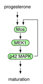
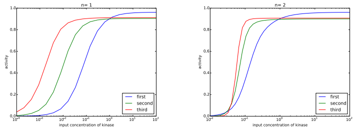
Cascades of enzymes can make responses ultrasensitive





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Biochemistry

An amplified sensitivity arising from covalent modification in biological systems

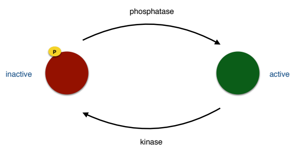
(protein modification/metabolic regulation/switch mechanism/enzyme cascades)

Albert Goldbeter† and Daniel E. Koshland, Jr.

Zero-order ultrasensitivity from a competition between two opposing enzymes: a kinase and a phosphatase

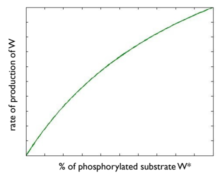
ABSTRACT The transient and steady-state behavior of a reversible covalent modification system is examined. When the modifying enzymes operate outside the region of first-order kinetics, small percentage changes in the concentration of the effector controlling either of the modifying enzymes can give much larger percentage changes in the amount of modified protein. This amplification of the response to a stimulus can provide additional sensitivity in biological control, equivalent to that of allosteric proteins with high Hill coefficients.

A "futile" cycle can generate ultrasensitive responses



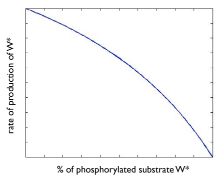
Consider the action of a phosphatase acting on a phosphorylated substrate:

$$W^* \longrightarrow W$$



Consider a kinase acting on a substrate:

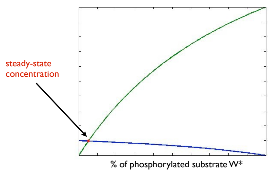
$$W \longrightarrow W^*$$



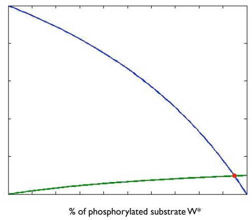
The system reaches steady-state when the rate of production of W* by the kinase matches the rate of production of W by the phosphatase.

$W \longrightarrow W^*$ kinase

$W^* \longrightarrow W$ phosphatase



As we increase the concentration of the phosphatase, the steady-state concentration of W* changes hyperbolically.



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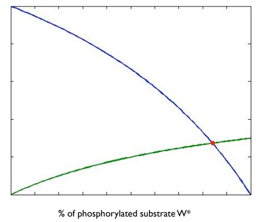

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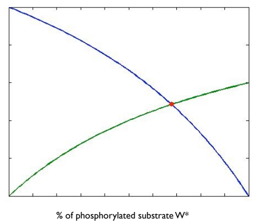

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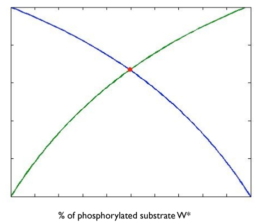

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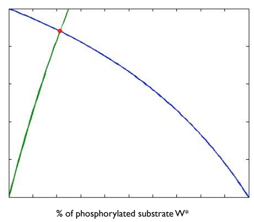

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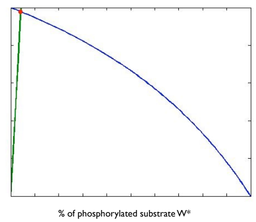
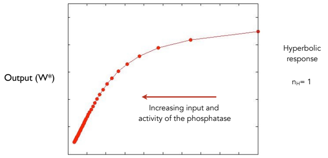
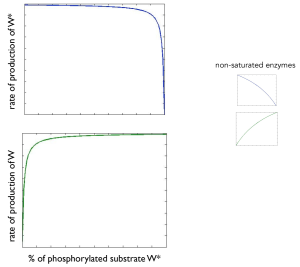


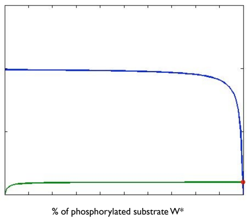
Therefore the change in the steady-state concentration of W* as the activity of the phosphatase increases is:



Let the amount of substrate saturate the kinase and the phosphatase.



As we increase the concentration of the phosphatase, the steady-state concentration of W* changes ultrasensitively.



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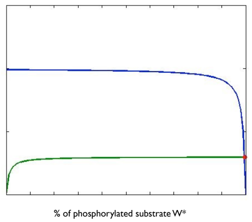

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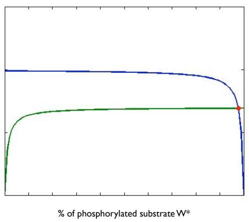

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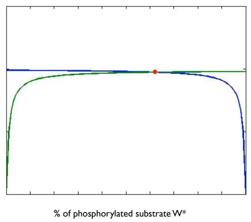

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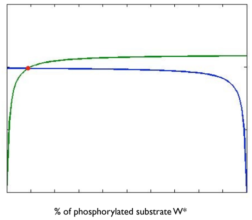

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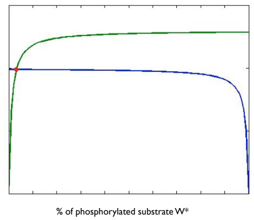

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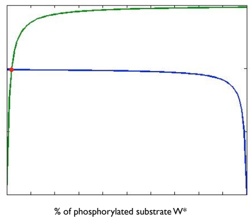
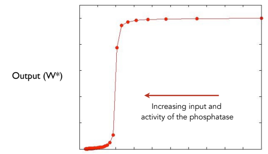


The change in steady-state concentration of W* varies ultrasensitively as the activity of the phosphatase increases.



When the enzymes work near saturation, the kinase is unable to compensate for increases in the activity of the phosphatase generating large changes in the steady-state concentration of W*.