Extracellular-to-intracellular signal transfer via G-proteins

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Abstract

We look at the problem of signal transduction by extracellular agonist binding to a receptor protein at the membrane (sensor) via binding of G-proteins (effectors) to a highly integrative target molecule, such as the second messenger cAMP (target). We explore the effects of binding times, effector assignment and effector pool size on the shape of the output signal under different input scenarios. We conclude that low rates of information transfer may sometimes coincide with a high probability or efficiency of plasticity induction.

Keywords: signal integration, G-protein, intracellular signaling, cAMP, calcium, plasticity

Introduction.

G-protein coupled signal transduction proceeds by receptor activation from extracellular ligands and intracellular transduction through a potentially limited and dynamically regulated pool of effector molecules (G-proteins, such as $G_s$ proteins, $G_i$ proteins). Evidence for this is found in the observation that certain receptors (e.g. dopamine D2 receptors) exist in distinct affinity states (low affinity vs. high affinity for the native ligand) dependent on their coupling to an effector G-protein [4]. We suggest a model with a set of input units for a number of receptors, a second set of units for effectors which can be linked to the receptors, and an output set of units for regulated concentrations as target values (e.g. adenylyl cyclase, calcium, cAMP). The binding times between receptors and effectors are regulated by proteins such as GRkinases, RGS or calcium sensors (NCS-1) [1]. The number of effectors is typically lower than the number of receptors, such that a number of receptors are ‘running empty’, i.e. they do not transmit any signals they receive to the output (see Fig. 1). Vice versa, overexpression of the active $G_{\beta\gamma}$ components has been shown to increase signal transduction.

The system operates by signal transmission from receptor to effector via variable binding times, a variable assignment of effectors to receptors via local competition (on a slower time-scale), and dynamical adjustment of effector pool size controlled by temporal integration over multiple output values in an encompassing feedback loop (see Fig. 1).

Figure 1: Competition for effectors and feedback regulation of effector pool size
Regulation of Binding Times.

At the level of receptor-G-protein interaction, regulation of GR kinases and RGS proteins plays a decisive role in the rate of binding and signaling of effector proteins to receptors. A critical issue for membrane receptors is temporal integration of signals from different ligands which have effects on the same target [3].

A NxJ matrix of inputs (with N sensors and a time series of inputs of length J) becomes transformed into an output vector of length J by mapping through a MxJ matrix, where M is dynamically regulated but typically smaller than N (filtering). Each sensor is linked to only one effector at a time. When a sensor receives a signal, it binds to an effector, which transmits a quantal effect on the target concentration, the amplitude of which may be additionally modulated (e.g., by the effects of adenylyl cyclases).

Now for several values of M, and different input signals, we can produce a raw output vector based on a summed integration of the effector values (see Fig. 2).

![Figure 2: Shapes of the output signal regulated by receptor-effector binding times. Input signals with periods of high or low concurrency are modulated by a cross-correlation filter defined by receptor-effector binding times. If binding times are long, correlation is increased (=correlation filter), if they are short, it is decreased (=decorrelation filter)](image)

The dynamical properties of second messenger concentration are an important part of their function, as has been shown for calcium. Brief, phasic increases have a different effect on downstream signaling than longer-lasting broader signals. By altering the binding times of R-G coupling [1], input correlation can thus be increased or decreased by a cell-internal cross-correlation filter.

We assume that a receptor can receive separate signals on the order of about 100 ms each. Binding times $\theta$ are typically one order of magnitude more, e.g. between 1-2 s, and resensitization times are equally variable (e.g., 2-4 s, the absolute values depend on the type of receptor [2]). When a receptor is activated, and a G-protein is associated with the receptor complex, it generates a signal proportional in length to its binding time. A receptor can produce more signals, when binding times are short. When binding times are longer, the window-size for integration increases (correlation filter), when they are shorter, the window-size decreases (decorrelation filter). We see this reflected in the output vector, comparing shorter with longer binding times, everything else being equal (cf. Fig. 3). This would allow, for instance, to either combine
or separate signals mediated by different ligands, such as by monoamine/neuropeptide release concurrency.

Figure 3: Simulating effector signaling with different binding times $\theta=1$ (top), $\theta=2$ (middle) $\theta=3.2$ (bottom) Short binding times separate more signals, longer binding times generate broader, lower signals when in phase. Mismatches of binding times with input signal frequency (bottom) generate the largest, but least modulated integrated signals.

There may be a specific structure of the input signal: periods of high coincidence of signals alternating with low incidence of signals. (cf. Fig. 3 left). If binding times are not well-matched to the temporal structure of the input, the output becomes similar to an ongoing tonic signal with few modulations (Fig. 3 bottom).

**Competition for effectors.**

The main insight into effective competition is the idea that the probability of losing an effector protein is inversely correlated to the activity at the receptor site ('sticky effectors').

Figure 4: (Left) Input signals to 8 different receptors, where signals 2, 3 and 4 show significant correlation. (Right) Allocation of effectors to input units. Receptors 2, 3 and 4 have strongest coupling.

This general principle, which can be implemented in a number of different ways, guarantees that strong inputs have a high probability of continuing influence on the output value and redistribution of effectors happens only during periods of low receptor activation. We illustrate this mechanism with variable input signals for 8 receptors (Fig. 4 left). Selection of the most important signals is facilitated by competition for a scarce set of effectors. In this case, receptors 2-4 show the most effector coupling, while assignment otherwise is probabilistic.

**Dynamic regulation of effector pool.**
The effector pool size which determines how many input signals are being transmitted depends on the output units of the system (see Fig. 5). For instance, effector pool size may increase for focused output signals with sharp peaks and degrade when signals are weak or diffuse. With appropriate delays, we will then observe an oscillation between periods of focused signal transduction (high receptor activity) and search for a strong signal (low receptor activity) (Fig. 5). When signal transmission is highly selective, focused output signals are generated. This output signal then increases effector pool size, and thus resets the system to a broader tuning in order to subsequently increase its chances of picking up new signals. Thus sharp focused peaks in the output signal lead to increases of effector size by feedback from the output signal. Accordingly, effector pool size decreases when signals are broad and unspecific. This may increase the probability of enhancing a new, specific signal through competition by receptors for scarce effectors.

Figure 5: The output signal (left) regulates effector pool size (right). Note the increase of pool size for time units 2-6 and decrease for time units 8-14. Individual signals are diminished by pronounced temporal integration in regulating pool size.

Conclusion.

The interesting result for the role of binding times as cross-correlation filters is that intracellular properties are able to either integrate or separate extracellular signals which occur in close temporal proximity. This is a central task for a neuron with a multitude of different G-protein coupled receptors. Furthermore, for phasic signals, when information transfer is lowest (tonic signals with few modulations), plasticity may be induced with high efficiency. This relation between low rates of information transfer which induce maximal plasticity requires further attention. Competition for effectors or binding partners in signal transduction pathways is a fairly ubiquitous phenomenon in intracellular computation. Here the concept of localized efficient computation maximizes information transfer when high activity events occur. Adjustment of effector pool size with long delays may induce an oscillation of effector availability that coincides with an oscillation of focused information transfer by high competition and broad signal search by low competition.

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