Steady-State Analysis of a Reversible Covalent Modification Cycle

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ABSTRACT

The properties of biological switches are shaped by competing selection pressures. Switches must be sensitive to their inputs, and their "on" and "off" states should be well-distinguished. At the same time, it is important for switches to exhibit a certain robustness to noise. A simple biological network motif that gives rise to switch-like behaviour is the Goldbeter-Koshland (GK) loop, in which the interconversion of two substrate forms is catalysed by two biased enzymes. In the context of the GK loop, it is possible to conduct a simple algebraic analysis to reveal that the degree of bias of each enzyme is the primary determinant of how switch-like the system is. The same analysis suggests a way that a switch might make itself robust to changes in enzyme concentrations—a trick that may underlie the importance of enzyme bifunctionality.

REACTION NETWORK — Background

In the GK loop, two enzymes, ***E*** and ***F***, catalyse the interconversion of substrates S_0 and S_1. We can summarize the salient features of each branch of the loop using a few numbers that describe how reversible the enzyme in question is and to what extent product rebinding occurs.

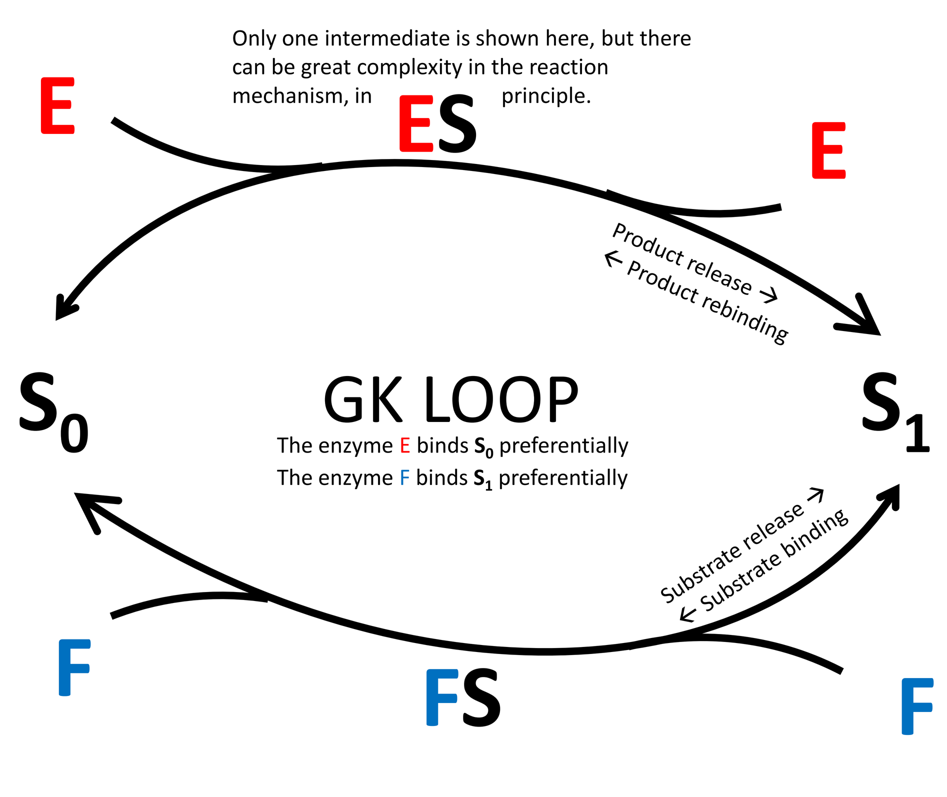


Figure: Schematic of a GK loop with a single intermediate form for each enzyme.

This work uses a mathematical framework laid out in: Y. Xu, J. Gunawardena, J. Theor. Biol. (2012).

TIME EVOLUTION

There is total substrate (S_{tot}) and enzyme (E_{tot} and F_{tot}) conservation throughout.

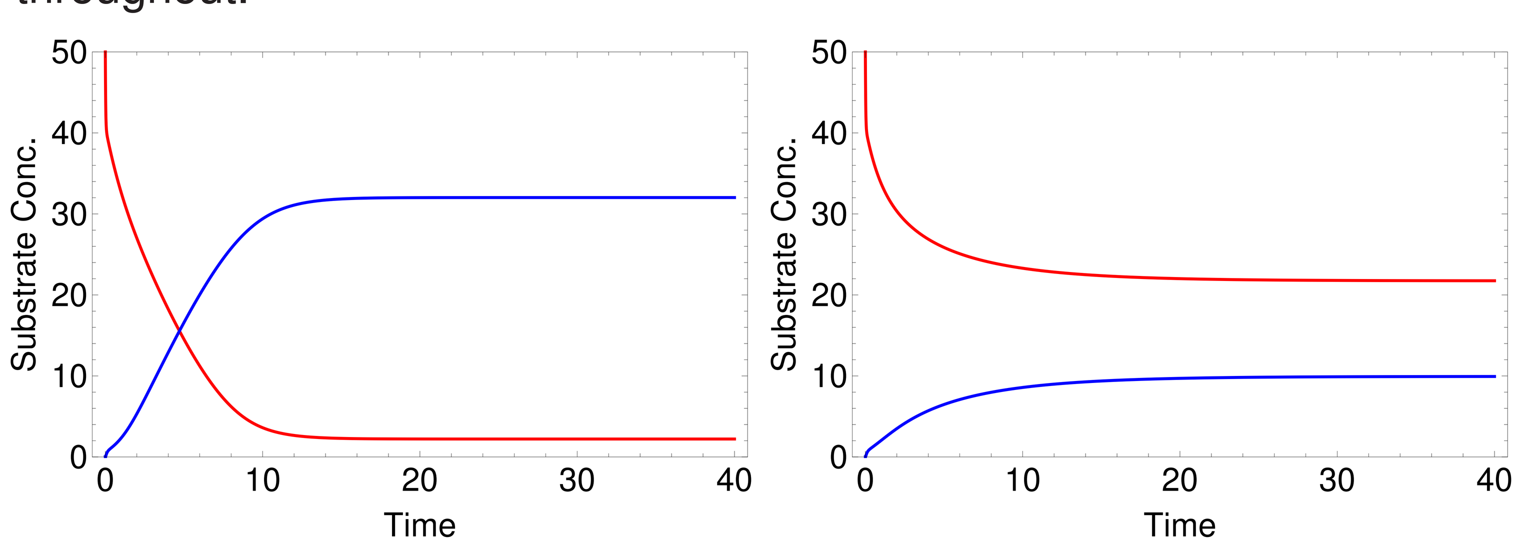


Figure: Depending on the total enzyme ratio and rate constants, either $[S_0]$ (blue) or $[S_1]$ (red), will be more prevalent at the loop's steady state.

STEADY-STATE INVARIANT — Results

The following equality holds at every steady state of the system:

$$f\left(\frac{E_{tot}}{F_{tot}}\right)(\beta u_0 + u_1)(u_0 - \mu u_1) = (u_0 + \alpha u_1)(u_1 - \rho u_0)$$

α, β = measure of prod. rebinding $\quad \rho, \mu$ = measure of reversibility

$$u_* = [S_*]/S_{tot}$$

SWITCH-LIKE BEHAVIOR

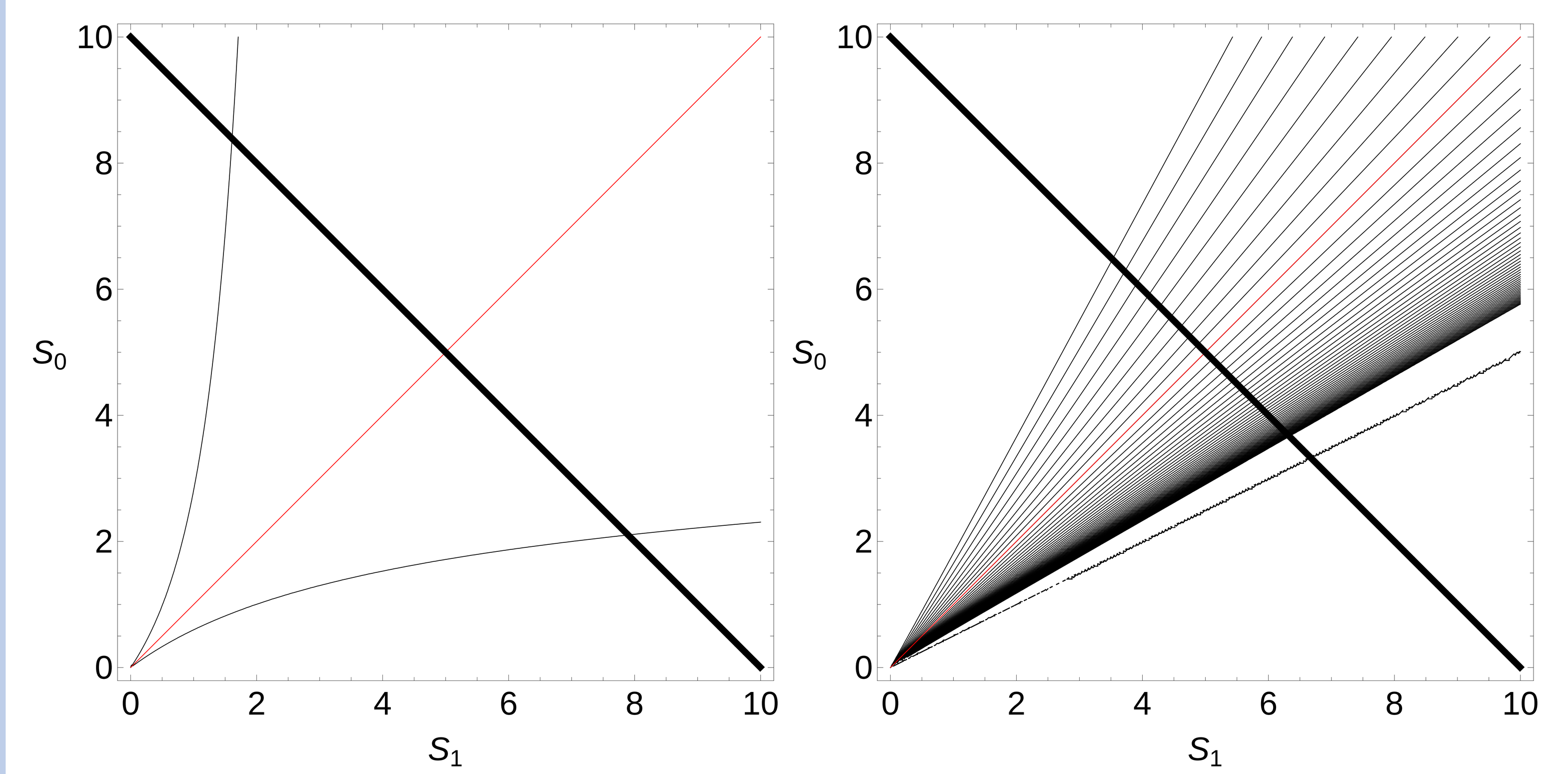


Figure: For each value of the enzyme ratio, the invariant describes a curve in $S_1 - S_0$ space. Combined with substrate conservation (black, diagonal), this completely determines the steady state given parameters and ICs. When the enzymes in the loop are irreversible (LEFT), the invariant sweeps across the whole $S_1 - S_0$ space. Not so in the reversible case (RIGHT), where the range is restricted.

$$\left(\frac{E_{tot}}{F_{tot}}\right) = \frac{(1+\alpha)(1-\rho)}{f(1+\beta)(1-\mu)} \implies [S_1] = [S_0]$$

Sensitivity at the transition point is:

$$\frac{f(\beta+1)^2(1-\mu)^2}{4((\beta+\mu)(1+\alpha)(1-\rho) + (\alpha+\rho)(1+\beta)(1-\mu))}$$

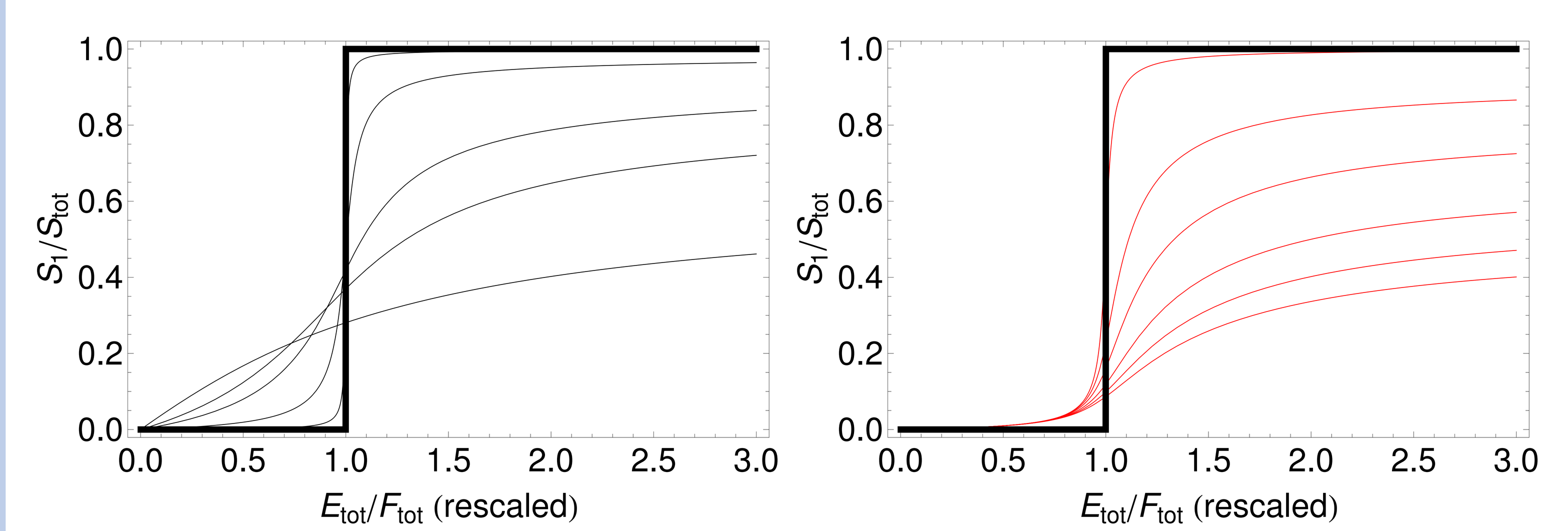


Figure: LEFT: the different curves correspond to increasing values of total substrate. RIGHT: the curves correspond to increasing product rebinding rates, α and β.

SENSITIVITY/DISCRIMINATION

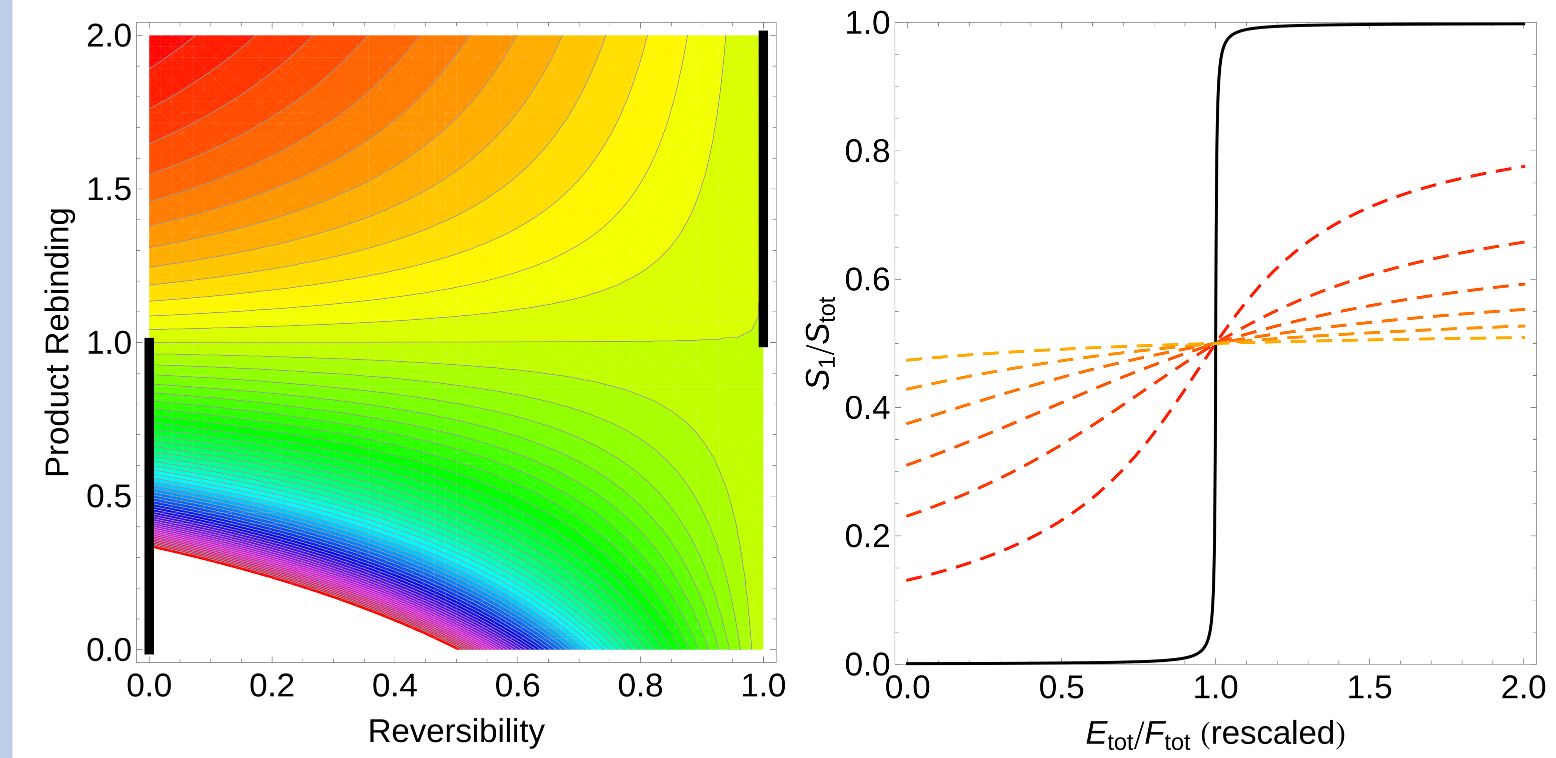


Figure: LEFT: An interplay of the product rebinding rate and reversibility determines the sensitivity of the switch (white = high, red = low). RIGHT: Increasing reversibility not only dulls the sensitivity, but also narrows the range of attainable values of $[S_*]/S_{tot}$

BIOLOGICAL SIGNIFICANCE

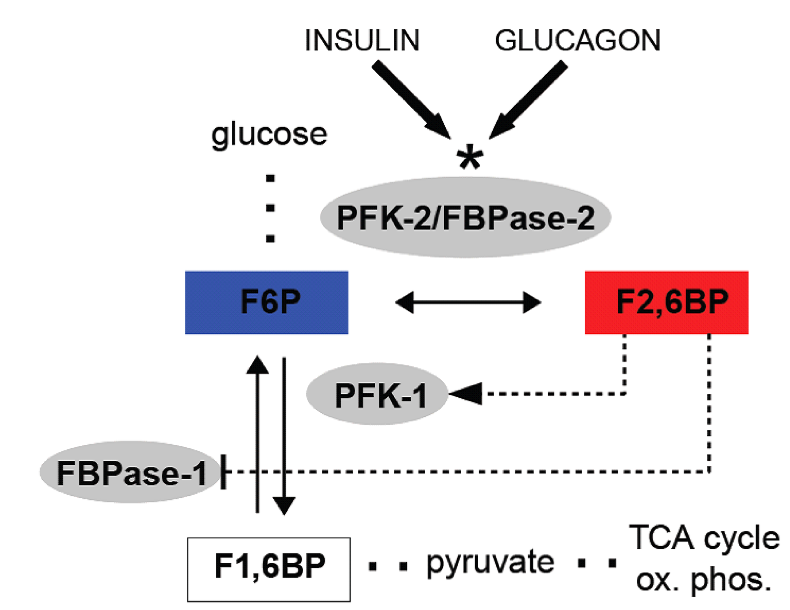
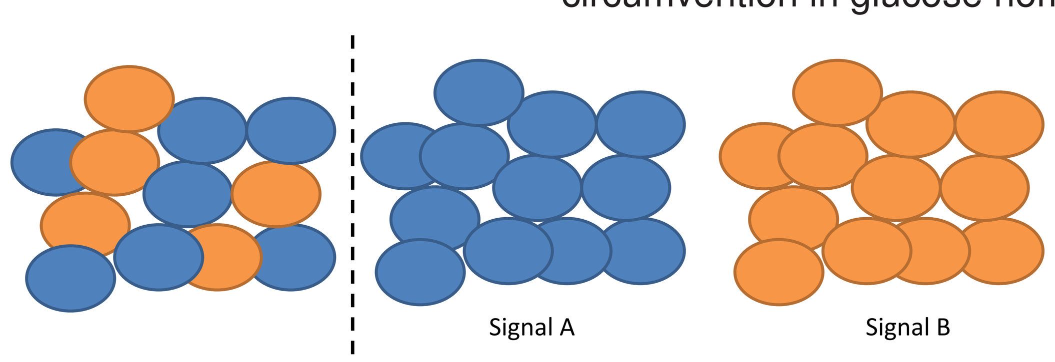


Figure: Schematic of a circuit through which glucagon and insulin exert control over glucose metabolism.

- A covalent modification cycle involving the bifunctional enzyme PFK2-FBPase-2 helps regulate glycolysis in the liver.
- Levels of individual enzymes may vary a great deal across a tissue, given rise to "mosaic" behavior.
- Bifunctionality may confer robustness by fixing the ratio of two enzymes, allowing coordinated response across tissue.

T. Dasgupta et al., "A fundamental trade off in covalent switching and its circumvention in glucose homeostasis"



CONCLUSIONS

- The sensitivity of the switch can be made arbitrarily large if and only if there is no product rebinding ($\alpha = \beta = 0$).
- Only when both enzymes are irreversible ($\rho = \mu = 0$) can the ratio S_1/S_0 reach both zero and ∞, at steady state.
- As long as product rebinding is low ($\alpha\beta < 1$), sensitivity is maximized when both enzymes are irreversible.
- The steady state of the GK loop depends on the enzyme concentrations only insofar as it depends on their ratio.
- This suggests a possible selective advantage of enzyme bifunctionality—by tying together enzyme abundances it may lend robustness to certain biological circuits.

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