Towards molecular level models of information processing in neurons

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Background or Purpose:
Brain function depends ultimately on complex molecular processes through which neurons respond to external stimuli and regulate their signaling. Molecular level models can shed light on the significant information processing and decision making taking place on the subcellular level (Bhalla, 2014), as well as providing important links to drug discovery and the effect of disease-linked mutations. A significant challenge when constructing these models is to find the set of parameters which quantitatively can account for all relevant experimental data. Here we discuss the possibilities of using molecular multi-scale modeling approaches to characterize and predict molecular interactions and to obtain thermodynamic and kinetic parameters, filling gaps in the experimental knowledge when building kinetic models of receptor induced cascades.

Methods:
We are extending a quantitative kinetic model framework of glutamate and dopamine signaling (Gutierrez-Arenas et al, 2014) for exploring two possible ways of interaction between Golf dependent and Gi dependent cascades converging onto AC5, the predominant adenylate cyclase in MSNs. We explore both interactions which can be classified as functionally competitive or non-competitive, and interpret the results in terms of how efficiently the cAMP response is controlled. In addition to AC5, AC1 and AC6 isoforms have also been shown to be regulated by Gi (Sadana and Dessauer, 2009). To predict the existence of a ternary complex, a prerequisite if non-competitive interactions are assumed, we have performed molecular electrostatic potential PIPSA analyses (Wade, 2001) of all membrane-bound AC isoforms (AC1-9) to find regions of high electrostatic potential similarity amongst AC1, 5 and 6 isoforms for identifying their likely sites of interaction with Gi.

Results and Conclusions:
Kinetic modeling predicts that when a dopamine transient is combined with a cholinergic dip, the deactivation of Gα and activation of Golf could interact synergistically to produce significant cAMP. Both the competitive and non-competitive interaction schemes can produce synergy for a limited parameter space, but the competitive scheme produces higher synergy values. However, transient changes in either the Gi or Golf signaling alone are instead detected better with the non-competitive scheme. Preliminary protein structural modelling results suggest that Gi interacts with AC5 in a position distant from the Golf binding site, supporting the non-competitive scheme, however further analyses are required to distinguish this from an allosteric competitive scheme. To the scope, Molecular modeling techniques, including protein/protein docking, protein/ligand Brownian Dynamics, all-atoms classical molecular dynamics (MD), ab initio MD and hybrid ab initio/MM MD approaches, and coarse-grained MD simulations (see e.g. Pasi et al, 2012; Zhang et al, 2012), are being used to characterize the interactions of AC5 with substrate and G-protein subunits effectors, to unravel the enzymatic reaction mechanism, and to estimate the associated kinetic and thermodynamic parameters.

References: