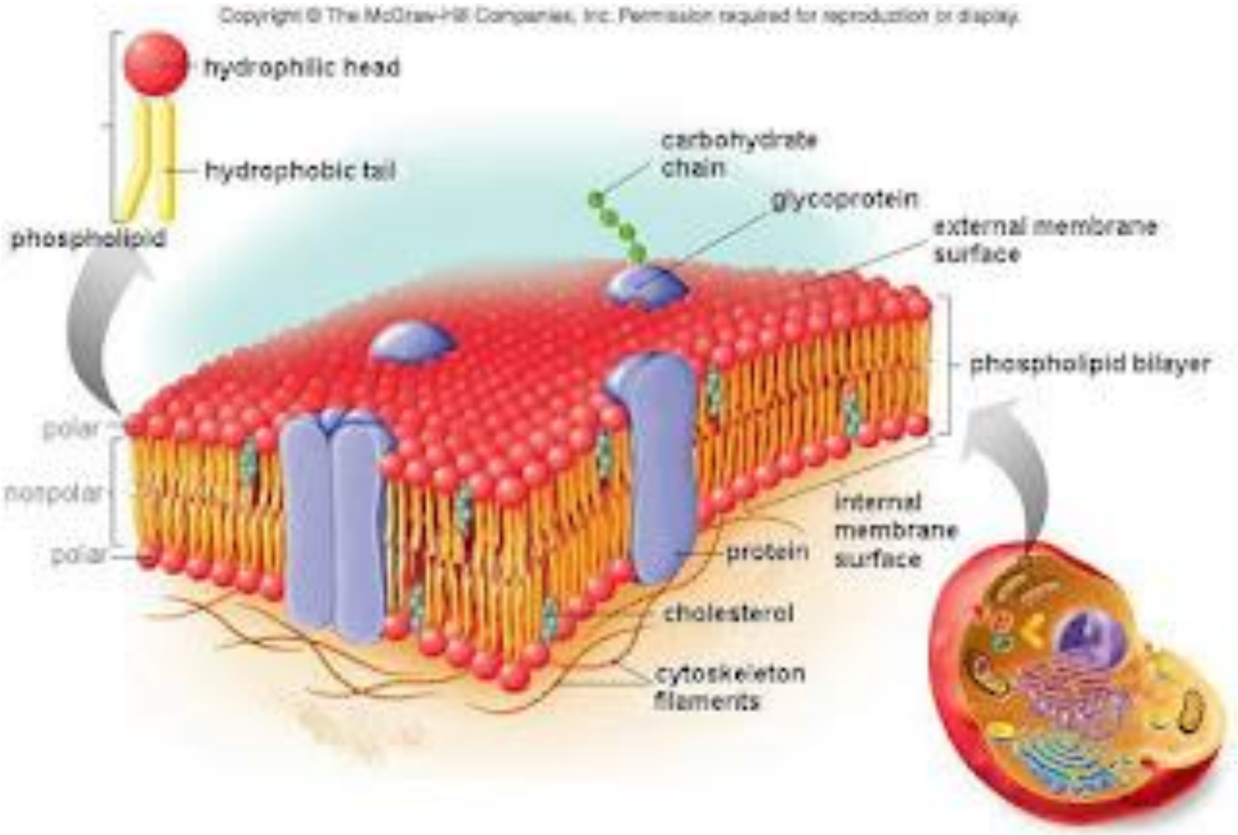
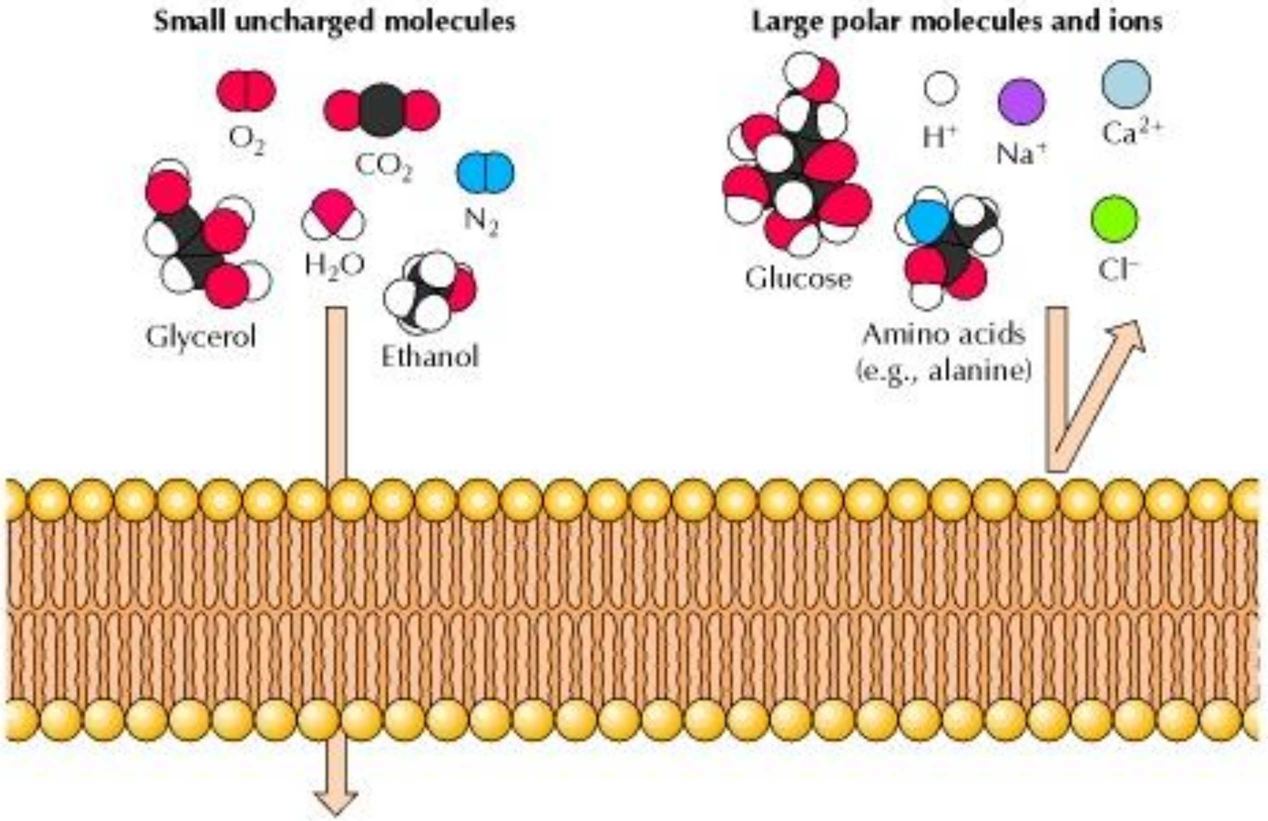
Modeling Ion Movement Through Channel Proteins

The Cell Membrane



The Problem…



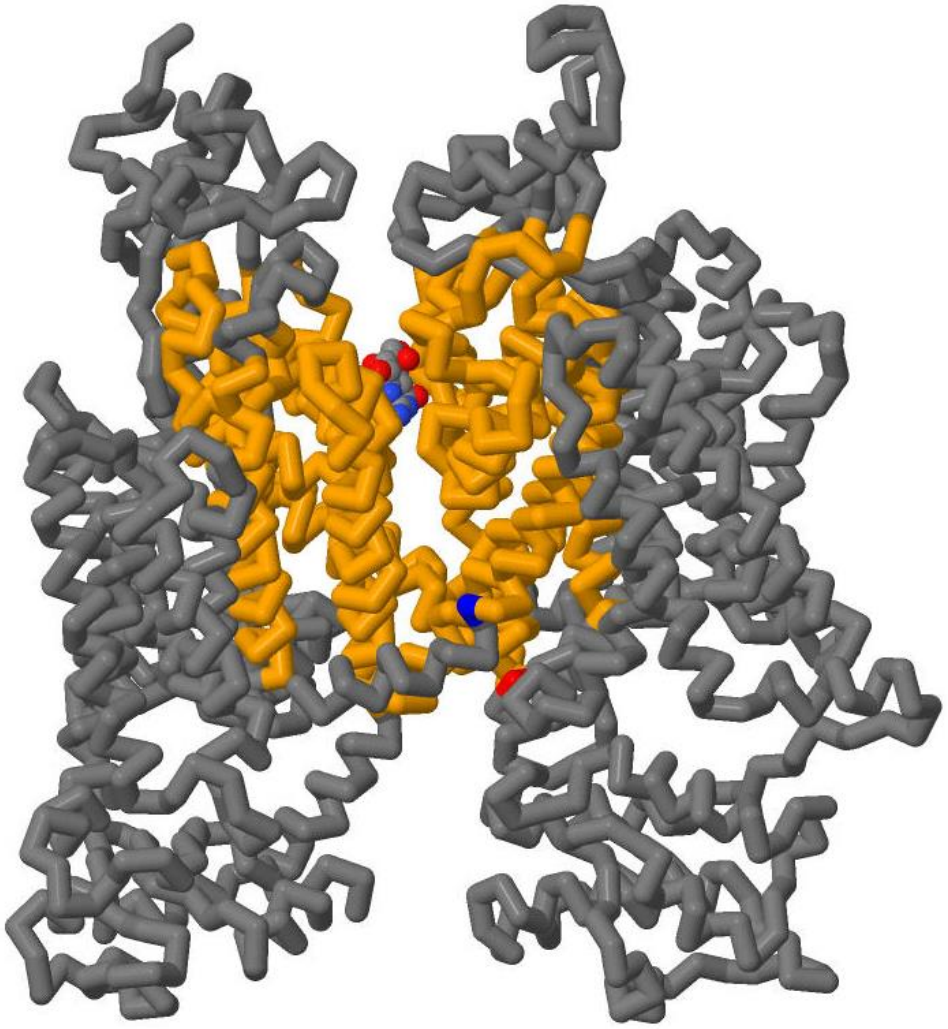
Small uncharged molecules
O_2
CO_2
N_2
H_2O
Glycerol
Ethanol
Large polar molecules and ions
Glucose
H^+
Na^+
Ca^{2+}
Cl^-
Amino acids
(e.g., alanine)

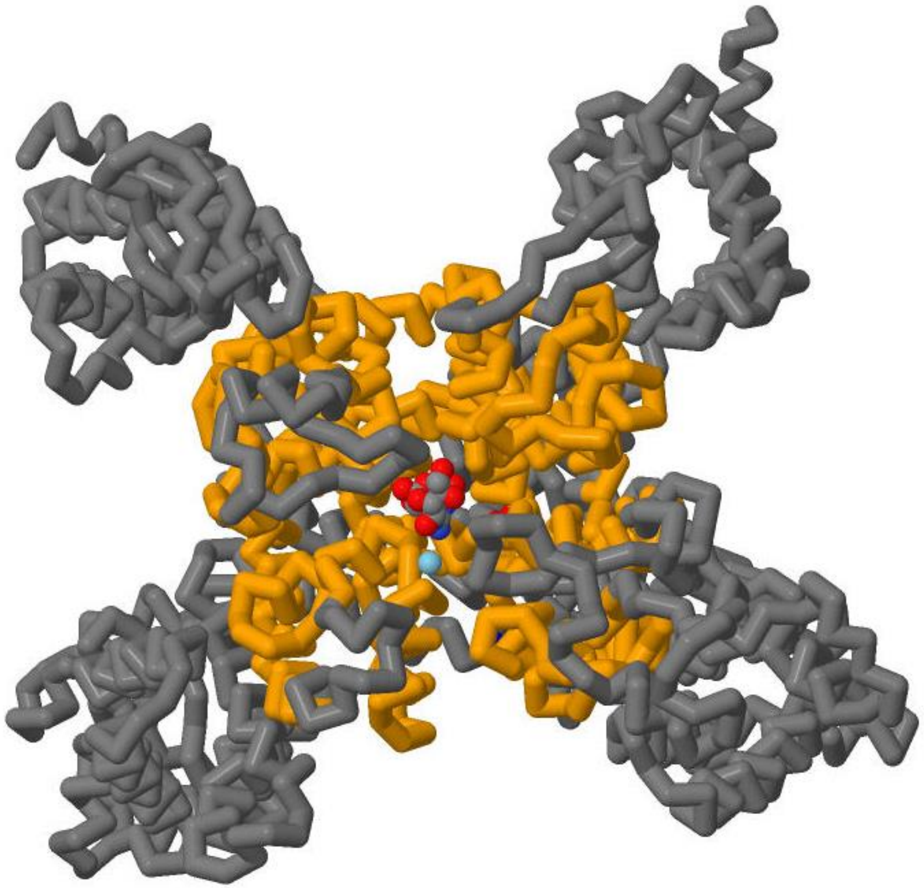
How does a channel “know” which ion to transport?

- They don’t…
- They follow the basic rules of chemistry!

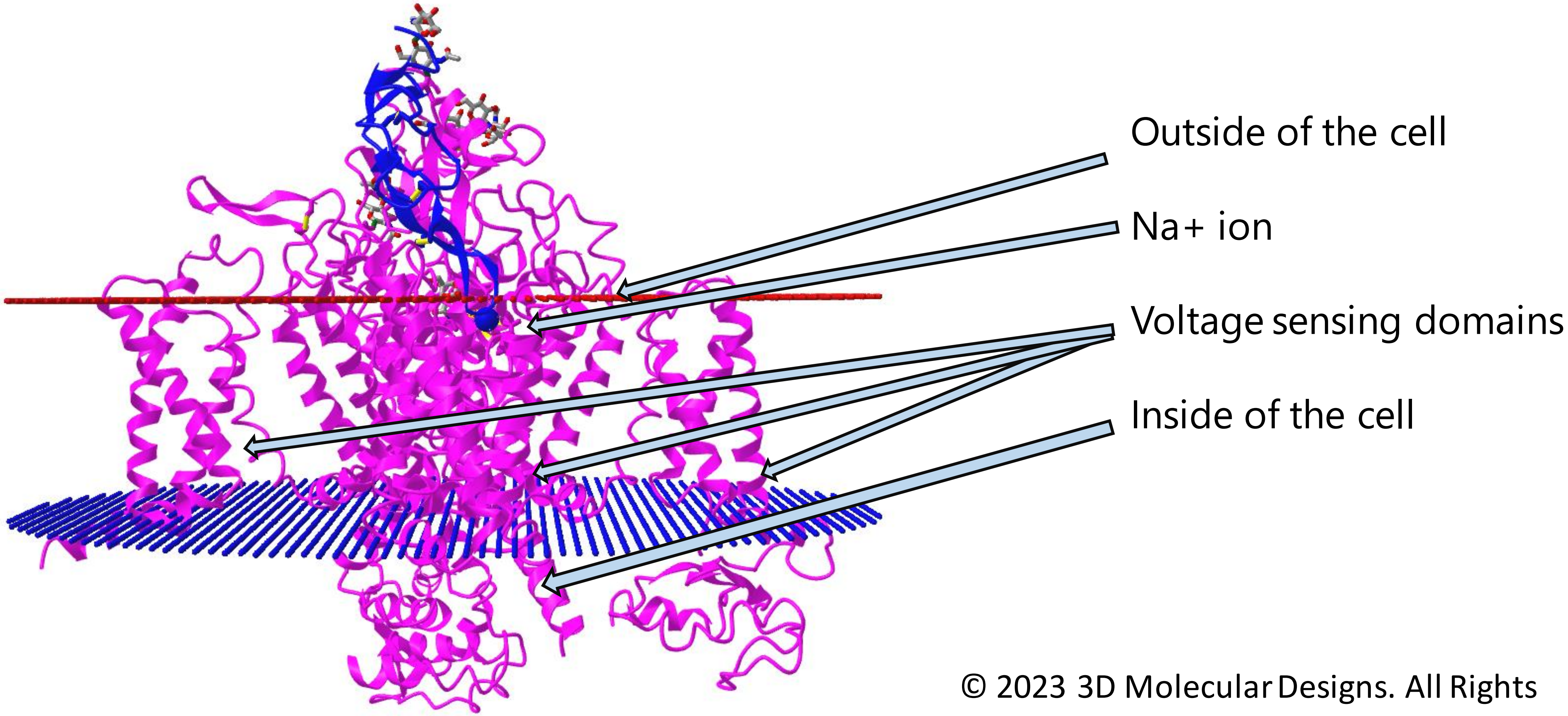
Let's look at the Sodium (Na+) Channel first

These are Voltage-Gated Na+ Channels - monomers





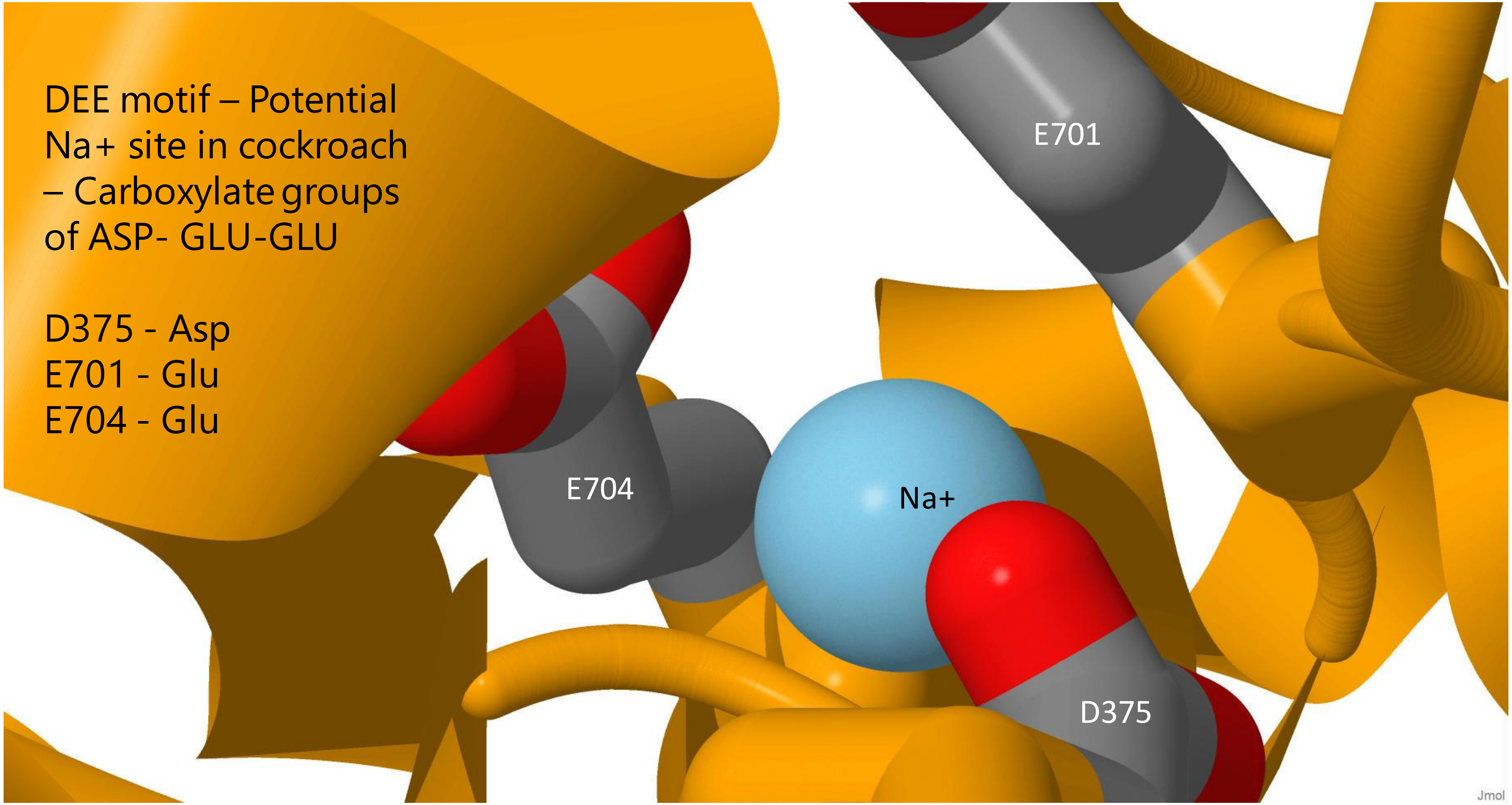
Membrane orientation



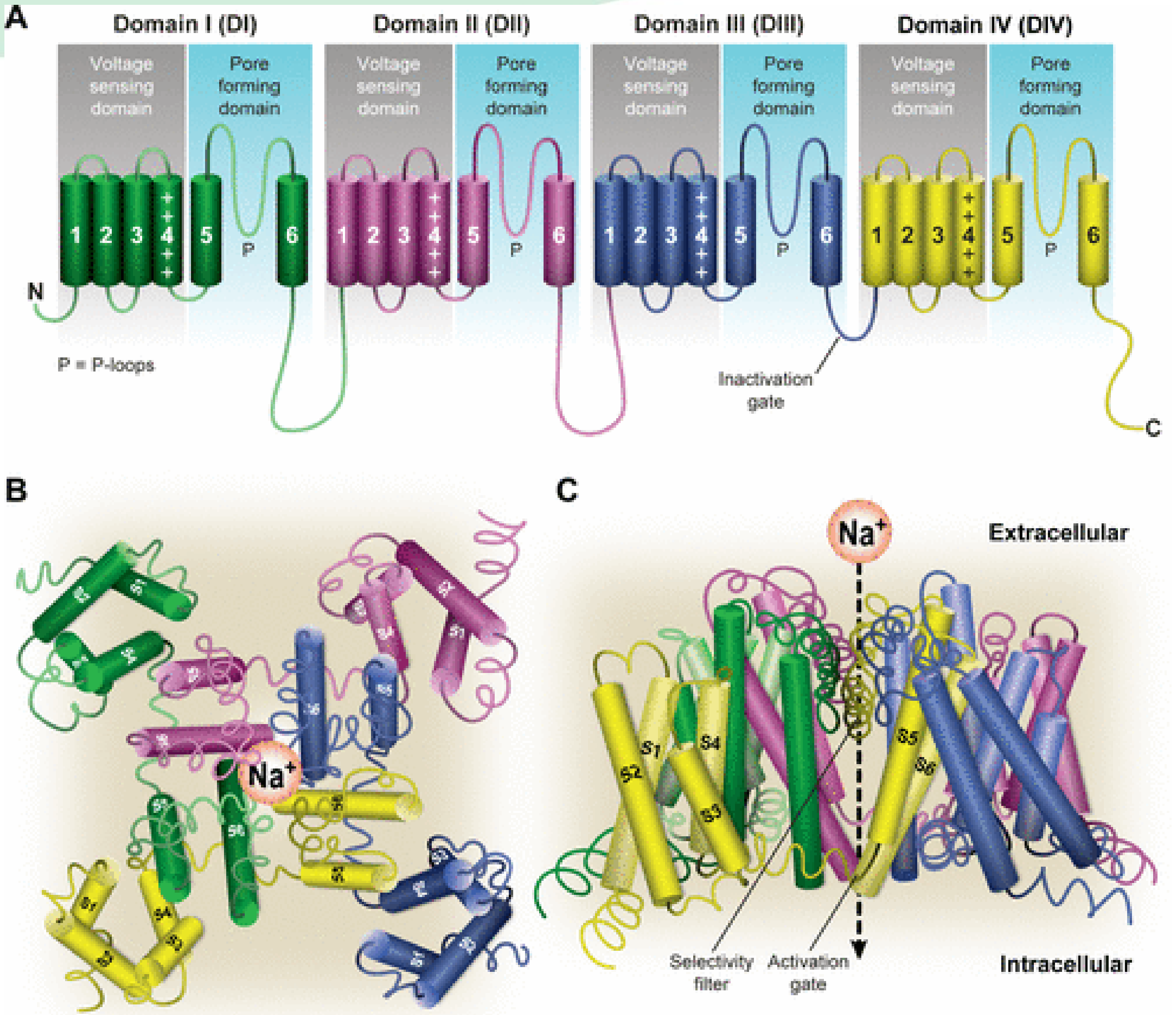
DEE acts as a selectivity filter for Na+ ion

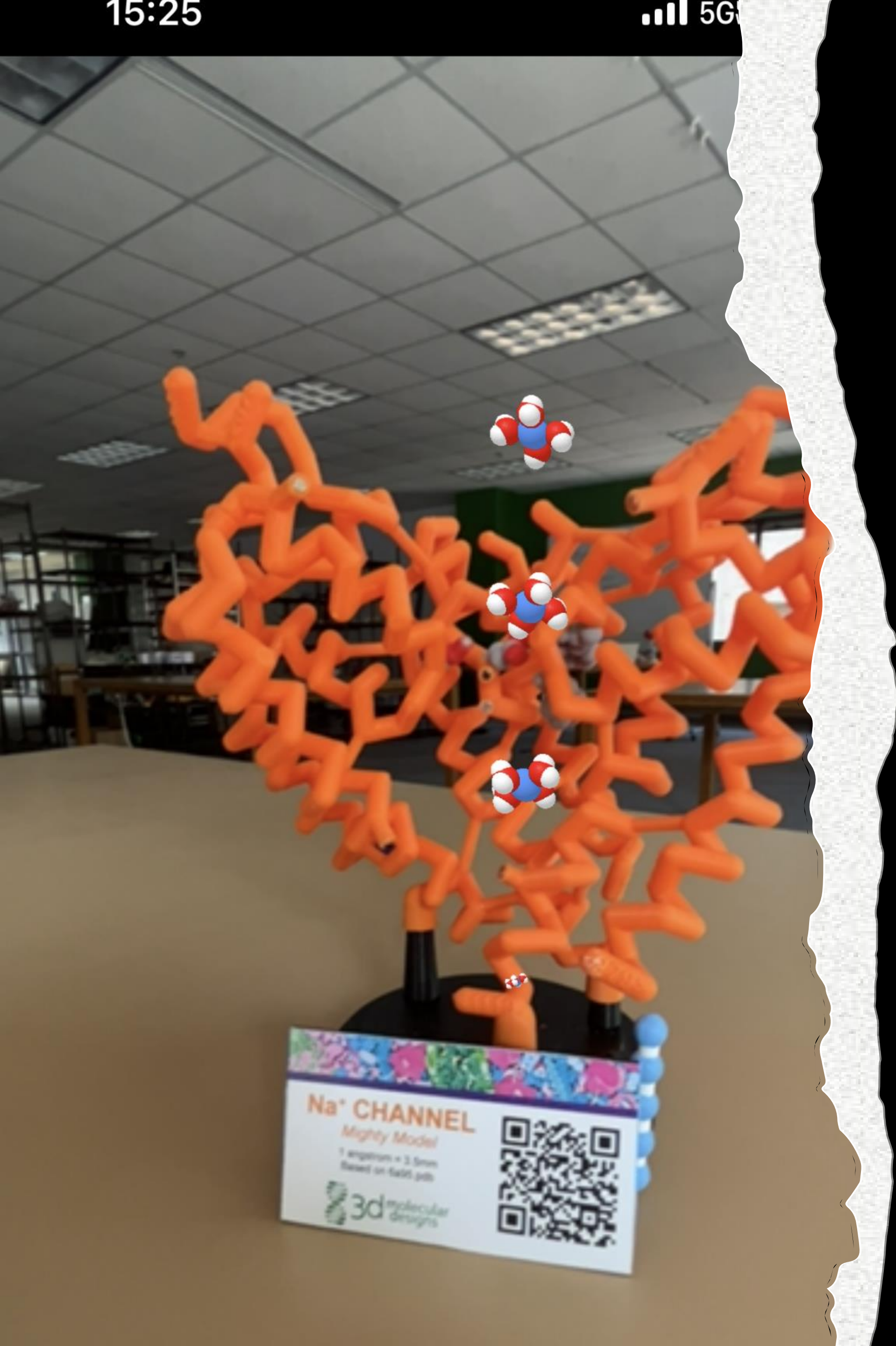
DEE motif – Potential Na+ site in cockroach – Carboxylate groups of ASP- GLU-GLU

D375 - Asp
E701 - Glu
E704 - Glu



Inactivation and refractory period

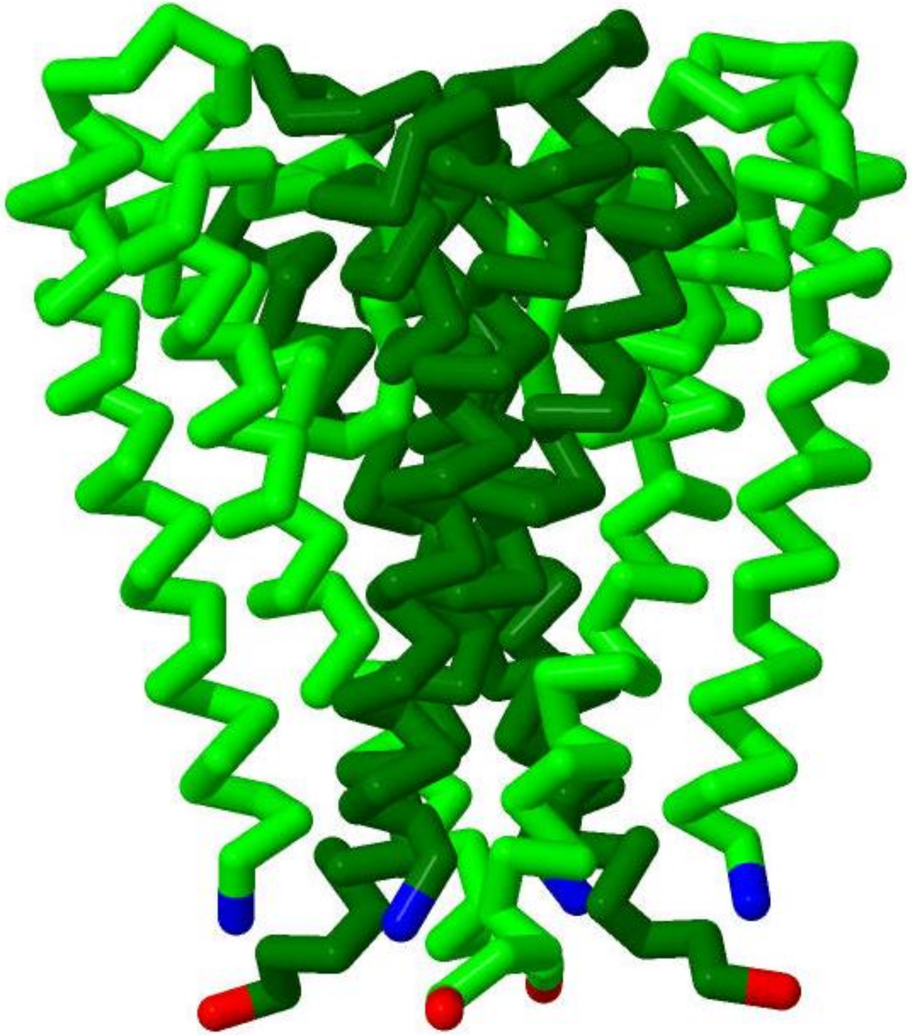




Use the QR code to see it in action-

- Note the direction of movement.
- What is the molecule around the Na+ ions?

Homotetramer



The K+ channel is made up of 4 identical subunits.

In our pdb file (2A9H), the channel is broken into 4 chains

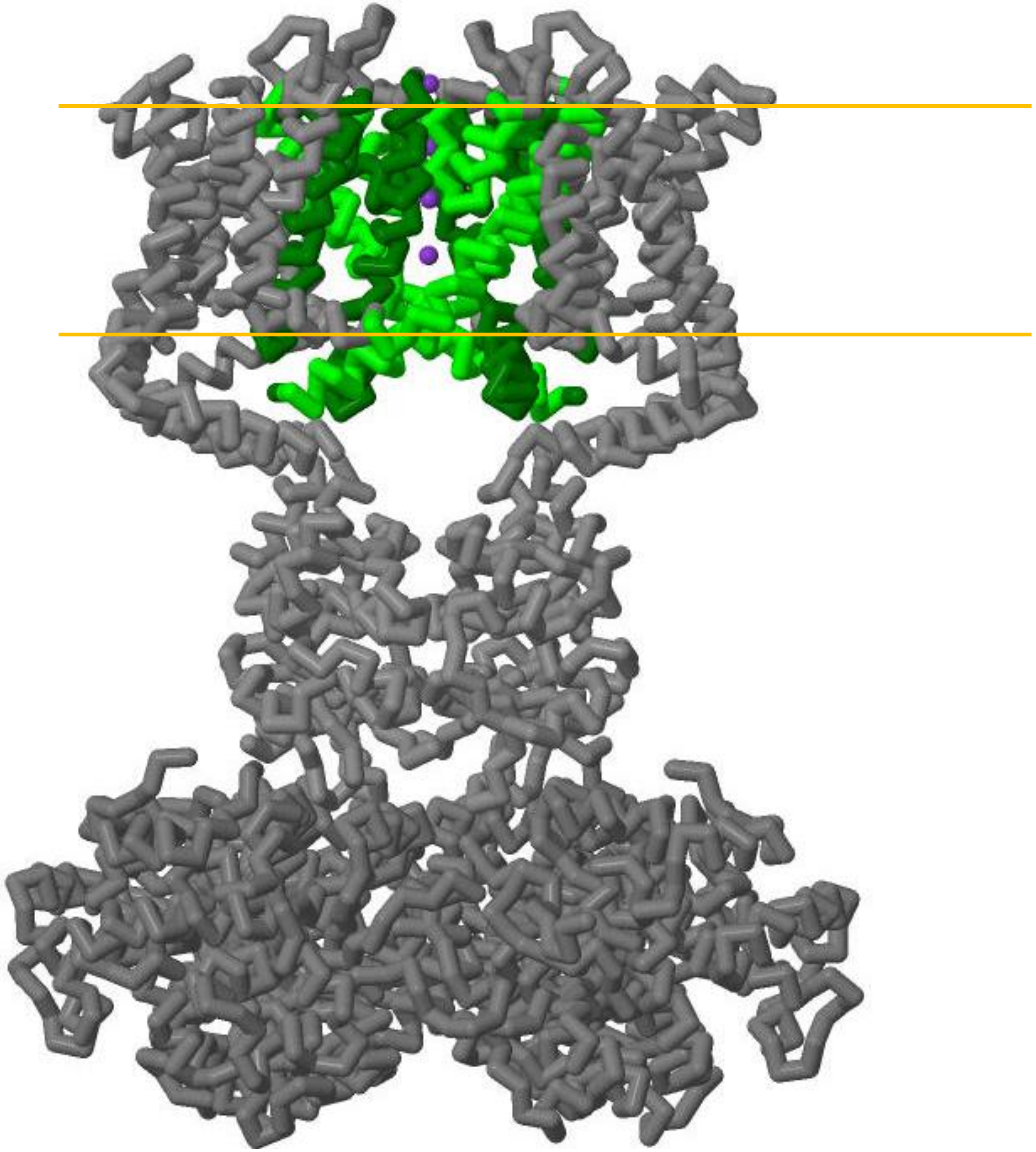
A:

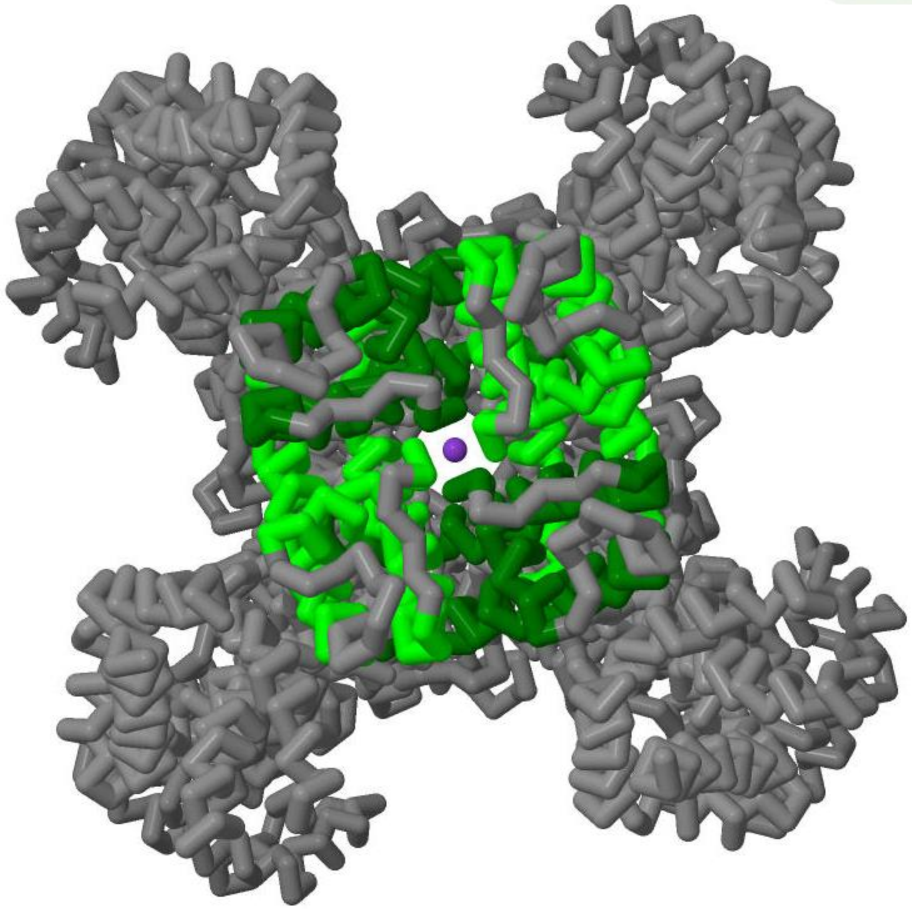
B:

C:

D:

This potassium channel is voltage-gated





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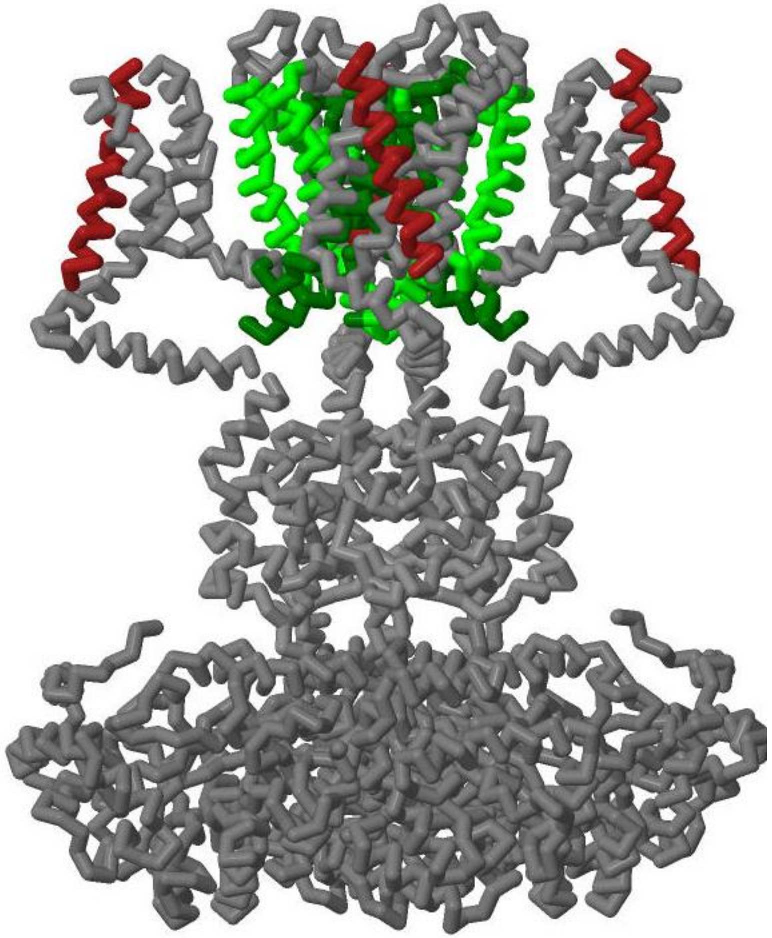
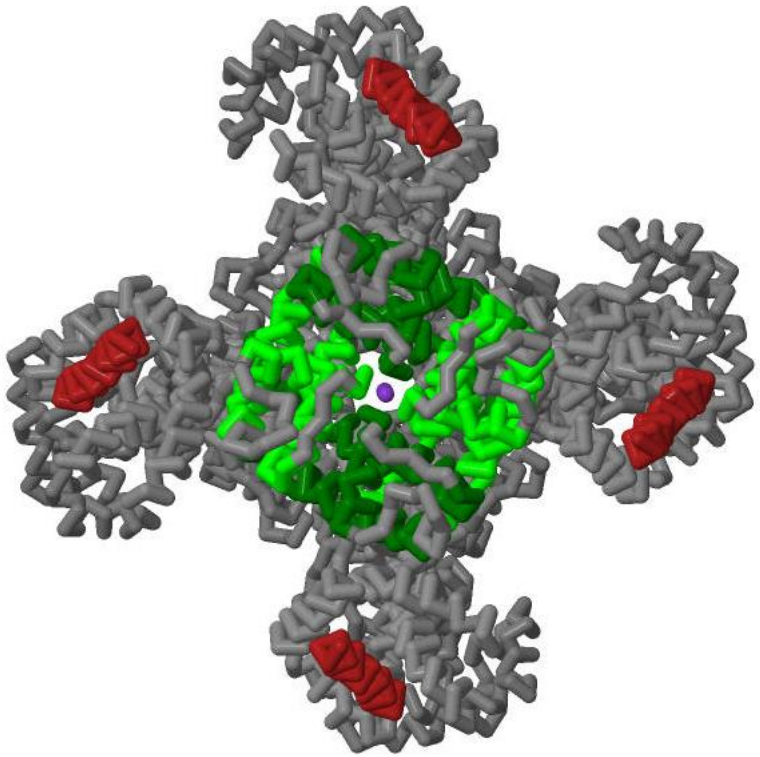
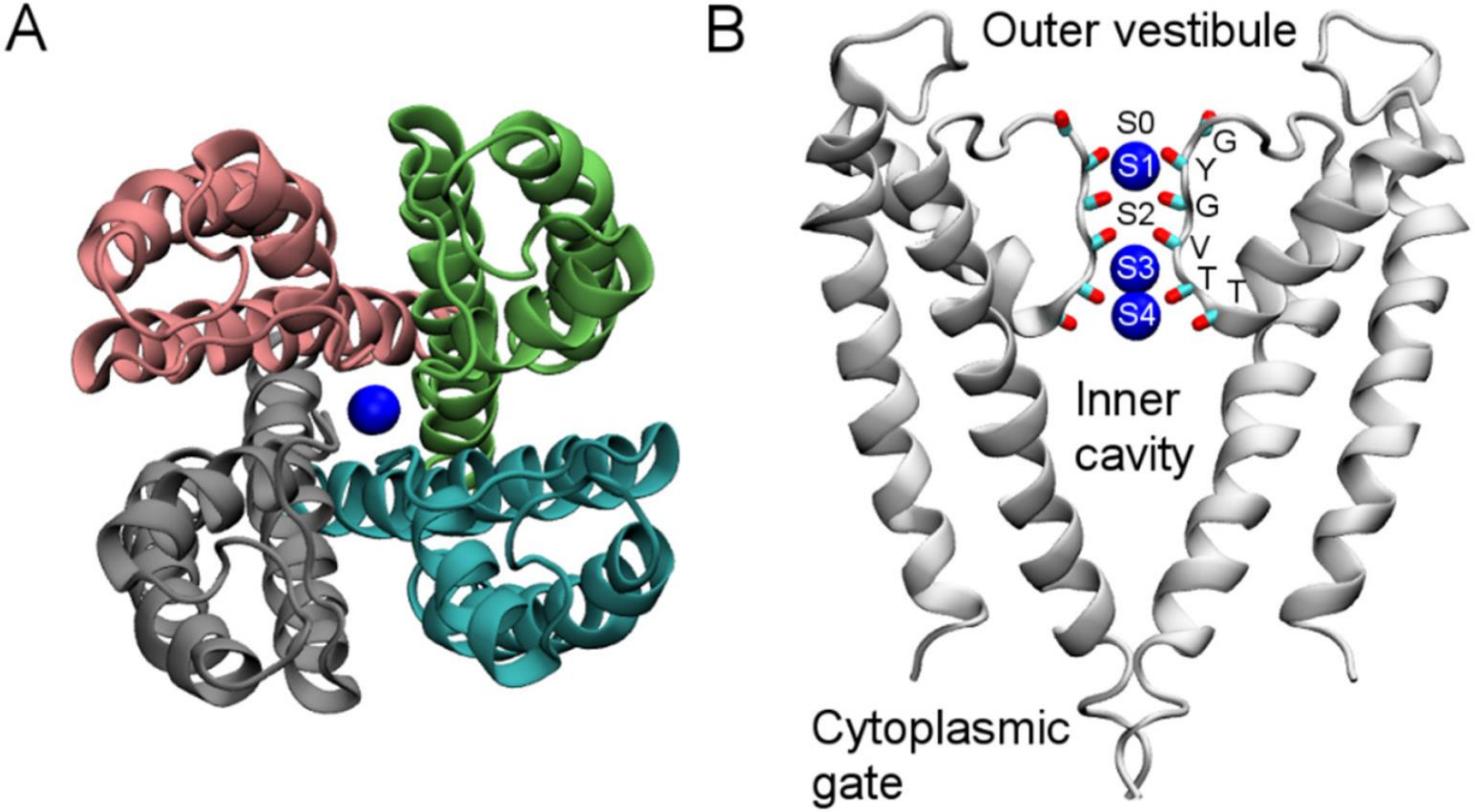




What does a K^+ channel do?

- K^+ channels play an important role in the nervous system and generating an action potential (message). K^+ channels are highly selective in the ions it allows to pass through.

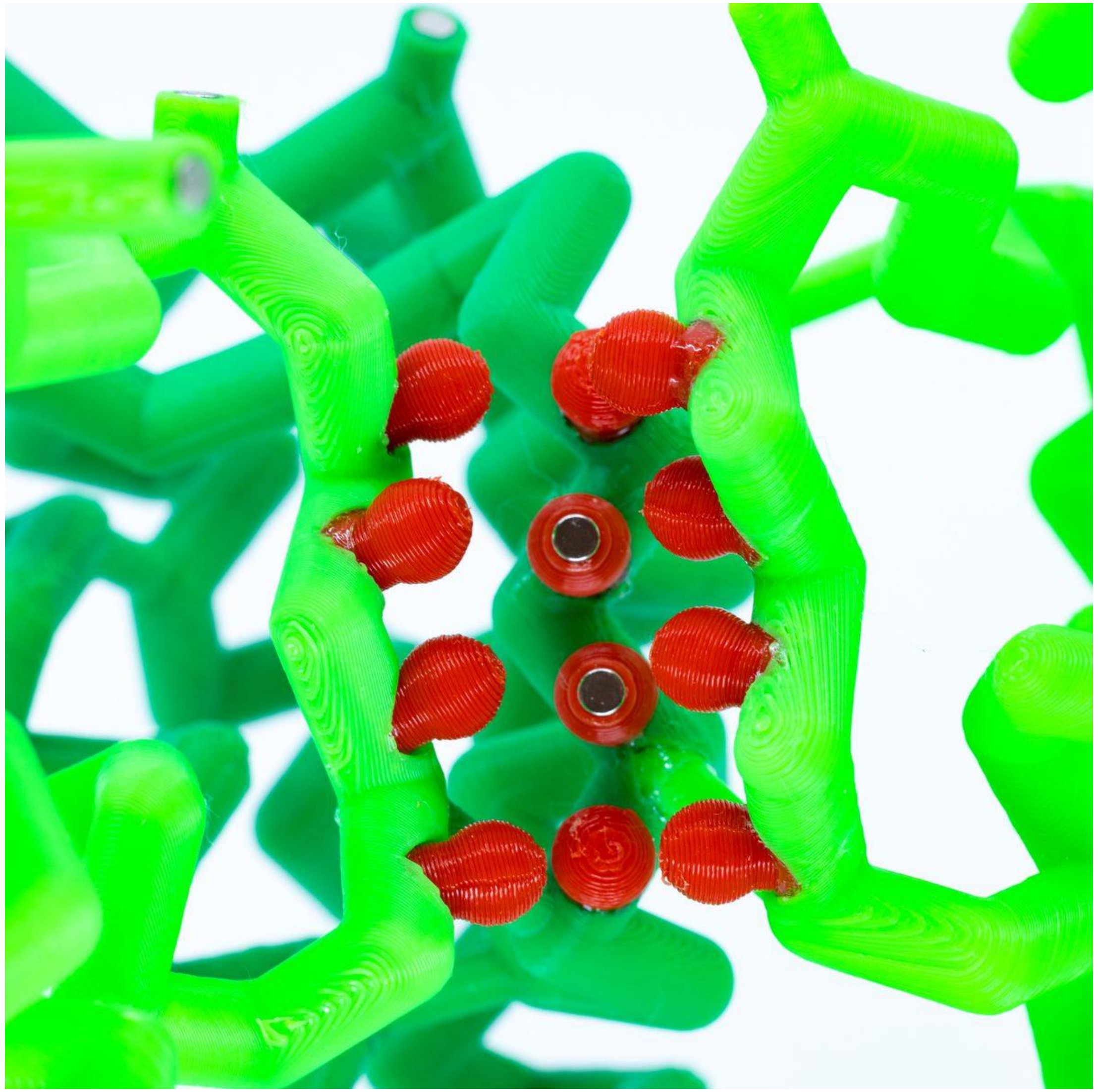


- *Why do you suppose this is important?*

Protein "Fingerprint":
TTVGYG

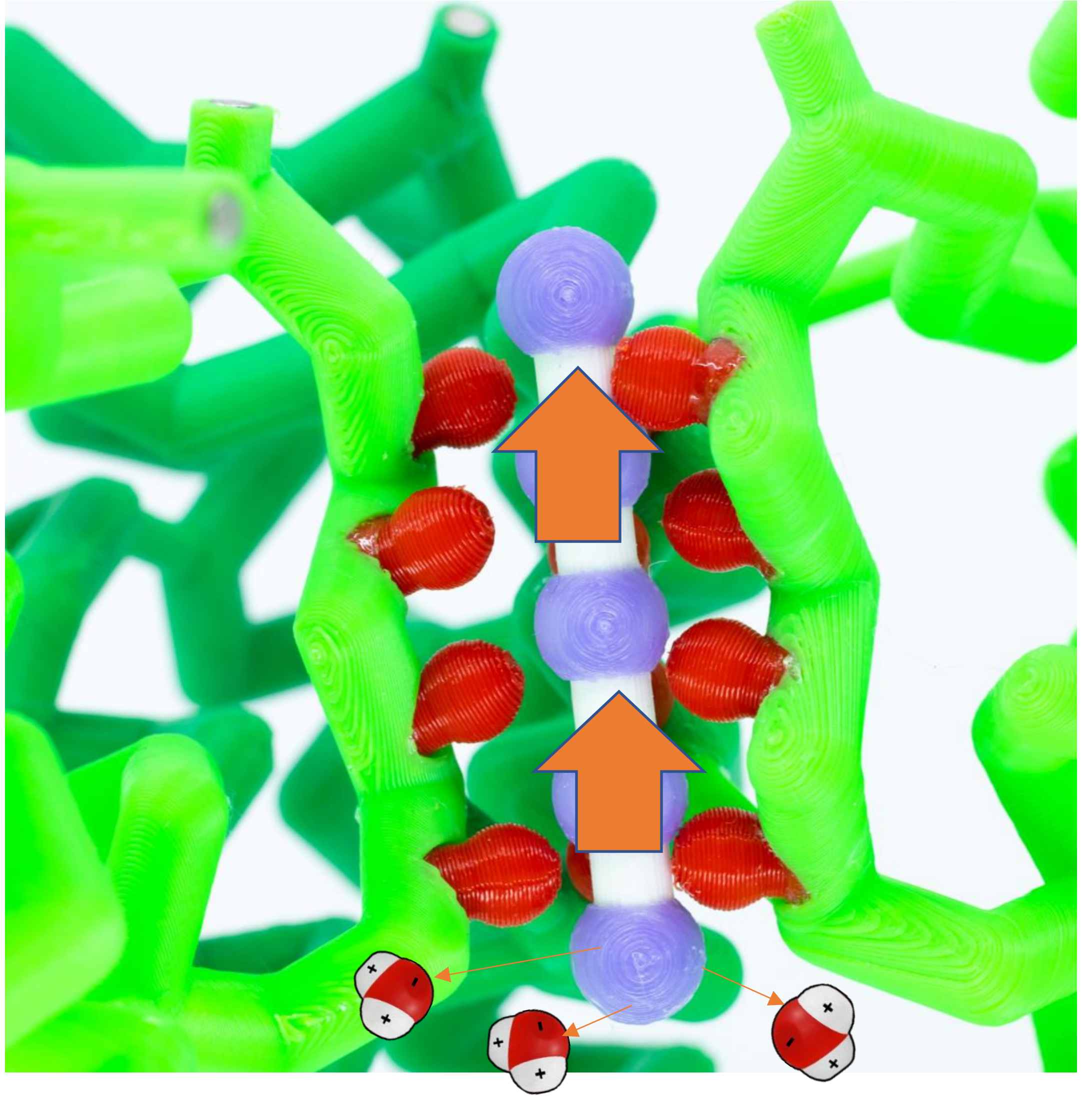
The carbonyl groups

The carbonyl oxygens of the 6 signature sequence amino acids (TTVGYG) in the backbone are oriented towards the pore.



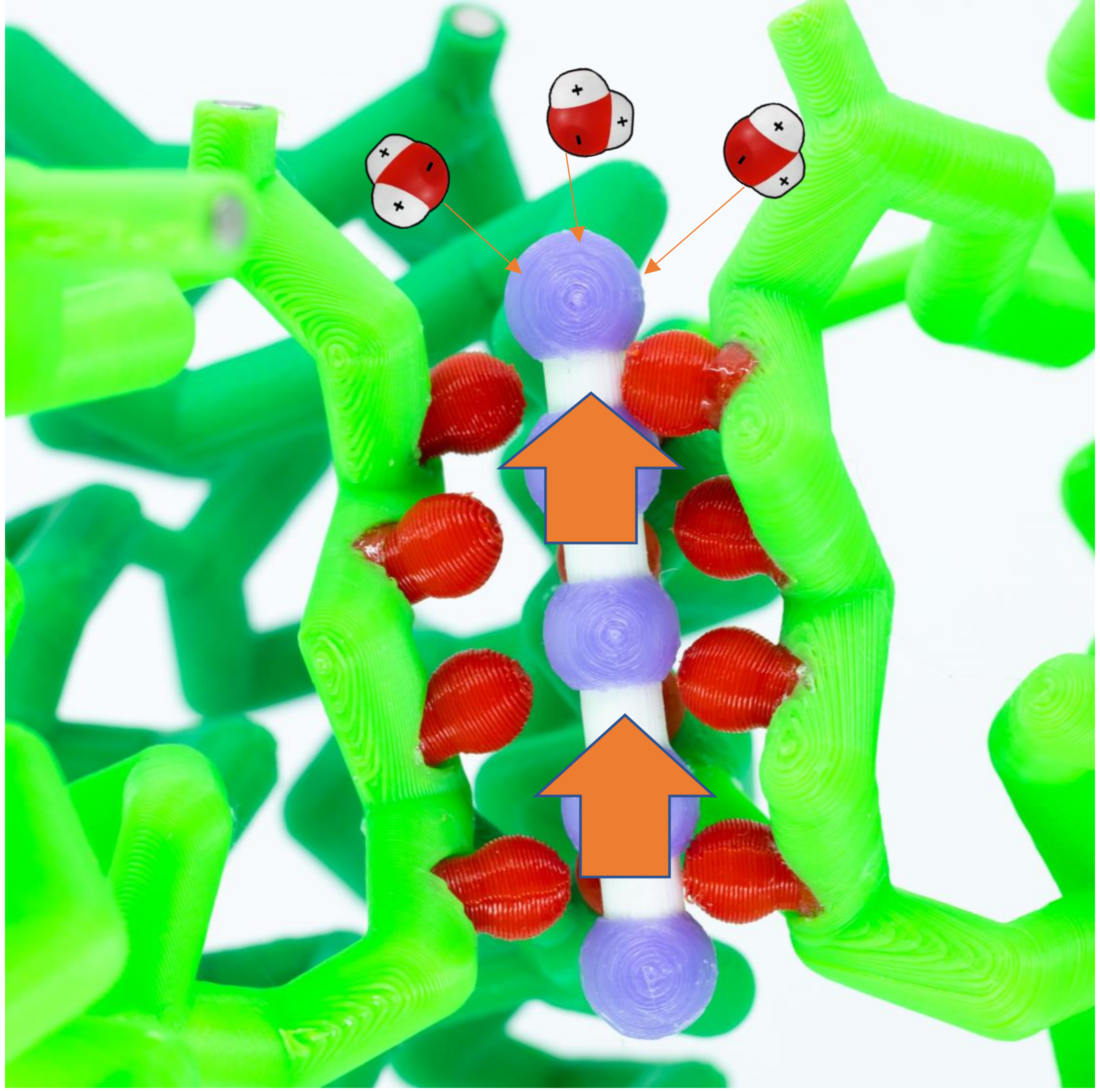
The carbonyl groups

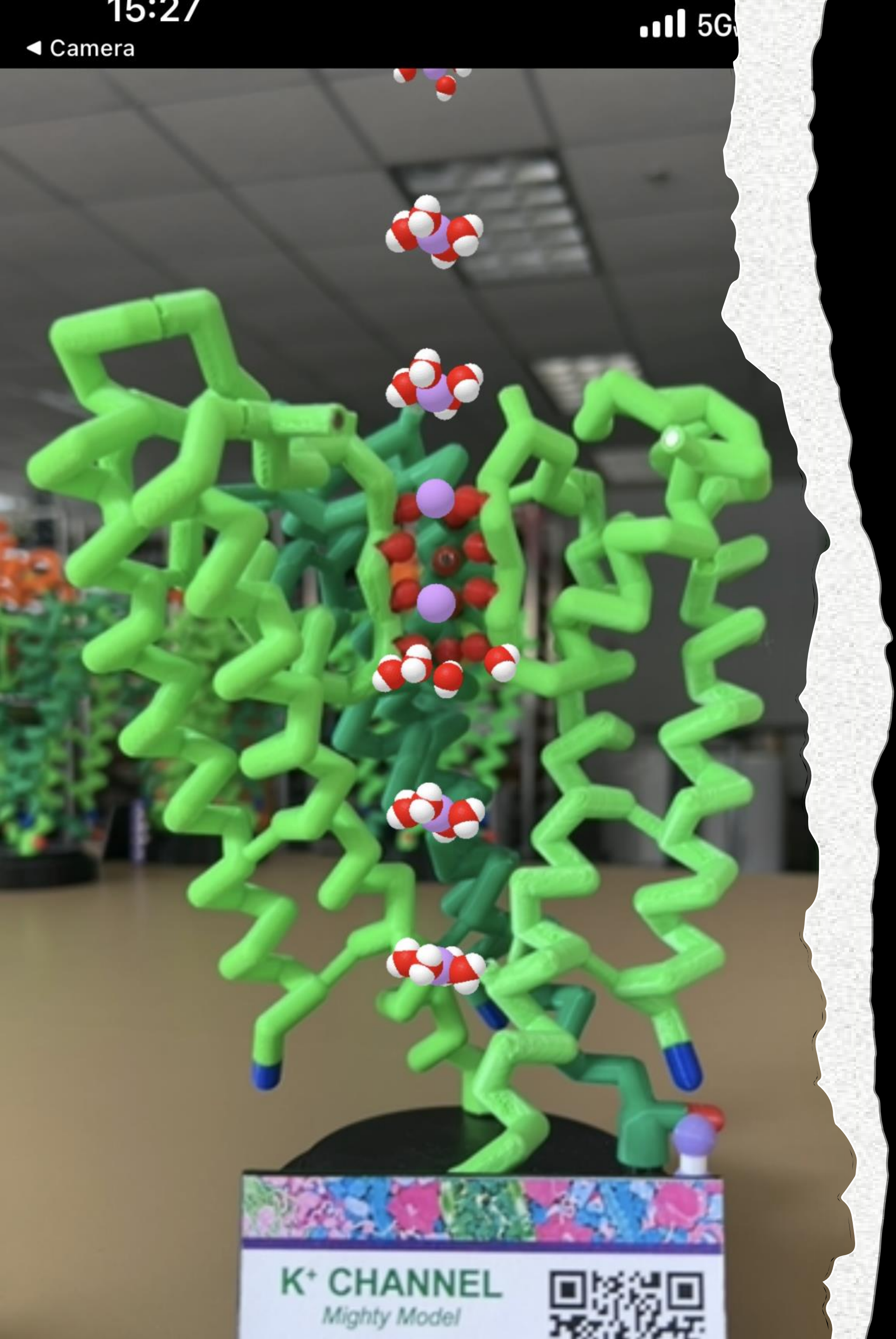
Then polarity of the carbonyl groups remove water from a hydrated K+ ion near the vestibule and facilitate its movement through the pore like an elevator.



The carbonyl groups

Potassium is immediately rehydrated once it transitions through the membrane.

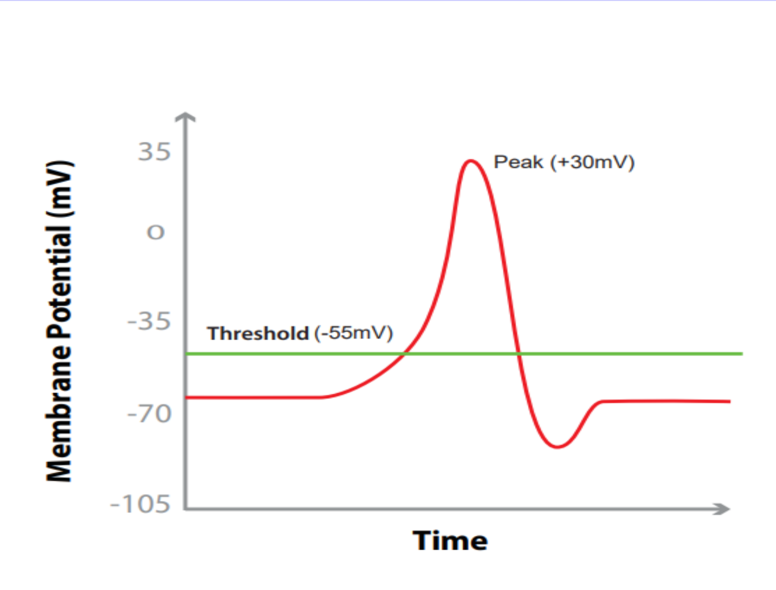




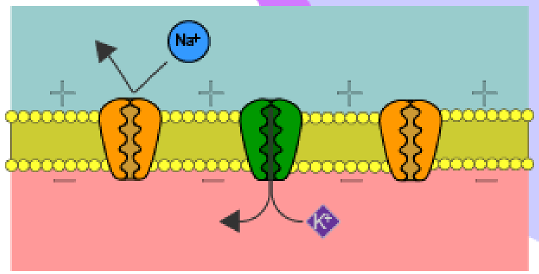
Use the QR code to see this in action!

How is this different from the Na+ Channel?

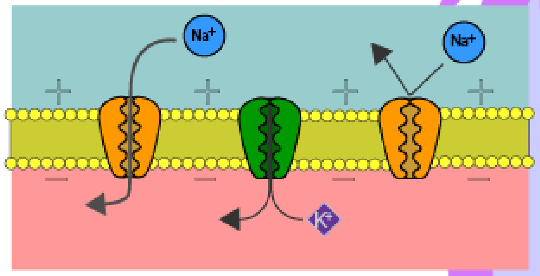
What are the similarities?



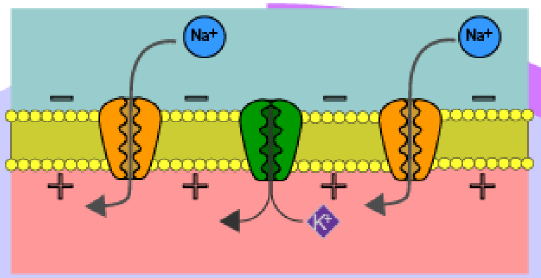
1 **Resting state**- The resting potential of the neuron is maintained by having the voltage gates closed in both Na+ and K+ channels.



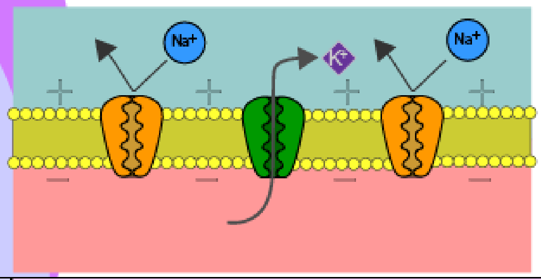
2 **Depolarization** – Some of the Na+ channel activation gates are opened by a stimulus. Na+ ions move through the channels and depolarize the membrane. If the depolarization reaches the threshold, it will trigger an action potential.



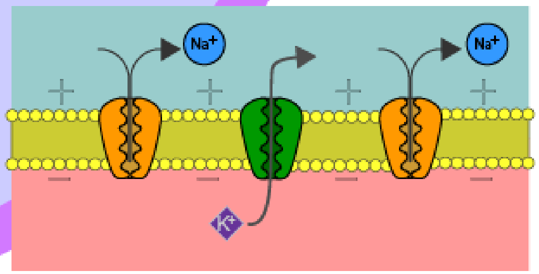
3 **Rising phase** – Most Na+ activation gates are now open, causing a large increase of Na+ ions inside the membrane. K+ channels remain closed. The higher concentration of Na+ ions make the inside of the membrane positive.



4 **Falling phase of the action potential** – K+ gates open, allowing K+ ions to move to the extracellular space. Na+ channels inactivation gates close, preventing the influx of Na+ ions. As more K+ ions leave the cell, the interior membrane becomes more negatively charged.



5 **Undershoot** - Activation and inactivation gates on Na+ channels are closed, but the gate on some K+ channels are still open. As the last K+ gates close, inactivation gates of Na+ channels open and the membrane is back at resting state.

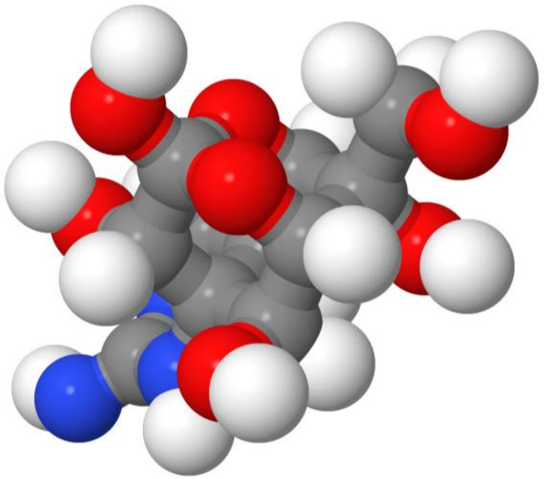


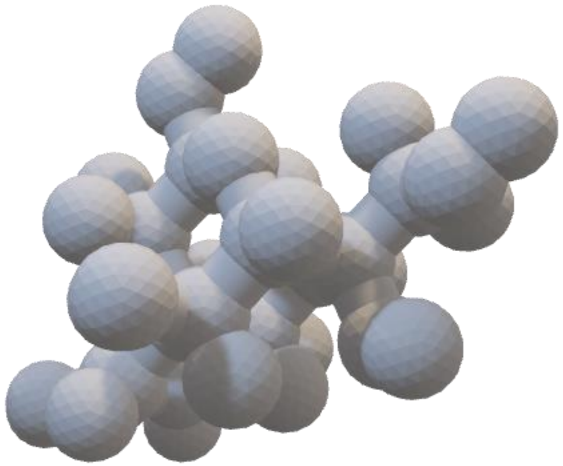
Link

Voltage-Gated Sodium Channel Inhibitor

TTX -> Tetradotoxin

Highly toxic – LD50 - 334ug/kg by ingestion and 8ug/kg by injection



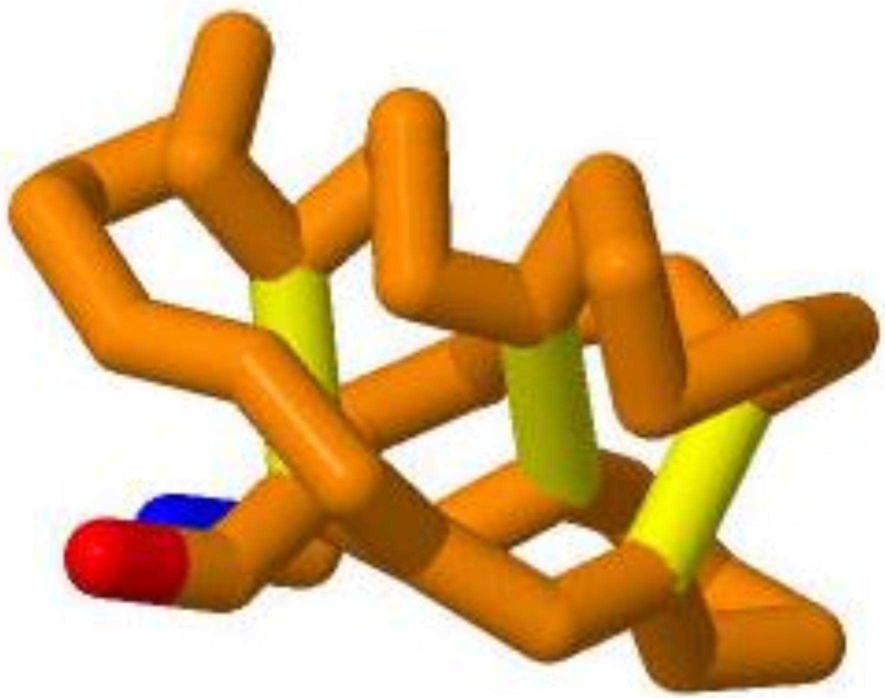


Explore this virtually and print this .stl file for use with you Sodium Channel Mighty Model!

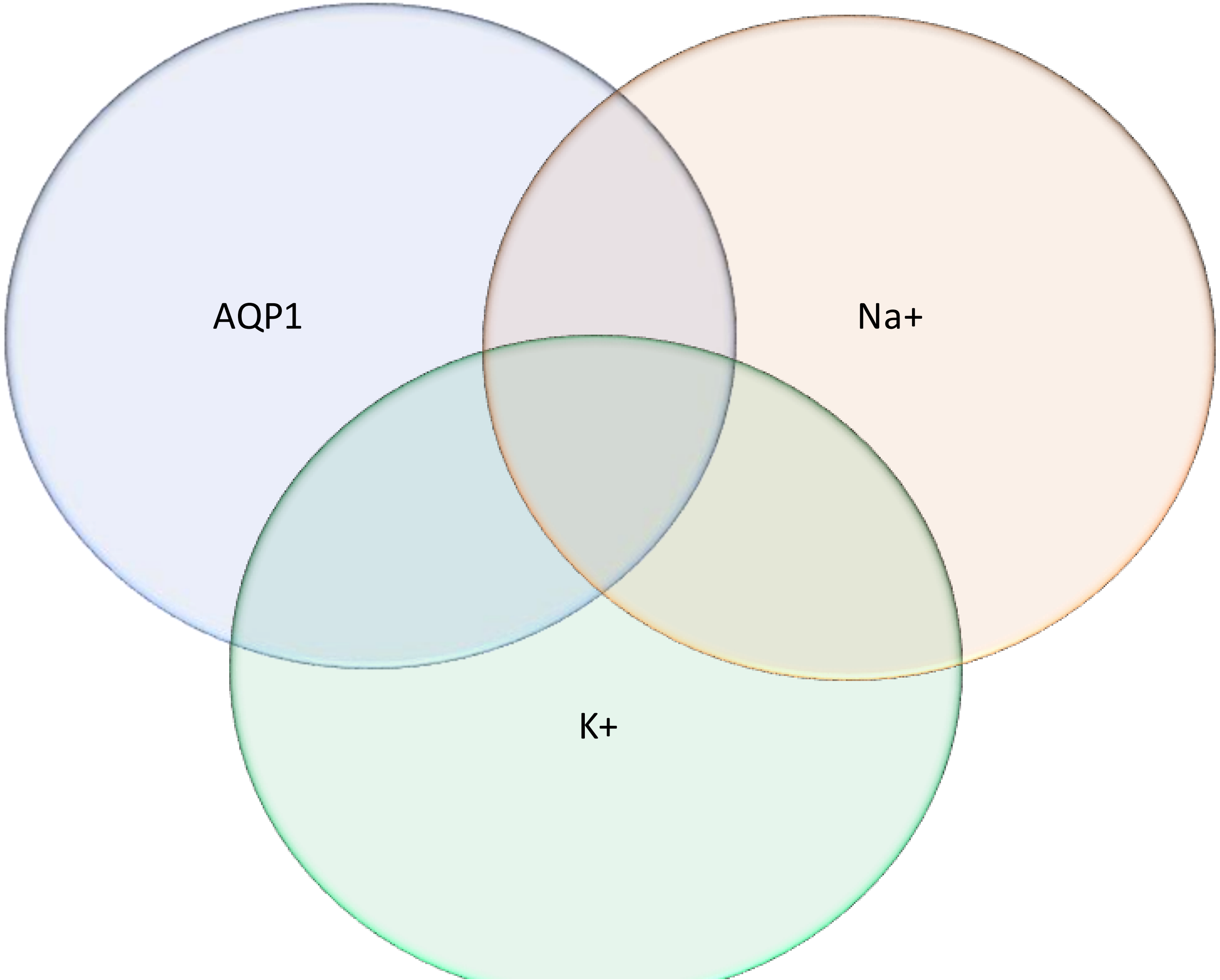
Charybdotoxin (CTX) is made of 37 Amino Acids. Six of them are cysteines. Statistically, it should only have two.

Write: Why do you think there are so many?

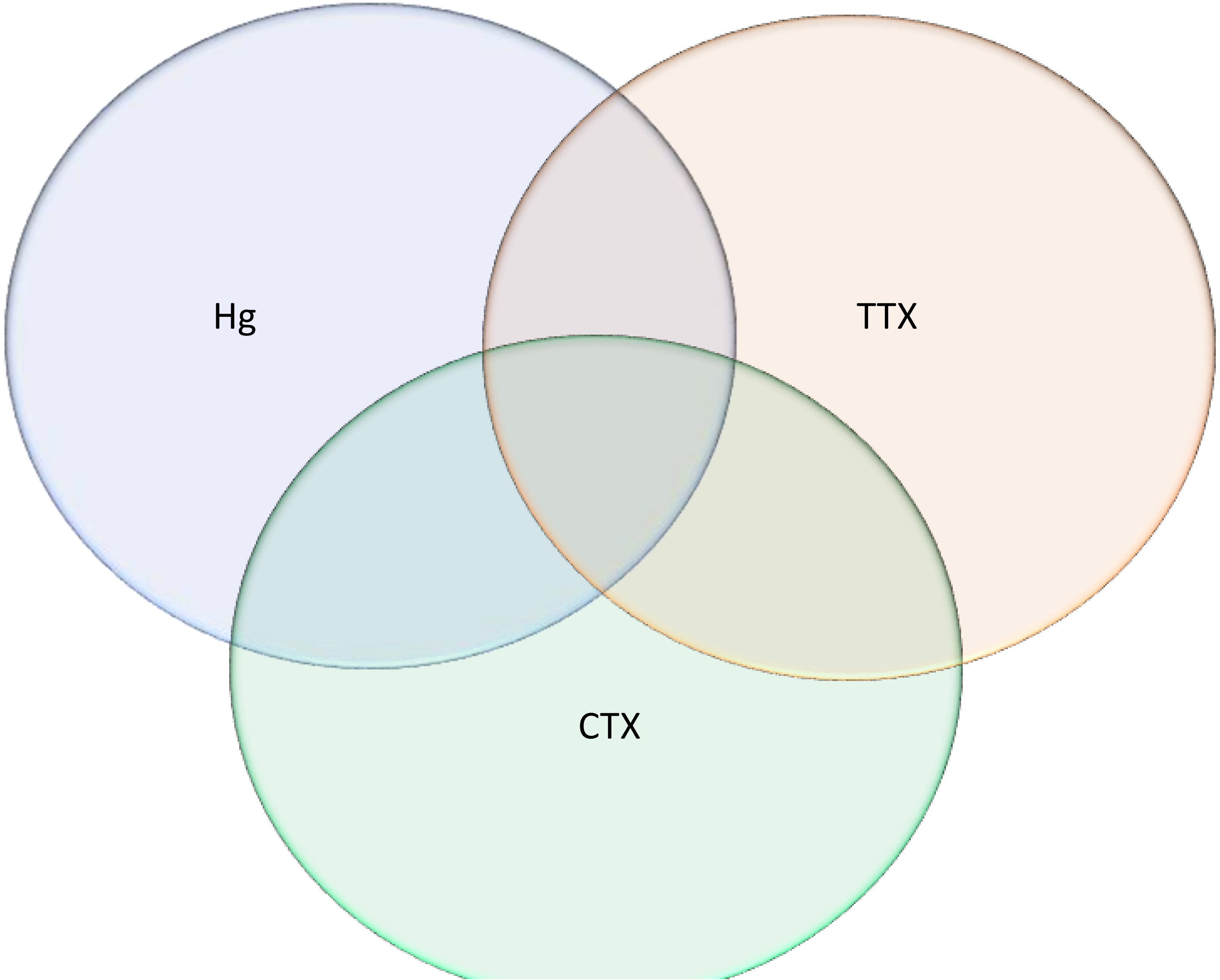
*Hint – the cysteines will form 3 disulfide bonds

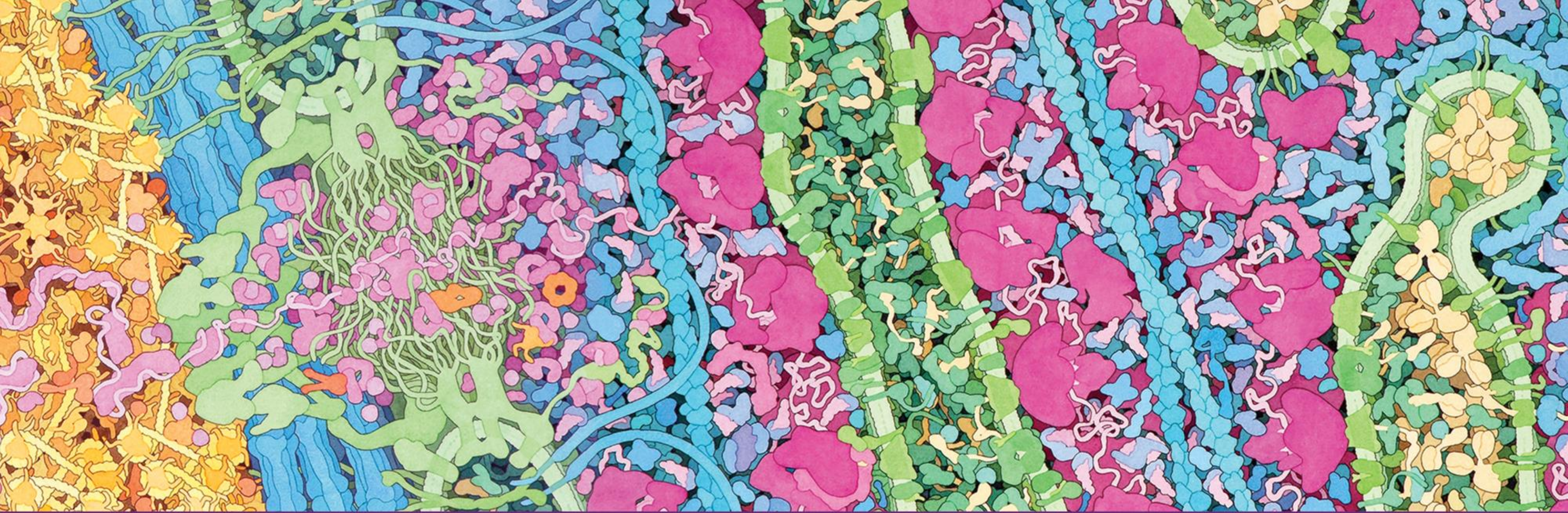


Compare and contrast our 3 channels



Compare and contrast our inhibitors





3d molecular designs

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