General description of the biological problem. It may be argued that the ultimate goal of structural biology as applied to ion channels (as well as transporters, GPCRs and enzymes) is to provide a picture of what the protein looks like in its different physiologically relevant conformational states. Remarkable advances have been made toward the structural characterization of ion channels in the last two decades. However, the assignment of well-defined functional states to the obtained structural models—a crucial aspect of the entire endeavor—has proved more elusive than anticipated and is often a matter of controversy. Undoubtedly, the problem arises because protein structure cannot, typically, be studied under the same conditions that are used to study protein function. For example, whereas the functional properties of ion channels are usually assessed in the context of a phospholipid membrane at room temperature, structure is frequently determined in detergent micelles at cryogenic temperatures, often under the constraints imposed by a crystal lattice. Although the structure of some ion channels has been determined by single-particle cryo-EM in lipid nanodisc-reconstituted samples (or using 2D electron crystallography of tubular crystals, in the case of the native *Torpedo* muscle-type nicotinic acetylcholine receptor), most cryo-EM structural determinations to date have been performed on detergent solubilized samples. A hitherto unrealized goal of ion-channel biology is to identify the conformation of ion channels in their different (physiologically relevant) conformational states. We are convinced that, in order to achieve this, we have to transition from detergent solubilized samples to lipid membrane-reconstituted samples. We are also convinced that structural-biology data on ion channels have to be buttressed by high-resolution electrophysiology (the main expertise of the Grosman lab) and quantitative molecular simulations (the main expertise of our collaborators, the Tajkhorshid lab).

The immediate goal of this project is to identify the conformation of members of the Cys-loop receptor superfamily of ion channels in their different conformations (“closed”, “open”, and various “desensitized” states) and liganded states (unliganded and liganded). In doing this, we hope to set an example of how this grand goal could be achieved with other ion-channel superfamilies, too. As for our ultimate goal, we think our work will contribute to the much broader area of rational drug design. We are of the opinion that a clear understanding of the relationship between structure and function of ion channels is absolutely required to be able to rationally design drugs.