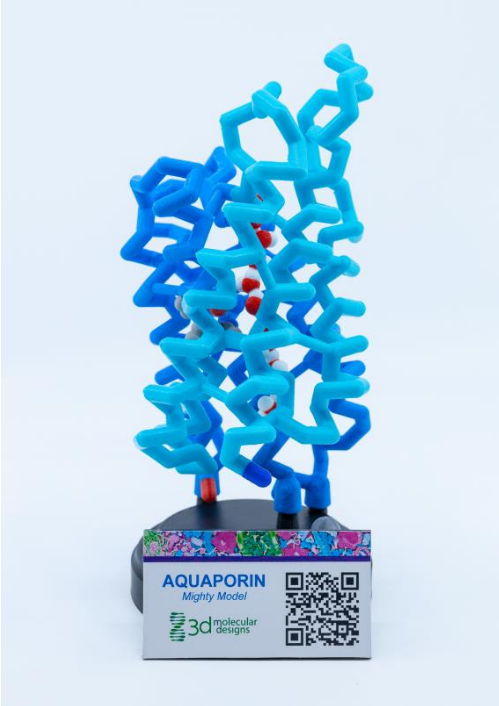
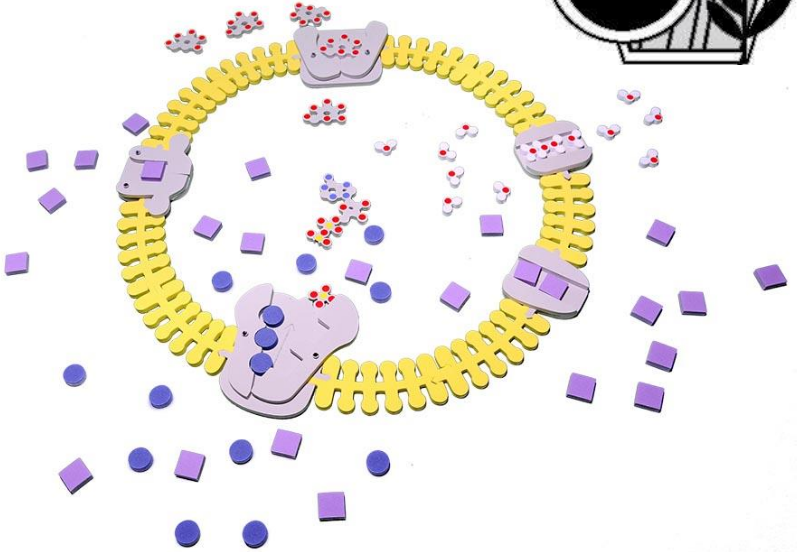




Water water everywhere… but how'd it get in there?

Mark Arnholt

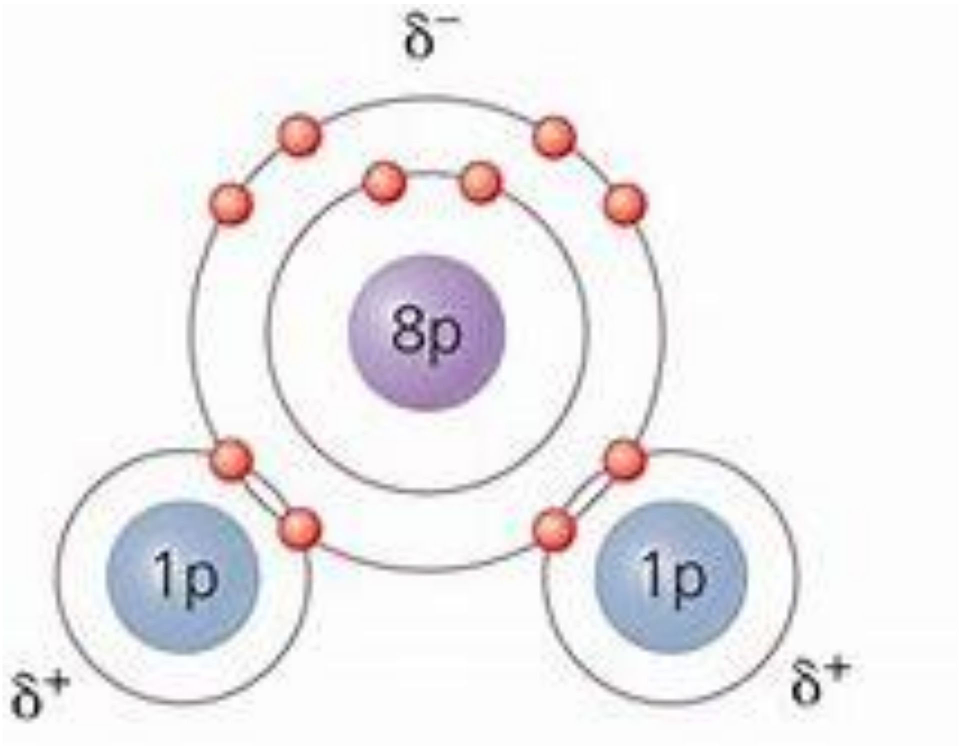
Science Educator

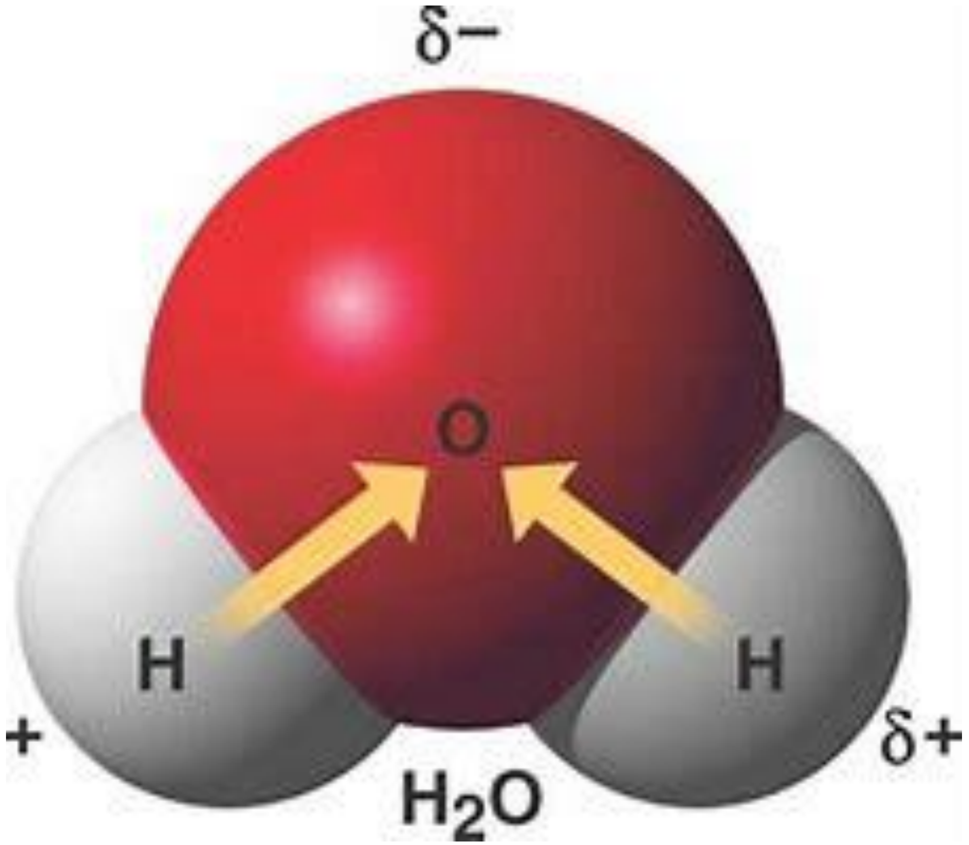
SMART Team Coordinator

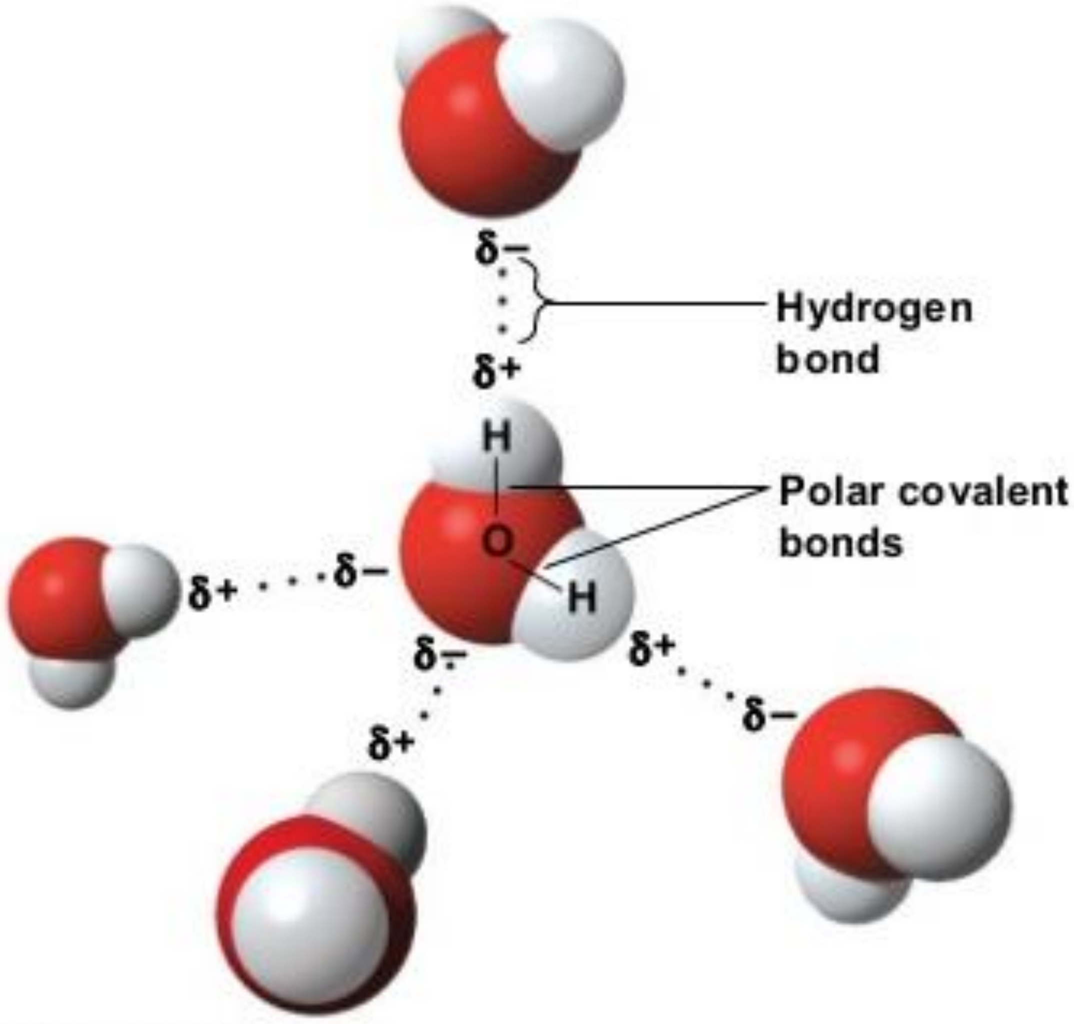
3D Molecular Designs

Milwaukee, WI

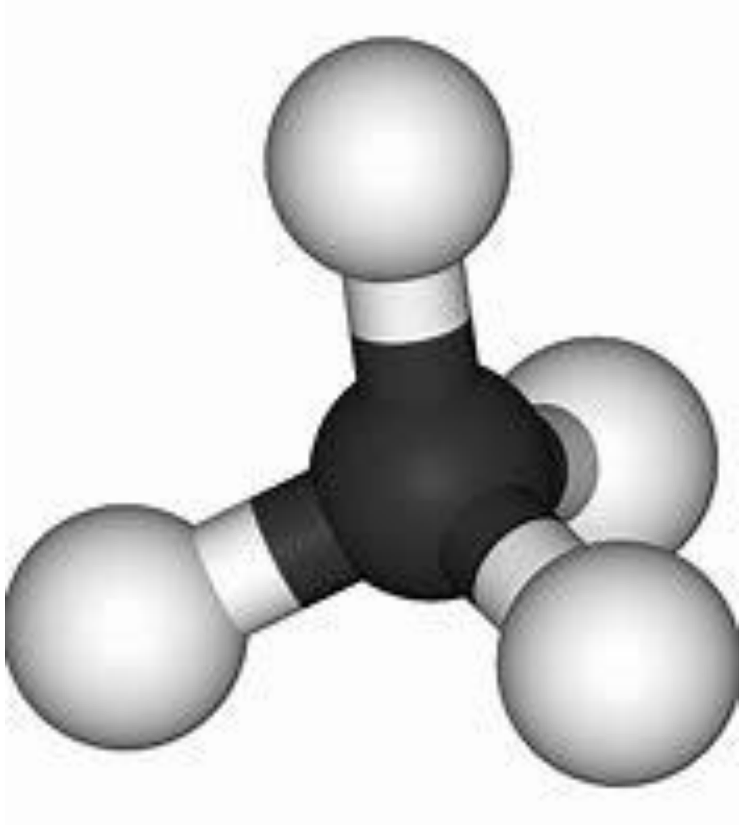
Water exhibits POLAR COVALENT bonds

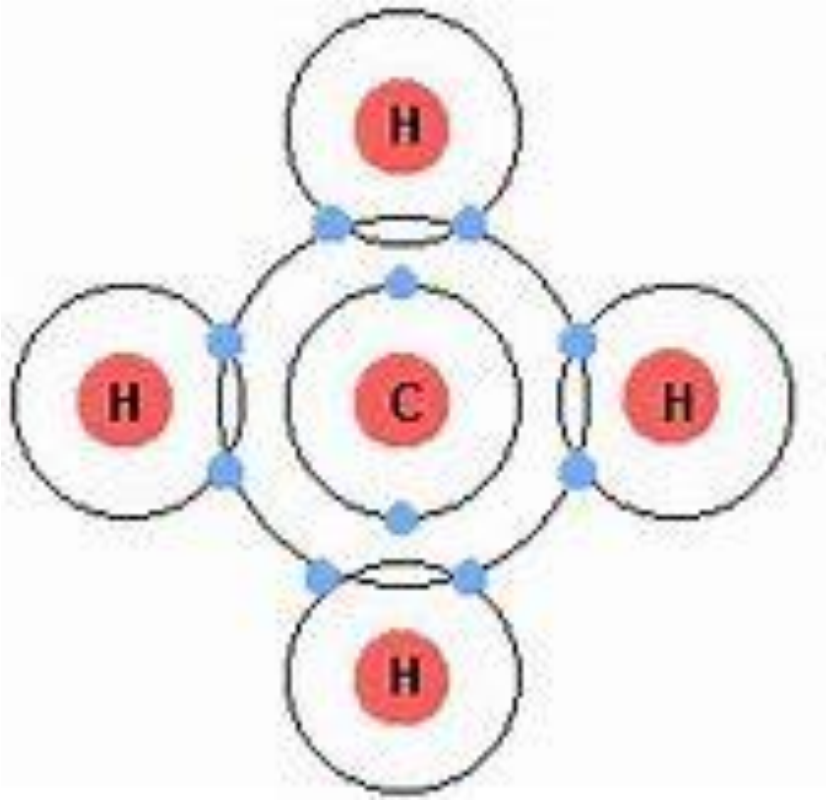




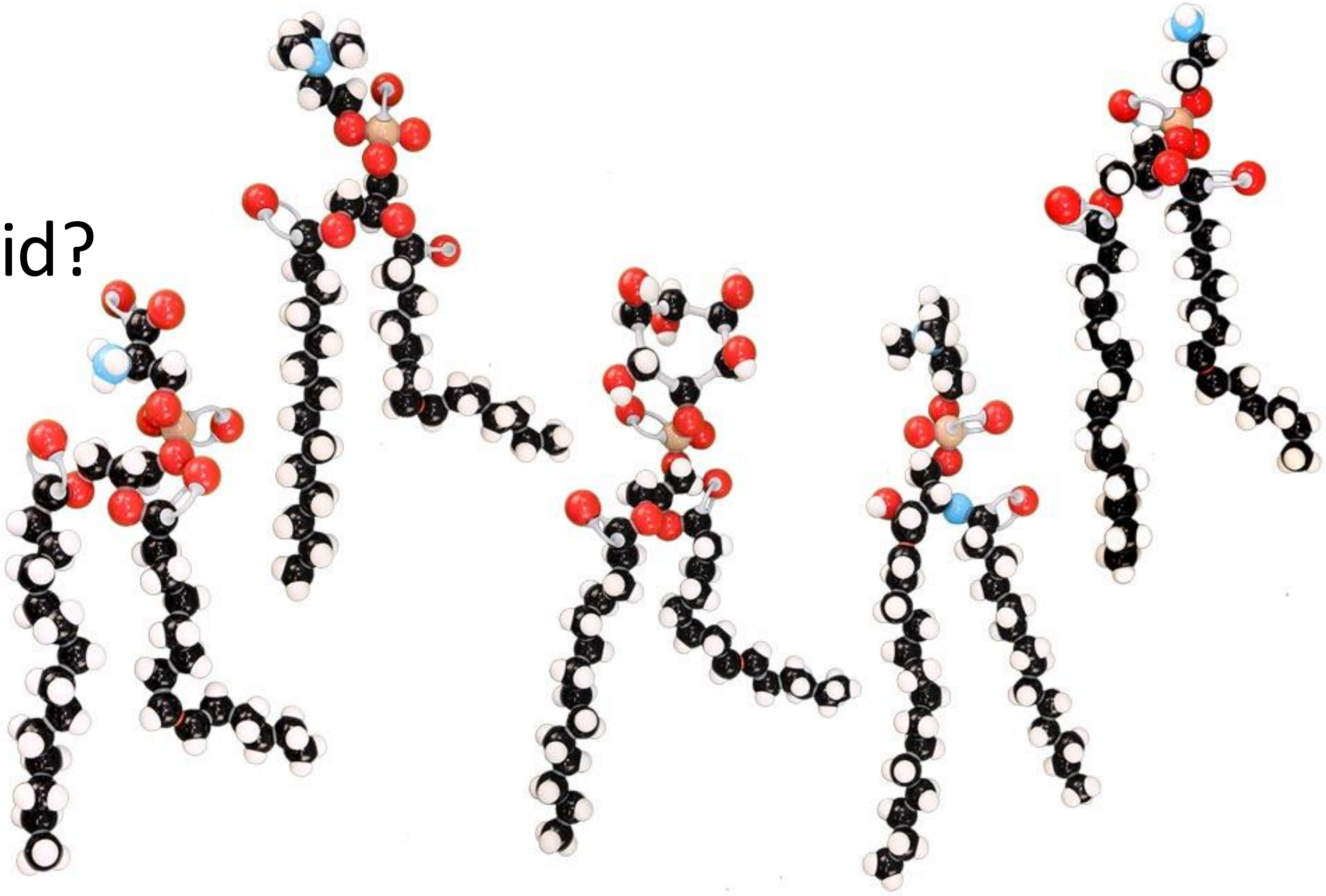

δ–
δ+
Hydrogen bond
H
O
H
Polar covalent bonds
δ+
δ–
δ–
δ+
δ+
δ–

What about Methane?

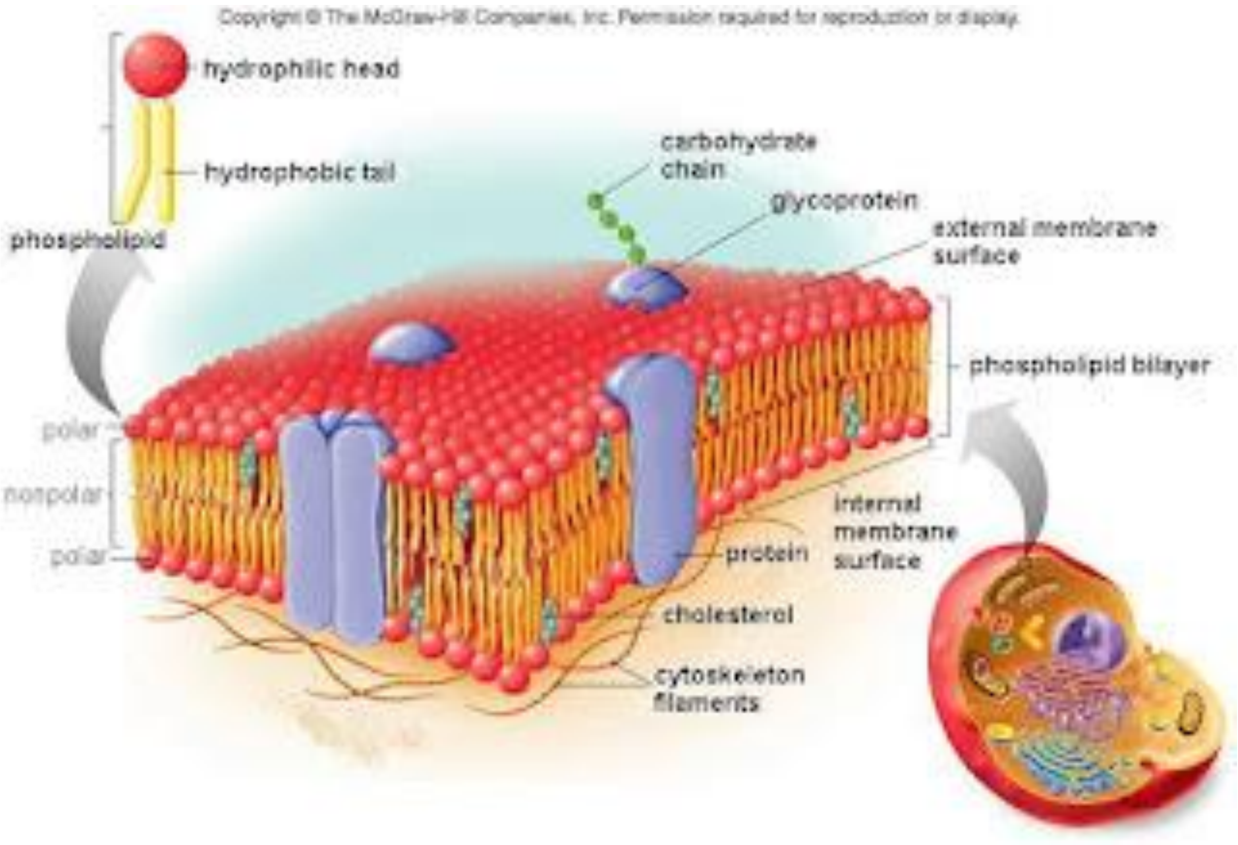




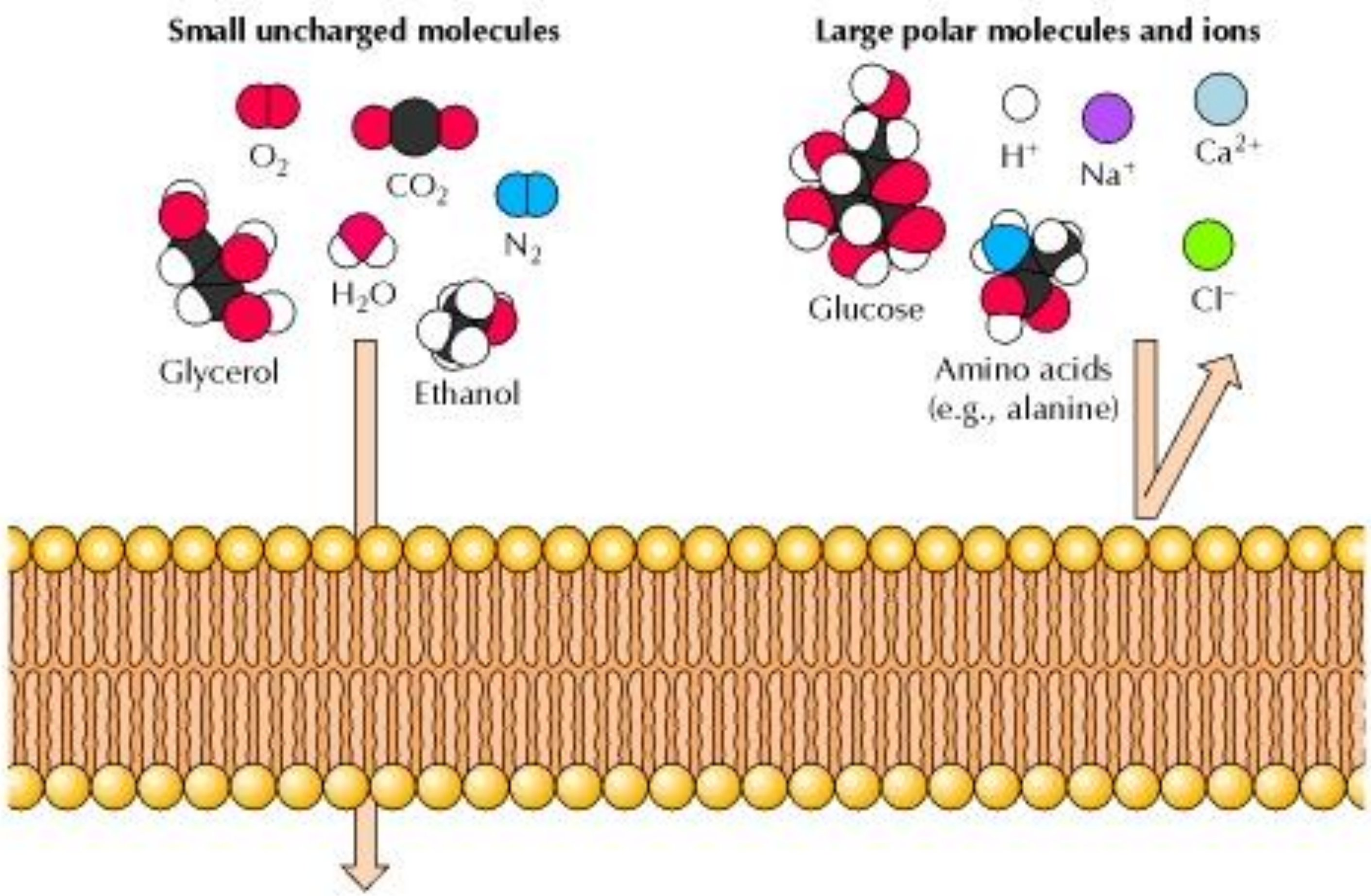
What about a phospholipid?
What do you notice?



The Cell Membrane



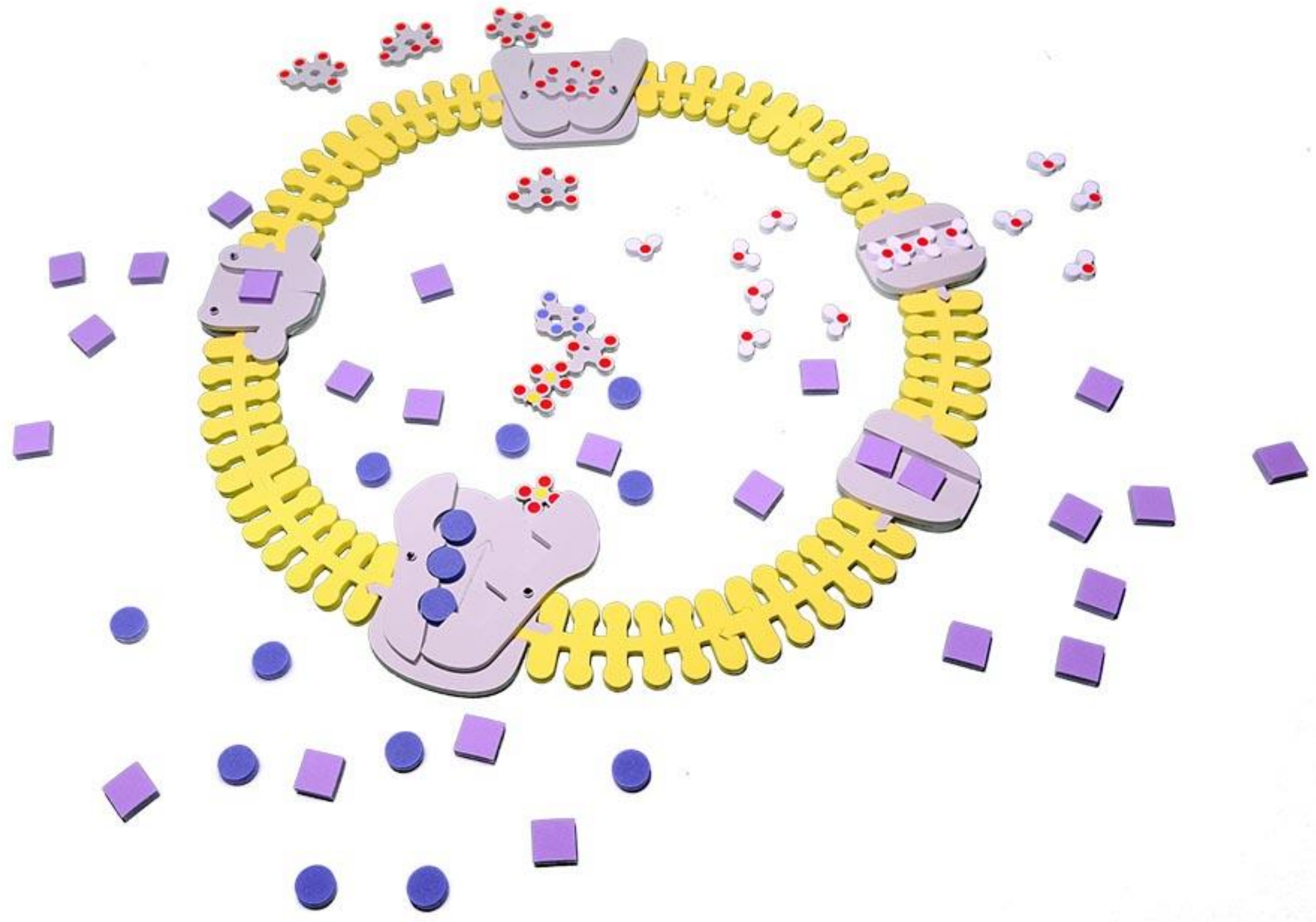
The problem…



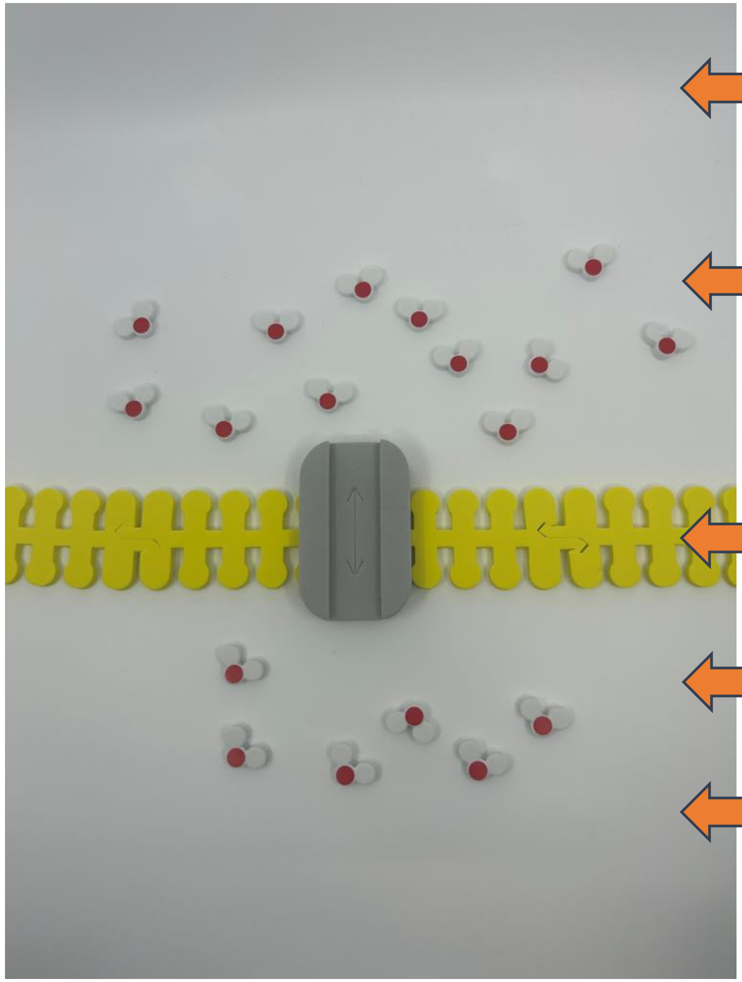
Small uncharged molecules
O_2
CO_2
N_2
H_2O
Glycerol
Ethanol
Large polar molecules and ions
Glucose
H^+
Na^+
Ca^{2+}
Cl^-
Amino acids
(e.g., alanine)

Let’s investigate some channel proteins!

There's a lot going on here, so let's simplify it!



Let's focus on water first – Add the following



Extracellular – Outside of the cell

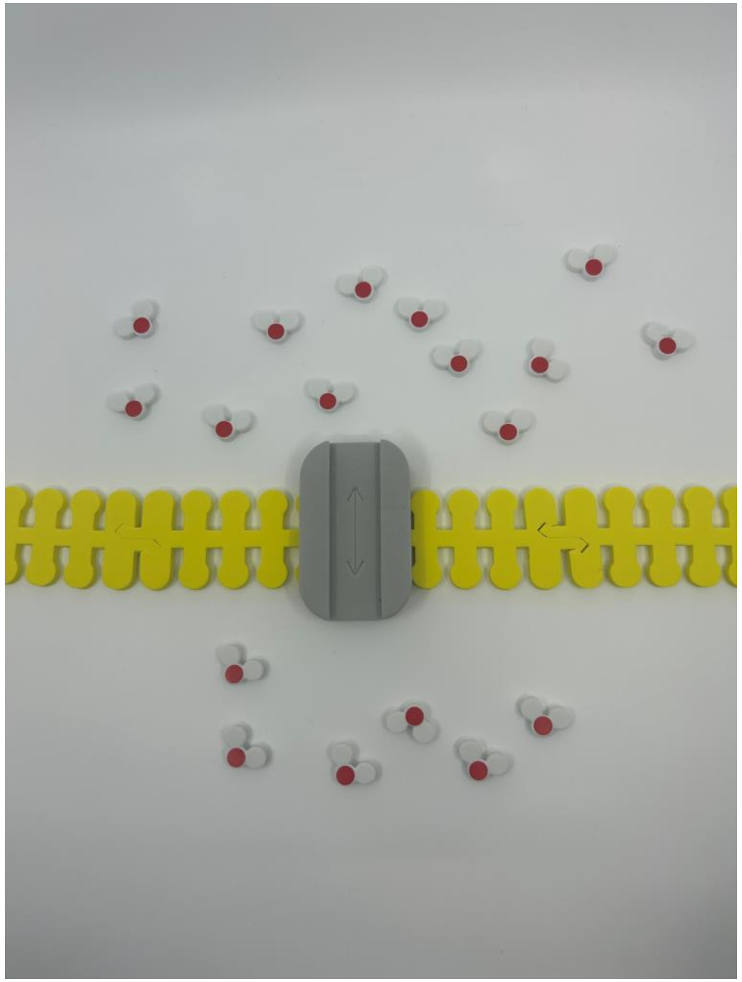
12 water molecules

Aquaporin and cell membrane

6 water molecules

Intracellular – Inside of the cell

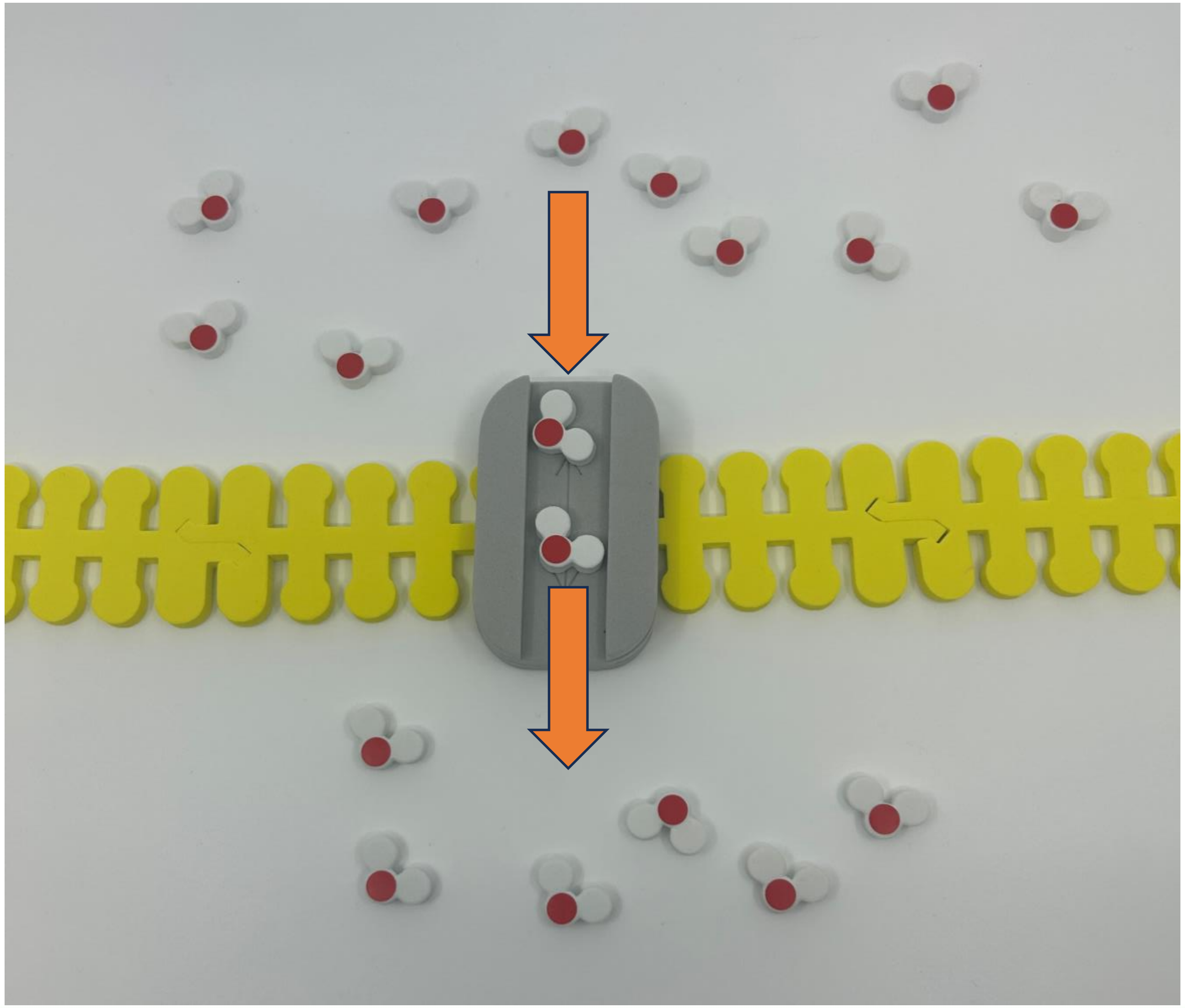
With an aquaporin in place...



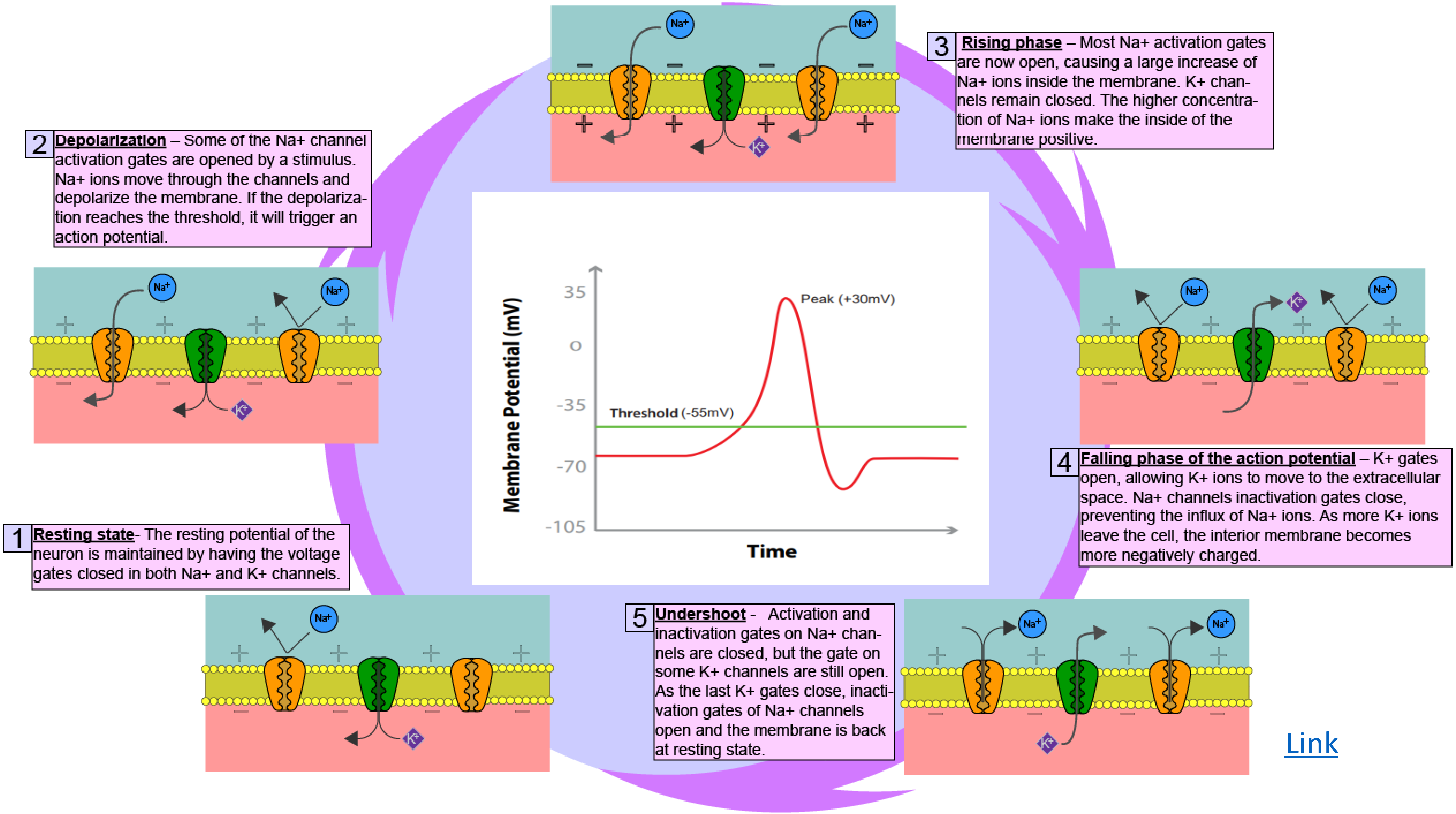
Based on what you know about water potential and osmosis, in which direction would the water molecules move?

How many water molecules should you move?

Move 3 water molecules across to reach equilibrium

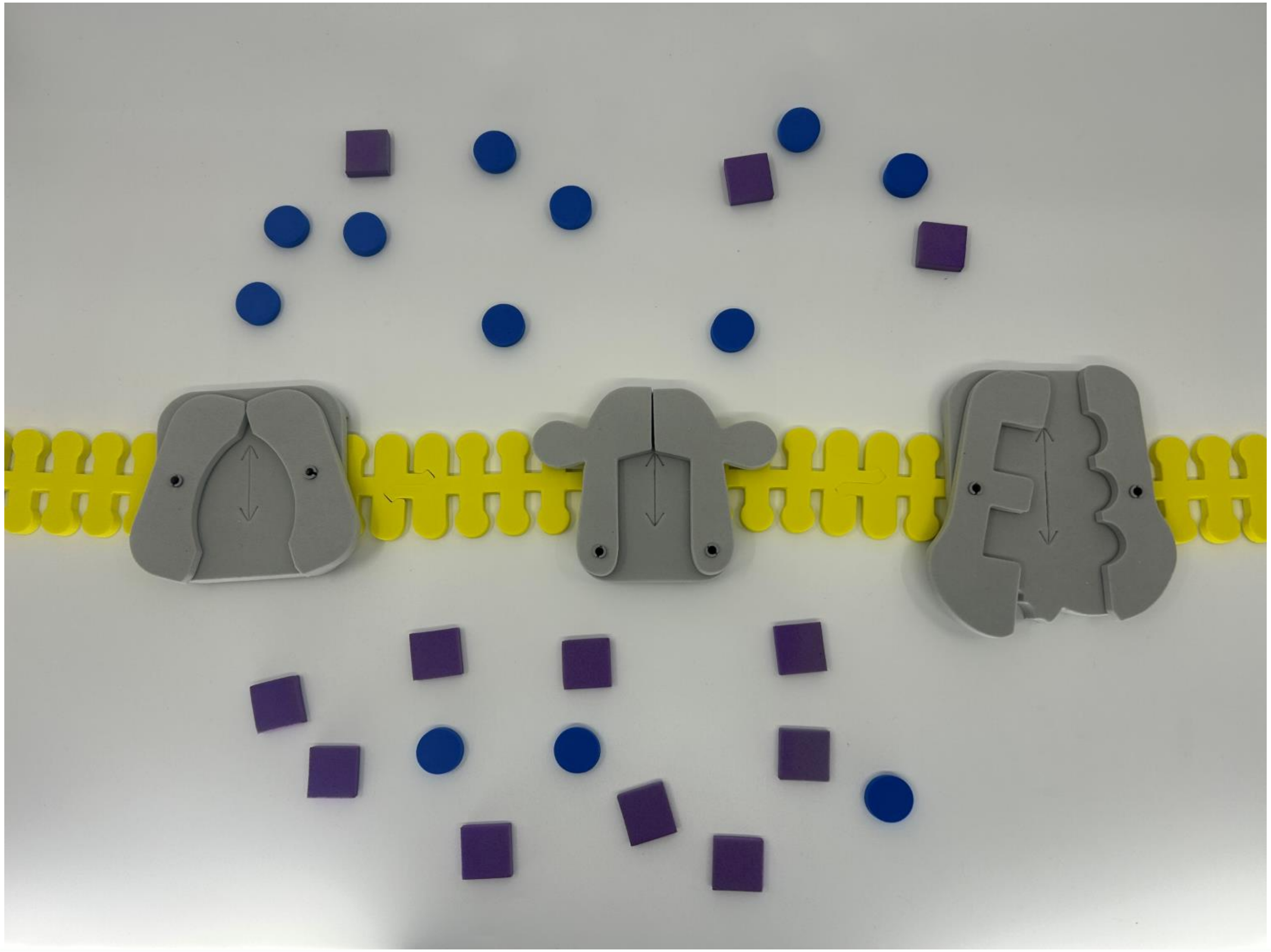


Life is complicated…

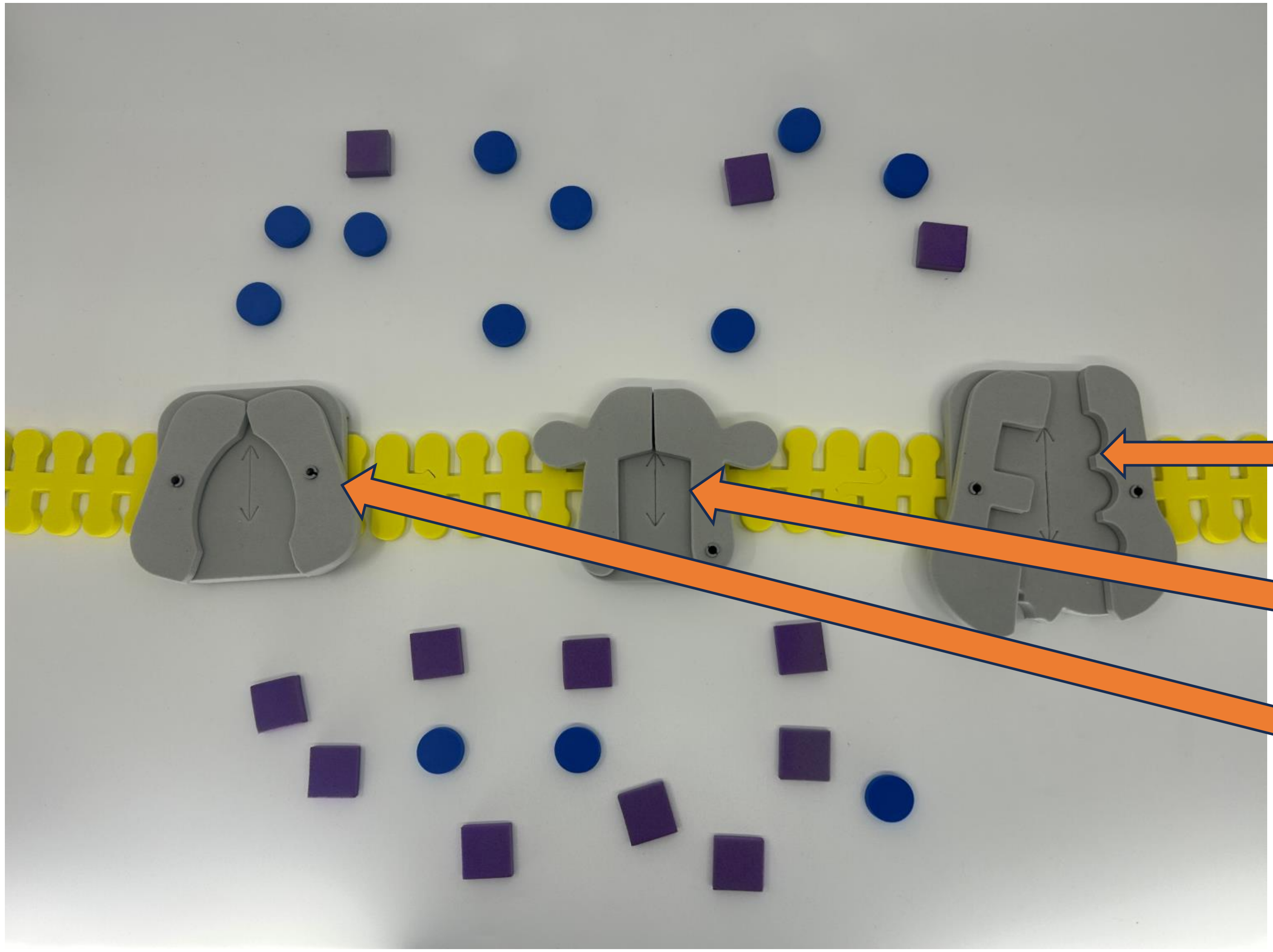


Link

Let’s model an action potential



Let’s identify everything



Na+ (x 12)

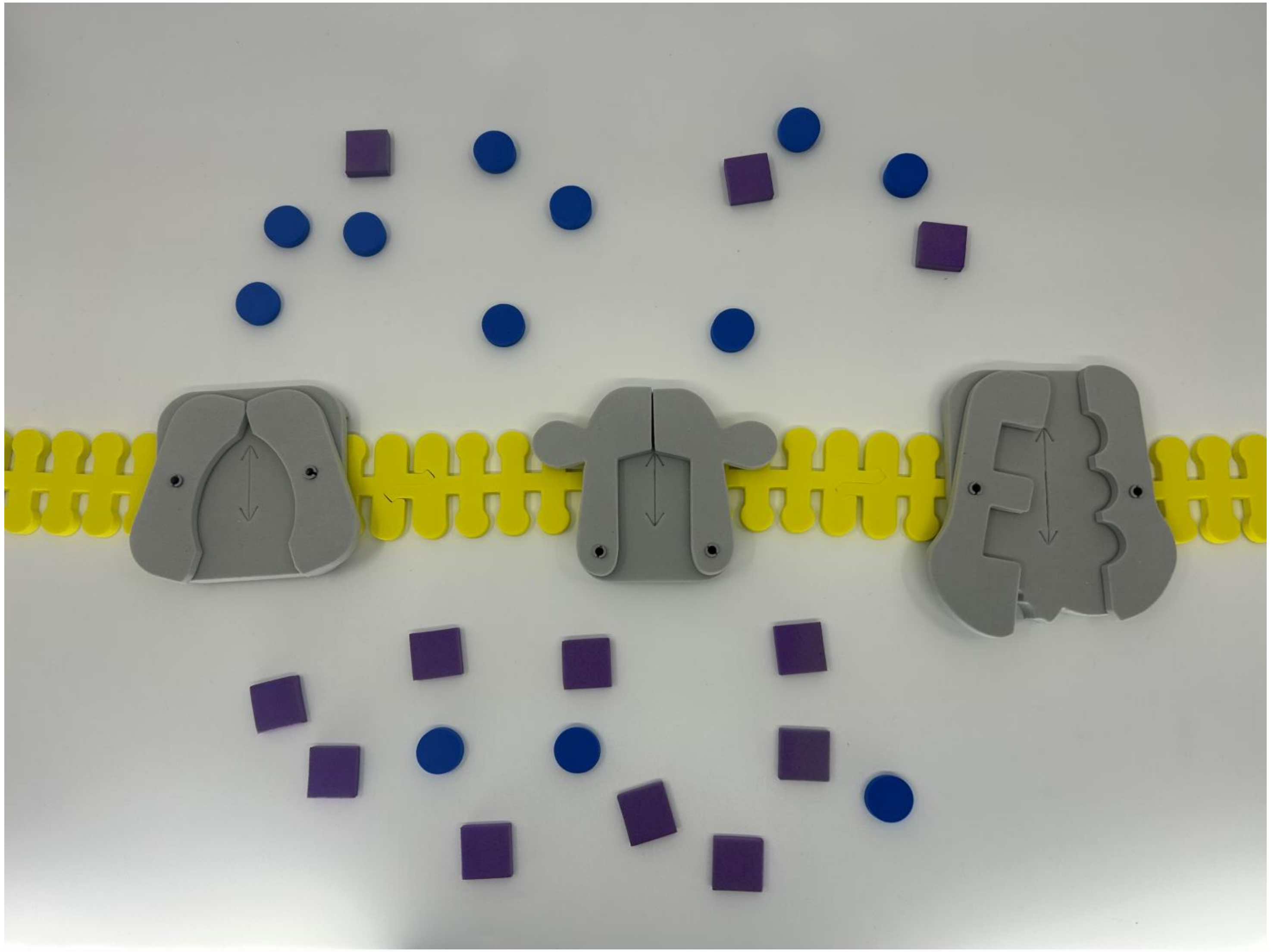
K+ (x 12)

Na+ / K+ Channel

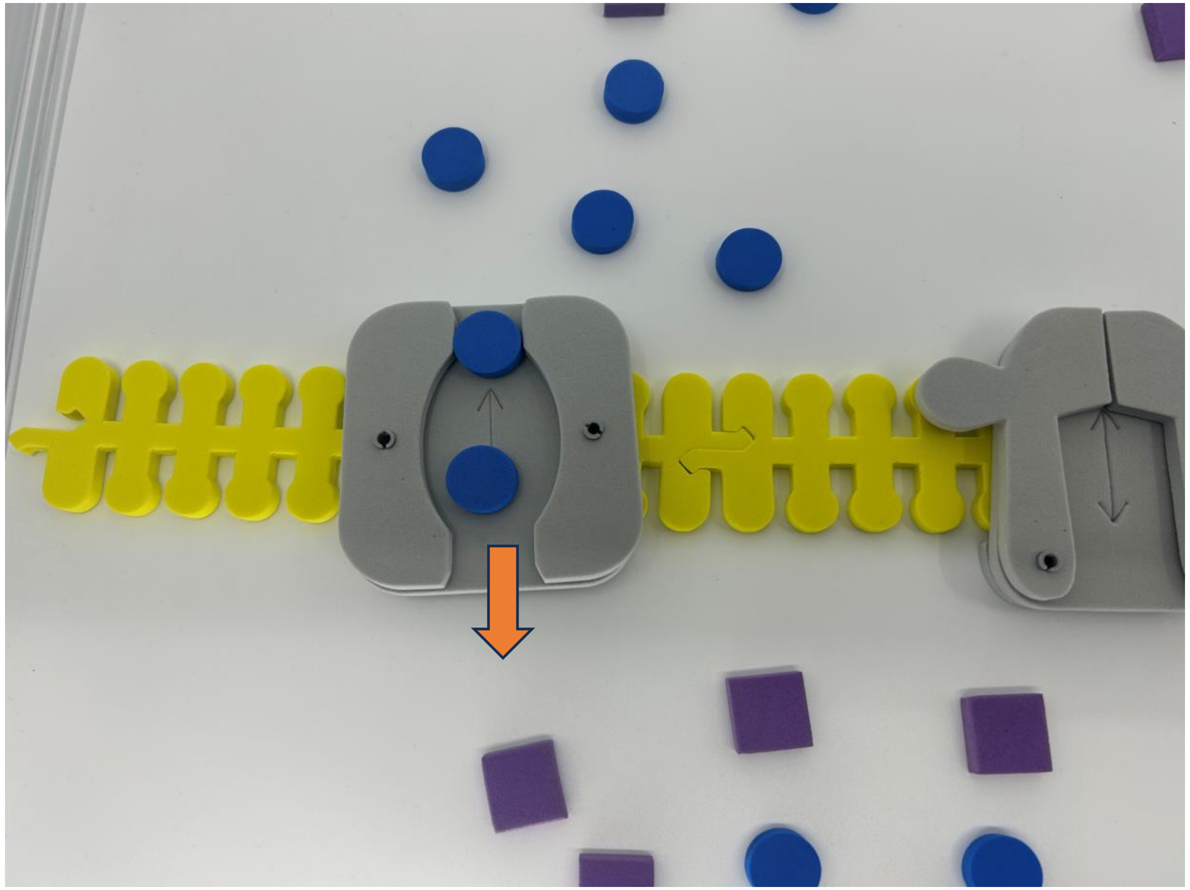
Gated Na+ channel (Simulated)

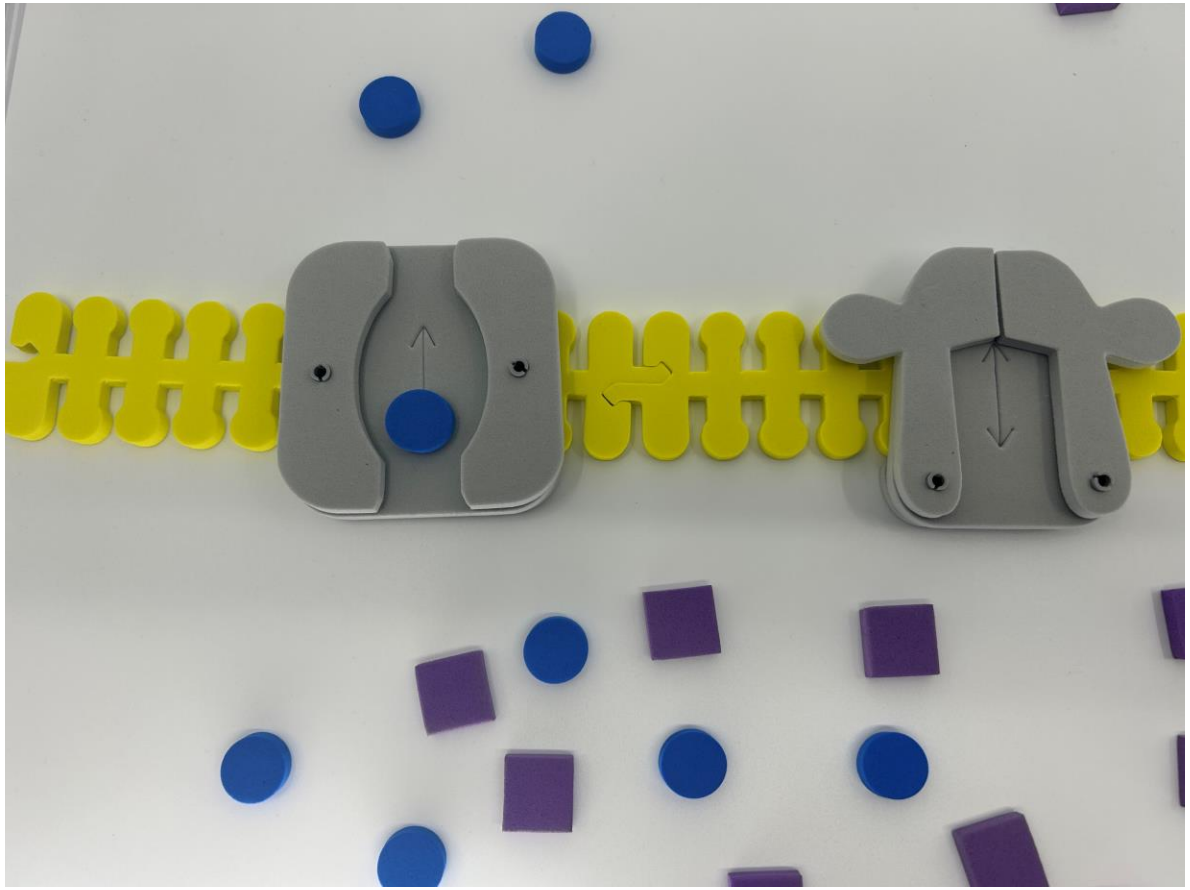
Gated K+ Channel

What do you notice?

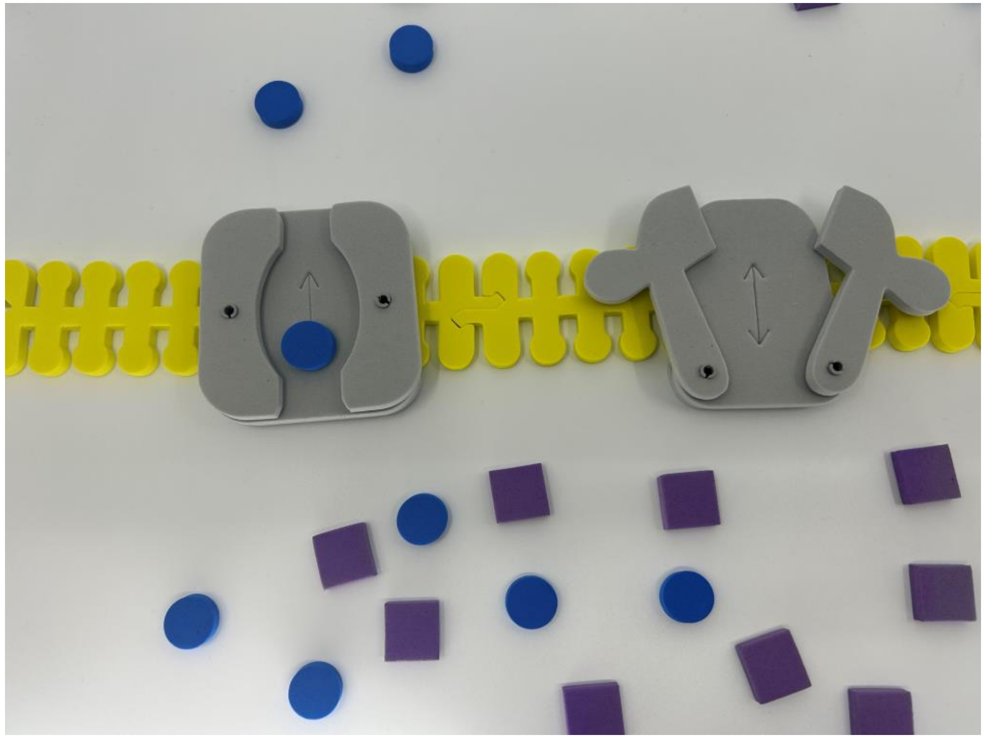


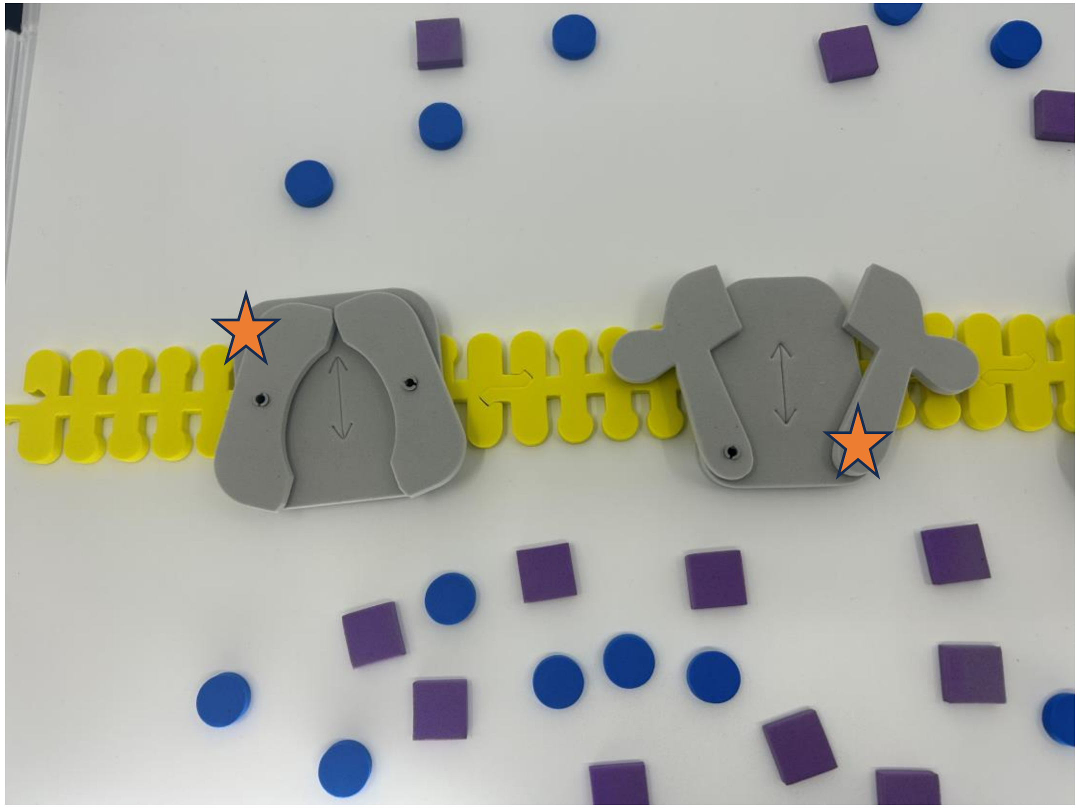
Sodium (Na+) first…



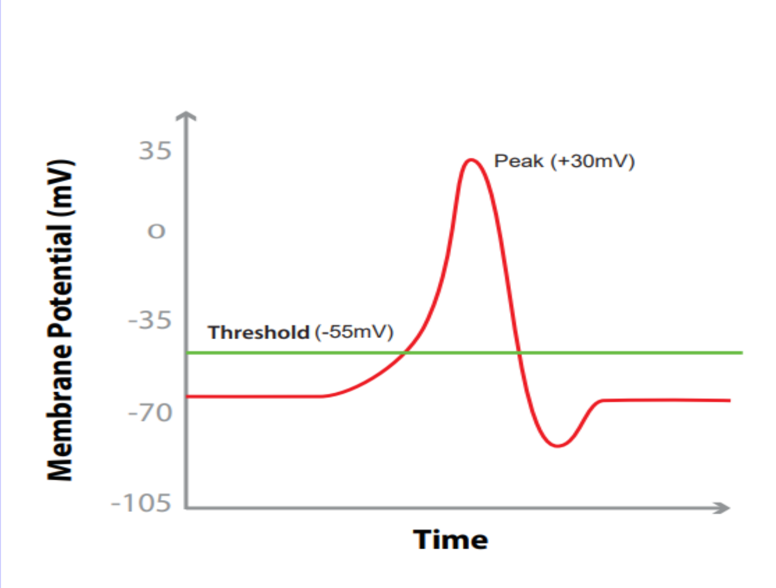


What happened to the charge inside the membrane?

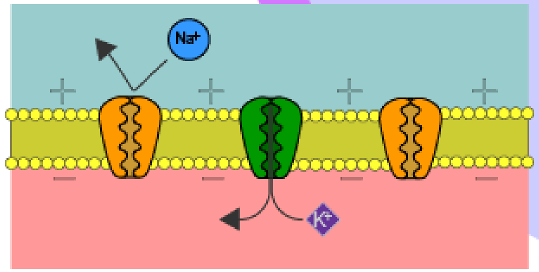




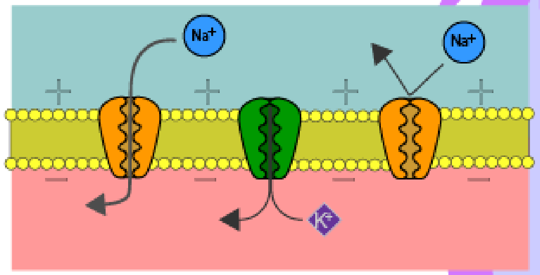
Life is complicated…



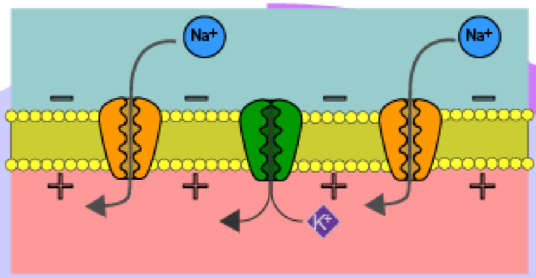
1 **Resting state**- The resting potential of the neuron is maintained by having the voltage gates closed in both Na+ and K+ channels.



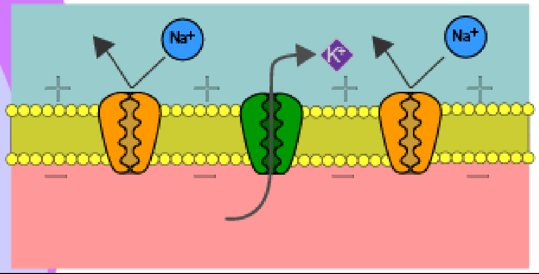
2 **Depolarization** – Some of the Na+ channel activation gates are opened by a stimulus. Na+ ions move through the channels and depolarize the membrane. If the depolarization reaches the threshold, it will trigger an action potential.



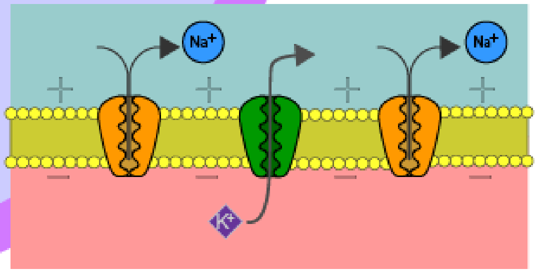
3 **Rising phase** – Most Na+ activation gates are now open, causing a large increase of Na+ ions inside the membrane. K+ channels remain closed. The higher concentration of Na+ ions make the inside of the membrane positive.



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.

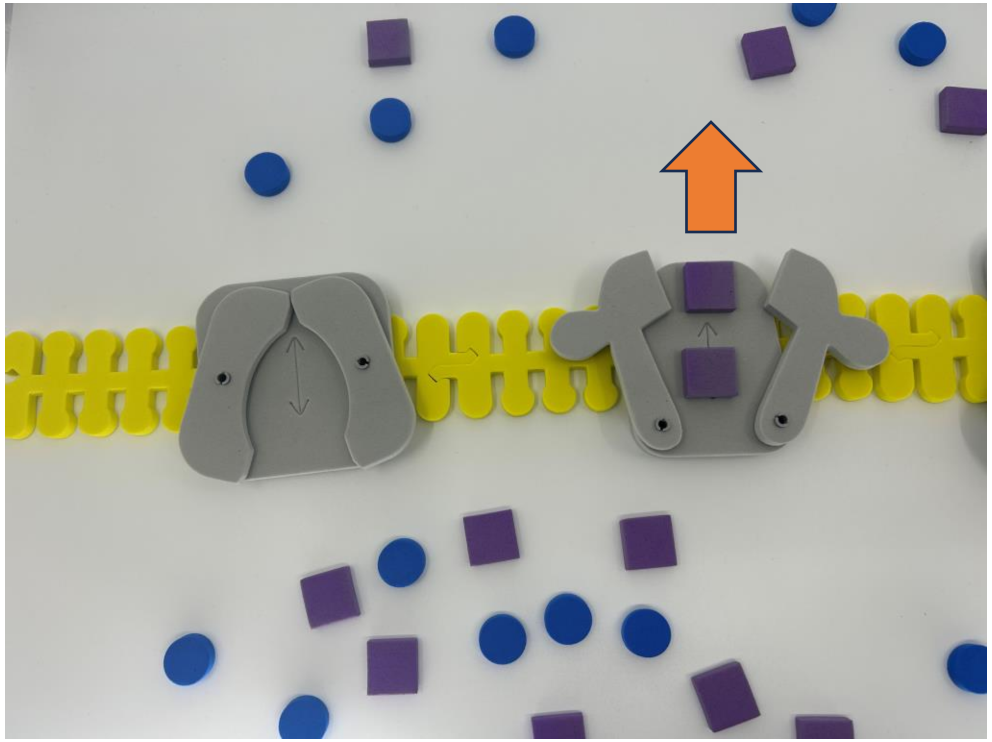


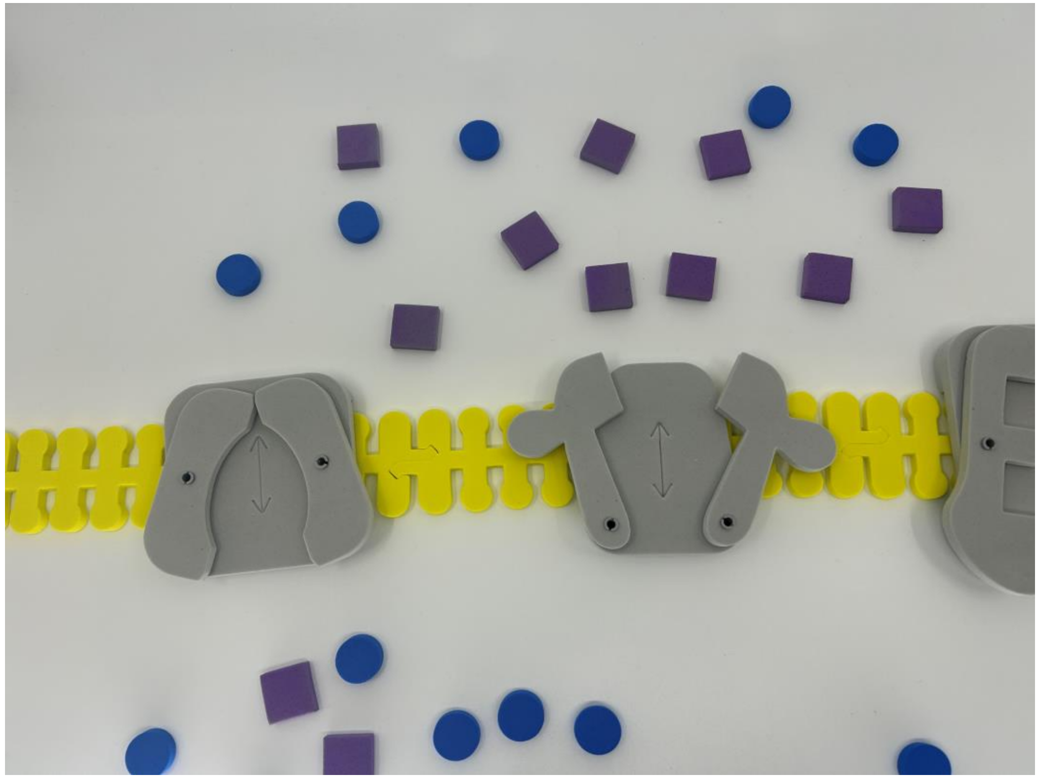
5 **Undershoot** - Activation and inactivation gates on Na+ channels are closed, but the gate on some K+ channels are still open. As the last K+ gates close, inactivation gates of Na+ channels open and the membrane is back at resting state.



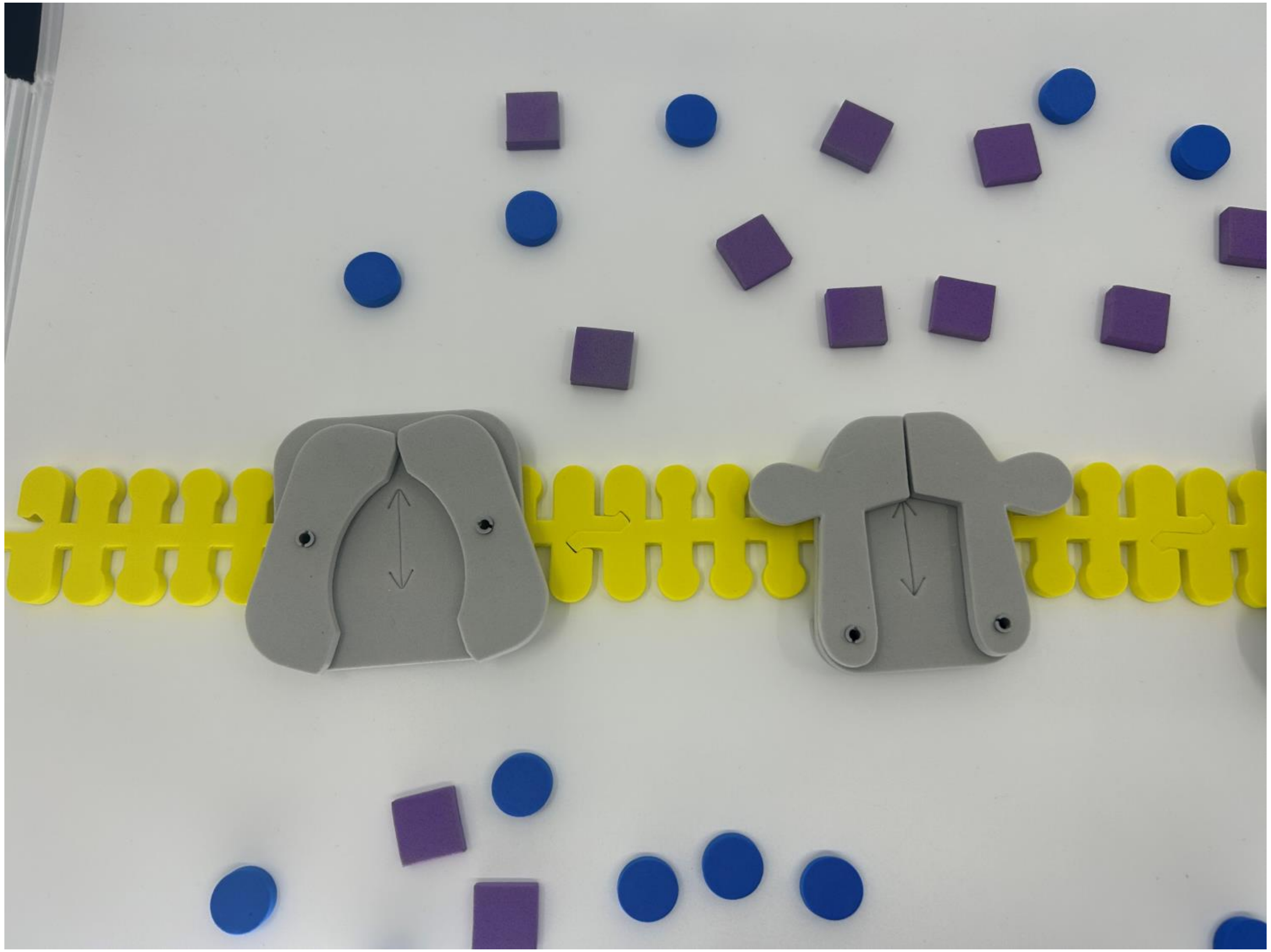
Link

Potassium (K+) moves next



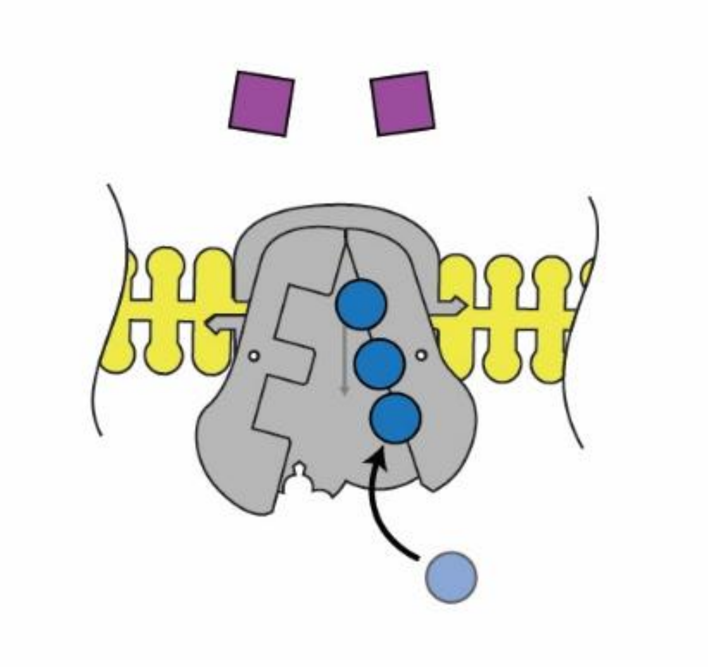


Each channel is "tuned"

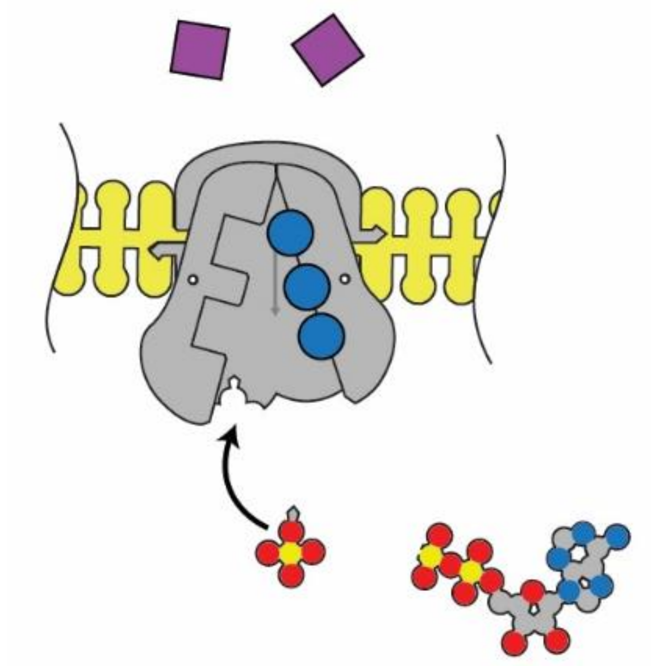


How do we get back to a resting potential?

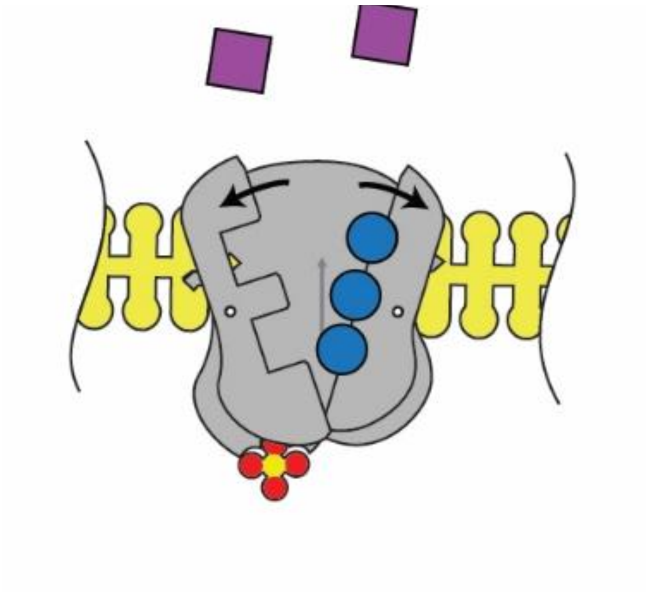
1. Sodium binds on the intracellular side.



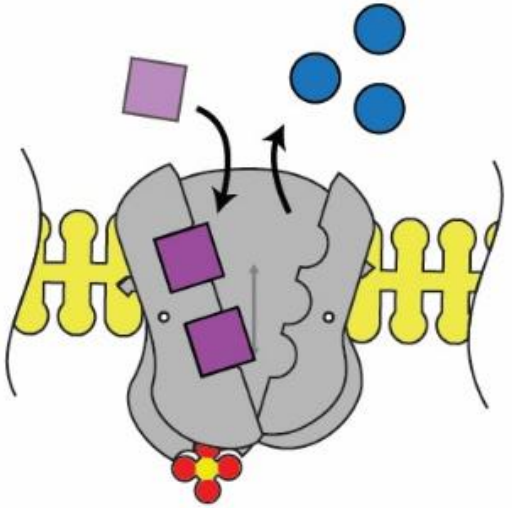
2. The pump is phosphorylated by ATP.



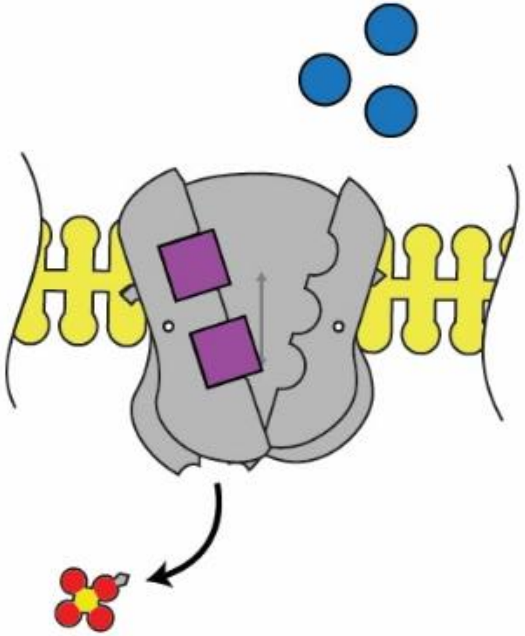
3. The pump shape changes, exposing the sodium to the extracellular space.



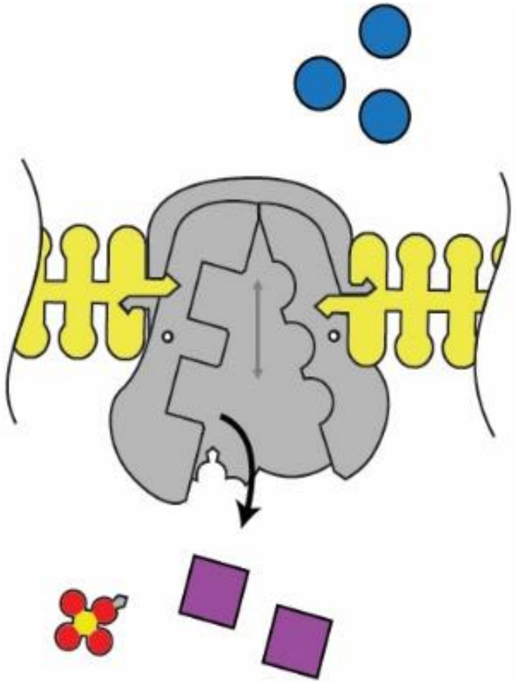
4. Binding affinity changes to release Na+ and take in K+.



5. Phosphate detaches.



6. Original shape is restored, releasing K+ into the cell.

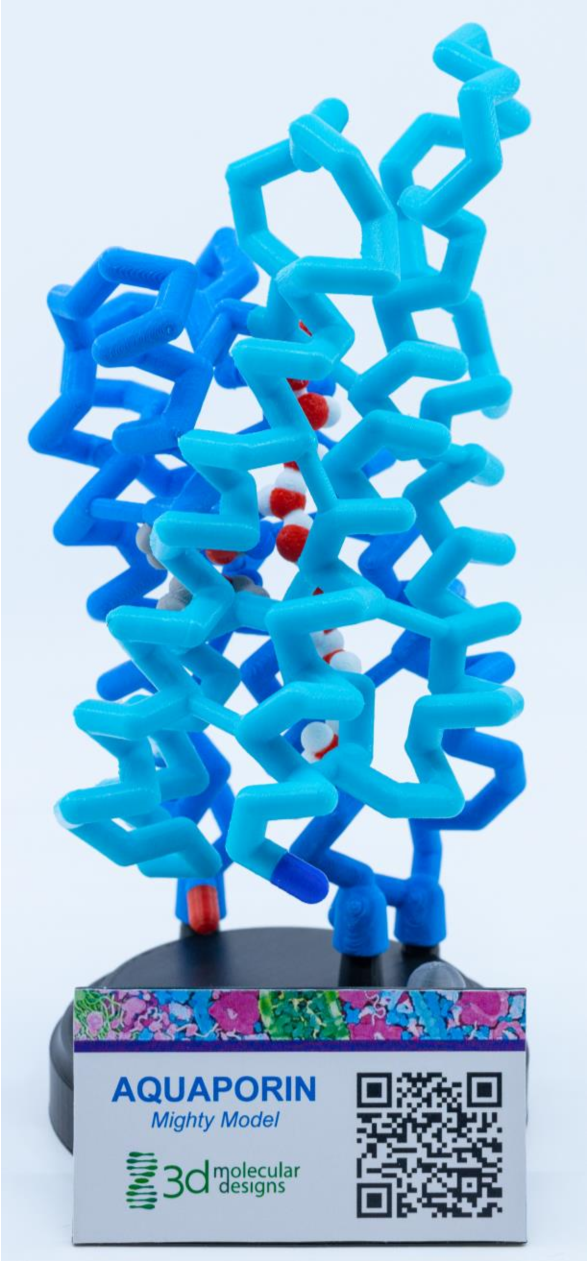


How does a channel “know” which ion to transport?

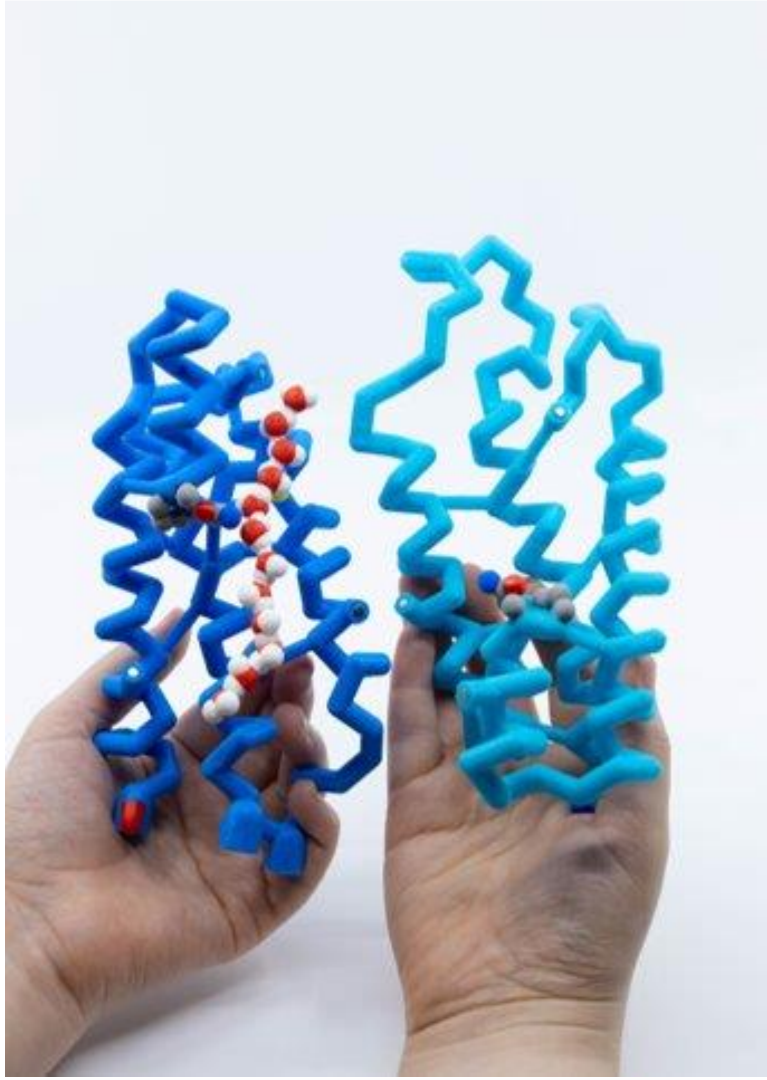
- They don’t…
- They follow the basic rules of chemistry!

How does Aquaporin move water?

- … and only water?



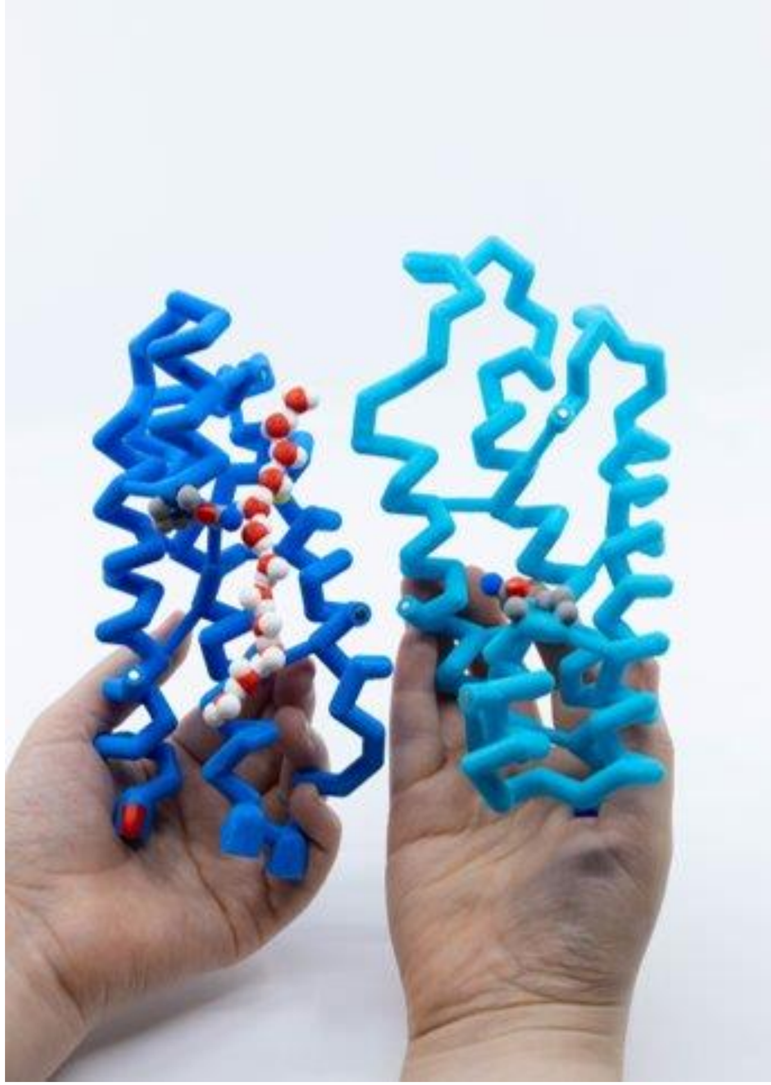
A closer look at water movement



Separate the two portions of the aquaporin monomer.
Remove the chain of water molecules.

What do you notice about the ability of water to enter the channel?

A closer look at water movement



Locate the two ***asparagine*** side chains (N78 and N194) inside the channel
Water molecules can move either way through the channel depending on concentration.

Notice the orientation of the oxygen atom and hydrogen atoms in reference to the inside and outside of the cell.

Speculate why there is a change in orientation.

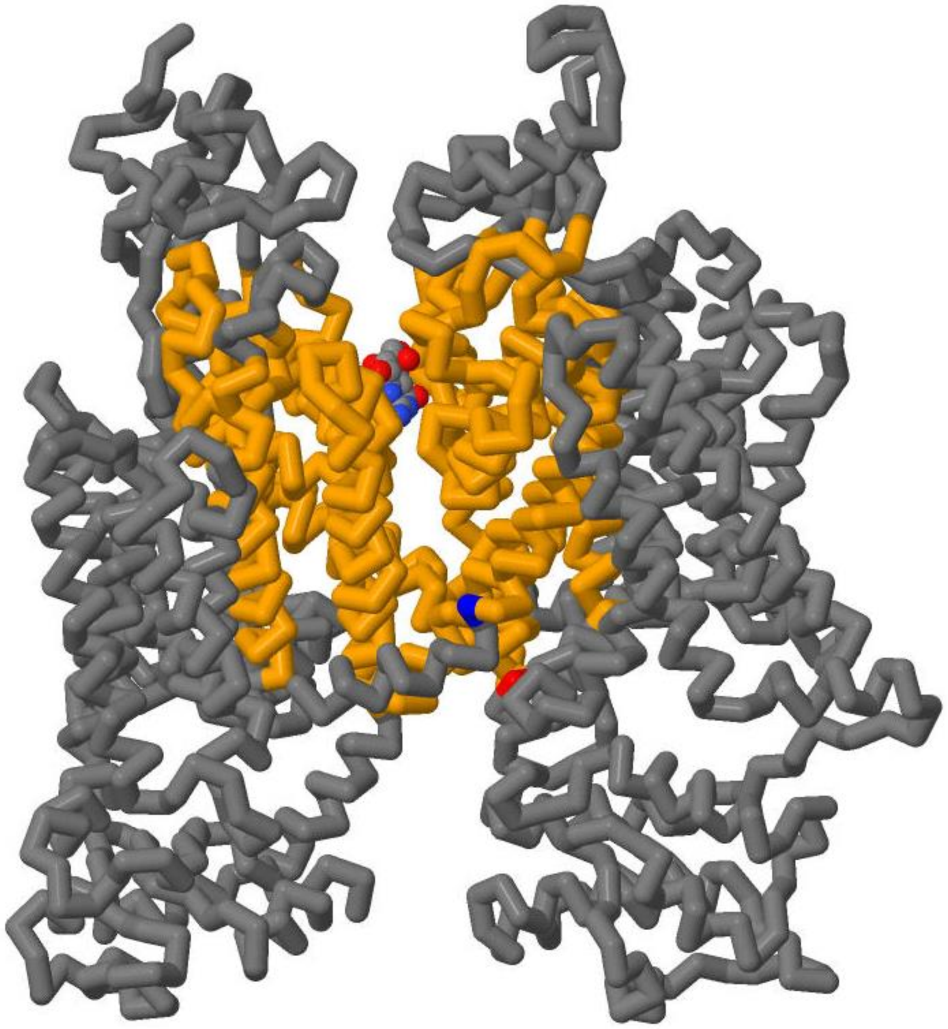
How could you model this?

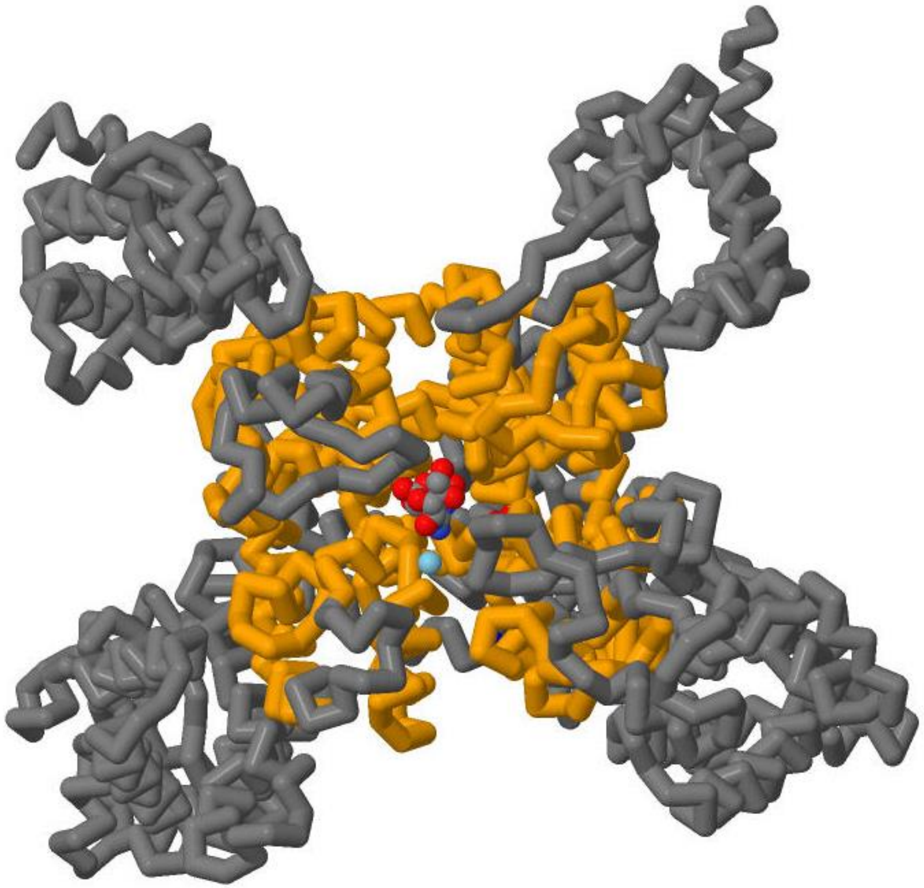
Use the QR code to see it in action-

- Note the direction of movement.
- What happens when you add the inhibitor? (Hg)

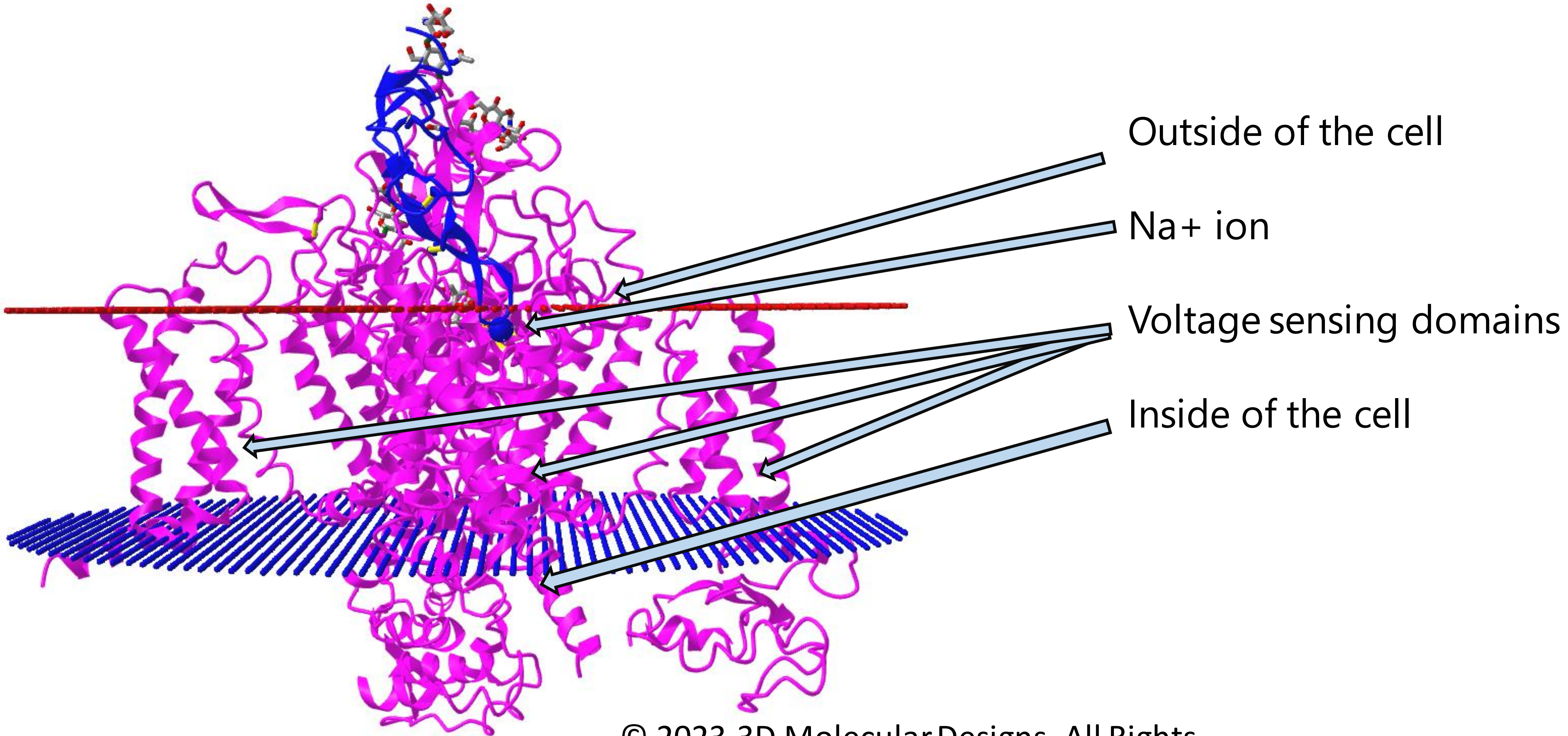
Let’s look at the Sodium (Na+) Channel

These are Voltage-Gated Na+ Channels - monomers





Here it is in a membrane



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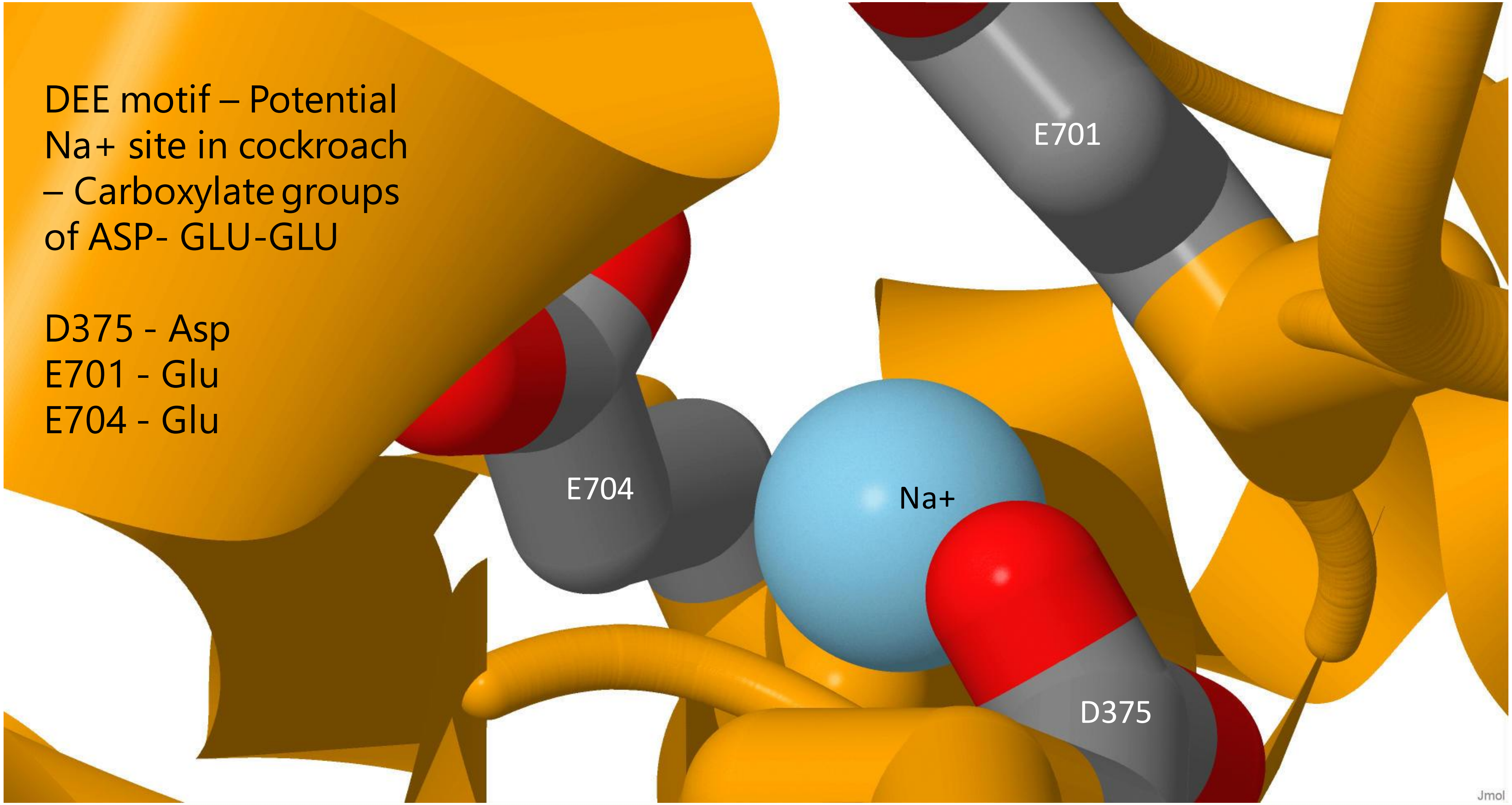
DEE acts as a selectivity filter for Na+ ion

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

D375 - Asp
E701 - Glu
E704 - Glu

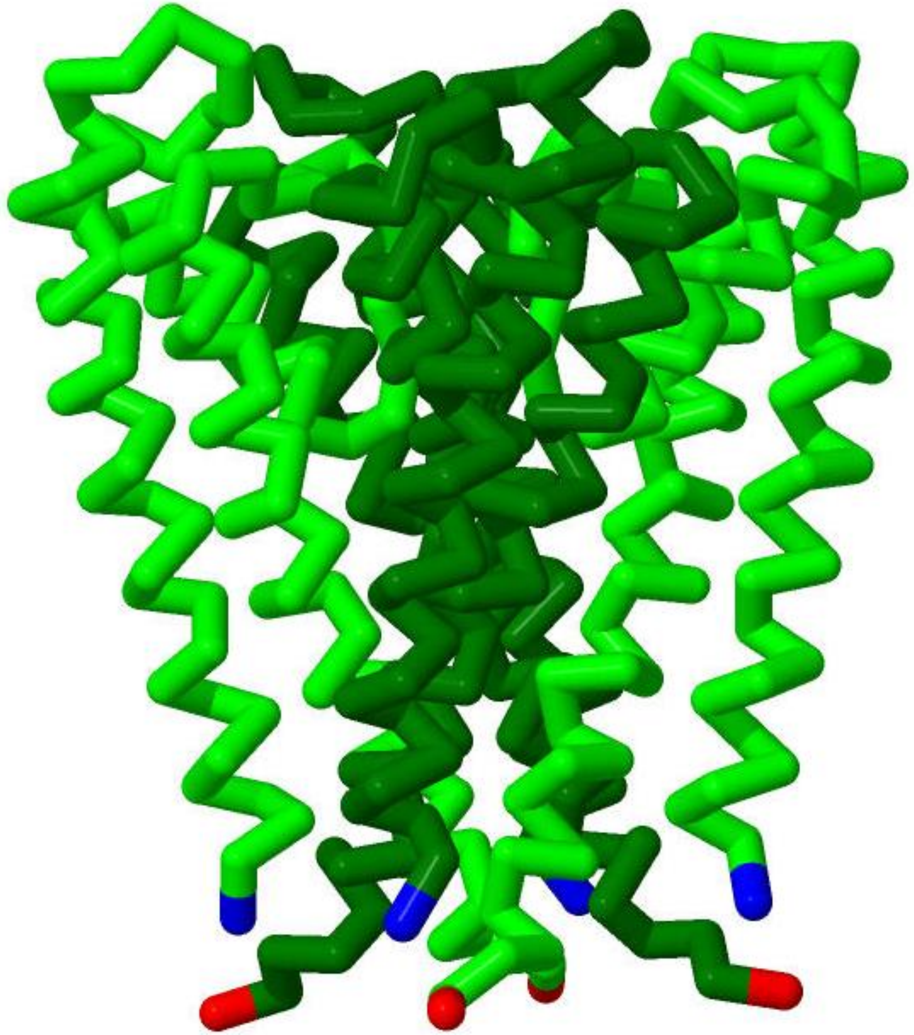


Use the QR code to see it in action-

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

Let's look at the Potassium (K+) Channel

Homotetramer



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

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

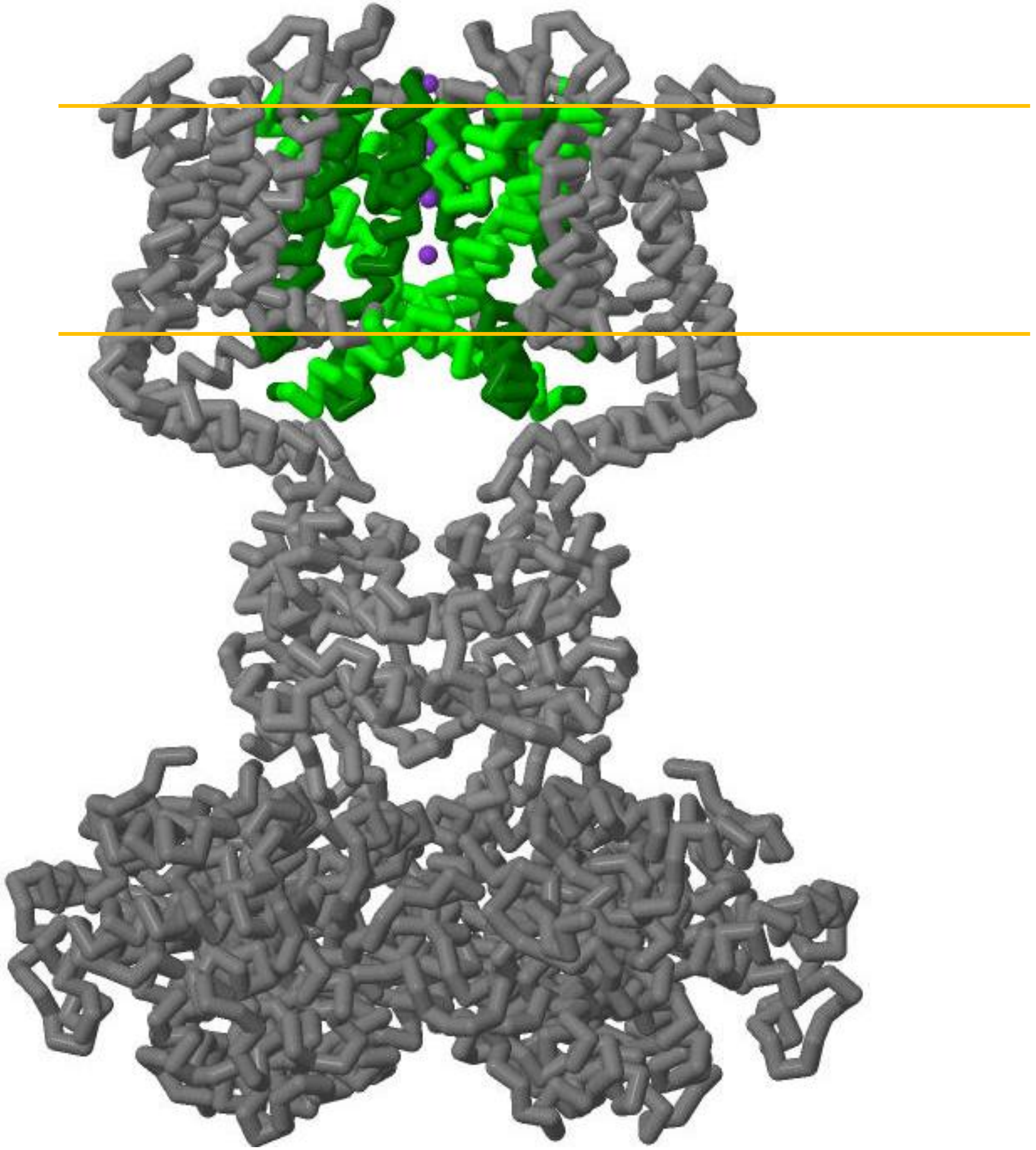
A:

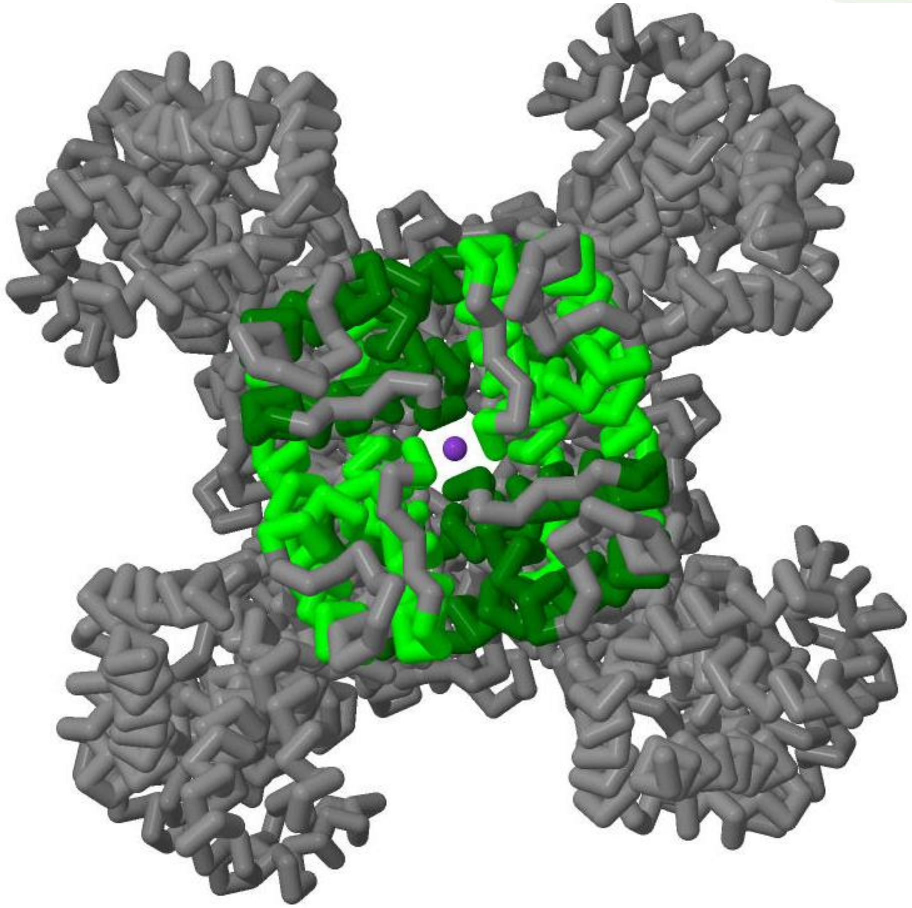
B:

C:

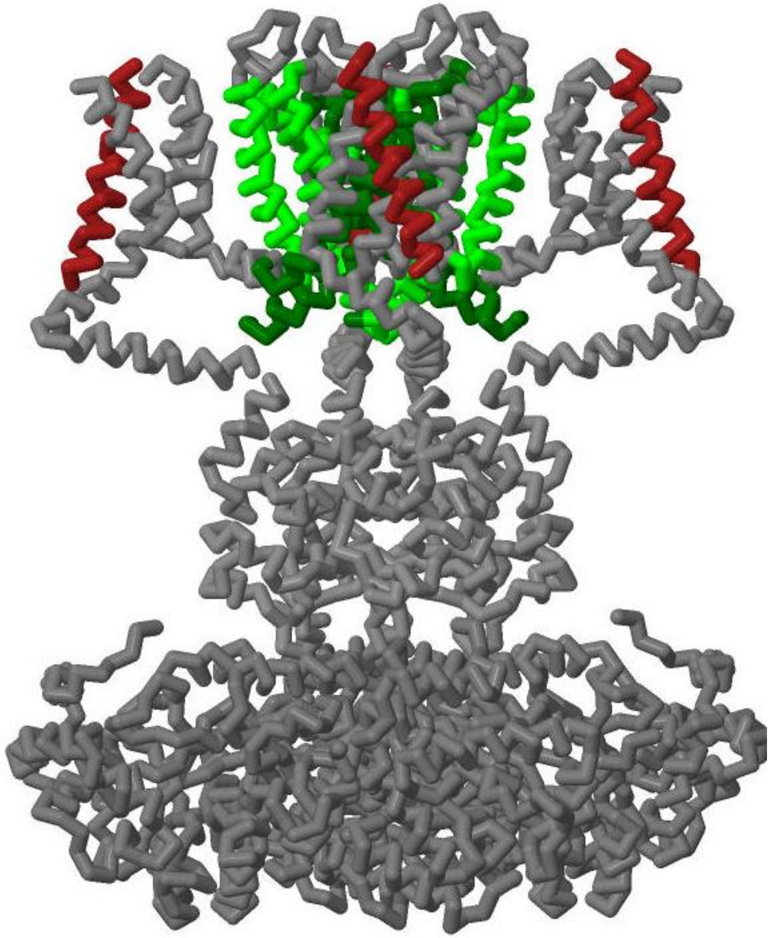
D:

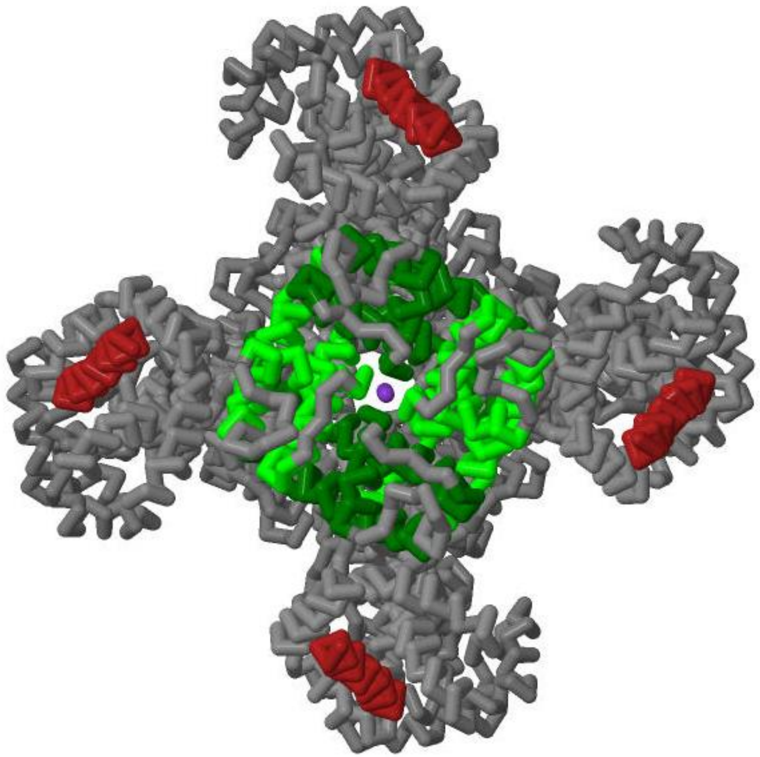
This potassium channel is voltage-gated





This potassium channel is voltage-gated

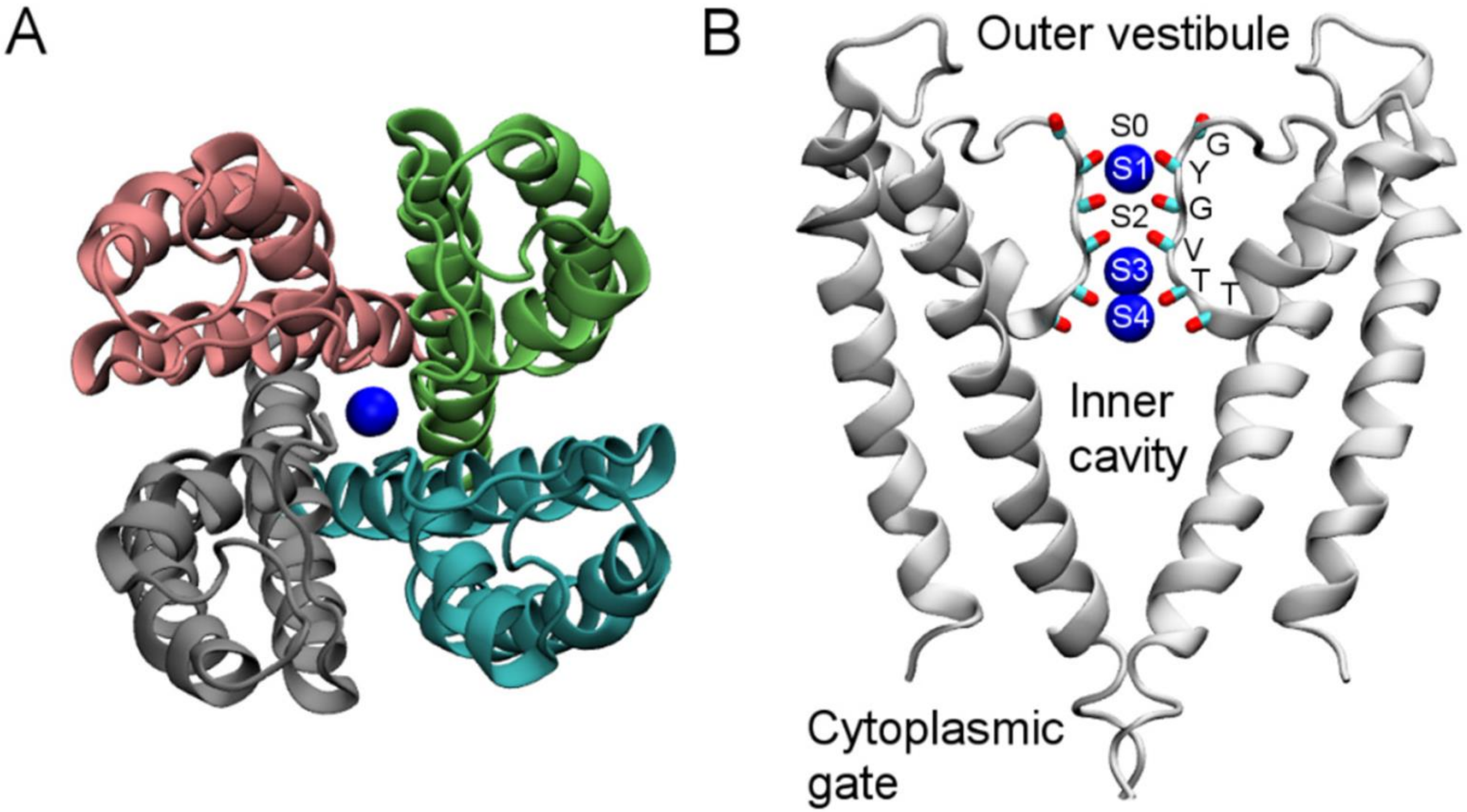




What does a K^+ channel do?

- 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.

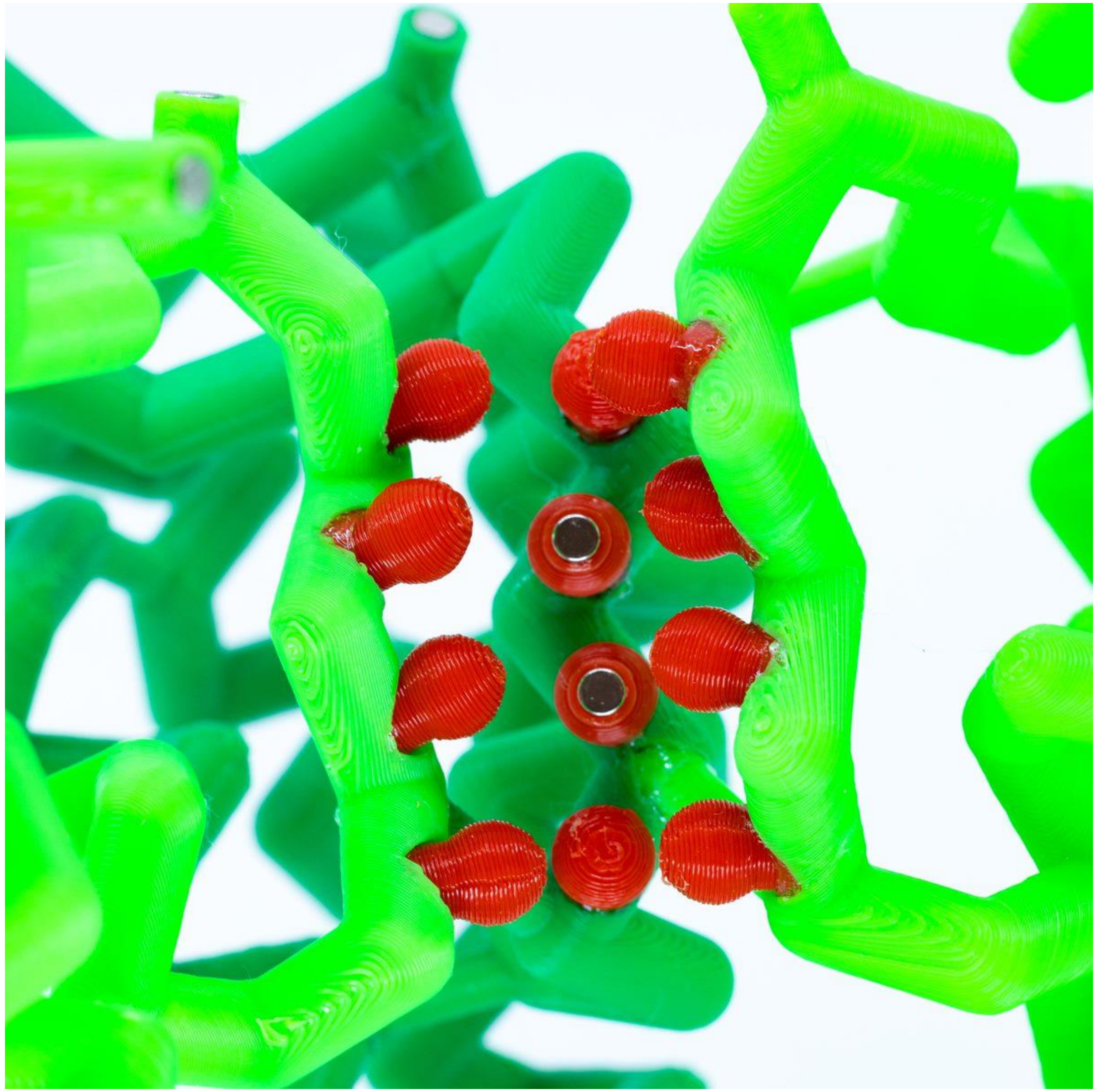
- *Why do you suppose this is important?*



Protein "Fingerprint":
TTVGYG

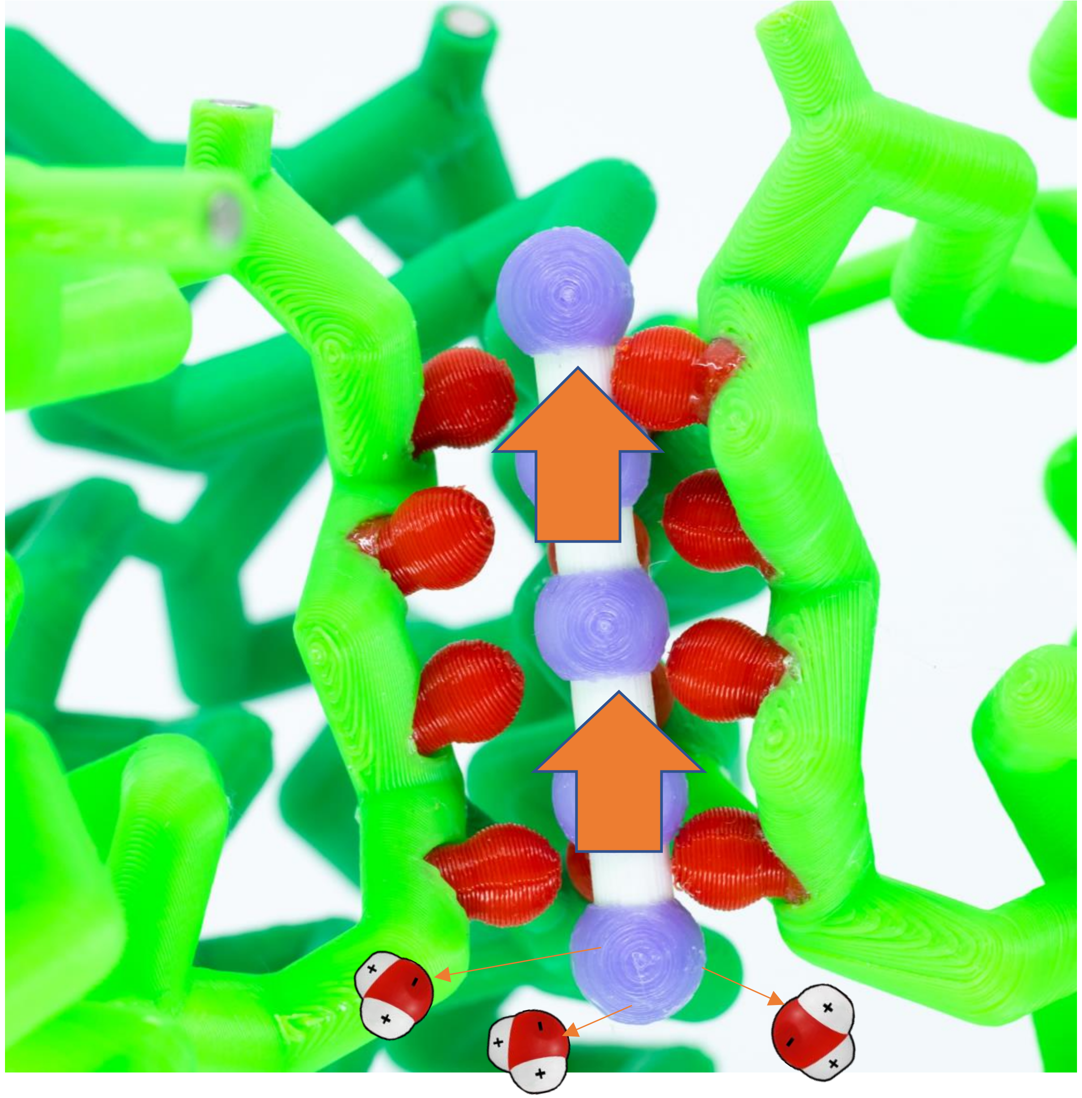
The carbonyl groups

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



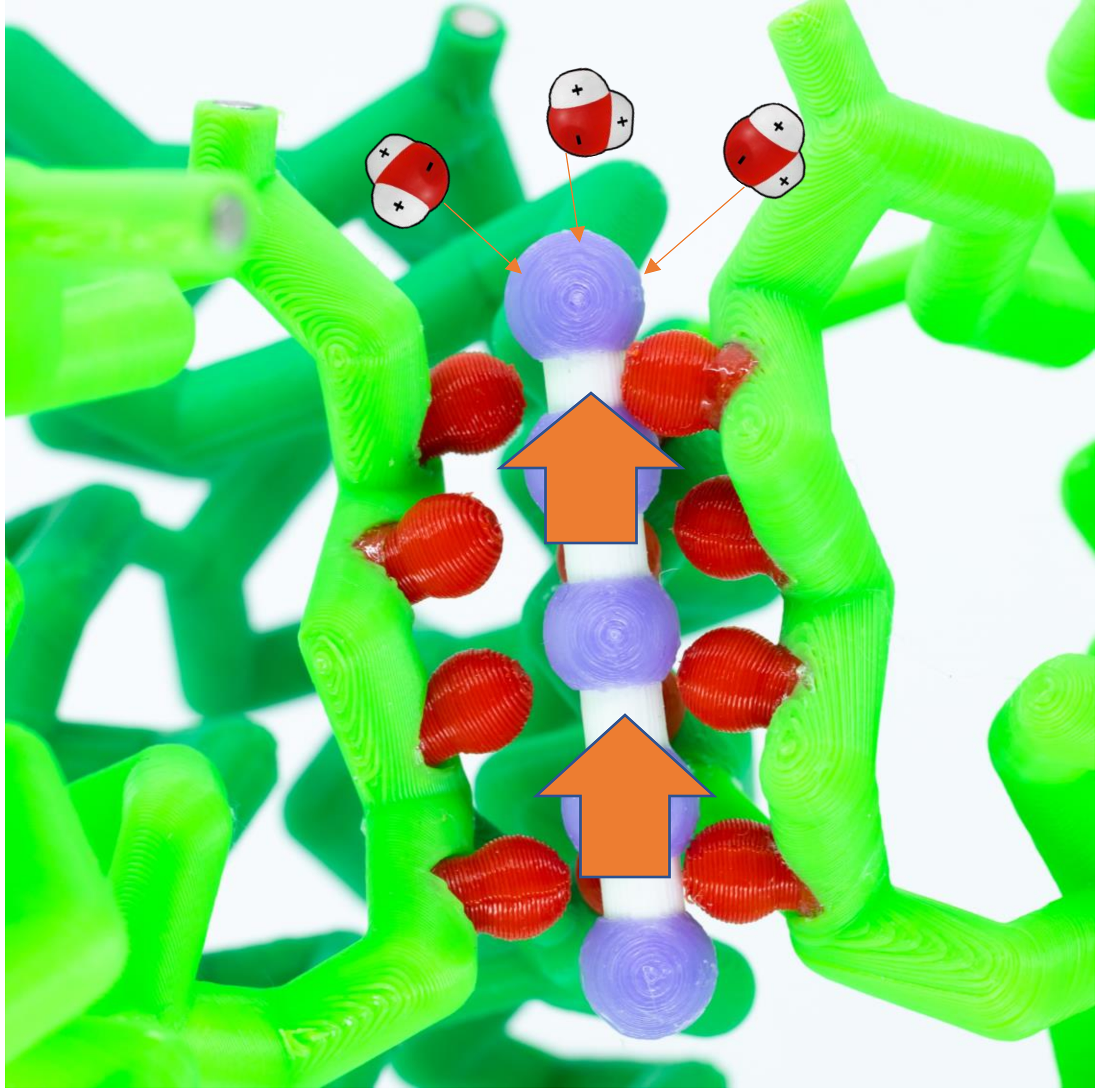
The carbonyl groups

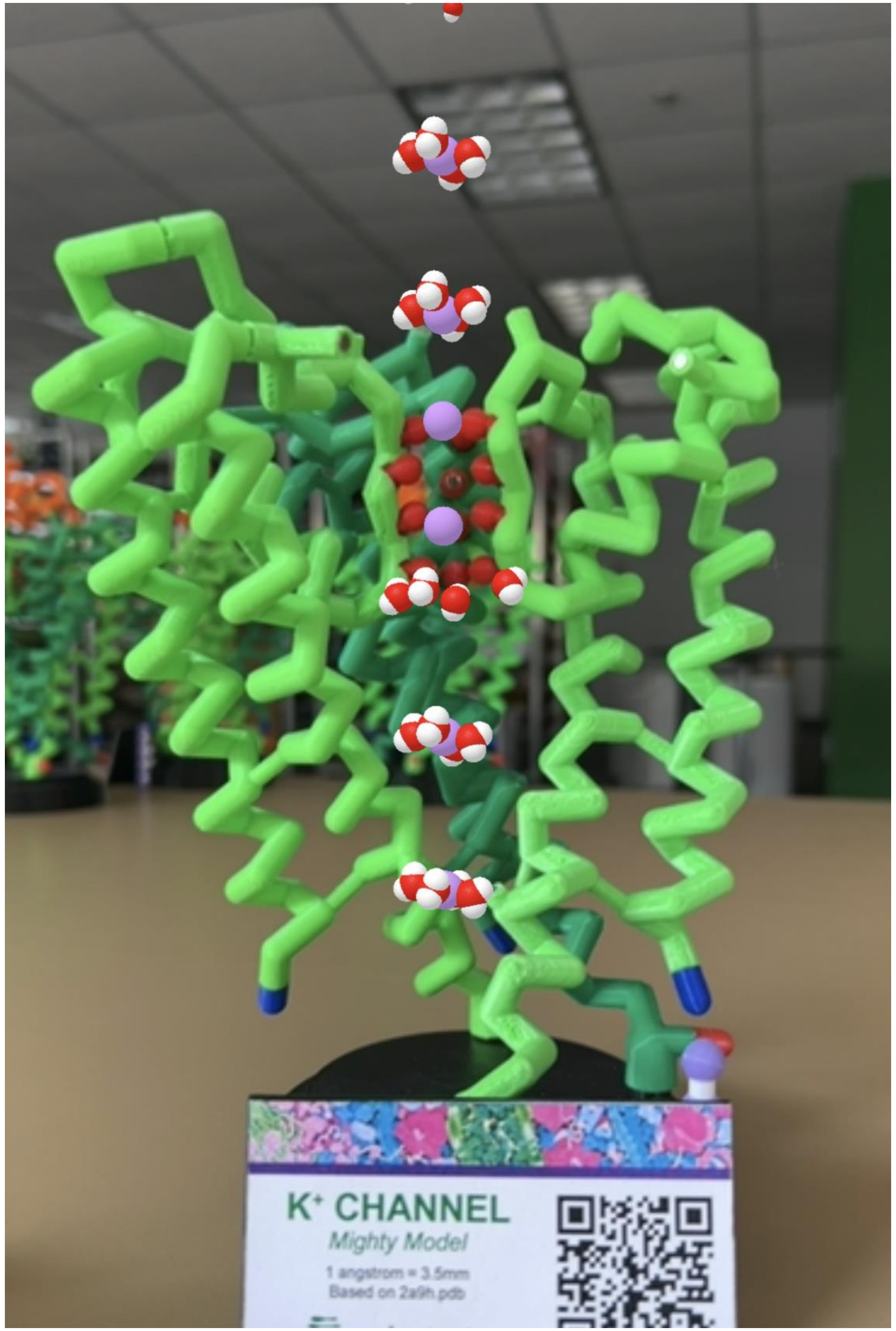
Then polarity of the carbonyl groups remove water from a hydrated K+ ion near the vestibule and facilitate its movement through the pore like an elevator.



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?

Do all the channels work this way?

- Yes and no -
- There are many different types of Sodium channel, Potassium channel, and Aquaporins

Why is this important?

- Drugs, Drug targets, and You… or your patients

- It has been suggested that the effects of some antidepressants may be mediated in part via sodium channel blockade.

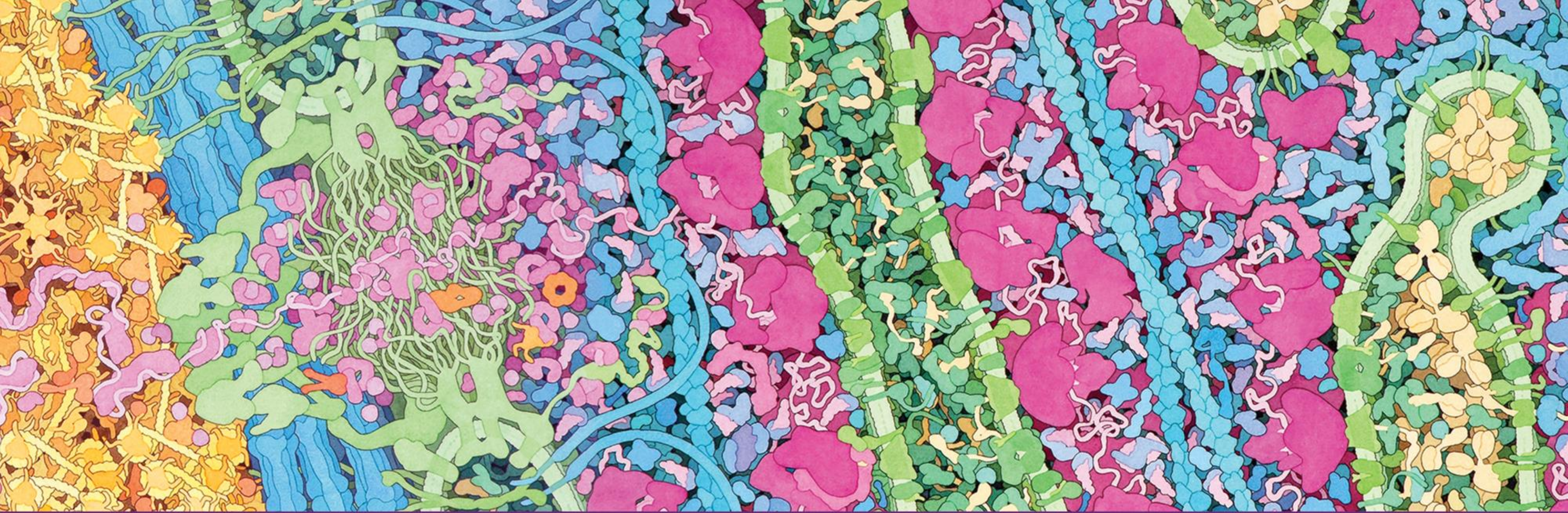
- Research has shown that CBD changes the fluidity of cell membranes and inhibits the activation of Na+ channels

- Linopirdine is a cognition-enhancing drug targeting K+ channels that can compensate for the age-related decline in acetylcholine release

Scan this QR code and fill out the survey!

... or head over to

https://bit.ly/3YFppC3



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