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Thirty-Fifth Anniversary of the Optical Affinity Sensor for Glucose: A Personal Retrospective

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Abstract

Since 1962 when Clark introduced the enzyme electrode, research has been intense for a robust implantable glucose sensor. An alternative "optical affinity sensor" was introduced by Jerome Schultz in 1979. The evolution of this sensor technology into a new methodology is reviewed. The approach integrates a variety of disparate concepts: the selectivity of immunoassays—selectivity for glucose was obtained with concanavalin A, detection sensitivity was obtained with fluorescence (FITC-Dextran), and miniaturization was achieved by the use of an optical fiber readout system. Refinements of Schultz's optical affinity sensor approach over the past 35 years have led to a number of configurations that show great promise to meet the needs of a successful implantable continuous monitoring device for diabetics, some of which are currently being tested clinically.

Keywords

glucose, glucose sensor, affinity, fluorescence, optical sensor, fiber optics

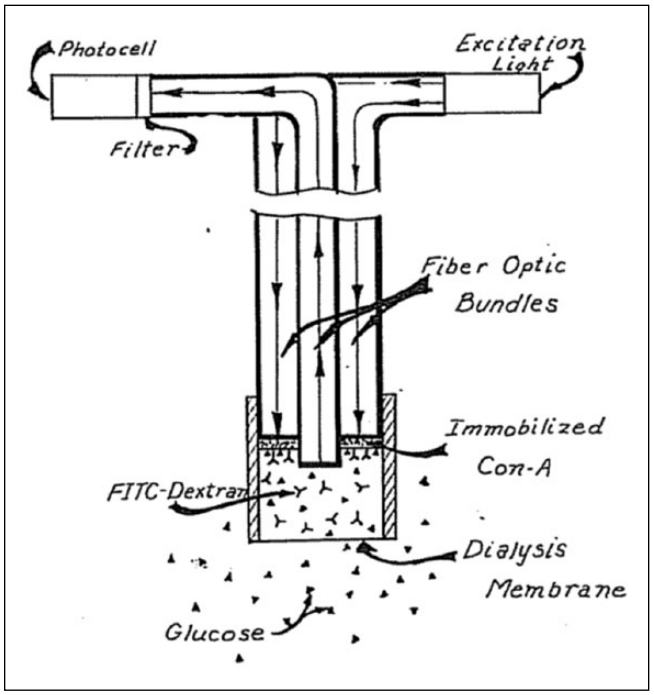

Figure 1. Schematic diagram of a fiber-optic affinity sensor for the measurement of glucose (not to scale). Increasing the concentration of glucose in the external solution, increasing the concentration of glucose in the sensor element. Fluorescent dextran is displaced from the immobilized Con-A and a greater emission intensity is measured.
Source: John Wiley

The article "Affinity Sensors for Individual Metabolites"[1] by Schultz and Sims in 1979 was to my knowledge the first publication that demonstrated the concept of constructing biosensors based on the principles of immunoassays and optical detection. An illustration of how this principle could be implemented into a sensor was shown in Figure 1 of this article and reproduced here.

This preliminary concept was fully evaluated in a single optical fiber glucose sensor system described in detail in a 1982 publication.[2]

The relevance of this work has become apparent in recent years with at least 2 clinical trials under way[3-5] and a recent optimistic review of optical methods by Klonoff.[6]

The impetus for my involvement in glucose monitoring started with a vision of physicians at the University of Michigan who anticipated the advantages of a regulated insulin infusion system for the treatment of diabetic patients. They were confident that the technology for reliable insulin infusion systems could be readily developed, but the technology for the continuous monitoring of glucose was the weak link. I was challenged to develop a method for reliably monitoring glucose continuously. During this period I was

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working with these physicians to evaluate biomaterials for NIH's Artificial Heart Program.[7]

As a biotechnologist I was aware of the Clark oxygen and glucose sensors based on enzymes and electrochemistry.[8] I visited Dr Clark to gain some of his insights on sensor technology. Clark's concept of isolating the detection system from the sample fluid by a semipermeable membrane was a key element that directed my thinking for a new glucose sensing technology. Of course, Clark's breakthrough technology was the basis for hundreds of new sensors—sometimes termed "enzyme electrodes."[9] A key feature of using enzymes in an analytical device for samples containing many analytes is the inherent specificty of enzymes, obviating the need to for separation techniques, such as chromatography, before making an assay.

However, there are some characteristics of enzyme-based sensors that can lead to issues if the sensor is used as an implanted device. One issue is the fact that enzyme-based sensors consume the analyte. This may not be an issue if the sensor is used in a flowing fluid (blood stream) or one that can be mixed. However, if placed in a stagnant environment (eg, implanted) the analyte tends to be depleted in the region directly in contact with the sensor. Through my involvement with the Artificial Heart Program I was aware of the tendency for capsule formation around implanted devices and that this behavior could lead to deterioration of the signal from an enzyme-based sensor. This concern led me to look for an alternative approach that had selectivity similar to enzymes without the consumption of the analyte. In addition to the selectivity element of a sensor the choice of the detection component is a critical feature for sensor sensitivity.

At that time my wife, Jane Schultz, was conducting research in the field of immunogenetics and through various conversations I became aware of the prevalence of immunoassays in biological research. A key feature of immunoassays is their extreme degree of specificity with appropriate selection of the antibody as demonstrated by the pioneering work of Berson and Yallow[10] for the measurement of insulin in body fluids. Another property of immunoassays is the fact that the binding reaction between antibody and antigen is reversible, and thus the antigen (analyte) is not destroyed in the process.

Typically, to achieve high levels of sensitivity in immunoassays, antibodies with high binding constants (avidity) of the antigen-antibody complex are sought. Because of these high binding constants the dissociation rates of the complex are slow (almost irreversible for practical purposes), and many immunoassay procedures include a step to separate the free and bound labeled analog antigen. However, for a continuous glucose sensor, rapid reversibility of the binding reaction is critical to be able to follow increases and decreases in analyte concentration.

At that time my search of the literature for an antibody to glucose was fruitless, but I did come across the use of lectins for agglutination studies.[11] Fortunately for me, Irwin J. Goldstein (an expert in lectin biochemistry) was a faculty member at the University of Michigan. I met with Prof. Goldstein to find an appropriate lectin to use as the recognition element for my proposed glucose sensor, and he suggested that we explore concanavalin A (Con A) for this application. His selection of Con A was based on the fact that the affinity constant for glucose binding to Con A was in the millimolar range,[12] and this is in the range of the concentration of glucose in blood. Furthermore, he indicated that the kinetics of association-dissociation would be very rapid in relation to diffusional processes.

The next important consideration was the selection detection method for measuring the extent of glucose binding to Con A. Previously I had been studying oxygen transport in blood and muscle as facilitated by hemoglobin and myoglobin, respectively, and I was involved in a project to develop a blood oxygenator with Dr D. Lubbers. During visits to Dr Lubbers's laboratory in Dortmund I became acquainted with his development of "optode sensors," a technology for measuring oxygen in tissue based on fluorescence quenching of chemicals encapsulated in beads[13] (a forerunner of "tattoo" sensors?). This innovative, partially noninvasive, technique persuaded me of the power of optical detection methods for monitoring biological phenomena and convinced me to look for an optical method for monitoring the extent of glucose binding to Con A. Around this time I happened to visit NIH and was shown a fiber-optic pH sensor under development by Peterson.[14] This appeared to be the ideal configuration for an optic fiber glucose sensor. Essentially their device consisted of a miniature porous test tube (a hollow dialysis fiber) placed at the end of a bifurcated optical fiber. A key feature of this technology is that analyte has access to the detection chamber by diffusion through the semipermeable membrane, but the active reagents within the chamber can be secured from leaving the chamber in some fashion, for example, immobilization and/or high molecular weight.

All these considerations led me to select immobilized Con A and FITC-Dextran (a glucose polymer) as the "antibody-antigen" couple for the glucose sensor. There are many ways to implement this technology, one of which is illustrated in Figure 1 above.

After obtaining some preliminary data that substantiated this technology, I submitted a disclosure statement to the office of intellectual property at the University of Michigan. They sent the information to the Battelle Memorial Institute, which served as a consultant to the U of M on patent matters. It was the opinion of Battelle that there was no market for an implantable glucose sensor, and based on this "expert opinion" the U of M decided not to apply for a patent on this technology. However, as this research was funded by a NIH grant, the patent disclosure was also sent to NIH. Officials at NIH decided that the technology was novel and important;

they obtained a release from the U of M and proceeded to file for a patent under the auspices of HEW. With my assistance the; "Optical Sensor of Plasma Constituents"[15] patent was issued to HEW in 1982. Note that the patent was not restricted to glucose because it can be implemented for any analyte-receptor pair. This patent has been cited by about 70 new patents issued since 2013, an indication of the current interest in optical/affinity technologies. I do not know if HEW ever licensed this patent.

Over the past 35 years, many variations of the "Schultz" optical affinity glucose sensor have been devised, some of them recently reviewed by Dr Klonoff.[6] Also, recent positive evaluations in animals and humans provide promising evidence that a clinically robust instrument will soon be available.

My hope is that once the affinity sensor principle has been clinically proven for glucose monitoring, that the method will be adopted broadly for other medically critical metabolites, drugs, and others as anticipated in my original publication and patent.

Abbreviation

Con A, concanavalin A.

Declaration of Conflicting Interests

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References

1. Schultz J, Sims G. Affinity sensors for individual metabolites. *Biotechnol Bioeng Symp*. 1979;9:65-71.
2. Schultz J, Mansouri S, Goldstein I. Affinity sensor: a new technique for developing implantable sensors for glucose and other metabolites. *Diabetes Care*. 1982;5(3):245-253.
3. Dutt-Ballerstadt R, Evans C, Pillai AP, et al. A human pilot study of the fluorescence affinity sensor for continuous glucose monitoring in diabetes. *J Diabetes Sci Technol*. 2012;6(2):362-370.
4. Dutt-Ballerstadt R, Evans C, Pillai A, et al. Acute in vivo performance evaluation of the fluorescence affinity sensor in the intravascular and interstitial space in swine. *J Diabetes Sci Technol*. 2013;7(1):35-44.
5. Müller A, Knuth M, Nikolaus K, Krivánek R, Küster F, Hasslacher C. First clinical evaluation of a new percutaneous optical fiber glucose sensor for continuous glucose monitoring in diabetes. *J Diabetes Sci Technol*. 2013;7(1):13-23
6. Klonoff D. Overview of fluorescence glucose sensing: a technology with a bright future. *J Diabetes Sci Technol*. 2012;6 (6):1242-1250.
7. Schultz J, Goddard J, Ciarkowski A, Penner J, Lindenauer S. An ex-vivo method for the evaluation of biomaterials in contact with blood. *Ann NY Acad Sci*. 1977;283:494-523.
8. Clark L, Lyons C. Electrode systems for continuous monitoring in cardiovascular surgery. *Ann NY Acad Sci*. 1962;102(1):29-45.
9. Gough D, Andrade J. Enzyme electrodes. *Science*. 1973;Apr 27;180(4084):380-384.
10. Berson S, Yalow R. Quantitative aspects of reaction between insulin and insulin-binding antibody. *J Clin Invest*. 1959;38:1996-2016.
11. Sharon N, Lis H. Lectins: Cell agglutinating and sugar specific proteins. *Science*. 1972;177:949-959.
12. So L, Goldstein I. On the number of combining sites on concanavalin A, the phytohemagglutinin of the jack bean. *Biochem Biophys Acta*. 1968;J65:398-404.
13. Lubbers D, Opitz N. The pCO_2/pO_2 optode: a new probe for measurement of pCO_2 or pO_2 in fluids and gases. *Z Naturforsch C Biosci*. 1975;30:532-533.
14. Peterson J, Goldstein S, Fitzgerald R, Buckhold D. Fiber optic pH probe for physiological use. *Anal Chem*. 1980;52(6): 864-869.
15. Schultz J. Optical sensor of plasma constituents. August 17, 1982. USP 4,344,438.