

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
الَّذِي عَلَّمَ بِالْقَلَمِ ۖ عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ

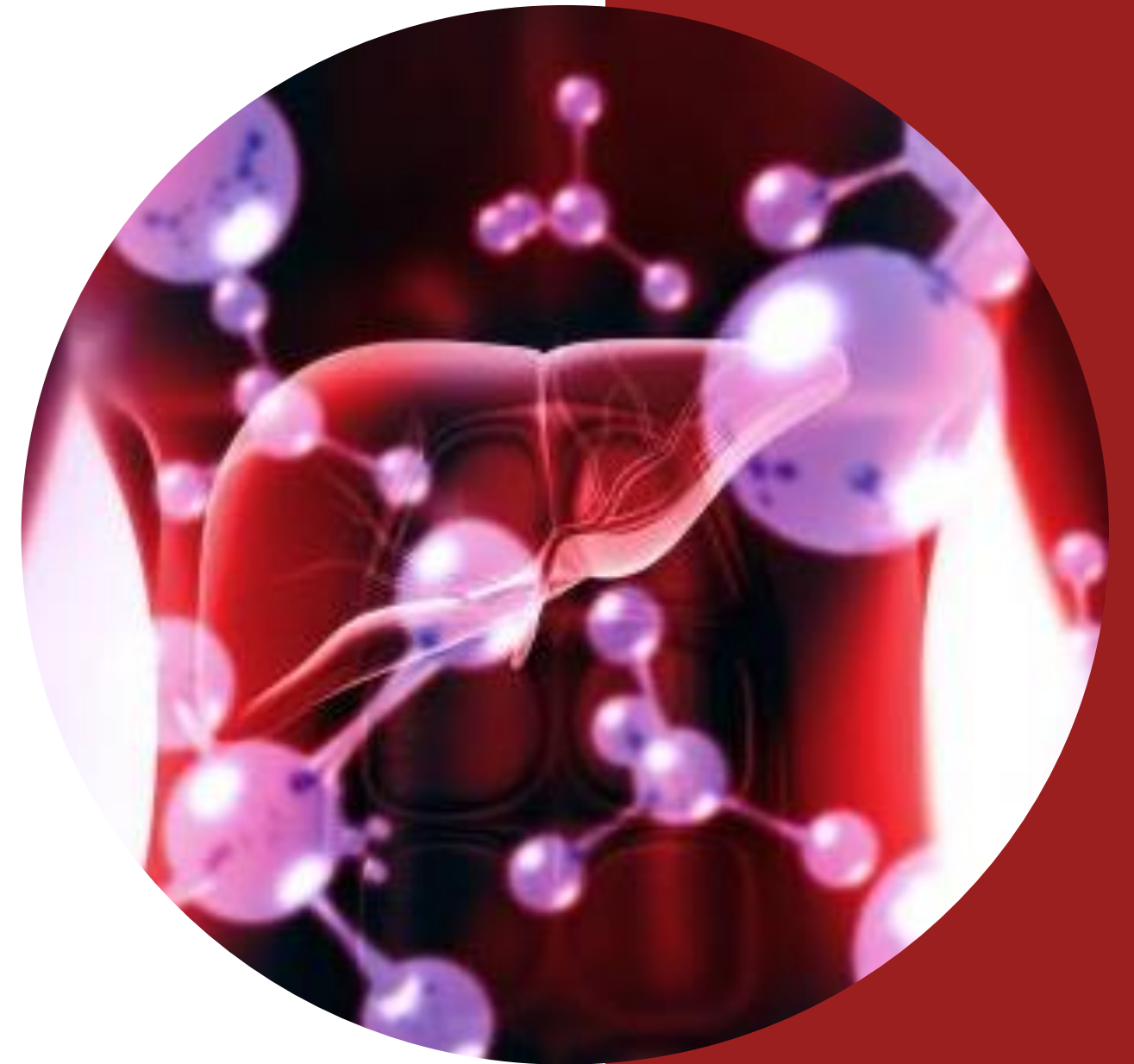
METABOLISM

MID | Lecture 2

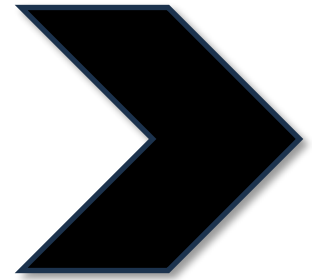
Bioenergetics & Thermodynamics 2

Reviewed by:

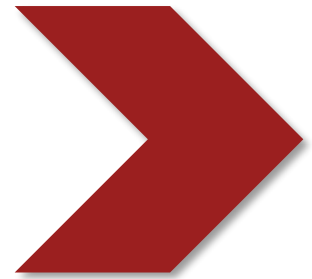
Karam Alquiam
Hala Marei
Raghad Farraj



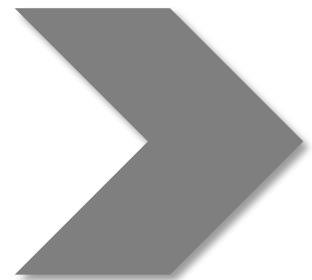
Color coding used in the modified:



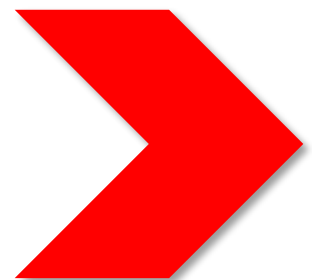
Black: the original slides



Maroon: the doctor's explanation/words



Gray: additional information and explanation



Red: important information

Quick revision

-All reactions(in living systems) are trying to avoid equilibrium state because it is (non functional) state

Where the net energy (driving force) is zero

-Remember : Equilibrium is an energy balance not a concentration balance

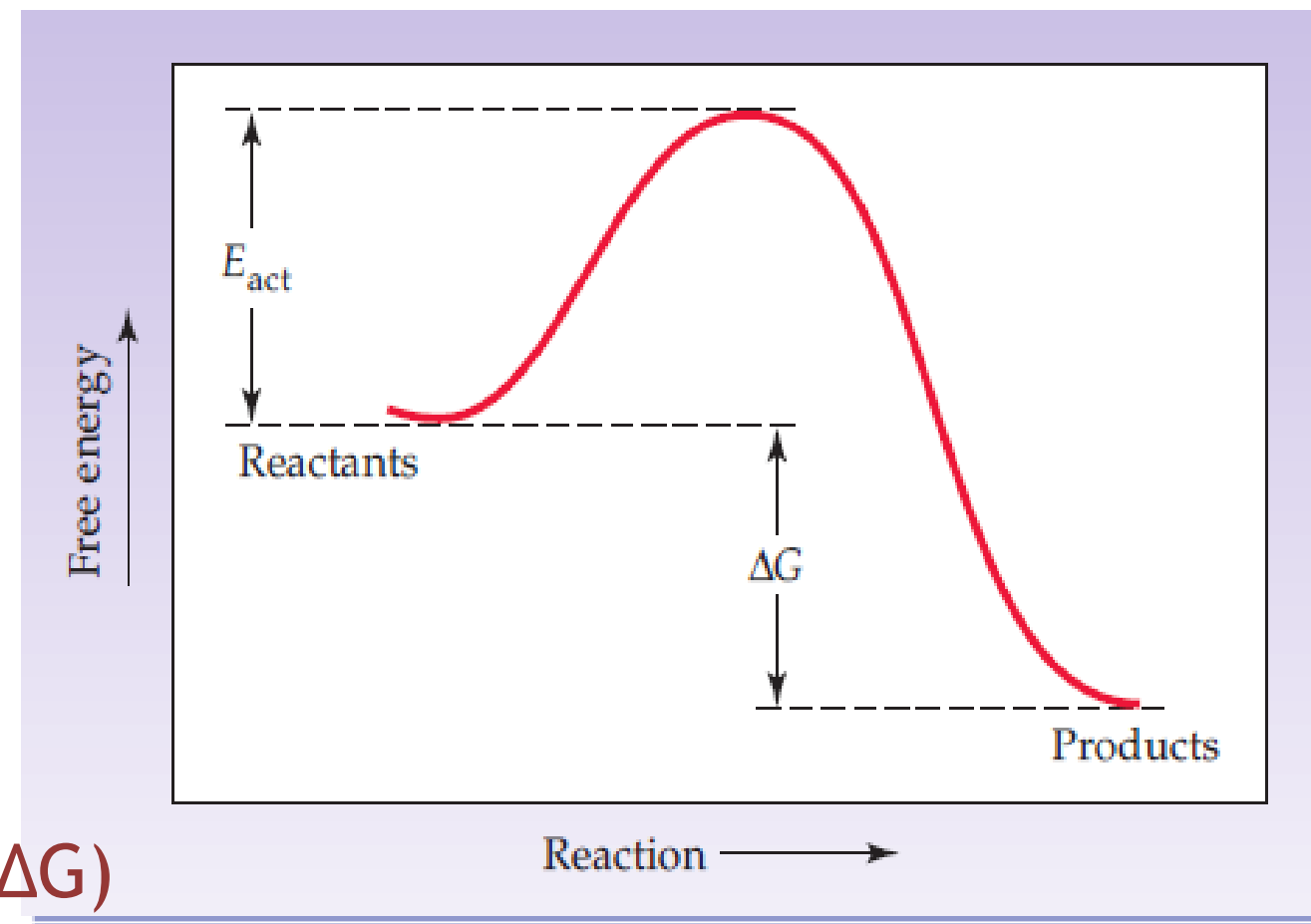
**-Concentration represents the amount of a substance per unit volume.
Equal numbers of moles of different substances do not necessarily mean
equal energy content.**

**- At equilibrium : the concentration of products divided by the
concentration of reactant represents the equilibrium constant**

WHY DO CHEMICAL REACTIONS OCCUR?

- The concept of activation energy
- ΔG and ΔG°

Activation Energy (E_a) Every chemical reaction needs some activation energy to get started. This is the energy barrier that must be overcome for reactants to turn into products.

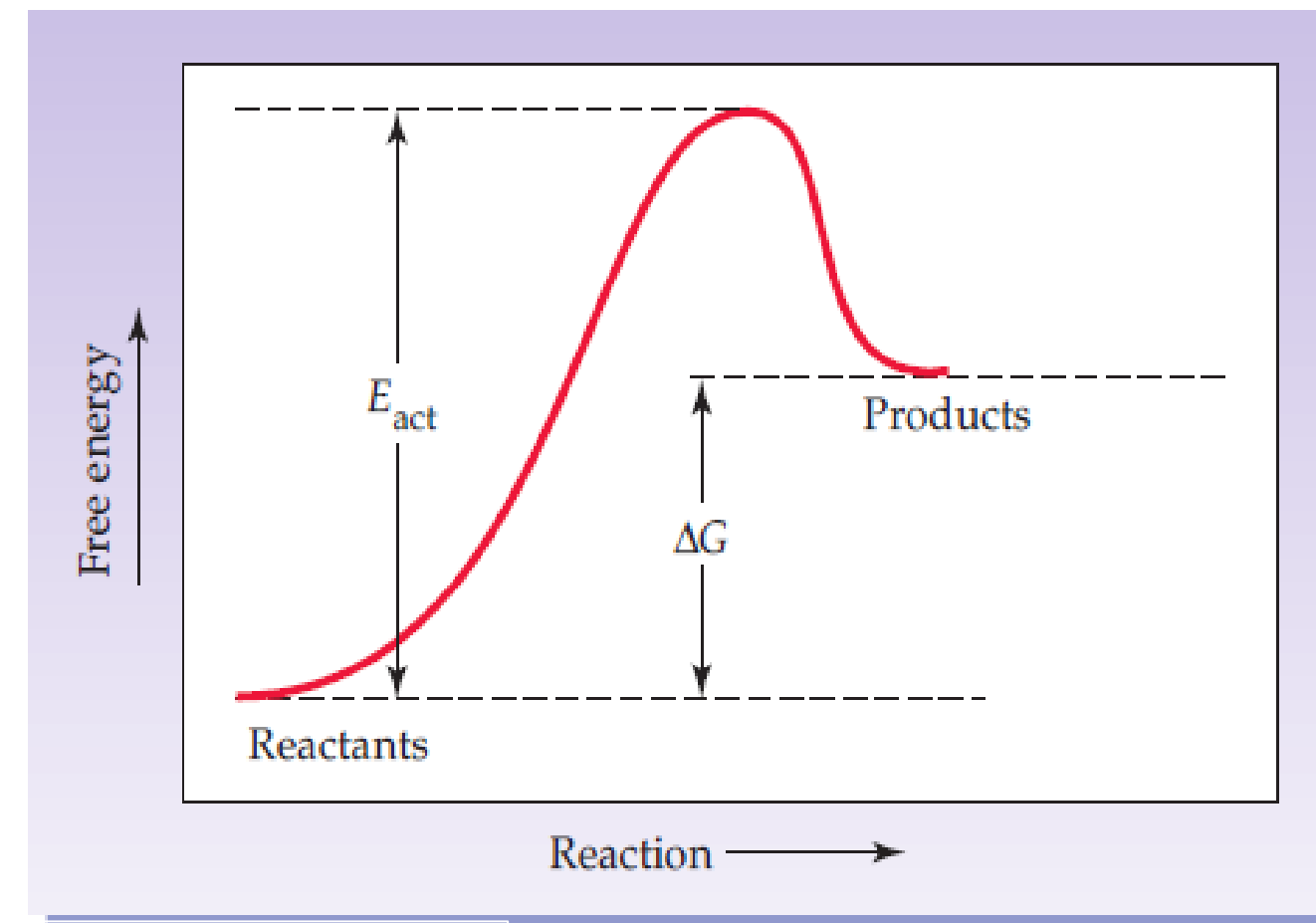


Negative ($-\Delta G$)

Releases energy

Spontaneous

(a) An exergonic reaction



(b) An endergonic reaction

Positive ($+\Delta G$)

Absorbs energy
Non-spontaneous

ΔG° vs ΔG

ΔG° = Standard free energy change (under standard conditions: 25°C, 1 atm, 1 M concentration).

ΔG = Actual free energy change in the cell, which **depends** on the **real concentrations** of reactants and products because R and T are not changing that much .

$\Delta G^\circ'$ represents the standard free energy change under biochemical conditions (the energy change for a reaction at pH = 7)

ΔG is a state function, meaning it depends only on the initial and final states, not on the path.

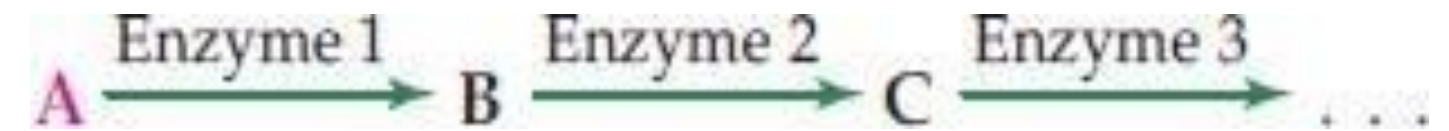
Example: Whether a reaction happens in one step or several steps, ΔG remains the same.

ΔG IS A STATE FUNCTION?!

- ΔG is not affected by the mechanism of the reaction

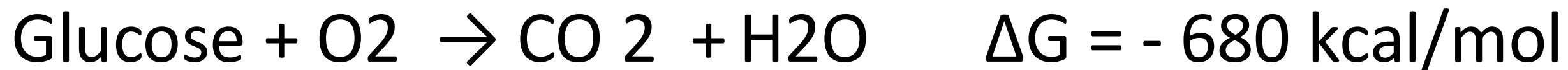
- $A \rightarrow B \rightarrow C$

$$\begin{aligned}\Delta G_{A \rightarrow B} &= \cancel{G_B} - G_A \\ \Delta G_{B \rightarrow C} &= G_C - \cancel{G_B} \\ \hline G_C - G_A &= \Delta G_{A \rightarrow C}\end{aligned}$$

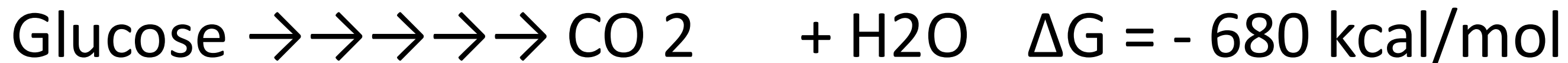


ΔG is independent of the reaction pathway because Gibbs free energy is a state function. It depends only on the initial and final states of the system, not on the pathway taken. Therefore, ΔG represents the difference in Gibbs free energy between the products and reactants.

- Combustion of glucose in calorimeter



In the cell



ΔG IS AFFECTED BY CONCENTRATION

Energy in glucose $\rightarrow$ energy in the bond, so can you calculate the energy in the bond? You should be. The energy should be affected by the concentration of products and reactants.



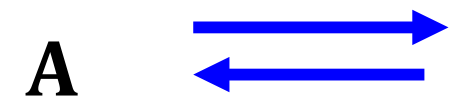
B

$$\Delta G = - - -$$



B

$$\Delta G = -$$



B

$$\Delta G = \text{zero}$$



B

$$\Delta G = + +$$

ΔG measures the tendency of a reaction to proceed towards equilibrium

B

$$\Delta G = - - -$$

There is a lot of A (reactant) and very little B (product). The reaction will go strongly forward because there are many reactants ready to react.

ΔG is very negative, meaning the reaction is spontaneous and releases energy

B

$$\Delta G = -$$

The reaction still goes forward, but less strongly.

B

$$\Delta G = \text{zero}$$

This means the reaction has reached equilibrium. The amount of A and B stays constant. $\Delta G = 0$ means no net energy change; the reaction goes in both directions equally.

B

$$\Delta G = ++$$

Now there is a lot of B (product) and very little A. ΔG becomes positive, so the reaction does not go forward. Instead, it tends to go backward to reach balance.

$$\blacksquare \Delta G = \Delta G^\circ + RT \ln \frac{[\text{Products}]}{[\text{Reactants}]}$$

ΔG° = standard free energy (constant, at 1M each)

ΔG = actual free energy (depends on concentrations) $Q = [\text{Products}]/[\text{Reactants}]$

Not at equilibrium state :

When [Reactants] are high, ΔG is negative $\rightarrow$ the reaction goes forward (exergonic)

When [Products] are high, ΔG is positive $\rightarrow$ the reaction goes backward (endergonic)

When [Reactants] = [Products], $\Delta G = \Delta G^\circ$

At equilibrium: $\Delta G = 0$

$$\Delta G^\circ = -RT \ln [\text{Products}]/[\text{Reactants}]$$

How ΔG and ΔG° relate?

- Concentrations of reactants and products = 1 mole/L

- $\Delta G = \Delta G^\circ + RT \ln \frac{[\text{Products}]}{[\text{Reactants}]}$

- $\Delta G = \Delta G^\circ + RT \cdot 2.3 \log \frac{[\text{Products}]}{[\text{Reactants}]}$

Logically if we have more products than the reactants, all the pathways in our body when we have extra amount of products will Undergo inhibition because the energy content itself prevents you, here we get back to the number concept, you have more molecules that contains more energy inside them. So when you raise the concentration of the products and decrease the concentration of the reactants, the ratio will increase the ($\ln$) will be positive. (so even in the standard conditions if we have a reaction with negative, delta G if we keep increasing the product, concentration and decreasing the reactant concentration you can end up with a positive value for delta G so this reaction won't be favorable in the forward direction.

This is important physiologically Because we will have inhibition energy wise. We're not talking about enzymes.

If we have ΔG° with a positive value, we can end up with a negative ΔG value by having a higher concentration of the reactants than products.

And this strategy is one of the greatest strategies that our body can do to overcome the non-spontaneous reactions (the endergonic reactions). Because we rarely ask for extra ATP we usually use the change in concentrations in these reactions.

At equilibrium the only thing that you are 100% sure of that the ΔG is zero.

The free energy change (ΔG) depends on **concentrations** at any given moment. It doesn't get affected by the pathway. It only depends on the reactants and the products.

If $[\text{Products}] / [\text{Reactants}] = 1$, then $\Delta G = \Delta G^\circ$
→ reaction at standard conditions).

If $[\text{Products}] / [\text{Reactants}] < 1$, ΔG becomes more negative
→ reaction is more spontaneous (favorable).

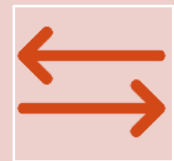
If $[\text{Products}] / [\text{Reactants}] > 1$, ΔG becomes less negative or positive
→ reaction is less favorable (or reversed).



THE STANDARD FREE-ENERGY CHANGE IS DIRECTLY RELATED TO THE EQUILIBRIUM CONSTANT (K_{eq})



Equilibrium is reached at the end!



At equilibrium: concentration are fixed; rates are exactly equal

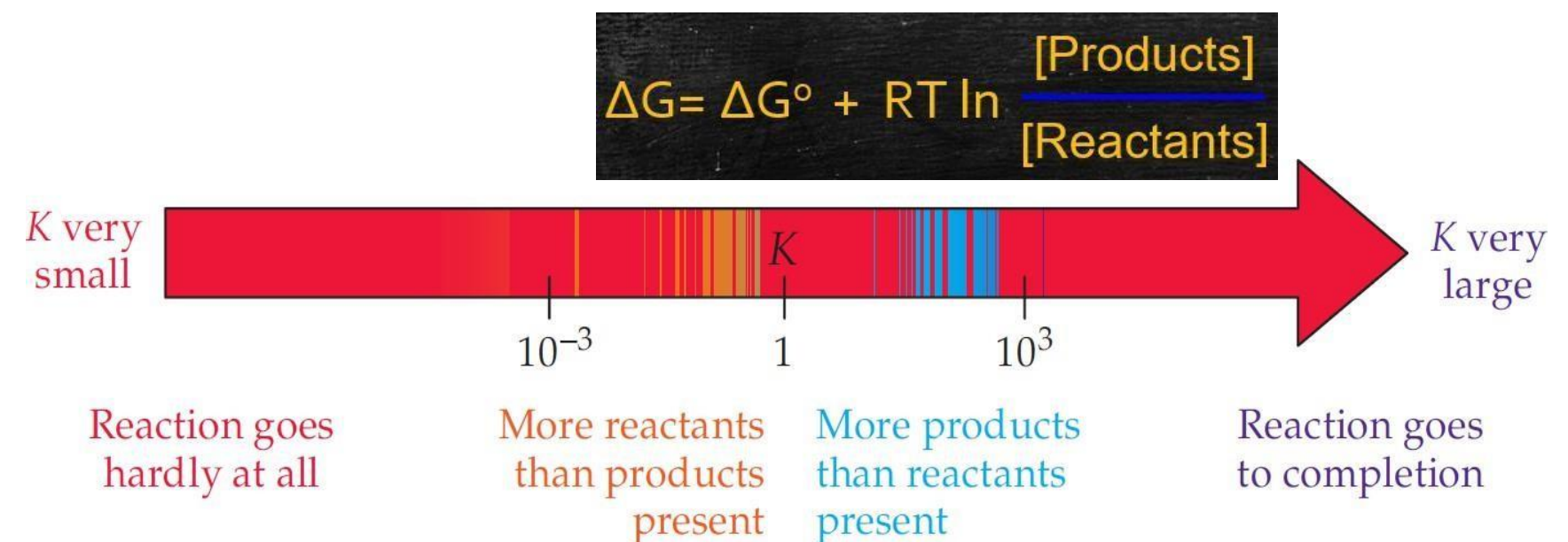


The concentrations define the equilibrium constant

✓ The equilibrium constant (K_{eq}) expresses the ratio of product to reactant concentrations at equilibrium



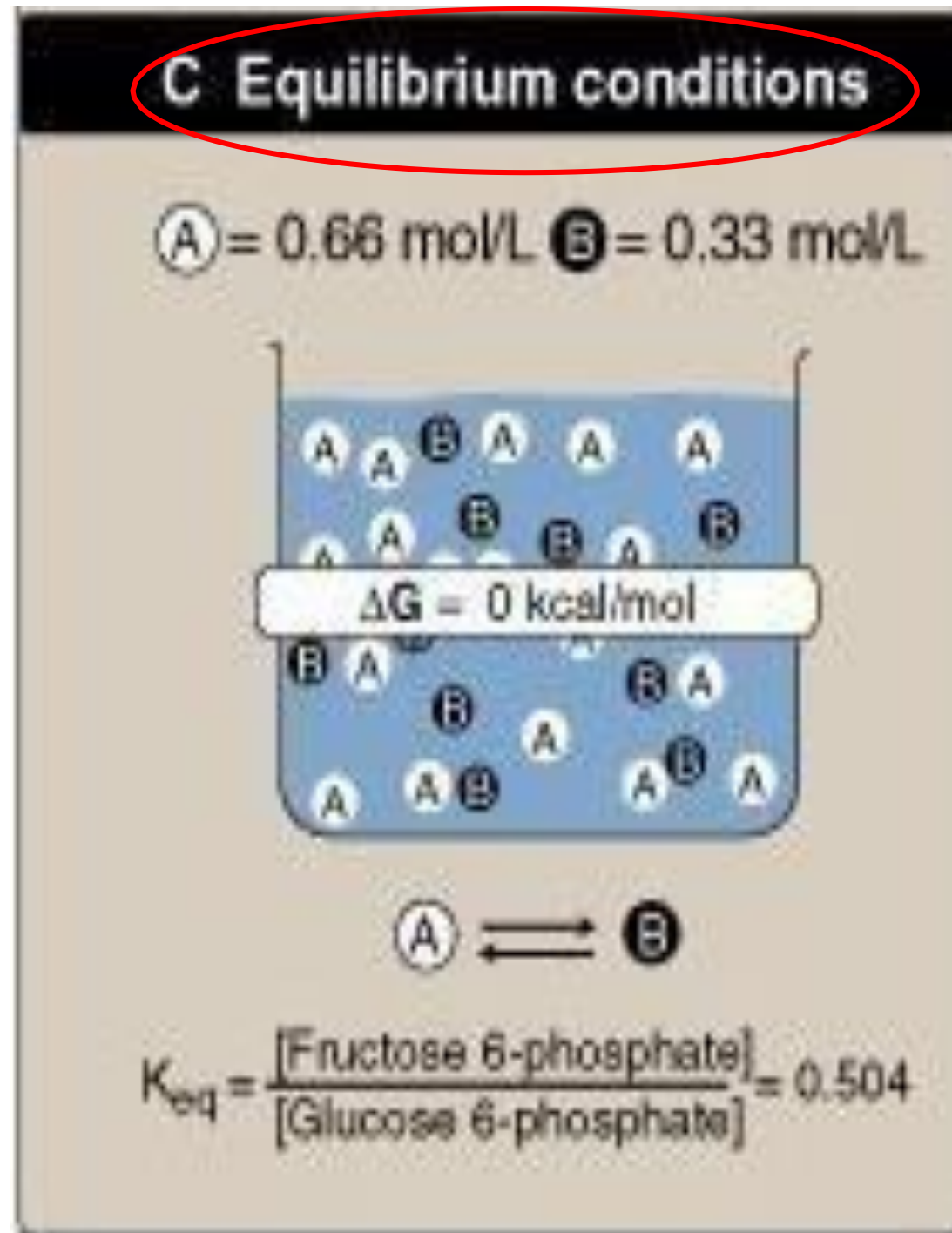
$$K_{eq} = \frac{[C]^c [D]^d}{[A]^a [B]^b}$$



Glucose 6- phosphate
0.66 mol/L



Fructose 6- phosphate
0.33 mol/L



$$\Delta G = \Delta G^\circ + RT \ln 0.33 / 0.66$$

$$\Delta G^\circ = +0.4 \text{ kcal/mol}$$

At equilibrium, $\Delta G = 0$ because the reaction is balanced in both directions.

When substituting the concentrations into the equation, we find that $\Delta G^\circ = +0.4 \text{ kcal/mol}$. The positive value means the reaction is not spontaneous under standard conditions.



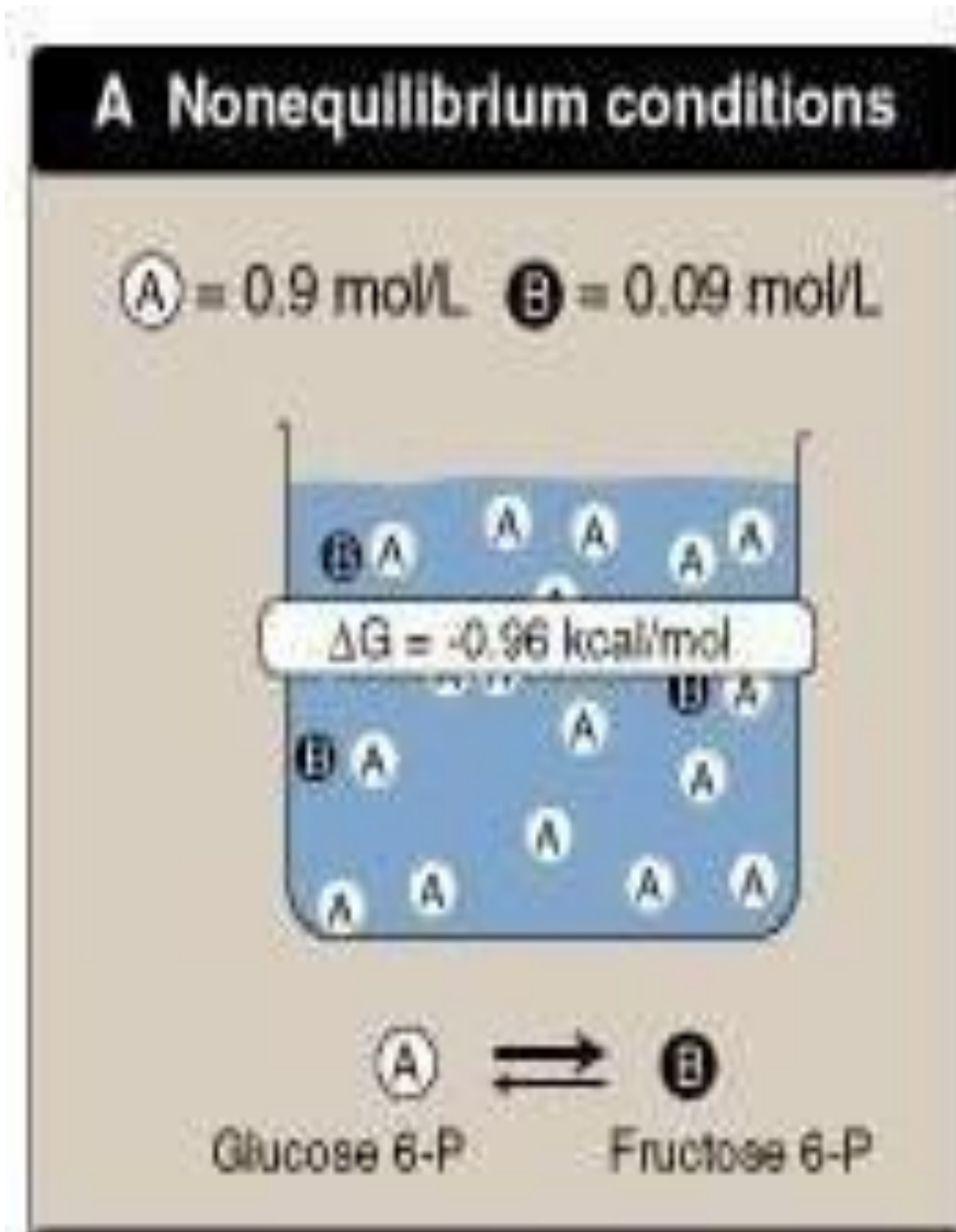
Constant at standard condition, it doesn't change regardless

$$\Delta G^{\circ} = + 0.4 \text{ kcal/mol}$$

$$\Delta G = \Delta G^{\circ} + RT 2.3 \log 0.09/0.9$$

$$\Delta G = - 0.96$$

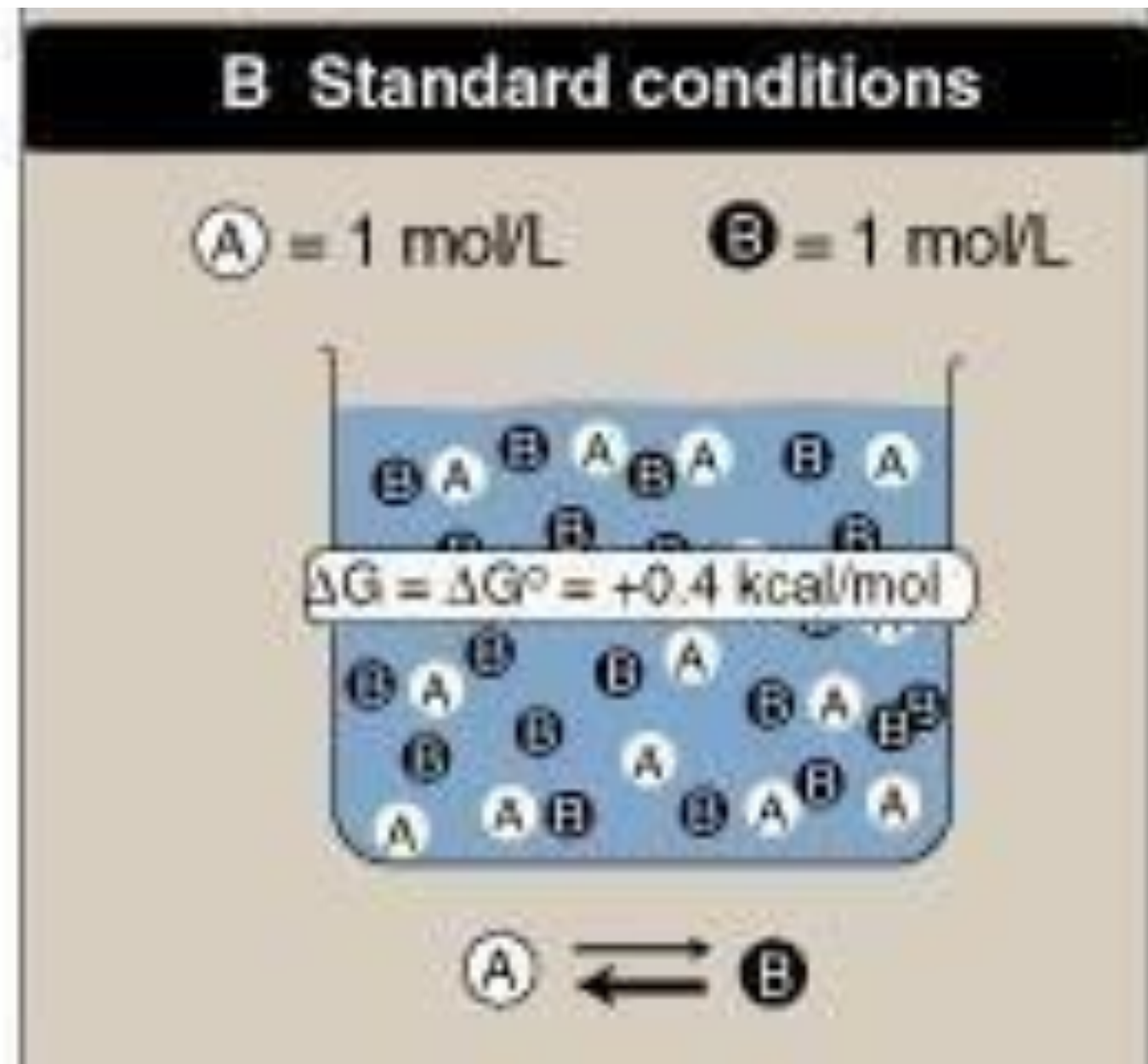
Since the ratio (0.09/0.9) is very small, the logarithm is negative, making ΔG negative. This means the reaction becomes spontaneous inside the cell, even though ΔG° is positive.



Glucose 6- phosphate
1 mol/L



Fructose 6- phosphate
1 mol/L



$$\Delta G = \Delta G^\circ + RT \, 2.3 \log 1/1$$

$$\Delta G = \Delta G^\circ$$

Under standard conditions: all substances are at 1 mol/L, so the log term equals zero.

Therefore, $\Delta G = \Delta G^\circ$, meaning the free energy change equals the standard free energy.

If the doctor say that we started the action with equal concentration of the reactants and the product and we were given the value of K_{eq} can we expect which direction is more favorable in this reaction?

We should all know that all the reactions are tending to reach the equilibrium. (so if we were given that the value of K_{eq} is 10 this indicates and it's low as the concentration of a product over the concentration of the reactants so as equilibrium, we will have thin folds of products to one fold of reactants, and we started with equal concentrations so it's absolutely shows that the forward direction is more favorable because the reaction is going toward the products so it can reach equilibrium)

And if the K_{eq} is this than one, it means that it is more favorable to go towards the reactants.

If it is one, it is already at the equilibrium.

Glycolysis is a 10 steps reaction that happens in our buddies in which we burn glucose. When we ate the glucose, it actually goes to our intestines then it gets absorbed and gets into the cell then it undergoes a glycolysis to give me pyruvate which gets dehydrogenated to give me CO_2 and acetylcholine then we go for Crips cycle, which gives us two CO_2 when we take the electrons and go to the electron transport chain then the four loaded oxygens are converted to water by the electrons.

When we burn woods which actually contains cellulose which is made of glucose (note that cellulose can't be there just by our buddies, but it can be digested by others so we don't get benefit when we actually eat it, but we get benefits when we burn it to get heat and a huge amount of energy) , we actually also burn glucose and this gives me a huge amount of energy as well as CO_2 and H_2O that evaporates by the heat.

What do we have to notice? the amount of energy does not change even if we change the steps of the reaction it only depends on the reactants and products. But we have multiple steps in our body so that we can harvest the energy in small amounts at different steps so that everybody does not explodes.

We only have to see the energy that are stored in the products and the energy that is stored in the reactants and subtract them from each other.

ΔG & K_{eq}

For a reaction $A + B \leftrightarrow C + D$

$$\Delta G = \Delta G^{\circ'} + RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

- At equilibrium, $\Delta G=0$
- Can a reaction has a +ve ΔG° & still be favorable?

K'_{eq}	$\Delta G^{\circ'}$ kJ/mol	Starting with 1 M reactants & products, the reaction:
10^4	- 23	proceeds forward (spontaneous)
10^2	- 11	proceeds forward (spontaneous)
$10^0 = 1$	0	is at equilibrium
10^{-2}	+ 11	reverses to form “reactants”
10^{-4}	+ 23	reverses to form “reactants”

$$\Delta G = \Delta G^{\circ'} + RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

$$0 = \Delta G^{\circ'} + RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

$$\Delta G^{\circ'} = - RT \ln \left(\frac{[C][D]}{[A][B]} \right)$$

$$\text{defining } K'_{eq} = \frac{[C][D]}{[A][B]}$$

$$\Delta G^{\circ'} = - RT \ln K'_{eq}$$

If $K_{eq} = 1$, it means that at equilibrium you have equal concentrations of reactants and products

If K_{eq} is more than one : you have more products than reactants but there is no favourability, because we are at equilibrium and at equilibrium ΔG is zero (theres no energy difference therefore no favourability)

For example: If K_{eq} is 1000, it means that at equilibrium we have 1000 folds of products compared to reactants.

when you reach K_{eq} of 1000 and more, the reaction is almost complete in one direction. If K_{eq} is 10^{-3} : This means we have 1000 folds of reactants compared to the product. (For each 1000 reactant molecules we have one product molecule)

When you reach K_{eq} of 10^{-3} and less the reaction is hardly going

ΔG° AND K_{eq}

When ΔG° is negative, $K_{eq} > 1 \rightarrow$ reaction is spontaneous (favors products).
When ΔG° is positive, $K_{eq} < 1 \rightarrow$ reaction is nonspontaneous (favors reactants).

K_{eq}	ΔG°
10^3	- 4.08
10^2	- 2.72
10^1	- 1.36
1	0
10^{-1}	1.36
10^{-2}	2.72
10^{-3}	4.08

How much change in delta G compared to changes in K_{eq}

If $K_{eq} = 1$, then $\Delta G^\circ = 0$

If $K_{eq} > 1$, then $\Delta G^\circ < 0$

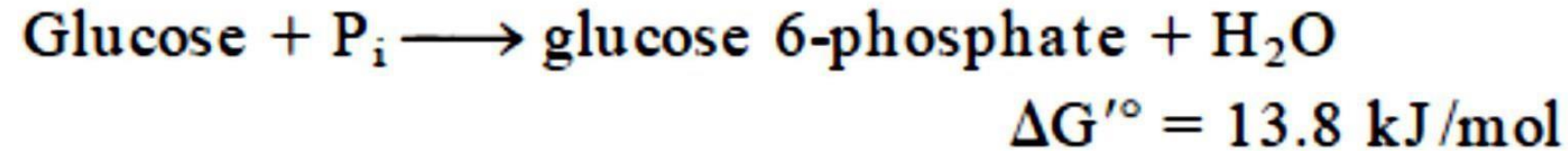
If $K_{eq} < 1$, then $\Delta G^\circ > 0$

$$\Delta G = \Delta G^\circ + RT \ln \frac{[\text{Products}]}{[\text{Reactants}]}$$

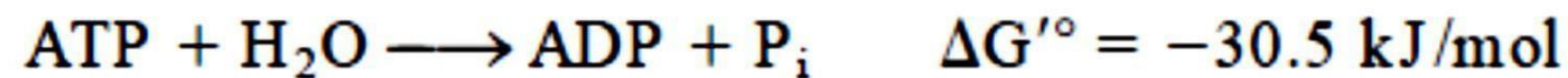
ΔG & K_{eq}

- ΔG is **additive** for multiple subsequent reactions
- K_{eq} is **multiplicative** for subsequent reactions

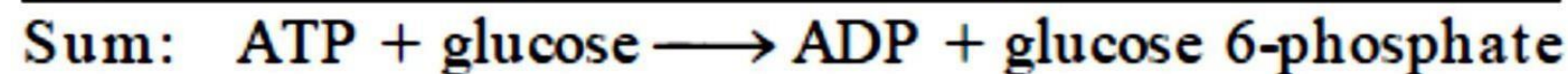
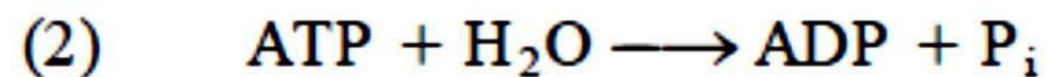
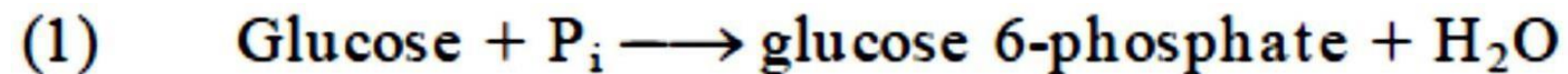
رَبَّنَا اغْفِرْ لِي
وَلِوَالِدَيَّ وَلِلْمُؤْمِنِينَ
يَوْمَ يَقُومُ الْحِسَابُ



$$K'_{eq_1} = \frac{[\text{glucose 6-phosphate}]}{[\text{glucose}][P_i]} = 3.9 \times 10^{-3} \text{ M}^{-1}$$



$$K'_{eq_2} = \frac{[\text{ADP}][P_i]}{[\text{ATP}]} = 2.0 \times 10^5 \text{ M}$$

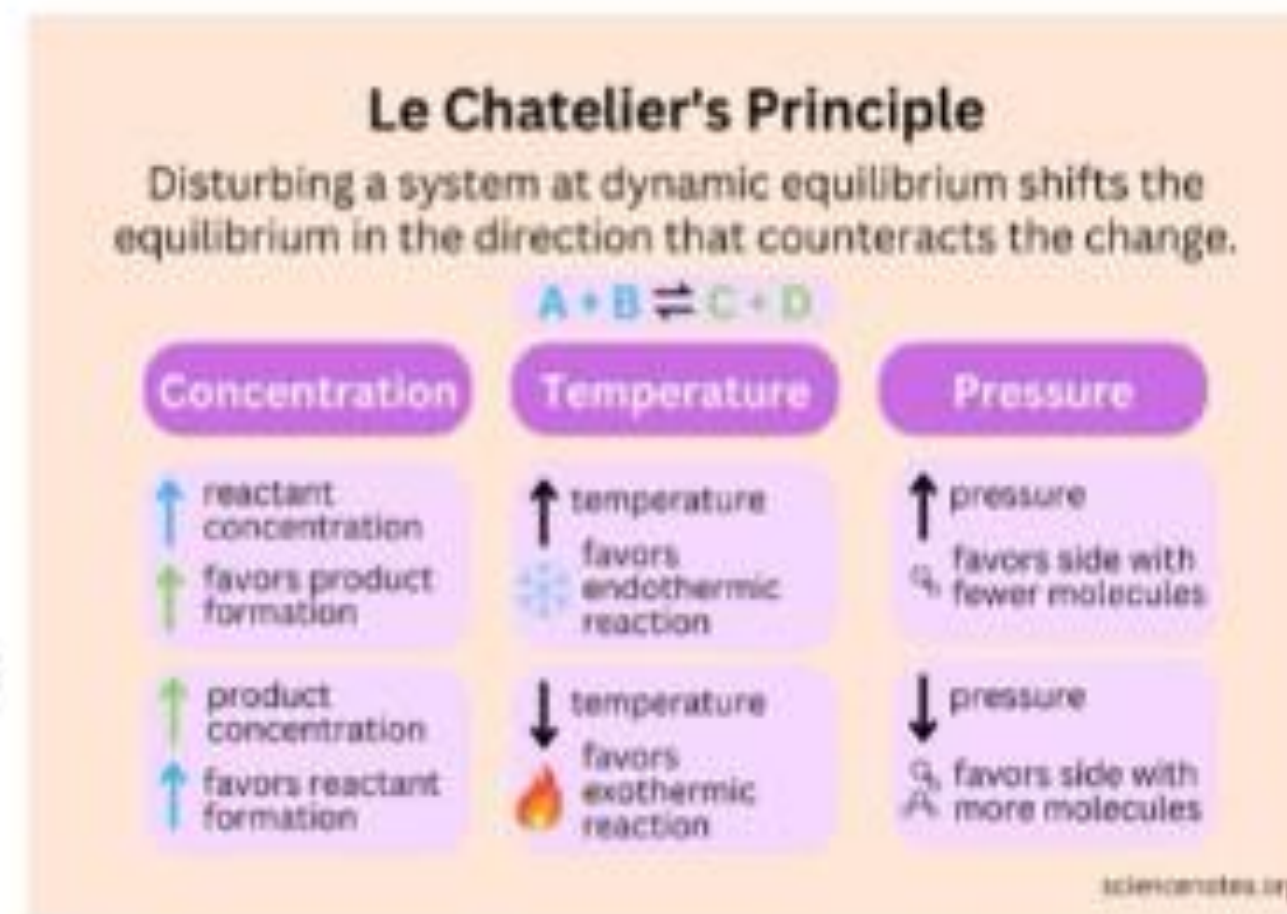


$$\Delta G'^{\circ} = 13.8 \text{ kJ/mol} + (-30.5 \text{ kJ/mol}) = -16.7 \text{ kJ/mol}$$

$$K'_{eq_3} = \frac{[\text{glucose 6-phosphate}][\text{ADP}][P_i]}{[\text{glucose}][P_i][\text{ATP}]}$$
$$= (K'_{eq_1})(K'_{eq_2}) = (3.9 \times 10^{-3} \text{ M}^{-1})(2.0 \times 10^5 \text{ M})$$
$$= 7.8 \times 10^2$$

THE EFFECT OF CHANGING CONDITIONS ON EQUILIBRIA

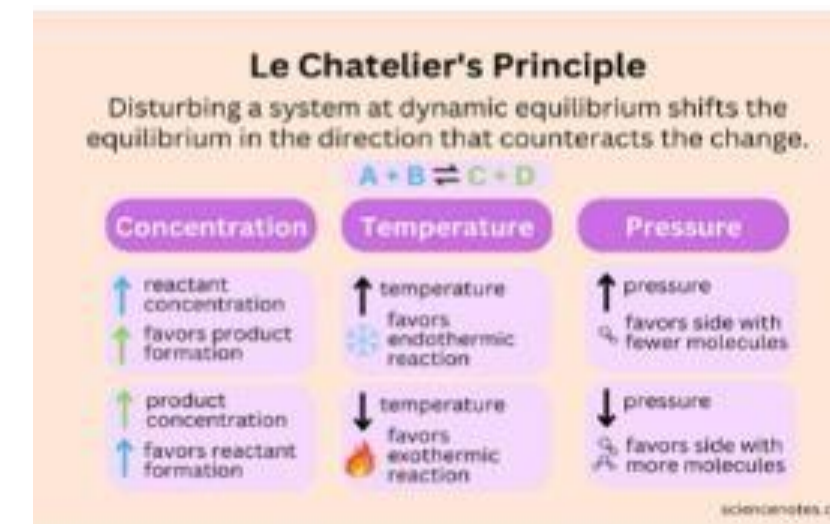
- When a stress is applied to a system at equilibrium, the equilibrium shifts to relieve the stress
- Effect of Changes in Concentration
 - What happens if a reactant/product is continuously supplied/ removed?
 - Metabolic reactions sometimes take advantage of this effect
- Effect of Changes in Temperature
 - Endothermic/exothermic are favored by increase/decrease in temperature, respectively.
- Effect of a catalyst on equilibrium



Le Chatelier's Principle: When a system at equilibrium is disturbed (by changing concentration, temperature, or pressure), it shifts in a direction that counteracts the disturbance to restore equilibrium.

Effect of a Catalyst:

An enzyme doesn't effect the energy content of either reactants or products, It helps reach equilibrium faster but does not change the equilibrium position or ΔG



Effect of Temperature

The direction of the shift depends on whether the reaction is endothermic or exothermic.

Endothermic reaction:

↑ Temperature → equilibrium shifts toward products because increasing temperature adds heat, which the reaction absorbs.

Exothermic reaction:

↑ Temperature → equilibrium shifts toward reactants because increasing temperature adds heat, which the reverse reaction absorbs.

We treat temperature as a reactant or product, for example : $\text{Heat} + \text{N}_2\text{O}_4 \rightleftharpoons 2\text{NO}$

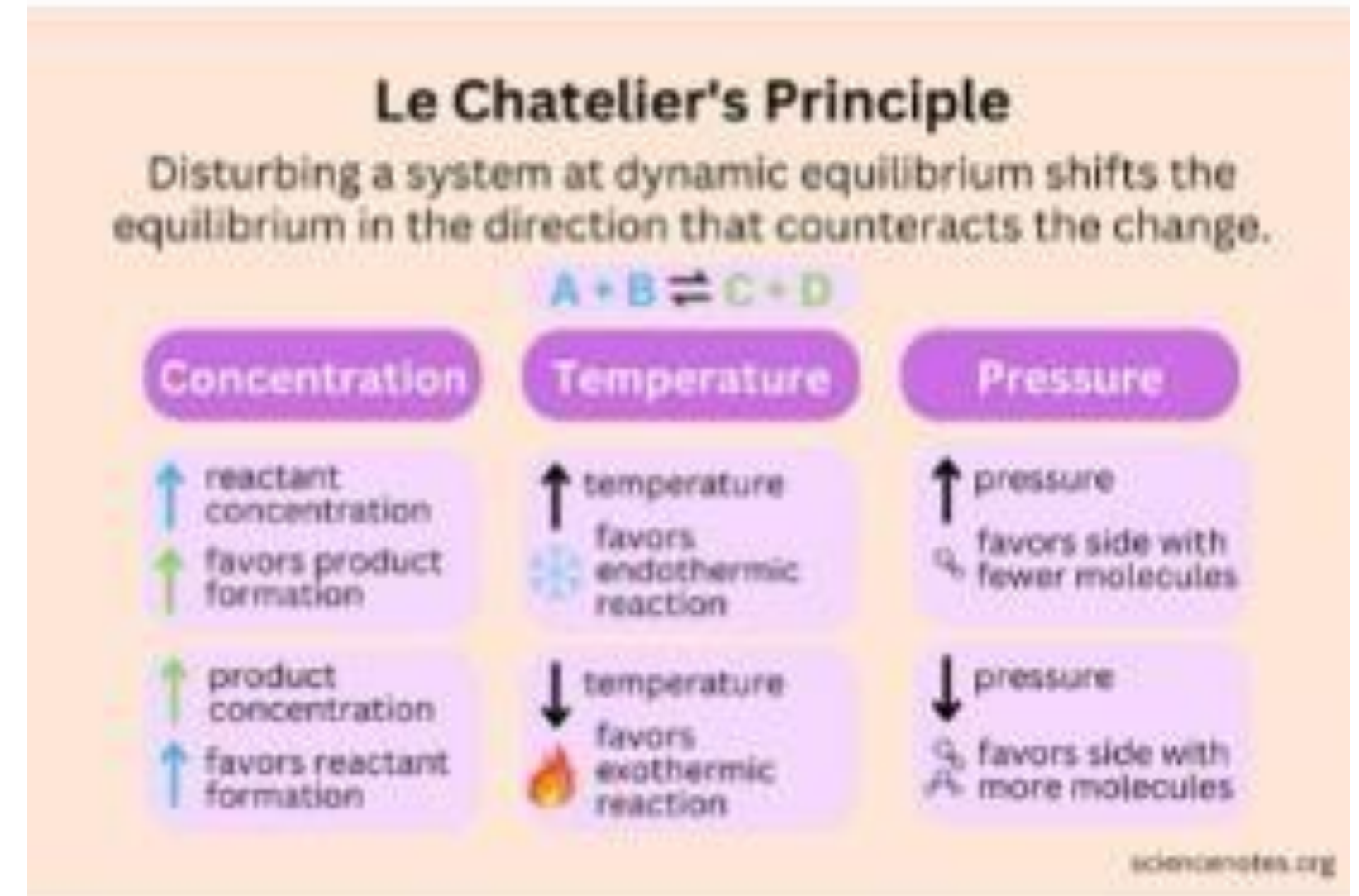
When heat increases it will drive the forward reaction in the endothermic perspective and the backward reaction from the exothermic perspective



Effect of Concentration

If the concentration of a reactant increases, the equilibrium shifts to the right (toward products) to use up the extra reactant.

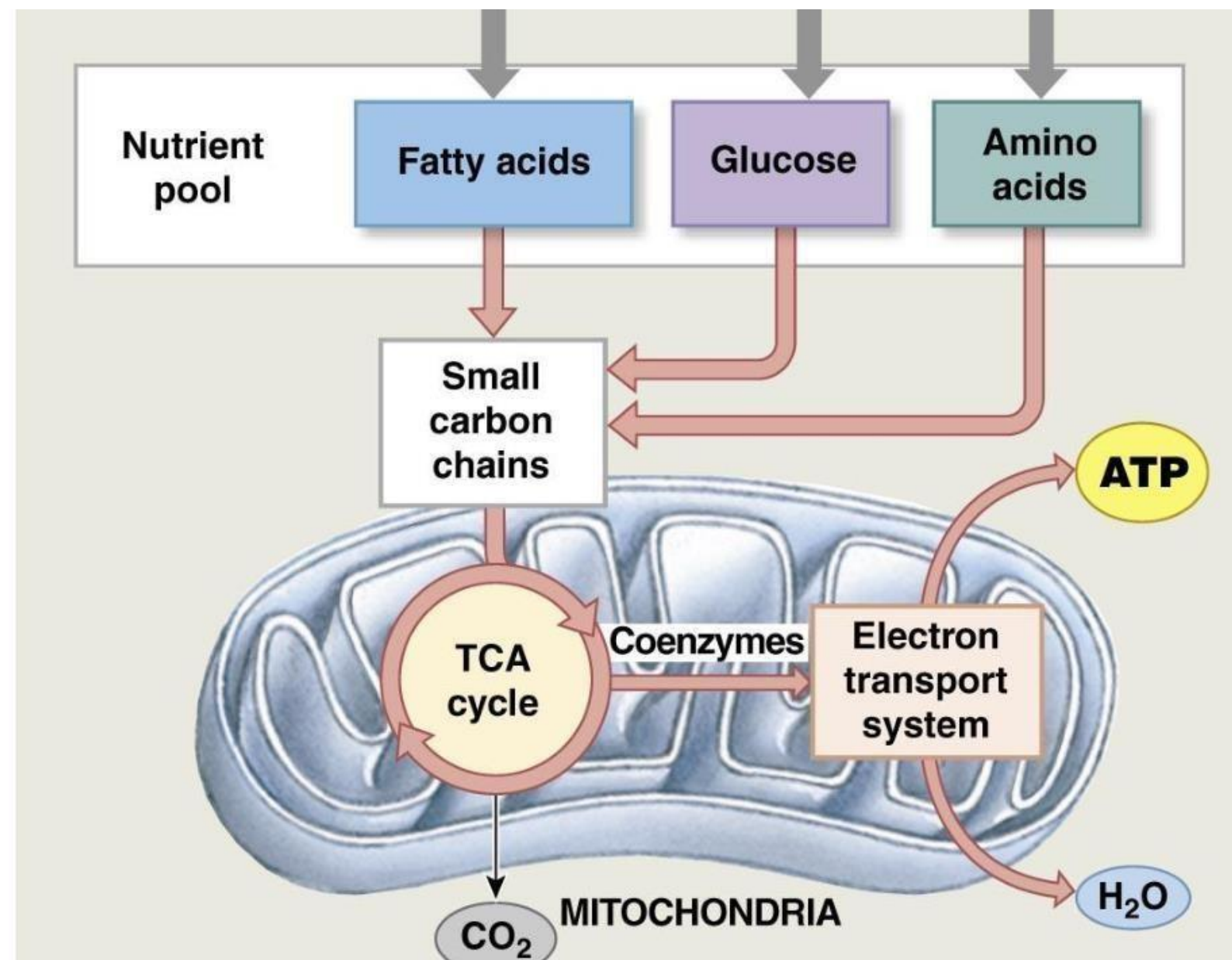
If the concentration of a product increases, the equilibrium shifts to the left (toward reactants) to reduce the product amount.



Principles of bioenergetics

2-Phosphoryl Group Transfers and ATP

THE ENERGY FLOW



- Ingestion, digestion, & absorption
- Metabolism (Acetyl CoA)
- TCA
- Oxidative phosphorylation

Energy flow stages

Slides 29 and 30 were made by 2024 students 

- First stage : ingestion ,digestion of food in GI tract , then absorption, molecules reach to the blood stream. Finally, it will be delivered to the cells .
- Second stage is (metabolism) the process through which the molecules from food are transformed inside the body to produce and use energy .
- and in this semester we are going to study the metabolism pathway, of carbs ,lipids , amino acids , nucleic acid .
- Acetyl CoA is a common shared molecule between more macromolecules that we are dealing with.

- Overview: How nutrients become Acetyl-CoA
- 1. Carbohydrates → Glucose → Pyruvate → Acetyl-CoA
- 2. Amino Acids → deamination → carbon skeleton → pyruvate Acetyl-CoA
- The acetyl CoA is the intermediate that enters (Krebs cycle , citric acid cycle) which is the third stage of energy metabolism
- Oxidative Phosphorylation is the forth stage of energy metabolism .

- Most of the second stage third stage and fourth stage happen in mitochondria Which is the organelle responsible for producing energy for your cells approximately 90% of your need 10% is produced by glycolysis which is in the cytoplasm.
- Why does glycolysis occur outside the mitochondria ? because some cells don't have mitochondria.

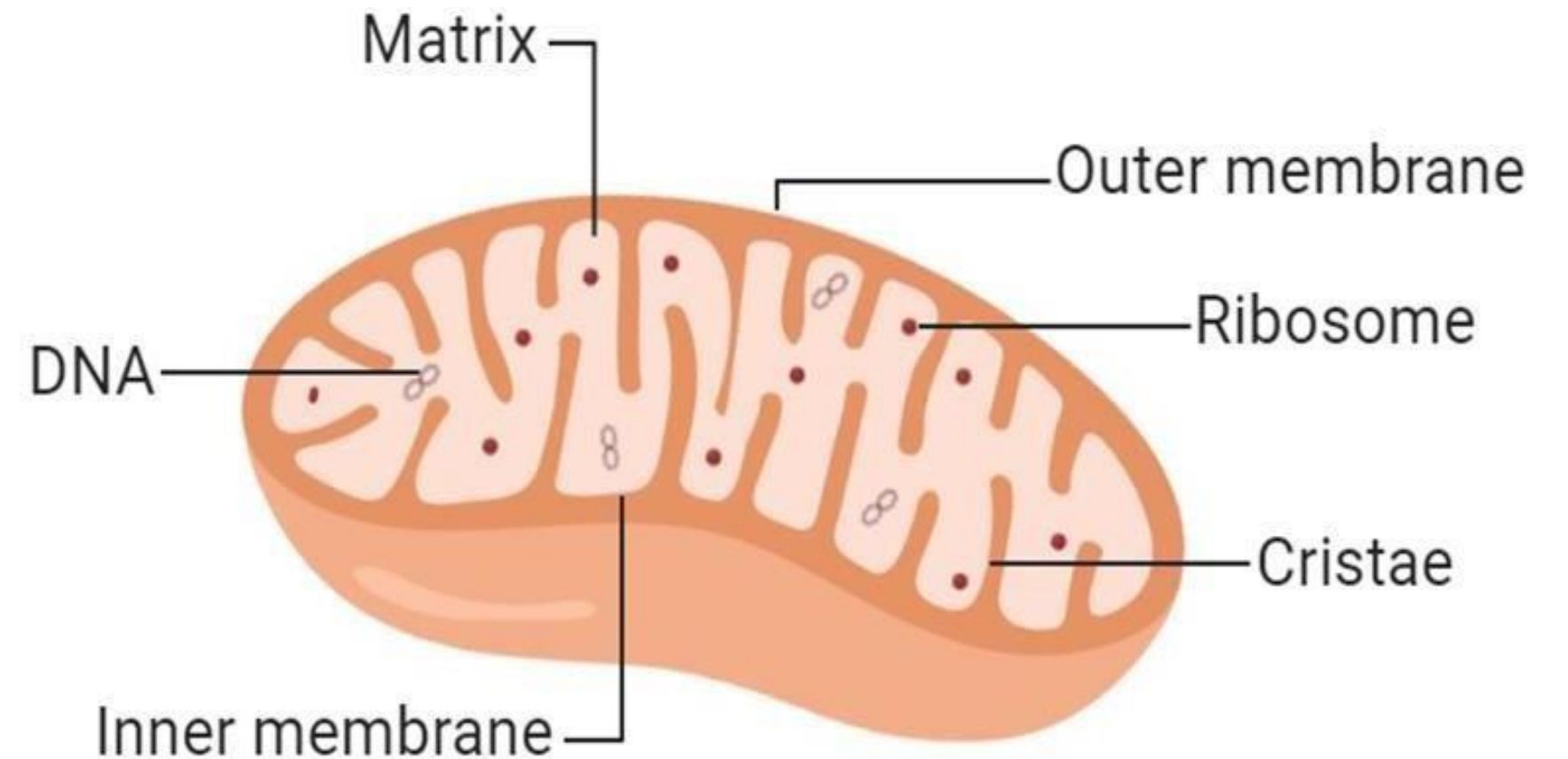
THE ENERGY MACHINERY OF THE CELL

- Prokaryotic cells vs. eukaryotic cells

The mitochondria (singular: mitochondrion) (90% body's energy ATP)

The energy harvesting process that takes place outside the mitochondria is glycolysis. It happens in the cytosol. It is important for cells that do not have mitochondria. (Like RBCs)

- The number of mitochondria is greatest in eye, brain, heart, & muscle, where the need for energy is greatest
- The ability of mitochondria to reproduce (athletes)
- Maternal inheritance



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
﴿إِنَّ اللَّهَ وَمَلَائِكَتَهُ يُصَلُّونَ عَلَى النَّبِيِّ يَا أَيُّهَا
الَّذِينَ آمَنُوا صَلُّوا عَلَيْهِ وَسَلِّمُوا تَسْلِيمًا﴾
اللَّهُمَّ صَلِّ وَسَلِّمْ وَبَارِكْ عَلَى نَبِيِّنَا مُحَمَّدٍ ﷺ

Evidences prove that mitochondria was bacteria :

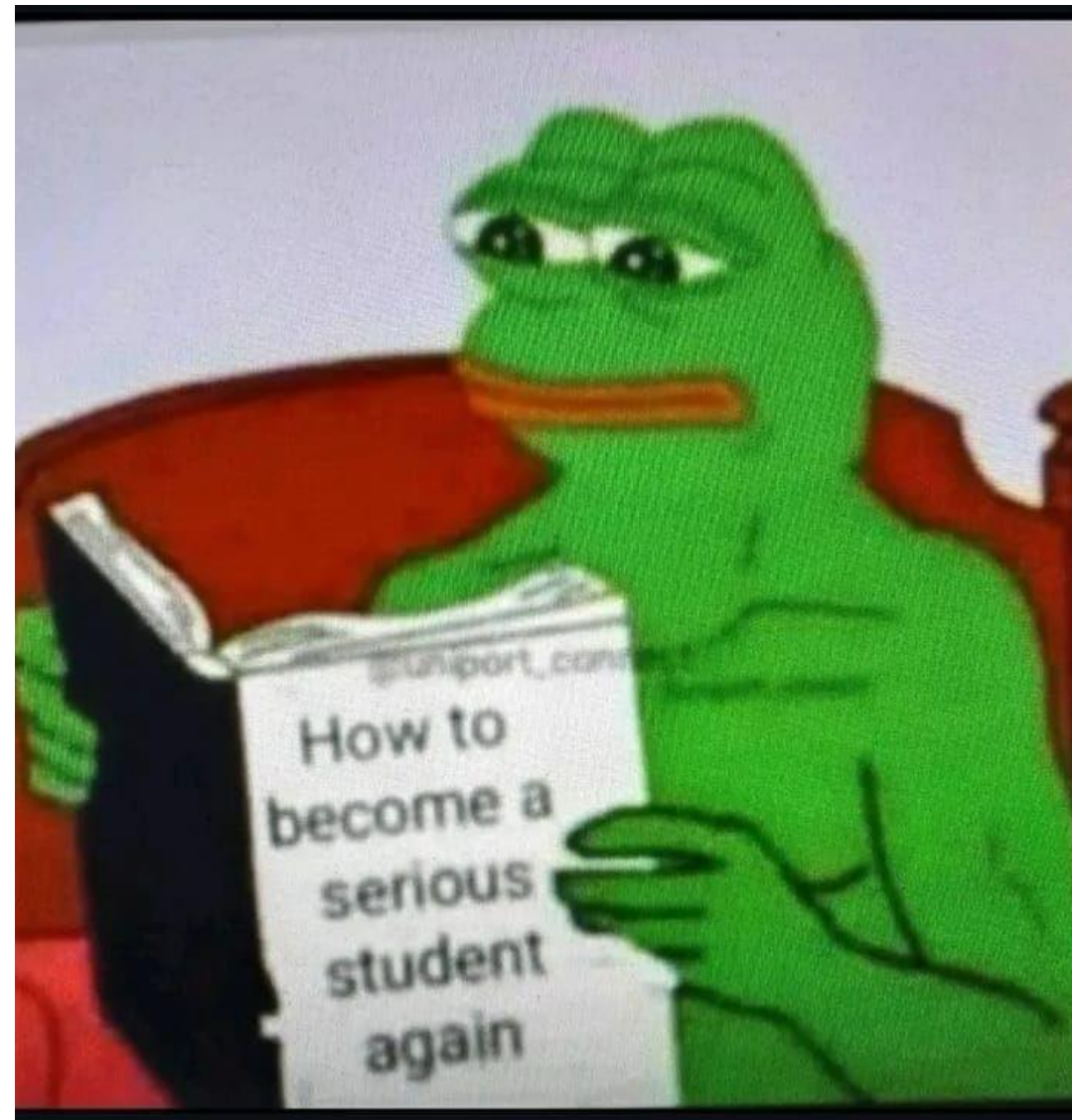
- It has its own DNA genetic material (circular as bacteria)
- It has double membrane:
 - **The outer one (mammalian membrane)** permeable to charged molecules dependent on their size (if they are 5kDalton or less they pass it)
 - **The inner one (mitochondrial membrane)** which is not permeable to any charged molecules even protons (the smallest charged molecule)
 - Achieved by :
 - Cardiolipins
 - The high density of proteins throughout the whole membrane
- It replicates/reproduces independently of the mother cells, but rather depending on the energy needs.
- It replicates by binary fission like bacteria (depending on energy needs, athletes have more mitochondria because of high energy needs which makes them having more tolerance because the muscles have a higher chance of undergoing aerobic respiration)



- When the mother cell replicates to give daughter cells the mitochondria will be distributed randomly. (There are no governors so a cell can have all mitochondria and the other has none)
- During embryonic development, mitochondria continuously divide and replicate their own DNA. A mutation may occur in mitochondrial DNA during this process. As embryonic cells divide and differentiate into different cell types, such as muscle cells and nerve cells, the mutation may be passed on to certain tissues but not others causing tissue-specific mitochondrial dysfunction
- When testing for a nuclear DNA mutation, almost any nucleated cell type, such as white blood cells, can be used. However, when testing for a mitochondrial DNA mutation, the choice of tissue is important because the proportion of mutated mitochondrial DNA can vary between tissues. Therefore, the tissue most likely to carry a detectable level of the mutation should be examined.
- This is called Heteroplasmy which is a feature of mitochondria only!

- Number of mitochondria per cell is 2000.
- Mutations can occur in:
 - 1. Nuclear DNA mutation: Nuclear DNA contains genes that encode most mitochondrial proteins (more than 1,000 proteins). If a mutation occurs in a nuclear gene encoding a protein that functions in the mitochondria, that protein may not work properly, causing mitochondrial disease.
 - Detection: A blood sample containing white blood cells (WBCs) can be used to analyze nuclear DNA.
 - 2. Mitochondrial DNA mutation: Mitochondrial DNA encodes 13 subunits that are synthesized within it, while it requires more than 1,000 types of proteins, which are encoded by nuclear DNA so The proteins of the mitochondria are synthesized from both mtDNA and nuclear DNA.
 - Detection: A biopsy of the affected tissue may be needed because the mutation might not be present at the same level in every tissue.
- The following will be discussed in the next modified!
- When an egg and sperm unite during fertilization, the egg provides almost all the cytoplasm and organelles, including mitochondria.
- The sperm's mitochondria are located in its tail, which usually does not enter the egg or is destroyed shortly after fertilization.
- Therefore, the embryo's mitochondria—and its mitochondrial DNA—come entirely from the mother's egg.
- So, if a mutation exists in the mother's mitochondrial DNA, all her children can inherit it, but only her daughters will pass it to the next generation.

Quiz



For any feedback, scan the code or click on it.



Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 34	Nuclear DNA produces proteins for mitochondria (13 subunits)	A paragraph was included and corrections regarding it were changed
V1 → V2			

Additional resources:

References Used:

لا يُهَمِّكَ كَثَافَةُ الْمَنْهَجِ وَضِيقُ الْوَقْتِ وَضُغُوطُ الْحَيَاةِ، أَنْسَيْتَ أَنَّ اللَّهَ خَلَقَ فِيكَ الصَّبْرَ وَالْقُوَّةَ وَالْإِرَادَةَ؟

Extra References for The Reader to Use:

لا تُضَيِّعْ جُهِدَكَ فِي التَّفَكِيرِ فِيمَا لَا يَدُ لَكَ فِيهِ
اغْرِسْ أَقْدَامَكَ فِي أَرْضِ الْعِلْمِ وَتَوَكَّلْ عَلَى رَبِّكَ
وَهُوَ حَسْبُكَ وَمُعِينُكَ.

رسالة من الفريق العلمي: