question of what factors regulate directed dendritic ingrowth. Mumm et al. suggest that the processes of cholinergic amacrine cells play a critical role in this process. Should this hypothesis be confirmed it would immediately raise the obvious next question: what is it about amacrine cell processes that directs the ingrowth and/or stabilizes the dendrites of developing RGCs? There are clearly many exciting things to come in our collective effort to understand the ways and means by which dendrites attain their mature state.

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# Dissecting the Coupling between the Voltage Sensor and Pore Domains

**The gating mechanism of $K_v$ channels is not known. In this issue of *Neuron*, Soler-Llavina et al. present fascinating results that support the concept of relatively independent voltage-sensing modules. However, they also find that its interactions with the pore domain are rather complex, with specific S4–S5 intersubunit contacts underlying the concerted transition leading to the channel opening.**

Voltage-dependent $K^+$ ($K_v$) channels undergo conformation changes in response to changes in the membrane potential, thereby allowing or blocking the conduction of ions. They are formed by four subunits surrounding a central aqueous pore for $K^+$ permeation. Each subunit comprises six transmembrane segments, S1–S6, the first four transmembrane segments, S1–S4, constituting the voltage sensor domain while the last two transmembrane segments, S5 and S6, form the pore (Bezanilla, 2000). Upon membrane depolarization, the voltage sensor in each subunit undergoes voltage-dependent transition from a resting to an activated state (R → A), resulting in a conformation that is permissive for pore opening (Bezanilla et al., 1994; Zagotta et al., 1994). Once all of the four subunits are in the A state, opening of the pore gate occurs cooperatively via a concerted transition (C → O) that is weakly voltage dependent (Ledwell and Aldrich, 1999).

To fully comprehend the "workings" of $K_v$ channels, one will ultimately need to "visualize," atom by atom, how the protein moves and changes its conformation as a function of time in response to the membrane potential. Little by little, progress is being made toward this ambitious goal. In the current issue of *Neuron*, Soler-Llavina et al. (2006) present fascinating results that shed light on the functional coupling between the voltage-sensing modules and the pore domain.

Structural information is a prerequisite to begin to understand voltage-gating channels. The crystal structure of $K_v1.2$ from rat brain has provided the first atomic-resolution view of a voltage-gated potassium channel (Long et al., 2005a). The interpretation of structural information in the case of multistate flexible allosteric proteins can be challenging because one must be able to assess which native functional state (if any) has actually been captured. These difficulties are further compounded in the case of membrane proteins due to the complexity of the lipid bilayer environment and the risk of inducing nonnative conformational distortions (Jiang et al., 2003). According to the experimental conditions, the crystallographic structure of $K_v1.2$ should correspond to an inactivated channel with its voltage sensors near their activated position. The overall topological features of the X-ray structure of $K_v1.2$ are in excellent accord with what had been previously deduced on the basis of a wide range of structural, functional, and biophysical experiments about the Shaker $K^+$ channel in its activated open state (Laine et al., 2003). That is, the voltage sensor is formed by a bundle of four antiparallel transmembrane $\alpha$ helices, S1–S4, each with their N- and C-terminal ends exposed alternatively to the intra- and extracellular solution. Seen from the extracellular side, the S1–S4 helices of the voltage sensor are packed in a counterclockwise fashion, and the S4 helix of a subunit is making contact with the S5 helix of the adjacent subunit in the clockwise direction (Laine et al., 2003). The good accord strongly suggests that the X-ray structure is in a near native conformation.

One striking feature of the X-ray structure is the modular nature of the voltage sensor domain and its lack of extensive interactions with the pore domain. About 66% of molecular surface of the transmembrane region of each voltage sensor S1–S4 is exposed to lipids; the interaction with the pore domain corresponds to $\sim$1250 Å$^2$. About 75% of the molecular surface area of S4 is buried by protein (the S1–S3 helices and the S5–S6 pore domain cover 50% and 25% of the total surface of S4, respectively). The large number of permissive mutations on S5–S6 tested by Soler-Llavina et al. support the general concept of relatively independent voltage-sensing and pore domains, consistent with the crystallographic structure.

As one is probing deeper into the mechanistic details of voltage gating, it was important to confirm that this structural feature captured in the crystal environment is in accord with observations based on functional channels in membrane bilayers. The modular nature of the voltage sensor and pore domains is also consistent with the functional chimeras engineered by substituting the pore domain of the KcsA channel into the voltage-gated Shaker channel (Lu et al., 2001) and naturally compatible with the allosteric model of channel gating developed by Aldrich and coworkers (Ledwell and Aldrich, 1999). The discovery of voltage sensors with high sequence similarity to the S1–S4 helices in two unrelated membrane-associated proteins lacking any channel-like central pore domain leaves no doubts about its recurrent and modular nature (Murata et al., 2005; Ramsey et al., 2006; Sasaki et al., 2006).

Once the concept of relatively independent voltage-sensing and pore domains is established, it begs the question of how and where they are coupled. In an extreme view, one might hypothesize that each S1–S4 helical bundle constitutes a complete functional voltage-sensing unit, able to work on its own in the membrane. In other words, the voltage-sensing domains float like "buoys" in the membrane and only need to be loosely attached to the central pore to confer voltage-gating properties. The careful study by Soler-Llavina et al. reveals that the coupling between the voltage sensor and the pore domain is, in fact, more complex than suggested by this naive view. They identified two regions where clusters of mutations display very different functional phenotypes. Mutations near the extracellular end of S5 affect mainly the R→A transition by making the activated state more unfavorable. Mutations toward the intracellular end of S5 seem to disrupt the coupling between the voltage sensors and the gate to the pore. On the one hand, these mutations make the transition R→A easier, but on the other hand, they make the concerted transition C→O much more difficult. By inspection of the $K_v$1.2 structure, those mutations are in physical proximity to the so-called ILT mutations in the S4 helix that are known to have a pronounced effect on the concerted transition C→O initially discovered by Aldrich and coworkers (Ledwell and Aldrich, 1999; Smith-Maxwell et al., 1998a, 1998b).

According to the $K_v$1.2 structure, the S4–S5 linker makes strong van der Waals contacts with the S6 helix forming the pore gate (Long et al., 2005b), a feature that was previously found to be essential for functional channels from the engineered Shaker-KcsA chimeras (Lu et al., 2001). Further examination also shows that 10 out of the 20 residues forming the transmembrane part of S4 are positioned within 4 Å of the S5 helix from the adjacent subunit. Thus, the idea that the voltage sensor lacks extensive interactions with the pore domain, while generally correct, needs to be carefully qualified in trying to dissect the coupling mechanism. The results of Soler-Llavina et al. indicate that the interactions between one face of the S4 helix with the S5 helix of the adjacent subunit most likely underlie the concerted transition leading to the channel opening.

These findings advance our fundamental understanding of the gating mechanism in $K_v$ channels and also raise numerous questions about the voltage-sensing modules in the phosphatase (Murata et al., 2005) and the proton pore (Ramsey et al., 2006; Sasaki et al., 2006) with those of $K_v$ channels. For example, does the modular unit formed by a single S1–S4 anticlockwise helical bundle have the ability to function as a voltage-sensing electromechanical "device" on its own? What molecular interactions are responsible for the transduction of the voltage-sensing signal to another protein? What aspect of those interactions might be conserved across different systems?

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# Synaptic Homeostasis on the Fast Track

**Synaptic homeostasis is a phenomenon that prevents the nervous system from descending into chaos. In this issue of *Neuron*, Frank et al. overturn the notion that synaptic homeostasis at *Drosophila* NMJs is a slow developmental process. They report that postsynaptic changes are offset within minutes by a homeostatic increase in neurotransmitter release that requires the presynaptic $Ca^{2+}$ channel *Cacophony*.**