INDRAPRASTHA INSTITUTE *of*
INFORMATION TECHNOLOGY
DELHI

HOMEWORK ASSIGNMENT - 3

INDRAPRASTHA INSITUTE OF INFORMATION TECHNOLOGY, DELHI

COMPUTER SCIENCE AND APPLIED MATHEMATICS

Introduction to Quantitative Biology (BIO213)

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Solution

Introduction

We know that, rate of production of Tryptophan will be directly proportional to k, or the constant rate at while Tryptophan is being produced and will be inhibited by the rate of degradation of the Tryptophan. This can be modelled as the following ODE:

$$\frac{\mathrm{d}T_r}{\mathrm{d}t} = k - k_d[T_r]$$

where,

$k \rightarrow$ the constant rate of Tryptophan prduction
$k_d \rightarrow$ the rate constant describing the decay rate of Tryptophan
$[T_r] \rightarrow$ the concentration of Tryptophan at time t

We know that, at equilibrium,

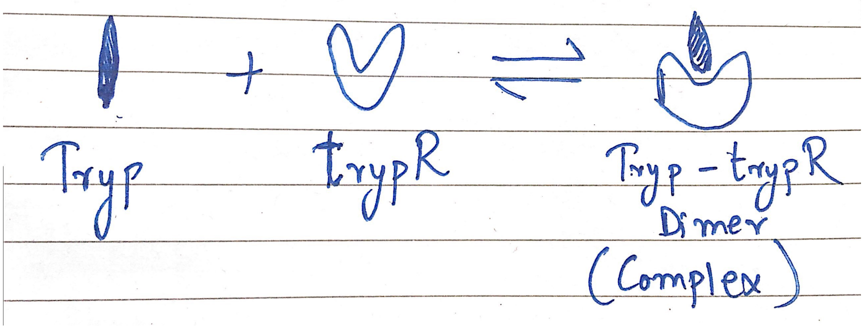
$$\frac{\mathrm{d}T_r}{\mathrm{d}t} = 0$$

Hence, we get,

$$[T_r] = \frac{k}{k_d}$$

Answer (a)

In the previous section, we talked about an ODE model to model the production rate of Tryptophan. However, we did not account for the effect of concentration of Tryptophan repressor ($trypR$) on the rate of generation of Tryptophan(T_r). The reason this happens is to inhibit the rate of formation of increasing Tryptophan.



The $\uparrow$se in the level of T_r also causes an $\uparrow$se in the levels of $trypR$ and this leads to a formation of a **dimer** between T_r and $trypR$.

Again, this can be represented by a simple ODE model:

$$\frac{\mathrm{d}T_r}{\mathrm{d}t} = k - k_d[T_r] - k_1^{'}[T_r]$$

where,
$k \rightarrow$ the constant rate of Tryptophan prduction
$k_d \rightarrow$ the rate constant describing the decay rate of Tryptophan
$k_1^{'} \rightarrow$ the rate constant for Tryptophan getting repressed
$[T_r] \rightarrow$ the concentration of Tryptophan at time t

Answer (b)

- As discussed in the previous answer, as the dimer of $T_r + trpR$ starts forming, we also see another effect.
- The formation of the dimer starts to **repress** the formation of $trpR$.
- This happens because the dimer ($T_r + trpR$) starts accumulating near the repressor formation site, and inhibits the formation of the repressor.
- This also leads to an $\uparrow$se in the concentration of T_r.

This situation can be modelled by the following ODE:

$$\frac{\mathrm{d}T_r}{\mathrm{d}t} = k - (k_1^{'} - k_2^{'}[R])[T_r] - k_d[T_r]$$

where,

$k \longrightarrow$ the constant rate of Tryptophan prduction
$k_d \longrightarrow$ the rate constant describing the decay rate of Tryptophan
$k_1^{'} \longrightarrow$ the rate constant for Tryptophan getting repressed
$k_2^{'} \longrightarrow$ the rate constant at which $trypR$ is being repressed
$[T_r] \longrightarrow$ the concentration of Tryptophan at time t
$[R] \longrightarrow$ the concentration of Tryptophan repressor ($trypR$) at time t

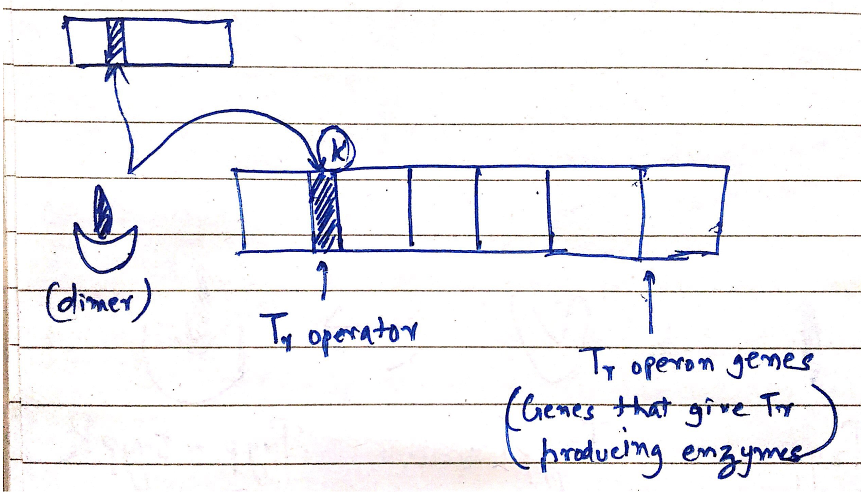
Here, we must also note that,

$$[R] = \left(\frac{[T_r]}{[T_r] + k_t}\right) R_0$$

where,
$k_t \longrightarrow$ constant of disassociation defined as:

$$k_t = \frac{k_b}{k_f} = \frac{\text{rate constant of backward reaction}}{\text{rate constant of forward reaction}}$$

and, R_0 = Total concentration of the repressor ($trypR$) at steady state.



This is how this regulatory circuit works:

- As the concentration of Tryptophan (T_r) goes up, it also kickstarts the formation of the Tryptophan repressor ($trypR$).

- The two of them form the ($T_r + trypR$) dimer which causes a decrease in the formation of Tryptophan (As shown in the above fig.). This is called **Negative Regulation**.

- At the same time, the formation of the dimer also causes a decrease in the repressor concentration. This causes Tryptophan concentration to go up. This is called **Positive Regulation**.

- Regulation does not cause any significant change at medium concentration of Tryptophan. It is noticeable and significant only at high concentration.

Answer (c): Biological Significance of Gene Regulatory circuit

- A gene regulatory circuit, is a representation of how protein synthesis is done, and how other factors represent the synthesis process. The circuit networks determine how cells adapt to the extra-cellular or intra-cellular environment changes. This is why, no external repressor is required to be injected in our bodies.

- Tryptophan is one such amino acid which is essential for basic biological processes in our body. They are essential for growth in infants and for balancing the amount of Nitrogen that is present inside adults.

- Too much of Tryptophan, can turn out to be poisonous whereas too less of it can lead to organ failure or malfunction of basic systems.

- Thus, the self-regulatory mechanism of Tryptophan ensures that we have just the right amount of it in our bodies.

Challenge problem

When there is excess Tryptophan, two molecules of Tryptophan, bind with one molecule of Tryptophan repressor, changing its structure and dynamics so that it can bind to the Tryptophan operator, thus, suppressing Tryptophan production. When the level of Tryptophan decreases, the Tryptophan molecules fall off from the Tryptophan repressor, making it inactive so that Tryptophan can finally be produced again.
The following equation can be used to depict the process:

$$T_r + trypR \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} T_r - trypR$$

$$\frac{\mathrm{d}[T_r]}{\mathrm{d}t} = -k_{on}[T_r][trypR] + k_{off}C$$

$$\frac{\mathrm{d}[trypR]}{\mathrm{d}t} = -k_{on}[T_r][trypR] + k_{off}C$$

$$\frac{\mathrm{d}C}{\mathrm{d}t} = k_{on}[T_r][trypR] - k_{off}C$$

where, $C \rightarrow$ complex that is formed when two Tryptophan molecules bind with one molecule of Tryptophan repressor
$[T_r][trypR] \rightarrow$ this represents the binding

References

- Dynamic regulation of the tryptophan operon: A modeling study and comparison with experimental data; Moisés Santillán and Michael C. Mackey (PNAS 98:1364-1369 (2001))
- Khan Academy's blog on Gene Regulation
- Wikipedia page of Tryptophan Repressor