In Silico Modeling of a Long-Term Implantable Continuous Blood Glucose Monitor—
A Joint Investigation by Glucotrack Inc. and TTP

Justin R. Buckland, PhD*; Ilya Tarotin, PhD; Sven Ernst, PhD; Sophie A. Meredith, PhD; Paul V. Goode, PhD; JP Thrower, PhD; Mark A. Tapsak, PhD

*author for correspondence: justin.buckland@ttp.com, TTP plc, TTP Campus, Cambridge Road, Melbourn, SG8 6HQ, UK

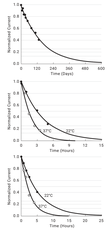
Learn more about Glucotrack

1021-P

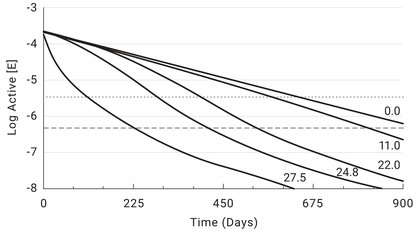
Background:

- The glucose oxidase reaction is well-established for glucose sensing, however, implementing this in an implantable continuous glucose monitor (CGM) is challenging due to deactivation of the enzyme over time and sensor drift
- A severe bottleneck in developing long-term CGMs is that it can take months, or years, to test sensor performance and longevity. In addition, electrochemical testing provides limited information about the complex processes that occur, making it challenging to compare multiple designs
- In 1994, Rhodes et al. developed a strategy for modelling the glucose oxidase reaction over many years by incorporating material transport properties and enzyme decay rates to predict sensor lifetimes.[1] Rhodes predicted a feasible sensor lifetime of ~1.5 years
- In this study, we extend this method to accelerate the development of Glucotrack's implantable continuous blood glucose monitor (CBGM)

Enzyme Decay Routes



Sensor Lifetime Prediction



Objectives:

Key design objectives for the CBGM are summarized below:

Essential requirements

- **Lifetime:** for implantation 2+ years
- **Response time:** to enable automated insulin delivery (AID) automatic meal bolusing

Preferable features

- **Stability:** to minimize calibration over the implanted lifetime
- **Linearity:** to increase accuracy and simplify calibration
- **Manufacturability:** tolerant of expected variations in layer thickness

Acknowledgments: Farah Almagham prepared electrode samples for experimental testing. Ted Peachey performed metrology to determine layer thicknesses.

References: **1.** Rhodes RK, Shults MC, Updike SJ. Predictions of pocket-portable and implantable glucose enzyme electrode performance from combined species permeability and digital simulation analysis. *Anal Chem*. 1994;66(9):1520-9. doi: 10.1021/ac00081a026. **2.** Ribeiro ASF, Ortona O, Tavares MFM, Simões SMC, Prazeres DMMV, Valente AJM *et al.* Binary mutual diffusion coefficients of aqueous solutions of sucrose, lactose, glucose, and fructose in the temperature range from (298.15 to 328.15) K. *J Chem Eng Data*. 2006;51(5):1836-1840. doi: 10.1021/je060061. **3.** Ping H, Bartels DM. Temperature dependence of oxygen diffusion in H2O and D2O. *J Phys Chem*. 1996;100(13):5597-5602. doi: 10.1021/jp952903s. **4.** van Stroe-Biezen SAM, Everaerts FM, Janssen LJJ, Tacken RA. Diffusion coefficients of oxygen, hydrogen peroxide and glucose in a hydrogel. *Anal Chim Acta*. 1993;273(1–2):553-560. doi: 10.1016/0003-2670(93)80202-Y. **5.** Squires T, Messinger R, Manalis S. Making it stick: convection, reaction and diffusion in surface-based biosensors. *Nat Biotechnol*. 2008;26:417-426. doi: 10.1038/nbt1388. **6.** Dou H-S, Khoo BC, Tsai HM. Determining the critical condition for flow transition in a full-developed annulus flow. *J Pet Sci Eng*. 2010;73(1-2):41-47. doi: 10.1016/j.petrol.2010.05.003. **7.** Incropera FP, DeWitt DP, Bergman TL, Lavine AS. External flow. In: Principles of Heath and Mass Transfer. 7th ed. John Wiley & Sons, Inc; 2011. 433-516. **8.** Time-dependent inactivation of immobilized glucose oxidase and catalase. *Biotechnol Bioeng*. 1987;29(9):705-13. doi: 10.1002/bit.260290607. **9.** Cai X, Tanner EEL, Lin C, Ngamchuea K, Fourd JS, Compton RG. The mechanism of electrochemical reduction of hydrogen peroxide on silver nanoparticles. *Phys Chem Chem Phys*. 2018;20(1608-1614. doi: 10.1039/C7CP07492A.

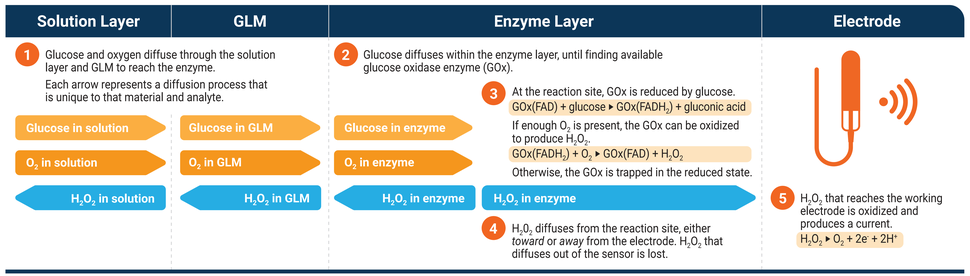
The Challenge:

Glucotrack's sensor uses a working electrode coated with a glucose oxidase enzyme layer and a glucose limiting membrane (GLM).

Sensor performance and lifetime are a combination of numerous interacting processes:

- Analyte and co-factor diffusion
- Reaction rates
- Multiple enzyme states and deactivation rates

Changes to any one of these processes can have complex, and sometimes surprising, implications for the sensor response.



Sensor response and linearity are affected by the balance of glucose and O_2 within the sensor, and the fraction of H_2O_2 that is detected at the electrode surface.

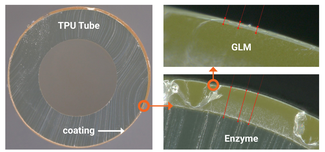
Sensor response time is affected by the rate of diffusion of each analyte through various materials.

Sensor longevity is affected by the concentration of enzyme in various states (ie, resting state, reduced state, or peroxide-complexed) and the respective decay rate for each state.

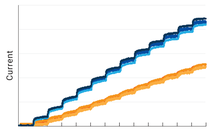
Experimental Methods:

- Sensors were built by dip coating electrodes to deposit each membrane
- Layer thickness was determined by taking cross-sectional slices of the samples and using white-light microscopy
- The sensor current was measured in response to various concentrations of glucose, O_2, or H_2O_2 in stirred beakers
- Response times and steady-state currents for multiple samples were extracted and compared to simulated results

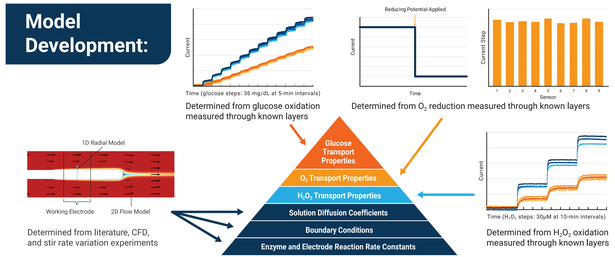
Cross-sectional Slice of Multiple Coated Layers on an Analogue Sample



Example Response to Increasing Glucose Steps; 2 Design Variants



Model Development:



The model is built from the "bottom up" by measuring each process independently, and then combining processes to predict emergent behaviors.

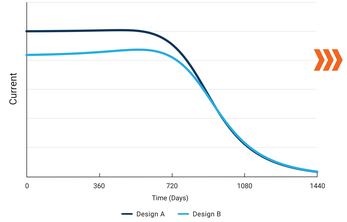
1. Analyze fluid flow and transport of glucose, O_2, and H_2O_2 in solution.[2-7]
2. Identify enzymatic and electrochemical reactions and rates, including enzyme states and decay rates.[1,8,9]
3. Determine transport properties for Glucotrack materials from experiment.

Results & Conclusions:

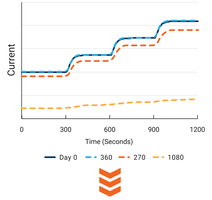
The preferred sensor design provides:

- Lifetime of >3 years
- Response time: <180 seconds
- Stability: <1% change in simulated response for >1 year
- Linearity: close to linear response, managed by 2-point calibration
- Manufacturability: <1% lifetime change in response to 20% layer thickness variation

Simulated Sensor Lifetime



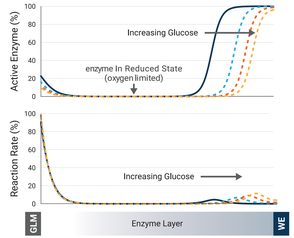
Glucose Step Response Over Lifetime



Sensitivity, Response Time, Linearity

- The model provides valuable insights into implantable CBGM sensor longevity. In silico modeling, coupled with sensor properties derived from in vitro testing, is an important tool for designing successful long-term glucose sensors
- Reaction dynamics and critical analyte concentrations for sensors with different layer thicknesses are understood. In particular, modeling results suggested significant design improvements to improve sensitivity, stability, and linearity

Initial Design



Preferred Design