In vivo glucose sensors modeled as a "source-sink, heterogeneous matrix" transport problem: Is that all there is?

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Tribute: Unlike passive implants, a glucose sensor is a "transport-dependent implant" where the interaction between the material and the tissue, and the tissue itself, impacts sensor performance. Taking the bi-directional interplay between the sensor and tissue into account, my research was profoundly impacted by the seminal work of Dr. James Anderson on the dynamics of tissue-material interactions and the foreign body response. I deeply appreciate the opportunity to honour Dr. Anderson with this presentation.

Introduction: All in vivo glucose sensors are designed to measure blood glucose either directly in the blood stream or indirectly through interstitial glucose. The two sensors that are FDA approved and marketed commercially from Medtronic and DexCom are robust and reproducible devices that that are capable of yielding stable readings for prolonged periods in glucose-spiked, buffered solutions. They have also performed well both animals and humans. However, when a given sensor is placed in vivo it cannot be predicted whether a given sensor will exhibit only minor signal drift, will become profoundly erratic, or somewhere in between. It is also true that when the sensor is removed, lightly rinsed, and recalibrated in vitro it regains its robustness and reproducibility almost immediately. This strongly implicates the metabolically active and dynamic in vivo environment, and not the sensor itself or the biofouling film accumulated at the senor surface, as the source of this behaviour.

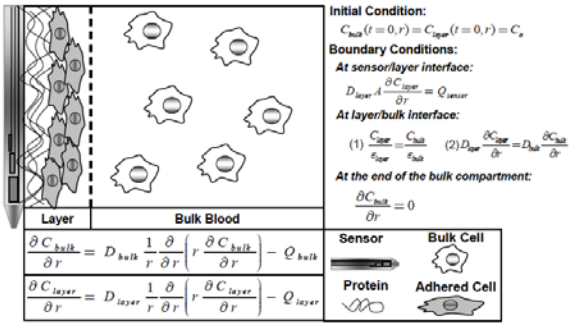

Figure 1: Schematic representation of diffusion through bulk blood and a layer of adsorbed proteins and cells.

Blood Studies: Following on the insights of Klueh et al. on the decay of glucose sensor signals in blood [ref], we adopted blood as a simple living system for testing in vivo glucose sensor response and then characterizing the results using transport modeling. Commercially available sensors (Medtronic Co.) were placed in a PBS solution spiked with a known solution of glucose at 37°C to gather a baseline sensor signal for two hours. Sensors were then moved into one of two different blood treatment categories: (1) whole blood or (2) PPP to see the effects of protein adsorption and cellular adhesion on sensor signals.

To examine whether blood and plasma allow sensors to behave in a stepwise fashion like PBS upon glucose additions, glucose incursions were made to the system. During the 10 hour incubation, blood and plasma glucose concentrations were measured via a OneTouch Ultra home blood glucose monitor. From these readings, enough glucose was added to double the concentration in each. Sensors were then allowed to gather a baseline over six hours and the process was repeated. OneTouch Ultra measurements were made at the beginning and the end of each incursion to see if sensor response mimicked a direct blood glucose concentration measurement.

Modeling: Figure 1 is a cartoon that depicts the sensor, the biofouling layer consisting of a protein adlayer and accumulated mat of cells, and the bulk blood comprised of dispersed cells. Also shown are the governing transport equations. Simulations were performed in MATLAB to examine whether the presence of inflammatory cells proximal to the sensor could create a depletion of glucose with respect to the distance away from the sensor via analyte uptake. Cellular glucose consumption was modeled using Michaelis-Menten kinetics. Red blood cells minimally metabolically active (give numbers) but are the most abundance blood cells; whereas monocyte/macrophages consume glucose at ?? times the rate as RBCs (give numbers) but are ??? times less abundant (give numbers). The participation of other blood cells and platelets were neglected. Therefore the decay of sensor signal Increases in cell number were approximated by increasing the reported maximal glucose uptake rate or V_{max} of macrophages.

Results and Conclusions: The results of PPP studies and modeling clearly show that the adsorbed protein film has a negligible effect as a transport barrier to glucose measurement. It is also clear from the whole blood studies that glucose consumption by leukocytes is the dominant factor in metabolic effects, and that the higher density of cells accumulated in the biofouling had the dominant impact. However, it is also apparent that there are other more minor factors cause the sensor response to differ strictly from the experimentally observed sensor traces in blood. These appear to be ???.