GENE REGULATION

Not all gene products are required by the cell all of the time. Some genes are expressed through out, i.e. they are constitutively expressed and are called **constitutive genes** or **housekeeping genes.** While, some are expressed only when the protein is required by the cell and are called **regulated genes**. This process of regulating the production of proteins by the gene is called gene regulation. Gene regulation is achieved by complex processes which is different for prokaryotes and eukaryotes.

GENE REGULATION IN PROKARYOTES

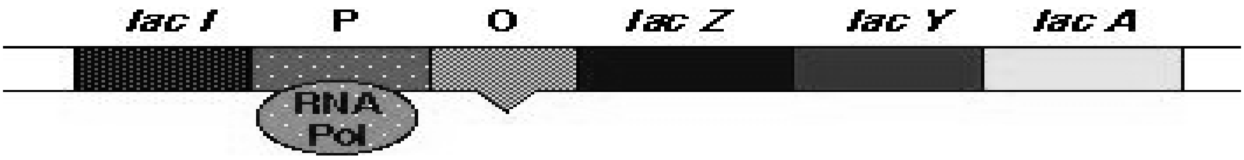
Prokaryotic gene regulation is well studied in bacteria. Jacob and Monad (1961) proposed the **operon model** to explain the regulation of genes in prokaryotes.

Operons

Genes that affect the same biochemical pathway in bacteria (for example, genes encoding proteins involved in metabolizing the sugar lactose) will all be expressed under the same conditions (such as when lactose is present). Therefore, it is economical to have all of these genes grouped together under the control of the same regulatory system. Such a grouping of similarly-regulated genes in bacteria is called an operon. An operon consists of a promoter, operator and structural genes. Some operons are inducible, others are repressible.

Inducible Operon

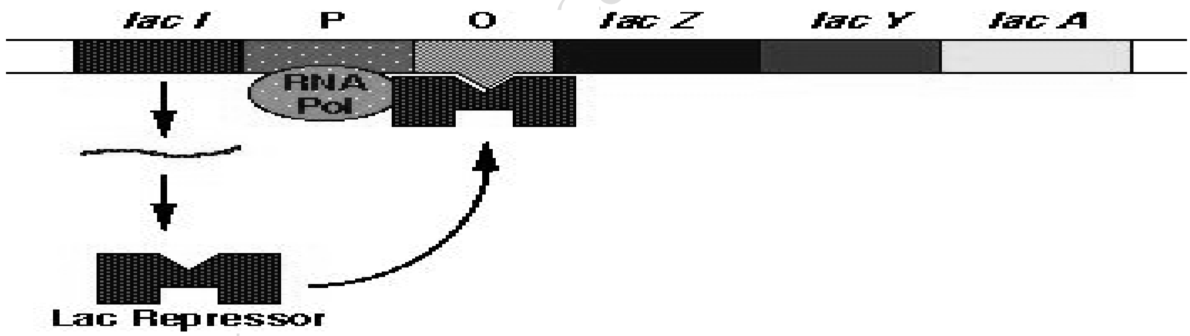
An example of an inducible operon is the **lactose operon** (lac operon for short), which contains genes that encode enzymes responsible for lactose metabolism. The lac operon looks like this:



The three structural (protein-encoding) genes of the lac operon are *lac Z*, which encodes the enzyme beta-galactosidase (which breaks down lactose into glucose and galactose), *lac Y*, which encodes a permease (that transports lactose into the cell), and *lac A*, which encodes a transacetylase. These three genes are under the control of the same promoter, designated P in the figure. The promoter is where RNA polymerase binds to the DNA and prepares to initiate transcription. The other regulatory element in an operon is the operator (designated O). This is the element that determines whether or not the genes of the operon are transcribed. In addition to all of the above, there is another gene, which is technically not part of the operon (it is controlled by a separate promoter, and is expressed all the time, or constitutively), but plays an important role in operon function. This is the *lac I* gene, which encodes a protein called the lac repressor. The lac repressor has two functional regions: one that binds to the DNA of the operator region, and one that binds to lactose. When the repressor binds to the operator, it prevents RNA polymerase advancing along the operon, and transcription does not occur. The regulation of the operon depends on regulating whether or not the repressor binds to the operator.

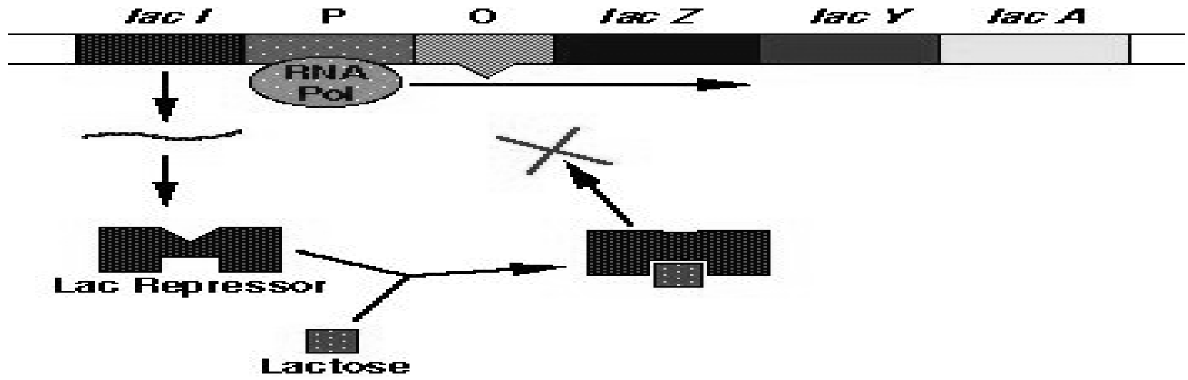
When Lactose is Absent

If there is **no lactose present** in the environment, the following series of events occurs:



The *lac I* gene is transcribed and the mRNA is translated, producing the lac repressor. The repressor binds to the operator, and blocks RNA polymerase. With RNA polymerase blocked, there is no transcription, and the enzymes for lactose metabolism are not synthesized. This is good, because there is no lactose to metabolize.

If **there is lactose** in the environment, the events unfold differently. A small amount of the lactose gets into the cell, and affects regulation of the operon:

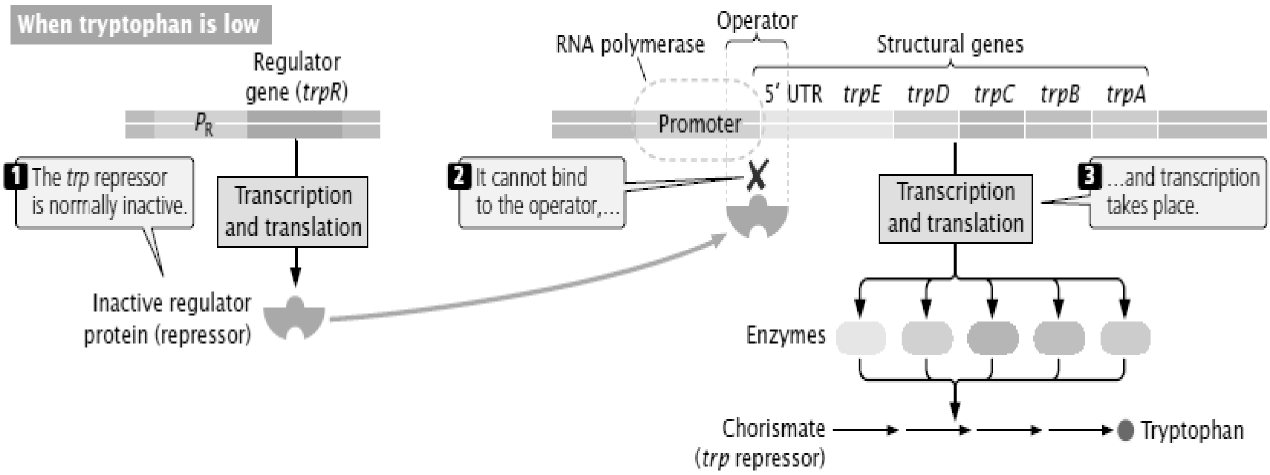


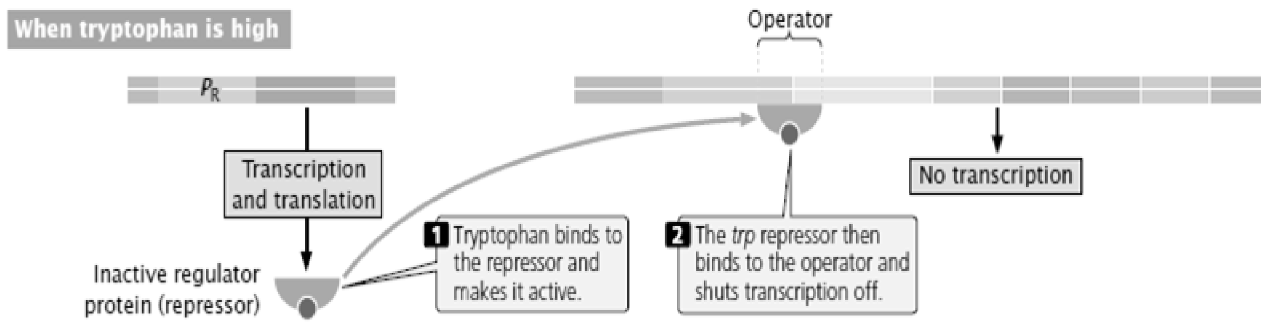
The lac repressor is still synthesized. As mentioned previously, the repressor can bind to lactose. When it does so, the repressor undergoes a **conformational change** (change of shape) and is unable to bind to the operator region. RNA polymerase is therefore not blocked, and is able to transcribe the genes of the operon. The enzymes encoded by those genes will be produced, the lac permease will transport more lactose into the cell, and beta-galactosidase will cleave the lactose into glucose and galactose, which can then be further metabolized by other enzymes, producing energy for the cell. Lactose, therefore, is able to **induce** the synthesis of the enzymes necessary for its metabolism (by preventing the action of the repressor). Thus, lactose is the **inducer** of the lac operon. When lactose is absent, lactose-metabolizing enzymes are not produced, and when lactose is present, those enzymes are produced.

Repressible Operons

Repressible operons are organized in much the same way as inducible operons: there are structural genes under the control of a promoter and operator, and there is a gene encoding a repressor. Repressible operons are regulated not by a reactant in the metabolic pathway (such as lactose was in its metabolic pathway), but by the end product of the pathway. An example of this is the **Trp operon**, which encodes enzymes responsible for the synthesis of the amino acid **tryptophan** (trp for short). The trp operon is regulated by trp, which is the product of the metabolic pathway.

The **trp repressor** only binds to the operator when trp is **present**. The repressor binds to trp, and undergoes a conformational change that allows it to bind to the operator, blocking transcription of the operon. Because trp is needed for repression, it is referred to as a **co-repressor** in this system. When trp is absent, the repressor will not bind to the operator, and transcription of the operon occurs. In this way, if there is plenty of trp around, no more is needed, so the operon is repressed. If there is no trp around, it needs to be synthesized, and the operon is transcribed, allowing the production of the enzymes for trp synthesis.





EUKARYOTE GENE REGULATION

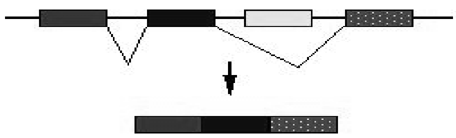
Eukaryotes consist of hundreds of different cell types, each differentiated to serve a different specialized function. Each cell type differentiates by activating a different subset of genes. Hence in eukaryotes gene regulation is a complex process and takes place at different levels. Regulation can occur at any point in the pathway of protein synthesis - at the levels of transcription, RNA processing, mRNA lifetime (longevity), and translation.

a. Regulation of RNA Processing

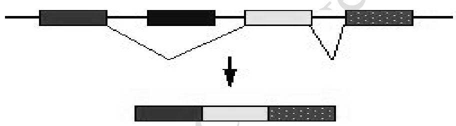
After transcription, the RNA must be processed before it can be translated. RNA processing involves addition of a 5' cap, addition of a 3' poly (A) tail, and removal of introns. Regulation can be of two types: a) whether RNA gets processed; and b) alternate splicing of exons in the mRNA.

The first type of regulation can determine whether or not an mRNA gets translated. If RNA is not processed, it will not be transported out of the nucleus, and will not be translated.

The second type of regulation can affect the function of the protein produced. Some genes have exons that can be exchanged in a process known as **exon shuffling**. For example, a gene with four exons might be spliced differently in two different cell types. In cell 1, exons 1, 2, and 4 would be used in the mRNA:



In cell 2 on the other hand, exons 1, 3, and 4 would be used:



In each of these cases, the polypeptide produced could have a different function. In *Drosophila*, **alternate splicing** of the *sex-lethal* RNA can produce an mRNA encoding a functional polypeptide, or one with a premature stop codon that encodes a short, non-functional polypeptide.

b. Regulation of RNA Longevity

Imagine two mRNA molecules: one lasts for five minutes in the cytoplasm before being degraded, while the other one manages to linger for an hour before being degraded. If both are translated continually while they exist, it is obvious that more of the second polypeptide will be produced than the first. This is the principle behind regulation of RNA longevity. mRNAs from different genes have their approximate lifespan encoded in them; this serves to help regulate how much of each polypeptide is produced.

c. Regulation of Translation

Whether or not an mRNA molecule is translated can be regulated as well. The various mechanisms of translational regulation are incompletely understood, but there are many documented examples of mRNA molecules that are present routinely, but are only translated under certain circumstances. For example, many animals sequester large amounts of mRNA in their eggs, and those mRNA molecules are not translated unless the egg is fertilized.

d. Regulation of Transcription

Whether or not a gene is transcribed is the major way that gene expression is regulated in eukaryotes, as it was in prokaryotes. There are some major differences between transcriptional regulation in prokaryotes and eukaryotes. For one thing, because of the complexity of eukaryotic patterns of gene expression, each eukaryotic gene needs its own promoter. In other words, **eukaryotic genes are not organized into operons**. Another difference is that prokaryotic genes are regulated primarily by repressors. Although repressors occasionally play a role in eukaryotes, eukaryotic genes are primarily regulated by transcriptional **activators**. These activators are **transcription factors.**