

Sensitivity amplification in biochemical systems

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I. INTRODUCTION

The sensitivity of biological systems to changes in environmental stimuli is connected with their regulatory properties. In order to achieve efficient control, these systems must respond to minute environmental variations by amplifying external stimuli to yield a significant response. To that end, biochemical systems have often evolved to a cascade organization in which the product of the n th reaction in a chain acts as a catalyst in subsequent transformations. The amplification properties of such cascades were first noticed in the process of blood clotting (MacFarlane, 1964, 1969) and visual excitation (Wald, 1965). Later on, a similar organization was noticed in hormonal control of metabolism (Bowness, 1964; Stadtman & Chock, 1977, 1978; Chock, Rhee & Stadtman, 1980).

In parallel with these studies on amplification, several authors have attempted to quantify the sensitivity of biochemical systems to changes in some control parameter. The idea of expressing sensitivity in terms of the relative variation of a response ϕ (e.g. the rate of an enzymic reaction) caused by a relative variation in stimulus S was first introduced by Higgins (1965), who took the ratio of relative changes, written in the above notations as

$$C = d \ln \phi / d \ln S \quad (1)$$

as a measure of 'control strength'.

Later on, Kacser & Burns (1968, 1973), Savageau (1971, 1976), and Heinrich & Rapoport (1974) used definitions similar to (1) to find the control points in a sequence of enzymic reactions. Ratio (1) or related versions of it, were termed *sensitivity coefficient* (Kacser & Burns, 1968), *response* or *controllability coefficient* (Kacser & Burns, 1973), *parameter sensitivity* (Savageau, 1971, 1976), *effector strength* (Heinrich & Rapoport, 1974), *sensitivity* and *signal amplification* (Stadtman & Chock, 1978)*.

Savageau (1971, 1976) explicitly linked the sensitivity of biochemical

* A similar measure of sensitivity has been used in other fields such as economics, where the relative change in responding variable compared to the relative change in stimulating variable is sometimes called *elasticity* (Boulding, 1970).

systems to their amplification properties by calling ratio (1) the *logarithmic gain*. Although the system originally considered by Savageau is of the cascade type, the concept of logarithmic gain is also applicable to a single reaction. As noted by many authors, the effect of a cascade organization serves to multiply the amplification factors obtained at each stage of the reaction sequence (MacFarlane, 1964; Wald, 1965; Levine, 1966; Savageau, 1971; Stadtman & Chock, 1978; Chock & Stadtman, 1977; Banks, Miech & Olson, 1980).

The purpose of this work is to quantify the amplification properties of biochemical systems which can cause a larger percentage change in output response relative to the percentage change in input stimulus. In the case of an enzyme, the output is an enzymic rate and the stimulus can be a substrate concentration. In general, however, the stimuli can be inhibitors, activators, light, sound, etc. and the output response can be an ion flow across a membrane, a voltage response in a synapse, the release of a hormone, etc. The mechanism of amplification and its limitations depend not only on the individual properties, such as co-operative subunit interactions and covalent modification, but also on the way these individual units are combined in the system. In the pages which follow, we will evaluate the amplification of finite changes in stimulus and find explicitly the relation between the size of the step, the initial and final values of the stimulus, and the resulting amplification. We will determine how a multi-step cascade can enhance or diminish the amplification observed in the discrete steps. In this way, we can obtain both the optimal value of stepwise increases and the decrease in the maximum amplification factor as one departs from optimal conditions.

Definition of terms

We will use ϕ to represent the output response and S to represent the input stimulus. The subscripts i and f will refer to the initial and final values respectively.

The sensitivity amplification factor, A_S , will be defined as shown in equation 2:

$$A_S = \frac{(\Delta\phi/\phi)}{(\Delta S/S)} = \frac{(\phi_f - \phi_i)/\phi_i}{(S_f - S_i)/S_i} \quad (2)$$

This discrete form of the ratio of output to input reduces to the logarithmic expression of equation (1) in the limit of infinitesimal changes in stimulus. The main reason which prompted Kacser & Burns (1968, 1973), Savageau (1971, 1976) and Heinrich & Rapoport (1974) to consider the continuous expression was the search for a

