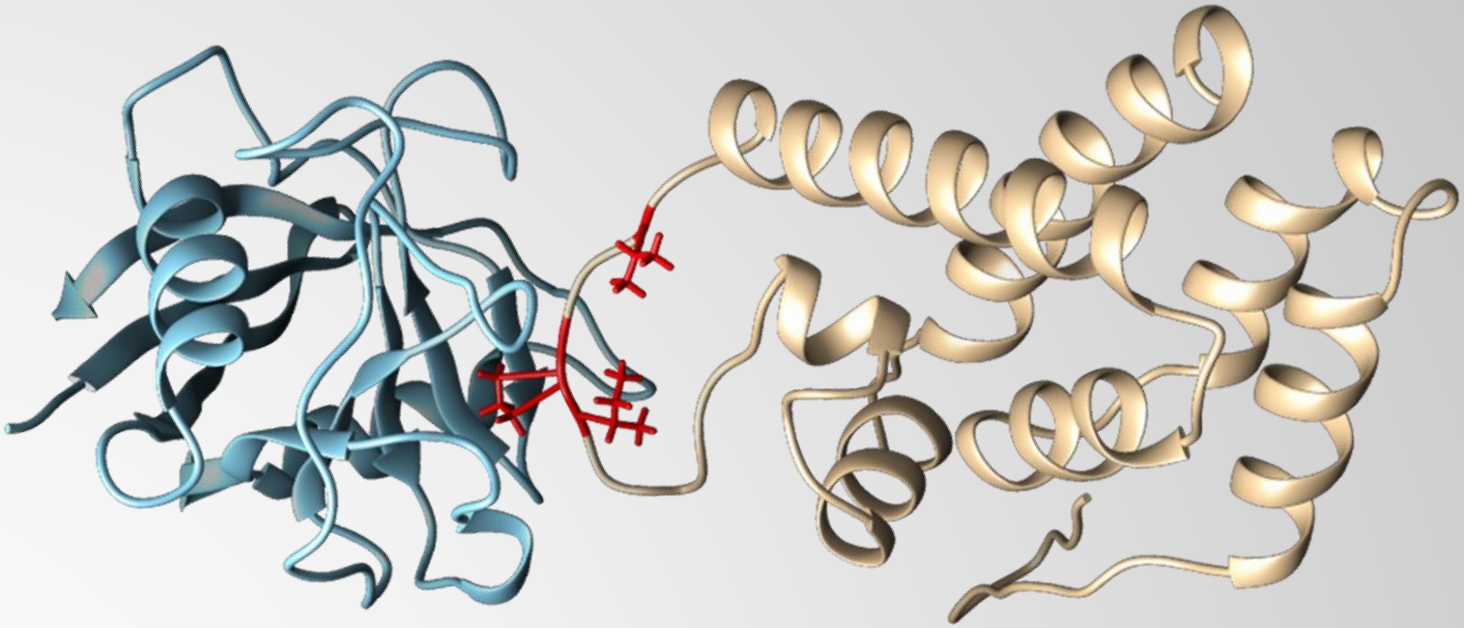
Seminar 8: exercises on protein binding and energetics



Biophysics

Course 2022-2023

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Exercises on protein-protein interactions

A reminder from last year chemistry...

$$aA + bB \rightleftharpoons cC + dD$$

The equilibrium constant

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

Exercises on protein-protein interactions

A reminder from last year chemistry...

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$$\downarrow$$

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

$$\Delta G = \Delta G^o + R \cdot T \cdot \ln(Q)$$

At equilibrium:

$$0 = \Delta G^o + R \cdot T \cdot \ln(K)$$

$$\downarrow$$

$$\Delta G^o = -R \cdot T \cdot \ln(K)$$

Exercises on protein-protein interactions

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Exercises on protein-protein interactions

The dissociation constant represents the concentration of protein and ligand at which 50% of the proteins are involved in a complex

$$A + B \longrightarrow AB$$

$$K_D = \frac{[A][B]}{[AB]}$$

[A][B] → Reactants

[AB] → Products

Exercises on protein-protein interactions

The dissociation constant represents the concentration of protein and ligand at which 50% of the proteins are involved in a complex

$$A + B \longrightarrow AB$$

Dissociation constant

$$K_D = \frac{[A][B]}{[AB]}$$

Reactants

Products

Equilibrium constant

$$K = \frac{[AB]^{ab}}{[A]^{a} \cdot [B]^{b}}$$

Products

Reactants

Exercises on protein-protein interactions

For PPIs, the equilibrium constant is the inverse of the dissociation constant, their logarithm has opposite sign

Equilibium constant

$$K = \frac{[AB]^{ab}}{[A]^{a} \cdot [B]^{b}}$$

Dissociation constant

$$K_D = \frac{[A][B]}{[AB]}$$

For interactions between proteins:

$$\ln(K) = \ln(K_D) \cdot (-1)$$

Exercises on protein-protein interactions

We can relate the equilibrium constant to the disociation constant from protein-protein interactions

$$\Delta G = -R \cdot T \cdot \ln(K)$$

$$\ln(K) = \ln(K_D) \cdot (-1)$$

$$\Delta G = R \cdot T \cdot \ln(K_D)$$

Exercises on protein-protein interactions

We can relate the equilibrium constant to the disociation constant from protein-protein interactions

$$\Delta G = -R \cdot T \cdot \ln(K)$$

$$\ln(K) = \ln(K_D) \cdot (-1)$$

$$\Delta G = R \cdot T \cdot \ln(K_D)$$

We can use this formula for mutations in protein-protein interactions

$$\Delta\Delta G = R \cdot T \cdot \ln(K_D^{mut}) - R \cdot T \cdot \ln(K_D^{wt})$$

Exercises on protein-protein interactions

Also, remember that the ΔG of a protein-protein interaction can be decomposed into different terms

$$\Delta G = \Delta G_{electrostatics} + \Delta G_{VanDerWaals} + \Delta G_{Solvation}$$

Exercises on protein-protein interactions

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$$\Delta G = \underbrace{\Delta G_{electrostatics} + \Delta G_{VanDerWaals}}_{\Delta G_{interaction}} + \Delta G_{Solvation}$$

Exercises on protein-protein interactions

Also, remember that the ΔG of a protein-protein inter...

be decomp...

Now try to solve exercise 1 from the protein-protein interactions section

Exercises on protein-protein interactions

In protein-protein or in protein-drug interactions we usually distinguish between receptor (R) and ligand (L)

Protein-protein interactions:

Receptor $\longrightarrow$ Bigger protein

Ligand $\longrightarrow$ Smaller protein

Protein-drug interactions:

Receptor $\longrightarrow$ Protein

Ligand $\longrightarrow$ Drug

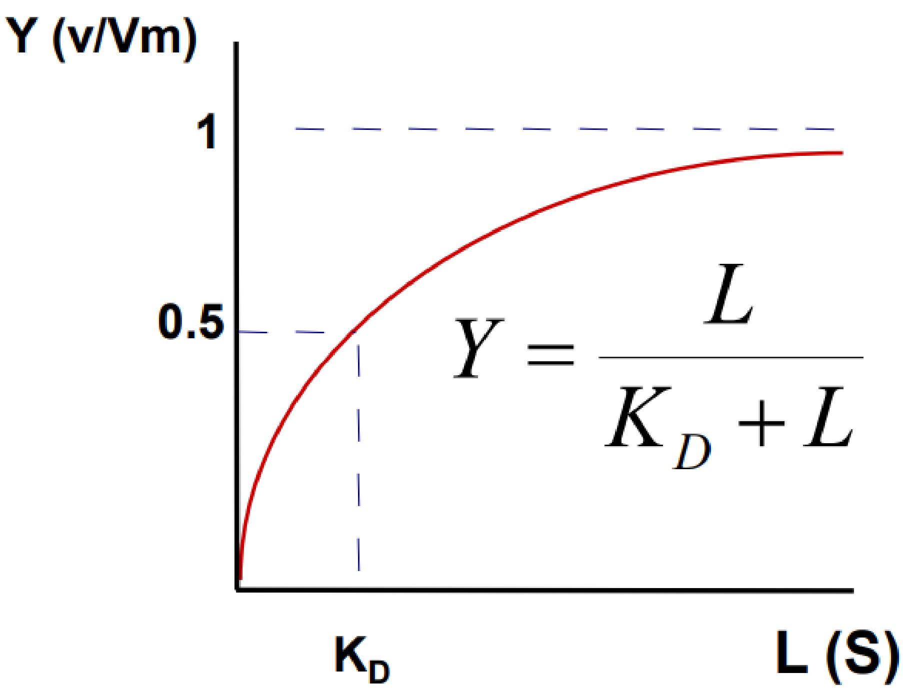
We no longer use A and B to represent the binding process, now we use:

$$R + L \longrightarrow RL$$

Exercises on protein-protein interactions

The saturation degree (Y) measures the percentage of receptor molecules that are involved in the interaction with a ligand

We can calculate the saturation degree from the value of the K_D and the concentration of ligand (L)



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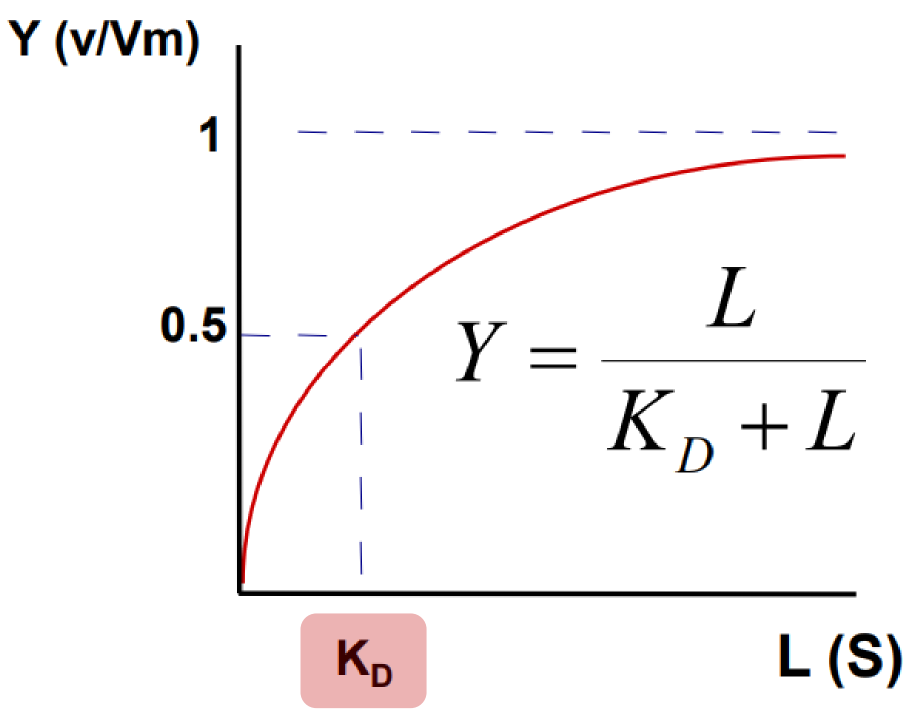


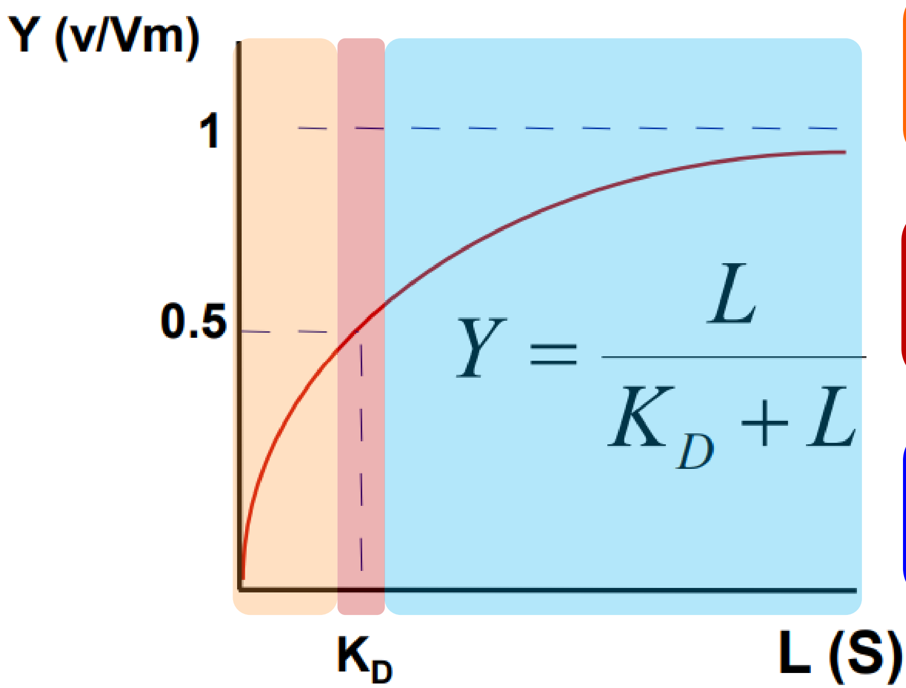
$$Y = \frac{L}{K_D + L}$$

K_D equals the concentration of ligand at which the saturation degree (Y) is 0.5

Exercises on protein-protein interactions

The saturation degree (Y) measures the percentage of receptor molecules that are involved in the interaction with a ligand

We can calculate the saturation degree from the value of the K_D and the concentration of ligand (L)

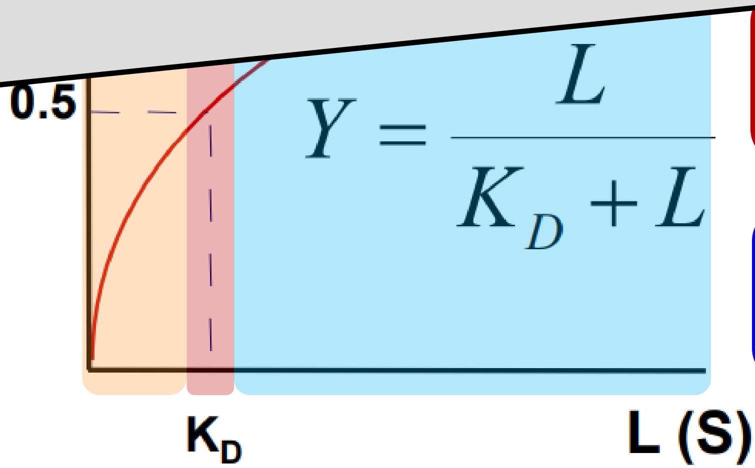


When L < K_D ; Y < 0.5

When L = K_D ; Y = 0.5

When L > K_D ; Y > 0.5

If we introduce mutations in this system what will change? The K_D or L?

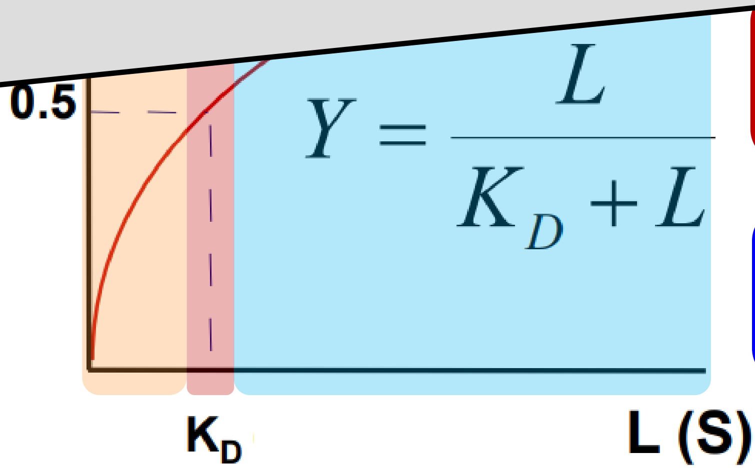


$$Y = \frac{L}{K_D + L}$$

When L = K_D ; Y = 0.5

When L > K_D ; Y > 0.5

With that in mind, try to solve exercise 2 from the protein-protein interactions section



$$Y = \frac{L}{K_D + L}$$

When L = K_D ; Y = 0.5

When L > K_D ; Y > 0.5

Exercises on protein-drug interactions

The inhibition constant (K_i) indicates the affinity between a protein (R) and a drug (L)

It is calculated exactly as the dissociation constant (K_D), the only difference is that it is used to describe protein-drug interactions.

$$R + L \longrightarrow RL$$

$$K_i = \frac{[R][L]}{[RL]}$$

When 50% of the protein is binding the ligand

Exercises on protein-drug interactions

The inhibition constant (K_i) indicates the affinity between a protein (R) and a drug (L)

Imagine that we keep the concentration of protein constant and we measure the K_i of two drugs, estimate the affinity of the drugs for

The drug with higher K_i

The drug with lower K_i

Exercises on protein-drug interactions

The inhibition constant (K_i) indicates the affinity between a protein (R) and a drug (L)

Imagine that we keep the concentration of protein constant and we measure the K_i of two drugs, estimate the affinity of the drugs for

The drug with higher K_i

The drug with lower K_i

Tip: since the concentration of protein is constant, the K_i is going to be proportional to the concentration of drug.

Exercises on protein-drug interactions

The inhibition constant (K_i) indicates the affinity between a protein (R) and a drug (L)

Imagine that we keep the concentration of protein constant and we measure the K_i of two drugs, estimate the affinity of the drugs for

The drug with higher K_i

Lower affinity

You need a higher amount of drug to achieve the 50% of binding

The drug with lower K_i

Higher affinity

You need a lower amount of drug to achieve the 50% of binding

Exercises on protein-drug interactions

The inhibit...

With that in mind, try to solve exercise 1 from the protein-drug interactions section

...drug to achieve the 50% of binding

You need a lower amount of drug to achieve the 50% of binding