Hebbian Learning by a Simple Gene Circuit

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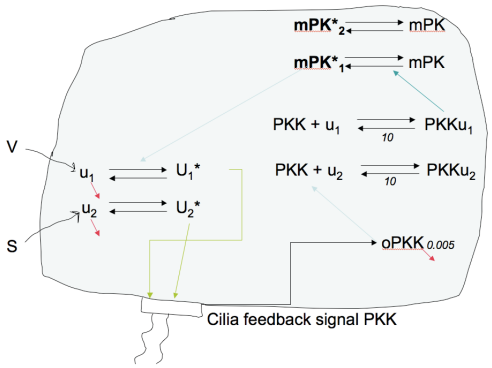

Figure 1: A network capable of approximating Hebbian learning. Two TFs, u_1 and u_2 can bind to the promotor only if they are activated. mPK_i molecules represent the weights, see text for details.

The single celled ciliate, Paramecium caudatum, can be classically conditioned therefore it must contain an intracellular circuit capable of associative learning. Hebbian learning was proposed as a mechanism for associative learning in neurons whereby synaptic weights would increase as a product of the correlated firing of pre and post synaptic neurons. Hebbian type learning by single cells could allow unsupervised self-organization of genetic receptive fields, or supervised training of gene expression patterns. One implementation of the circuit is shown in figure 1. Although the paramecium is used to illustrate the circuit we propose, the actual mechanism of classical conditioning in paramecia is more likely to use a variant of the adenylyl cyclase, cAMP, Ca^{2+} channel system involved in associative learning in Aplysia. Let V represent the conditioned stimulus (vibration) and S represent the unconditioned stimulus (shock). Assume they activate transcription factors u_1 and u_2 which do not bind to the promotor unless modified (e.g. phosphorylated) into the U_1* and U_2* forms respectively. Upon binding of the transcription factor , the cilia beat to produce the avoiding response, but in addition produce a re-entrent signal kinase oPKK, which is an internal representation of the extent of cilia beating. This kinase oPKK is activated specifically by binding rapidly to either u_1 or u_2. If it binds to u_1 then it activates another kinase mPK_1 and if it binds to u_2 it activates the kinase mPK_2. These second level kinases are in a slow equilibrium and so effectively integrate the concentration of activated oPKK over time. They specifically phosphorylate the transcription factors and allow them to bind the promotor. In analogy with Hebbian learning, the transcription factor concentrations represent the pre-synaptic activities, the cilia activity and the oPKK concentration represents the post-synaptic activity, and the concentrations of mPK_i represent the synaptic weights. Figure 2 shows a simulation of the classical conditioning training procedure. Initially the concentration of mPK_2* is high, so that only shock activates the cilia, not vibration. However, when shock is paired with vibration, the concentration of mPK_1* increases, such that when vibration is subsequently presented alone, the transcription factor u_1 is now able to bind to the promotor and cause cilia beating. We have demonstrated how associative learning could be implemented in a single cell. When Donald O. Hebb proposed his principle in the book entitled "The Organization of Behaviour" in 1949, there was no evidence for it, and no means to verify it. We suggest that researchers working on cellular networks should explicitly search for Hebbian mechanisms acting in single celled and multi-cellular Eukaryotes. Also, applications immediately suggest themselves in which cells can be engineered to express a gene under conditions modifiable by training, for example a therapeutic gene could learn to anticipte the conditions under which it should be expressed.

Categories and Subject Descriptors: J.J.3 [Biology and genetics]**General Terms: Algorithms**

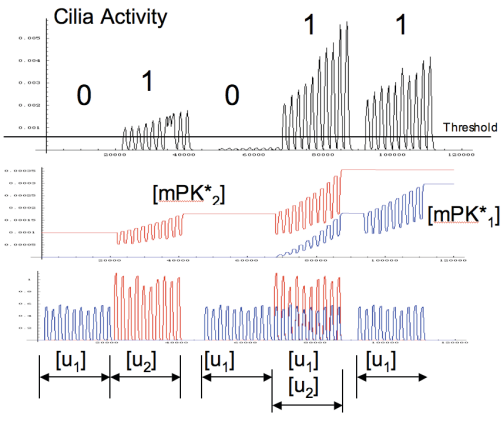

Figure 2: A classical conditioning experiment.

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