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► **To cite this version:**

Giuseppe Iurato, Andrei Igamberdiev. Some historical remarks on Jacob-Monod operon model. 2021. <hal-03741817>

**HAL Id: hal-03741817**

**<https://hal.science/hal-03741817v1>**

Preprint submitted on 1 Aug 2022

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# Some historical remarks on *Jacob-Monod operon model*

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**Abstract.** In this brief note, we wish simply to point out again that the *operon model*, due to 1965 Nobel laureates François Jacob and Jacques Monod in the 1950s, might be laid out within the historical framework of the epigenetics, as well as one of its first biological models making use of a systemic approach, at the crucial crossroad from prokaryotes to eukaryotes.

## 1. Introduction

François Jacob (1920-2013) and Jacques Monod (1910-1976) have been central figures of modern science, recalled as founders of modern molecular biology. They worked mainly at the laboratories of the Institut Pasteur of Paris, where they directed the unities of bacterial genetics and cellular biochemistry. In these places, from 1960s onward, new ideas on Neo-Darwinism were worked out within the new framework of molecular biology of DNA, were pursued, fitting together genetic variability with natural selection assumption. The DNA, seen as a structured set of genes, undergoes to a linear combinatorial logic which may have various dimensions of combination, as a 1-dimensional, a 2-dimensional, until to a 3-dimensional one, to give rise spatially arranged living organisms, with a certain geometrical shape, where also a fourth dimension may be added, as the one related to the temporal dimension. In such a combinatorial building up of life, the chance, the contingency or the possibility play a very fundamental role, so that what we get in as a real living world is only one of the many possible worlds which we should have could get; so, the strict necessity in getting out a certain living organism, is not absolute in biology, but there exist yet constrains which force nature to have certain configurations rather than others. Jacob and Monod, just from their remarkable work in the new molecular biology, devoted much of their time to think and reflect also in epistemology of natural sciences, giving deep and valuable contributions to the philosophy of biology and natural sciences, besides to open new perspectives of research (Mayr, 1982; Monod, 1970; Morange, 1998; Piattelli Palmarini, 1987; Redi, 2018; Rheinberger & Müller-Wille, 2017).

It is just the case considered in this paper, in which we wish to recall, another time, what crucial and valuable perspectives opened Jacob and Monod around the late of 1950s when they published some works of the molecular biology of bacteria which will give first theoretical models upon the gene expression regulation in prokaryotes, with their so-called *operon model*, whose importance will be later acknowledged with Nobel prize in 1965, won together with André Lwoff (1902-1994). We would like to recall briefly such a model, hence to highlight what outcomes were achieved by it in the field of molecular biology, with a particular attention to the biological trend of *epigenetics* and the systemic approach later called *systems theory* in biology. The operon model, as we stand out in this paper, just provides first patterns of epigenetics, through a systemic approach based on feedback mechanisms, as well as it has provided new insights about the crucial bifurcation from prokaryotes to eukaryotes. Monod started to study bacteria cultures since 1940s, and observed that,

also in presence of sugars, bacterial growth was yet quite anomalous, so inferring that enzymatic synthesis depended on environment conditions and the related needs. His further researches were pursued just on such an “environmental adaptation” of enzymatic synthesis, studying in particular the role of either environment and hereditary factors on it. In doing so, Monod established a collaboration with André Lwoff, who introduced the study of viruses in French, and François Jacob (1920-2013), within Pasteur Institut in Paris, in the 1950s, together the American biologist Arthur B. Pardee (1921-2019) during an his sabbatical period of research in Paris (Duris & Gohau, 1997).

In the late of 1950s, Jacob, Monod and co-workers introduced the notable notion of *operon*<sup>1</sup>, as a structural group of contiguous genes whose biofunction is ruled by another brief consequent group of genes said to be *operator*, together the as many important notions of *structural gene*, *regulator gene* and *induction/repression* of enzymatic synthesis. The operon was therefore conceived as the minimal unity of coordinated expression, by the operator, of a group of structural genes that it rules. The operator, on its turn, is influenced by other external proteins, which act as either inductor or repressor of enzymatic synthesis, by ruling the control function of the operator through allosteric effects. What had to be clarified better concerned the mechanisms with which such processes taken place, so Jacob and Monod hypothesized new types of RNA to accomplish to such ends: precisely, they introduced mRNA and pRNA, as chief means to transport and transfer genetic information, hence identified in the early 1960s, also in collaboration with Jean-Pierre Changeux (1936), the so-called *allosteric regulation*, i.e., new stereodynamic mechanisms (later called *allosteric processes*) ruling repression and induction processes by means of certain external proteins said to be *allosteric effectors* (Duris & Gohau, 1997).

The 1950s work of Jacob, Monod and co-workers, on the molecular biology of prokaryotes, then acknowledged by Nobel prize in 1965, given the first models of gene expression regulation of cells, although limited to prokaryotes, analyzing, in particular, how does protein synthesis to take place, hence clarifying phenotypic manifestation processes, from the epigenetic standpoint therefore. They also pointed out how environmental conditions may influence these latter, so identifying possible mechanisms just based on a systemic approach of feedback type. Their models were also of help in deducing analogous patterns for the gene expression regulation in the eukaryotic case, as well as in clarifying the crucial bifurcation from prokaryotes to eukaryotes and their typical features (like cells differentiation and replication). Therefore, after having briefly recalled the main basic notions of molecular biology need to understand better operon model and lay out it within the right biological framework, we discuss the chief aspects of such a pattern, highlighting which are its notable results of interest for epigenetics and the systemic approach in biology.

## **2. Molecular biology and Darwinian evolutionism: basic ideas and concepts**

Darwin’s theory of *evolution* is based on the so-called *natural selection* which occurs by means of *mutations* that, although everyone is quite rare (about,  $1:10^9$ ), have yet selection power due to their collective accumulation into a certain population, which therefore evolves phylogenetically. Along the biological evolution, it has been possible to identify certain *invariants*, as cellular organization, some basic metabolic processes, genetic code and its capability to transmit genetic information by *reproduction*. This last, with the capability to evolve, are the common traits of all living organisms

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<sup>1</sup> See (Jacob et al., 1960), hence (Jacob & Monod, 1961).

structurally done by cells (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982).

Historically, i.e. from a phylogetical standpoint, it has been hypothesized that cell sprung out from a unique, initial pre-cellular pattern which, on its turn, arisen from a previous (prebiotic) chemical phase in which an accumulation of certain organic substances took place, with substances able to warrant its replication by self-catalysis, this latter due to other simplest chemical substances which, along evolution route, have become ever more specialized until up to give rise the first biological form of a primordial *pre-cell*, basically surrounded by a protective membrane, and having a certain hereditary patrimony together a set of catalysts able to bring to the *replication* of such an heritage, hence to the *duplication* of such a pre-cell. The basic uniqueness of such a pre-cell pattern justifies the substantial analogies amongst the next cellular organization of all living organisms (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982).

Afterwards, from such a basically unique primordial chemical *pre-cell*, then developed that basic morphophysiological unit of living organisms which will be the biological *cell*, whose fundamental structure and function are quite analogous to all living organisms. What has, instead, marked the first, remarkable differentiation amongst the various types of cells, has been the net distinction between *prokaryotes* and *eukaryotes*, the first being characterized by a simple cellular organization, while the latter have a more complex and articulated cellular organization. This distinction between cellular types, has also been the major of the discontinuities along the phylogenetic evolution of the living organisms (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982).

The genetic material, which warrants cell reproduction, growth and development, is done by DNA, which, in turn, rules protein synthesis and cellular characteristics. These latter are, in turn, stated by proteins themselves (*cellular proteins*), so the synthesis of these, by genetic material contained into DNA, is a fundamental biochemical process for any living organism and its characters. Structurally, DNA is done by *genes* (as traits of DNA, which are ordered sequences of certain *nucleobases*) and groups of genes (*chromosomes*), which are also sequentially ordered. Proteins, in turn, are ordered sequences of amino acids<sup>2</sup>, which are determined exactly by traits of DNA. A *mutation*, then, is a variation of DNA of a cell, which may entail a modification of the amino acids sequence of a certain protein, with a consequent alteration of those cellular functions depending on such a protein (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982).

A protein, as made by amino acids, may have either an enzymatic or a structuring function, in dependence on the 3-dimensional arrangement of its constituent amino acids, of which it is possible to identify a *primary*, a *secondary*, a *tertiary* and a *quaternary structure*, mainly through X-rays diffraction methods, characterizing its biological activity; such a 3-D structure is, in turn, specified by DNA. The synthesis of a protein takes place thanks to *ribosomes*, which are particular cellular subunits done by proteins linked by *ribosomal RNA* (rRNA), through the information brought by *messenger RNA* (mRNA), arising from a splitting of DNA double helix into two single helices, and reaching ribosomes, where the protein synthesis takes place by means of one out of the two helices sprung out from such a DNA splitting, with nucleobases sequences complementary of each other, and that forming mRNA being a filament of many ribonucleobases, first attached to DNA, then,

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<sup>2</sup> The four nucleobases of DNA combine according to simple dispositions of class 3 (which are totally  $4^3=64>20$ ) to give rise proteins formed by sequences of 20 amino acids (polypeptides sequence). Thus, genetic information of DNA is elicited by triplets (*codons*).

after splitting, migrating to ribosomes to produce proteins (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982).

The splitting of DNA double helix, to give rise one single helix of mRNA (whose sequences of ribonucleobases, moulded by DNA, will be then translated into sequences of amino acids), is due to a particular enzyme, said to be *polymerase* RNA (pRNA), which sticks up on certain sequences of nucleobases (or better genes, of one of the two DNA helices), said to be *promoters*, to give rise then mRNA. Such a process, through which nucleobases sequences of DNA (having, therefore, genetic information) are transcribed into new sequences of (ribo)nucleobases of mRNA, is said to be *genetic transcription*, while the process through which proteins are synthesized, is said to be *genetic translation*, in that new information is got by the passage from sequences of nucleobases triplets (of mRNA) to sequences of amino acids, so we have a kind of “change of linguistic register”, from the one done by sequences of nucleobases, to the one made by sequences of amino acids; the *genetic code* just allows such a passage, from one register to the other (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982).

In these molecular biology processes, related to the protein synthesis of living organisms, what is interesting, from our enquiry standpoint, regards the way in which a triplet of one DNA helix, then transcribed in a triplet of mRNA, determines the insertion of a certain amino acid into a polypeptide chain, that is to say, how the translation process (by genetic code) takes place. In this regard, some years later the discovery of the DNA structure (1953), it was conjectured the existence of a specific molecule able to insert a given amino acid into a polypeptide chain; such a molecule, therefore, has the main role to “adapt”, inside a ribosome oscillating along mRNA filament<sup>3</sup>, a certain amino acid to the triplet of nucleobases of mRNA, after having recognized both. Such a molecule, later discovered, was named *transfer* RNA (tRNA). It has a low molecular weight (with respect to the other types of RNA), is – geometrically – formed by a unique filament made by 80 nucleobases, amongst which there are some new bases, as the methylated ones. This filament is refolded on itself, and, at its two extremities, there are two triplets of nucleobases, one (said to be *anticodon*) able to recognize the other one, a complementary triplet of nucleobases (*codon*) lying on mRNA (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982).

### **3. First instances of epigenetic phenomena: the enzymatic synthesis and its regulation**

Enzymes are proteins useful for metabolic processes, and some biological processes in which they are involved, may provide remarkable examples of how environment conditions may influence their biological activity, so having first epigenetic phenomena. For instance, yeasts work either in aerobic and anaerobic conditions, notwithstanding that their genetic patrimony remains unchanged: in fact, yeasts usually work in anaerobic conditions via fermentation processes (anaerobic metabolism), but if environment conditions change, for instance imposing aerobic conditions, then the fermentation processes cease to work (*Pasteur effect*), and yeast itself so starts to synthesize new enzymes (which are absent in aerobic conditions), allowing to work now in aerobic conditions (aerobic metabolism). And all this takes place without changing of genetic patrimony of yeasts, yet they are able to change own metabolic processes in dependence on environment conditions according to biological abilities or regulative mechanisms, evolutionarily selected for the advantage of yeast cells themselves and

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<sup>3</sup> The molecular system made by ribosomes oscillating along the same filament of mRNA, is said to be a *polysome*.

their metabolic processes (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997).

The example just exposed above – regulation of enzymatic synthesis – is a modality of regulation of the cell metabolism, through the synthesise of proteins. It relies on the main fact for which not all the possible proteins, of which a cell has their genetic patrimony, are however synthesized, but only those strictly necessary for the cell metabolism or for other biological processes or phenomena in which it is involved. Therefore, it follows that the synthesis of proteins, which takes place through gene expression, is then ruled in dependence on the various needs and contingent conditions in which cell is embedded. For instance, some enzymes are synthesized only when, in the environment of growth of a cell, are present certain, other *inducing substances* (as *inductors*) which allow their synthesis; in such a case, we speak of *inducible enzymes*. First genetic models about gene regulation in prokaryotes were worked out by François Jacob, Jacques Monod and André Lwoff in the 1950s and 1960s at Pasteur Institute of Paris, so providing historically first explicit instances of epigenetic processes for prokaryotes, which are yet quite different from those regarding eukaryotes, except in part DNA methylation which are also involved partially in prokaryotes enzyme synthesis<sup>4</sup> (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997; Seong et al., 2021; Willbanks et al., 2016).

#### 4. A historical case-study of inducible enzyme: the $\beta$ -Galactosidase of *Escherichia Coli*

In the history of molecular biology, the first and best known instance of inducible enzyme is the so-called  $\beta$ -Galactoside (in short,  $\beta$ -G) of the bacterium<sup>5</sup> *Escherichia coli* (in short, *E. coli*); the related synthesis process is called  $\beta$ -Galactosidase<sup>6</sup>. Such an enzyme, which catalyzes hydrolytic splitting of lactose and other galactosidases, it is need for cell may use such substrates in its metabolism, so that cells devoid of such an enzyme cannot grow up in a culture environment having only lactose as a unique source of carbon. Usually, *E. coli* cells do not contain  $\beta$ -G enzyme, but they synthesize it when are into a culture containing lactose, so that  $\beta$ -G is an inducible enzyme, while lactose and galactosidases are inducing substances (which, in turn, are, in general, substrates of the induced enzyme). However, the presence of lactose only, as a unique source of carbon for *E. coli* cells metabolism, induce  $\beta$ -G together other two enzymes<sup>7</sup>, namely the  $\beta$ -Galactoside permease (in short,  $\beta$ -Gp) and the  $\beta$ -Galactoside transacetylase (in short,  $\beta$ -Gt), that allow other biological processes inside *E. coli* cells (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997).

From the evolutionary biology standpoint, it has been a biological advantage the enzyme synthesis in that, a cell may survive in different environments choosing optimally what type of enzyme to use, hence generate (this being always possible at genetic level), in the suitable metabolic process need for the cell. The regulation of such an enzyme synthesis has just been defined also optimal because

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4 See (Willbanks et al., 2016). On the other hand, methylation processes are already involved in tRNA phenomena, which were discovered just by François Jacob and Jacques Monod in the late of 1950s, in studying biology of *E. coli*. See (Jacob & Monod, 1961).

5 This bacterium is particularly suitable for such type of studies as it contains a mixture of many different enzymes.

6 See (Jacob & Monod, 1961).

7 And these two other enzymes are always produced concomitantly to the production of  $\beta$ -G.

it synthesizes just the right and strictly necessary enzymes needed for, but not others which might turned out to be superfluous. Thus, *E. coli* cells, when are in presence of both glucose and lactose, do not synthesize any enzyme for metabolic purpose, because the glucose only is faster usable as a source of carbon rather than synthesize  $\beta$ -G (hence, also  $\beta$ -Gp and  $\beta$ -Gt) for the presence too of the lactose, a synthesis which might at the same time be triggered as a further process; to be precise, this latter does not take place until up glucose is present, as it just explicates the double function<sup>8</sup> of *inhibition* (or *repression*) of such an enzyme synthesis or of *induction* of it, which run basically according to a *feedback* mechanism, hence through a *systemic* fashion, so making optimal the cell metabolism (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997). These two main mechanisms – of *repression* and *induction* – are basically periodic in their formal nature, in agreement with their positive/negative feedback feature (or systemic fashion), so they may be also mathematically described through certain formal models based on periodic oscillations, either genetically and/or environmentally controlled, which rule many important cellular and subcellular processes, like enzymatic synthesis and activity, guarantying certain levels of induction of enzymes also to some next generations<sup>9</sup>. This justifies, in the context of mathematical biology, the name of *epigenetic oscillations* given to those related to enzymatic synthesis, and of *metabolic oscillations* given to those related to enzymatic action, as done by Ilya Prigogine and Gregoire Nicolis in the 1970s, who achieved remarkable researches and studies in this field, just after the pioneering works by Jacob and Monod of the 1950s, in turn based on many, previous works done by other scholars on *E. coli* biological phenomenology (Prigogine & Nicolis, 1981).

**The *Jacob-Monod pattern*.** The mechanisms of repression and induction of enzyme biosynthesis of above, have many similarities and analogies. Indeed, as pioneeringly pointed out by François Jacob and Jacques Monod in the late of 1950s, such repression and induction mechanisms arise, respectively, from the deactivation and activation of the transcription of those structural groups of genes containing that genetic information related to the enzymatic biosynthesis. Each of such specific groups of *structural genes*, was said to be *operon*; in general, its genes are sequentially ordered along DNA and attached of each other<sup>10</sup>. Alongside any operon, there is attached a particular chromosomal segment (i.e., a set of genes), said to be *operator* (in short, O), which mainly controls and regulates the gene expression of the operon to which it is attached, allowing mRNA to work for the transcription, via pRNA, of the whole operon. So, the starting point of DNA replication is just in the operator. Jacob and Monod hypothesized a molecular mechanism for the regulation of the operon genes, working out a theoretical model, then called *Jacob-Monod pattern*, to explain the induction of  $\beta$ -G and other related phenomena (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997).

Jacob and Monod, therefore, from *E. coli* case-study, supposed that, besides the genes (of DNA) appointed to the protein synthesis, that Monod calls *structural genes* (and forming the *operon*), other particular genes (of DNA) exist and are in charge of regulate the activation (*induction*) or the

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8 Which should be meant from a *systemic* standpoint, because it acts according to a feedback mechanism: if the concentration of glucose is not zero, then such an inhibition occurs; if the concentration of glucose is zero, then such an inhibition does not take place, hence enzymatic synthesis starts as the concentration of lactose is not zero.

9 So, these last facts have just epigenetic nature.

10 In the case of *E. coli* and the related synthesis of  $\beta$ -G, such an operon is called *lac*.

inactivation (*repression*) of the structural genes, that Monod calls *regulating* (or *regulator*) genes<sup>11</sup> (acting upon the *operator*), still synthesizing another specific protein which will be said *inductor* or *repressor* in dependence on the regulation function elicited by it. Further, the gene sequence of the operator O is just placed between the place where pRNA (i.e., the promoter) sticks up (for the transcription, with the consequent production of the related mRNA) and the sequence of structural genes (i.e., the operon). It follows that, when, for example, the repressor sticks up on O (i.e., the operator), then the synthesis of mRNA cannot take place (as promoter has not access), hence the genes of the operon remain not expressed. Likewise, inductor acts on the stereodynamics of the repressor meant as a protein, to be precise, it does a conformational modification (of *allosteric* type) on the spatial structure of repressor<sup>12</sup> in such a manner that this latter cannot anymore stick up on the operator. So, in the case of *E. coli* studied by Jacob and Monod, when the inductor – i.e., the lactose – is present, the repressor is unable to block the synthesis of mRNA because lactose prefers<sup>13</sup> to stick up to repressor, which therefore cannot run, hence the transcription of structural genes (of the operon) may start, with consequent synthesis of  $\beta$ -G,  $\beta$ -Gp and  $\beta$ -Gt (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997).

Moreover, Jacob and Monod considered also the case of enzymes which are *repressible*: namely, in the case of *E. coli* cells, if these are in a culture rich of nutrients, and containing all need amino acids, then no one enzyme, need to biosynthesize these latter, is present, hence they are repressible enzymes<sup>14</sup>; nevertheless, these latter appear as soon as the amino acid synthesized by them, or some its substrate, becomes present, so any final product of their biosynthesis acts as a *corepressor*. In fact, in the case of biosynthesis of the histidine, it is just the histidine-tRNA to act as a corepressor, activating the repressor of the related operon of the histidine, so blocking the biosynthesis of the many enzymes typically attending at the synthesis of histidine. Therefore, in presence of histidine, formation of histidine-tRNA takes place, hence a corepression process starts to block the synthesis of all the enzymes occurring in the biosynthesis of new histidine. In a few words, corepressor works as an activator of the repressor of the related operon, which so starts its usual function of repression of the synthesis of enzymes (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997).

So, repressor plays a very important role in influencing the whole functioning of the DNA system {Operator (O) + operon (SGs)}, often called *lac operon*, where SGs stands for structural genes of the operon. As we have seen above, the *repressor* R, as a protein, mainly runs in dependence on the possible (allosteric) configuration that it may assume amongst a variety of – at least – two possible stereodynamic configurations<sup>15</sup>, say R and R'. To this end, the regulator genes, as a kind of molecular switch, establish, with the help of another external substance, said to be *effector* E, what

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11 Therefore, Monod considered the existence of genes which rule other genes, via complex molecular mechanisms of regulation (Borek, 1965).

12 In this regard, the so-called *allosteric* proteins act in analogous manner. more

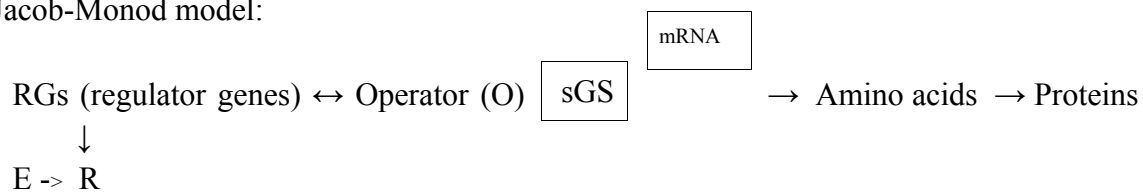
13 Probably, because the chemical reaction {lactose + repressor} is thermodynamically more advantaged with respect to other possible reactions.

14 Such enzymes are obviously biologically advantaged, this quality having been acquired in an evolutionistic way.

15 As genes of the operon cannot be permanently locked, so repressor, as a kind of switch, must allow sometime the free expression of such operon genes; this may be possible only when at least two different stereodynamic configurations of the repressor exist, with one spatially compatible with the operator configuration, and the other not, so leaving unlocked it to act on the operon genes (Morchio, 1982).

stereodynamic configuration the repressor R has to assume on the basis of the interaction  $E \rightarrow R$ . Therefore, the effector is that substance with respect to which the operator O (and, accordingly, the related operon) has to be activated or blocked, so it is the chief element that rules the whole functioning of the genetic system  $\Omega = \{\text{operator O} + \text{operon}\}$  (*lac operon*), of whose environment, E is an its element (e.g., the  $\beta$ -G in the case of *E. coli*). The action of such an external (with respect to  $\Omega$ ) element E, to activate or block the operator O through the repressor R (which is produced by the genetic system  $\Omega$  – so that, it is an its internal element, differently from E – in, at least, two allosteric configurations, say R and R'), is optimally functional to the production or not of certain enzymes having metabolic ends; moreover, such a molecular process explicates through a clear systemic approach of feedback type, as it constantly verifies the presence or not of the enzyme to be produced, hence activate or not R on the basis of its concentration and use rate, through E (which is also able to change R in R', or vice versa, in dependence on the metabolic needs<sup>16</sup>) (Frontali & Schiesser, 1989; Lattanzi, 1974; Lehninger, 1975; Morchio, 1982; Morpurgo, 1997).

To sum up, we may consider the following, very simple scheme explaining the basic mechanisms of Jacob-Monod model:



where E stands for effector, R for repressor, RGs for regulator genes, and SGs for structural genes (of the operon). The Jacob-Monod pattern was basically verified experimentally by Walter Gilbert and Benno Müller-Hill in 1967, identifying some components of the *lac operon*; further empirical proves were then found by Jonathan R. Beckwith and co-workers, some years later. Anyhow, the operon model due to François Jacob and Jacques Monod is acknowledged as the first pattern to understand the complex interactions between the regulation of gene function or expression and the phenotypic development for both prokaryotes and eukaryotes (Yavin et al., 2011), as well as it promoted the notion of regulatory circuits in biology besides to have been a precursor of either the systemic approach to biology and the developmental systems theory<sup>17</sup> (Baylin, 2016; Cavalli, 2011; Gann, 2010; Tajbakhsh et al., 2011); in particular, Jacob-Monod works stimulated further multidisciplinary researches, and the gene regulatory circuits, whose notion just started with such a pattern, have showed to own the main property to propagate the memory of a specific gene regulatory state long after it has been established and even when the original inducer is no longer present, this last feature being clearly an emblematic epigenetic phenomenon (Cavalli, 2011). So, phenotypic expression of genes depends on the complex interactions and networks of genetic programmes according to a model first postulated just by Jacob and Monod in the late of 1950s, for a simple bacterial system, more than half of a century ago (Rheinberger & Müller-Wille, 2017).

<sup>16</sup> E (i.e., the effector) may also be an environment condition, like the lacking of a certain substance for metabolic ends, which, in this case, rules suitably R or R' in such a manner that it may be now synthesized; this is the case of histidine, for the *E. coli*.

<sup>17</sup> The pioneering work of Jacob and Monod, later acknowledged with Nobel prize in 1965, besides to have pointed out the systemic functioning of gene expression regulation in prokaryotes, stood out too that DNA follows a Boolean logic, hypothesizing that every other biological gene regulation system obeys to such a basic combinatorial logical principle (Monod, 1970).

## 5. The comparison with the eukaryotic case

From an historical standpoint, in this paper we have briefly recalled *Jacob-Monod pattern* about the  $\beta$ -G synthesis (Jacob & Monod, 1961), as well as, we have pointed out that it might be also seen as one of the first attempts to shed light on epigenetics of prokaryotes, to which will follow then the epigenetics of eukaryotes that, although much more complex than the former, it has yet received help by epigenetics of prokaryotes and, in general, by genetics of bacteria and its basic mechanisms, notwithstanding the remarkable differences between prokaryotes and eukaryotes. For instance, in eukaryotes, genes appointed to enzymatic synthesis are not sequentially ordered one attached to the other in contiguity, differently from the case of prokaryotes in which it has been possible to identify a sequential unity of contiguously ordered genes, forming an *operon*, ruling the enzymatic synthesis itself whose mechanisms depended on such a structurally ordered genes' set; and this does not hold for eukaryotes, supposing therefore that other types of enzymatic synthesis methods hold. Likewise, enzymatic synthesis control seems to have a relatively different role in prokaryotes and eukaryotes, being much more important for the former than the latter. Yet, these aspects may play a certain role in trying to understand the crucial biological evolution bifurcation from prokaryotes to eukaryotes: in fact, as an instance, at the present in none eukaryote, even the most primitive one, it has not been found any operon, which therefore is a structure typical of prokaryotes only<sup>18</sup> (Gann, 2010; Lattanzi, 1974; Morpurgo, 1975; 1997).

Although epigenetic mechanisms inherent to eukaryotes are quite different from those related to prokaryotes, nevertheless a comparative study of either prokaryotes' epigenetics and eukaryotes' epigenetics, with the related mechanisms, might turn out to be useful from an evolutionary biology standpoint to try to understand better, for instance, the basic and crucial passage from prokaryotes to eukaryotes (Gann, 2010; Willbanks et al., 2016). Indeed, as has been said above, a main difference between prokaryotes and eukaryotes relies on the fact that enzymatic syntheses are quite different for it, with the latter having biosynthetic processes not based on the ordered structure in operons of DNA genes devoted to biosynthesis as in the former, in that eukaryotes have a more specialized and articulated biological development, temporally scanned, so genes (for biosynthesis) have their own specific and distinct moment of expression, which should have been impossible for a contiguously ordered genes as in prokaryotes. Thus, eukaryotes have biosyntheses quite different from those of prokaryotes, in particular these processes do not depend on environment in regulating genes expression (diversely from prokaryotes case, where this closely depends on environment conditions through E, hence R), that is, they should have much more autonomy and independence from the environment<sup>19</sup>, which are also guaranteed by a more complex and articulated internal cellular structure than prokaryotic cells case (Morpurgo, 1975; 1997).

Indeed, biological evolution of eukaryotes from prokaryotes has been featured just by the attempt to reach an higher internal autonomy of cell, and to keep constant its internal environment, an aim which was achieved thanks at first with the construction of a cellular membrane, so allowing cell to be independent, as soon as possible, from environment. From this step, it followed an enrichment of

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<sup>18</sup> And therefore, as operons are ordered structures, we may also suppose that, their absence in eukaryotes, might be due to the occurrence of symmetry breaking phenomena, to be precise, the breaking of an ordered symmetry (just typical of operons), during such a crucial evolutionary biology bifurcation.

<sup>19</sup> For this reason, such processes are specifically said to be *constitutive syntheses*.

the internal cell organization, with the rising of new biological constituents and settings<sup>20</sup> which entailed a cell autonomy from the external context of the cell, whose structure went gradually to become ever more self-organized<sup>21</sup>, specialized, integrated and articulated until up to reach first primitive forms of eukaryotic cellular nature. At the same time, this latter stored gradually nutritive reserve substances to become ever more self-sufficient in the metabolism as well as independent from the environment, although for a limited time range, with the establishment of new type of biosyntheses processes now depending rather on an internal program than on environment fluctuations as in the prokaryotic case. At the same time, the gaining of cell autonomy from environment has entailed structural/functional enrichment, cellular and biological differentiation, morphogenesis as well as the rising of new mechanisms of replication/duplication (Lawrence, 2002; Morpurgo, 1975; 1997; Ralston, 2008).

Operon genes in prokaryotes, especially in bacteria, are almost simultaneously coregulated as they need to change and adapt rapidly in dependence on environment conditions and the related nutrients available, just these latter being rapidly changing. Such a typical feature of prokaryotes to have the genes grouped into operons, and to be coregulated all together by a common control mechanism, is possible for their simple cellular structure and organization, as well as for their need to adapt fastly to rapid environment changes, a necessity which would not be easily satisfied or accomplished if prokaryotic cell structure weren't very simple, and not so articulated and rich as in the eukaryotic case. Notwithstanding that, prokaryotes have an highly organized genome, as well as are efficiently able to control and regulate their genes and the related expression in dependence on environment conditions and changes (Lawrence, 2002; Morpurgo, 1997; Ralston, 2008).

## 6. Conclusions

As has been said above, prokaryotic mechanisms of gene expression regulation are quite different from those of eukaryotic cells mainly because of the major complexity of the structure, organization and biological function of these latter with respect to the former. If protein synthesis mainly takes place at two chief levels of regulation, the first one being the level of *control of transcription* (from DNA to pRNA/mRNA) and the second one the level of *control of translation* (related to the setting, the beginning and the velocity of synthesis of polypeptide chains), then we may say that the first level mainly regard the prokaryotic case, while both levels are instead involved in eukaryotic case, even if the control of transcription seems to be more economic at molecular level. However, just due to cellular differentiation, gene expression regulation in eukaryotic case operate above all at the translation and post-translational level in a irreversible way, by new mechanisms of gene regulation, typical of higher cells, and nowadays studied by epigenetics of eukaryotes. Furthermore, most of eukaryotic genome is irreversible and constantly repressed, differently of prokaryotic case, besides to have *totipotency*<sup>22</sup> yet not owned by prokaryotes; thus, genome of eukaryote, although potentially totipotent, expresses only a minor part of it, the one appointed to that specific biofunction to which

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20 Like, the important thermal homeostasis.

21 About further and in-depth mathematical aspects of self-organization of living organisms, comprised the *E. coli* case, see (Prigogine & Nicolis, 1981), above all Chapters 14 and 15.

22 That is, any eukaryotic cell contains the genetic information related to the whole living organism to which it belongs, and potentially able to ontogenetically develop it.

it is devoted, leaving unexpressed (or repressed) the remaining part, permanently (Bonaldo et al., 2019; Lehninger, 1975).

Empirical evidence has yet ascertained the basic invalidity of Jacob-Monod pattern (worked out for prokaryotes) for eukaryotes, even if some biofunctional aspects might be considered valid for both types of cells. Higher biological specialization, an enriched cellular structure and differentiation as well as a major degree of internal cellular self-organization with a wider biochemical irreversibility for eukaryotic cells, have made Jacob-Monod pattern inapplicable to eukaryotes, yet remaining a still valid model for prokaryotic cells and their epigenetics. Nevertheless, later models of the genes regulation expression for eukaryotes, like the *Britten-Davidson pattern*<sup>23</sup>, have been then worked out just starting from the Jacob-Monod pattern, which may be seen as first models of an epigenetics of prokaryotes and eukaryotes (Gann, 2010; Lehninger, 1975; Pardee, 2013; Yavin et al., 2011). Therefore, Jacob-Monod pattern, as a valid model for the epigenetics of prokaryotes, may be considered, from an epistemology of biology standpoint, as a prolegomenon for the epigenetics of eukaryotes, which, nowadays, is a central and innovative trend of modern and contemporary biology, as well as a useful starting point to compare epigenetic models to be put into reciprocal comparison to clarify the evolutive biological line from prokaryotes to eukaryotes as well as to understand deeper which may have been the possible causes or reasons about this crucial biological bifurcation, upon which a useful comparison between prokaryotic and eukaryotic epigenetics might turn out to be clarifier (Gann, 2010).

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23 Due to Roy J. Britten and Eric H. Davidson in the late of 1960s; see (Britten & Davidson, 1969) and also (Yavin et al., 2011). A further, remarkable model of regulation of gene expression in higher cells based on Jacob-Monod one, was due to Georgii P. Georgiev in about the same period; see (Georgiev, 1969).

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