P048 Systems biochemistry approaches to vertebrate phototransduction: toward a molecular understanding of disease

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Phototransduction in vertebrates represents a paradigm of signalling pathways, in particular those mediated by G protein-coupled receptors. The variety of protein-protein, protein-ion and protein-nucleotide interactions makes up an intricate network, which is finely regulated by activating-deactivating molecules and chemical modifications. The holistic systems properties of the network allow for typical adaptation mechanisms, which ultimately result in fine adjustments of sensitivity and electrical response of the photoreceptor cells to the broad range of light stimuli.
We discuss a novel bottom-up strategy to study the phototransduction cascade in rod cells starting from the underlying biochemistry. The resulting network model can be simulated and the predicted dynamic behaviour directly compared with data from electrophysiological experiments performed on a wide range of illumination conditions. The advantage of applying procedures typical of systems theory to a well studied signalling pathway is also discussed. In particular, we show that global sensitivity analysis provides both a way to test model robustness and to suggest novel experiments to highlight the key interactions and components in the network. The recently developed model is compared to other holistic modelling approaches, and the potential for applications to the study of molecular basis of retinal diseases is highlighted through a practical example, namely the simulation of conditions related to Leber congenital amaurosis.