Bioinorganic Chemistry
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Lecture – 02
Metals in Biology: Nature’s Selection [Part-1 of 4]

Today we will talk about Metals in Biology: Nature’s Selection.

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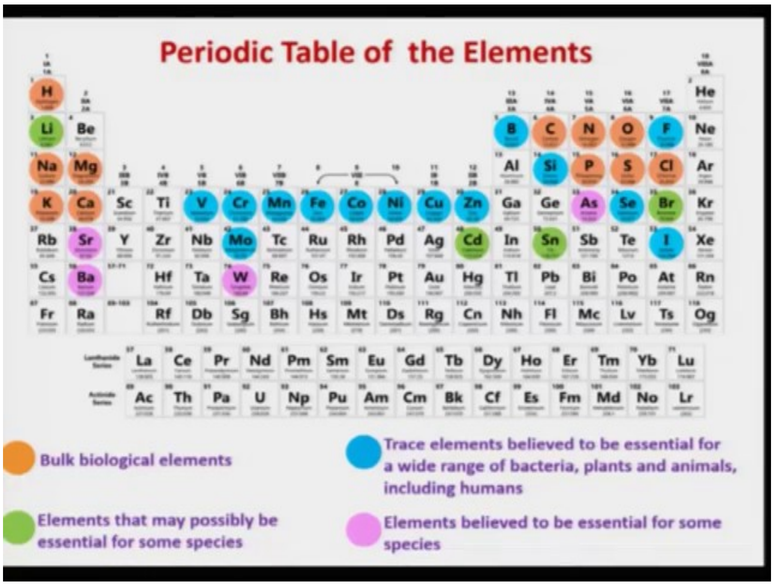

Look at the periodic table of elements; as you can see there are some elements are highlighted which are present in biological system. For example: the brown color gives the element which are present in bulk amount in the biological system like hydrogen, sodium, potassium, magnesium, calcium, carbon, nitrogen, oxygen, phosphorus, sulphur, chlorine.

Then the blue one is the trace element which are believed to be essential for a wide range of bacteria, plants and animals, including humans. These are mostly the 3d elements vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, molybdenum then boron, silicon, fluorine, selenium, iodine. There are also some elements which are colored as green those elements may possibly be essential for some species such as lithium, cadmium, and tin.

And some elements which are colored in pink these elements are believed to be essential for some species such as strontium, barium, tungsten, arsenic.

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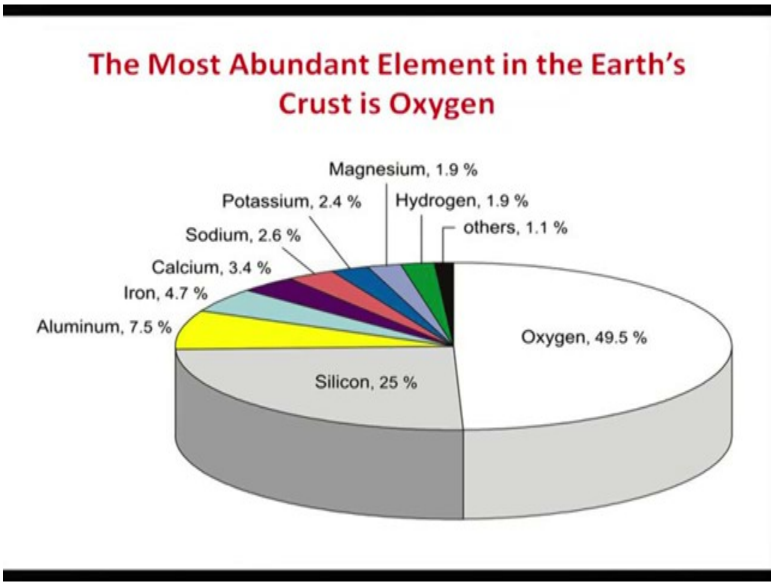

So, most abundant element in the earth crust is oxygen. As you can see that oxygen percentage very high around 50% , then the next abundant is silicon around 25% , then aluminum 7.5, iron 4.7, calcium 3.4 % and then sodium, potassium, magnesium, hydrogen, and other elements.

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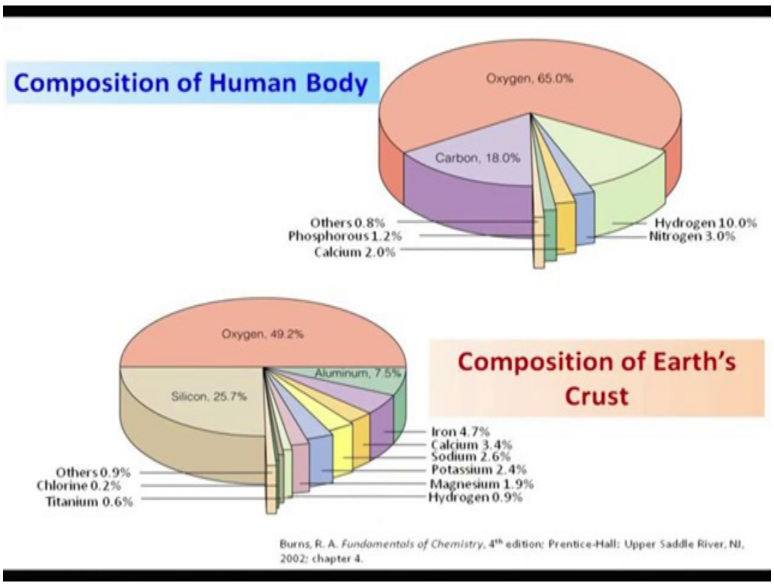

Now, here I have compared the composition of earth crust and also composition of human body. You see that the diagram is completely different Although oxygen concentration is a largest in both the system, but look at the silicon which is around 25.7% in earth crust is completely absent in human body. While, carbon which is very small concentration in the earth crust and in human body it is around 18%. also the hydrogen which is around 1% in the earth crust present around 10% in human body.

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Percentage of Atoms in the Human Body

Elements	Atom (%)
Hydrogen	62.8
Oxygen	25.4
Carbon	9.4
Nitrogen	1.4
Other	**1.0**

The term "**bio-inorganic**" which is a composite of biology and inorganic, is used to describe the occurrence and properties of inorganic elements in living systems.

Now, if we look at the overall percentage of atoms in human body what you find hydrogen 62.8% is atom percent, oxygen 25.4, carbon 9.4, nitrogen 1.4, and the other elements is just 1% . At first sight the idea of inorganic chemistry associated with the life may appear to be a rather narrow field of study, as we tend to think of living matters as being just organic.

However, it is affected without certain inorganic elements no organism could adjust. The term bioinorganic which is a composite of biology and inorganic is used to describe the occurrence and properties of inorganic elements in life systems.

So, these 1% elements are very crucial for our day to day survival.

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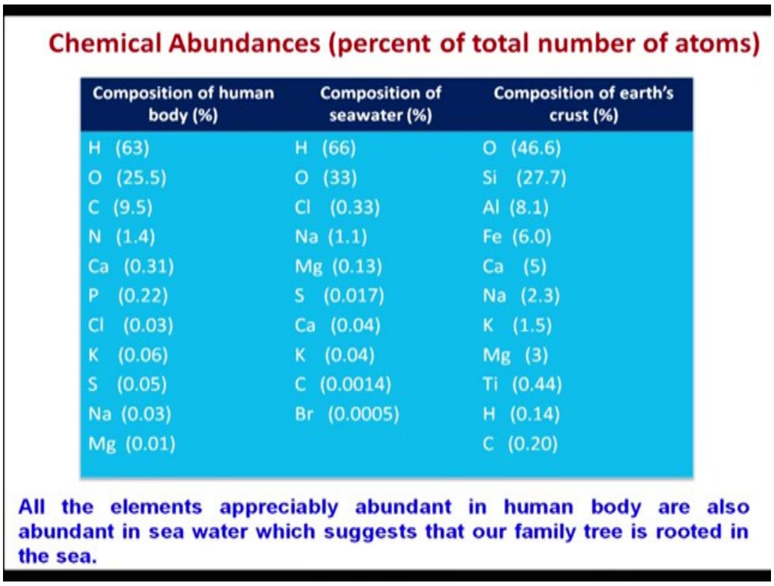

Chemical Abundances (percent of total number of atoms)

Composition of human body (%)	Composition of seawater (%)	Composition of earth's crust (%)
H (63)	H (66)	O (46.6)
O (25.5)	O (33)	Si (27.7)
C (9.5)	Cl (0.33)	Al (8.1)
N (1.4)	Na (1.1)	Fe (6.0)
Ca (0.31)	Mg (0.13)	Ca (5)
P (0.22)	S (0.017)	Na (2.3)
Cl (0.03)	Ca (0.04)	K (1.5)
K (0.06)	K (0.04)	Mg (3)
S (0.05)	C (0.0014)	Ti (0.44)
Na (0.03)	Br (0.0005)	H (0.14)
Mg (0.01)		C (0.20)

All the elements appreciably abundant in human body are also abundant in sea water which suggests that our family tree is rooted in the sea.

Now, here I have compared the chemical abundance. So, composition of human body, composition of seawater, and composition of earth crust are compared. If you look very carefully what you can see that composition of human body is similar to the composition of seawater which suggest that all elements appreciably abundant in human body are also abundant in seawater which suggest that our family tree is rooted in the sea which inorganic elements are important biologically, 99% human body is comprised of only 11 elements.

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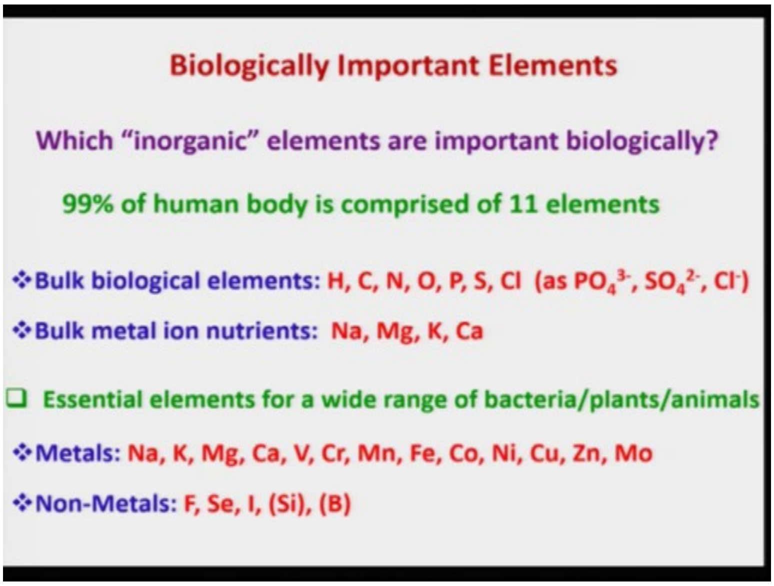

Out of 11 elements the bulk biological elements are hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, chlorine, bulk metal ions are sodium, potassium, magnesium, calcium. And essential elements for a wide range of bacteria, plants, animals are given here like metals mostly sodium, potassium, magnesium, calcium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, molybdenum and nonmetals fluorine, selenium, iodine, silicon, boron.

I should mention over here, it is not always clear whether an element is essential or not indeed some elements are only essential for a particular species not for all. It should be noted here however, that just because an element is present in an organism it does not mean that it is necessarily essential.

For example the average human contains approximately 300mg of strontium which chemically resembles to calcium. But it is not believed to be essential for our health, it is also fortunate for us not toxic. However, strontium is believed to be essential for somecorrected Corals.

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Now, the elements which are deduct for our activity comes through our diet we take every day. Here I have been showing the elements like potassium rich foods, sodium rich food, cobalt, calcium, iron rich food. You see that these foods we take every day in our life.

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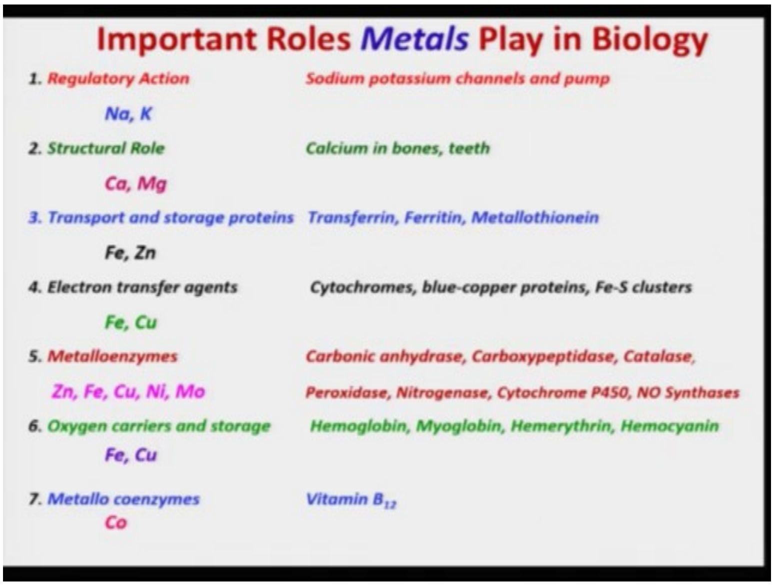

Now, the important roles the metals play in biology. Actually these metals are responsible for various activity in our day to day life. Some of this important activities I am highlighting over here say regulatory action sodium and potassium, they are actually responsible for sodium potassium channels and pumps. Structural role: calcium and magnesium are mostly responsible for the bones, teeth. Iron and zinc, they are present in the transport and storage proteins for example, transferrin, ferritin and metallothionein. Electron transfer agents such as cytochromes, blue copper protein, iron, sulphur clusters and iron and copper are mostly involved as a key component in those agents.

Metalloenzymes, a large number of metalloenzymes are used for our day to day activity. Some of them are carbonic anhydrase, carboxypeptidase, catalyst peroxidase, nitrogenase, cytochrome p450. And zinc, iron, copper, nickel, molybdenum, they are mostly involved during this process. Oxygen carrier and storage proteins such as hemoglobin, myoglobin, hemerythrin, hemocyanin, and iron, coppers are mostly involved during this process. Metalloenzymes such as vitamin B12 and cobalt is involved in this process.

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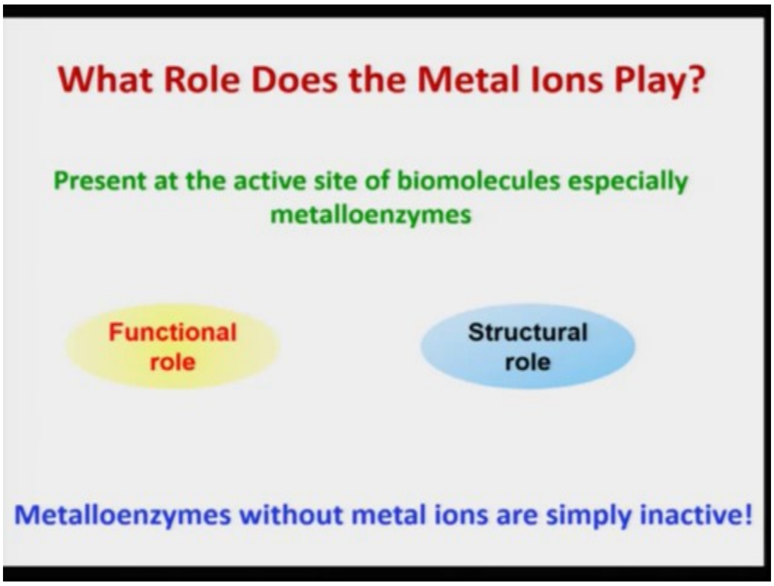

Now, what role does this metal ions play? This metal ions present at the active site of biomolecules, especially the metalloenzymes. They have functional role and or structural role. However, metalloenzymes without metal ions are simply inactive.

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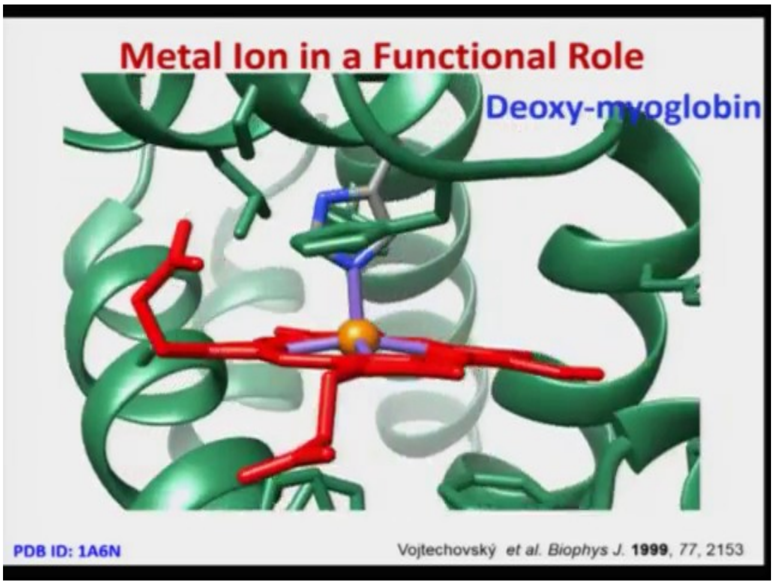

I will give you a simple example to show that how metal ion is responsible for functional role. You will see in details that hemoglobin and myoglobin they are actually responsible for carrying dioxygen in our body.

So, this is the myoglobin, the protein structure is shown over here. And as you can see that there is a huge protein chain which are wrapping the molecule the heme center and you see a tiny iron is sitting at the middle.

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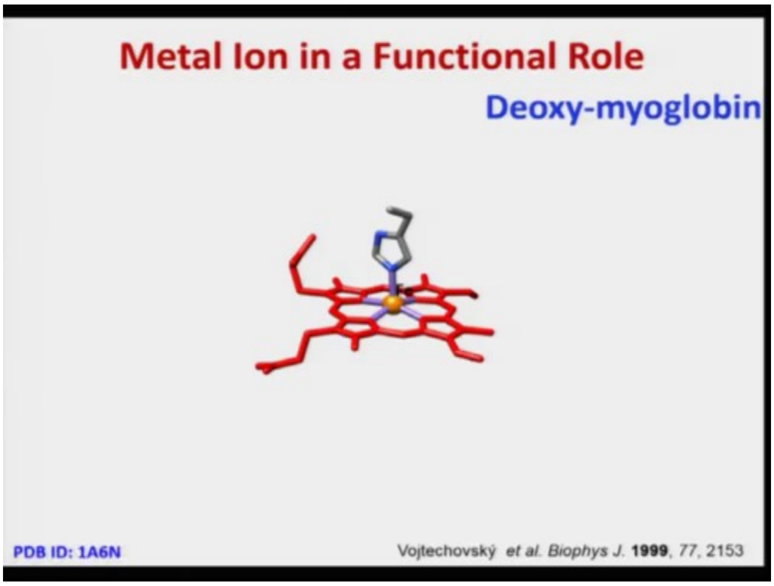

Here iron which is actually plays the active role in binding dioxygen.

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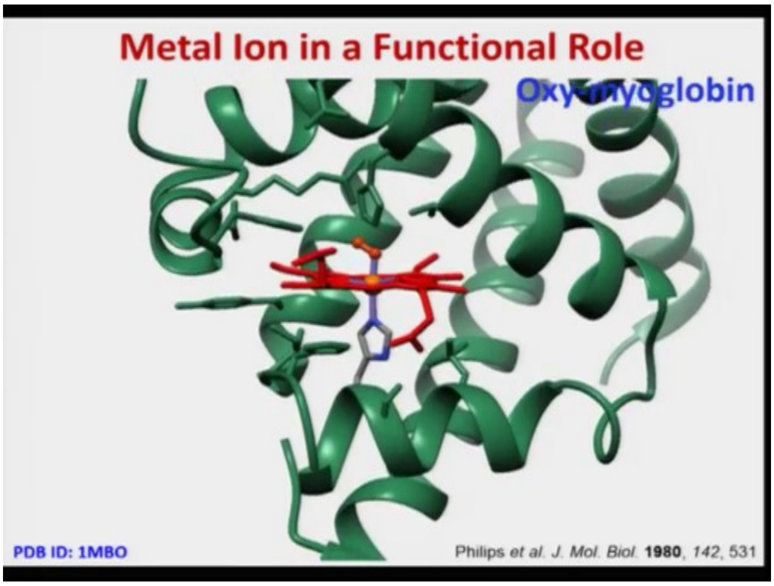

You see that oxy-myoglobin structure over here the huge protein chains, but is small heme unit and also the iron center which is playing the key role of binding dioxygen, and responsible for our survival.

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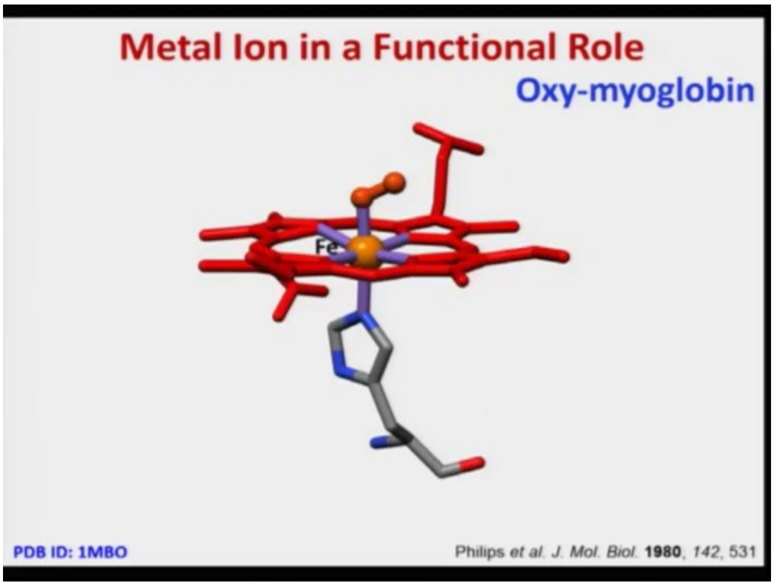

And without iron this molecule cannot bind oxygen anymore.

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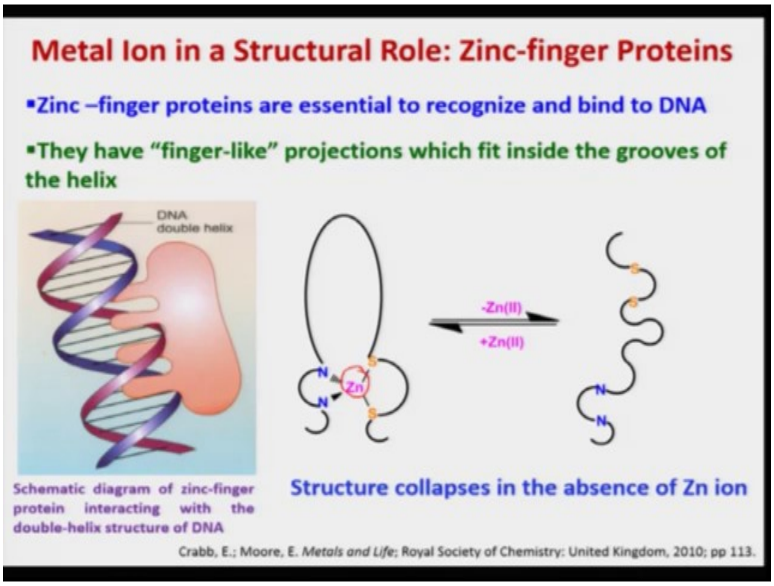

Now, I will show another example for structural role: zinc finger proteins. You see that zinc finger proteins are essential to recognize and bind to DNA. Here I have shown the DNA double helix, and how finger like proteins are fitting inside the groups of the helix. And this is the finger like proteins which are shown over here and at the center zinc ion is present. However, if you remove this zinc the entire structure collapse.

So, you see that how the metal ion is important for its structure.

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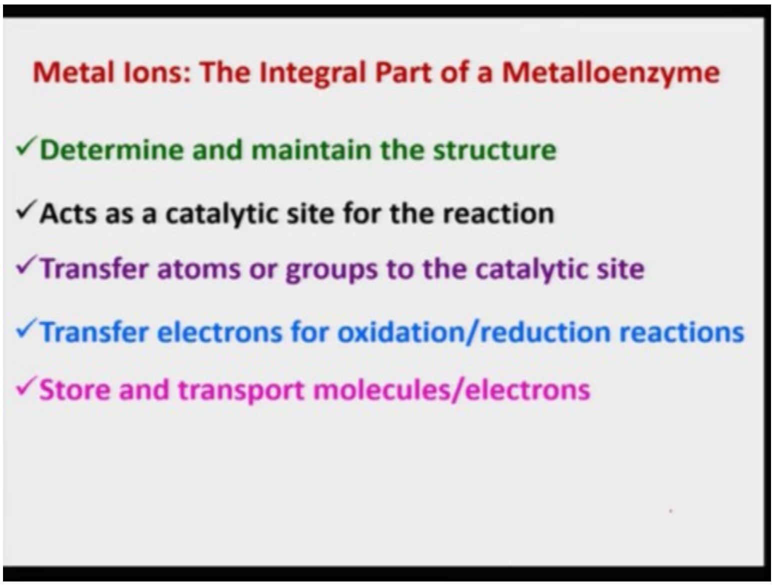

Now, metal ions the integral part of a metalloenzymes, what it is actually doing? It determines and maintains the structure as we have just seen. It acts like a catalytic site for the reaction, it transfers atoms or groups to the catalytic site, it transfers electron for oxidation or reduction reactions, it also store and transport molecules, electrons.

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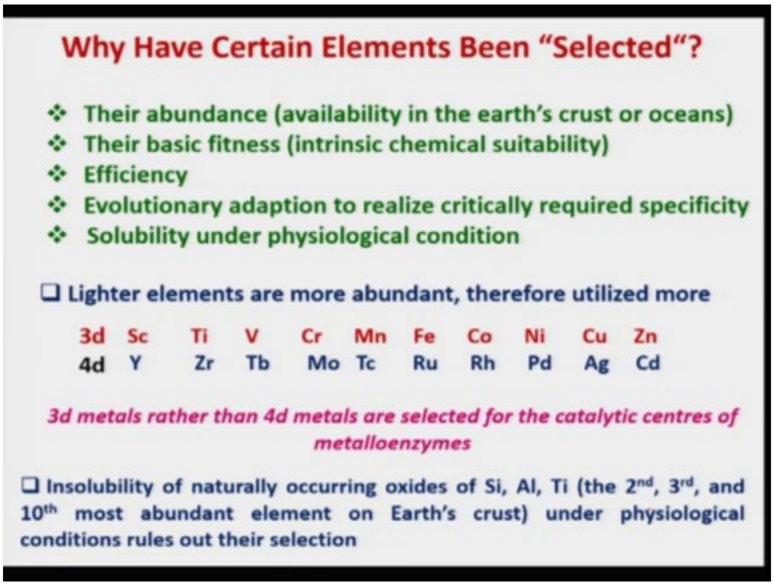

Why has certain elements being selected out of so many element present in the periodic table? Which has followed certain guiding principle while selecting the elements. Some of these principles are their abundance in the earth crust or in ocean. Their basic fitness the intrinsic chemical stability, the elements should be fit for the post their efficiency, evolutionary adoption to realize critically required specificity and also solubility under physiological condition.

As lighter elements are abundant, therefore utilized more. For example, 3d elements and 4d elements, out of these two series 3d elements are more abundant than 4d elements. And that is the reason why 3d elements are being chosen for the catalytic center of the metalloenzymes. In solubility of naturally occurring oxides of silicon, aluminium, titanium, under physiological conditions ruled out their selection for any biological activity although, they are highly abundant in the earth crust.

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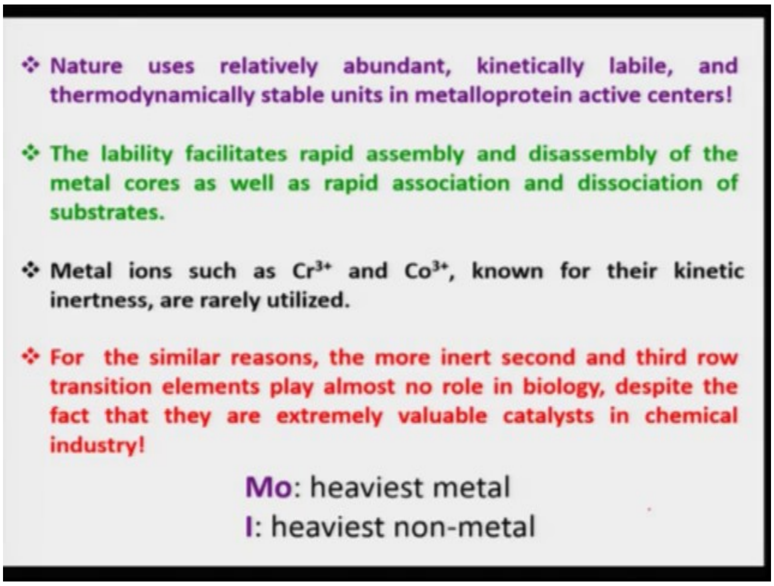

Now, nature basically used relativity abundant, kinetically labile, and thermodynamically stable units in the metalloprotein active centers. The liability basically facilitates rapid assembly and disassembly of the metal cores as well as rapid association and dissociation of the substrate. This is particularly very important for the catalytic activity.

Metal ion such as Cr^{3+} and Co^{3+} known for their kinetic inertness are really utilized in biology. For the similar reason the more inert second and third row transition elements play almost no role in biology, despite the fact that they are extremely valuable catalyst in chemical industry. However, there are exceptions Say molybdenum, which is heaviest metal and iodine which is heaviest non metal also essential for our day to day activity.

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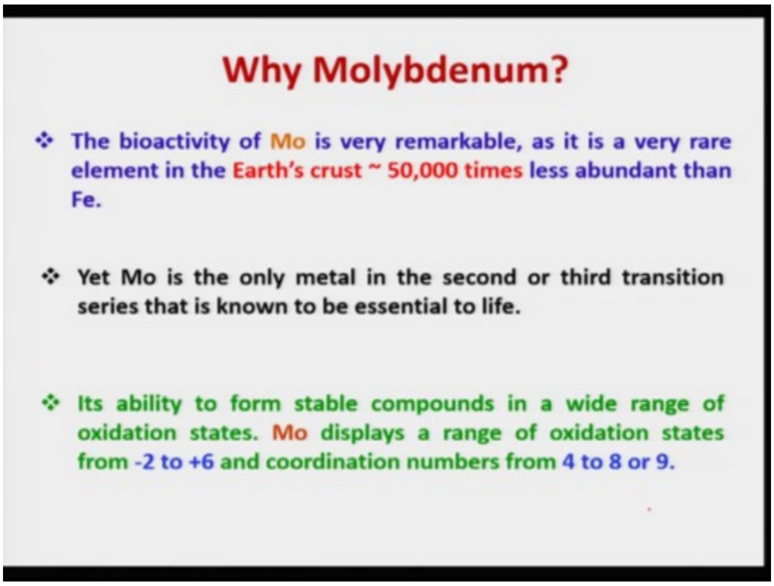

Now, the question is that why molybdenum? why nature get select molybdenum? The bioactivity of molybdenum is very remarkable, as it is a very rare element in earth crust around 50000 times less abundant than iron. Yet molybdenum is the only metal in the second or third transition series that is known to be essential to life its ability to form stable compounds in a wide range of oxidation states. Molybdenum displays a large range of oxidation states starting from -2 to +6 and also coordination numbers from 4 to 8 or even 9.

And these are the characteristic features which is responsible for its selection.

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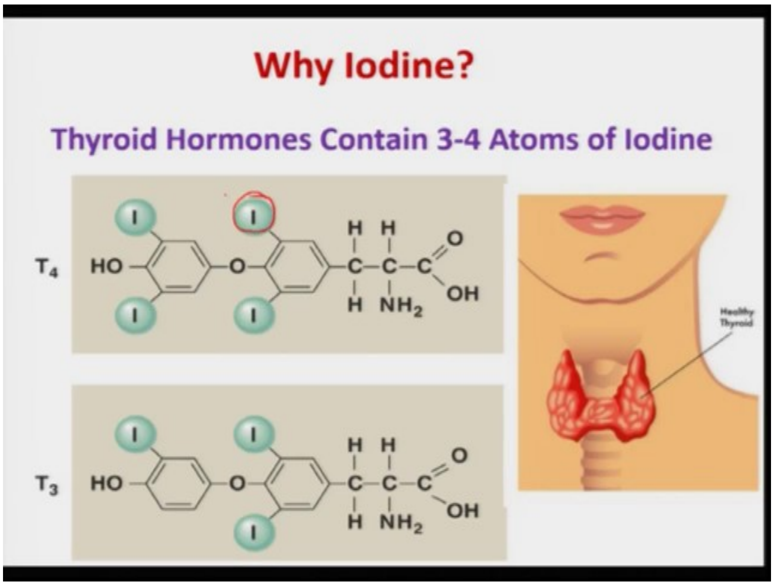

Similarly, why iodine being selected? As you can see in this particular slide that thyroid hormones contains 3 to 4 atoms of iodine, this is T_3 and T_4 is shown over here and as you can see that this iodine is present. And these hormones are secreted from the thyroid gland present in the neck. And this is essential and that is why iodine being selected.

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Chemical Abundances (percent of total number of atoms)

Composition of human body (%)	Composition of seawater (%)	Composition of earth's crust (%)
H (63)	H (66)	O (46.6)
O (25.5)	O (33)	Si (27.7)
C (9.5)	Cl (0.33)	Al (8.1)
N (1.4)	Na (1.1)	Fe (6.0)
Ca (0.31)	Mg (0.13)	Ca (5)
P (0.22)	S (0.017)	Na (2.3)
Cl (0.03)	Ca (0.04)	K (1.5)
K (0.06)	K (0.04)	Mg (3)
S (0.05)	C (0.0014)	Ti (0.44)
Na (0.03)	Br (0.0005)	H (0.14)
Mg (0.01)		C (0.20)

All the elements appreciably abundant in human body are also abundant in sea water which suggests that our family tree is rooted in the sea.

Now, as I have shown earlier that composition of human body is closely resembles to the composition of sea water.

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How a Particular Element is Concentrated or Diluted by Humans?

Element	[Sea water] /mol dm^{-3} × 10^{-8}	[Human plasma] /mol dm^{-3} × 10^{-8}	Concentration/ dilution factor
Sodium	4.6×10^{7}	2×10^{5}	~4×10^{-3}
Magnesium	5.3×10^{6}	9×10^{4}	~0.02
Potassium	9.7×10^{5}	2×10^{5}	~0.2
Calcium	1.0×10^{6}	1×10^{6}	~1
Vanadium	4.0	17.7	~4
Chromium	0.4	5.0	~14
Manganese	0.7	10.9	~15
Iron	0.005-2*	2230	1100-450,000
Cobalt	0.7	0.0025	3.6×10^{-3}
Nickel	0.5	10.4	~21
Copper	1.0	1650	1650
Zinc	8.0	1720	215
Molybdenum	10.0	1000	1000

* Dependent on pH.

Concentration of these elements in human plasma greatly exceeds that in sea water, suggesting the existence of efficient mechanisms to deal with the process of storage and transport!!!!

However, there are certain elements which are either getting concentrated or diluted by humans.

In this particular table as you can see that their concentration in seawater and human plasma are compared. And then the concentration or dilution factor is also calculated. If you see the sodium sea water concentration is much higher compared to the human plasma and so it has been diluted by a factor of 4×10^{-3} in humans. Magnesium, potassium, calcium, vanadium, chromium, manganese, there are also some of them are comparable between sea water and human plasma.

However, if you look at iron which concentration in seawater is very low certainly it is dependent on the pH of the solution. However, as you know that in human plasma this is very high concentration. And it has been found that the concentration increased by a factor of around 1100 to 4,50,000 times. Nickel, copper, zinc, molybdenum also getting concentrated in the human plasma to a large extent with an exception that cobalt; cobalt the concentration in seawater was more while in human plasma it is less. So, it is diluted by a factor of 3.6×10^{-3}.

Thus the concentration of these elements in human plasma greatly exceeds that in seawater which suggests the existence of efficient mechanism to deal with the process of storage and transportation.

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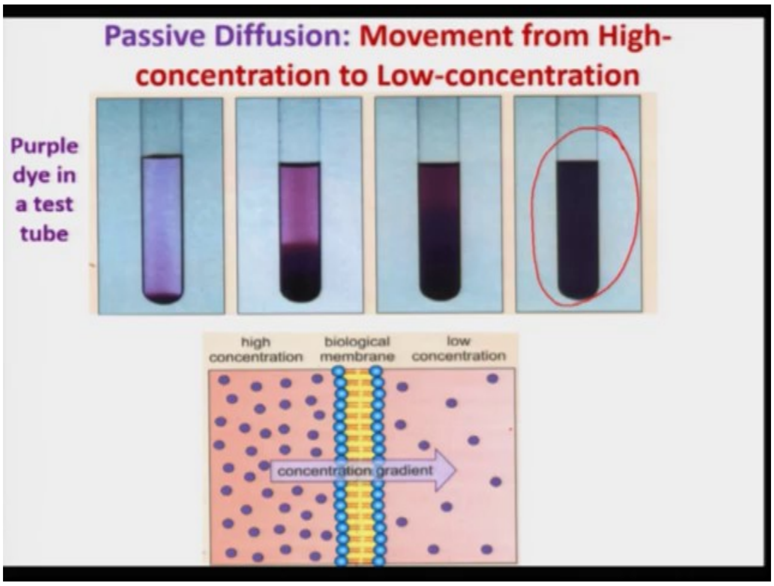

So, let us look at that how these elements comes inside the cell. Before we discuss let us take a very simple example of passive diffusion, basically the movement from high concentration to low concentration.

So, the purple dye is taken in a test tube with lots of water and if you keep it with time slowly diffuse. And in the last in this test tube as you can see the concentrations becomes equal throughout out of such passive diffusion process. This is what exactly happening in biological system also. When the concentration of an element is high outside the cell and the concentration of the element is low inside the cell, then because of this passive diffusion spontaneously the element passes through the biological membrane from high to low. You do not need any energy this is spontaneous process.

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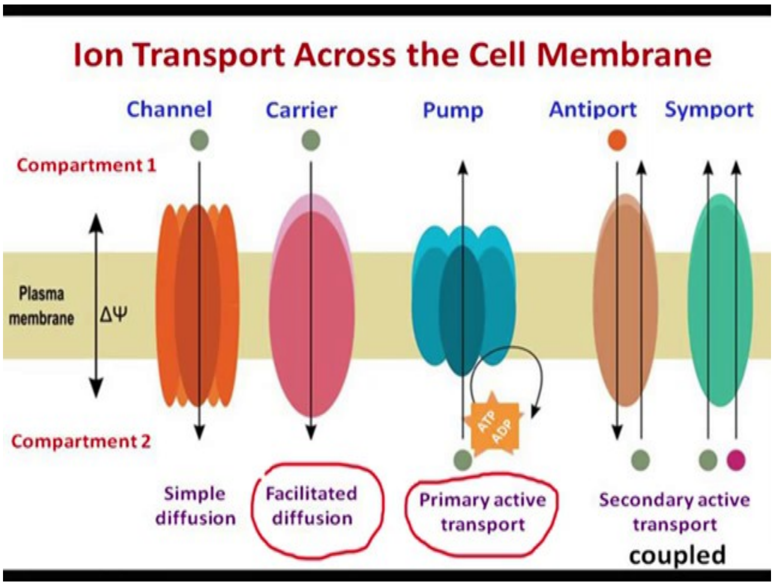

Let me tell you that the mechanism on which a ion transport across the cell membrane. So, these are component 1 and component 2. So, there can be a simple diffusion process you passing through a channel. There can be a carrier which is carrying that element or ion and passes through the cell membrane, we call it as a Facilitated Diffusion. There can be a situation that ion has to go against concentration gradient. That means, from a low concentration situation to a high concentrated system and it is against the passive diffusion process.

So, it requires energy and ATP would be converted to ADP produces energy we call it Primary Active Transport, because energy is required it have to be pumped. There can be a situation where two ions they actually coupled, energetically coupled with each other, either go at the same time say at the time one go out and the other ion comes inside the cell or both of them either go out or come inside the cell. And this is called Secondary Active Transport.

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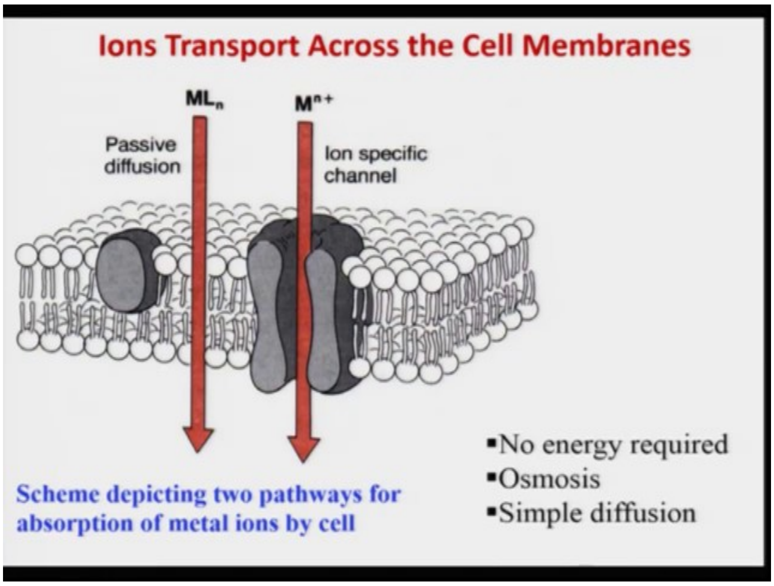

Now, ion transport across the cell membrane here is a schematic diagram. Two possible pathways one is just a passive diffusion, where a ion comes spontaneously across the concentration gradient, no energy is required, is a just a simple diffusion. Also there can be a situation where ion specific channel actually facilitate the passive of this metal ion to come inside the cell. And there are also no energy is required, because it is across the concentration gradient.

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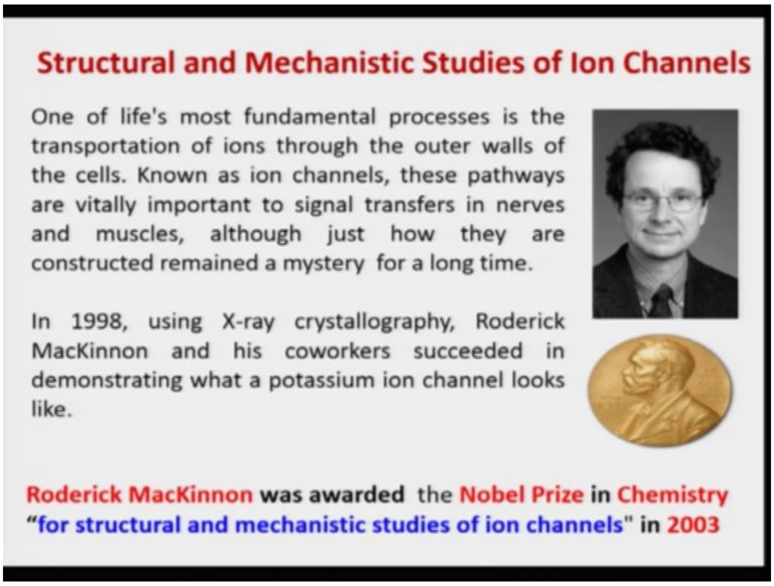

Now, one of life's most fundamental processes in the transportation of ions through the outer walls of the cell known as ion channels. These pathways are vitally important to signal transfer in nerves and muscles, although just how they are constructed remained a mystery for a long time.

In 1998, using X-ray crystallography Roderick MacKinnon and his coworkers succeeded in demonstrating what a potassium ion channel looks like. And Roderick MacKinnon was awarded Nobel Prize in Chemistry for 'Structural and Mechanistics Studies of Ion Channels' in 2003.

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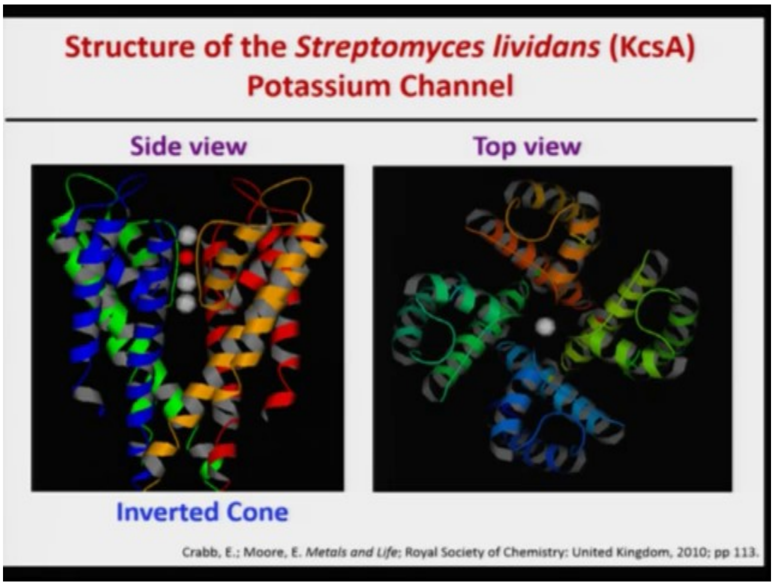

So, here the X-ray structure of potassium ion channel is shown. As you can see that this is like a inverted cone and on a side view and top view is shown over here. And the potassium ion goes in through this cavity, the channels, and highly selective in nature and four subunits as you can see here, there are four subunits and they selectively filter potassium to goes through that channel.

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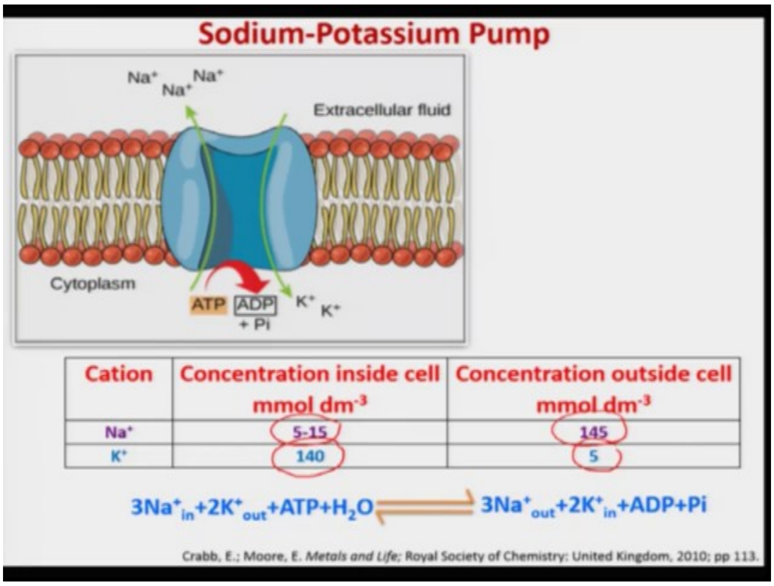

Now, I will talk about sodium potassium pump.

So, as you can see that sodium goes outside the cell potassium comes inside the cell, and equal in energy to facilitate this process. And if you look at the concentration of sodium and potassium inside and outside the cell what you see, you see that in sodium the concentration inside the cell is much less whereas, outside the cell is much more. In contrast potassium is just opposite inside the cell it is much more 140 and outside cell is just only 5 mmol dm^{-3} .

So, what is exactly happening that $3Na^{+}_{In}$ + $2K^{+}_{out}$ converted to $3Na^{+}_{out}$ + $2K^{+}_{in}$, at the cost of some energy.

So, this is we call it active transport and requires energy.

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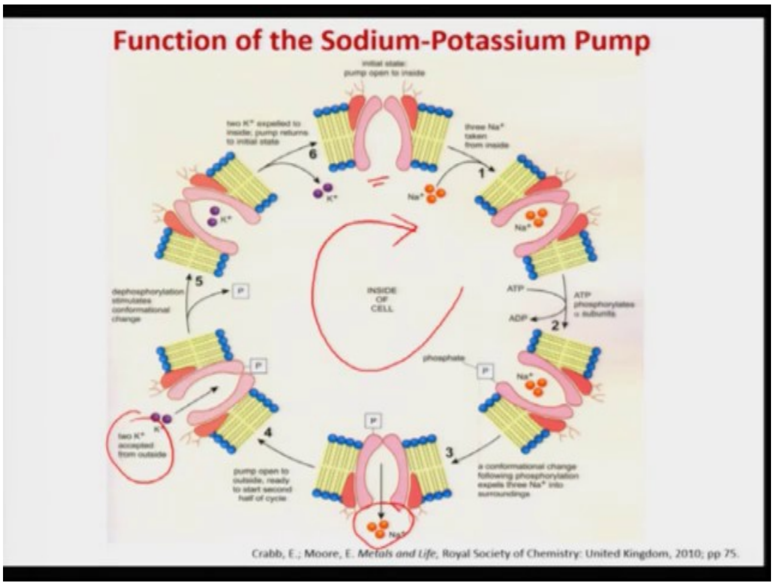

Now, we will show a schematic diagram of their function. So, initial state as you can see that the pump opens to inside. Now when three sodium taken inside and then this ATP phosphorylase α-subunit, then a conformational change following phosphorylation expelled three sodium ion into surroundings as shown over here. The pumps the open to outside ready to start second half cycle two potassium accepted from outside, dephosphorylation stimulates conformational changes once again, two potassium expelled to inside, pump returns back to initial state where it takes three sodium ion again and this catalytic cycle is going on.

So, this is the way Sodium-Potassium pump works.

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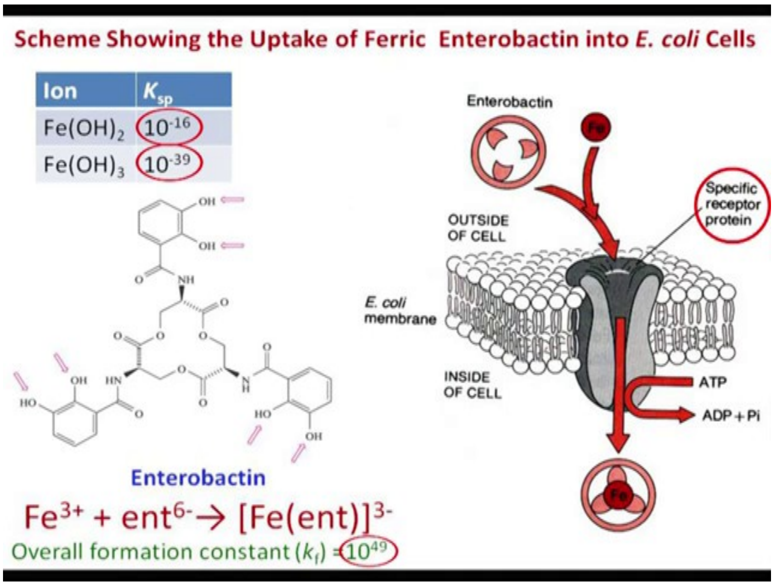

Now, it is interesting to see that how iron comes inside the cell. If you look at whether it is $Fe(OH)_2$ or $Fe(OH)_3$ if you look at their solubility product, if $Fe(OH)_2$ the solubility product is 10^{-16}, $Fe(OH)_3$ solubility product is 10^{-39}, so low, so low concentration.

Now, this being the case how iron comes inside the cell in such a high concentration. This is what is happening this siderophores are actually designed which binds this Fe^{3+} very tightly. The siderophores are released by the bacteria into its environment. This sequesters iron, solubilizing it in complex form that one specifically taken up into the cell where it is subsequently released. As you can see that this siderophore here one example is enterobactin. And which is a chelating agent as you can see that there are hexa-dentate chelator which binds with Fe^{3+} very strongly overall formation constant is 10^{49} so high.

And this enterobactin have to be such that specific receptor protein can allow them going inside the cell. And of course, since it is against the concentration gradient the energy is required. So, 1 unit of ATP converts to ADP and gives rise to energy so that this process becomes spontaneous. And this is the way the siderophores actually increases the concentration of iron and brings iron inside the cell.

So, we have discuss so far the importance of inorganic element in biological system and also how those elements are being selected out of so many elements present in the periodic table. We also have seen today, how the elements are transported across the cell membrane. In my next lecture I will showcase how our life is affected directly out of such elements and causes various diseases in our daily life.

Thank you.