Ion Channels at the Origins of Life. M. A. Wilson[1,2] and A. Pohorille[1,2], [1]Dept. Pharmaceutical Chemistry, University of California, San Francisco, CA 94143, [2]Exobiology Branch, NASA Ames Research Center, Moffett Field, CA 94035, Michael.A.Wilson@nasa.gov, Andrew.Pohorille@nasa.gov .

Introduction: The membranes of contemporary cells are almost impenetrable to ions, and ion transport occurs through membrane-spanning channels that contain water-filled pores. Contemporary ion channels are large, complex and highly-evolved protein assemblies that facilitate ion transport in an efficient, selective and highly regulated fashion. This raises the question of what were the evolutionary origins of complex channels? What comprised the earliest ion channels and what were their properties?

The ancestors of modern cells (protocells) might have utilized fatty acids and long chain alcohols to form membranes which are sufficiently leaky to allow for ion transport. However, once phospholipid membranes emerged, facilitated ion transport would have been required to maintain the osmotic equilibrium between the environment and the protocell. This implies that the earliest channels could have formed from α-helices that became inserted into the membrane, and then associated to form water-filled pores.

This view of the origins of ion channels leads to a puzzle: It is thought that the ability to form a structure enclosing a pore is a prerequisite for a channel to function, but if the intermolecular interactions between neighboring monomers are not sufficiently strong, the channel could open to the side, completely disintegrate or collapse, and presumably loose its ability to conduct ions. It would appear that only a small number of privileged amino acid sequences sufficiently long to span the membrane could assemble to stable, pore forming structures. How then did they appear for the first time? They could not have evolved from non-functional assemblies because natural selection does not operate on the latter. There is also no clear mechanism for their evolution from shorter peptides, since such peptides would not extend across the membrane. Of course, peptides capable of forming channels endowed with structural integrity might not be as rare as anticipated, and emerged from random amino acid sequences by chance. Alternatively, more common, but highly flexible structures that did not fully enclose a pore all the time might have been functional and developed into stable structures through familiar evolutionary processes. Such assemblies, however, have not been observed experimentally or computationally.

Discussion: Here we report computer similations of two ion channels: antiamoebin[1] (AAM), an antimicrobial peptide from fungi, and the LS3 peptide[2], a designed 21-mer containing leucine and serine arranged in a heptad repeat so that the helical peptide has well-defined hydrophilic and hydrophobic faces. Experimentally, both peptides form ion conducting channels which are thought to be formed from parallel, hexameric bundles of monomers.

In simulations, LS3 forms a well-defined structure, which persists over μ-sec time scales whereas AAM undergoes significant structural fluctuations, but retains its ability to conduct ions. The conductance of LS3 is in good agreement with experiments. The ion currents in AAM are highly non-uniform, but on average the calculated conductance is in a good agreement with single-channel recording measurements.

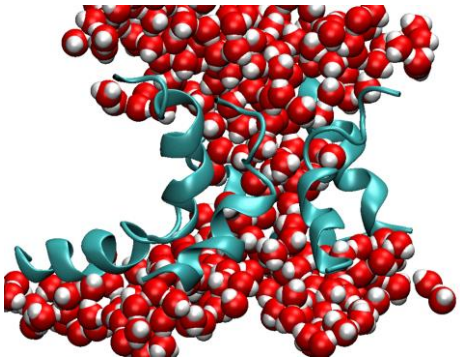

Figure 1: Side view of the antiamoebin ion channel showing the disordered, water-filled pore.

The AAM channel appears to represent a class of ion channels with characteristics that have not been observed experimentally or computationally. AAM is unusual flexible, but still capable to efficiently conduct ions. It is possible that a number of other natural channels might have similar properties. These small channels cannot retain their structural integrity through strong interhelical, knob-in-the-groove interactions. This greatly limits their possible functions in contemporary biological systems. However, in the ancient history of protein-assisted ion transport they might have been the "missing link" between even simpler and shorter ion carriers and well packed channels that resembled contemporary ones. In contrast, LS3 is an example of an ion channel endowed with a rigid structure that is achieved from a very simple sequence.

References: [1] M. A. Wilson, et al. (2011) Biophys. J. 100, 2394–2402. [2] J. D. Lear et al. (1988) Science 240, 1177-1181.