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Julian Chela-Flores

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GENETIC DISORDERS AS COLLECTIVE PHENOMENA *

Julian Chela-Flores **
International Centre for Theoretical Physics, Trieste, Italy
and
Instituto Internacional de Estudios Avanzados, IDEA, Caracas, Venezuela.

ABSTRACT

Genetic disorders due to human chromosome aberrations in number are discussed from the point of view of Molecular Genetics. The etiology of trisomy is discussed in the light of the collective variables recently introduced and an age-dependent metabolic disorder is suggested as a possible etiological factor.

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** Also at the Physics Department, Universidad Simon Bolivar, Apartado 80659, Caracas, Venezuela.

1. INTRODUCTION

The degree of maturity implied by the discovery of the genetic code in the sixties, and the development of biotechnology in the seventies has led to the undertaking of new areas of research for Molecular Genetics, as well as to new aims.

Amongst the new areas emerges Molecular Psychiatry. Some aspects of this topic which have recently been clarified are.

-Mental retardation in trisomic-21 individuals has been shown to be intimately related (Barnes, 1987) with senile dementia in patients suffering from Alzheimer's disease (Katzman, 1986).

-The above relationship is suggested by the presence in chromosome 21 of the gene coding for the amyloid protein, which plays a role in the cerebral lesions typical of Alzheimer's disease.

-The neuritic plaques which are deposited in the brains of victims of this condition - as well as in the brains of trisomic-21 individuals - contain a core of amyloid protein.

Amongst the new aims of research in Molecular Genetics we single out the search for mechanisms responsible for the simultaneous activation, or repression of a large number of genes. This work is related to the inactivation of the X-chromosome in female mammals early in embryogenesis, a phenomenon which has not yet been understood from the point of view of Molecular Genetics (Alberts et al, 1983).

In a recent work (Chela-Flores, 1987) we have attempted to approach this question by careful use of cooperative (i.e., collective) variables, rather than variables characterizing a wide variety of bio-

chemical processes which may, separately, contribute to the whole process of genetic expression in the eukaryotic cell, but which may individually be considerably difficult to separate out in a given experimental assay.

In the present work we propose to study the genetic basis of the psychiatric disorder observed in trisomic individuals (mongolism, as well as the Patau and Edwards syndromes). Thus the phenomena underlying trisomy, namely, the nondisjunction of bivalents in meiosis I, will be considered within the approach to Molecular Genetics in terms of collective variables.

This paper is laid out as follows: In Sec. 2 we discuss the mechanics of the chromosomes during normal meiosis. In Sec. 3 we consider the exceptional cases where primary nondisjunction occurs, leading to chromosomal aberrations in number. Then, in Sec. 4 we present the arguments in favour of Collective Biology in terms of standard Biochemistry, instead of Physics as in our earlier work, in order to facilitate the understanding of the repressor parameter. This leads, in Sec. 5, to a discussion of the specific case of human autosomal trisomy in chromosome 21 in terms of collective variables. Finally, in Sec. 6, we discuss briefly the implications of the specific metabolic disorder and Down's syndrome.

2. THE MECHANICS OF THE CHROMOSOMES

Some of the most important insights into the mechanics of the chromosomes may be obtained by studying aberrations in structure and number. An example of the latter is an aneuploid, in which addition or subtraction of chromosomes from a normal set occurs. A common type occurring in humans is trisomy in the autosomes, particularly in chro-

mosome 21 (Down's syndrome). For the sake of brevity, we omit a discussion of trisomy in the sex chromosomes.

In the zygotene, the second stage of meiosis, the chromosomes are partially condensed, ready to join their identical copies with respect to their constituent genetic loci (homologues). This process, synapsis, ends when four chromatids are securely joined together into what is known as a bivalent. The actual coupling is guaranteed by a new structure: the synaptonemal complex. The next stage, the pachy - tene, marks the onset of a very extended temporal period. Together, the zygotene and the earlier leptotene last typically at most a few hours. On the other hand, pachytene may last up to days, or even weeks.

The signal for the onset of the next stage, the diplotene, is the uncoupling of the bivalent, allowing the homologous chromosomes the opportunity of receding from one another. The temporal development of this stage is long, implying that abundant flow of metabolic energy, E_m, is available so as to motor the bulk of cell growth. It follows that E_m is sufficiently large to supply the energy required for desynapsis. Yet the bivalent structure is not completely lost, since there is still coupling at one or more chiasmata; complete decoupling is delayed until the anaphase I stage.

3. GENETIC DISORDER: THE PND ANOMALY

On the other hand, the above meiotic stages do not always proceed as expected. A bivalent may fail to uncouple, and its displacement occurs towards one of the poles. In the case of genetic order such displacement was intended for the homologous chromosomes. In the case

that now concerns us, therefore, such an important anomaly has been given the name of primary nondisjunction (PND).

The end product of meiosis in the phase of the PND anomaly is the production of gametes with an abnormal chromosome number. In other words, two of the four haploid nuclei will have an extra chromosome, and the remaining two haploid nuclei will lack that chromosome. Some instances of these trisomies are not aborted automatically, but we shall confine our attention on a specific autosomal trisomy. Before we do so, however, we shall consider briefly the repressor parameter (Chela-Flores, 1987) in purely biochemical terms.

4. THE COLLECTIVE BIOLOGY OF THE GENE: THE QUESTION OF GENETIC EXPRESSION

In order to present the repressor parameter in terms of familiar biochemical concepts, the following remarks need to be considered.

As a given reaction is initiated in the living cell, covalent bonds of macromolecules must be broken. This implies that such bonds must acquire temporarily certain additional energy, which has been called the activation energy E (a). This amount of energy is responsible for making the bonds less stable; in other words, E (a) is responsible for making the bonds more reactive (Keeton, 1980).

The activation energy is fundamental for life, since there is a wide variety of macromolecules that must perform their physiological functions in the living cell without altering these very functions as, for example, histones and DNA in chromatin. Certain enzymes achieve a catalytic reduction of E(a) in such a manner that this energy barrier may be overcome by normal thermal perturbations of the macromolecules at physiological temperatures, thus initiating a given reaction.

In particular, the enzyme RNA-polymerase catalyzes the synthesis of a copy of RNA from a sequence of nucleotides in a certain region of DNA. This process is known as DNA transcription, which occurs while this nucleic acid is closely linked with proteins in units called nucleosomes.

Nevertheless, in order for RNA-polymerase to transcribe DNA, some temporal change in the conformation of the nucleosome is required. Such process requires activation energy E (a). However, this situation is not unique, since other macromolecules shall also require certain further activation energy, so as to achieve an adequate control of genetic expression.

In fact, methylation of genes implies the addition of a methylic group $-CH_3$ to the fifth atom of the cytosine ring. High levels of me - thylation seem to be correlated, in some cases (Bird, 1986) with a reduction of genetic expression. The activity of the enzyme methylase, then plays a role in the regulation of transcription. For its activity this enzyme requires a certain activation energy E'(a). With these examples we can see that, in general, gene expression requires the accessibility of a definite amount of metabolic energy capable of activating different molecular processes:

$$E(a) + E'(a) + \ldots = \triangle \quad , \qquad (1)$$

where the dots denote factors which may contribute to the full expression of the genes; we have merely illustrated two such factors which are well documented with many experiments. In terms of $\triangle$, for example, we

were able to formulate the Lyon hypothesis analytically, thus suggesting a spectrum of possibilities for modelling genetic phenomena (Chela-Flores, 1987).

5. GENETIC DISORDERS AS COLLECTIVE PHENOMENA

The above convenient choice of collective variables may contribute some insights into the etiology of human trisomies. In fact for over sixty years some etiological factors have been considered, in particular altered thyroid function (Vogel & Motulsky, 1986). This suggestion has been difficult to confirm, but this may be due to a longer time interval between birth of the affected children and examination of the mother (Nilsson et al, 1975). In the light of these remarks we shall consider the phenomena underlying the PND anomaly, restricting ourselves to autosomal trisomy in humans in chromosome 21 (the trisomic-13 and trisomic-18 viable aneuploids may be understood similarly).

In terms of the repressor parameter we may interpret some facts that are well-known about the incidence of this syndrome per number of births. In fact, for women up to the age of 20 years the incidence of this syndrome is 1/2300 births; in the range 20-25 years the incidence has already increased to 1/1600 births (Ayala & Kiger, 1984). We may conclude that the failure to trigger the desynapsis in the diplotene may be due to insufficient flow of metabolic energy E_m required to overcome the minimum threshold Δ ($E_m < \Delta$),so that the various enzymatic processes that may be needed to drive desynapsis do not have available their corresponding activation energy E (a).

The metabolic disorder that gives rise to trisomy is clearly age-dependent since it will be more frequent as the age of the mother ranges between 20 and 45 years, the frequency of Down's syndrome reaching the high value of 1/46 births.

Such a metabolic disorder is not surprising, since evidence has been gathered indicating that normal cells undergo some deterioration as a function of age. Essentially this follows from purification of specific enzymes from young and old animals, pointing out the fact that there exists some difference in activity (Murray & Holliday, 1981). The merit of the collective approach to these genetic disorders is that the attention is shifted from the separate molecular anomalous processes to the various physical parameters that may be playing a decisive, pathological role.

6. DISCUSSION AND CONCLUSIONS

In order to illustrate further some advantages of turning our attention from the biochemical aspects of Molecular Genetics to the collective variables such as the repressor parameter, we must look a little closer to the various etiological factors that may affect trisomy in humans.

There may, in fact, be a combination of a purely age-dependent factor (characterized by $E_m < \Delta$) as well as, for instance, hyper - thyroidism, as we have already seen in Sec. 5. A further factor may be related to hyperthermia, since temperature T is known to have an important effect on normal human development. Analytically we would summarize this option by the expression $\Delta = \Delta(T)$. A clinical

observation may illustrate this point: for maternal temperatures greater than 38.9° C, occurring during embryonic days E21-E28 there may occur a variety of neural tube defects such as microcephaly (a condition which is associated with mental retardation), anencephaly, and spina bifida (Lindquist, 1986).

In the presence of such a potentially complex etiology, $\triangle$ may in principle be a function of several physical variables:

$$\triangle = \triangle(E_m , T, \ldots) , \qquad (2)$$

where the dots denote further variables that may play a role as, for example the degree of packing of chromatin, as already suggested (Chela-Flores, 1987). In the present work we have only discussed two such variables, namely temperature T and the inflow of metabolic energy E_m required for providing the activation energies that drive a variety of enzymatic processes. Modelling gene expression may thereby prove to be a valid approach to investigate this important, but unfortunate condition of human development; however, modelling as such lies beyond the scope of the present work.

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REFERENCES

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K. & Watson, J.D. (1983) Molecular Biology of the Cell, pp. 458-459, New York: Garland Publishing Inc.

Ayala, F. J. & Kiger, J.A. (1984) Modern Genetics, 2nd ed. p. 721 Menlo Park, California: Benjamin/ Cummings.

Barnes, D. M. (1987) Science 235, 846.

Bird, A. P. (1986) Nature 321, 209.

Chela-Flores, J. (1987) J. Theor. Biol. (in press).

Katzman, R. (1986) New Eng. J. Med. 314, 964.

Keeton, W. T. (1980) Biological Sciences , 3rd ed. p. 67, New York: W. W. Norton & Co.

Lindquist, S. (1986) Ann. Rev. Biochem. 55, 1151.

Murray, V. & Holliday, R. (1981) J. Mol. Biol. 146, 55.

Nilsson, C., Hansson, A. & Nilsson, G. (1975) Hereditas 80, 157.

Vogel, F. & Motulsky, A. G. (1986) Human Genetics: Problems and Approaches, 2nd ed. p.345, Berlin: Springer-Verlag.