO, 422 million people suffer from it worldwide (8.5% of the adult population in 2014), a number that is expected to increase due to aging populations, unhealthy diets and lifestyles and population growth. The economic cost of diabetes-related healthcare has been estimated to be 827 billion US$. Two types of diabetes are most common, type 1 being an autoimmune disease characterized by a lack of pancreatic insulin production and therefore high blood sugar. Type 2 is a result of the body's ineffective use of insulin. A majority (~90%) of diabetes cases are of type 2, which has been shown to be associated with lack of physical activity, bad diets, obesity and sedentary lifestyle as well as age. The 1.5 million diabetes-related deaths in 2012 tend to disproportionately affect low- or middle-income countries lacking sophisticated healthcare systems. Risks of adverse effects on health increase with late stage diagnosis. Effects of

imbalances of blood glucose include seizures, strokes, loss of consciousness, amputations, heart-, kidney-, nerve- and eye damage.[38]

Therefore, in order to effectively manage and diagnose diabetes, it is crucial to monitor blood glucose levels. This detection needs to be simple (home diagnosis by patients), precise, cheap and stable (shelf-life), criteria that favor biosensors over traditional detection methods. Which is why the glucose sensor market, according to Grand View Research Inc. is estimated to be worth over 15 billion US$ in 2015, is dominated by biosensors.

The first biosensor by Clark et al. assayed glucose concentration by measuring the change in oxygen concentration caused by immobilized glucose oxygenase catalyzing the oxidation of glucose. Iterations of the original design relying either on measurement of oxygen or hydrogen peroxide (formed as by regeneration of cofactor FAD+) are still in use today and are classified as 1st generation sensors. Limitation of this approach include the restricted solubility of oxygen in biological fluids and interference of endogenous electroactive species with the detection process. Second generation glucose biosensors replace oxygen with non-physiological electron acceptors (redox mediators), most current commercial biosensors apply similar approaches. 3rd generation glucose biosensors are based on the direct transfer of electrons between enzyme and electrode, avoiding toxicity issues of 2nd generation redox mediators.[39]

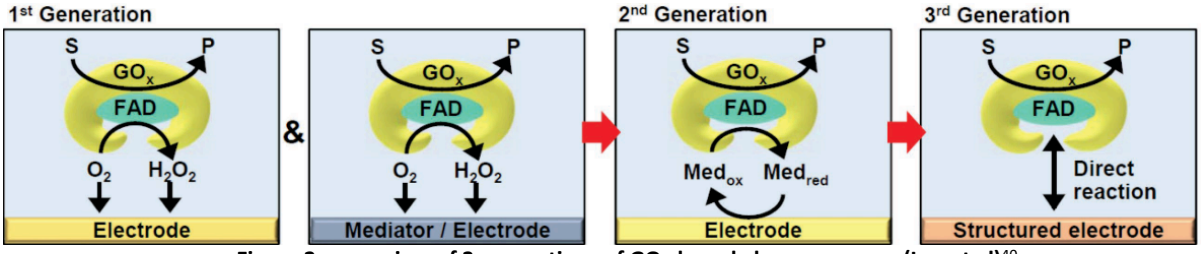

Figure 2 – overview of 3 generations of GOx based glucose sensors (Lee et al)[40]

The economic demand and the supply of biosensor innovations drove the commercial success of glucose biosensors

Patients need point of care devices that are simple to use and effectively offer a therapeutic strategy to maintain salubrious blood sugar levels. To that end, machine manufacturing was able to satisfy the demand of billions of disposable sensors per annum. Printing electronics reduced the cost of biosensors to ~6 US cents per strip when produced in quantity. Together with advances in sampling techniques and consumer accessibility (only µl of sample required per measurement), by the 1990s the stage was set for a wide implementation of glucose biosensors.[5,39,41]

However, one remaining fundamental flaw of the current state of glucose biosensors is the lack of continuous monitoring. Current point of care devices require the patient to periodically puncture the skin, extract a small quantity of blood and analyze it on a disposable strip to adjust insulin dosage. Ideally, a device would continuously monitor blood sugar without requiring the use of a needle and subsequently administering the appropriate amount of insulin. Innovative approaches using wearables (glucose-sensing contact lenses, subcutaneous implants) and research into using sweat, tears, saliva or breath as a sample have yielded mixed results and no wide commercial application yet.[5,40,42]

While the exact conditions that led to the success of glucose biosensors might not apply everywhere, lessons regarding the implementation and scaling up of other biosensors can be drawn nevertheless: The huge demand and impact of glucose monitoring paired with the simplicity of sample preparation

for patients, major improvements in manufacturing techniques and the resulting significant cost degression of biosensors were the critical factors of success for large scale adoption.

Nucleic acid biosensors

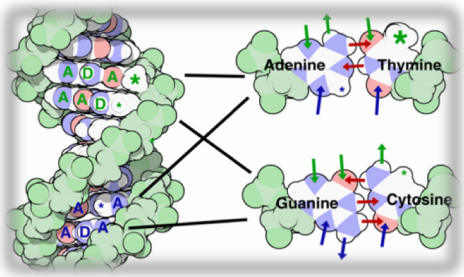

Figure 3 – DNA double helix and base pairing (David Goodsell)

Nucleic acid biosensors are based on the specific pairing of complementary base pairs due to formed hydrogen bonds (Figure 3).[43] This allows for a fast, reliable and sensitive detection of sequence-specific information of small analyte concentrations in environmental, clinical, research, and food analysis. The principal advantage of DNA derived biosensors is the availability of tools to synthesize, quantify and manipulate DNA based structures. Unlike antibodies, DNA biosensors are also reusable. PCR reactions additionally offer signal amplification which significantly increases sensitivity.[44]

The structure of DNA biosensors is essentially based on immobilized oligonucleotides of 20-60 base pairs. Immobilization of the probe is critical, and two methods have been prevalent. Biotinylated DNA probes can be attached by exploiting the strong biotin-avidin interaction on the electrode surface. The other method uses thiolated DNA, which is covalently bound onto gold transducers via alkanethiol-based monolayers, termed SAM (**s**elf-**a**ssembled **m**onolayers).[31]

Analyte detection is facilitated by hybridization to complementary sequences which is often inferred indirectly via labels. For example, an increase in current is detected due to redox indicators recognizing hybridized dsDNA molecules.[31] Signal transduction is versatile and application dependent. Hybridization can lead to detectable changes in mass, optical or electrical properties or milieu pH. Electrochemical DNA biosensors allow for rapid response times and high sensitivity. Piezoelectric DNA biosensors have also been engineered relying on a change in oscillatory frequency caused by hybridization of DNA strands.[17] SPR has also proved to be a reliable signal transductor. Optical transduction methods rely on labels detecting hybridization and changing optical properties of the biosensors, for example via intercalating fluorescent dyes, and are most prominent in research applications. [45]

Generally, detection can either be indirect (label based; fluorescence, radioactivity etc.) or direct (label-free). One label-free way of detection is the measurement of changes in conductance of polymers bound to the DNA probes.[31] The advantage of label-free detection is the reduced detection time and cost and that no interference of the labels with the detection occurs (steric hindrance).

DNA biosensors have found wide application in the sequence specific detection of infectious diseases such as avian influenza virus, vibrio cholerae, HIV, or environmentally problematic species such as the algae microcystis aeruginosa.[34,35,46,47] DNA biosensors can in principle detect every DNA sequence and therefore also all organisms as long as their DNA is accessible, even GMOs and biowarfare agents.[27,48] Besides the monitoring of organisms, DNA biosensors already see vast application in health and life sciences. They can detect mutations in clinically relevant genes, for example p53.[29,49] DNA biosensors can be used to detect a single sequence of interest or be scaled up, in the form of microarrays allowing for the simultaneous assaying of thousands of sequences, usually by immobilizing a large variety of oligonucleotides on a glass, plastic or silicon support structure and labelling them. Hybridization-based detection and analysis can be automated and allows the researcher to extract a significant amount of information out of a sample. Most microarrays use fluorescence for signal transduction but SPR, enzyme labelled, colorimetric, Raman scattering spectroscopy and enzyme-based methods have also

been engineered with success. These microarrays have found widespread application in healthcare and life sciences. By using a reverse transcriptase processing step, RNA sample analysis can also be included.[50]

Nucleic acid biosensors allow for detection of complementary sequences and progress in scaling (microsensors) and sensitivity (PCR) have made them a valuable tool in healthcare and life sciences. Several efforts have been made to improve upon the scope of detection and the stability by resorting to semi-synthetic design of nucleic acids to expand the scope of detection as well as improve the performance in biosensors.

For example, engineered peptide nucleic acid (PNA) are a modified DNA molecule where the sugar-phosphate backbone is replaced by a pseudopeptide. PNAs have been shown to bind with higher affinity and specificity to the complementary DNA/RNA strain. Mismatches in a PNA/DNA duplex have a much more destabilizing impact on the structural integrity when compared to a DNA/DNA duplex. This allows for a significantly improved specificity when determining SNPs.[51] PNAs have seen wide applications in drug discovery, analytical chemistry, gene repair, and diagnostics and can showcase the advantages of integrating semi-synthetic design solutions to improve upon existing biosensors.[52]

Not only do these semi-synthetic approaches offer ways to improve the performance and stability of biosensors but they can also increase the scope of detectable analytes. Nucleic acids cannot only bind to their complementary sequence but can catalyse reactions and bind ligands. One notable example are aptamers, short (20-60 nucleotide) ssRNA or ssDNA molecules that can bind various target molecules. Generation of large varieties of aptamers is cheap (compared to antibodies) and can be performed in a high-throughput fashion. They also require less sample, are non-toxic and non-immunogenic and can inhibit target enzymes, which are qualities especially relevant for *in vivo* diagnostics and therapeutics. They can be conjugated with toxic or radioactive substances and allow for local concentration of these substances at target sites (e.g. tumor).[53] Another interesting use of aptamers are riboswitches. Riboswitches are small RNA elements allowing for ligand-dependent gene control and therefore have a significant potential for application in biosensors and biotechnology. Currently research is focusing on the expansion of new aptamer domains available for riboswitches and novel expression modules, but so far riboswitches represent a useful tool to engineer ligand dependent transcriptional biosensors.[54]
In contrast to antibodies, the aptamer design and production pipeline is significantly cheaper and can be automated to a large degree. **S**equential **E**volution of **L**igands by **EX**ponential enrichment, or SELEX, is an iterative design process leading to the generation of aptamers capable of binding target molecules with a high degree of specificity and selectivity due to their tertiary structure. Randomized libraries of $10^{14\text{-}18}$ oligonucleotides are tested for binding to the target molecule, successful candidates eluted, PCR amplified and subsequently subjected to another round of SELEX. The process can also be modified to select for enzymatic activity. Several cycles of this yield aptamers with a high degree of specificity. [55] This process offers a production pipeline scaling and expanding the already vast amounts of detectable analytes and allowing for biorecognition of toxic compounds.

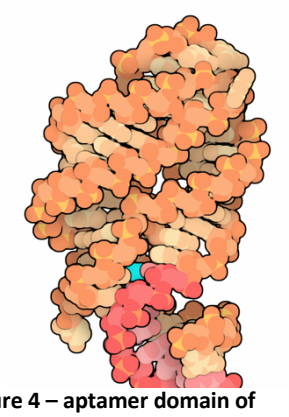

Figure 4 – aptamer domain of guanine riboswitch (David Goodsell)

While RNA aptamers offer a greater structural diversity than DNA aptamers, they are also significantly more unstable and degrade easily. Attempts to improve stability, such as engineered resistances to exonucleases, have led to the first FDA approved aptamer therapeutics (Macugen) for treating age-related macular degeneration. Therapeutic applications have struggled with controlling the pharmacokinetics, cross-reactivity, and renal excretion of aptamers in patients.[56] Aptamer microarrays for drug discovery and diagnostics have yielded more applications.

Given the apparent advantages of aptamers (cheap, existing production pipeline, specificity, scalability and automation, a wide array of detectable analytes) and semi-synthetic design strategies, why is the share of aptamers in biosensors and therapeutic devices relatively low? First off, clinical diagnostics and therapeutics require a significant financial commitment (for example for clinical trials).[57] The first monoclonal antibody was developed in 1975, the first antibody based drug 11 years later and the second antibody based drug 18 years after the first monoclonal antibody. Aptamers and semi-synthetic biosensors are relatively novel developments and require time to penetrate markets and establish themselves. Improvements in performance and applicability together with the increased demand for biosensors will give biosensors a competitive advantage over traditional detection methods and help establish them commercially.

Conclusion

The interdisciplinary development of biosensors exploiting the biorecognition benefits of biological systems, miniaturization advantages of nanotechnology, design philosophies of engineering and data analysis provided by computer science offer promise in disrupting analyte detection in healthcare, life sciences, and analytical chemistry.
The key advantages of biosensors over traditional detection methods are their high specificity, wide range of detectable analytes, small sample (and reagent) volume, re-usability, cheap production and their miniaturization. Biosensors allow for easy and user-friendly detection and do not necessarily require a trained professional and expensive instrument to operate.[58] Due to the large required initial high-risk investment for a biosensor to be developed into a mature consumer-grade product, commercial penetration of biosensors will most likely be in high-demand markets in excess of a 100 million USD. [5] As production cost deceases and performance increases, biosensors will become competitive in other smaller markets.
Whether a biosensor or a more traditional detection mechanism is appropriate is highly dependent on the application. Expensive, high-throughput, laboratory biorecognition instruments are of interest for drug development, metabolic engineering and detecting a variety of industrially relevant analytes. These kinds of machines rely on the broad potential of bio-recognizable analytes but also have to compete against traditional methods such as chromatography and mass spectroscopy. Both will, for the foreseeable future, have their place in the detection of analytes. Bulky mass spectroscopy and chromatography instruments cost thousands of dollars and are difficult to operate and maintain. In contrast, biosensors can be simple to operate and cheap to produce and their production is scalable.
The printing electronics revolution has reduced cost and throughput of production, allows for mass produced, consumer friendly, single-use biosensors. I believe the greatest potential for commercial application lies in over-the-counter personal bio-diagnostic and monitoring devices.

Analysis of key metabolic, genetic and physiological parameters by the patients can be enabled by biosensors that do not require a trained professional to operate. Even if these home diagnostic devices do not offer the same performance as a large, expensive, high throughput device, they can address a different market. A patient can self-test for cancer biomarkers, risk factors, therapeutically relevant parameters, sexual diseases, parasites and other illnesses. This decentralized diagnostic strategy can capitalize on weaknesses in countries with poor healthcare infrastructure and reduce the burden on healthcare institutions. For example, off-grid cell phone based biosensors can assist HIV detection in a decentralized manner.[59]
Patients can monitor themselves and use accessible bioinformatics tools to aid in the analysis. The case study of glucose biosensors demonstrated that consumer friendly biosensors can reach wide implementation and acceptance, given the right conditions. As we begin to unravel more and more

risk factors for diseases, so will our capacity to recommend suitable therapeutics. The rise of theranostics, the combination of specific targeted therapy based on specific targeted diagnostics, will also contribute to the demand for biosensors. Additionally, as our methods for analyzing big data sets improve, so will our demand for data collection.[60] More data, not only on patients seeking treatment but also on healthy individuals, will increase data sets and likely lead to improved diagnostics.

Ultimately, continuous monitoring offers benefits that single-use biosensors cannot. Imagine a diabetes patient not having to worry about their blood sugar level but a sensor and insulin pump automatically regulating it. This would have a significant impact on their quality of life. Of course, for that to become common practice would require a new level of sophistication of implant devices, biological stability and an immensely reliable and precise biosensor. Not having to manually test for an analyte would not only be advantageous in health care but also in other sectors.

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