# Metals in Biology

**Prof. Debabrata Maiti**
**Department of Chemistry**
**Indian Institute of Technology, Bombay**

## Lecture - 34
## Pumps and channels

Hello welcome back. Today, we will discuss little bit different topic which we were thinking to discuss at the beginning, but postponed it ok. So, today's focus will be on Pumps and channels; you must be wondering how a particular metal ion is gated to the cell? How cells are able to take the metal ions inside it or able to expel from inside to outside?

Well, let me tell you that it is done by pumps and channels; pumps as you know will require some sort of external force; that means, forcefully it will be taking out or taking in a particular metal. Channels are those where it is passed through a let us say cell membrane, but without an external energy put on it or set on it.

We will see that pumps are of course, energy driven, channels are more of a natural; more of present in many places, but works very seemingly simple way we will try to focus on both pumps and channels throughout this class today.

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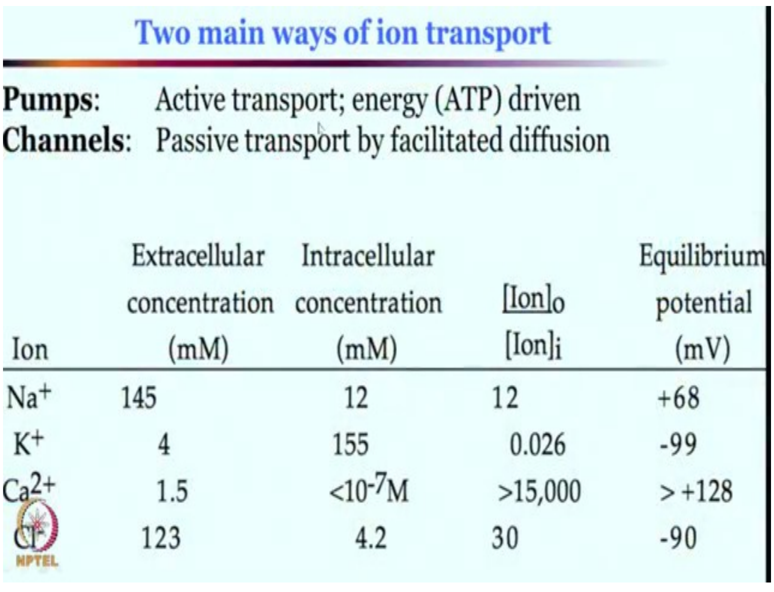

**Two main ways of ion transport**

**Pumps:** Active transport; energy (ATP) driven
**Channels:** Passive transport by facilitated diffusion

| Ion | Extracellular concentration (mM) | Intracellular concentration (mM) | $\frac{[Ion]_o}{[Ion]_i}$ | Equilibrium potential (mV) |
|---|---|---|---|---|
| $Na^+$ | 145 | 12 | 12 | +68 |
| $K^+$ | 4 | 155 | 0.026 | -99 |
| $Ca^{2+}$ | 1.5 | $<10^{-7}$M | >15,000 | > +128 |
| $Cl^-$ | 123 | 4.2 | 30 | -90 |

While as I was saying pumps are involved in active transport, this is energy or ATP driven. Channels are passive transport facilitated by diffusion, you may have already noticed inside our cell different metal centers are present. These metal center could be or metal ions could be sodium, potassium, calcium or other an ions such as chloride, but if you notice that extracellular concentration and intracellular concentrations are completely different.

So, outside sodium is present in large concentration, but inside it is present in very low concentration. On the other hand, potassium a outside is present in very little amount, but inside it is; inside the cell it is quite high amount. Similarly, calcium is present largely outside, but inside concentration is very less. So, we will try to see how ions concentration are controlled in the means of pumps and channels so that ion can pass through the membrane and can maintain a particular concentration; that is good for our body.

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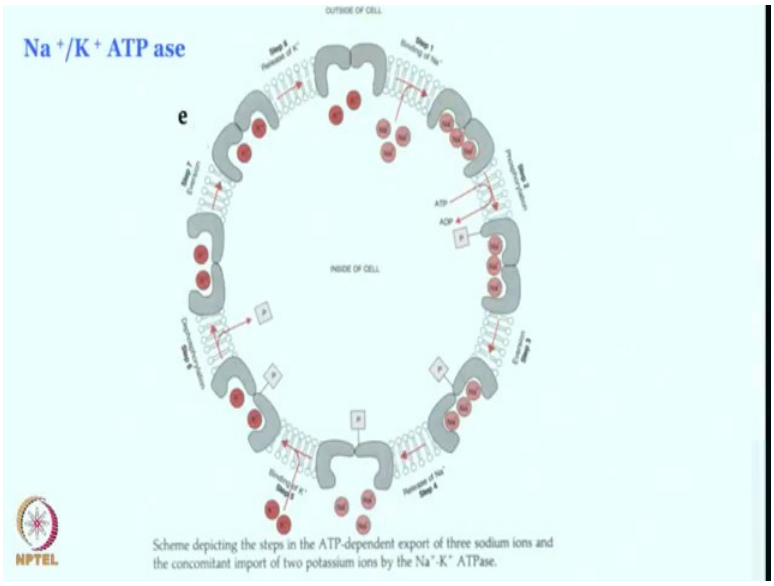


Well let us see this process of taking sodium outside the cell. So, let us say sodium is present in some amount inside the cell as you have seen sodium is present very little amount inside the cell maybe it is not too much required and that is why we are trying to see how these intracellular concentration can be decreased for sodium and taking them from inside the cell to outside the cell; how it is happening through pumps.

So, as I said pumps are energy driven process some energy is involved into the process overall there is a site in the membrane, where sodium can bind as you see over here we are depicting 3 sodium binding in this pocket and overall ATP is converted to ADP and then phosphate is bound with this pocket. Now this sodium binding will subsequently; so, this energy driven process will cause the eversion of this pocket to throw the sodium outside the cell. Release of sodium plus will then happen over all to ensure that sodium goes outside the cell from inside the cell.

So, sodium was inside the cell through this pumping it goes outside the cell, but of course, the cost is in the form of ATP to ADP and phosphate generation. Over all this energy driven process make sure that sodium is launched or placed outside the cell. This pocket then can bind with potassium; two of the potassium gets in the cell through once again by dephosphorylation catching and releasing inside the cell. So, this is a cycle that goes on quite very well because sodium is required more on the outside, not too much required inside, but potassium is required more in the inside this process of pumping in potassium and pumping out sodium goes on quite seemingly well with the help of this ATP driven process.

Therefore, this is a good pump it is just pumping out the sodium and taking in the potassium.

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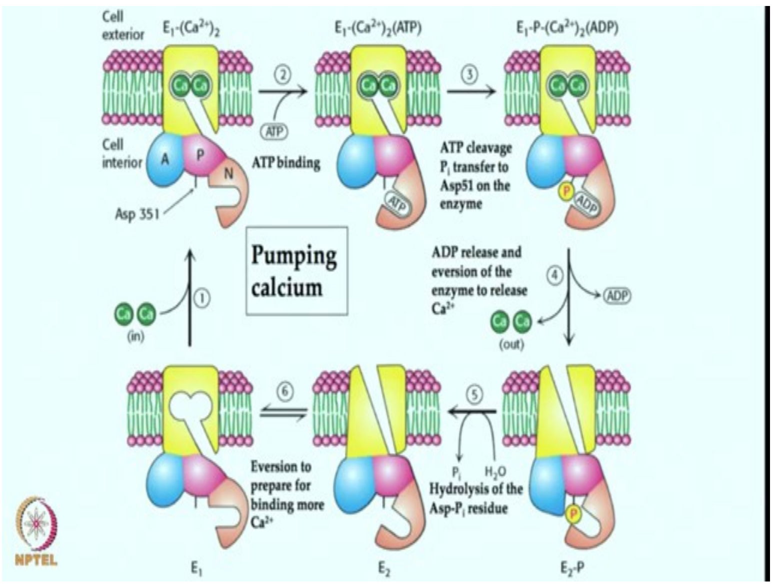

There is similar pump for calcium also of course, you can called it as calcium pump. This is the cell extruder and this is cell intruder overall you have aspartate 351 which is the ATP binding site. ATP binds over there in the pocket and calcium gets in to this cavity where in ATP cleavage and the phosphoryl transfer to aspartate 51 on the enzyme. This aspartate 51 phosphate transfer upon binding of ATP will lead to the ADP and phosphate generation and this energy driven process, then will start to rupture or to release the calcium outside the cell.

So, both the ATP release and inversion happens of the enzyme to release calcium ok. So, this is the enzyme that is involved overall this enzyme helps us pumping out calcium from inside the cell to the outside of the cell. This hydrolysis of the aspartate P I residue also takes place, where in the water will assist in this de phosphorylation reaction, overall then this is getting ready once again to bind; bind the calcium. So, eversion happens once again to prepare binding more calcium 2+ into this pocket and the process goes on. It is almost a catalytic cycle and calcium is pumped from inside the cell to the outside the cell by this ATP driven process.

You can read more from the book, but these sort of pumping out of calcium is quite important for the physiological function. Well, as we have discussed not the not transport of every metal ions or incorporation of every metal ions are done through the pumps; it is a very high energy demanding process, it is a little bit hectic process.

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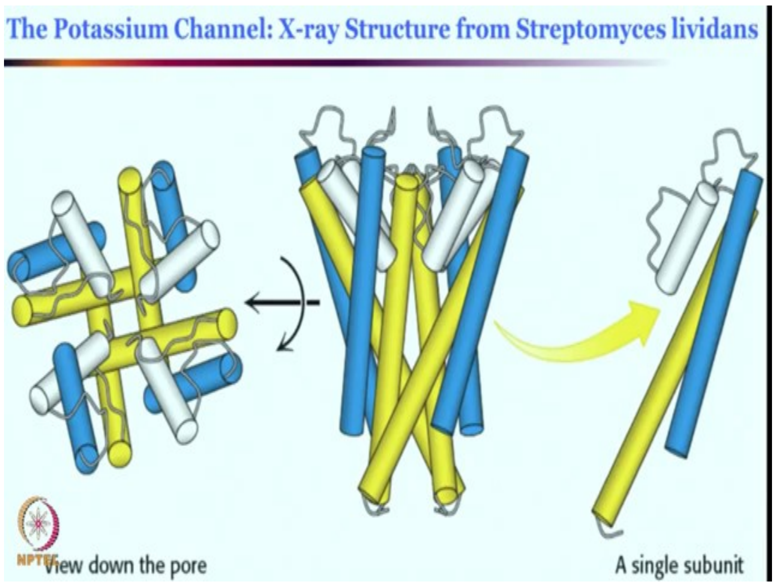

But the diffusion control process which are rather simple no energy is lost in the process and rather happening quite naturally and quite importantly everywhere it is happening and we have now understanding of these processes how these diffusions are happening. So, these are the protein residues as you see that they can assemble in such a way so that a hole or passageway can be created.

So, these overall orientation gives rise to this passage through which perhaps different metal ions can be passed through. But more importantly how this passage is controlling a particular metal passage only, but not allowing other metal to pass through this is quite interesting to know. These are the single subunit these are multiple subunit put together and making the whole channel for a particular metal ion. So, this is the one with the potassium channel and many extra structures are the reason why we perhaps started understanding the channel quite effectively and these are quite active areas of research and quite fascinating areas of the science.

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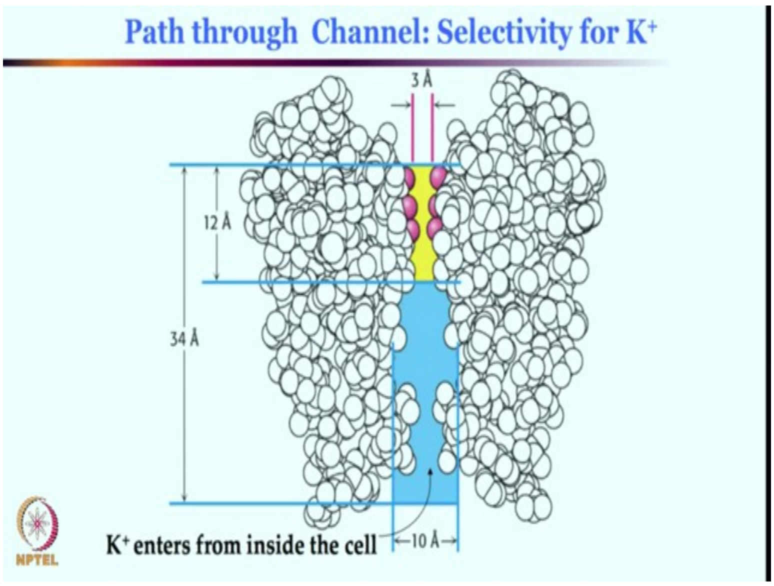


So, here is the cross section or the inner view of this selective potassium channeling or this is the particular channel through which potassium will pass through. Potassium plus from inside the cell we are going to get it outside the cell, but this is not through a pump this is by simple diffusion. As you can see the passage is wide in some case and very narrow in some phase.

So, if you have a very narrow passage this ensures that the bigger metal ion will not be passing through this narrow passage. So, one can perhaps think of the average radii if radius is something like 1.5 Angstrom this channel will not be able to pass those metal ions.

If it is much smaller or smaller than this 1.5 Angstrom then there is a possibility that they can pass through although you see that there are further narrower passage among this or inside this channel. So, there is every chance that the metal which are only having much less than 1.5 Angstrom radius will pass through this narrow phase of the channel. On the other hand, the large distance from inside cell to outside cell nearly 30; nearly this would be nearly 22 Angstrom distance can be traveled by many different metal even the bigger one. Because as you see here the diameter is quite high; so the metal ion such as all lithium sodium potassium rubidium cesium all perhaps can pass through this channel.

Now, the question is then how the selectivity is obtained in these cases? So one case that we have discussed so far that the bigger ions will get stuck here and therefore, they will not be able to pass through, the smaller ions will pass through all these and that also. For example, lithium and sodium is smaller than potassium, but why lithium and sodium is not passing all the way from inside the cell to outside the cell through this channel of potassium?

Why so specific; why is it so specific for potassium, but sodium and lithium cannot pass through this channel? Well I think that is a very difficult question to answer at the beginning, but the relentless studies many crystal structure and significant contribution from many different research group has now obtained an answer for this.

Once again the bigger one will be eliminated naturally because of the narrow passage and smaller one should in principle all be passed through this but not really only the medium sized potassium goes through, but lithium and sodium cannot even pass through, although size wise they fit perfectly to pass through. Let us try to look at what is the selectivity factor that governs or that controls this sort of lithium sodium passage or prevents their passage and allows only potassium passage.

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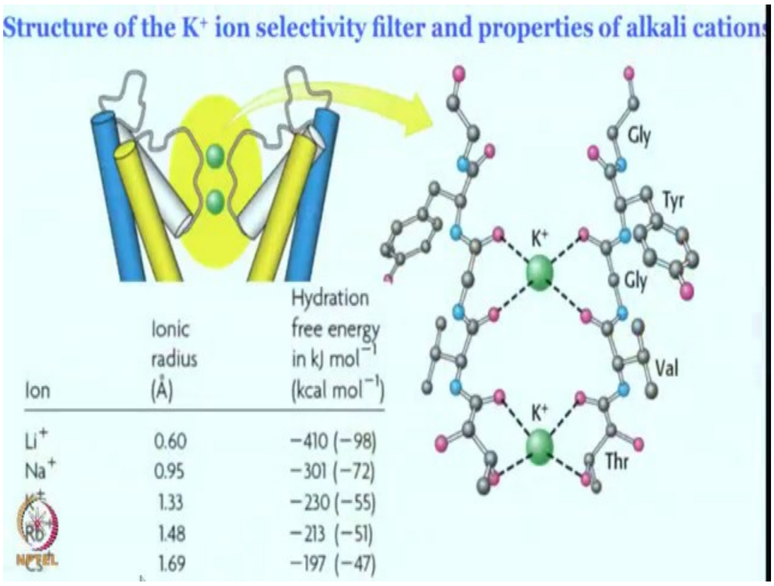


As you can see the size of the rubidium and cesium are quite high the radius is nearly 1.5 or higher; so these will be excluded by default be due to those molars passage. Lithium and sodium are small very small compared to potassium, but still they cannot pass through. And this is mainly due to the fact that the hydration free energy or the hydration energy of lithium and sodium are quite high.

So, for example for 10 and 301, so while they are getting hydrated they want to stay hydrated. They do not want to go through this passage because during passing through some of the water molecule has to be displaced and the metal has to interact with the protein backbone. For instance when potassium is passing through this channel; the protein residue from this protein backbone different amino acid backbone, this peptide backbone or amino acid residues will be interacting with the potassium center.

And that is what is happening here as you can see making the life for potassium easy as it is passing through. But of course, potassium has to lose if it is interacting with 4 different centers with the peptide backbone. So, it has to lose 4 water molecules after losing 4 water molecules, then only this sort of interaction will be possible and it will be possible to make them pass through this.

Now losing such water molecule is feasible for potassium because the hydration free energy is relatively less. So, losing the water molecule and rebonding with the peptide backbone is compensated for the dehydration energy. So, the bond breaking from the water potassium aqua complex and removal of water from the potassium aqua complex is ok; because these new bonding can compensate those hydration free energy loss.

On the other hand, for lithium and sodium since these hydration free energy is quite high; water molecule from lithium and sodium would not like to drop off from the lithium and sodium primary coordination sphere. And therefore, they would like to stay as lithium aqua complex and sodium aqua complex which is having the large radius compared to of course, these are ionic radius for free lithium and potassium with aqua molecule it becomes very big.

Unless it can lose out those water pretty easily and can interact with these protein backbone in this channel, it will not be possible for the metal ions to pass through and this is precisely the reason why we see potassium ion selectivity.

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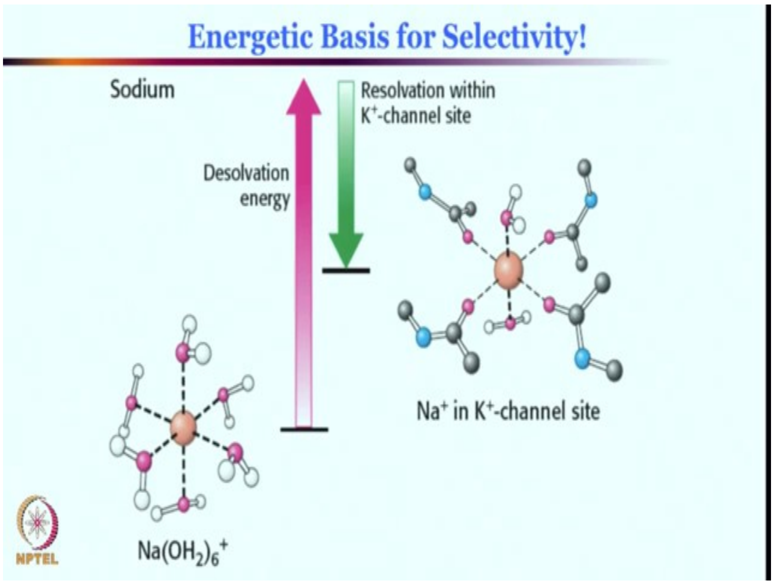


So, there is another thing; so this is hexa aqua sodium, as you see the desolation energy is pretty high. Means meaning if you want to remove these let us say 4 of the water molecule from here the desolation energy will be this much. The energy gained due to the protein backbone interaction with the metal ion at the cost of these 4 water molecule is not that very high; as you can see only this much.

If it was able to compensate this amount, then only potassium would have been sorry sodium would have been able to go through the channel. So, this is really a wonderful design by nature which ensures despite lithium and sodium being smaller in size, but having higher dehydration energy prevents them in participating these interaction with the protein backbone and therefore, if their effective size becomes much higher than the then what one of their atomic radii would give rise to the size cannot be shortened because this water molecule cannot be released.

Therefore, we see that potassium having higher atomic radii, but easier ability to remove this water molecule because the hydration energy is less. And therefore, we see that selectively potassium ion can go through this channel. Let us get back again rubidium and cesium cannot pass through some part of the channel because there is very small aperture or very small opening and therefore, it cannot pass through it get stuck. Lithium and sodium in principle should pass through very easily, but they are incapable of losing their water molecule; since they have high hydration free energy.

Potassium on the other hand is in the middle which has moderate hydration energy and moderate size which is perfectly matching for this passage through the channel and the size is absolutely fantastic provided it can lose out the water molecule and can interact with this protein residue which is feasible in this case, but not feasible with lithium and sodium therefore, they are missing out the fun of passing through this potassium channel. So, the selectivity can be answered by this way; however, if that is the case; why show effectively potassium ion; of course, selectivity factor we now understand perhaps, but why potassium ion passage is so fast and so effective?

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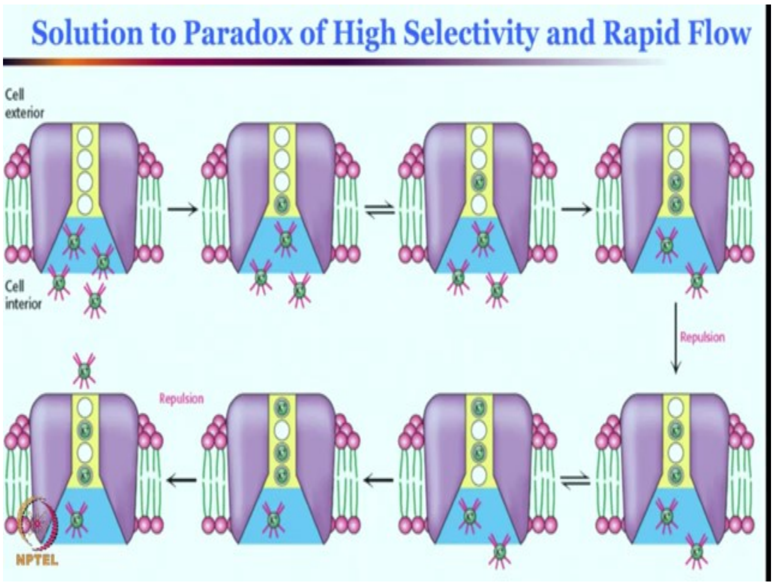


So, not only high selectivity, but still a rapid flow can be maintained. Why is that? And this is precisely due to the repulsion among the potassium ion; that is quite interesting. So, a cationic potassium will ripple each other right; same charges repel with each other.

So, let us say cell interior will have this 4 potassium ion, they want to pass through the channel. So, one of them will diffuse through this channel; it will start diffusing, it comes over here, but you know this process may be slow to pass through this channel and this is when the second potassium ion which is also trying to get through this channel will come into the picture. They will repeal each other as soon as the potassium is trying to approach this potassium channel; this channel.

This repulsion among these potassium ion will ensure that this potassium which is already in the channel gets repealed and passed in because of the repulsion it gets; it gets close of each other. So, this potassium will be moved in and then that will create a vacancy for the next potassium ion. If that is the case, if there is a vacancy in the next potassium ion which is in the queue for diffusion can get in right.

Now since they are now very close to each other; once again they repel each other and the first potassium ion, then can move one place further to go a little bit more up. In this situation, another third potassium comes in who wants to get in and then ends up repealing this second potassium and therefore, the second potassium moves inside and then also repel this one and that move in. So, systematically the first potassium is now very close to be out of the cell.

Now, once again the next potassium comes in, it repels each other, it goes up and during this process the repulsion of this second potassium with the first potassium that causes this first potassium to come out and that is how from cell interior to cell exterior a potassium ion can move out.

So, what you have just seen is natures beautiful architecture by which a potassium ion; not only can be selectively passed through this channel, but in ensures that a rapid flow of potassium ion is possible. So, overall what we have seen then pumps can be very effective in delivering or taking out a particular metal from inside the cell to the outside the cell or it can take a particular metal ion from outside the cell to the inside of the cell.

These are energy driven process; ATP driven process, but perhaps a most desirable mode of ion passage could be those through channel. We have seen here how potassium ion is the winner among many different metal ions; that is present let us say inside the cell. How potassium ion being larger in size compared to lithium and sodium still can passage through as narrow channel; whereas, lithium and sodium being smaller still cannot go through it.

Rubidium cesium which are such larger in size compared to potassium obviously, get stuck or get prevented or cannot approach due to the narrow passage of the channel. The main region behind lithium and sodium inability to pass through this channel as we have seen is really the dehydration energy. Since their hydration energy is quite high they lack to keep the water with them, they do not want to get rid of the water and therefore, their effective volume is quite big and cannot pass through the channel.

During the passage through the channel one needs to ensure that those metal ions are able to interact with the channel backbone. That interaction requires some of the water molecule to get dissociated from the metal ions, which is not becoming feasible for lithium and sodium. On the other hand, potassium being perfect in size and also are in a position where they can lose the water molecule of course, they lose some energy, but the gain of energy due to the bonding from the protein backbone of the channel ensure that it can compensate those loss due to the water release.

This compensation and the perfect matching of energy and the size ensured that only potassium can pass through the potassium channel; this does explain why there is a selectivity for potassium. But this does not explain why so rapidly potassium can pass through the channel and this is precisely due to the fact as we see over here that there is a repulsion among the same charge such as potassium in this case. This repulsion causes the potassium to stepwise move out from the inside the cell through the channel. The same charge repulsion is quite effective and can be a particular reason why we get the rapid flow.

Right, keep studying we will come back soon in the next class we will try to summarize the metal activities, those metal chemistry that we have discussed so far we will try to summarize to make it easy for you for the exam purpose. I hope you are enjoying, please do study more from the book of Lippard and Berg; Lipid Bug, you can read from any other book of your choice, but please keep studying and try to understand the principle behind this bio inorganic chemistry. If you have any questions or queries, please do not feel shy stop by send an email ask a question to TA or to me directly.

Thank you very much.