Direct knock-on of desolvated ions governs strict ion selectivity in K⁺ channels

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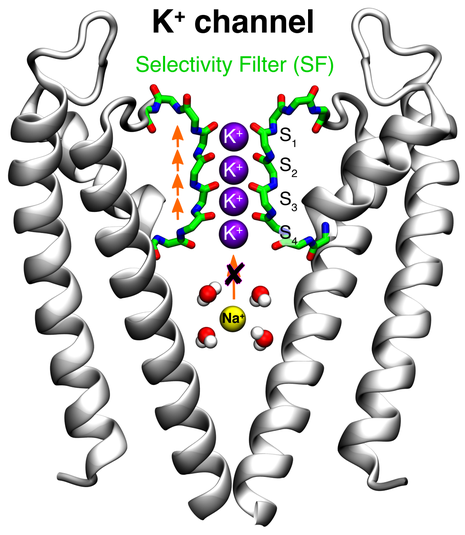
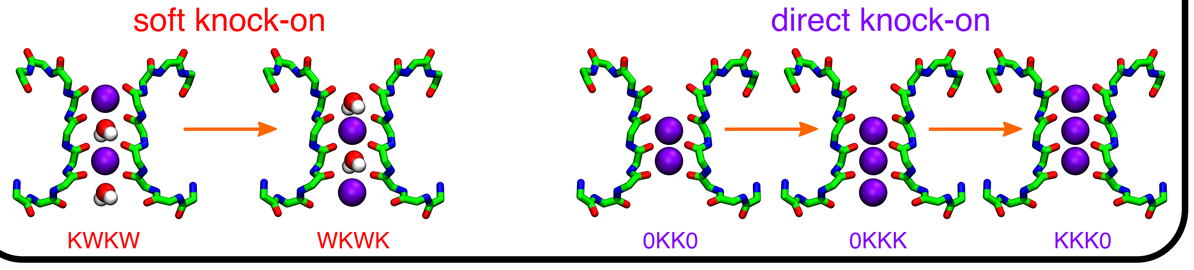
Introduction

Potassium channels facilitate the passage of K⁺ ions through membranes to near-diffusion limited rates, while reliably excluding smaller Na⁺ ions [1]. A clear separation between K⁺ and Na⁺ currents is necessary to ensure sharp action potentials in excitable cells. A unified explanation for how K⁺ channels maintain strict K⁺ selectivity under maximal ion conduction rates has remained elusive.

Recently, a novel mechanism of K⁺ ions conduction - the direct knock-on - was proposed [2], that involves close contacts between the ions in adjacent ion binding sites, in contrast to the previously accepted soft knock-on, where water molecules separate ions in the SF [3]. As all previous models of ion selectivity assumed soft knock-on between the ions, the mechanism of ion is likely to be very different than previously thought.



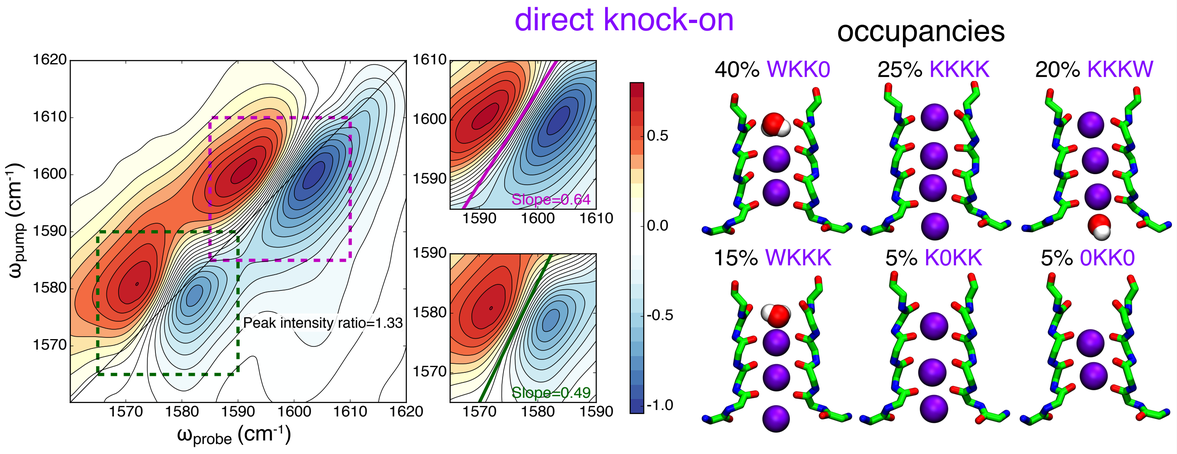


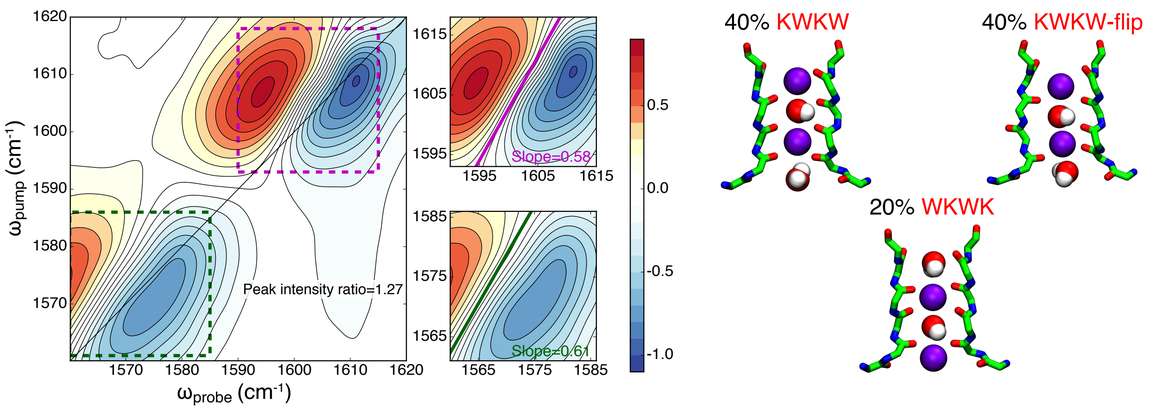
Questions

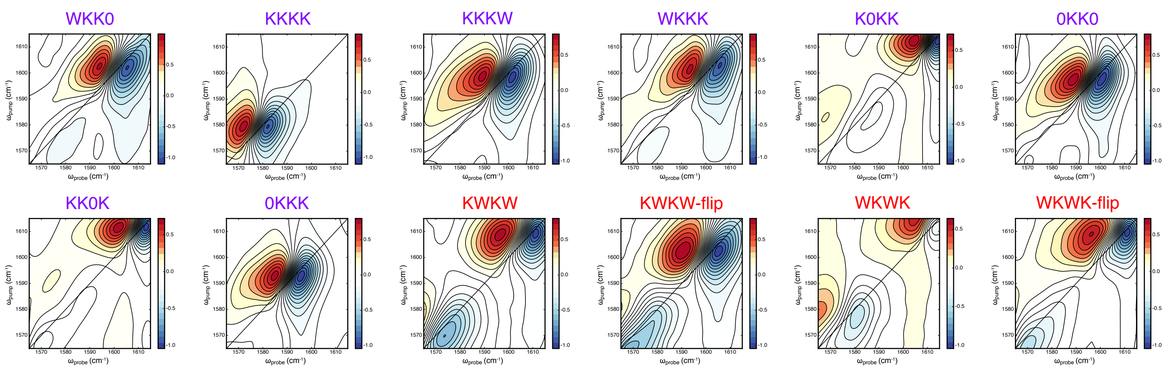
- Is the direct knock-on compatible with 2D IR measurements [4]?
- How do K⁺ channels achieve high conduction rates while simultaneously excluding Na⁺ ions from permeation?
- How does ion permeation differ in related, but non-selective channels with only three ion binding sites (NaK2CNG)?

2D IR calculations

Recently, 2D IR spectra of the synthetic KcsA channel were recorded and interpreted by calculations of theoretical spectra of different ion and water occupancy of the KcsA's selectivity filter [4]. It was reported that only 2D IR spectra that were predicted from simulations of states characteristic for the soft knock-on were compatible with the experimental spectrum. However, different averaging schemes were applied to simulations showing soft knock-on and direct knock-on. To reconcile this apparent discrepancy, we repeated 2D IR calculations for all relevant states for both permeation mechanisms.

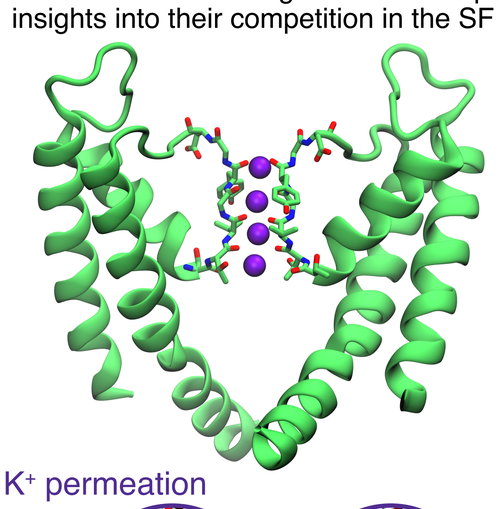


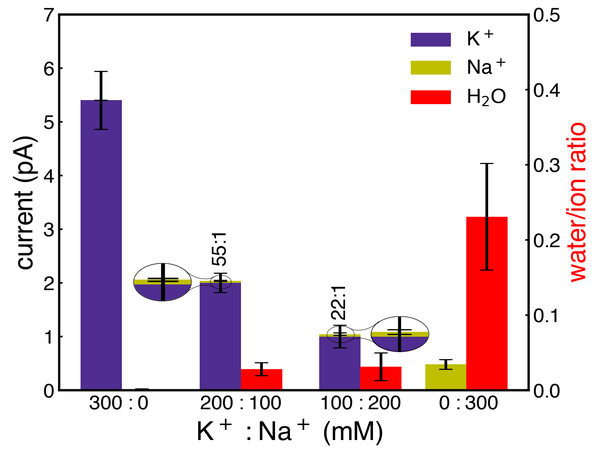




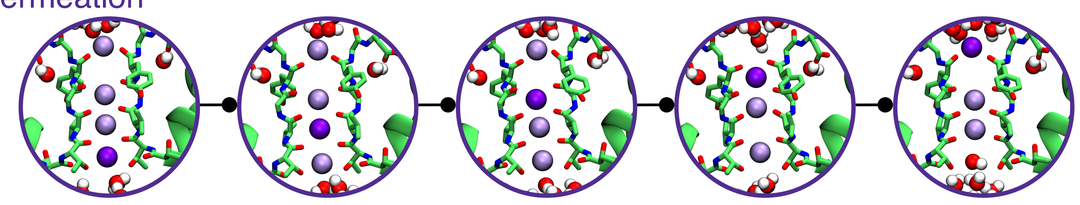
KcsA

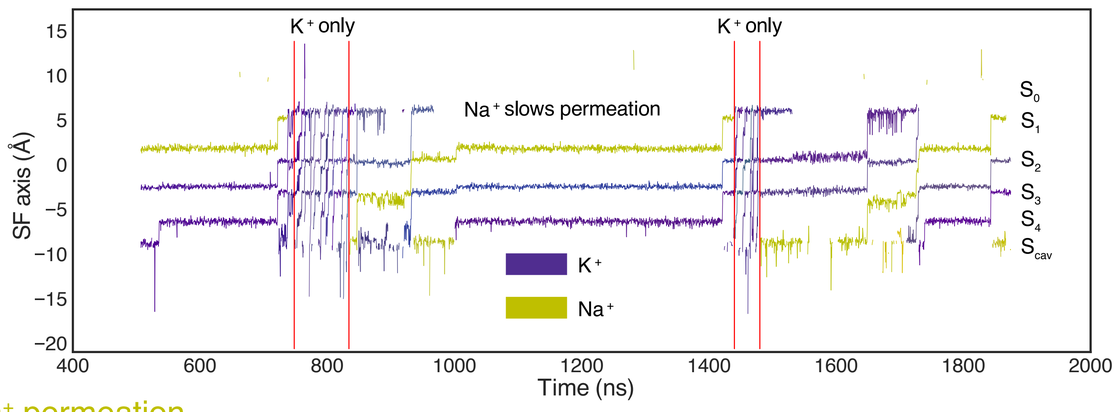
To study ion permeation and selectivity in atomistic detail, we used both electrochemical gradients and applied electric field to generate membrane voltages in MD simulations. These acted as driving forces for the permeation of K⁺ and Na⁺ ions, providing an unfiltered insights into their competition in the SF of the model K⁺ channel KcsA.



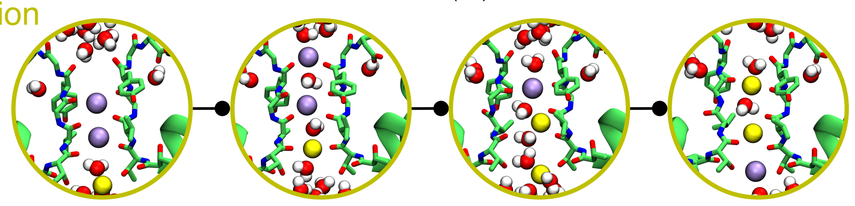


K⁺ permeation



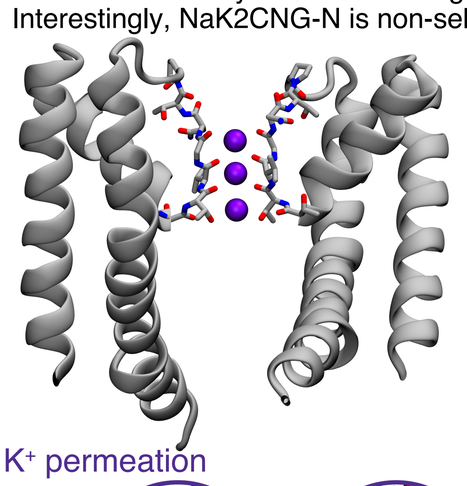


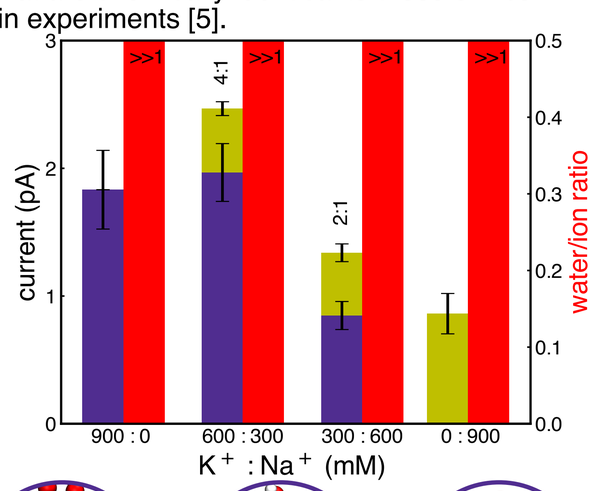
Na⁺ permeation



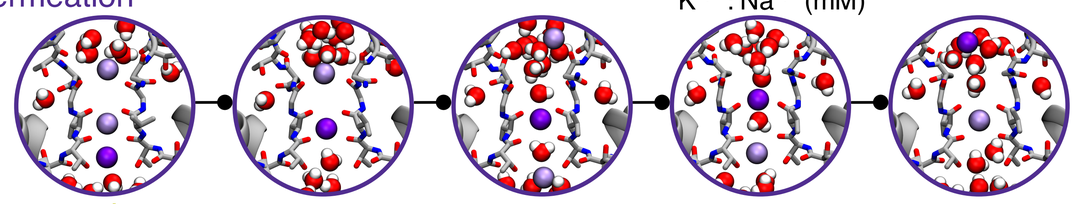
NaK2CNG-N

Next, we used the same methodology to study ion permeation in the NaK2CNG-N channel, whose SF has only three ion binding sites, that are chemically identical to those of KcsA. Interestingly, NaK2CNG-N is non-selective in experiments [5].

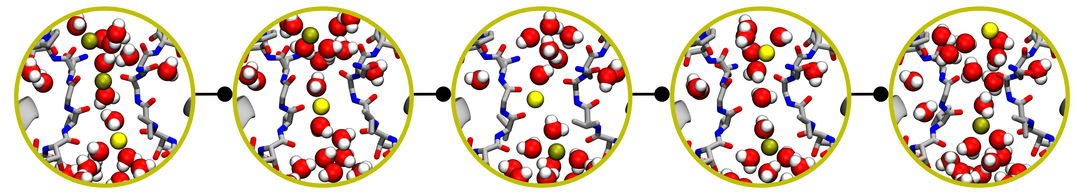




K⁺ permeation



Na⁺ permeation



Conclusions

- Both mechanisms of ion conduction in K⁺ channels can explain 2D IR spectroscopy data equally well.
- Canonical K⁺ channels with four ion binding sites display the direct knock-on mechanism of ion permeation, which leads to both efficient and selective conduction of ions, due to full dehydration of permeation ions.
- Channels that allow for high levels of water permeation conduct ions in a non-selective manner.

References

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