What is your biosensor good for?

We predict the range of biochemical values that you can measure **accurately**.

A model to predict the accuracy of biochemical measurements made with two-state biosensors

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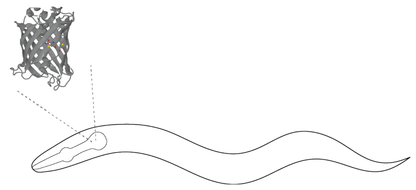
Introduction

Two-state biosensors change conformation and spectral properties in response to a specific biochemical input.

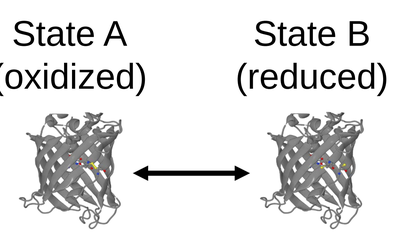
We use the roGFP1_R12 two-state biosensor to make absolute quantitative measurements of glutathione redox potential (E_{GSH}).

Existing two-state biosensors measure pH, [ATP], and more.

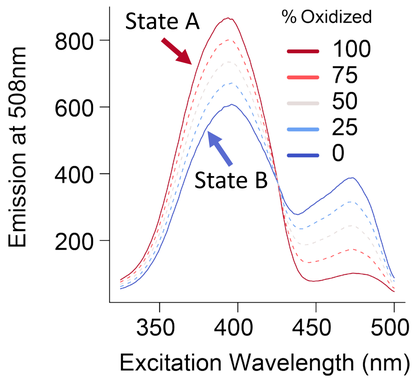
Previous work developed a map between fluorescence ratio (R) and E_{GSH}.



We express a fluorescent biosensor (roGFP1_R12) in the pharynx.



Two-state biosensors change conformation in response to a specific input.



Methods

Error propagation from ratio fluorescence (R) to biochemical measurement (E_{GSH}, pH, [ATP], etc.) was modeled on paper and then simulated in R.

Sensor spectra was collected from literature and email and then digitized.

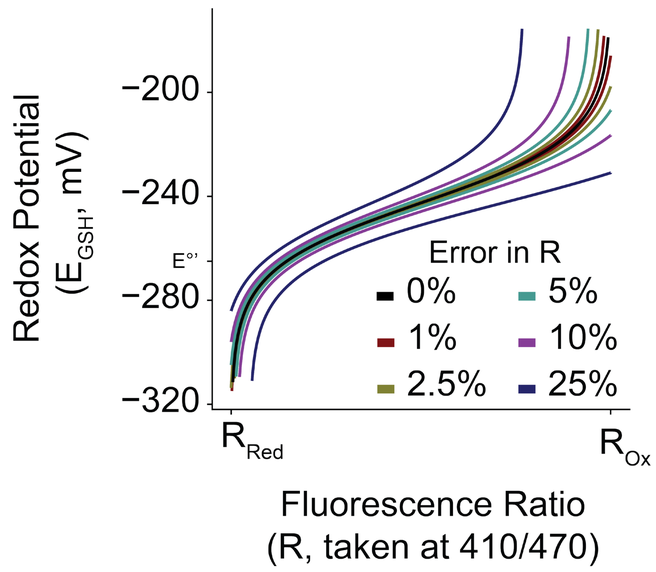
Microscopy errors were calculated retrospectively from fluorescent images accumulated from >6 years of experiments. Timeseries data was fit using a GCV-optimized spline; residuals were error. For non-timeseries data, standard deviations were error.

Web application was built with R Shiny.

Results

Errors propagate from ratio fluorescence into redox potential via a non-linear map that explodes near its edges.

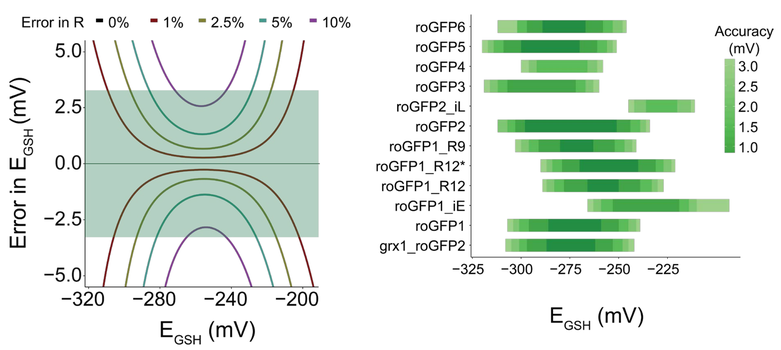
This map allows us to predict the error in E_{GSH}.



The relationship between fluorescence (R) and redox potential (E_{GSH}) at different levels of microscopy error.

Using a constant microscopy error, we predict the ranges of redox potential that roGFP sensors can measure accurately.

Our prediction of well-suited ranges can be applied to most two-state fluorescent sensors.



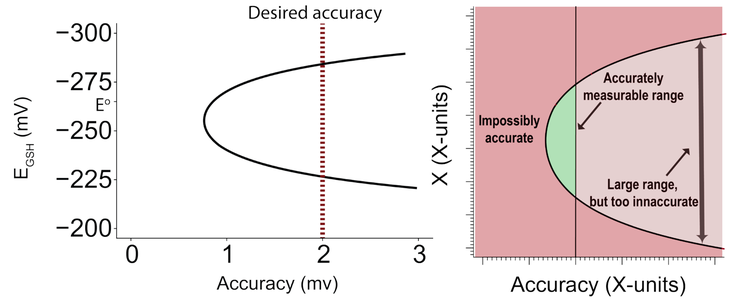
Left: Errors in E_{GSH} for roGFP1_R12. Right: The ranges of E_{GSH} that redox biosensors can measure given empirical microscopy errors.

Discussion

Our framework enables us to:

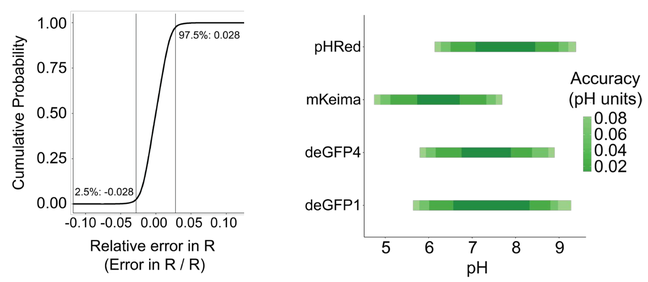
1. Estimate the E_{GSH} values roGFP1_R12 is well-suited to measure.
2. Quantify how much accuracy is changed by optimizing microscopy methods.
3. Identify biosensors best suited for measuring different ranges of E_{GSH}, pH, etc.
4. Reclaim underused sensors.
5. Identify which new biosensors are needed.

To repeat our analysis, we developed an R shiny web application: **https://sensoroverlord.org**.



The map between E_{GSH} and accuracy as a phase plot (left) for roGFP1_R12 (right) in general.

Additional figures



Left: empirical distribution in microscopy error using roGFP1_R12. Right: ranges that two-state pH sensors are well-suited to measure.

(A) $$\frac{F_{Ox}}{F_{Ox}+F_{Red}} = \frac{R - R_{Ox}}{R - R_{Red} + \delta_{\lambda_2}(R_{Ox} - R)}$$

(B) $$\frac{State_A}{State_A + State_B} = \frac{R - R_{State_B}}{R - R_{State_B} + \delta_{\lambda_2}(R_{State_A} - R)}$$

(C) $$E_{GSH} = E'^{\circ} - \frac{RT}{2F}\ln\left(\frac{Reduced}{Oxidized}\right)$$

(D) $$pH = pK_a - \log\left(\frac{[HA]}{[A^-]}\right)$$

Maps from: (A) R to F_{Ox}, (B) R to F_A (C) F_{ox} to E_{GSH}, (D) F_{prot} to pH.

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Take photos!