

The Matrix: Phylogenetic Studies of Ion Channels and Other Microbial Transporters

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Functional classification and phylogeny of voltage-gated ion channels: The starting point for this subproject is a comprehensive alignment of all potassium channels in microbes, plus all potassium channels in completely sequenced eukaryotic genomes. Potassium channels can not be automatically aligned by existing alignment tools, because of the extreme diversity they exhibit in all regions of the sequence except for the permeation pathway. In effect, potassium channels are not one superfamily, but rather many families that have incorporated the potassium channel permeation pathway as a device to transduce the signals to which they are sensitive into an electromotive force across a membrane. In this study we present:

- a. A survey of the diversity of potassium channel sequences.
- b. A demonstration by consurf analysis that the structural organization of the permeation pathway has been preserved from the prokaryotic origins of potassium channels through the potassium channels of modern humans.
- c. The discovery that classification of potassium channels (including presence of regulatory domains) can be determined from the homology of the permeation pathway alone and, as a corollary of this discovery, an enhanced classification scheme for human channels.
- d. An exploration of the phenomenon of hyperconservation (very strong conservation over the entire gene for hundreds of millions of years of evolutionary time) for particular classes of potassium channels
- e. An overall reconstruction of potassium channel evolution from prokaryotes to eukaryotes including an identification and analysis of the emergence of sodium and calcium channels from potassium channels.

Phylogenetic profiling of microbial transport proteins: In this subproject we started with NCI Blast to build a high-throughput blast and parsing program called NCSA Blast. We used NCSA Blast to ascertain the mutual homology between the Transport Commission Data Base (developed in the Saier lab of University of California, San Diego) and all the completed microbial genomes. The core result is a matrix with dimensions (# of transporter classes x # of microbial genomes) describing what transporter classes are contained in what genome. The core matrix is transformed into a co-existence matrix with dimensions (# of transporter classes x # of transporter classes) and into a tree, with clusters representing putative networks of interacting transporters. The tree will be displayed with interpretative commentary.

The power of High-Resolution Displays: We have visualized the trees and matrices on an NCSA Mosaic Wall Tile Display, which essentially permits a display on an entire wall with the resolution of a high-quality desktop monitor. This display has enabled us to make inferences about functional and evolutionary pathways much faster than conventional small displays combined with zooming and numerical analysis.

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