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Genes for adaptation and learning spanning evolution: computational comparison between synaptic transmission and chemo-tactic signaling protein networks

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Plasticity at the synapse and adaptation in bacterial chemotaxis are two prominent examples of biological regulation and signal processing in response to noisy, time-varying stimuli [1,2]. Both regulatory systems process glutamate stimuli (as neurotransmitter and food respectively) to determine whole-cell response to future changes in glutamate concentration. These two evolutionary distant protein networks thus perform a common computational function (adaptation to stimulus patterns) on glutamatergic inputs. Moreover, the bacterial glutamate receptor is an evolutionary ancestor of mGlu and NMDA receptors in the mammalian synapse [1,3]. Thus, we were curious if common regulatory principles of both networks and specifically if their proteins had common evolutionary roots. We investigated this hypothesis by performing a comparative bioinformatics study to test if the amino acid sequences of these two protein networks are conserved across 600 Million years.

We focussed on mouse (*M. Musculus*) post-synaptic proteins [4] and the 23 proteins involved in bacterial chemotaxis of *E.coli*[2,5], both available on the UniProt protein database. We measured protein similarity by aligning the sequences of all synaptic *M.Musculus* proteins (tagged as “synapse” related in UniProt) with all 23 bacterial chemotaxis proteins, using the local pairwise Smith-Waterman algorithm [6]. Because the algorithm’s similarity score is sequence length dependent and evolutionary distance between proteins results in considerable genetic drift, the comparison is difficult [7]. Therefore,

we developed a normalization method to establish significance of alignments (cf. Figure): We established two baseline sets of alignments: we aligned 300 generic (non-synaptic) proteins from *M.Musculus* (with similar length as the synaptic proteins) with the 23 bacterial chemotaxis proteins and vice versa 100 generic (non chemo-tactic) *E.coli* proteins (of similar length as the chemo-tactic proteins) with the 84 synaptic proteins from *M.Musculus*. Any significant sequence similarity score between synaptic and chemotactic proteins would have to stand out from the large set of scores of the baseline sets: We normalised the alignment score S_{ij} , between a synaptic protein i , and a chemo-tactic protein j , using the mean μ_{ij} , and standard deviation σ_{ij} of the baseline score distributions. Thus, alignments between synaptic and chemo-tactic proteins with positive normalized scores, indicated strong sequence similarity.

We found a set of a dozen synaptic and chemotactic proteins that show high sequence similarity across this vast evolutionary gap. The highest scoring one was, for example, the methyl-accepting chemotaxis protein III in bacteria and the glutamate receptor interacting 1 (GRIP1) associated protein in synaptic transmission. GRIP1 is an adapter protein linking AMPA receptors associated to increase synaptic efficiency [8], whereas methyl-accepting chemotaxis protein III is involved in adaptation by varying the level of methylation to allow bacteria to remain sensitive to changes in average glutamate concentration [9]. This novel link suggests regulatory networks for adaptation and learning at the synapse have common ancestors and possible common principles (see also [10]). We pose the idea, that like Mitochondria (which were bacteria integrated into

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eukaryotic cells to supply energy) so could 'learning' at the chemical synapse be the result of integrating the chemotaxis network into early neurons.

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