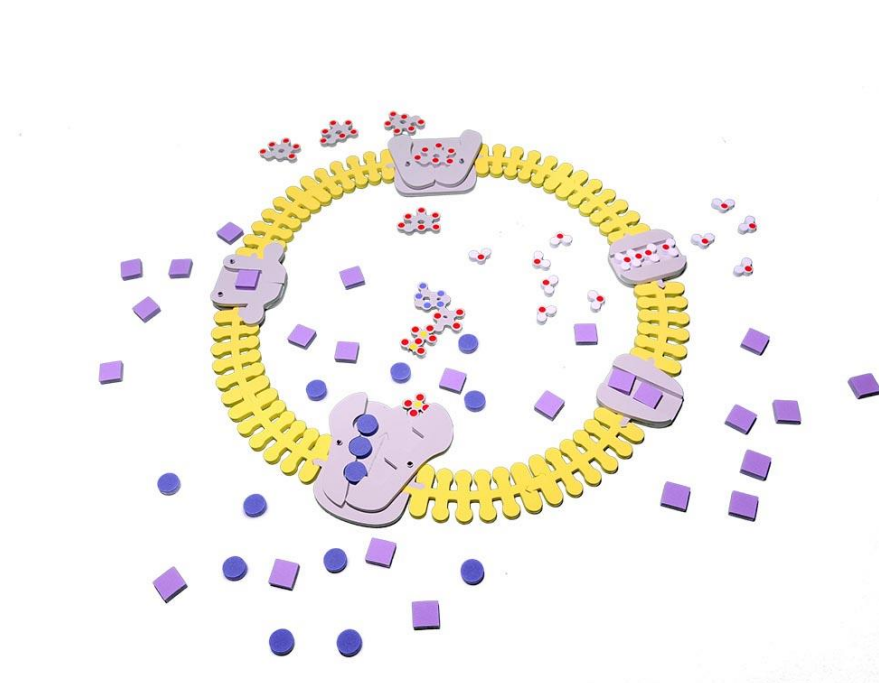
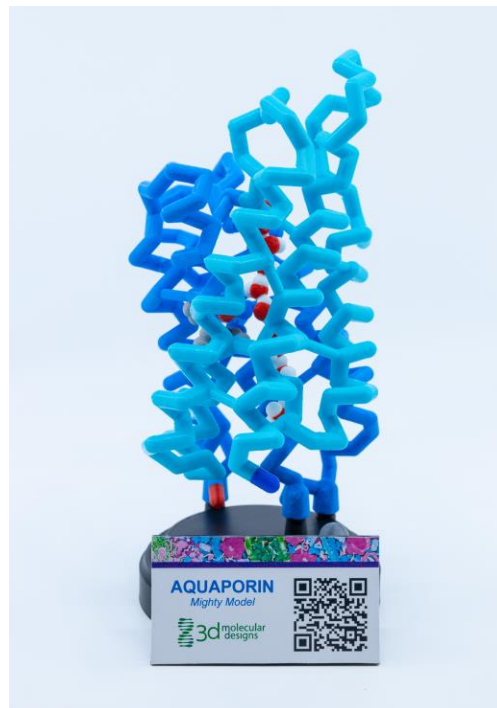




**Water water
everywhere... but
how'd it get in there?**

Mark Arnholt

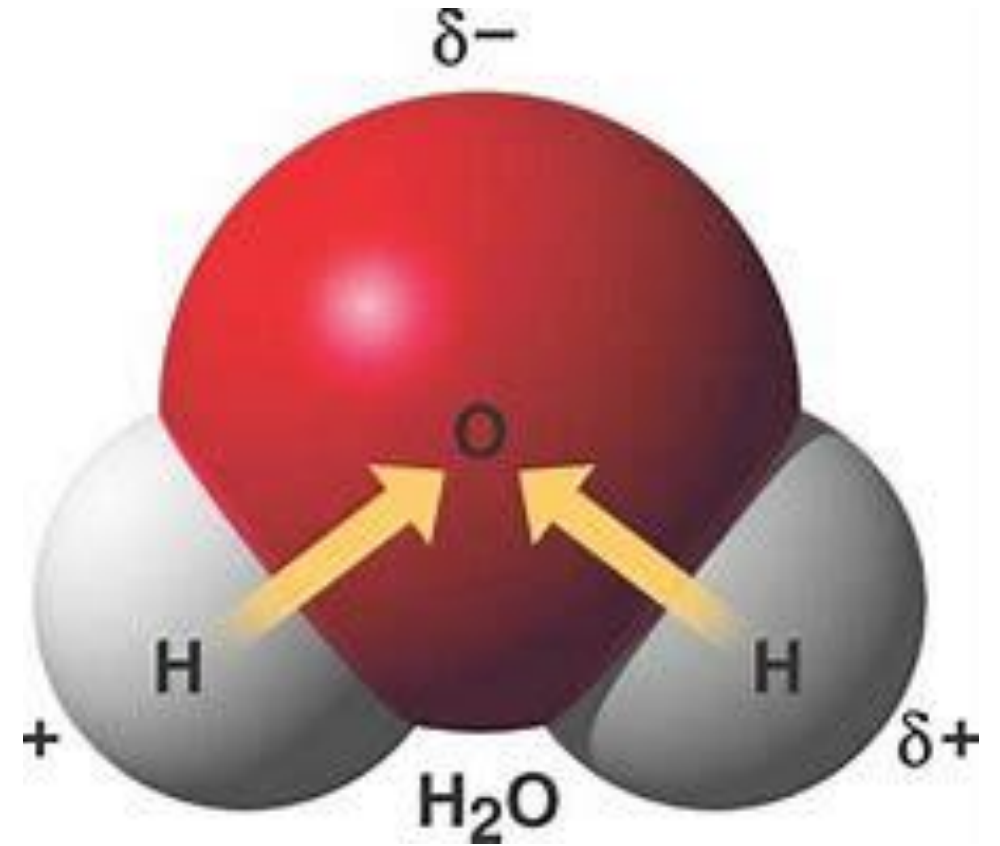
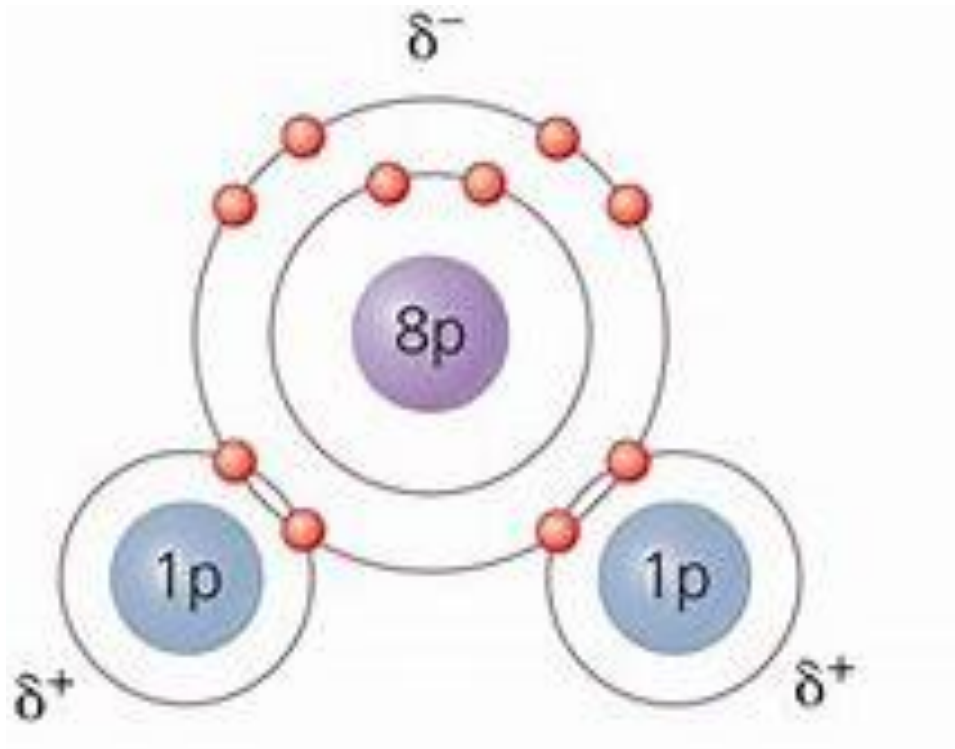
Science Educator

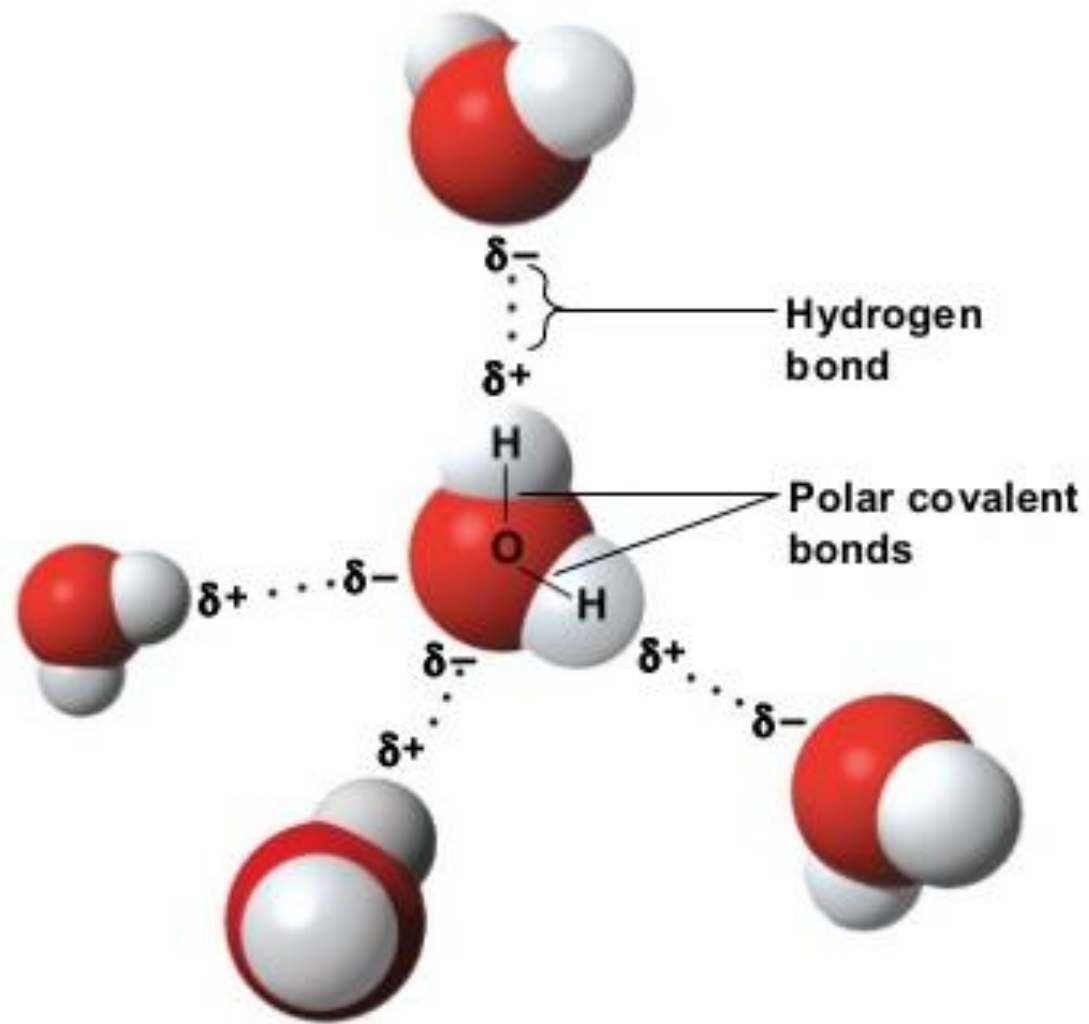
SMART Team Coordinator

3D Molecular Designs

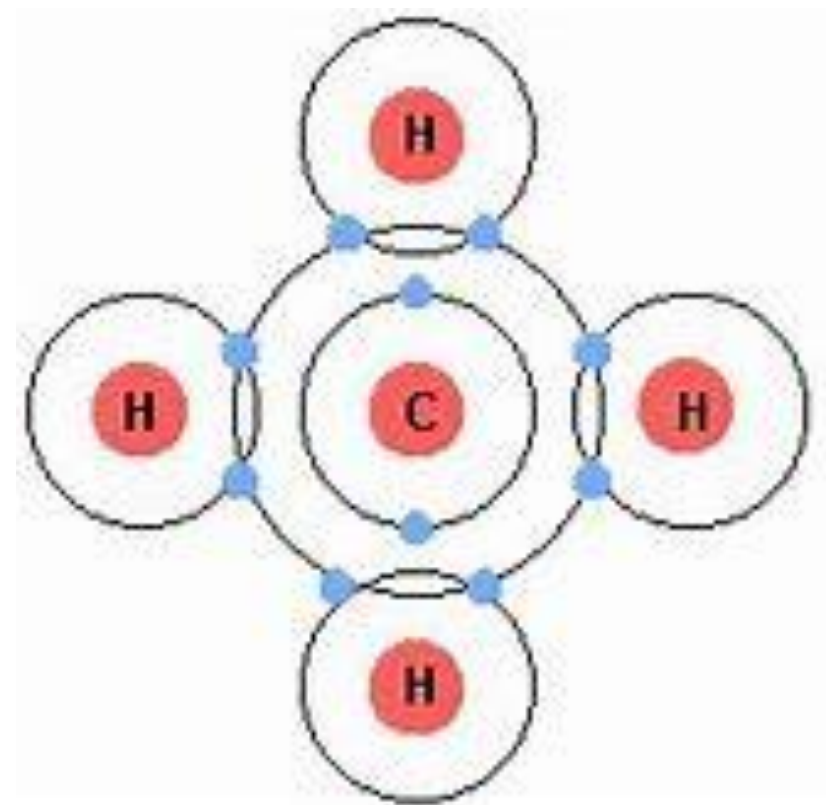
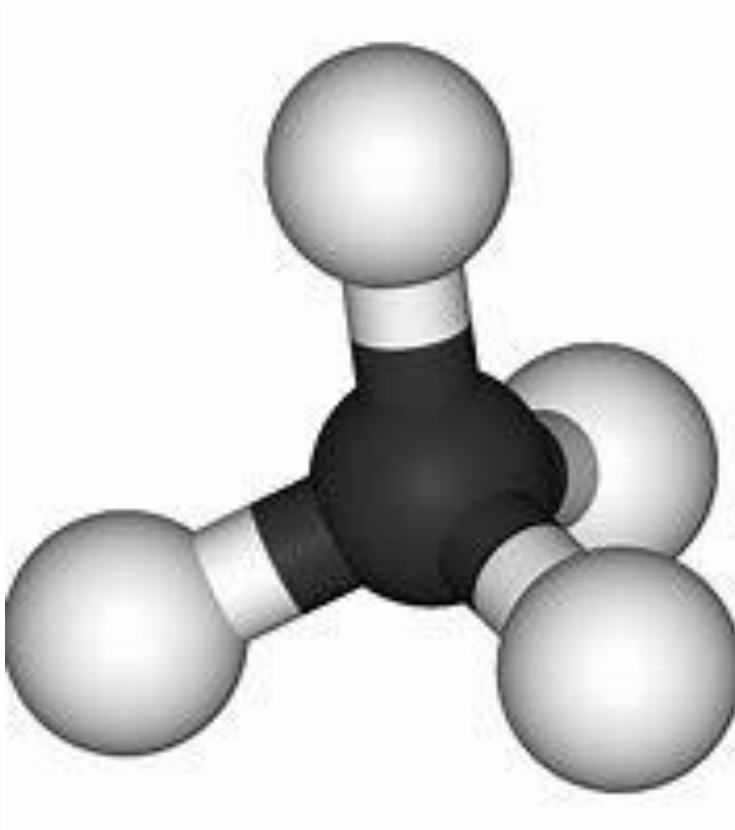
Milwaukee, WI

Water exhibits POLAR COVALENT bonds

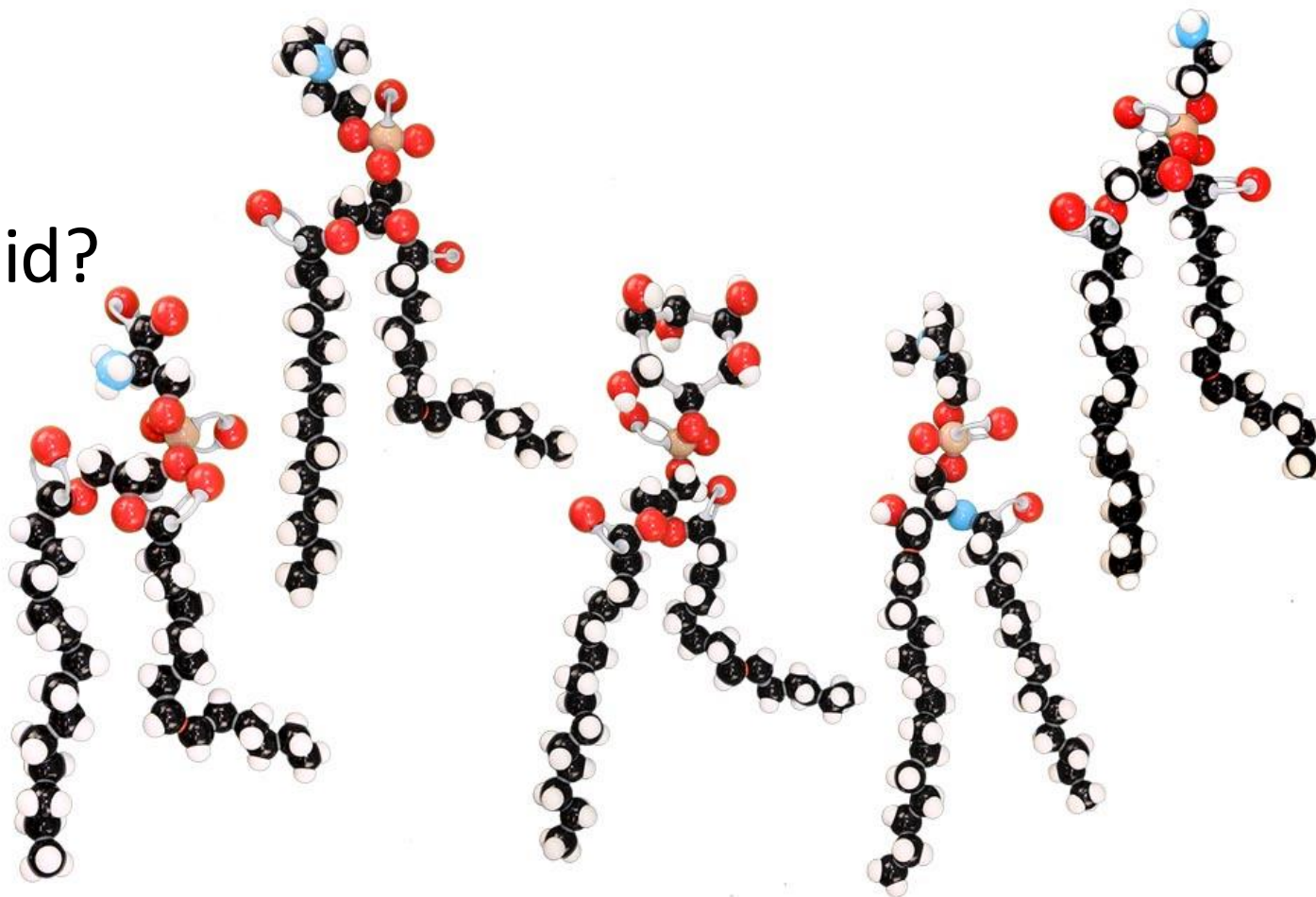




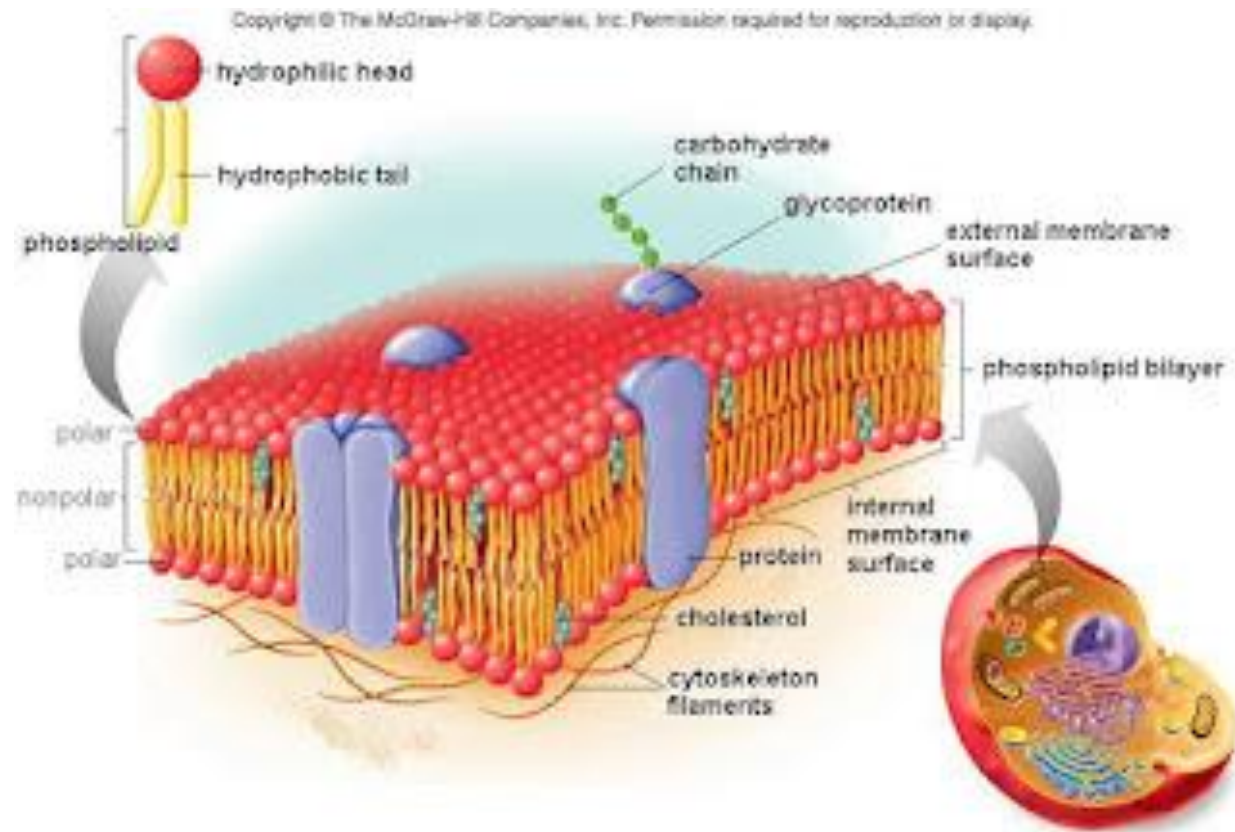
What about methane?



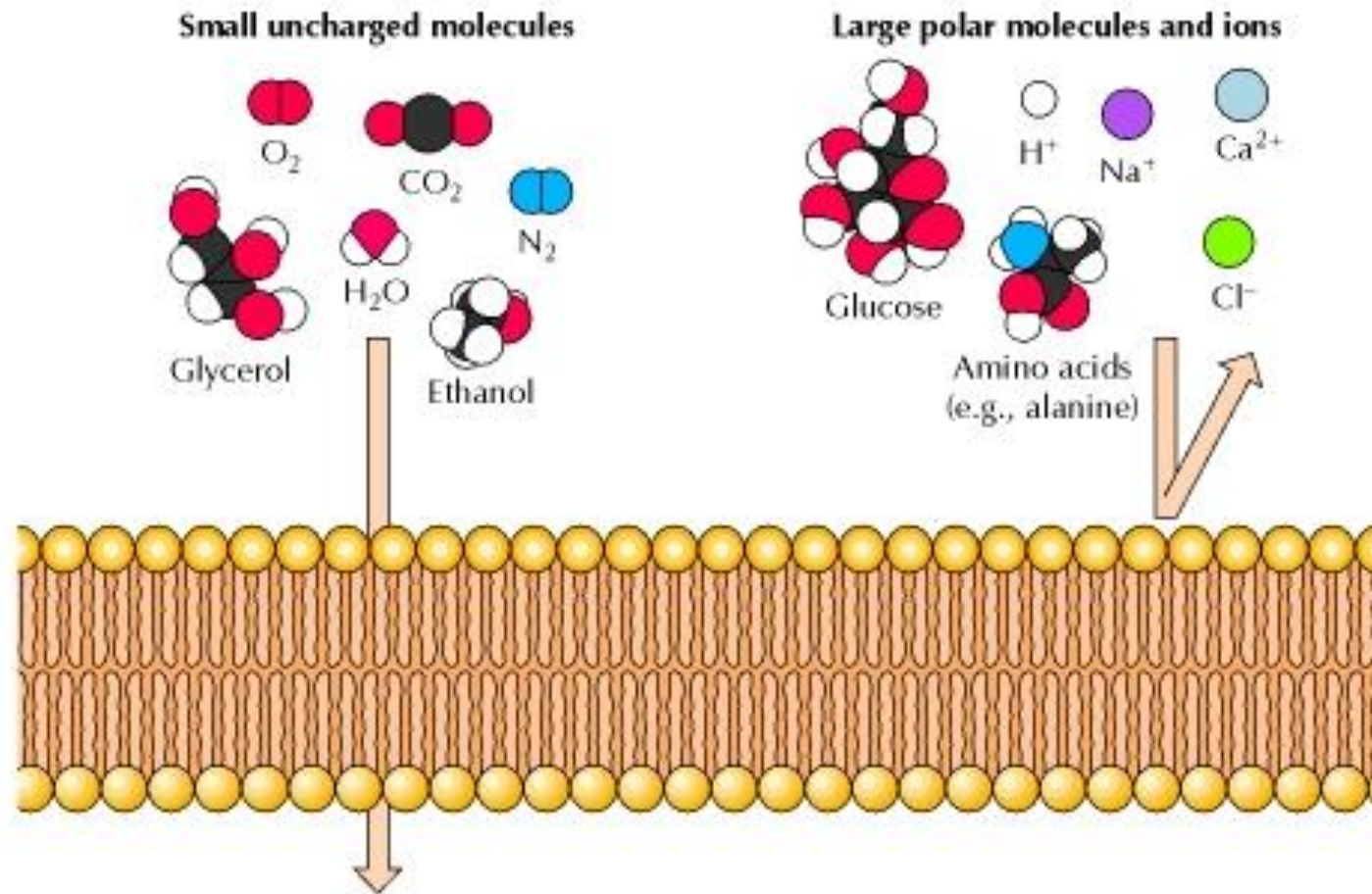
What about a phospholipid?
What do you notice?



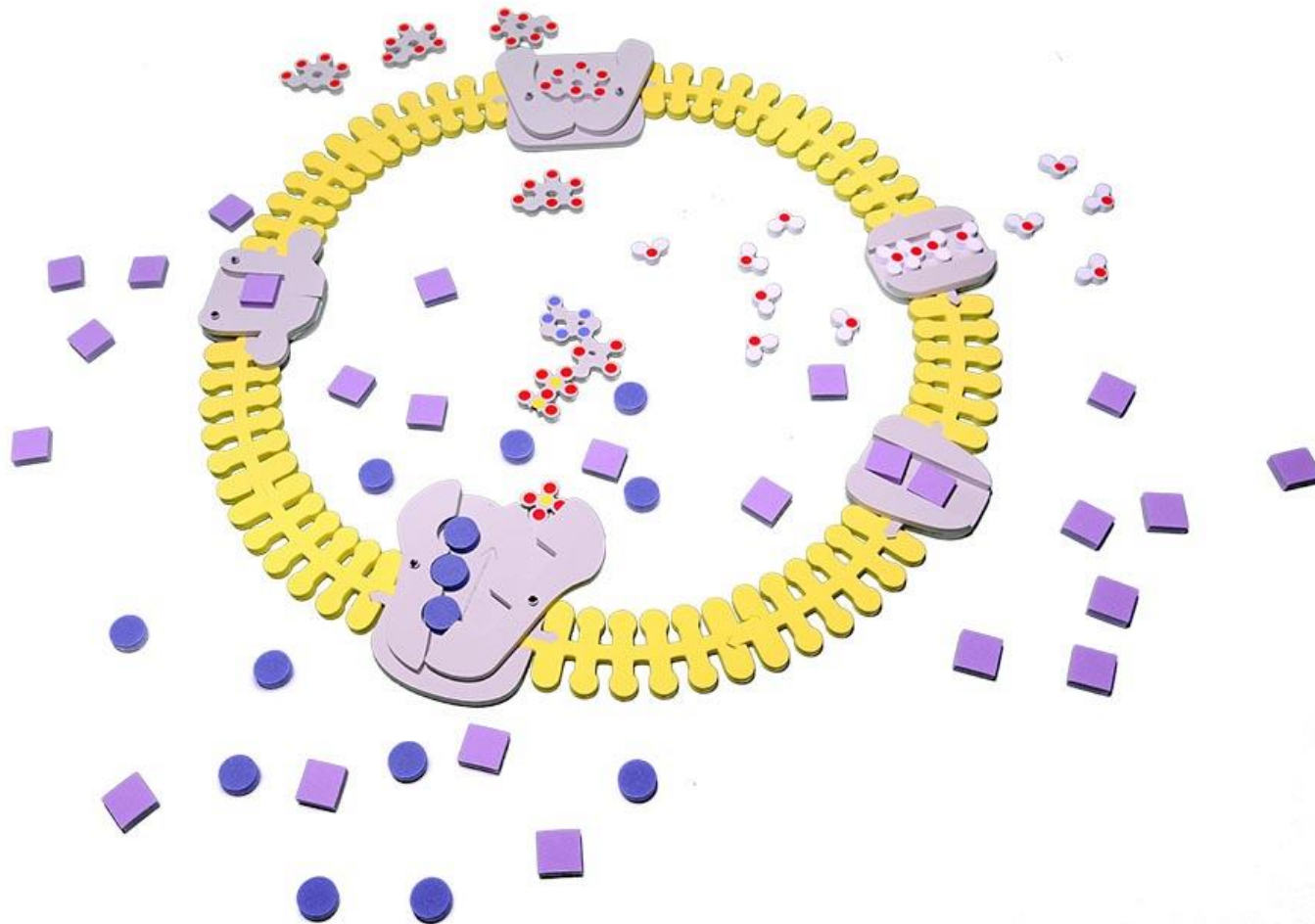
The Cell Membrane



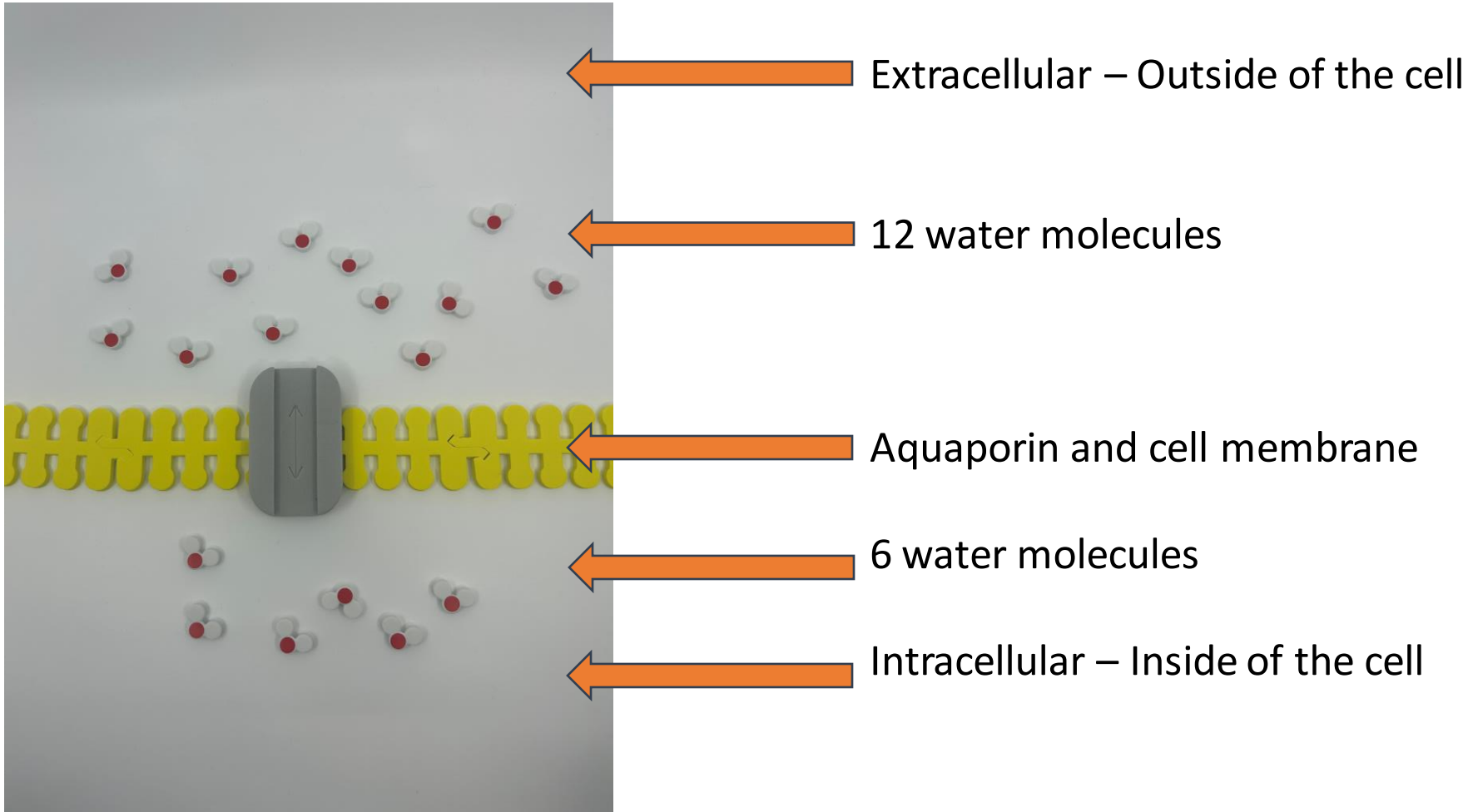
The problem...



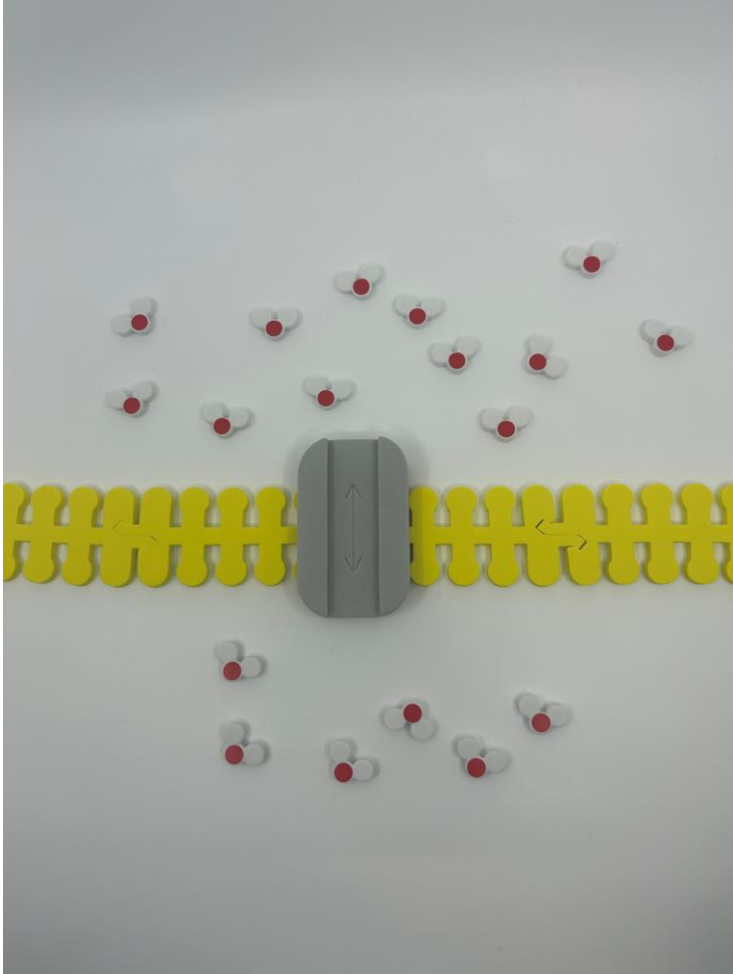
There's a lot going on here, so let's simplify it!



Let's focus on water first – Add the following



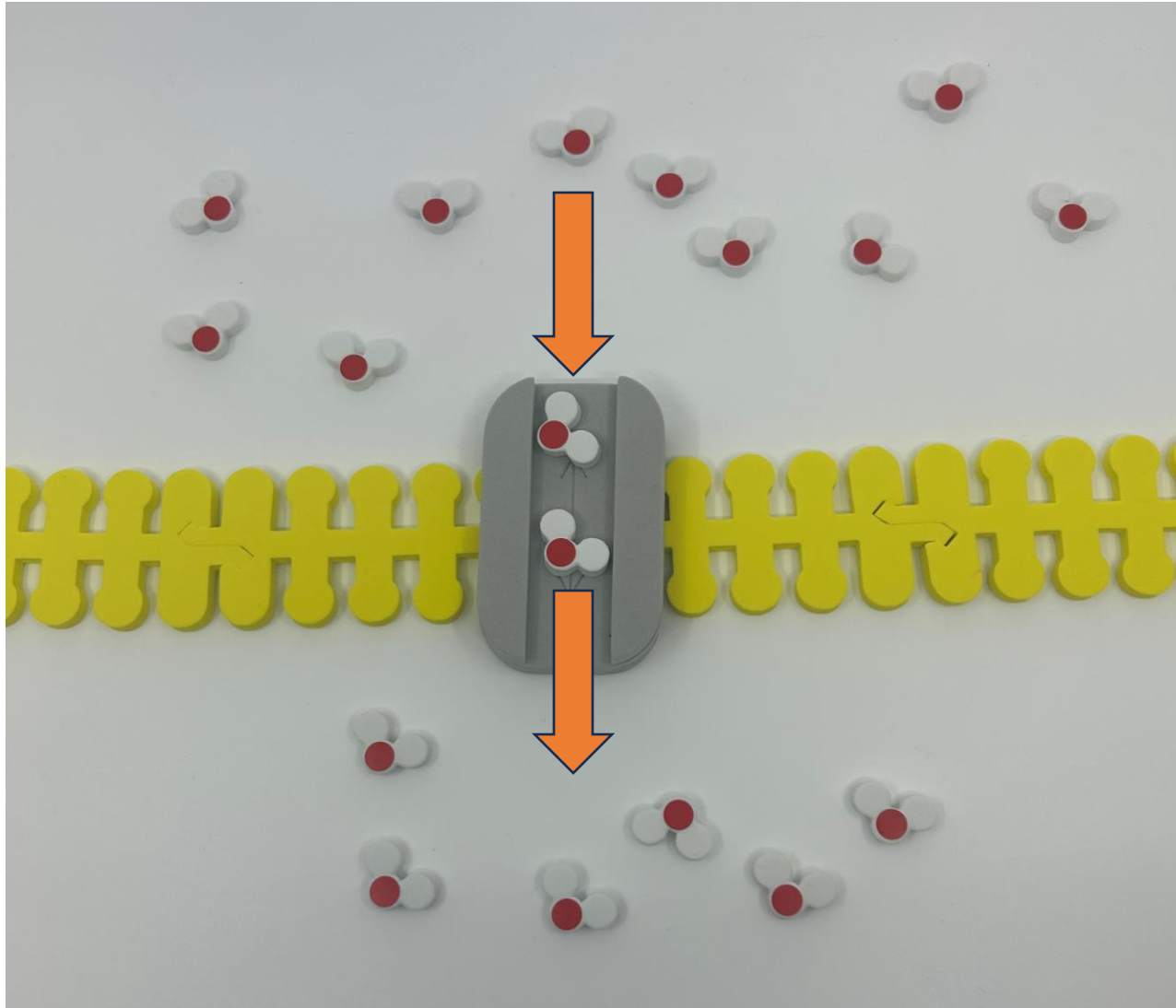
With an aquaporin in place...



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

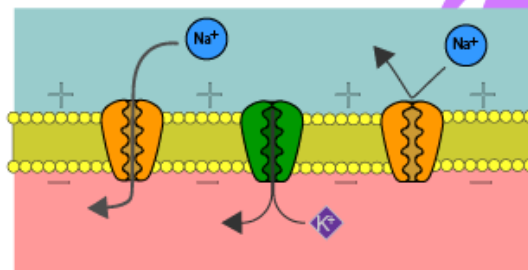
How many water molecules should you move?

Move 3 water molecules across to reach equilibrium

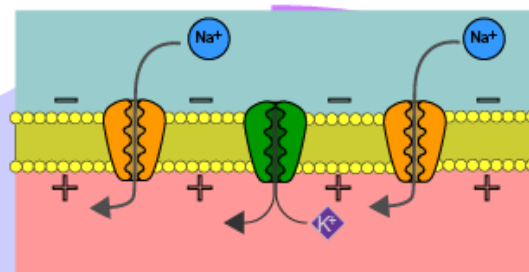


Life is complicated...

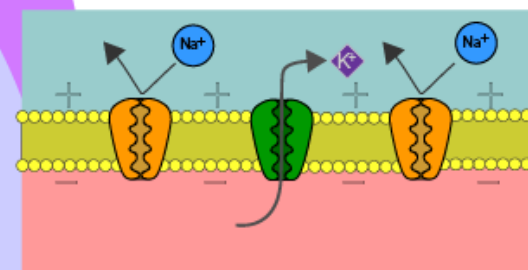
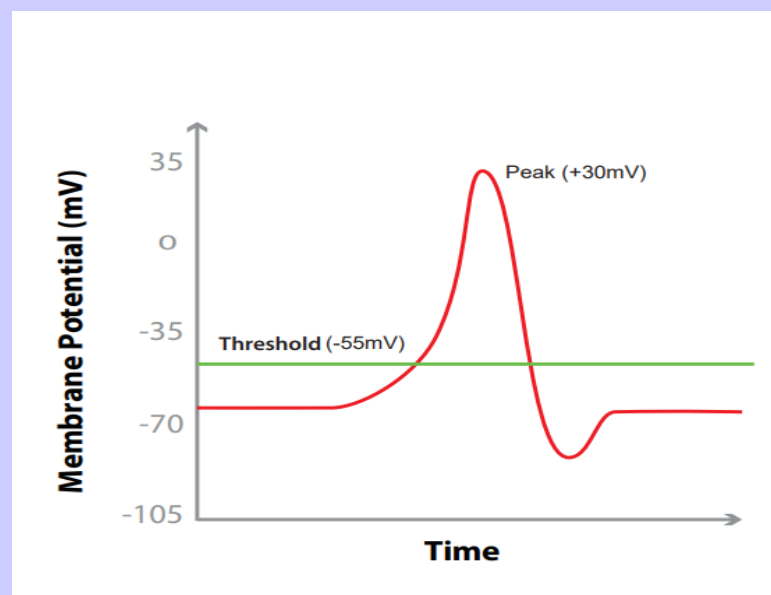
1 Resting state - The resting potential of the neuron is maintained by having the voltage gates closed in both Na⁺ and K⁺ channels.



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.

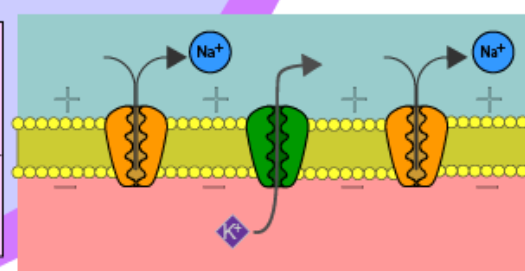
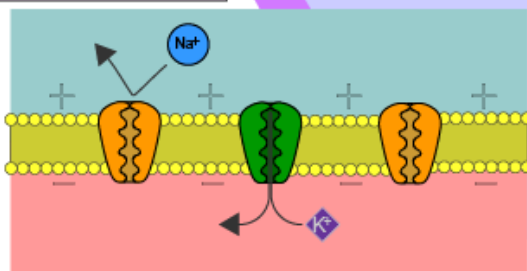


3 Rising phase - Most Na⁺ activation gates are now open, causing a large increase of Na⁺ ions inside the membrane. K⁺ channels remain closed. The higher concentration of Na⁺ ions make the inside of the membrane positive.



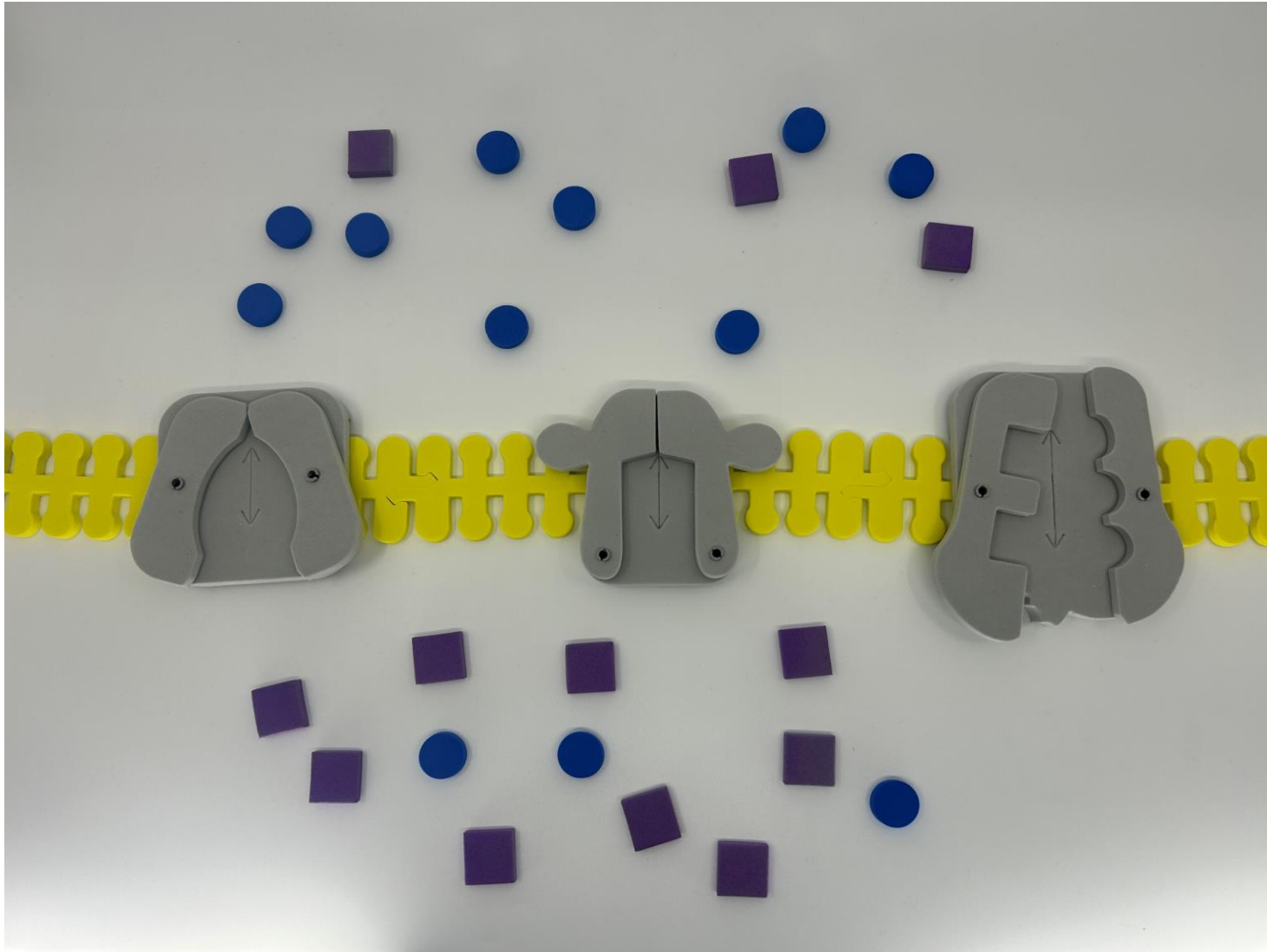
4 Falling phase of the action potential - K⁺ gates open, allowing K⁺ ions to move to the extracellular space. Na⁺ channels inactivation gates close, preventing the influx of Na⁺ ions. As more K⁺ ions leave the cell, the interior membrane becomes more negatively charged.

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.

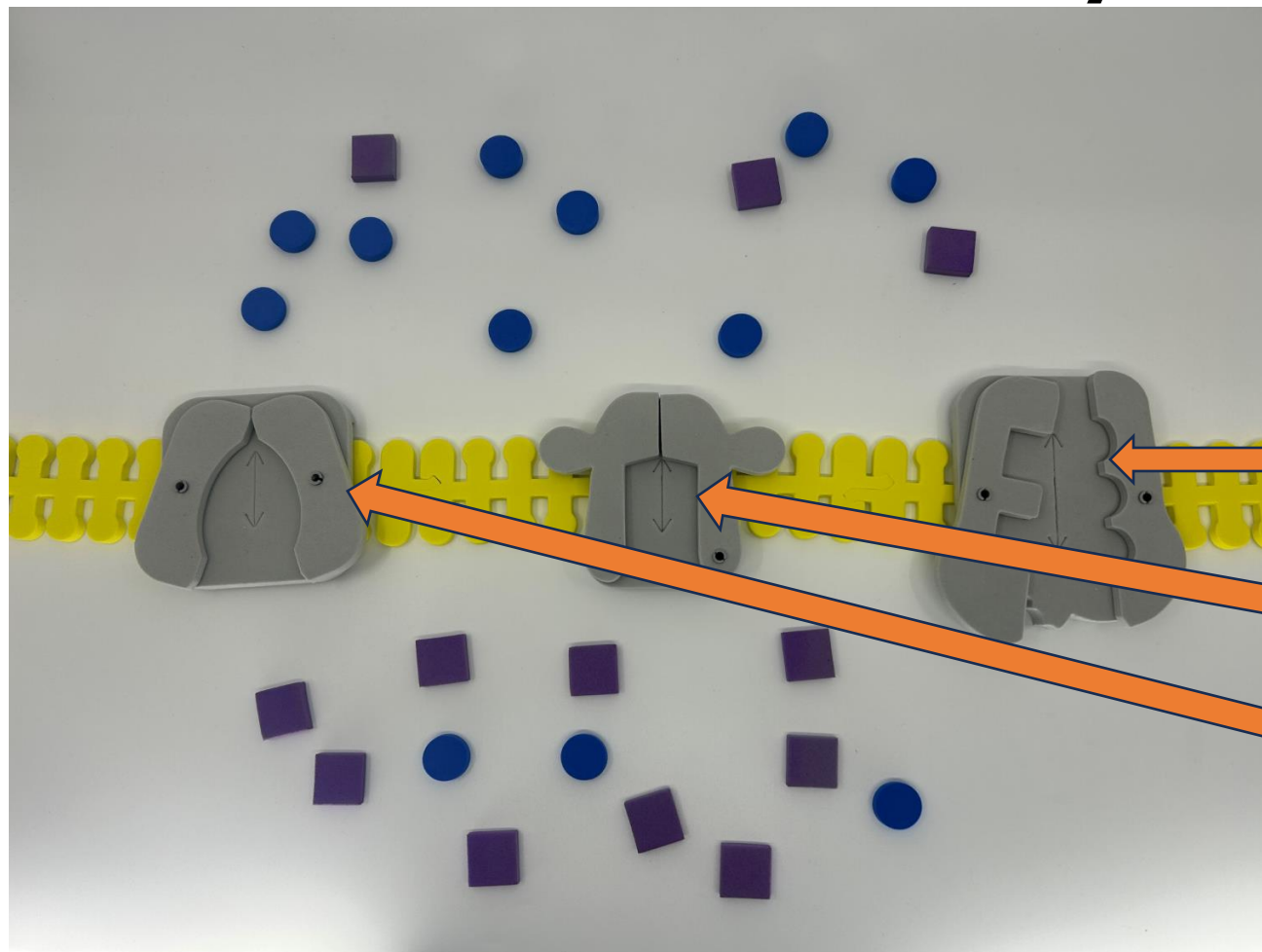


[Link](#)

Let's model an action potential



Let's identify everything



Na⁺ (x 12)



K⁺ (x 12)

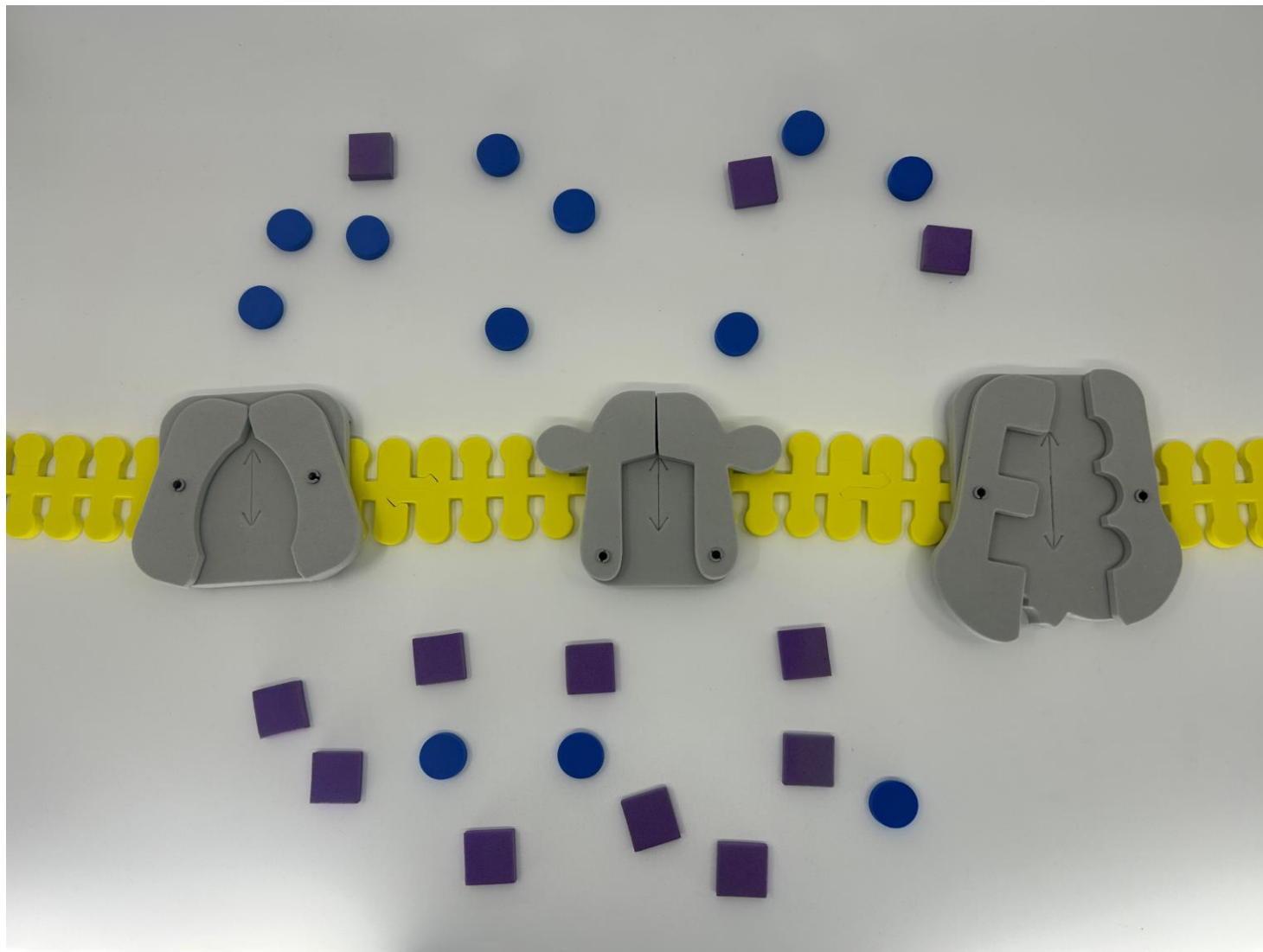
Na⁺ / K⁺ Channel

Gated Na⁺ channel (Simulated)

Gated K⁺ Channel

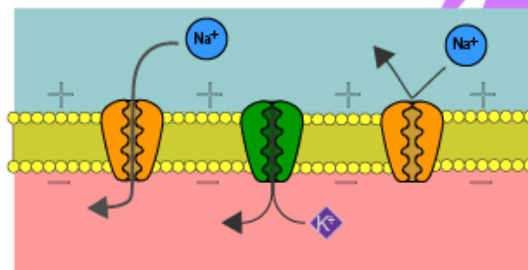


What do you notice?

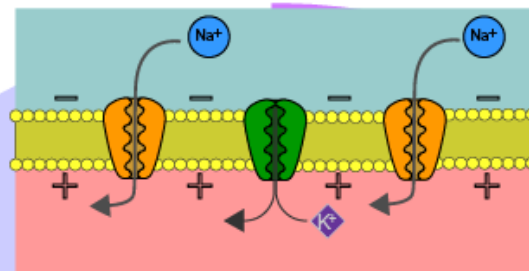


Life is complicated...

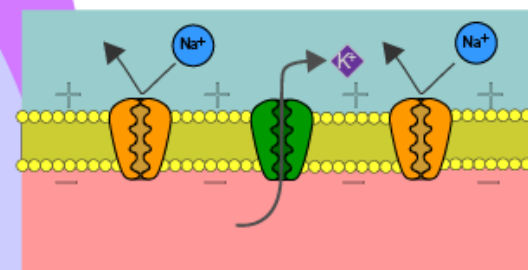
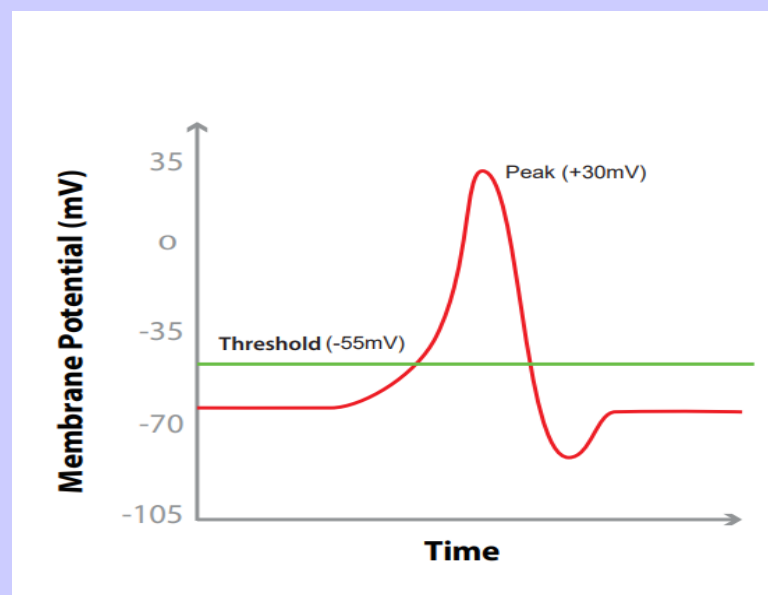
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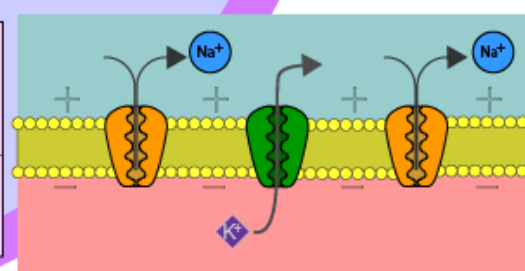
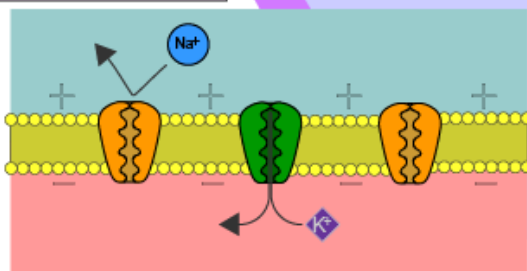


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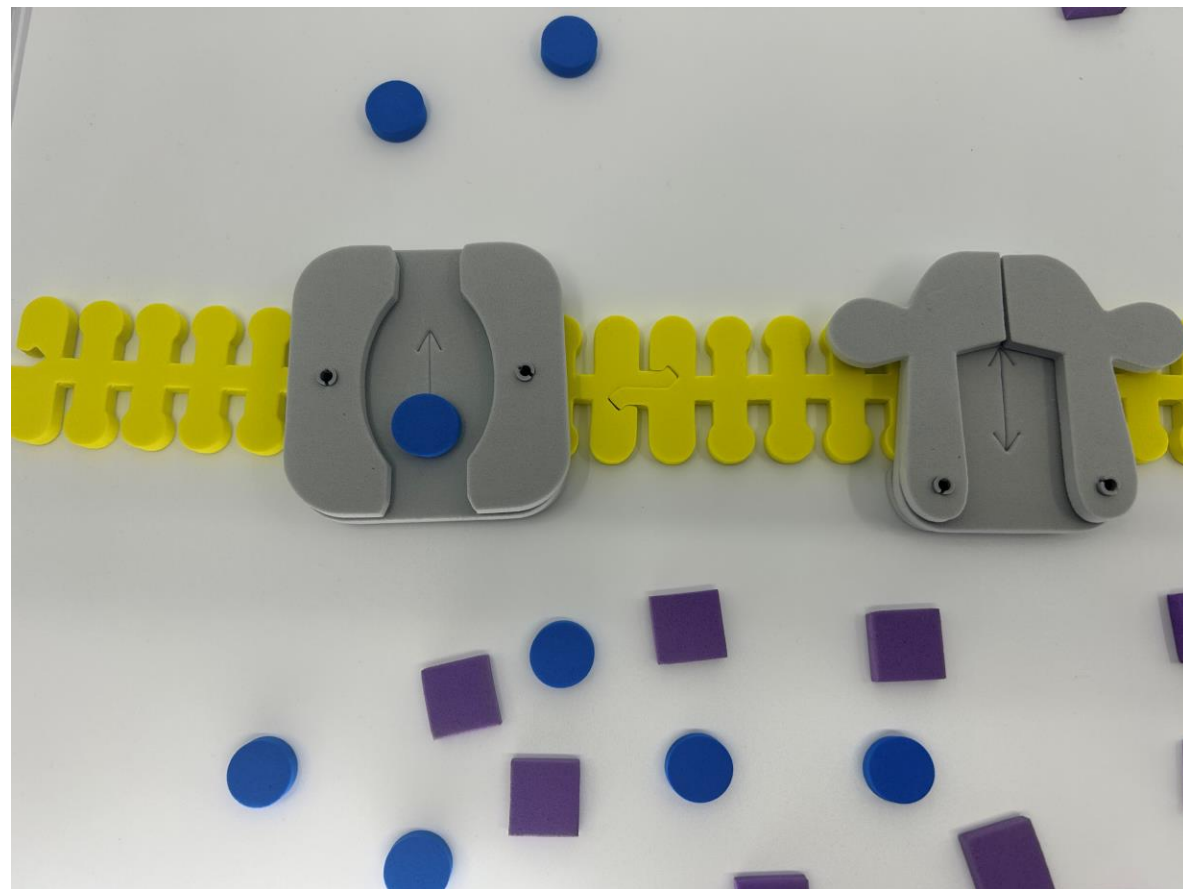
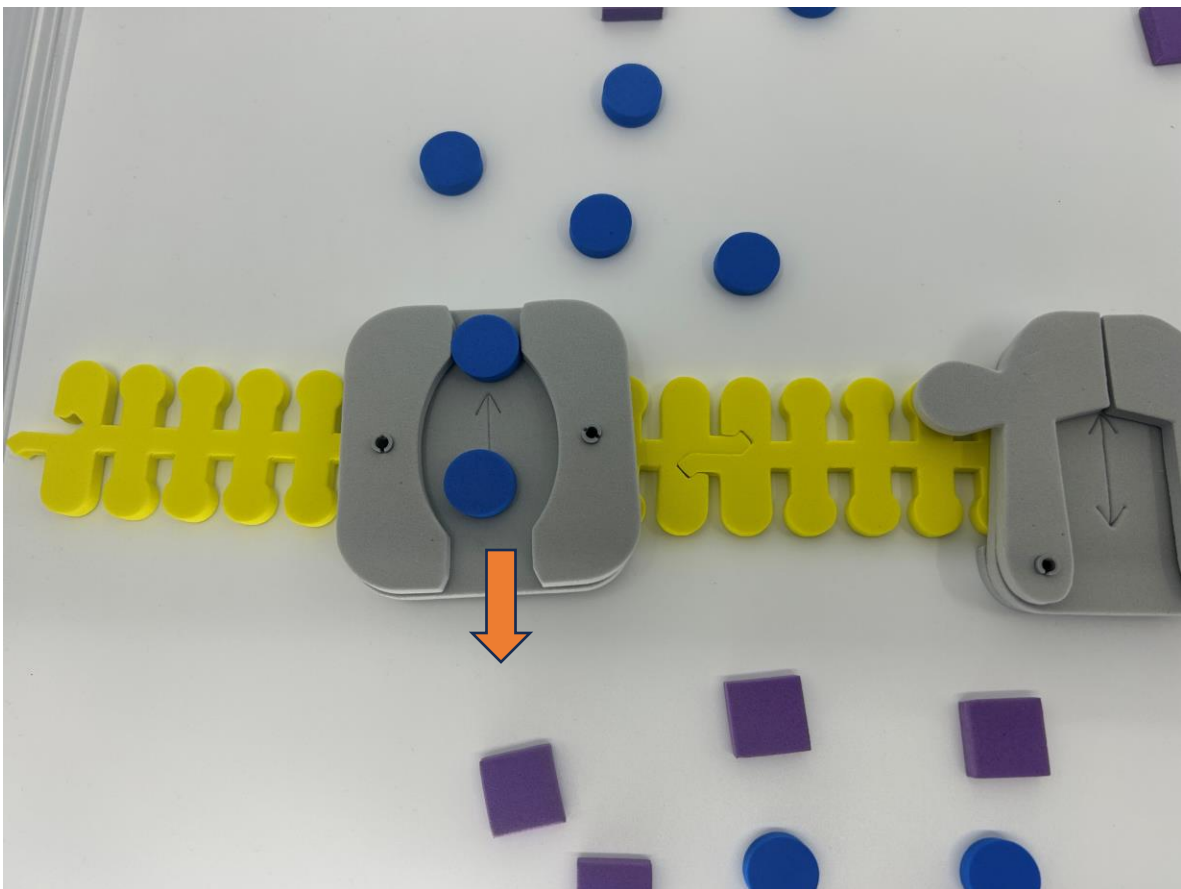
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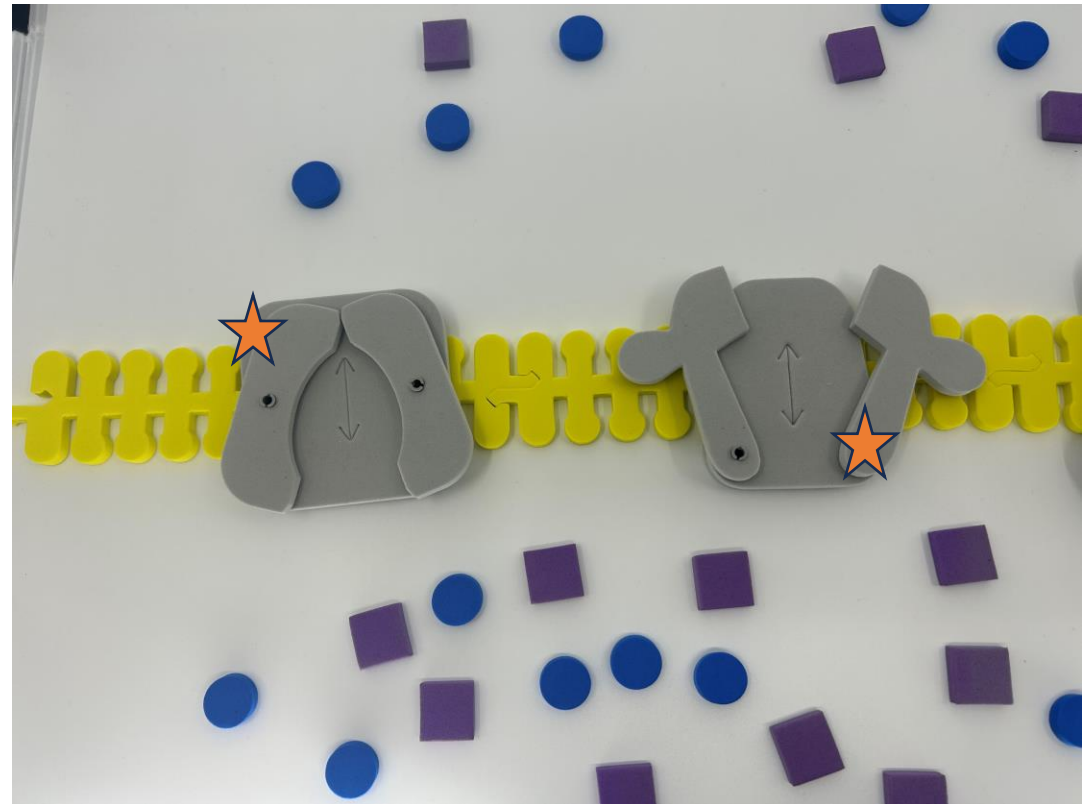
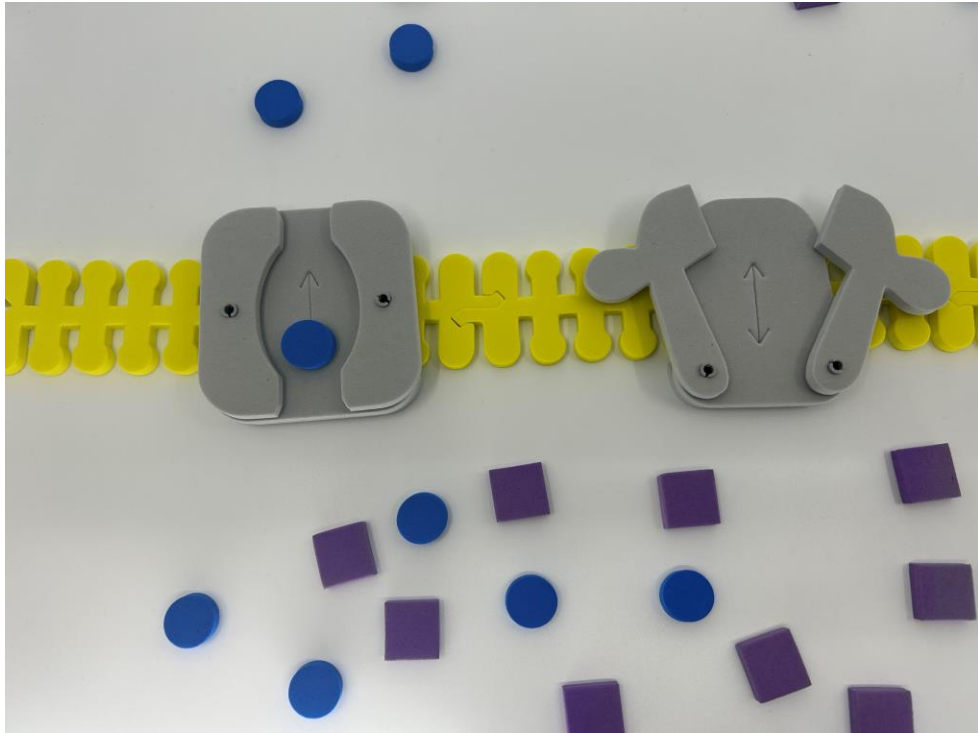


[Link](#)

Sodium (Na^+) first...

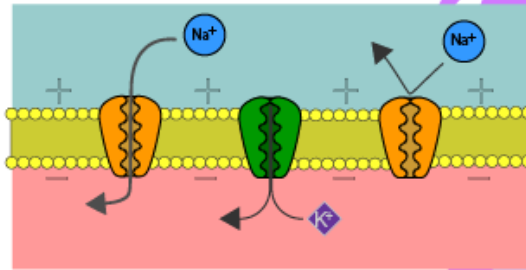


What happened to the charge inside the membrane?

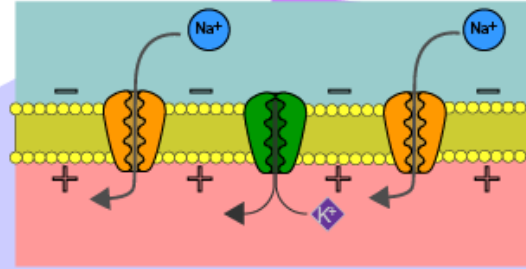


Life is complicated...

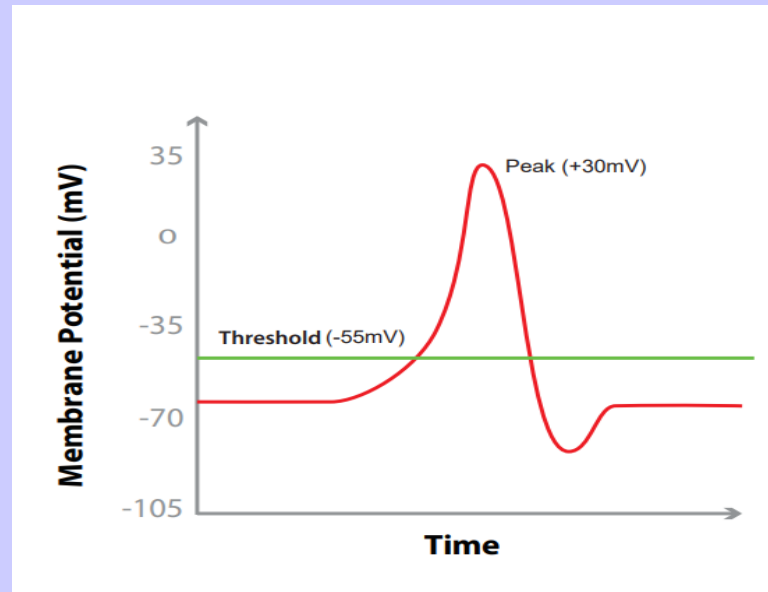
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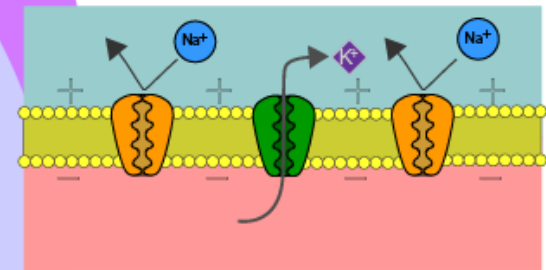
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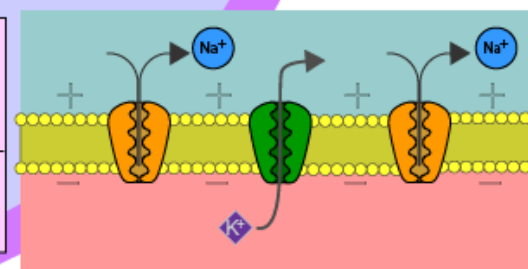
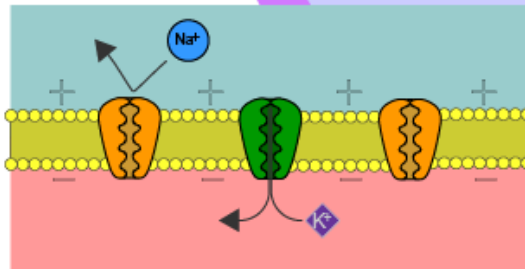
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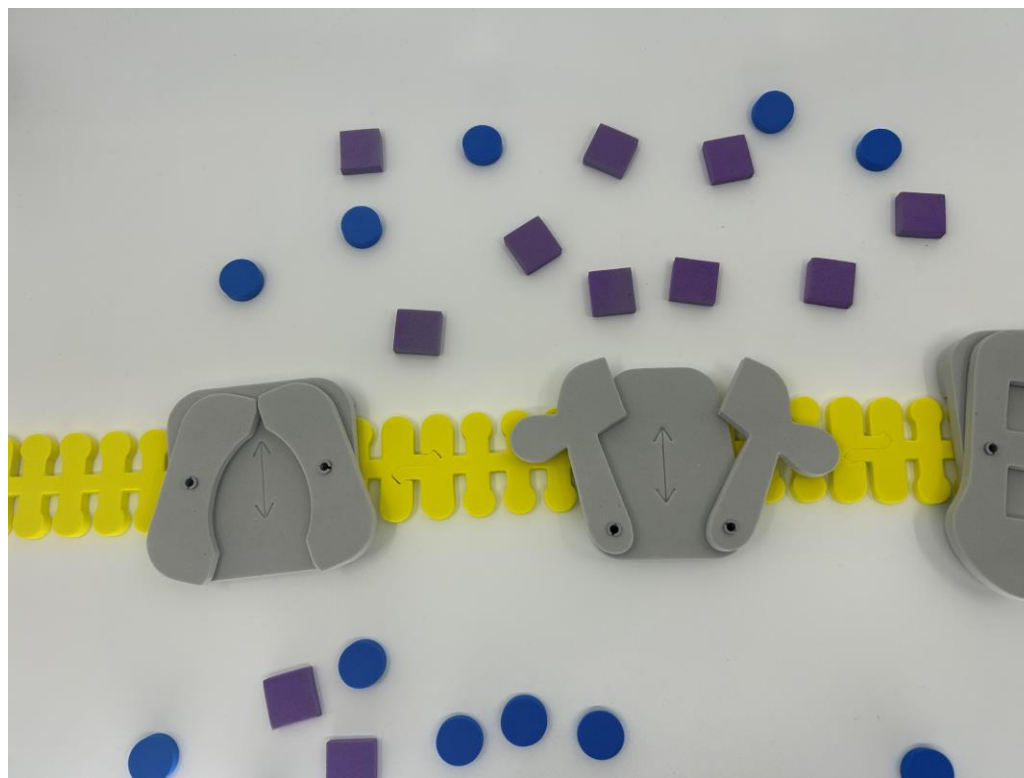
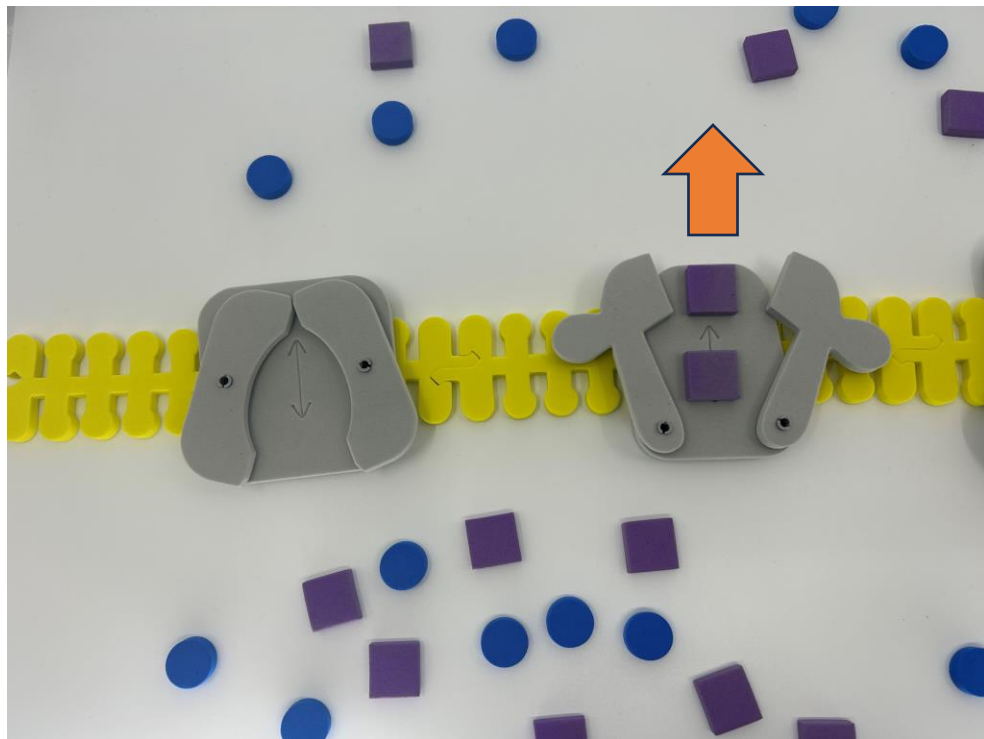


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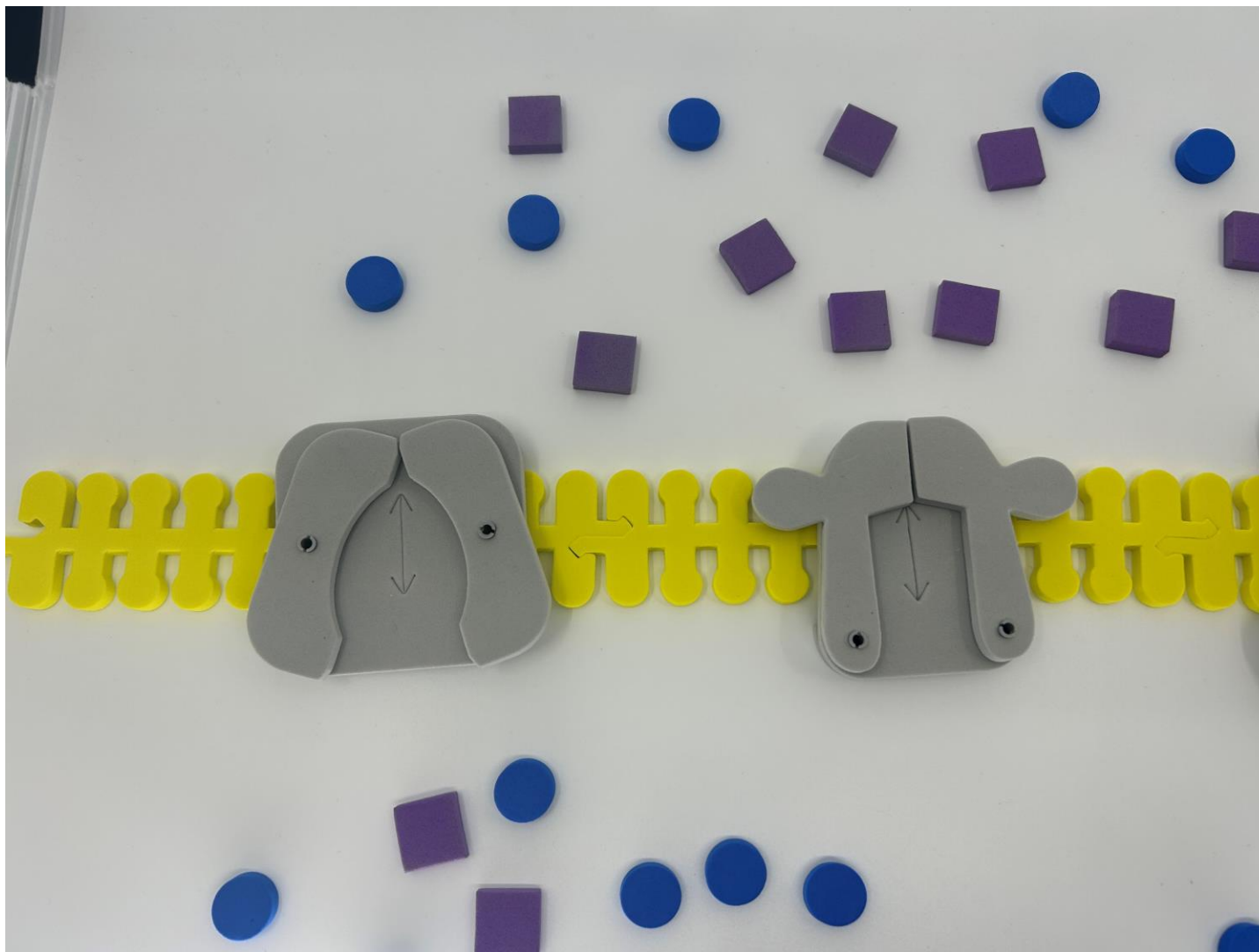


[Link](#)

Potassium (K^+) moves next

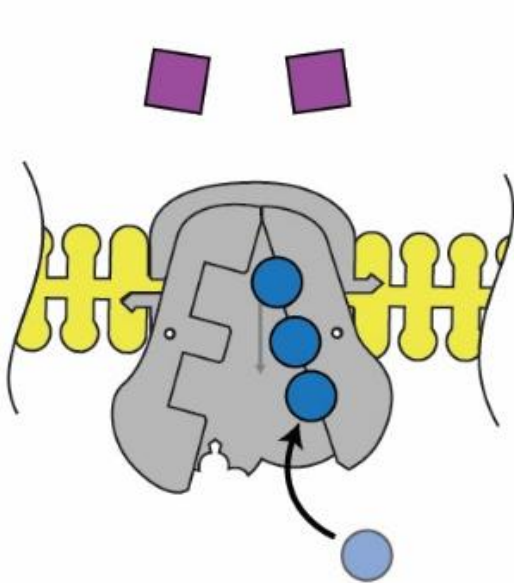


Each channel is “tuned”

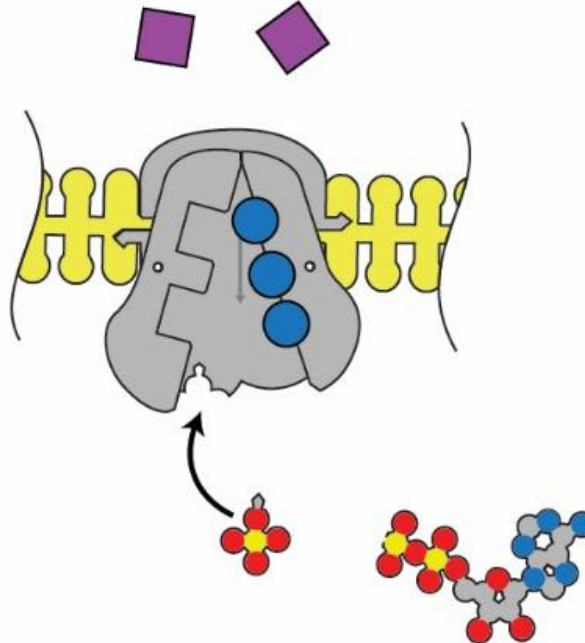


How do we get back to a resting potential?

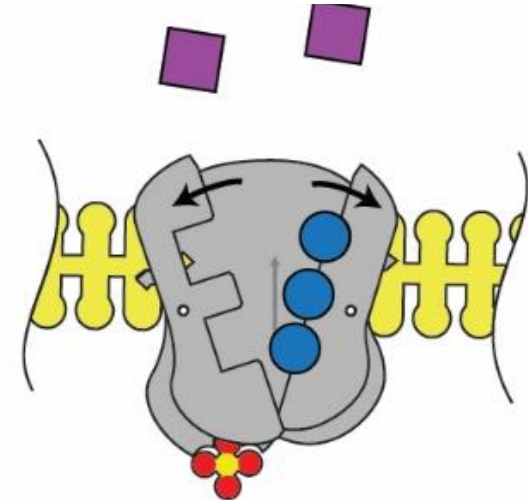
1. Sodium binds on the intracellular side.



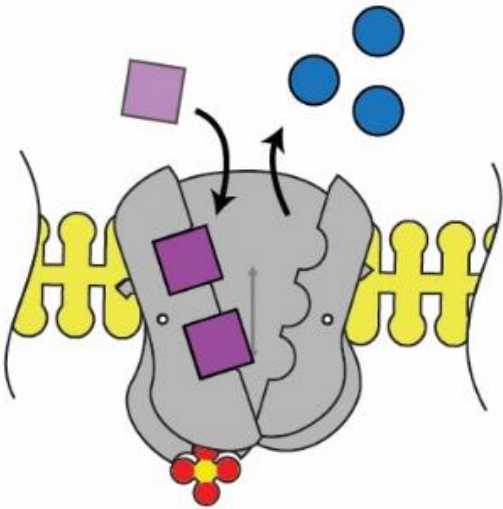
2. The pump is phosphorylated by ATP.



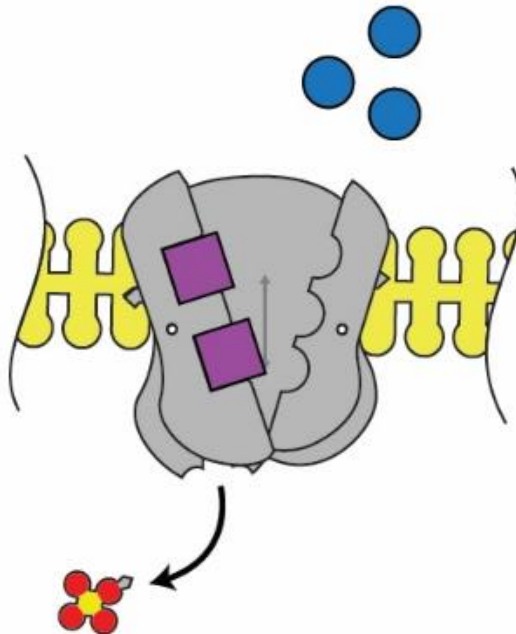
3. The pump shape changes, exposing the sodium to the extracellular space.



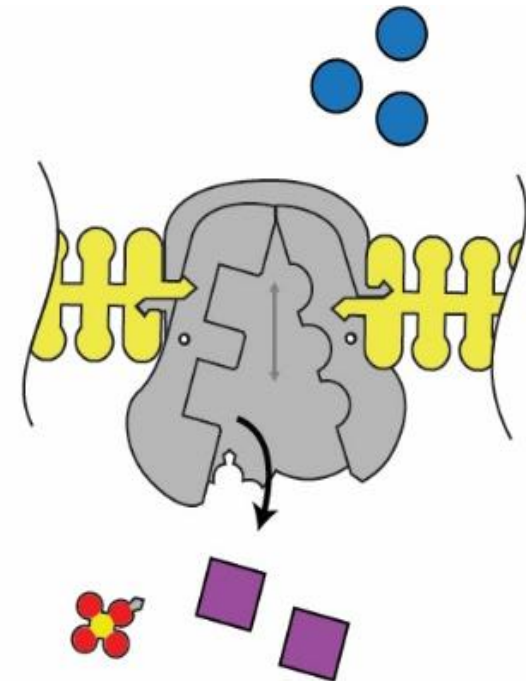
4. Binding affinity changes to release Na^+ and take in K^+ .



5. Phosphate detaches.

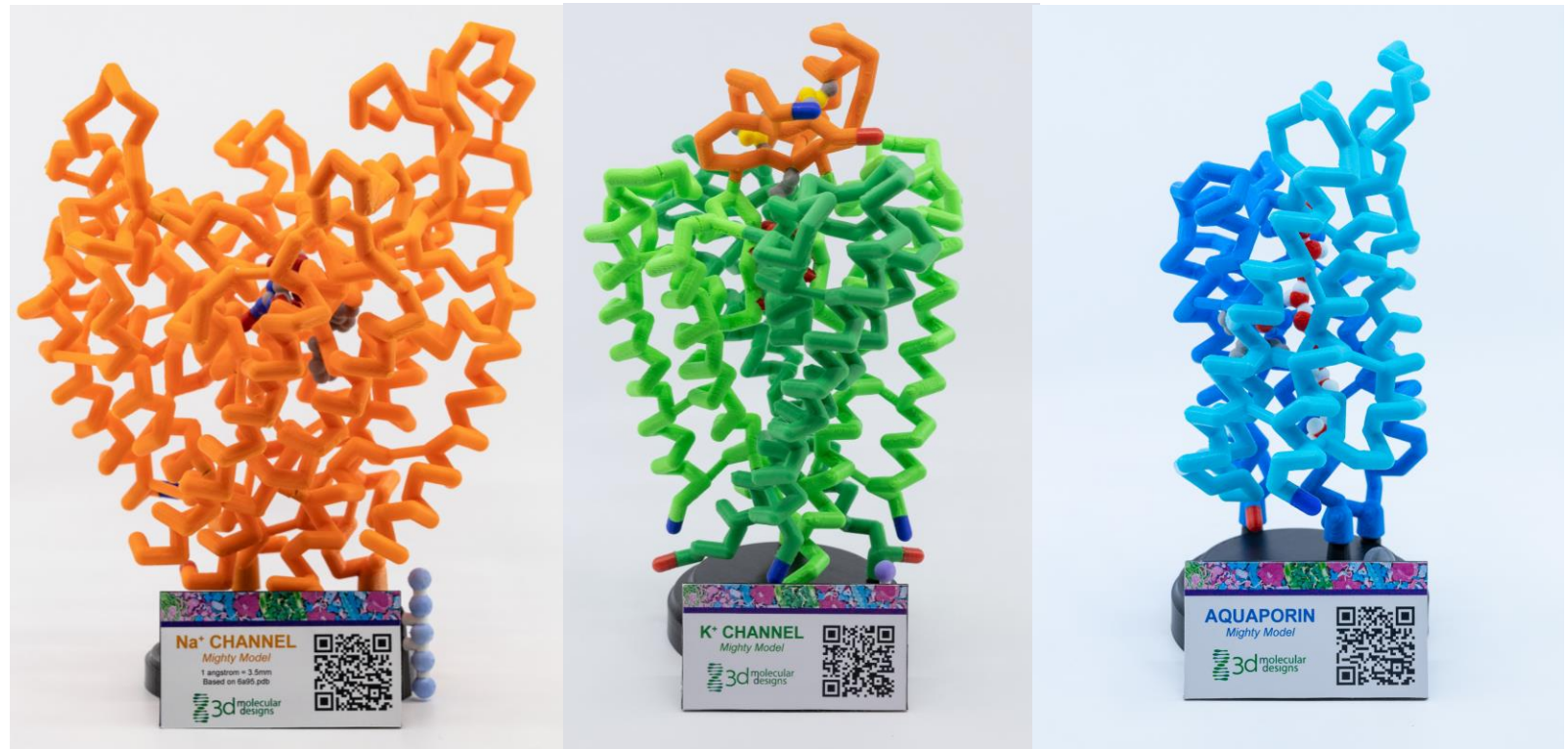


6. Original shape is restored, releasing K^+ into the cell.



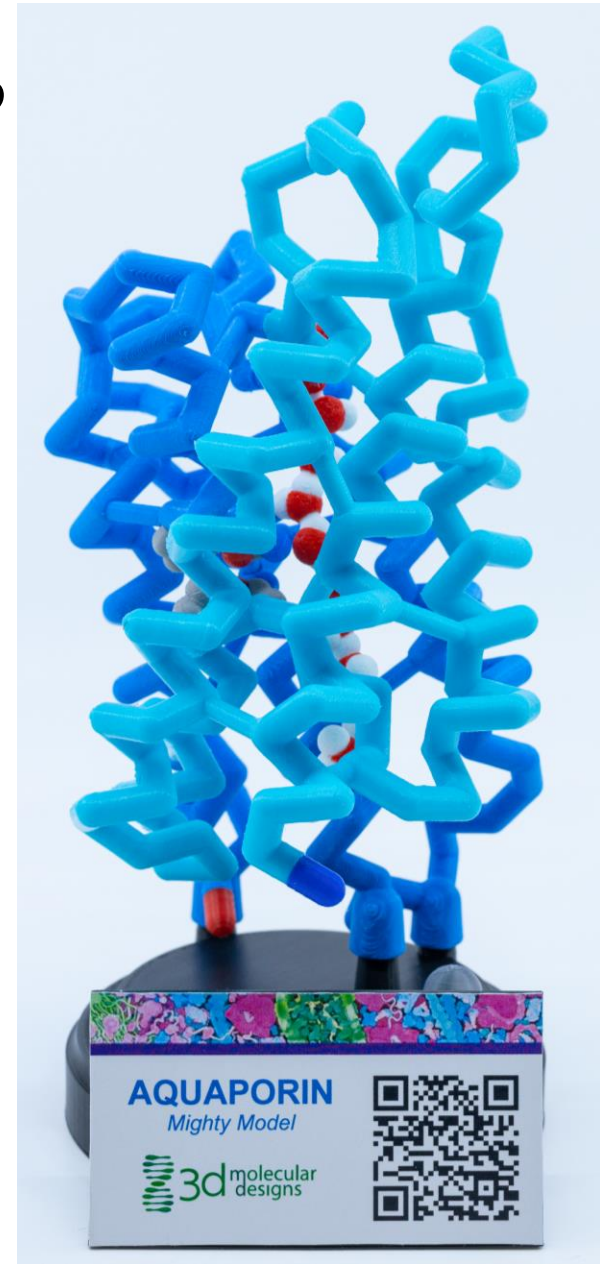
How does a channel “know” which ion to transport?

- They don't...
- They follow the basic rules of chemistry!

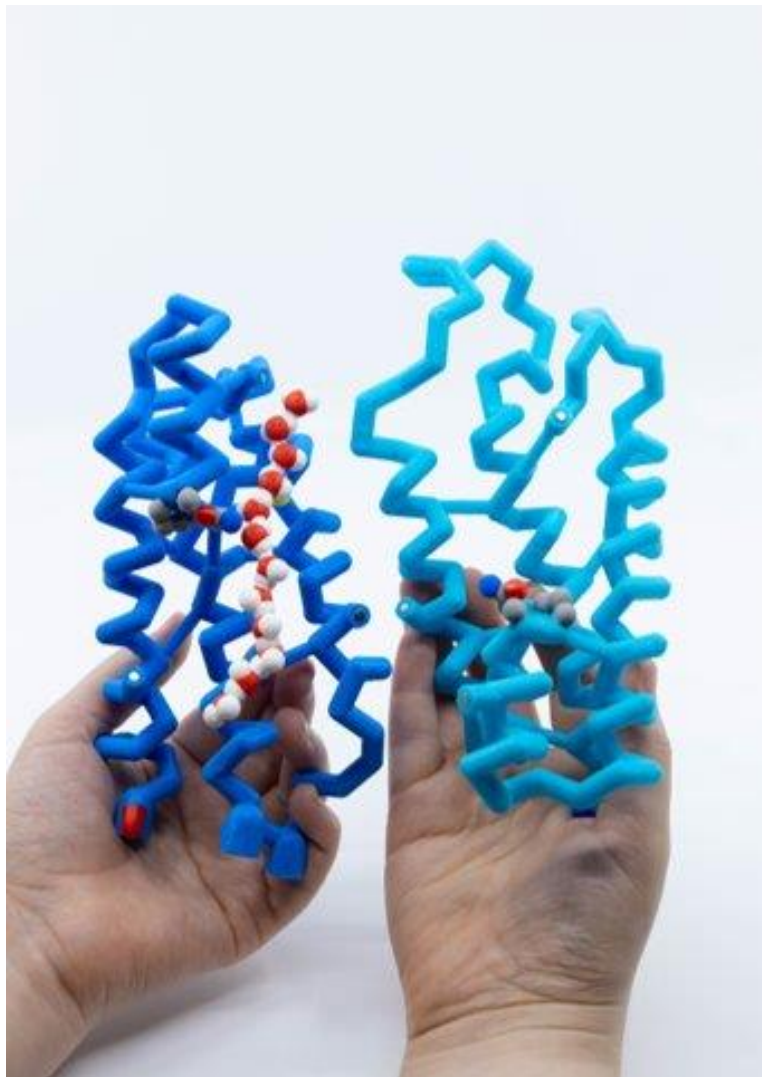


How does Aquaporin move water?

- ... and only water?
- It only allows 1 hydrogen atom for every 1,000,000 water molecules



A closer look at water movement

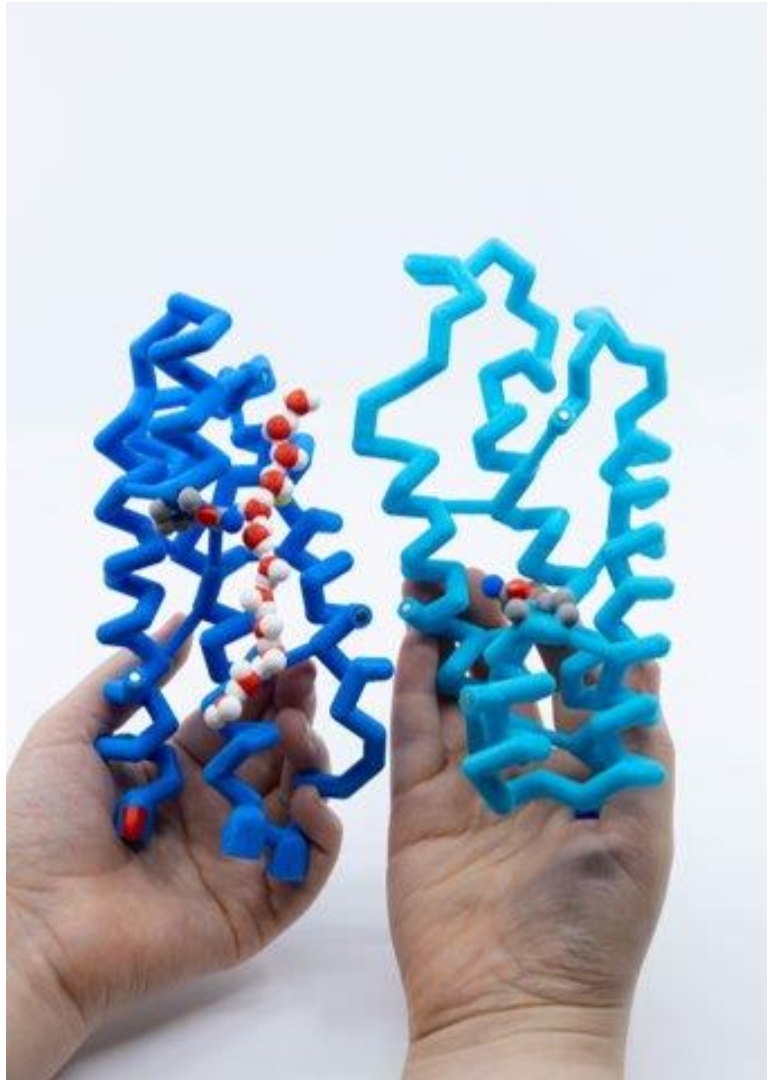


Separate the two portions of the aquaporin monomer.
Remove the chain of water molecules.

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



A closer look at water movement



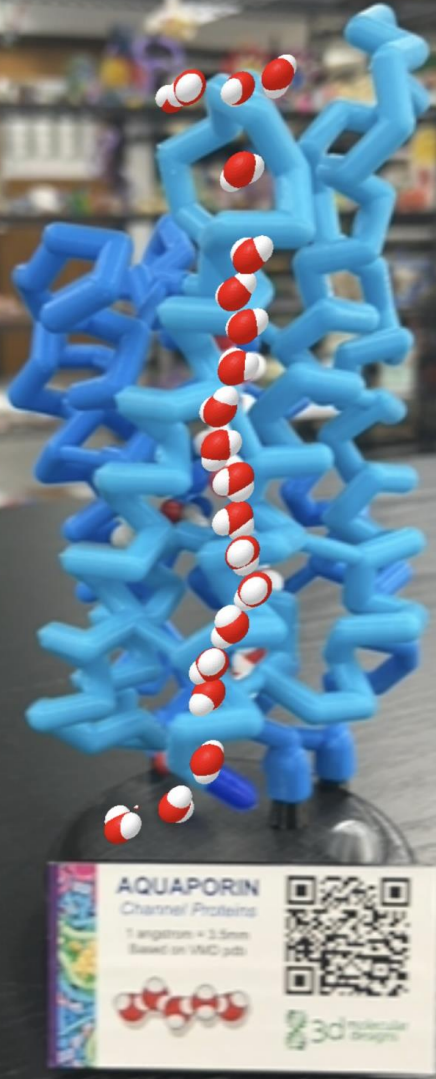
Locate the two *asparagine* side chains (N78 and N194) inside the channel
 Water molecules can move either way through the channel depending on concentration.

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?





Add Inhibitor

Use the QR code to see it in action-

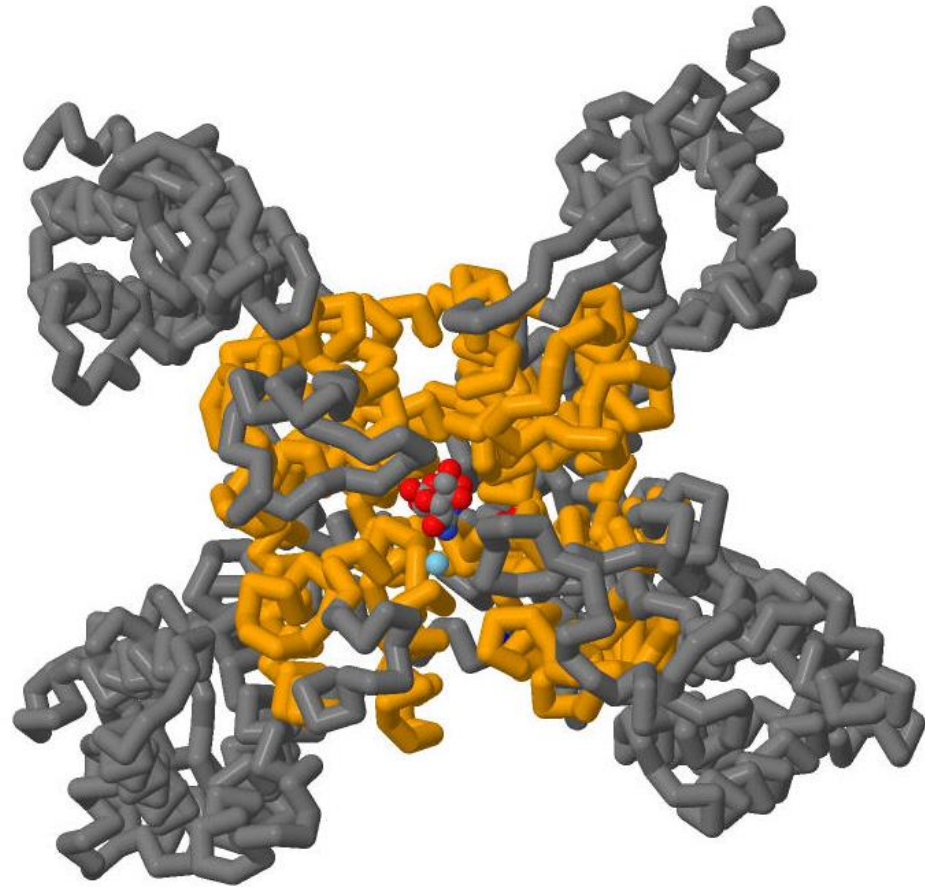
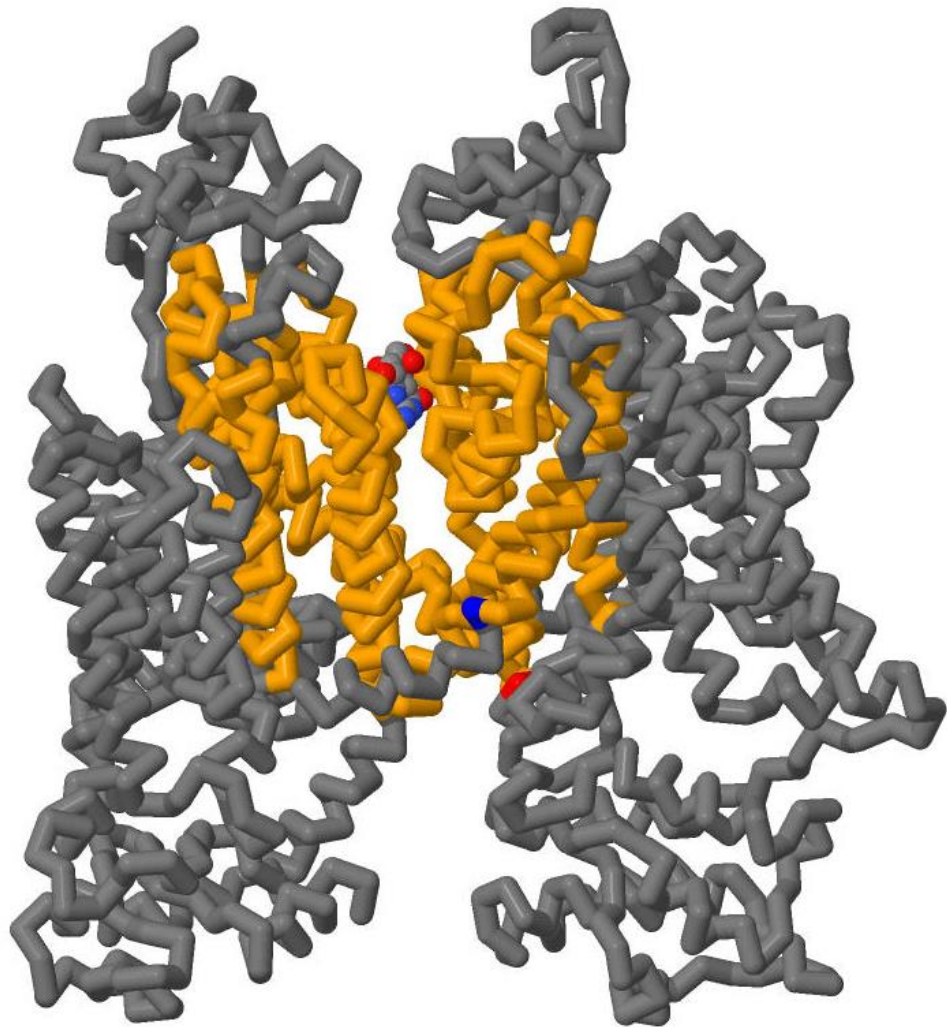
- Note the direction of movement.
- What happens when you add the inhibitor? (Hg)



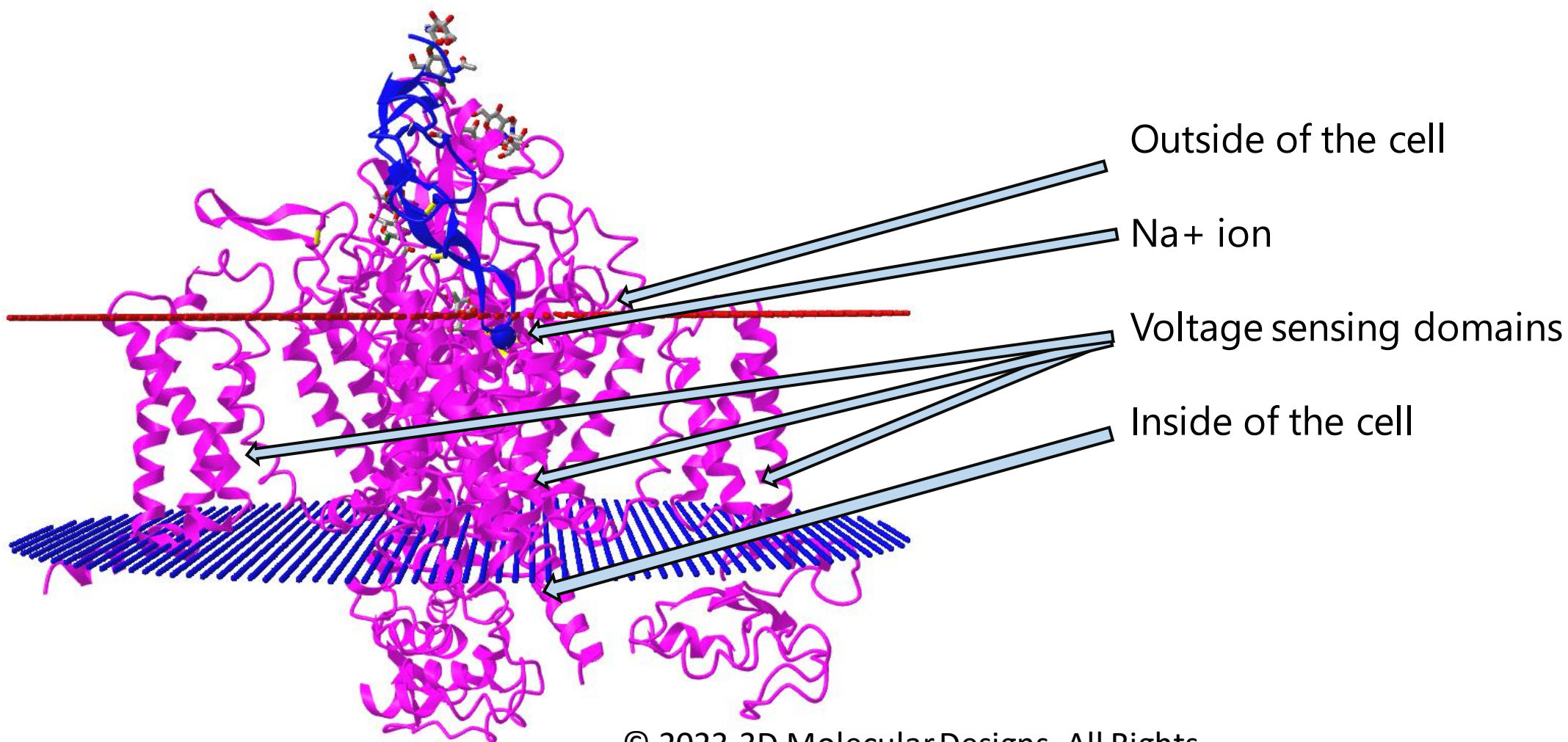
Let's look at the Sodium (Na⁺) Channel



These are Voltage-Gated Na⁺ Channels - monomers



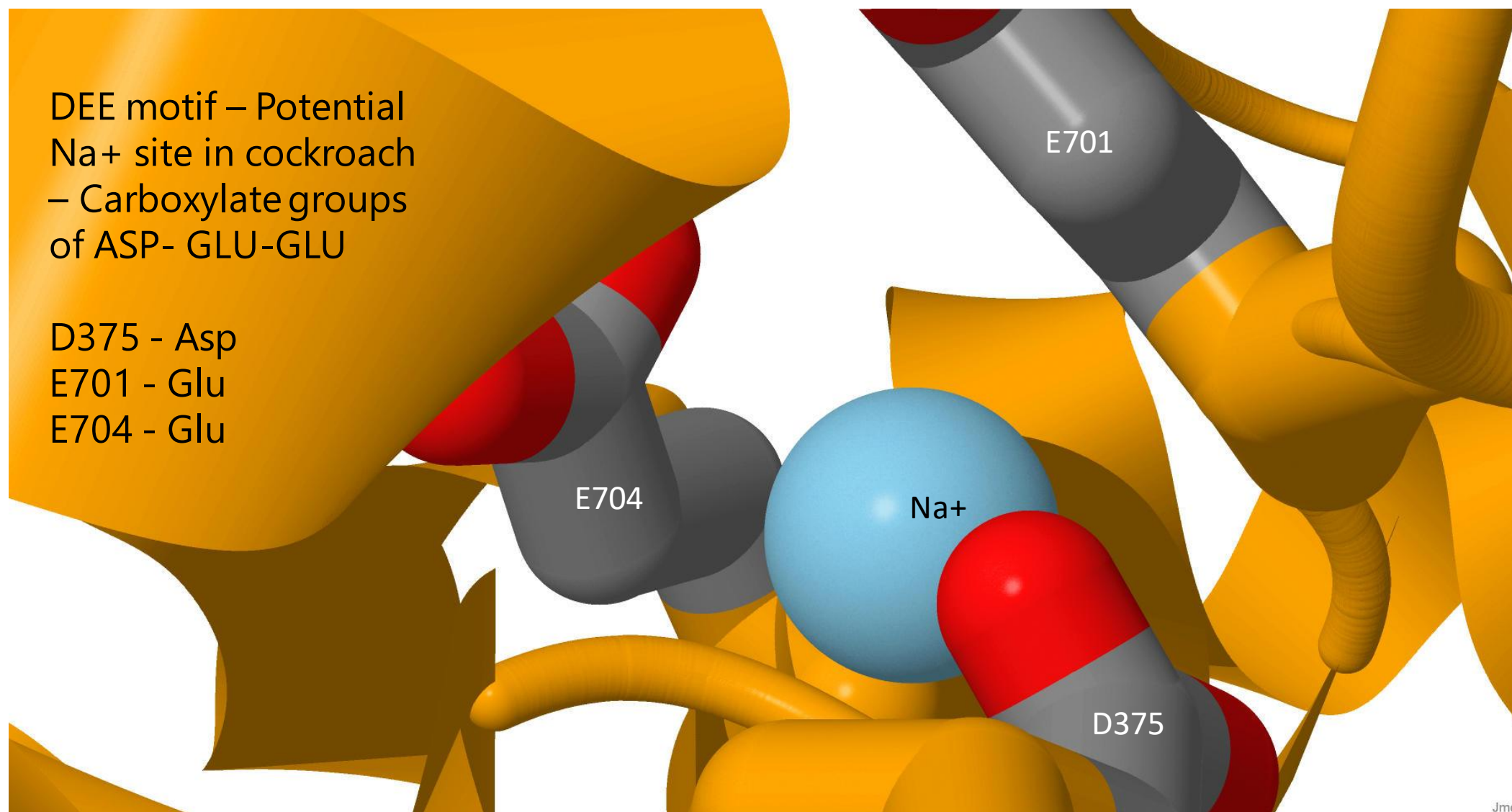
Here it is in a membrane



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-

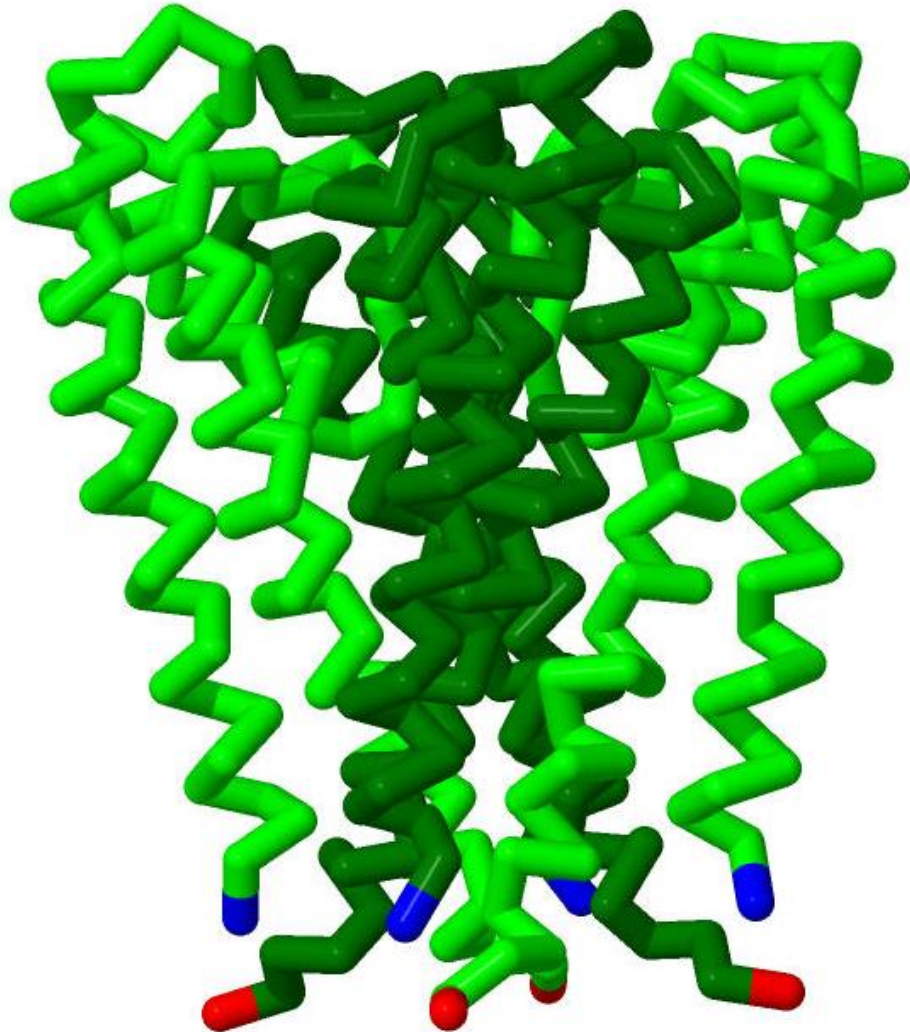
- Note the direction of movement.
- What is the molecule around the Na⁺ ions?



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

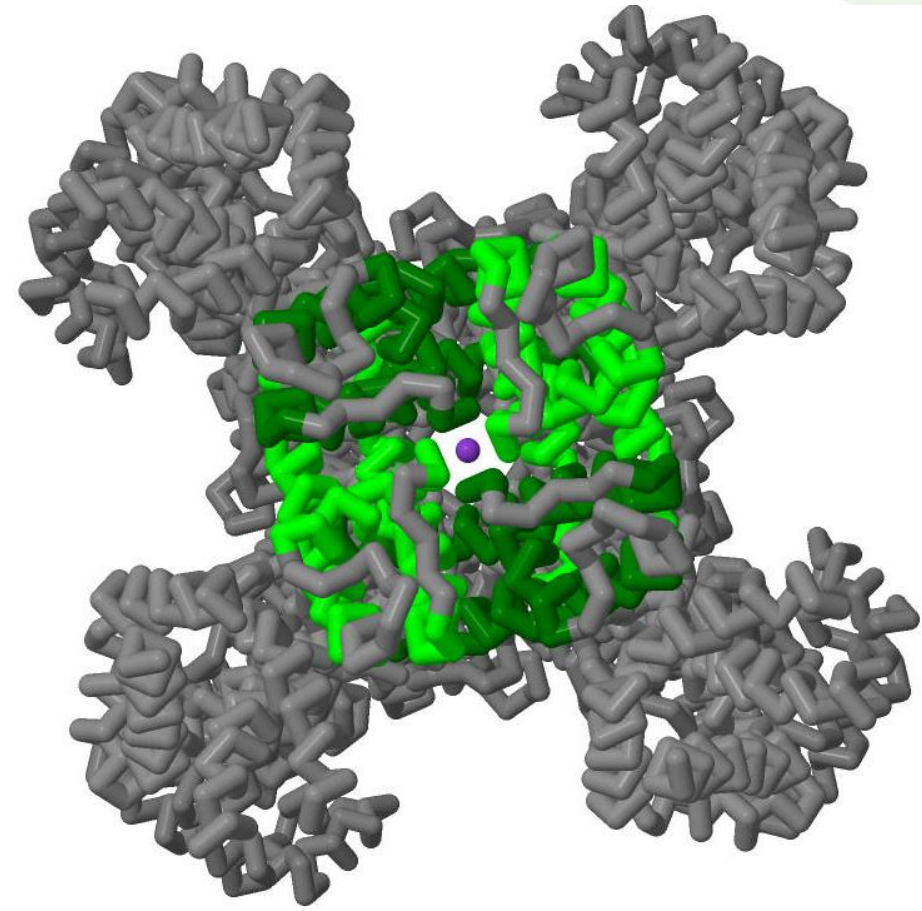
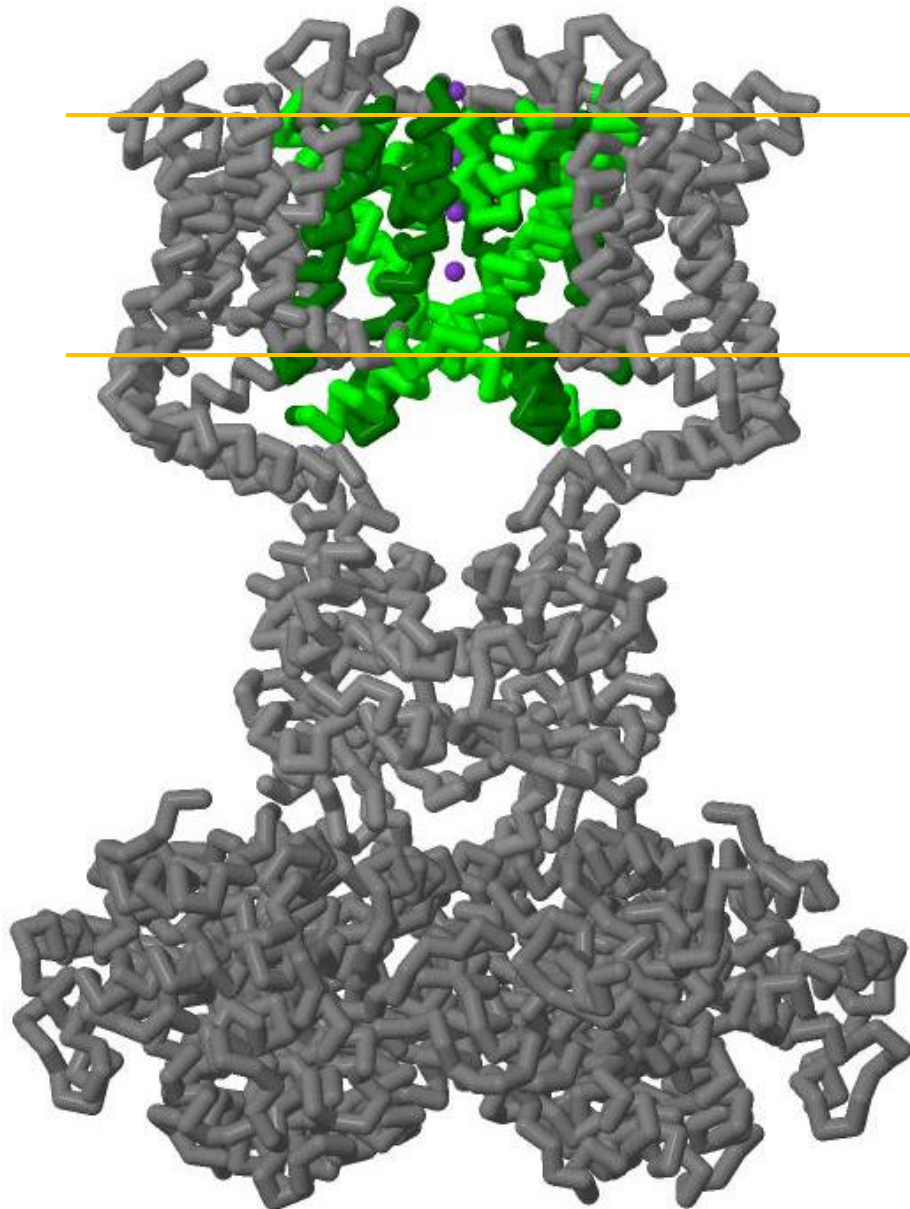
A:

B:

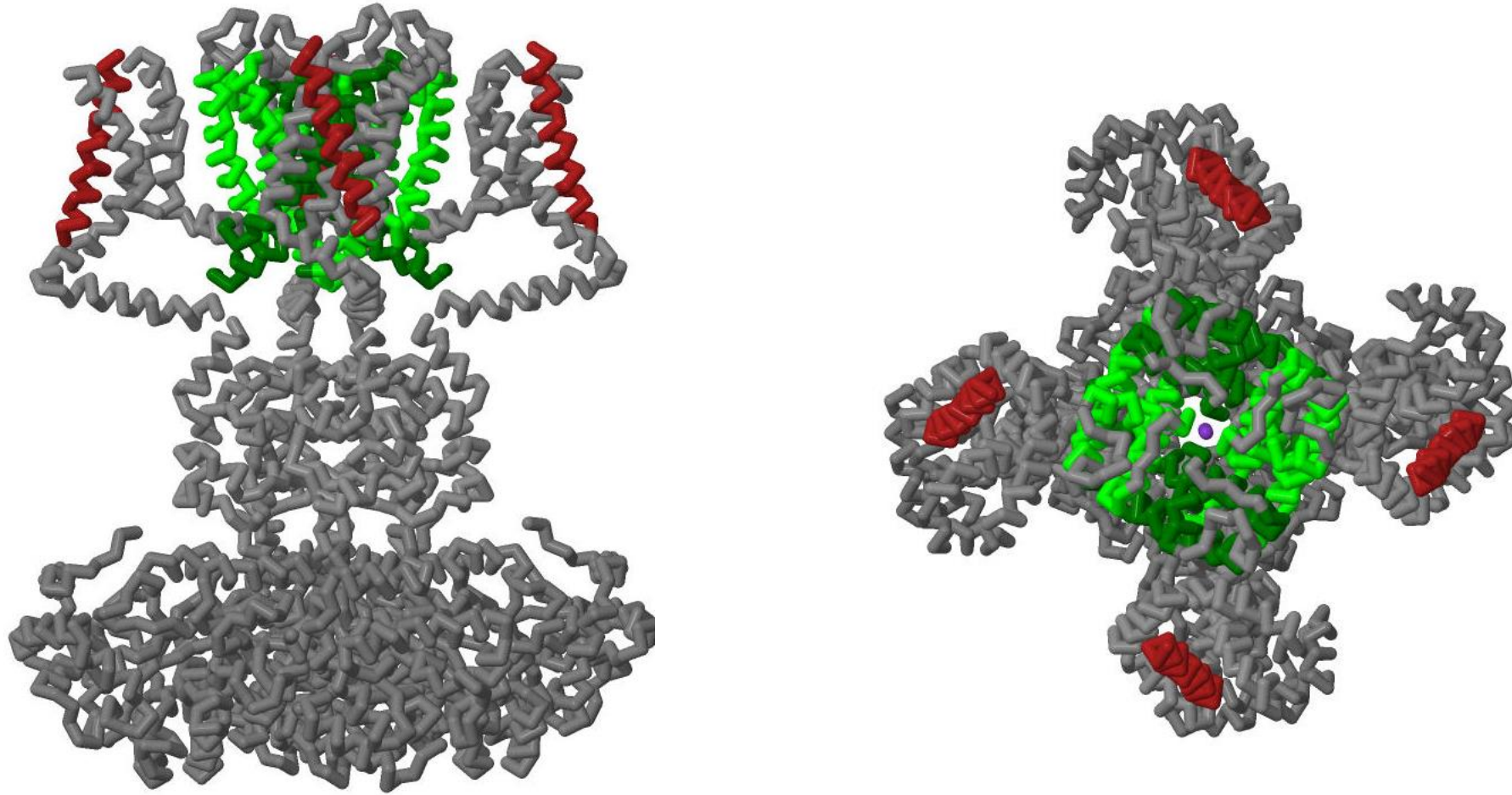
C:

D:

This potassium channel is voltage-gated



This potassium channel is voltage-gated



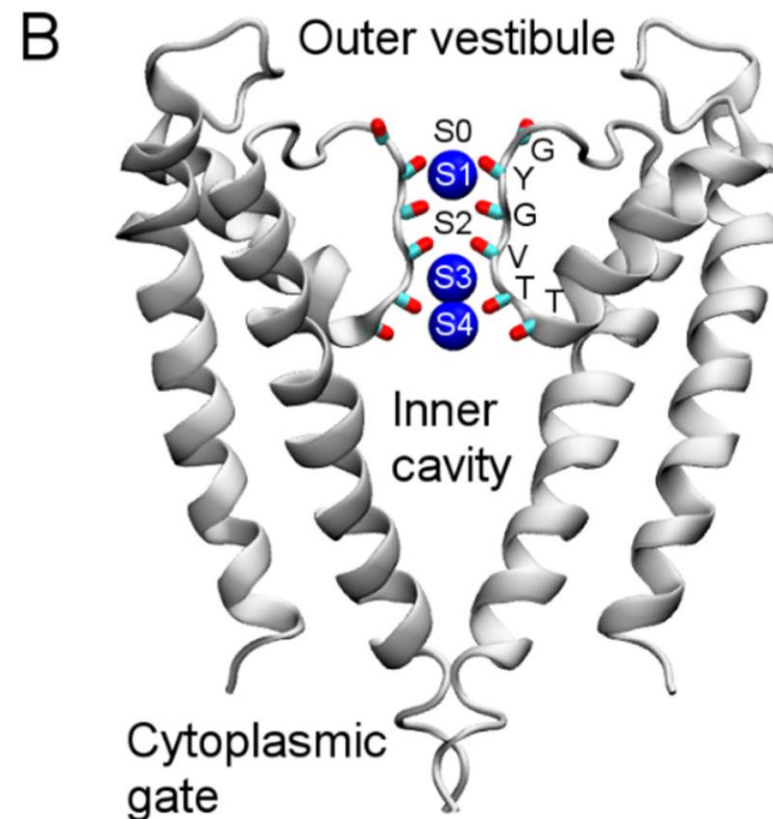
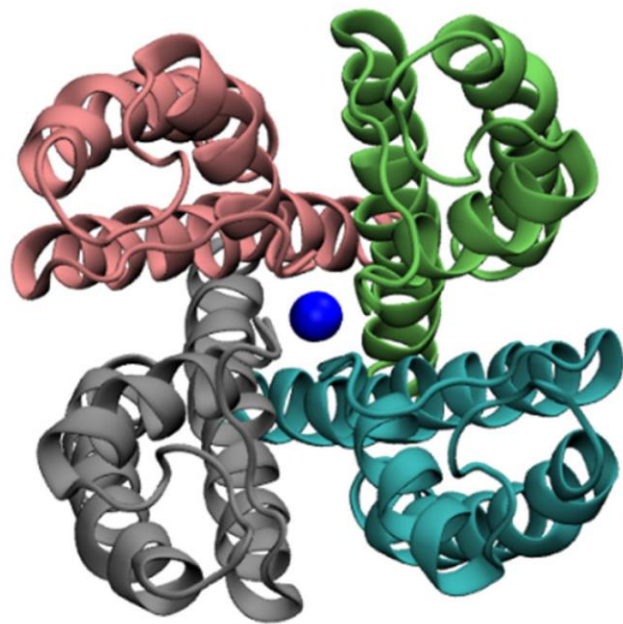


What does a K⁺ channel do?

- 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. A

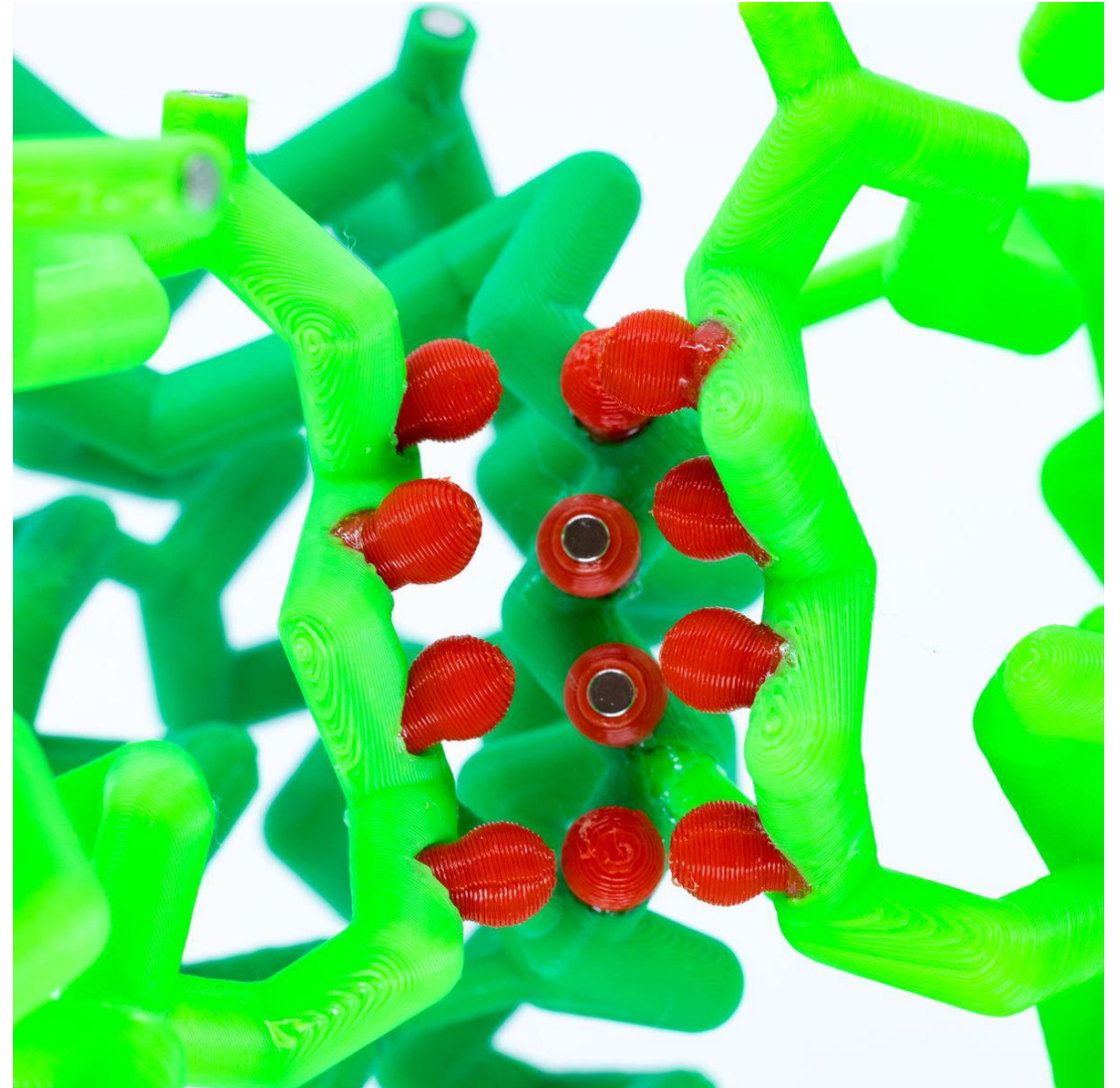
- *Why do you suppose this is important?*

Protein "Fingerprint":
TTVGYG



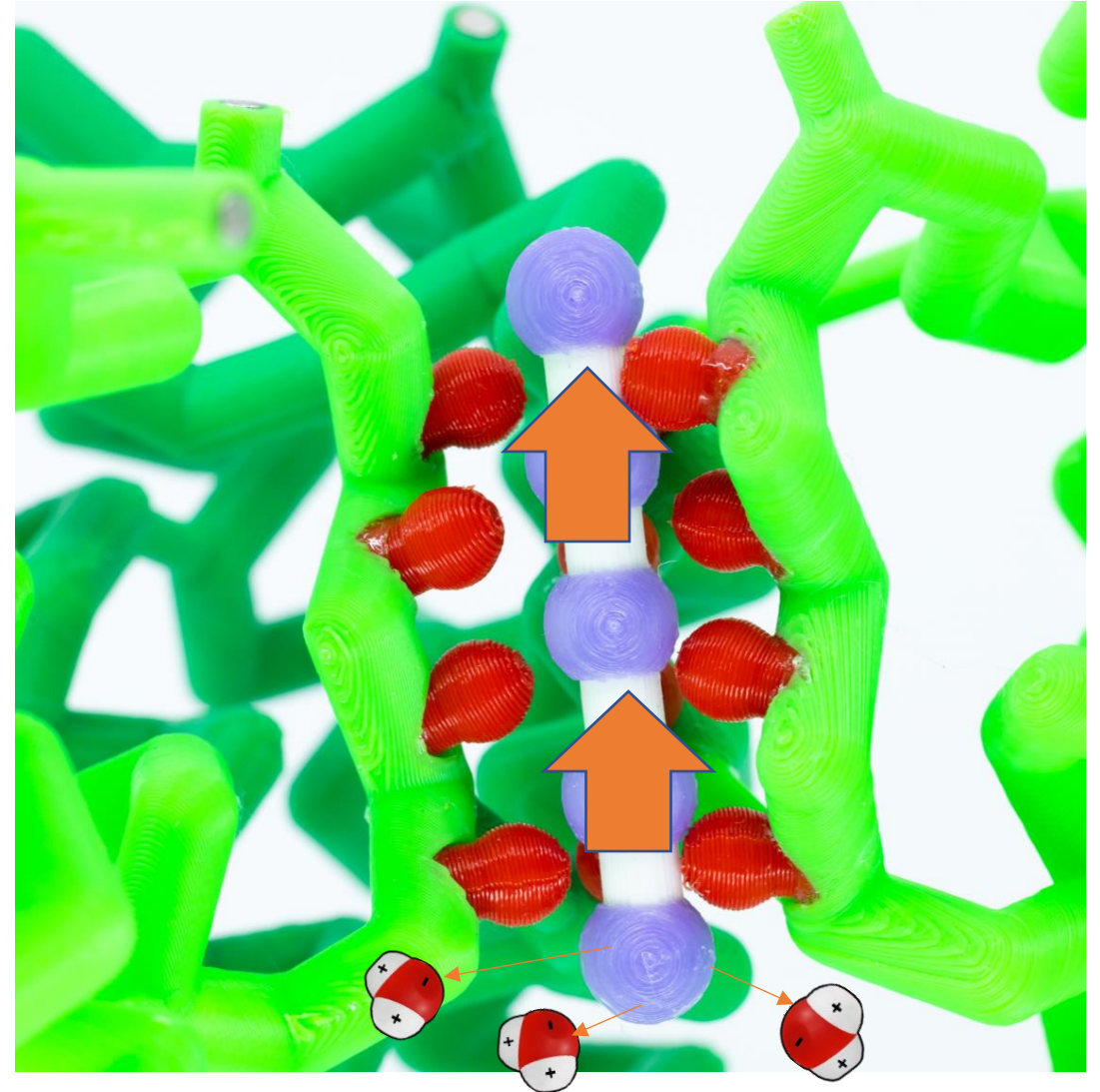
The carbonyl groups

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



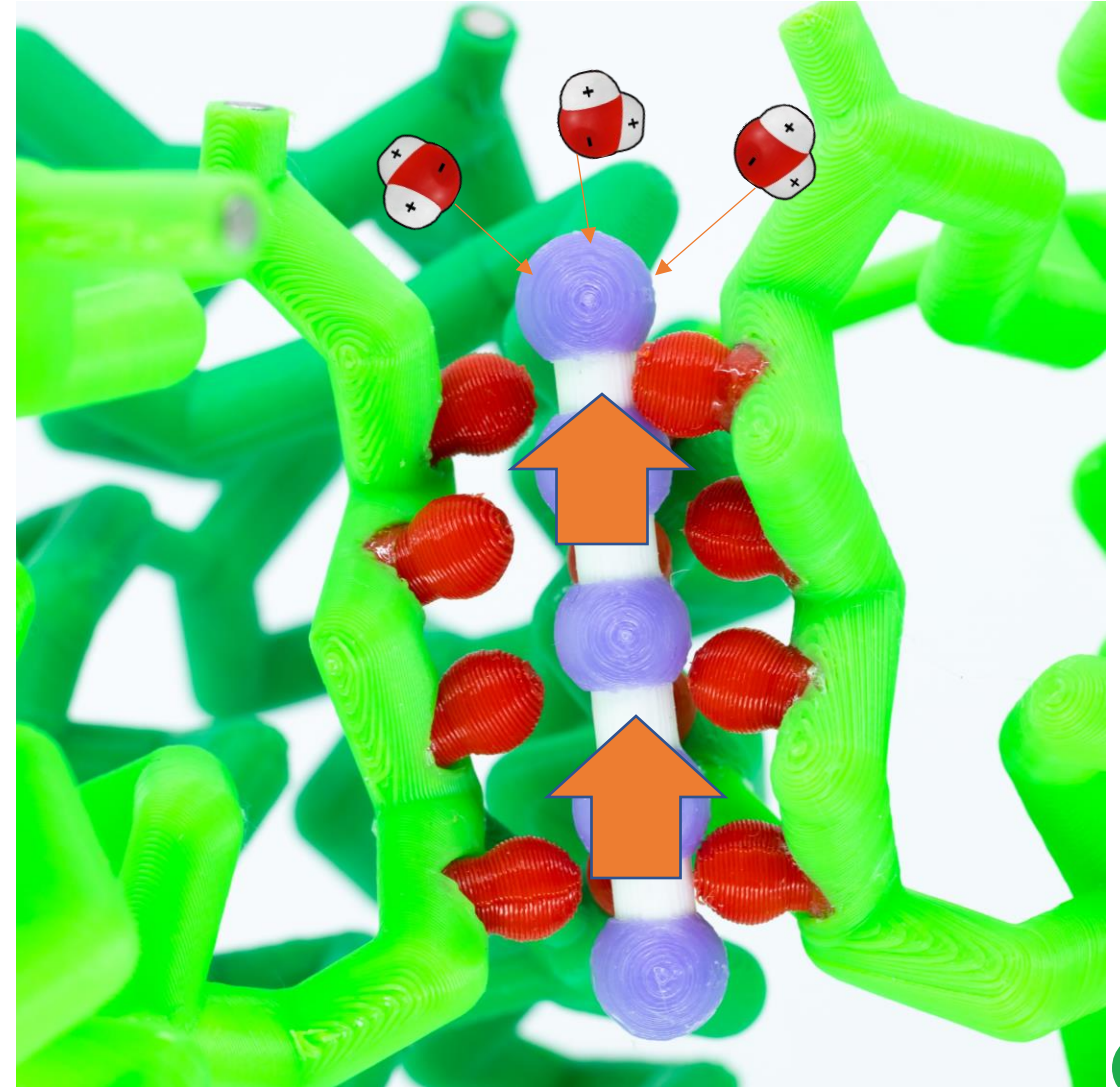
The carbonyl groups

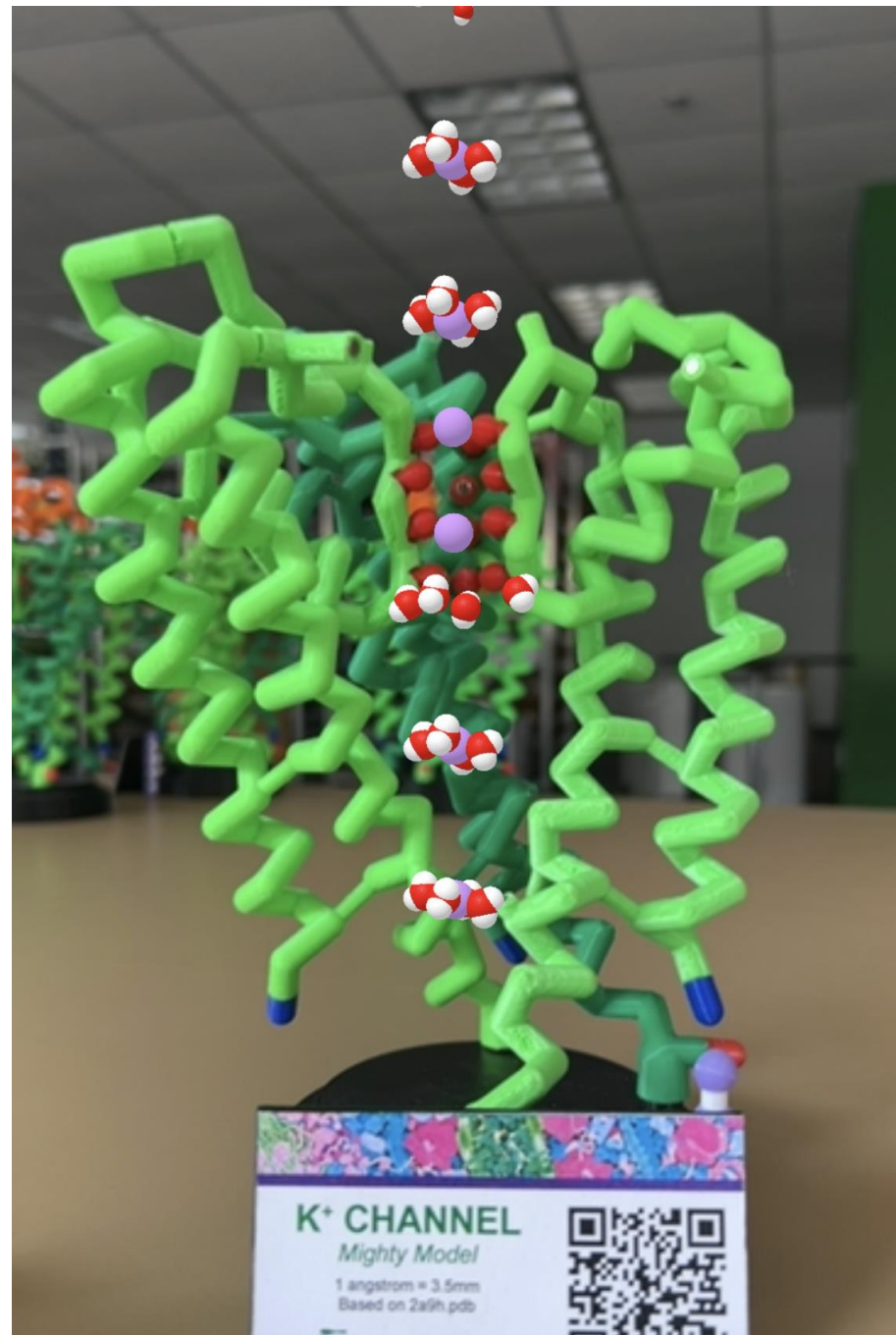
Then polarity of the carbonyl groups remove water from a hydrated K^+ ion near the vestibule and facilitate its movement through the pore like an elevator.



The carbonyl groups

Potassium is immediately rehydrated once it transitions through the membrane.





Use the QR code to see
this in action!

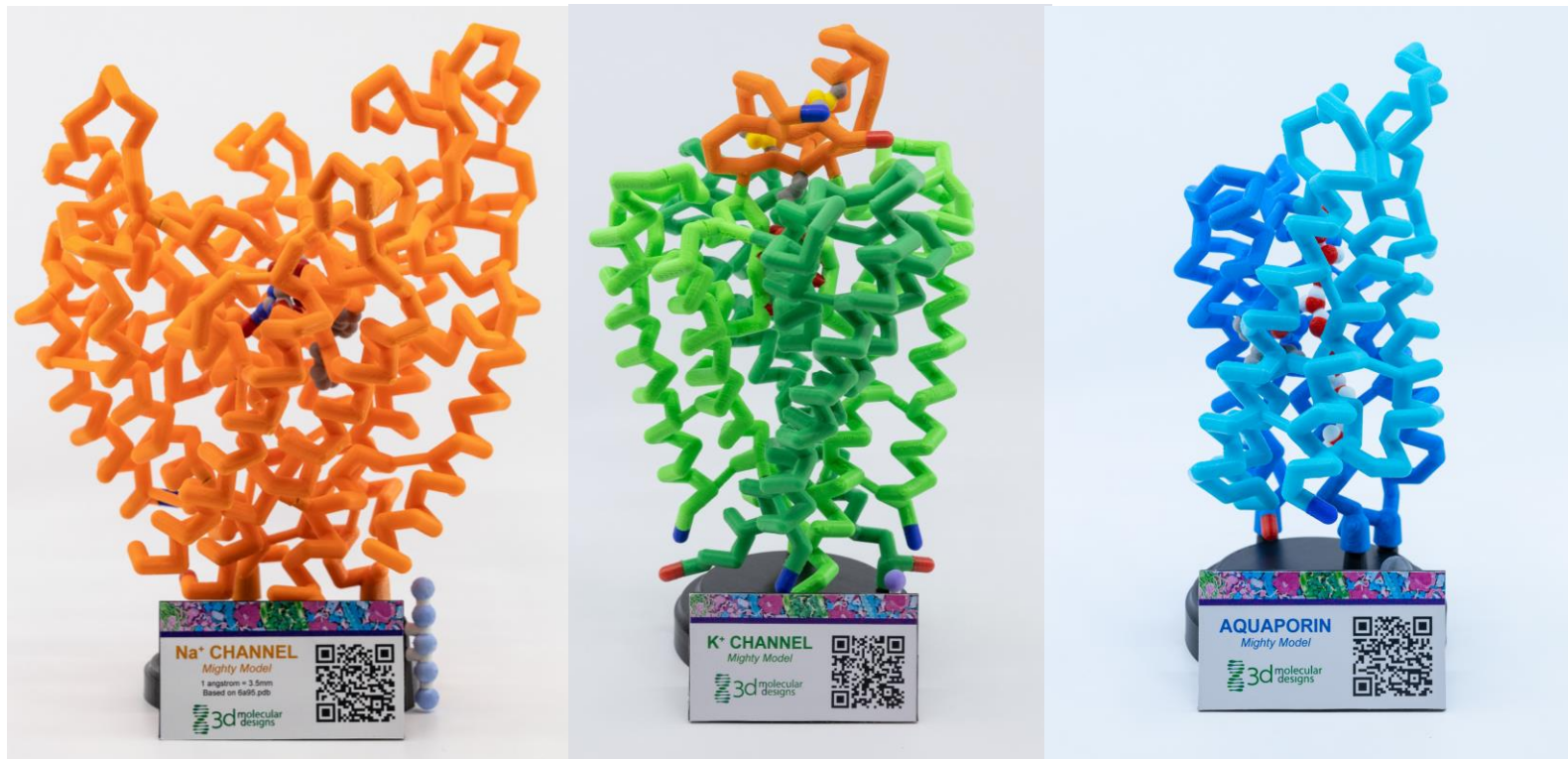
How is this different from
the Na⁺ Channel?

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



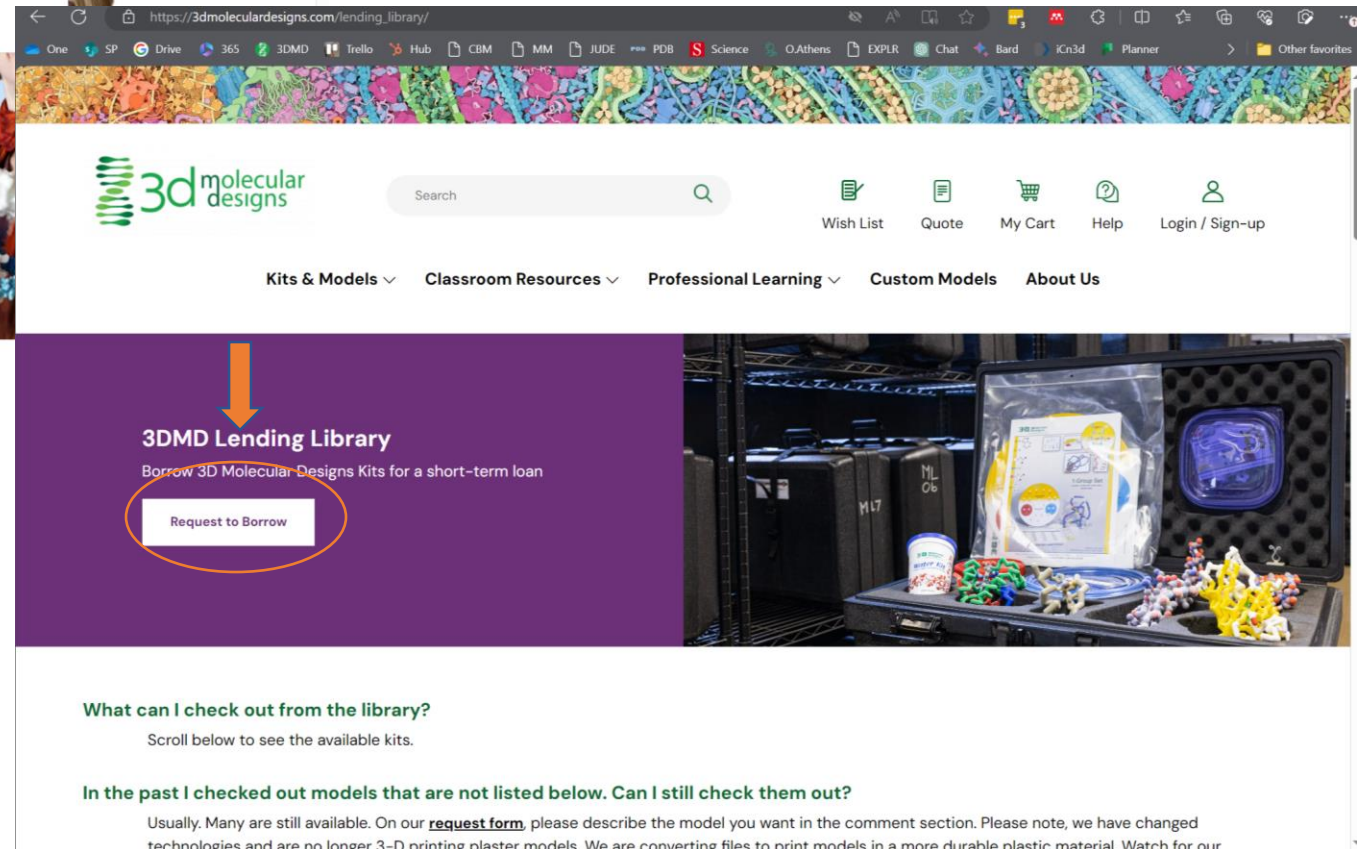
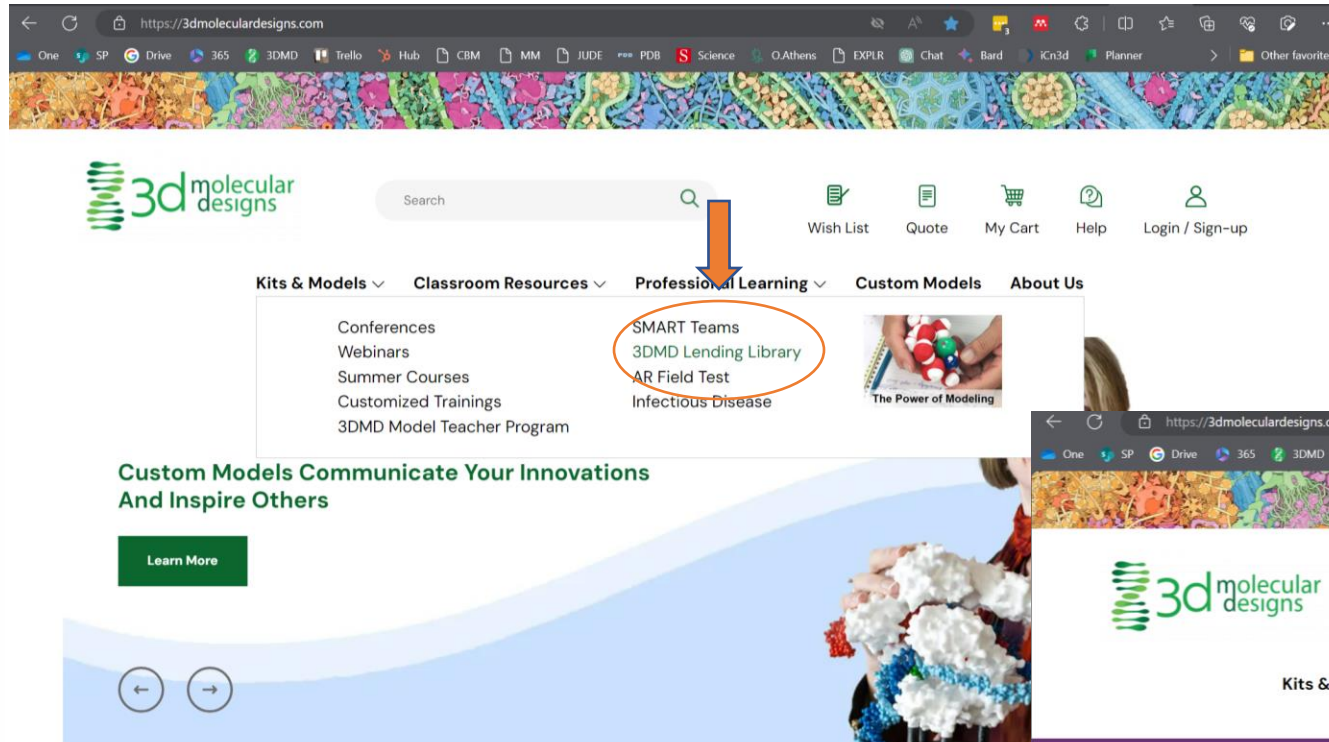


Why is this important?

- 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



Lending Library



Scan this QR code and fill out our survey!

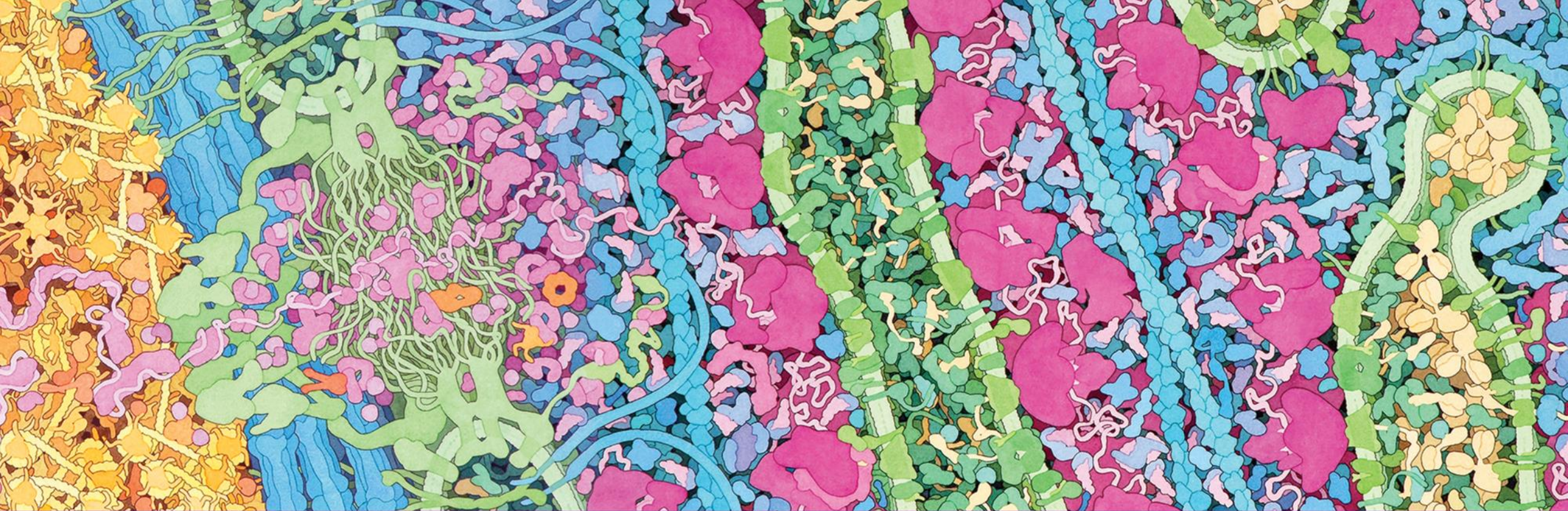


Show me your DNA molecule image
and I'll give you a model with AR
enhancement as a thank-you gift!



Next Generation Science Standards

Science and Engineering Practices	Cross Cutting Concepts	Disciplinary Core Ideas
Scientific Investigations Use a Variety of Methods	Stability and Change	HS-LS1-3
Developing and Using Models	Systems and System Models	HS-LS1-2
Constructing Explanations and Designing		



3d molecular
designs

Transforming Science Learning