Anchoring patterns and point mutations in pairwise alignments using AlignMe

X-ray crystal structures have revealed that numerous membrane proteins, such as GPCRs or some secondary transporters, despite the lack of any detectable sequence similarity between them, still share very similar 3D structures. Moreover, some proteins were originally categorized into different sequence families but after their structural models became available, it has been revealed that they may share the same evolutionary ancestor. One of the representative examples is LeuT-fold transporters. Their core consists of two units of 5TM helices, whose conformations have been proposed to exchange to form the two alternate states required for transport. That these two units are related implies that LeuT-like transporters evolved from gene-duplication and fusion events. However, the lack of significant sequence similarity requires sensitive sequence search methods for analyzing their evolution. To this end, we developed a software application called AlignMe and subsequently a webserver, which can use various types of input information, such as residue hydrophobicity, to perform pairwise alignments of sequences and/or of hydropathy profiles of (membrane) proteins. In addition, we modified the dynamic programming algorithm such that it allows to flexibly connect positions in the sequences that are being aligned. The novel feature allows the user to define any number of anchors with varying strength for improving the quality of pairwise alignments in challenging cases lacking notable sequence similarity. The information about possible anchors can be obtained from the experimental studies, expert knowledge of specific motifs or even from the alignments of hydropathy profiles. There are manifold applications in homology modeling as well as in the context of mutagenesis experiments, and all this makes the tool useful in detection of the structural similarity of membrane proteins and in the analysis of the evolutionary relationships.