Reprint - Classics in Biology

Vol. 4, No. 1 (2020)
ISSN: 2532-5876

DOI: 10.13133/2532-5876/16963

Stochastic or Deterministic? That is the Question

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Commentary on: Kupiec, JJ 2020, A probabilist theory for cell differentiation, embryonic mortality and DNA C-value paradox, *Organisms: Journal of Biological Sciences*, vol. 4, no. 1 pp. 80-85. DOI: 10.13133/2532-5876/16955

Citation: Paldi, A, 2020, "Stochastic or Deterministic? That is the Question", *Organisms: Journal of Biological Sciences*, vol. 4, no. 1 (2020), pp. 77-79. DOI: 10.13133/2532-5876/16963.

Scientific progress depends essentially on new ideas. Nevertheless, in biology, it is usually difficult to trace back with precision their origin. There are multiple reasons for this. Perhaps the most important of them is the simple fact, that truly new ideas are usually met with doubt and receive little attention at the moment of their publication, usually in a specialized journal. The paper entitled "A probabilist theory for cell differentiation, embryonic mortality and DNA C-value paradox" by J.J Kupiec reproduced in this issue of "Organisms" is a good example. It was published in 1983 and represents the first step toward a new theory of cell differentiation, the theory called ontophylogenesis. According to the main propositions of the paper differential gene expression during cell differentiation and embryonal development is provoked by random interactions between molecules. The apparently predetermined gene expression patterns that characterise the defined cell phenotypes are the results of a selective stabilization of some patterns through interactions between the cells. This way of framing one of the modern biology's central questions calls for the same reasoning Charles Darwin proposed to explain the evolution of biological species. The idea that spontaneous variation followed by selective stabilization of some of these variants can account for the emergence of new cell types during ontogenesis places the evolution of the species and cell types on the same theoretical ground.

The theory outlined in the 1983 paper and developed further in his subsequent publications by J.J. Kupiec found a favorable echo in the community of theoretical biologists and philosophers and stimulated further thinking and discussions. This was not the case in the community of experimental biologists. The paper remained virtually undetected for many years. With hindsight, this is not surprising. Such a theory could not gain high popularity during the heyday of the molecular genetics. The latter considers that embryonal development is a sequence of molecular and cellular events programmed by the genome and there is no place for random changes in development. Such a deterministic framing of the issue is closely related to the pre-Darwinian view of biological diversity and has been criticized many times. Yet, a softer than the original version of the genetic program narrative is still dominating the scientific literature. This version acknowledges the existence of some variations during ontogenesis, but considers them as environmentally- induced that are counteracted by the robustness of the DNA-encoded program. The molecular genetic vision makes predictions on individual cells, genes and molecules on the basis of the averages measured experimentally on populations. The variation between cells or molecules is deliberately ignored because considered irrelevant. While variation is in the *blind spot* of molecular genetics, it is the most important element of the probabilistic model proposed

by Kupiec. Until recently, it was technically challenging to measure variation among the cells. This is now changing; the resolution of the analytical techniques is increasing. It is becoming easy to detect single molecular events in individual cells, analyze the mRNA or protein composition of single cells or measure the dynamic changes of individual cells in vivo. Now, almost 40 years after its publication we realize that the basic assumptions and predictions formulated in Kupiec's 1983 and later papers (Kupiec 1996, 1997, 2000, 2009) are confirmed without exception.

The first such assumption is stochastic gene expression. Transcription of the genes, as any other biochemical reaction in the cell, depends on the interaction between molecular species, each represented by a small number of copies in the cell. For example, there are usually only two copies of a given gene in eukaryotes. The number of transcription factor molecules of a given type is much lower than the number of binding sites of that factor. Therefore, the rate of gene transcription is limited by their diffusion and diffusion is a random process. Although sporadic data had been published earlier (Hume, 2000), the scientific community became aware of the inherent randomness of gene expression after the publication of a key paper (Elowitz et al 2002). This report, using fluorescent microscopy, provided visual demonstration of the stochasticity in living cells. Since then, the phenomenon gained substantial interest and the ubiquity of the stochastic nature of gene expression is not a surprise anymore. A direct consequence of the randomness of gene expression is the spontaneous generation of phenotypic variability. Indeed, substantial differences between cells within the same tissue or clonal populations have been detected. The variation was much higher than expected. In the classical view, such variability is a nuisance that serves as an impediment to reliable behavior (Raj & Oudernardeen 2008 Cell). In Kupiec's framing it is the opposite; spontaneous variation is essential to maintain the capacity of the cell to respond to environmental changes and, eventually, to differentiate. The requirement of continuous phenotypic fluctuation is the second important assumption of the model.

However, if variation is an obstacle that the living cell must overcome to achieve normal function, as considered by the deterministic vision, then there should be evolved mechanisms by which the effects of noise are minimized. Many studies were conducted to investigate the effect of regulatory feed-back or forward loops, cascades and networks on "noise" propagation and a number of interesting individual examples were described (Eldar & Elowitz 2010). Nevertheless, one of the most important discoveries was the demonstration that the capacity of the living cell to reduce molecular fluctuations is fundamentally limited (Lestas 2010). This study demonstrated that the noise (variation in abundancies of the molecular components) decreases with the quadratic root of the number of signaling events. In other terms, it requires sixteen times more investment to simply double the accuracy of a regulatory process. The cell simply can't afford such a high energetic cost required to reduce the fluctuations to a level where regulatory systems can work in a deterministic way. Stability is not an intrinsic property of an individual cell, constant variation is. Therefore, stochastic variation represents a constraint that can't be dismissed, they have to be part of the explanatory scheme of the stability of biological systems.

The third assumption of the Kupiec model states precisely, that stability of cell states in multicellular organisms is the result of cell-to-cell or cell-environment interactions. In this way, multicellular organisms are analogous to an ecosystem where cells are individuals and cell types are species. In fact, the role of cell-to-cell interactions in embryonal development is already well known. The only difference between the deterministic and probabilistic explanation is that the former considers cell-to-cell interactions as an inducer of changes, contrary to the latter, that sees them as stabilizing force. Some recent observations however, are not only compatible with the probabilistic model, but directly refute the deterministic interpretation. For example, in the Drosophila embryo early-expressed genes exhibit the same degree of transcriptional variability. Precise expression profile in the embryo is generated by spatiotemporal averaging (Little et al. 2013).

An explicit prediction of the probabilistic model formulated by Kupiec is the transitory increase of cell-to-cell variation. This prediction is now firmly confirmed. The first observations on hematopoietic stem cells were published as early as 1997 (Hu et al. 1997). They showed that before committing to a cell fate, these cells go through a period of disordered gene expression, when many different genes typical for mutually exclusive cell fates are co-expressed. The authors called this state as "multilineage-primed". This observation has been

confirmed several times (Pina et al. 2012; Moussy et al 2017). Similar observations were reported on other experimental cell systems also (Richard et al. 2016, Mojtahedi et al 2016). Recently, the rise-then-fall profile of the transcriptional variation has been reported to be a universal feature of cellular differentiation (Gao et al 2020).

The 1983 paper was the first step on a long road. Now, 40 years later, far beyond the initial theoretical speculations and conjectures, with a substantial body of evidence as support, the probabilist theory of cell differentiation is on the way to become an alternative to the deterministic view of ontogenesis and to help definitively getting rid of the cryptic finalism hidden in it.

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