Operon

Subjects: Biology
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operon evolution | histidine metabolic pathway | piecewise model

1. The “Operon Model”: Story of an Idea

In the review article entitled “Genetic Regulatory Mechanisms in the Synthesis of Proteins”, François Jacob and Jacques Monod reinforced contemporary discoveries on genes’ structure and expression patterns into an exhaustive and of great impact theory of gene regulation: the “Operon Model” [1]. This article, published in June 1961 by the Journal of Molecular Biology, can be considered as the starting point in the emergence of a new scientific era [2].

The story of the discovery of the operon concept is a story of passion for science, sharing of ideas, and convergence of (apparently) independent research lines. At one end of a corridor at the Pasteur Institute were André Lwoff, Elie Wollman, and François Jacob. Jacques Monod and his group were at the other end of the hallway. Lwoff worked on lysogenized *Escherichia coli* bacteria able to produce bacteriophage without infection. In the same bacterium, Monod was focusing on the properties of the enzyme β-galactosidase, required for lactose metabolism and synthesized only in the presence of galactosides in the culture medium. As reported by Jacob himself “to all and sundry the two systems appeared mechanistically miles apart. But their juxtaposition would produce a critical breakthrough for our understanding of life, demonstrating that we cannot presume to know how new ideas will arise and where scientific research will lead” [3][4].

In 1957, Jacob, Monod, and the American scientist Arthur Pardee, who was spending a sabbatical year in Monod’s laboratory, performed a crucial experiment that is generally known as PaJaMo, i.e., the initials of the three scientists’ names [5]. The PaJaMo experiment represents the starting point that led to the proposal of a model of negative regulation. Moreover, it generated two other fundamental concepts: the messenger RNA and the operon [5]. In both systems (that of the regulation of the synthesis of β-galactosidase and that of the control of bacteriophage λ lysogeny), they proposed that the product of a regulator gene, the **repressor,** controls and coordinates a group of genes with related functions. This group of genes constitutes an **operon**, and the region on the DNA that responds to the repressor was named **operator**. The repressor can act in *trans*, while the operator functions in *cis* to the operon. In the absence of an inducer, the expression of the genes that constitute the operon is inhibited by the binding of repressor to the operator. Otherwise, when the repressor is induced, it detaches from

the operator and the genes are transcribed [2]. Since its conception, this model has been validated various times [5]. The 1961 review article reports and summarizes these experiments and their effects [6]. These papers transformed thinking about gene regulation, introducing for the first time the concept of **regulatory genes**, a new class of genes with no metabolic or structural function, but with the ability to control the expression of metabolic functions [2][7]. The operon model, indeed, described two events: (i) how coding genes' expression works, and (ii) how this expression is regulated [8].

The ideas presented in these papers were rapidly and widely accepted and welcomed among biologists [2][7], and in 1965, André Lwoff, Jacques Monod, and François Jacob shared the Nobel Prize in Physiology and Medicine "for their discoveries concerning the genetic control of enzyme and virus synthesis" [5][9]. Starting from the beginning of the 1960s, the operon concept matured quickly, and it became manifest that regulatory systems were hugely versatile and plastic. Indeed, it was found out that (i) bacterial genes could be regulated by activators, be subjected to both positive and negative regulations, or be synergistically controlled by combinations of regulatory proteins, that (ii) repressors could also behave as activators, and that (iii) the activity of a given transcription factor often changes depending on the promoter [10].

The idea that the synthesis of bacterial proteins is structured in tangled regulatory circuits was introduced by the operon model. Such circuits could be compared to complex machines control mechanisms, electric circuits, or programs in computers. Indeed, Jacob and Monod can be viewed as promoters of the cybernetics concept in biology [2], as they paved the way for the first synthetic gene networks that, in 2000, introduced the branch of synthetic biology [1].

2. Definition of Operon

The term operon was first coined by Jacob and Monod in 1961 [6] to describe a cluster of genes whose expression was regulated by an operator. Now, any group of adjacent genes that are transcribed from a promoter into a polycistronic mRNA are defined as operons [11]. All bacterial and archaeal genomes hold operons, and clustered genes with related functions have been reported also for many eukaryotic organisms such as yeasts, fungi, insects, vertebrates, and plants [12][13].

Operons represent one of the principal schemes of gene organization and regulation in prokaryotes [14][15]; about half of all protein-coding genes of a typical prokaryotic genome are organized in multigene operons [16][17], including from two to dozens of genes [18]. They often encode enzymes belonging to the same functional pathway [19], although there are some exceptions such as the Macromolecular Synthesis (MMS) operon, made up of genes involved in replication, transcription, and translation [20]. Moreover, genes in operons often encode proteins that physically or functionally interact, such as enzymes of consecutive steps in metabolic routes ([21] and references therein).

Nevertheless, among prokaryotes, operon conservation is not as common as one would expect [14]. Indeed, prokaryotic genomes are quite unstable [22], and only 5–25% of genes belong to strings shared by at least two

distantly related species [23], suggesting that the conservation of operons might be neutral during evolution [22]. Moreover, the operon structure seems to be quite heterogeneous [24], since operons can carry “alien” (genes having homologs in other species but that apparently are not involved in the same metabolic pathway of the other genes of the operon) [24] and/or “ORFan” genes (without homologs in closely related species), and show a different degree of compactness, with closely or widely spaced genes [16].

Most operons are controlled by a single transcriptional promoter situated upstream of the first gene [17]. Nonetheless, many operons are under the control of multiple promoters, regulators, and regulatory sequences [16]. Gene expression can be altered by the organization and order of genes in operons, when specific regulatory mechanisms, such as translational coupling and/or polarity, are involved. Moreover, gene expression increases linearly with the distance from the start of a gene to the end of the operon (“transcription distance”). This is due to (i) a longer time for translation to occur during transcription, and (ii) a six-fold greater translation initiation rate for an mRNA during transcription than after its release, both resulting in an increased gene expression [25].

In the early 1990s, structures similar to canonic prokaryotic operons were found in the genome of the nematode *Caenorhabditis elegans* [26]. Genes in nematode and ascidian genomes are known to be often organized in operons (comprising up to 15–20% of the coding genome) [27] and operons can be horizontally transferred from prokaryotes to eukaryotes [28]. However, the derived polycistronic mRNA is then trans-spliced into monocistronic mRNAs that are individually translated [29].

Recently, numerous computational strategies have been developed to predict operon structures in prokaryotes, based on (i) the intergenic distances between open reading frames (ORFs) of the same operon, (ii) gene cluster conservation among different organisms, (iii) functional relations between genes, since genes in operons often lead to the synthesis of the same protein complex, or enzymes involved in a unique metabolic pathway, (iv) the occurrence of DNA motifs and other sequence elements such as transcription factor binding sites, promoter sequences, and transcriptional terminators, (v) experimental evidences derived from DNA microarray experiments and, more recently, from RNA-seq data, since genes belonging to the same operon are expected to show comparable expression patterns [30][31].

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