

# Dynamic Regulation of Receptor/G-Protein coupling

Gabriele Scheler, Johann Schumann <sup>1</sup>

**Keywords:** affinity state, receptor, G-protein coupling, intracellular signaling

## 1 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,  $G_{olf}$  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. 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). Typically, the number of effectors is smaller 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 increases signal transduction.

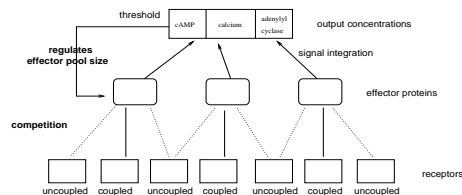


Figure 1: Competition for effectors and feedback regulation of effector pool size

The system operates by a variable assignment of effectors to receptors, but on a slower time-scale than signal transmission from receptor to output. Effectors may be assigned on the basis of local signaling activity (e.g. within a neuronal dendrite) and the overall effector pool may also be dynamically adjusted during the lifetime of the system, but on an even larger temporal and spatial scale (such as the whole cell), and due to (slow) processes of protein synthesis. Effector pool size can thus be expected to be controlled by temporal integration over multiple output values in an encompassing feedback loop, while assignment to receptors would involve local competition orchestrated by receptor activation.

## 2 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'). 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

<sup>1</sup>Stanford University [scheler@stanford.edu](mailto:scheler@stanford.edu) and NASA/RIACS [schumann@email.arc.nasa.gov](mailto:schumann@email.arc.nasa.gov)

this mechanism with variable input signals for 8 receptors (Fig. 2, 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.

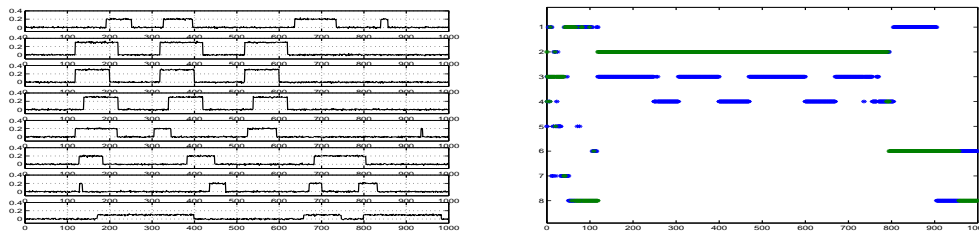


Figure 2: (Left) Input signals to 8 different receptors, where signals 2, 3 and 4 show significant correlation. (Right) Allocation of effectors to input units. Receptors 2, 3 and 4 have strongest coupling.

### 3 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. 1). For instance, effector pool size may increase for focused output signals with sharp peaks and degrade when signals are weak or diffuse. Essentially we will then observe then an oscillation between periods of focused signal transduction (high effector-receptor coupling) and search for a strong signal (low effector-receptor coupling). 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. Vice versa, 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.

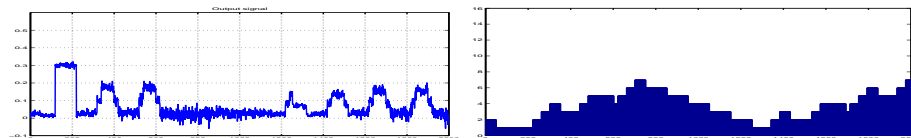


Figure 3: The output signal (left) regulates effector pool size (right). Note the increase of pool size for time units 2-6 and decrease for time units 8-14. Individual signals are diminished by pronounced temporal integration in regulating pool size.

### 4 Conclusion.

Competition for effectors or binding partners in signal transduction pathways is a fairly ubiquitous phenomenon in intracellular computation. Competition and adjustment of effector pool size contribute to signal analysis and may be controlled by characteristics of the input and output signals, respectively.