THE ORDER OF CONCEPTION PRIORITY

The importance of the order of conception priority in understanding gene regulation

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Abstract

An ongoing problem in Biology can be formulated into the question of how can a complex organism come from a single cell? Or equivalently, how can a *zygote*[1] become an *embryo*? In fact, a *zygote* undergoes *mitosis*, that is, a process through which a cell gives rise to two identical cells; and *cell differentiation*, which is a process by which cells become specialized ones, resulting into a *multicellular organism*, or better, an *embryo*. What is fundamental so as to go from an *unicellular organism* to a *multicellular organism*? What characterizes the process through which a *primitive cell* becomes a *stable cell type* with a certain *purpose* and *functionality*? Or equivalently, how do non-specialized cells, that is, *stem cells* differentiate into *stable cell types*? Further in this chapter, we will suitably touch upon the concept of a *stem cell*.

In order to give an answer to the latter questions, we rely upon an argumentative approach based on the order of *conceptual priority*. We shall behold that the latter approach will reveal a *rational strategy* to evaluate *Huang's model* of *cell differentiation* which will also be applied to size up an extension thereof: *Semrau-Huang's model*. Furthermore, it will allow us to project our analysis onto the realm of the *philosophy of logic* by exploring the primitive nature of the concept of *knowledge* and *judgment* turning our attention toward *perspectivalness* by means of different forms of *epistemic access* to an *epistemic object* which, in turn, will point us out to the necessity of a better clarification of the role of the *first-person perspective* in the *evaluation* and *analysis* of a *phenomenological mathematical model*.

The notion of the order of *conceptual priority* was introduced by Dr. Per Martin-Löf in [1]. In fact, a *concept* precedes another one if the *definition* of the later one is dependent upon the definition of the former. Having defined that, if we draw upon the *epistemic status* of cell activity then we can say that we know that there are specific *molecules* within the cell that catalyze *biochemical reactions* which, in fact, are involved in a variety of cellular processes including *cell growth*, *cell division*, *cell proliferation* and *cell death*. In light of their particular function, those *molecules* actually receive a more sophisticated name, that is, they are known as *enzymes*. The latter *concept*, i.e. being an *enzyme* is solely functional and structural determined.

In order to unveil an entanglement of *notions* paved by the order of *conceptual priority*, we must ask ourselves questions regarding the synthesis of an *enzyme* in the cell environment. Or equivalently, How is an *enzyme* produced in the cell? In fact, if we rely upon the *epistemic status* of the concept of an *enzyme* (see [13]) then we can say that an *enzyme* is a *protein* or a *ribozyme*. Furthermore, the set

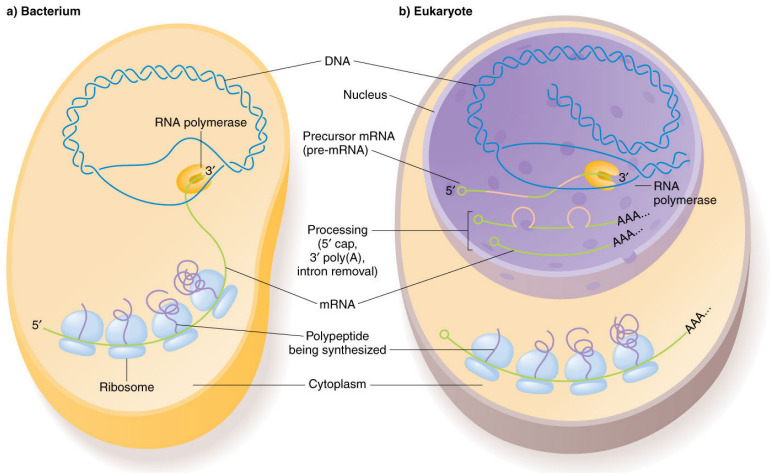

Figure 1 This *cartoon* has been taken from [11]. Here, one sees the depiction of the process of *transcription* and *translation* in a *prokaryotic cell (bacterium)* and in a *eukaryotic cell*. In contrast to a prokaryotic cell, in which translation presumably begins right after transcription, the eukaryotic apparatus is much more complex involving at least three levels of regulation prior to translation: mRNA capping, polyadenylation and RNA splicing.

of enzymes, which are proteins, and the set of enzymes, which are ribozymes, are mutually exclusive. But, what is a *protein*? And, what is a *ribozyme*? Actually, both of them are considered as a *gene-product*. Now, we know that the concept of an *enzyme* is conceptually dependent on the notions of a *protein* and a *ribozyme*, which, in turn, are conceptually dependent on the notion of a *gene*. However, what is a *gene*? Despite the controversy over the concept of a *gene* (see [2] and [3]), we adopt a definition that serves the purpose of our analysis. In fact, according to Gerstein et al [2], a *gene* is a *DNA coding sequence* or a *DNA functional non-coding sequence*. But, the latter concepts are conceptually dependent on the concept of a *DNA*. So, what is a *DNA*? In fact, a *DNA* is a *double-stranded polymeric macromolecule* that contains *genes* carrying instructions for the whole *life cycle* of a *living organism*. What is intriguing about their proposed concept of a *gene*? It is a *circular definition*, due to the fact that it depends on the concept of a *DNA* which, in turn, refers back to the concept of a *gene*. The latter circularity suggests that there might be something essential about trying to capture the notion of a *gene*. In fact, one has that the concept of a *gene* seems to be a *primitive notion*, or equivalently, a notion that cannot be defined in terms of previously well-defined notions whose definitions do not depend conceptually upon the notion being defined. However, how can we understand such a primitive notion then? Further in this thesis, we shall appropriately turn ourselves toward the latter question.

If we want to apprehend their proposed definition of the concept of a *gene* then we need to clarify the notions of a *DNA coding sequence* and a *DNA functional non-coding sequence*. But, such a clarification amounts to answering the following questions. How can a *gene* give rise to a *protein* or a *ribozyme*? How is this synthesis regulated then? Or rather, how does *gene regulation*, that is, the control of the turning on and off of a *gene*, occur? In order to cast light on the latter questions, we need to invoke the *central dogma*, or rather, the central hypothesis of molecular

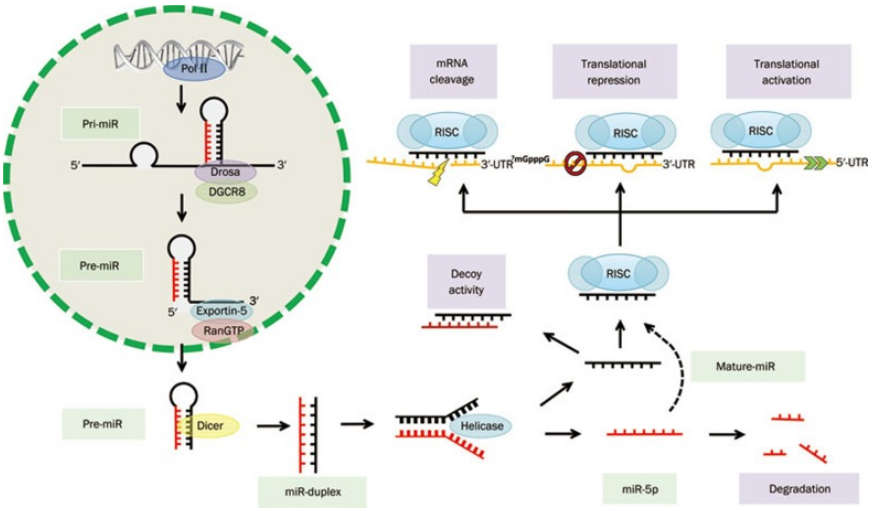

Figure 2 This cartoon has been taken from [10]. MicroRNA mechanism: RNAp II (RNA polymerase II: a ribozyme) transcribes pri-miR (primary microRNA); DGCR8-Drosha complex (DGCR8: a protein; Drosha: a RNase III: a RNA enzyme, that is, a ribozyme that catalyzes degradation of RNAs in small fragments) processes pri-miR into pre-miR; Exportin 5-RanGTP complex (Exportin 5: a protein; RanGTP: a protein) transports pre-miR out of the cell nucleus to the cytoplasm; Dicer (a RNase III) processes pre-miR into mature miR; RISC (a multiprotein complex) binds to miR to provoke repression of the translation of mRNA; RISC binds to miR to cleave mRNA; RISC can promote translation of mRNA by binding to its $5'$ untranslated region ($5'$ *UTR*).

biology as illustrated in Figure 1. Indeed, the *central dogma* is a *dogmatic mechanism* for *gene regulation* that comprises a finite set of *regulatory proteins*, that is, the *transcription factors (TFs)*, which bind specific sites of *DNA* in the surroundings of a *gene* of interest. Thereby, those specific sides in *DNA* bound by *TFs* gives rise to the concept of an *operator*. What do *TFs* bind an *operator* for? In fact, when bound to *DNA*, *TFs* change *DNA-conformation* so they can either repress the activity of the respective *RNA polymerase* (*RNAP*) or facilitate its binding to a fixed DNA sequence, which is defined as the *promoter*. Regarding the later case, *RNAP* will thereupon initiate the process of *transcription* of *DNA* into a *RNA*. In this regard, we identify *TFs* involved in the *repression* of *RNAP* as the *repressor* whereas *TFs* involved in the facilitation of *RNAP* are thought to be the *activator*. Hence, in this hypothetical mechanism[2], the *promoter* can be thought as being in one of the states: *active* or *inactive*.

But, what is a *RNAP*? It is a *RNA enzyme*, or equivalently, a *ribozyme*. More specifically, *RNAP* catalyzes the *transcription* of *DNA* into *RNA*. So, the concept of *RNA polymerase* is conceptually dependent upon the concepts of *RNA* and *enzyme*. But, what is a *RNA*? According to the *central dogma*, a *RNA* is a *polymeric molecule* synthesized during the process of *transcription*. If a *RNA* can be translated into

[2]It might be misleading to use *hypothetical mechanism* in this context if we rely upon several papers in which one can find irrefutable evidences supporting the *falsifiable status* of the *central dogma*, but as the author of this thesis is not able to argue to what extent the central dogma is "true" and if the question is relevant in some "complex organism", he chooses to assign the *hypothetical status* to it.

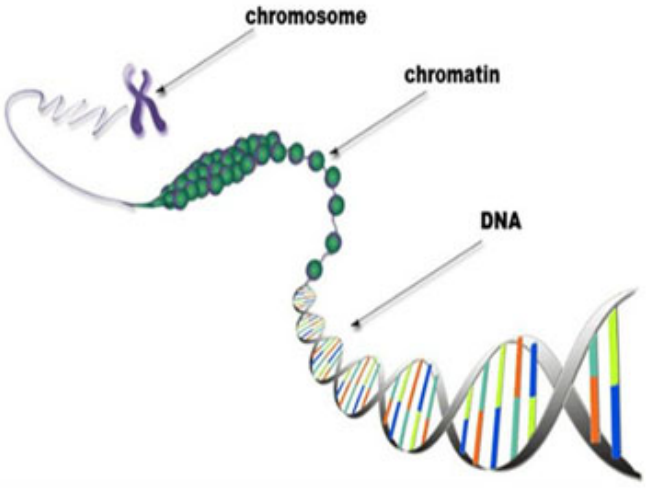

Figure 3 This *cartoon* has been taken from [26]. A *chromosome* as a compacted *chromatin*, or equivalently, a compacted structure consisting of *DNA* wrapped around *histone proteins*.

a *protein* then it is said to be a *coding RNA*. On the other hand, if a *RNA* is already functional, such as *RNAP*, and cannot be translated into any *protein* then it is defined to be a *functional non-coding RNA*. But, what do we mean with a *RNA* being translated into a *protein*? In fact, in this case, a *RNA* is regarded as a messenger *RNA*−a *mRNA*.

Mainly driven by diffusion[3], that is, by performing a *random walk*, one has that a *mRNA* will be transported to the cytoplasm wherein it will be bound by a *ribosome*. But, what is a *ribosome*? It is a *complex molecule* consisting of *non-coding RNAs*, known as *ribosomal RNAs* or *rRNAs*, and lots of distinct *proteins*. The latter will perform the *translation* of a *mRNA* into an *amino acid sequence (polypeptide)* which, in turn, will thereafter fold into a three-dimensional functional molecular structure defined as a *protein*. Now, if we assume that there is a one-to-one correspondence between the set of *DNA coding sequences* and *coding RNAs*; and between *DNA non-coding sequences* and *non-coding RNAs* then we can, in so doing, capture the essence of the definition of the concept of a *gene* introduced by Gerstein et al [2].

What guarantees that a *RNA* really suits the purpose? Or better, how can a *RNA* be correctly transcribed by a *RNAP*? In fact, if an error occurs during the process of *transcription* then *RNA polymerase* can pause *transcription* so as to cleave the error away from that sequence. So, *RNA polymerase* can fluctuate between an *active state* and an *inactive state*, or rather, a *backtracked state* and a *paused state*. The latter mechanism of fidelity in the *transcription* process gives rise to the notion of *proofreading* [14, 15, 16]. How can we conveniently apprehend *RNAs* at the conception level? In fact, *RNAs* can be regarded as the union of two mutually exclusive sets, that is, the one consisting of *coding RNAs*, such as *mRNAs*, and the one formed by *non-coding RNAs*. The latter can be categorized in *non-coding functional RNAs* and *non-coding non-functional RNAs*. As for *non-coding functional RNAs*, one can

[3]Not necessarily true for *prokaryotes*, seeing that there is no *membrane-bound nucleus* so *DNA* is already floating loosely in the cytoplasm.

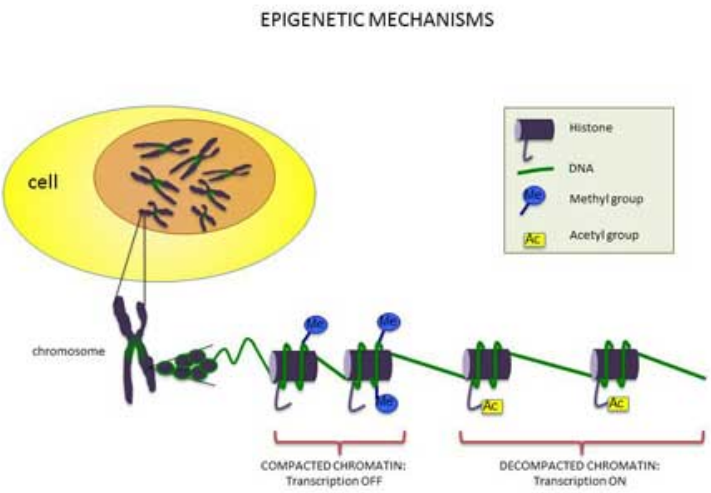

Figure 4 This *cartoon* has been taken from [8]. Here, one sees an illustration of the process of *histone acetylation* and *cytosine methylation*. In fact, HAT enzymes introduce an acethyl group to histone proteins which causes DNA to uncoil itsef. That allows TFs to bind target DNA sequences culminating in the transcription process performed by RNAPs, while HDACs enzymes removes the acethyl group from histone proteins what abrogates TFs due to the coiling of DNA.

reefer to *RNAPs* and to *microRNAs* (*miRNA*; *miR*) as genuine examples. In fact, *microRNAs* are small *non-coding functional RNAs*, as reported in [25], which bind target *messenger RNAs* preventing them from being bound by *ribosomes*. So, it results in *mRNA-degradation* what corroborates the *repression*[4] of the related *gene* as illustratted in Figure 2. The latter process leads to the notion of *gene silencing*. Therefore, in the introduced conceptual framework, one has that the *concept* of a *microRNA* suggests a *stratification* of the notion of *gene regulation* so it can be divided into *pre-transcriptional* one and *post-transcriptional* one.

In *eukariotic cells*, if we want to be a little bit more specific as to *post-transcriptional* regulation then we can also tell that a transcribed piece of *coding RNA* primarily consists of *introns*, that is, *DNA sequences* of a *gene* not used for *translation*, and *axons*, which, in turn, are defined as DNA sequences of a *gene* that will be definitely used for *translation*. Thus, the latter concepts of *axons* and *introns* give rise to the notion of a *pre-mRNA*[5], that is, a *coding RNA* containing *introns* and *axons*. In order to prevent a *pre-mRNA* from being clove by *RNases*, which are ribozymes specialized in catalyzing the *degradation* of *RNAs*[6], one has that a *pre-*

[4]However, it has been also reported that *microRNAs* can promote translation of a mRNA by binding to its 5′ untranslated region (5′ *UTR*) as one can verify in [21].
[5]It is fundamental to noting that *introns* are not necessarily wrong sequences. In fact, *introns* and *axons* in a transcribed sequence, are defined in relation to a specific protein what the respective gene code for. Actually, an unique *gene* can encode many proteins as reported in [17, 18].
[6]Such as RNA viruses.

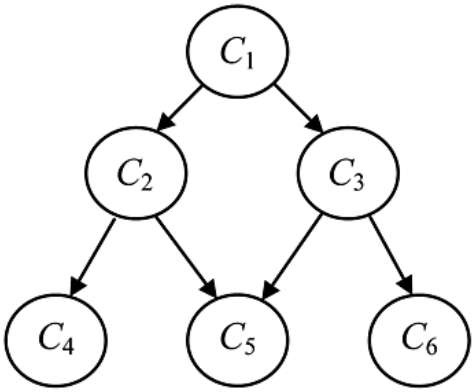

Figure 5 This *cartoon* has been taken from [6]. Here, one sees a "*directed graph*" in which the "nodes" represent the *concepts*. The direction of each "*edge*" is determined by the "*conception order*" which means that the concept C_1 is conceptually dependent upon the concepts C_2 and C_3 and so forth. However, the concepts C_2 and C_3 are not conceptually related to each other. That means that $\{C_1, C_2, C_3, C_4, C_5, C_6\}$ is "partially ordered". Furthermore, the concepts C_1, C_2 and C_3 can be thought as the most fundamental notions or as the irreducible ones, that is, the primitive ones. Therefore, at the conceptual level, one might regard gene regulation as a partially-ordered hierarchical graph.

mRNA undergoes physico-chemical modifications right after *transcription*. In fact, those modifications include the addition[7] of a *cap tail* to its *five-prime end* $\left(5^{'}cap\right)$, and the annexation of a *poly(A) tail* to its *three-prime end* $\left(3^{'}poly(A)\right)$ as shown in Figure 1. In this regard, one has the emergence of the concepts of *mRNA capping* and *polyadenylation*, respectively. Next, that modified *mRNA* undergoes another physico-chemical modification through which its *introns* get extracted by highly complex *macromolecules* made of several *proteins* and *RNAs*. Those molecules are known as *spliceosomes*. So, the latter dwindling process gives rise to the concept of *RNA splicing*. In light of that process, a *pre-mRNA* becomes a *mature mRNA*, that is, a *messenger RNA* ready for *translation*. In sum, in *eukaryotic cells*, one has that a necessary condition for *translation* to occur is that a pre-mRNA goes through *mRNA capping*, *polyadenylation* and *RNA splicing*. Therefore, *stratification* of *gene regulation* flows rationally in the direction of the *conceptual order*. Moreover, one might also assert that the notion of *stratification* of *gene regulation* is actually equivalent to the concept of *layers of gene regulation* introduced by Dr. Stefan Semrau in [24].

Likewise, if we appeal to the *central dogma* to deepen our understanding about the changes in *DNA-conformation* caused by *TFs* then we can assert that *gene regulation* can be separated into *pre-translational* one and *post-translational* one as well. Indeed, for instance, how can a target site of *DNA* become accessible for *TFs*? This is actually controlled by epigenetic mechanisms. But, what are epigenetic mechanisms? Those are mechanisms of *gene regulation* that cause *DNA* to change its conformation without altering *DNA-sequence*. So far, we have brought up the notion of *DNA-conformation* without explaining it sufficiently. So, what do we mean with *DNA-conformation*? It is defined as any feasible spatial arrangement

[7]For biochemical details see [19].

that *DNA* can have. In order to understand it intuitively, we might build upon the order of *conception priority* by invoking the concept of a *chromosome*, which is a compact structure carrying *DNA*. But, how is that compact structure organized? That consists of a coiled *DNA* wrapped around *histone proteins*, which, in turn, gives rise to the concept of a *chromatin*. Hence, a *chromosome* can be defined as a compacted *chromatin* as illustrated in Figure 3. Therefore, consistently, the concept of a *chromosome* is conceptually dependent upon the concept of a *chromatin* which, in turn, is conceptually dependent upon the concepts of a *DNA* and a *protein*.

As an example of such epigenetic mechanisms, one has *histone acetylation* and *cytosine methylation*. As for the former, it consists of the insertion of an *acetyl group* by specific *enzymes*, that is, *Histone Acetyltransferases (HATs)*, to *lysine aminoacids* on *histone proteins*. Hence, a *post-translational* protein modification, that is, *acetylation* of *histone proteins*, cause *DNA* to uncoil itself which creates physical accessibility for *TFs* to bind target *operators* enabling *RNAPs* to access the *activator* so as to initiate the process of *transcription* as illustrated in Figure 4. As for the latter, it is described as the inclusion of a *methyl group* to *cytosines*[8] in the *DNA sequence*, causing *DNA* to get condensed what abrogates DNA-binding proteins *(TFs)* as depicted in Figure 4. Moreover, concerning the respective reversal mechanisms, one has *histone deacetylation* and *cytosine demethylation*. In fact, *histone deacetylation* is the removal of an *acetyl group* from *histone proteins* by *Histone Deacetylases (HDACs)* inducing coiling in *DNA* while *cytosine demethylation* is the extraction of a *methyl group* from *cytosines*, that is, the removal of a barrier switching off *DNA target sequences*[9].

If it is true that most of the *DNA* is useless then it is reasonable to know how genes are actually distributed in the *DNA*. As reported in [12], genes are not randomly distributed in the *DNA*, but they form clusters of genes that are likely to be coexpressed without having necessarily any functional relation. That means that genes belonging to the same cluster in the *DNA* are highly likely to be related to each other at the *transcriptional level* but not necessarily at the *translational level*. Although it seems to be counter-intuitive that neighboring genes might be functionally unrelated to each other, they argue in [12] that a plausible explanation for that is based on *natural selection*, which is the underlying *mechanism* of *evolution*. Indeed, this cluster organizational structure observed in the distribution of genes in the *DNA* has been achieved by fine-tuned evolutionary processes so as to reduce *gene expression noise*.

But, what was the purpose in reducing *gene expression noise*? In fact, a high *noise* in *gene expression* can have a negative effect on *cell fitness*[10]. In order to give an argument for that, we might draw upon the molecular morphology of *ribosomes* and its important roll in the process of *translation*. Indeed, as we described earlier, one has that *ribosomes* are highly *complex macromolecules* consisting of *rRNAs* and many different *proteins*. Besides that, according to [27], the 'total number of ribosomes' in a *mammalian cell (eukariotic cell)* is around 10^7, which, for example,

[8] *Cytosine, adenine, guanine* and *thymine (uracil)* are the four *bases* found in *DNA*.
[9] Or equivalently, *DNA coding sequences* or *DNA functional non-coding sequences*.
[10] A measure of the *health state* of a cell concerning its ability of reproducing itself.

amounts[11] to 0.00002% of the total volume of an *egg cell*. So, if one regard the latter percentage as a significant one then it might be used as a reasonable justification for an eventual use of the notion of *concentration* in an argument referring to the level of ribosomes in the cell. If not then one can also use "the total number of ribosomes" instead. In fact, in no way will the latter choice alter the conclusion of our argument.

However, as we shall see, even though our argument is not contingent upon the notion of the 'level of ribosomes in the cell' being used, it offers a suitable occasion to bring up the issue of *ribosomal heterogeneity* in the control of *gene expression*. To begin with, also according to [27], the number of *ribosomal proteins* in each *ribosome* amounts to 80. So, it is reasonable to imagine that ribosomes might be selective in translating *mRNAs*. In fact, it has been hypothesized that *translation* does depend on the interactions among *mRNAs* and *ribosomal RNAs and proteins*, or equivalently, cells presumably build specialized ribosomes for the synthesis of proteins. The later hypothesis is known as the *ribosome filter hypothesis* as broadly discussed in [28]. But, is there an evidence for that? In [29], it was shown that the variability in the total number of specific *ribosomal proteins* in *mouse embryonic cells (mESCs)* correlates with *cell fitness*.

But, what does the *conceptual order* have to do with how we ought to be conveniently addressing the stoichometry of ribosomes in the cell with respect to the ongoing question? In fact, the concept of *ribosome* is, in particular, conceptually dependent upon the concept of *protein*. Moreover, despite the fact an eukaryotic organism can have approximately 5868 types of proteins with up to 4.2×10^7 protein molecules in average per cell, the synthesis of most of the types of *proteins* reveals a number of approximately $10^3 - 10^4$ protein molecules in average per cell as reported in [30], which, in turn, amounts to 0.000004% of the total cellular volume. How can we arrive at the latter estimation? In [30], they used *saccharomyces cerevisiae* as a model organism, whose diameter is approximately $3 - 4\mu m$. So, our estimation is predicated upon the assumption that a cell and a protein have a spherical shape and on the calculations performed in [31] for the diameter of a protein. However, one has that a single protein type corresponds to $0.002 - 0.02\%$ of the total number of protein molecules in the cell. Hence, if we invoke that a *protein* is structural and functional determined then one has that the *conceptual order*, under the *ribosome filter hypothesis*, perhaps rules out an eventual use of the concept of *concentration* so as to refer to the stoichometry of ribosomes in the cell.

So, an argument for the current question reads as follows. As the 'total number of ribosomes' must be maintained *stable* in the *cytoplasm* for a normal cellular function then a low *noise* in the expression of their respective *DNA coding sequences* and *DNA non-coding sequences* is a favourable condition for *cellular growth, division* and *proliferation* [22], which, in fact, are essential processes for *embryogenesis*. On the other hand, another *via positiva* argument for that, can be given from a *mechanical perspective* given that *gene expression* involves changes in *DNA-conformation* [23]

[11]This estimation was calculated by the author of this thesis by using that the diameter of an *egg cell* is approximately equal to $1.0mm$ and of an *ribosome* is around $25nm$. Moreover, he has been also predicated upon the assumption that their volumes might be approximated by the volume of a sphere.

caused by the binding and unbinding of *TFs*, which, in turn, embroils the *stress-strain*[12] relationship with that. Thereby, a high *expression noise* could potentially increase the chance of damage in the *DNA* structure, causing certain *mutations* to occur, that is, alterations in a *DNA coding sequence* or *DNA non-coding sequence*. Those *mutations* in *DNA* would presumably lead to severe implications for a normal cellular function which, in turn, would impair *embryonic development*.

If the latter arguments are plausible then we should ask ourselves what is fundamental to understanding them as a whole? It is irrefutable that knowing the meaning of the involved *concepts* is a necessary condition for that. However, we argue that apprehension of the notions might not be sufficient to know how the above arguments are interlocked with each other. In fact, the order of *conceptual priority* enables us to make such an connection between them seeing that the concept of a *ribosome* is conceptually dependent on the concept of a *rRNA* and on the concept of a *protein* which, in turn, are both reducible to the concept of a *gene*. How can we connect the above arguments then? In fact, the definition of the concept of a *gene* has been given in terms of the notions of *DNA coding sequence* and *DNA non-coding sequence*. The latter concepts have been clarified in terms of *transcription*, which entails changes in *DNA-conformation*, and *translation*, which involves the binding of *ribosomes* to a target *mRNA*. Therefore, that suffices as an argument of how the aforementioned arguments can be put in perspective to one another.

Are there *non-primitive concepts* in *gene expression* that are non-comparable, or rather, that are conceptually independent upon one another? Yes, the concept of a *mRNA* and the concept of a rRNA are both dependent upon the concept of a *RNA*, but their definitions do not refer back to none of them, which is illustrated in Figure 5. So far, we have argued that understanding how possible *events* in *gene expression* are interrelated to each other requires knowledge of the involved concepts and of their *conceptual order* in relation to one another. Is knowing the concepts and their *conception order* a sufficient condition for us to know *events* in *gene expression* as a whole? No, it is not; and an argument for that relies upon the fact that the notion of *knowledge* is a *primitive concept*. In fact, if *knowledge* is understood as a justified true belief then, intuitively, we cannot conceive of the idea that *knowledge* of all *events* in *gene expression* as a whole can be logically deduced at the conceptual level. That can be done if we know all the phenomena related thereto, that is, if we know all mechanisms involved in *gene expression*, and their agents, which, in this case, are supposed to have been properly conceptualized. Hence, the latter elucidation points us out to the primitiveness of the concept of *knowledge*.

Withal, from a *mechanistic perspective*, we assert that if we know the concepts and their *conception order* in relation to one another then we can potentially know *events* in *gene expression* as a whole. Why? Because *actuality* precedes *potentiality* [*Actus est prior potentia*] as categorically stated by Dr. Martin-Löf in [1]. In fact, if one claims that "something" is potentially doable then it means that it can actually be done. But, what do we mean with knowing *events* in *gene expression* as a whole? The answer for this question is implicit in the aforementioned *mechanistic perspective* of *gene expression*, that is, a *dynamical system perspective* thereof, from

[12] Or better, force and deformation.

which one has that a *behaviour* of a *system* is strictly determined by the interaction among its parts. So, knowing the *conceptual order* of its parts can provide access to the way in which their interaction actually occurs in the *system*. Therefore, this view presumably gives us a systematic approach to get information about the *underlying mechanisms* in *gene expression* by solely using *analytical thought*. Furthermore, it perhaps offers a *rational recipe* to model *gene expression*.

What is essential in this view? Finding the *entailment of notions* with respect to a set of *events* of interest is of utmost importance. This process will unveil the most fundamental notions and, of course, if feasible, the primitive ones. That gives a thinking directionality completely determined by the *conceptual order*. Can we give an example for that? Yes, we can refer to the *birth-death model* of *gene expression* as described in [20]. In that model, it is essential to know that the notion of *transcription* precedes *translation* and that the concepts of a *protein*, a *mRNA* and a *promoter* are entailed with each other in this respective order with regard to the *conceptual order* so that the notion of a *promoter* is the most fundamental one in that sequence of concepts. Further in this thesis, we shall see that the aforesaid *mathematical model*, to some extent, enables us to understand *gene expression*.

References

1. Per Martin-Löf. A path from logic to metaphysics. Atti del Congresso Nuovi problemi della logica e della filosofia della scienza. Viareggio, 8-13 gennaio, 1990.
2. Mark B. Gerstein, Can Bruce, Joel S. Rozowsky, Deyou Zheng, Jiang Du, Jan O. Korbel, Olof Emanuelsson, Zhengdong D. Zhang, Sherman Weissman, and Michael Snyder. What is a gene, post-ENCODE? History and updated definition. Genome Research, 7, 669-681, 2007.
3. Pesole G. What is a gene? An updated operational definition. Gene. 417(1-2):1-4, 2008.
4. Stefan Semrau, Johanna E. Goldmann, Magali Soumillon, Tarjei S. Mikkelsen, Rudolf Jaenisch, Alexander van Oudenaarden. Dynamics of lineage commitment revealed by single-cell transcriptomics of differentiating embryonic stem cells. Nature Communications, 23;8(1):1096, 2017.
5. Arnon Levy and Adrian Currie. Model Organisms are Not (Theoretical) Models. Brit. J. Phil. Sci., 66, 327-348, 2015.
6. C. Laih and S. Wang. Merging: An Efficient Solution for a Time-Bound Hierarchical Key Assignment Scheme in IEEE. Transactions on Dependable and Secure Computing, vol.3, 1, 91-100, 2006.
7. Huang S. The molecular and mathematical basis of Waddington's epigenetic landscape: a framework for post-Darwinian biology? Bioessays;34(2):149-57, 2012.
8. Florean, C. Food that shapes you: how diet can change your epigenome. Science in School, 28, 2014.
9. Furusawa C., Kaneko K. Dynamical-Systems View of Stem Cell Biology. Science, vol.338, 6104, 215-217, 2012.
10. Li, Haoran and B Yang, Burton. Friend or foe: The role of microRNA in chemotherapy resistance. Acta Pharmacologica Sinica, 34 (7), 2013.
11. Peter J. Russel. iGenetics: A Molecular Approach. Pearson new international edition, 2014.
12. Kustatscher G., Grabowski P., Rappsilber J. Pervasive coexpression of spatially proximal genes is buffered at protein level. Molecular system biology, 13, 937, 2017.
13. Doudna J.A., and Lorsch J. R. Ribozyme catalysis: not different, just worse. Nature Structural Molecular Biology volume 12, 395–402, 2005.
14. Schiessel H. Biophysics for beginners: a journey through the cell nucleus. Pan Stanford Publishing, pages: 274-285, 2014.
15. Hopfield, J. J. Kinetic proofreading: a new mechanism for reducing errors in biosynthetic processes riquiring high specificity. Proc. Natl. Acad. Sci. USA 71, 4135-4139, 1974.
16. Depken M., Parrondo J.M., Grill S. W. Intermittent transcription dynamics for the rapid production of long transcripts of high fidelity. Cell Reports 5, 521–530, 2013.
17. Venter, J.C. et al. The sequence of the human genome. Science 291, 1304-1351, 2001.
18. Lander, E. S. et al. Initial sequencing and analysis of the human genome. Nature 409, 860-921, 2001.
19. Albert J. Courey. Mechanisms in transcriptional regulation. Blackwell Publishing, pages: 44-45, 68; 2008.
20. Vahid Shahrezaei and Peter S. Swain. Analytical distribution for stochastic gene expression. *PNAS* **105**, n0.45, 2008.
21. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. Science; 318: 1931–4, 2007.
22. Hunter B. Fraser, Aaron E. Hirsh, Guri Giaever, Jochen Kumm, Michael B. Eisen. Noise Minimization in Eukaryotic Gene Expression. PLoS Biology, vol.2, issue 6, 834-838, 2004.
23. Yekaterina A. Miroshnikova, Michele M. Nava, Sara A. Wickström. Emerging roles of mechanical forces in chromatin regulation. Journal of Cell Science,130, 2243-2250, 2017.

24. Stefan Semrau, Alexander van Oudernaarden. Studying lineage decision-making in vitro: emerging concepts and novel tools. Annu. Rev. Cell Dev. Biol. 31, 317-345, 2015.
25. Lyudmila F. Gulyaeva, Nicolay E. Kushlinskiy. Regulatory mechanisms of microRNA expression. Journal of Translational Medicine, 14: 143, 2016.
26. Uttaranchal, P.G.: College Of Bio-Medical Sciences Hospital. Zoology Department, Lecture notes, 2018.
27. Mitch Leslie : There are millions of protein factories in every cell. Surprise, they're not all the same. Science posts, 2017.
28. Filipek K. ; Derylo K. ; Michalec-Wawiórka B. : The ribosome filter hypothesis and specialized ribosomes. World Scientific News, 32-42, 2018.
29. Slavov N., Semrau S., Airoldi E., Budnik B., van Oudenaarden A. : Differential stoichiometry among core ribosomal proteins. Cell Reports, vol. 13, 2015.
30. Brandon Ho, Anastasia Baryshnikova, Grant W. Brown : Unification of Protein Abundance Datasets Yields a Quantitative Saccharomyces cerevisiae Proteome. Cell Systems 6, 1-14, 2018.
31. Erickson, Harold P. : Size and Shape of Protein Molecules at the Nanometer Level Determined by Sedimentation, Gel Filtration, and Electron Microscopy. Biological Procedures Online 11, 32–51, 2009.