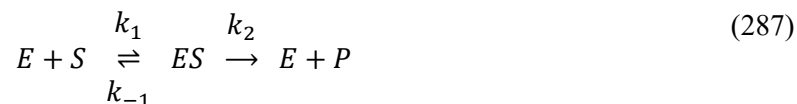## ❖ Competitive and Non-Competitive Inhibition

An enzyme inhibitor is a compound that binds to an enzyme and decreases its overall activity, and the phenomenon is typically known as "enzyme inhibition". Two of the most common enzyme inhibition processes will be discussed in this section.

➤ *Competitive Inhibition*

In the case of competitive enzyme inhibition, the binding of an inhibitor prevents the binding of the substrate and the enzyme. This type of behavior is actually achieved by blocking the binding site of the target molecule (the active site) by some means. The competitive enzyme inhibition can be classified into two types as discussed below.

1. Fully competitive inhibition: The fully competitive inhibition occurs when an enzyme (E) binds with the substrate (S) and inhibitor (I) separately, and it is only the enzyme-substrate complex (ES) that will convert into the product. This whole process can be described mathematically as

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\longrightarrow} E + P \tag{287}$$

$$E + I \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} EI \tag{288}$$

After applying the steady-state approximation on ES, we have

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0 \tag{289}$$

$$k_1[E][S] = k_{-1}[ES] + k_2[ES] \tag{290}$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2} \tag{291}$$

When $[S_0] \gg [E_0]$, we can assume $[S_0] \approx [S]$, and also

$$[E_0] = [E] + [ES] + [EI] \tag{292}$$

$$[E] = [E_0] - [ES] - [EI] \tag{293}$$

Now recalling the equilibrium constant for inhibition equilibria i.e.

$$K_3 = \frac{k_3}{k_{-3}} = \frac{[EI]}{[E][I]} \tag{294}$$

$$K_I = \frac{1}{K_3} = \frac{[E][I]}{[EI]} \tag{295}$$

Hence, we can say

$$[EI] = \frac{[E][I]}{K_I} \tag{296}$$

After using the value of $[EI]$ from equation (296) into equation (293), we have

$$[E] = [E_0] - [ES] - \frac{[E][I]}{K_I} \tag{297}$$

$$[E] = \frac{K_I[E_0] - K_I[ES] - [E][I]}{K_I} \tag{298}$$

$$K_I[E] = K_I[E_0] - K_I[ES] - [E][I] \tag{299}$$

$$K_I[E] + [E][I] = K_I[E_0] - K_I[ES] \tag{300}$$

$$[E] = \frac{K_I[E_0] - K_I[ES]}{K_I + [I]} \tag{301}$$

Using the above-derived result in equation (291), we have

$$[ES] = \frac{k_1[S]}{k_{-1} + k_2} \frac{K_I[E_0] - K_I[ES]}{K_I + [I]} = \frac{[S]}{K_m} \frac{K_I[E_0] - K_I[ES]}{K_I + [I]} \tag{302}$$

$$[ES] = \frac{K_I[E_0][S] - K_I[ES][S]}{K_m K_I + K_m[I]} \tag{303}$$

Now rearranging further for $[ES]$, we get

$$K_m K_I[ES] + K_m[I][ES] = K_I[E_0][S] - K_I[ES][S] \tag{304}$$

$$K_m K_I[ES] + K_m[I][ES] + K_I[ES][S] = K_I[E_0][S] \tag{305}$$

$$[ES] = \frac{K_I[E_0][S]}{K_m K_I + K_m[I] + K_I[S]} \tag{306}$$

Since the rate of formation of product is

$$r_0 = k_2[ES] \tag{307}$$

Using the value of $[ES]$ from equation (306) in equation (307), we get

$$r_0 = \frac{k_2 K_I[E_0][S]}{K_m K_I + K_m[I] + K_I[S]} \tag{308}$$

Since $k_2[E_0]$ is r_{max}, the equation (308) takes the form

$$r_0 = \frac{r_{max} K_{\mathrm{I}}[S]}{K_m K_{\mathrm{I}} + K_m[I] + K_{\mathrm{I}}[S]} \tag{309}$$

Taking the reciprocal to get Lineweaver-Burk plot

$$\frac{1}{r_0} = \frac{K_m K_{\mathrm{I}} + K_m[I] + K_{\mathrm{I}}[S]}{r_{max} K_{\mathrm{I}}[S]} \tag{310}$$

$$\frac{1}{r_0} = \frac{K_m K_{\mathrm{I}}}{r_{max} K_{\mathrm{I}}[S]} + \frac{K_m[I]}{r_{max} K_{\mathrm{I}}[S]} + \frac{K_{\mathrm{I}}[S]}{r_{max} K_{\mathrm{I}}[S]} \tag{311}$$

$$\frac{1}{r_0} = \left(\frac{K_m}{r_{max}} + \frac{K_m[I]}{r_{max} K_{\mathrm{I}}} \right) \frac{1}{[S]} + \frac{1}{r_{max}} \tag{312}$$

Rearranging further and using initial substrate concentration, we get

$$\frac{1}{r_0} = \frac{K_m}{r_{max}} \left(1 + \frac{[I]}{K_{\mathrm{I}}} \right) \frac{1}{[S_0]} + \frac{1}{r_{max}} \tag{313}$$

After comparing with equation without enzyme inhibition i.e.

$$\frac{1}{r_0} = \frac{K_m}{r_{max}} \frac{1}{[S_0]} + \frac{1}{r_{max}} \tag{314}$$

it is clear that the intercepts in both the equations are the same whereas the slope has been increased from K_m/r_{max} to $(K_m/r_{max})(1 + [I]/K_{\mathrm{I}})$. This implies that enzyme inhibition changed the K_m to $K_m(1 + [I]/K_{\mathrm{I}})$.
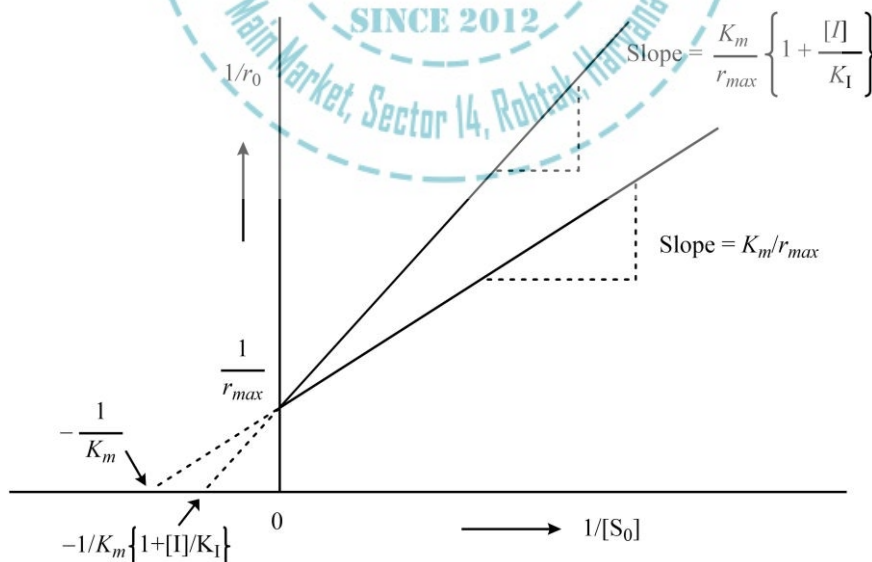
Figure 5. Lineweaver-Burk plot for enzyme-catalyzed reaction with fully competitive enzyme inhibition.

2. Partially competitive inhibition: The partially competitive inhibition occurs when the enzyme (E) binds with the substrate (S) and inhibitor (I) simultaneously, and complex ES and EI also combine with I and S to give EIS. Also, besides the enzyme-substrate complex (ES), the complex EIS will also convert into the product with the same rate of reaction. This whole process can be described mathematically as

$$E + S \overset{K_1'}{\underset{}{\rightleftharpoons}} ES \overset{k_2}{\longrightarrow} E + P \qquad (315)$$

$$E + I \overset{K_2'}{\underset{}{\rightleftharpoons}} EI \qquad (316)$$

$$EI + S \overset{K_3'}{\underset{}{\rightleftharpoons}} EIS \qquad (317)$$

$$ES + I \overset{K_4'}{\underset{}{\rightleftharpoons}} EIS \qquad (318)$$

$$EIS \overset{k_2}{\longrightarrow} EI + P \qquad (319)$$

According to classical Michaelis-Menten equation $K_m = (k_2 + k_{-1})/k_1$; however, if $k_2 \ll k_{-1}$, we have $K_m = k_{-1}/k_1$ or $K_m = 1/K_1'$. Now, set the following results

$$K_m = \frac{1}{K_1'} = \frac{[E][S]}{[ES]} \qquad (320)$$

$$K_2 = \frac{1}{K_2'} = \frac{[E][I]}{[EI]} \qquad (321)$$

$$K_3 = \frac{1}{K_3'} = \frac{[EI][S]}{[EIS]} \qquad (322)$$

$$K_4 = \frac{1}{K_4'} = \frac{[ES][I]}{[EIS]} \qquad (323)$$

Following enzyme conservation, we have

$$[E_0] = [E] + [ES] + [EI] + [EIS] \qquad (324)$$

Using values of $[ES]$, $[EI]$ and $[EIS]$ from equation (320-322) into equation (324), we get

$$[E_0] = [E] + \frac{[E][S]}{K_m} + \frac{[E][I]}{K_2} + \frac{[E][I][S]}{K_2 K_3} \qquad (325)$$

$$[E] = \frac{K_m[E_0]}{K_m(1 + [I]/K_2) + [S](1 + K_m[I]/K_2 K_3)} \qquad (326)$$

The overall reaction rate of product formations should be

$$r_0 = k_2[ES] + k_2[EIS] \tag{327}$$

After using values of $[ES]$ and $[EIS]$ from equation (320, 322) into equation (327), we get

$$r_0 = k_2\frac{[E][S]}{K_m} + k_2\frac{[E][I][S]}{K_2K_3} \tag{328}$$

Substituting the value of $[E]$ from equation (326) in (328), and rearranging at initial substrate concentration

$$r_0 = \frac{k_2[E_0][S_0]}{\{K_m(1 + [I]/K_2)/(1 + K_m[I]/K_2K_3)\} + [S_0]} \tag{329}$$

Since $k_2[E_0]$ is r_{max}, equation (329) takes the following form after the reciprocal to get Lineweaver-Burk plot

$$\frac{1}{r_0} = \frac{\{K_m(1 + [I]/K_2)/(1 + K_m[I]/K_2K_3)\}}{r_{max}}\frac{1}{[S_0]} + \frac{1}{r_{max}} \tag{330}$$

After comparing with equation without enzyme inhibition i.e.

$$\frac{1}{r_0} = \frac{K_m}{r_{max}}\frac{1}{[S_0]} + \frac{1}{r_{max}} \tag{331}$$

it is clear that intercepts in both the equations are the same whereas the slope has been varied from K_m/r_{max} to $\{K_m(1 + [I]/K_2)/(1 + K_m[I]/K_2K_3)\}/r_{max}$. This implies that enzyme inhibition changed the K_m to $\{K_m(1 + [I]/K_2)/(1 + K_m[I]/K_2K_3)\}$.
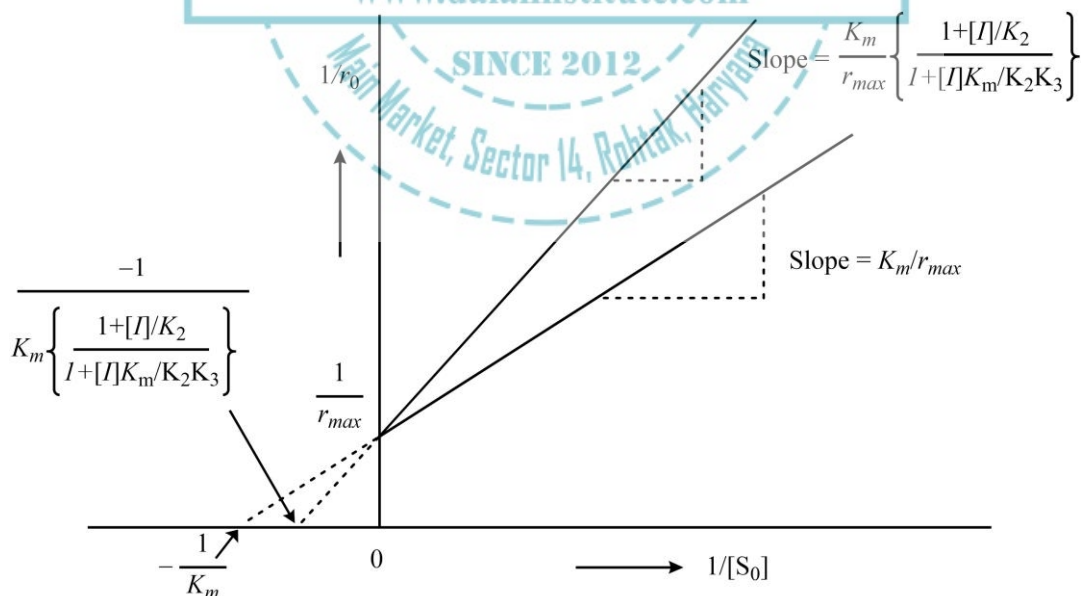
Figure 6. The Lineweaver-Burk plot for partially competitive enzyme inhibition.

➢ *Non-Competitive Inhibition*

Non-competitive inhibition may simply be defined as the enzyme inhibition where the inhibitor decreases the activity of the enzyme catalysis and binds equally well to the enzyme whether or not it has already bound the substrate. The non-competitive enzyme inhibition can be classified into two types as discussed below.

1. Fully non-competitive inhibition: The fully non-competitive inhibition occurs when an enzyme (E) binds with inhibitor (I), and complex ES and EI also combine with I and S to give EIS. However, it is only the enzyme-substrate complex (ES) that converts into the product. This whole process can be described mathematically as

$$E + S \;\; \underset{}{\overset{K_1'}{\rightleftharpoons}} \;\; ES \;\; \overset{k_2}{\longrightarrow} \;\; E + P \tag{332}$$

$$E + I \;\; \overset{K_2'}{\rightleftharpoons} \;\; EI \tag{333}$$

$$EI + S \;\; \overset{K_1'}{\rightleftharpoons} \;\; EIS \tag{334}$$

$$ES + I \;\; \overset{K_2'}{\rightleftharpoons} \;\; EIS \tag{335}$$

According to classical Michaelis-Menten equation $K_m = (k_2 + k_{-1})/k_1$; however, if $k_2 \ll k_{-1}$, we have $K_m = k_{-1}/k_1$ or $K_m = 1/K_1'$. Now, set the following results

$$K_m = \frac{1}{K_1'} = \frac{[E][S]}{[ES]} = \frac{[E][S]}{[EIS]} \tag{336}$$

$$K_I = \frac{1}{K_2'} = \frac{[E][I]}{[EI]} = \frac{[ES][I]}{[EIS]} \tag{337}$$

Following enzyme conservation, we have

$$[E_0] = [E] + [ES] + [EI] + [EIS] \tag{338}$$

$$[E] = [E_0] - [ES] - [EI] - [EIS] \tag{339}$$

Using values of $[ES]$, $[EI]$ and $[EIS]$ from equation (336-337) into equation (338), we get

$$[E_0] = [E] + \frac{[E][S]}{K_m} + \frac{[E][I]}{K_I} + \frac{[E][I][S]}{K_m K_I} \tag{340}$$

$$[E] = \frac{[E_0]}{(1 + [S]/K_m)(1 + [I]/K_I)} \tag{341}$$

The overall reaction rate of product formations should be

$$r_0 = k_2[ES] \tag{342}$$

After using values of $[ES]$ from equation (336) into equation (342), we get

$$r_0 = k_2 \frac{[E][S]}{K_m} \tag{343}$$

Substituting the value of $[E]$ from equation (341) in (343), and rearranging at initial substrate concentration

$$r_0 = \frac{k_2[E_0][S_0]}{(K_m + [S_0])(1 + [I]/K_I)} \tag{344}$$

Since $k_2[E_0]$ is r_{max}, the equation (344) takes the form

$$r_0 = \frac{r_{max}[S_0]}{(K_m + [S_0])(1 + [I]/K_I)} \tag{345}$$

Taking the reciprocal to get Lineweaver-Burk plot

$$\frac{1}{r_0} = \frac{K_m}{r_{max}}\left(1 + \frac{[I]}{K_I}\right)\frac{1}{[S_0]} + \frac{1}{r_{max}}\left(1 + \frac{[I]}{K_I}\right) \tag{346}$$

After comparing with equation without enzyme inhibition i.e.

$$\frac{1}{r_0} = \frac{K_m}{r_{max}}\frac{1}{[S_0]} + \frac{1}{r_{max}} \tag{347}$$

it can be clearly seen that intercept is increased from $1/r_{max}$ to $(1/r_{max})(1 + [I]/K_I)$ whereas the K_m has remained the same.
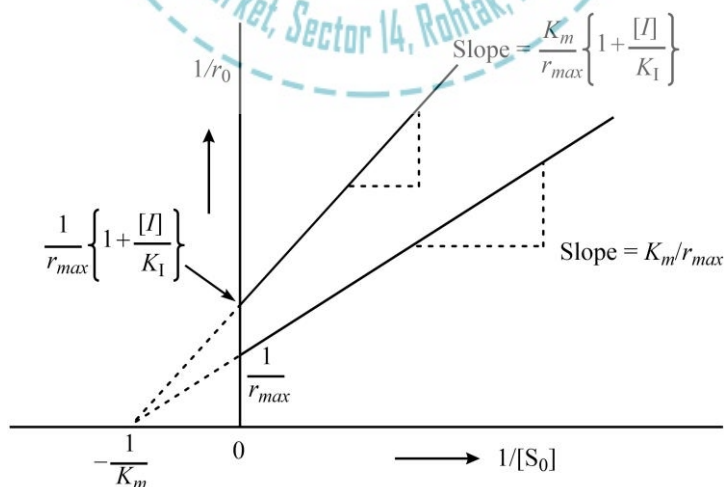
Figure 7. The Lineweaver-Burk plot for fully non-competitive enzyme inhibition.

2. Partially non-competitive inhibition: The partially non-competitive inhibition occurs when an enzyme (E) binds with inhibitor (I), and complex ES and EI also combine with I and S to give EIS. However, unlike fully non-competitive inhibition, besides the enzyme-substrate complex (ES), the complex will also convert into the product. This whole process can be described mathematically as

$$E + S \underset{}{\overset{K_1'}{\rightleftharpoons}} ES \overset{k_2}{\longrightarrow} E + P \tag{348}$$

and

$$E + I \overset{K_2'}{\rightleftharpoons} EI \tag{349}$$

and

$$EI + S \overset{K_1'}{\rightleftharpoons} EIS \tag{350}$$

and

$$ES + I \overset{K_2'}{\rightleftharpoons} EIS \tag{351}$$

and

$$EIS \overset{k'}{\longrightarrow} EI + P \tag{352}$$
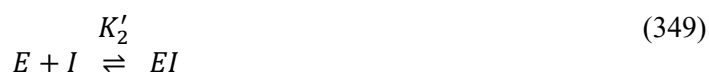
According to classical Michaelis-Menten equation $K_m = (k_2 + k_{-1})/k_1$; however, if $k_2 \ll k_{-1}$, we have $K_m = k_{-1}/k_1$ or $K_m = 1/K_1'$. Now, set the following results

$$K_m = \frac{1}{K_1'} = \frac{[E][S]}{[ES]} \tag{353}$$

and

$$K_I = \frac{1}{K_2'} = \frac{[E][I]}{[EI]} \tag{354}$$

and

$$K_m = \frac{1}{K_1'} = \frac{[EI][S]}{[EIS]} \tag{355}$$

and

$$K_I = \frac{1}{K_2'} = \frac{[ES][I]}{[EIS]} \tag{356}$$

Following enzyme conservation, we have

$$[E_0] = [E] + [ES] + [EI] + [EIS] \tag{357}$$

Using values of $[ES]$, $[EI]$ and $[EIS]$ from equation (353-356) into equation (357), we get the following expression.

$$[E_0] = [E] + \frac{[E][S]}{K_m} + \frac{[E][I]}{K_I} + \frac{[E][I][S]}{K_m K_I} \tag{358}$$

or

$$[E] = \frac{[E_0]}{(1 + ([S]/K_m)(1 + [I]/K_I)} \tag{359}$$

The overall reaction rate of product formations should be

$$r_0 = k_2[ES] + k'[EIS] \tag{360}$$

After using the values of $[ES]$ and $[EIS]$ from equation (353-356) into equation (360), we get the following result.

$$r_0 = k_2 \frac{[E][S]}{K_m} + k' \frac{[E][I][S]}{K_m K_I} \tag{361}$$

Now, substituting the value of $[E]$ from equation (359) in (361), and rearranging at the initial substrate concentration

$$r_0 = \frac{(k_2[E_0][S_0] + k'[E_0][S_0][I]/K_I)/(1 + [I]/K_I)}{K_m + [S_0]} \tag{362}$$

Using $k_2[E_0]$ is r_{max} and then taking the reciprocal to get the Lineweaver-Burk plot, we get the following relation.

$$\frac{1}{r_0} = \frac{K_m(1 + [I]/K_I)}{(r_{max} + k'[E_0][I]/K_I)} \frac{1}{[S_0]} + \frac{(1 + [I]/K_I)}{(r_{max} + k'[E_0][I]/K_I)} \tag{363}$$

After comparing the result given above with the general equation without enzyme inhibition, i.e., we can conclude some important points.

$$\frac{1}{r_0} = \frac{K_m}{r_{max}} \frac{1}{[S_0]} + \frac{1}{r_{max}} \tag{364}$$

it can be clearly seen that intercept is increased from $1/r_{max}$ to $(1 + [I]/K_I)/(r_{max} + k'[E_0][I]/K_I)$ whereas the K_m has remained the same.
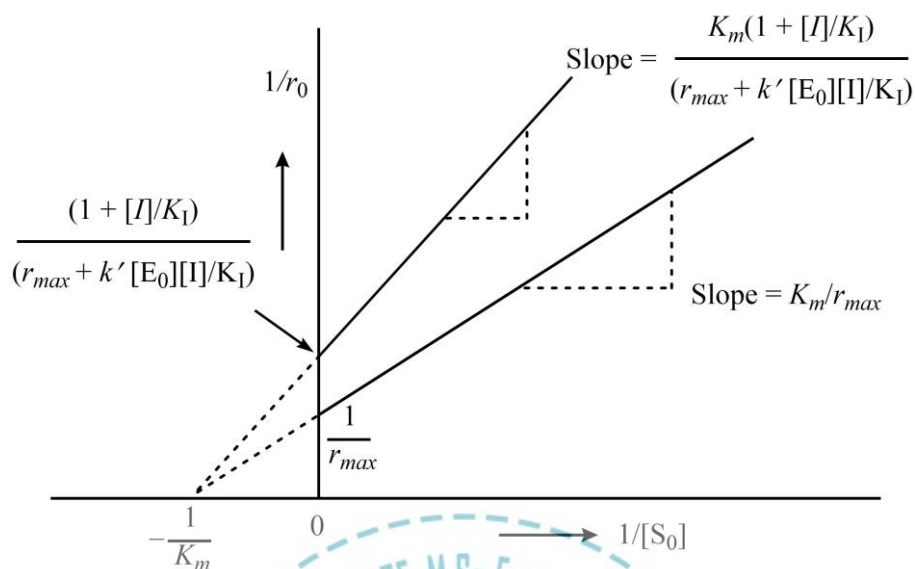
Figure 8. The Lineweaver-Burk plot for partially non-competitive enzyme inhibition.

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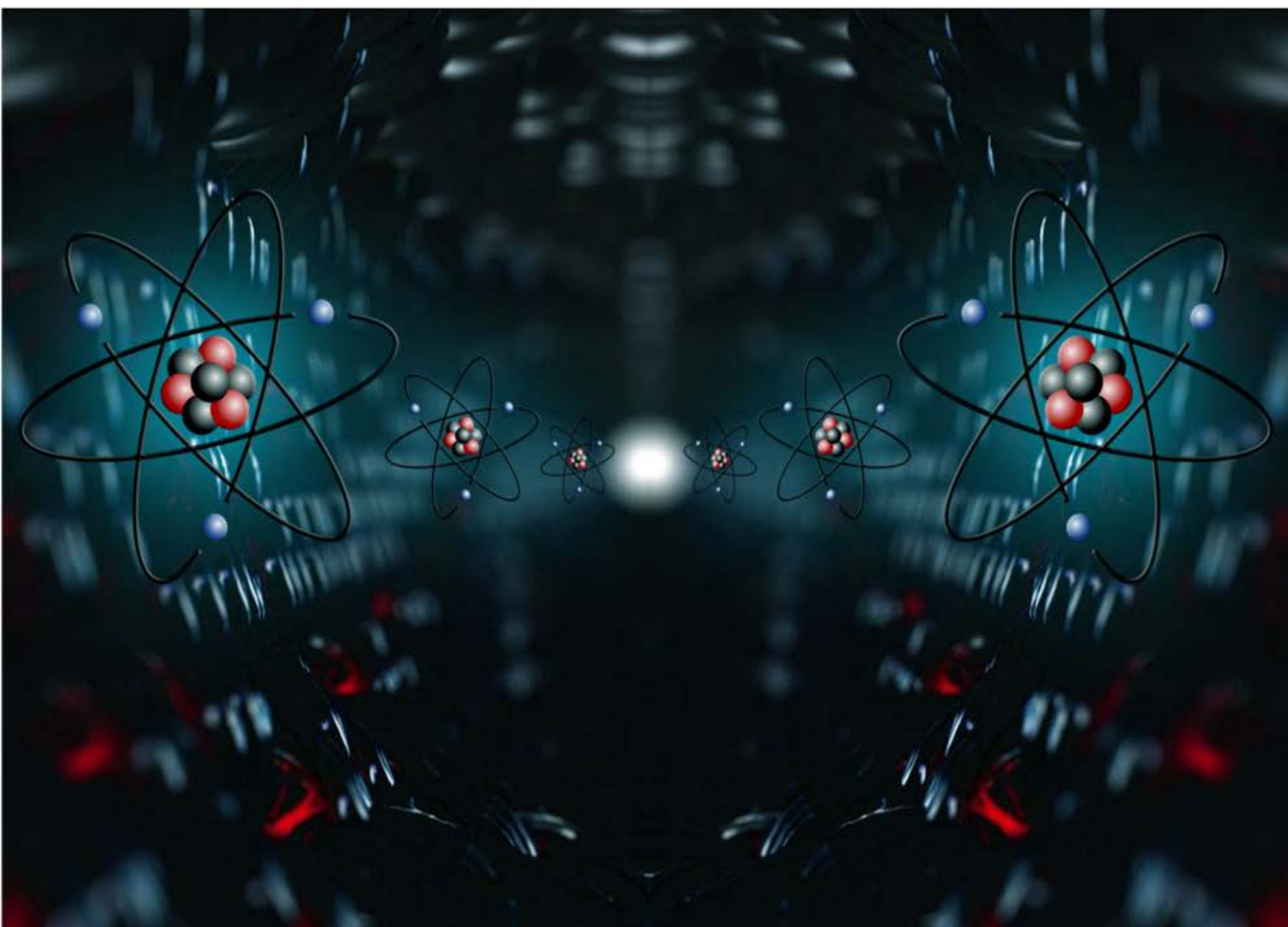
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