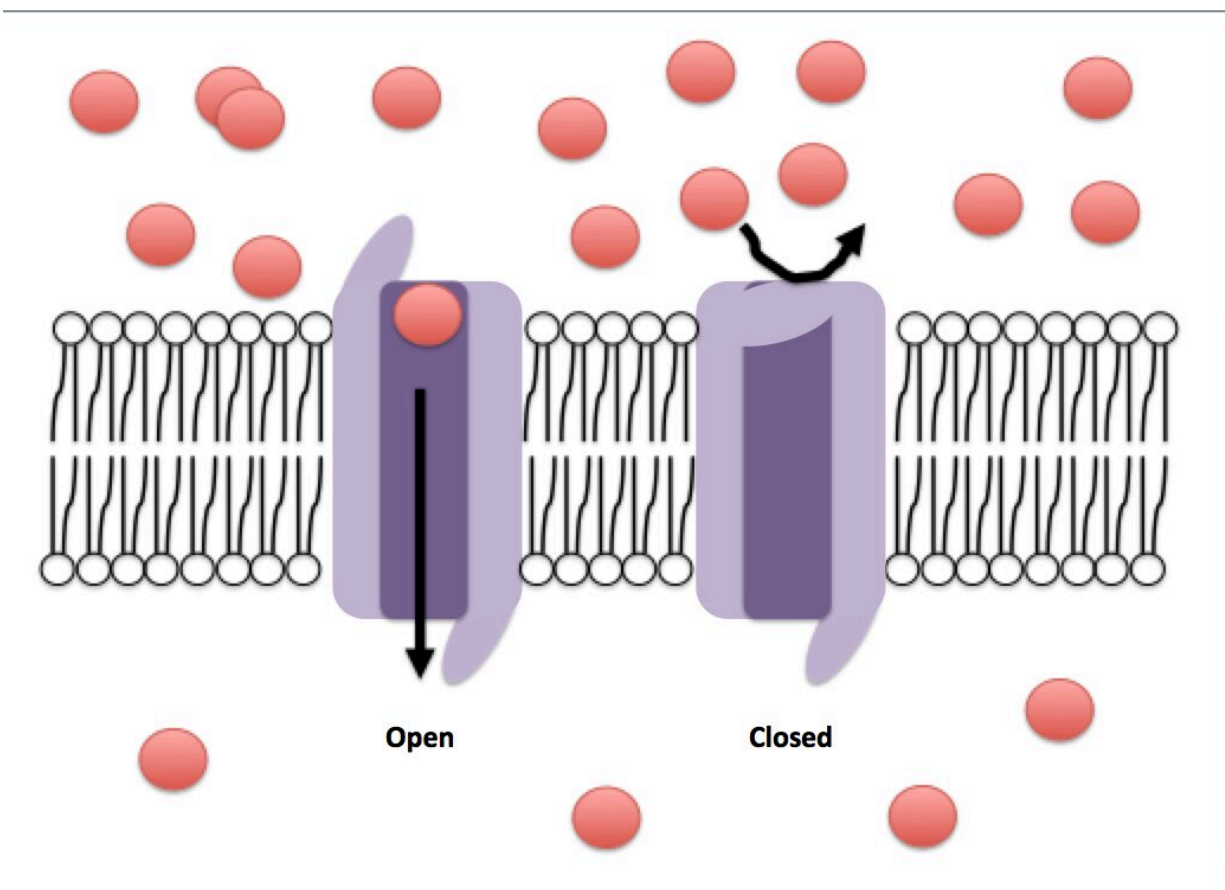


# Research reveals surprising inactivation mechanism for a voltage-gated ion channel

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Scientists at St. Jude Children's Research Hospital are studying voltage-gated ion channels (VGICs). Their work revealed a previously unknown

mechanism of inactivation for one such channel that plays an important role in how neurons and muscles respond to electric signals sent by the nervous system. A paper on the work appeared today in *Molecular Cell*.

VGICs are [transmembrane proteins](#) that form a pore that opens and closes to allow the passage of ions into or out of a cell. Cells such as neurons and muscle cells respond to electric signals by opening (activating) and closing their VGICs. Proper activation and closing of VGICs allows these cells to properly coordinate their functions.

The researchers used cryogenic electron microscopy (cryo-EM), biochemistry and electrophysiology approaches to study a VGIC called Kv4. Mutations in Kv4 are linked to neurological and cardiac conditions. Understanding how Kv4 functions may help researchers identify therapeutic strategies to treating such disorders.

"Neuronal communication is based on how electro-signals are transmitted, which is mediated by the action of proteins in the neuronal membrane. Many researchers are interested in studying this process, but it has been difficult to capture," said corresponding author Chia-Hsueh Lee, Ph.D., St. Jude Department of Structural Biology. "We were able to capture multiple states of this specific ion channel to get a better picture of how this protein works in molecular detail. We were excited to find that Kv4 functions in a way that is distinct from other types of VGICs."

The researchers were able to complement and validate the structural findings with electrophysiology work from collaborators at University of California San Francisco.

## **Finding out why the car won't go: Understanding Kv4 inactivation**

VGICs occupy different states to function. The channels can transition from resting/closed to activated/open states. Think of a car: when turned off, it is like the VGIC in the resting/closed state. When you've turned it on and are driving, that is like the VGIC in the activated/open state. However, Kv4 can also enter an inactivated state, where the pore is closed and unresponsive. Imagine a car where the engine is on and you're stepping on the gas, but the car won't go, because the handbrake is applied.

The researchers wanted to understand how Kv4 transitions between these different states. Using cryo-EM, they initially captured the channel in three different conformations (shapes), corresponding to the activated/open, inactivated and intermediate states. Those structures revealed the mechanisms behind Kv4 inactivation, which featured an unexpected symmetry breakdown from four- to two-fold symmetry.

Like other VGICs, Kv4 is composed of four identical copies of a protein (imagine a four-leaf clover), and in the activated/open and intermediate states, all four copies adopt the same conformation. In contrast, in the inactivated state, the two pairs facing each other have different conformations. To capture Kv4 in its resting/closed state, the researchers needed to "lock" the channel into that position, using protein engineering and certain reagents.

This is the first time that researchers have identified the mechanism for closed-state inactivation, and the approaches used here could be applied to other [ion channels](#).

"I think our study is quite exciting for the field because we were able to get multiple structures that are related to functional states for one ion channel," said first author Hongtu Zhao, Ph.D., St. Jude Structural Biology. "Being able to determine several structures of the same protein and in a single study enabled us to draw a lot of information from

comparing them. This really reflects the power of cryo-EM."

**More information:** Wenlei Ye et al, Activation and closed-state inactivation mechanisms of the human voltage-gated KV4 channel complexes, *Molecular Cell* (2022). [DOI: 10.1016/j.molcel.2022.04.032](https://doi.org/10.1016/j.molcel.2022.04.032)

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