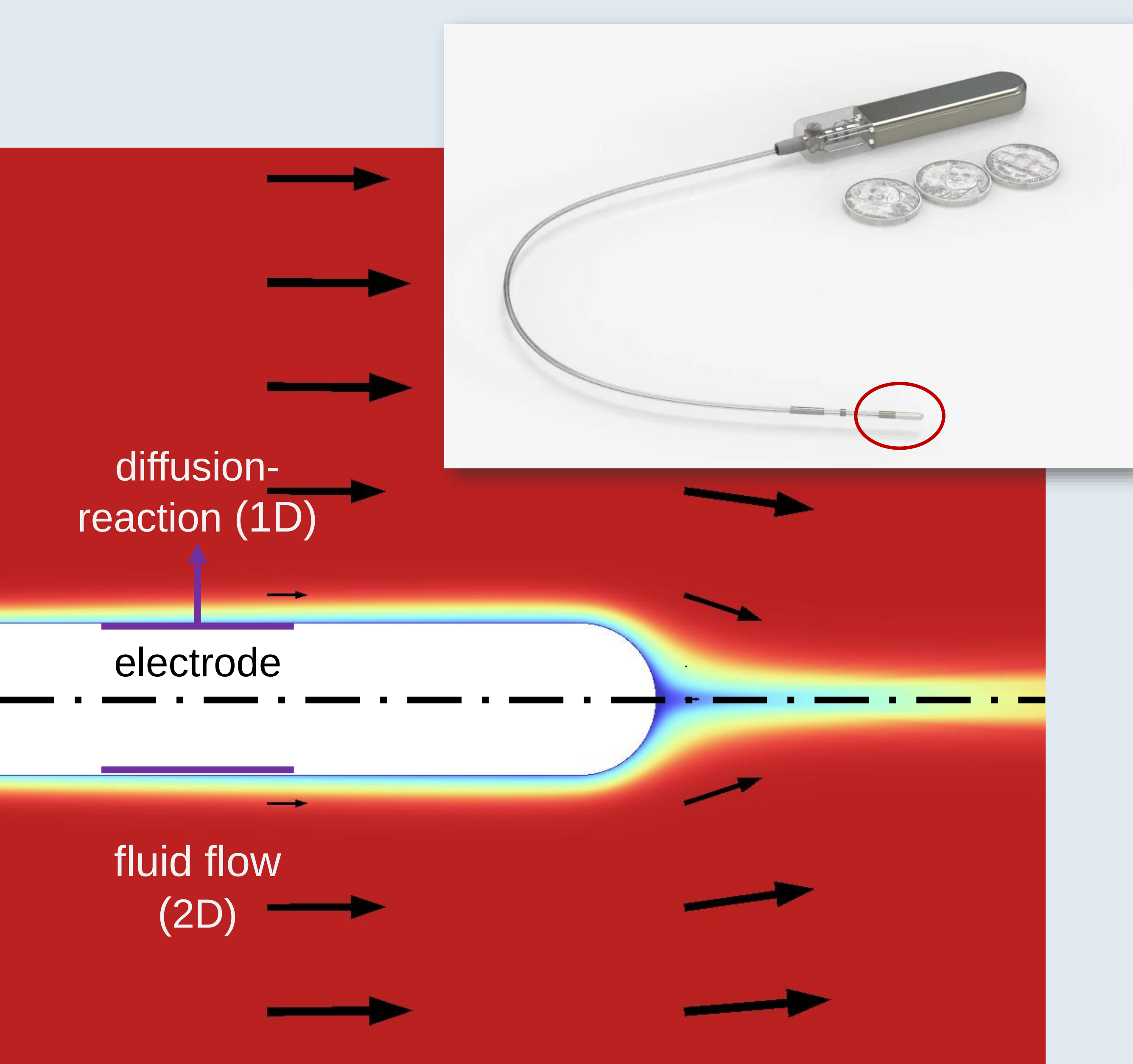




In silico modelling of a long-term implantable continuous blood glucose monitor

Simulations of the internal diffusion and reaction processes that govern glucose sensor performance, and degradation over time due to enzyme deactivation, provide detailed understanding critical to the development of long-term implantable devices.

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Introduction:

Continuous glucose monitors (CGMs) are used to monitor the glucose levels of people living with diabetes, typically in the form of patches worn for 10-15 days. Glucotrack is developing a fully implantable device to measure glucose over multiple years.

Most CGMs use a well-established glucose oxidase sensing mechanism, but developing an implantable sensor is challenging due to deactivation of the enzyme over time and resulting sensor drift. A severe development bottleneck is that it can take months, or years, to

test sensor performance and longevity in the lab. In addition, electrochemical testing provides limited information about complex internal processes, making it challenging to compare multiple designs.

In 1994, Rhodes et al. simulated diffusion, reactions and enzyme deactivation, predicting a lifetime of ~1.5 years.¹ We extend this approach to represent surrounding blood flow, and use it to predict sensitivity, response time and linearity, accelerating development of Glucotrack's implantable continuous blood glucose monitor (CBGM).

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

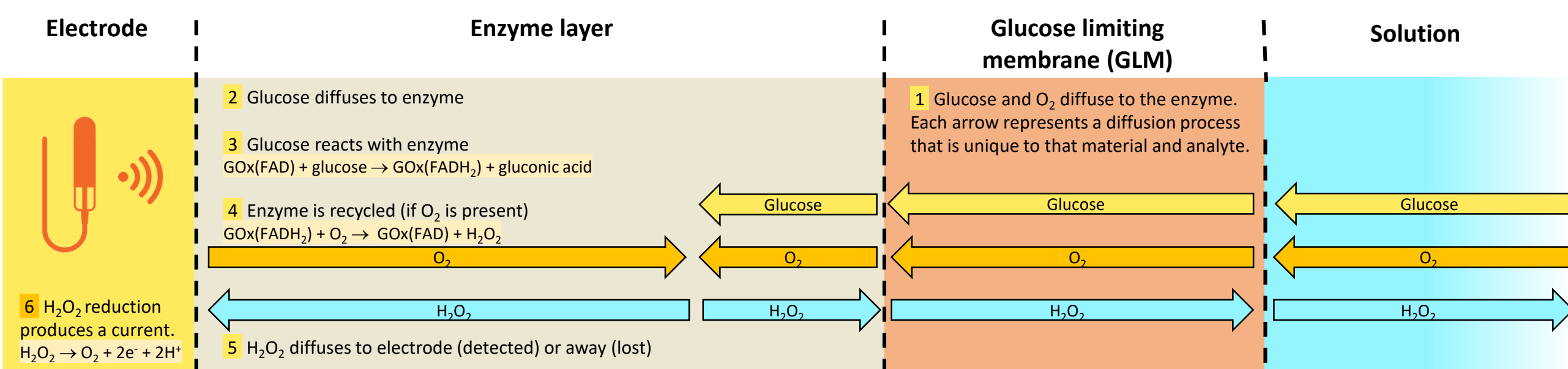
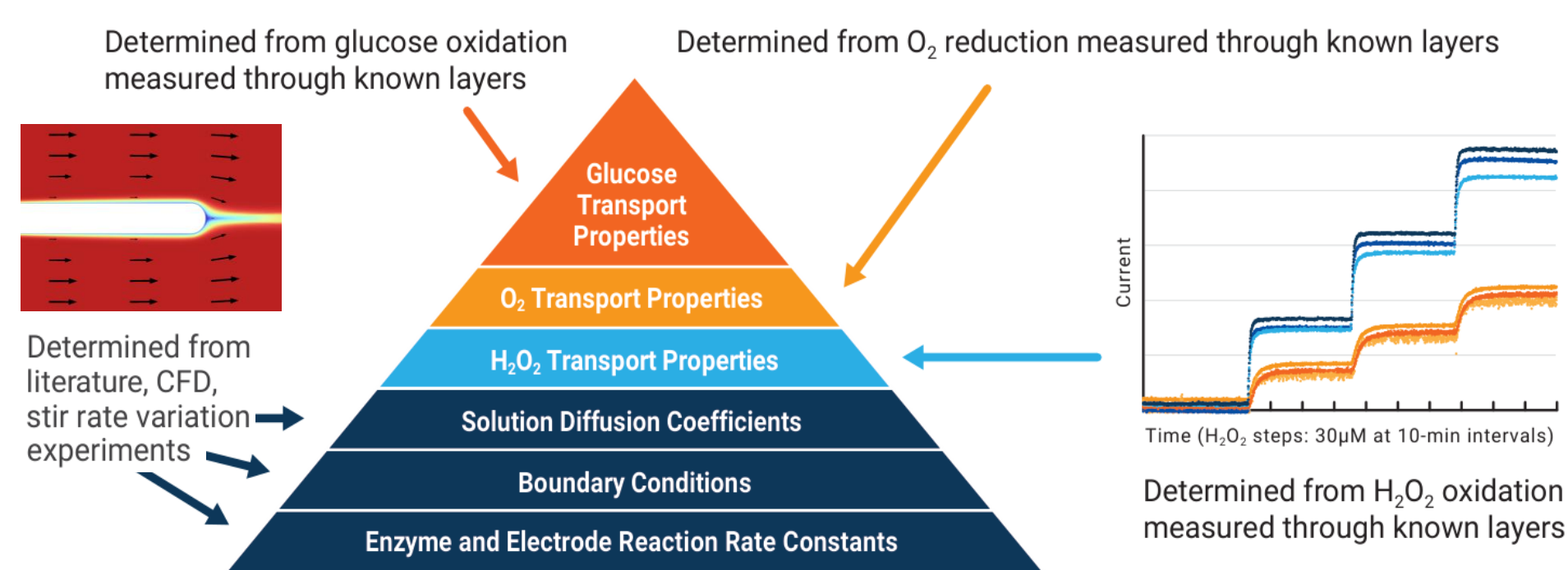


FIGURE 1. Model inputs were derived from experimental tests, CFD simulations and literature to identify transport properties for each species and layer, depletion layer thickness in solution, and reaction rate constants.

Methodology:

A 1D time-dependent diffusion-reaction model was used to enable computationally efficient simulation of the sensor output over life. A three-layer diffusion model with layer-specific diffusion and partition coefficients was combined with reactions in the enzyme layer. Solution layer boundary conditions were chosen to match the bulk concentration and depletion layer thickness for glucose, O_2 and H_2O_2 in the surrounding fluid flow.

The sensor output current was determined from H_2O_2 consumption at the electrode, with fast electrode kinetics representative of the operating voltage.

Linearity and response time were derived from simulated glucose step-response tests, interspersed with long periods at constant glucose concentration to monitor sensitivity. Layer thickness and composition were varied to explore the sensor design space and improve lifetime.

Results:

The preferred sensor design meets key performance requirements:

- Lifetime: >3 years
- Response time: <180 seconds
- Linearity: close to linear response, managed by 2-point calibration
- Manufacturability: <1% lifetime change with 20% thickness variation.

The model provides valuable insights into implantable CBGM sensor longevity. In silico modelling, 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, modelling results suggested significant design improvements to improve sensitivity, stability, and linearity.

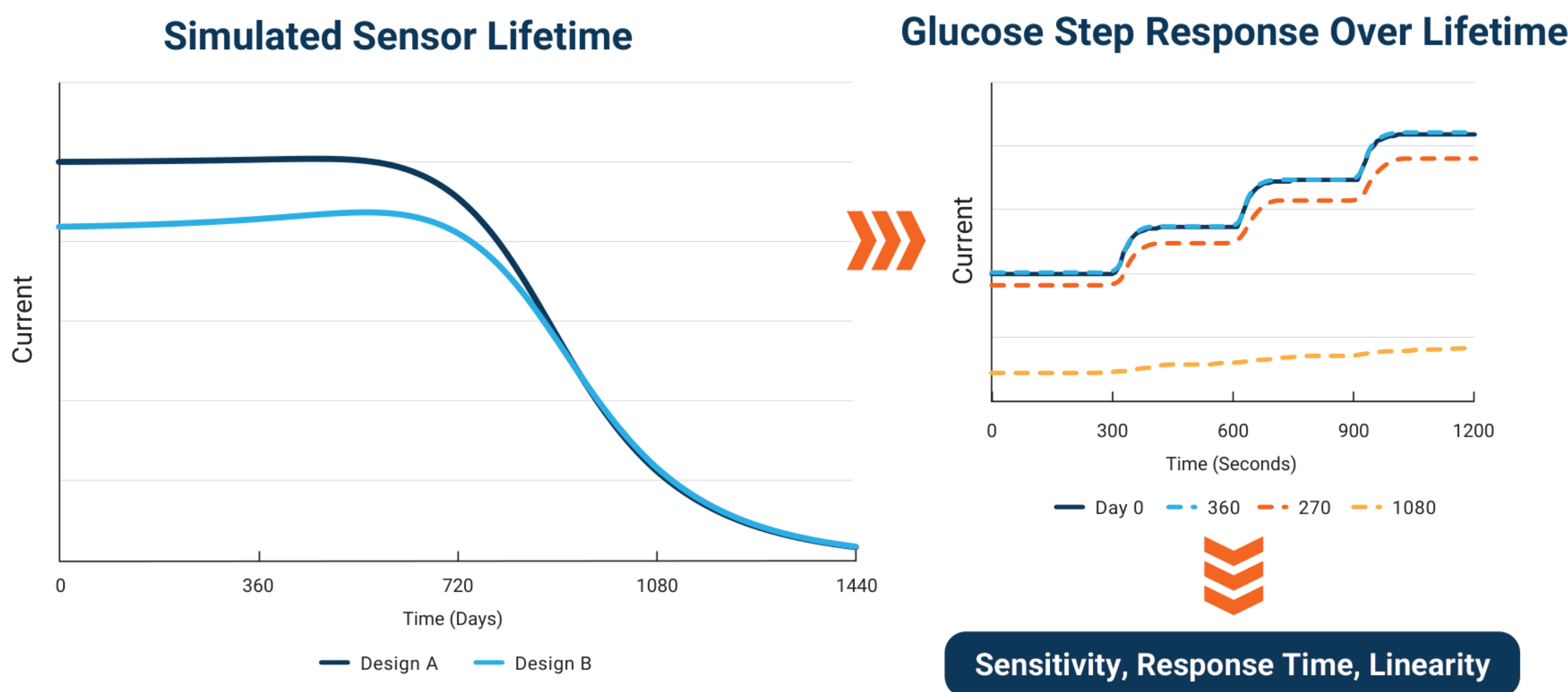


FIGURE 2. Left: simulated sensor output comparing two designs, with stable operation for two years followed by exponential decay as the sensor transitions from diffusion limited to enzyme limited output. Right: linearity and response time are derived from simulated glucose concentration step tests, with increasing response time at end of life.

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