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On the developmental self-regulatory dynamics and evolution of individuated multicellular organisms

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Abstract

Changes in gene expression are thought to regulate the cell differentiation process intrinsically through complex epigenetic mechanisms. In fundamental terms, however, this assumed regulation refers only to the intricate propagation of changes in gene expression or else leads to non-explanatory regresses. The developmental self-regulatory dynamics and evolution of individuated multicellular organisms also lack a unified and falsifiable description. To fill this gap, I computationally analyzed publicly available high-throughput data of histone H3 post-translational modifications and mRNA abundance for different *Homo sapiens*, *Mus musculus*, and *Drosophila melanogaster* cell-type/developmental-period samples. My analysis of genomic regions adjacent to transcription start sites generated a profile from pairwise partial correlations between histone modifications controlling for the respective mRNA levels for each cell-type/developmental-period dataset. I found that these profiles, while explicitly uncorrelated with the respective transcriptional "identities" by construction, associate strongly with cell differentiation states. This association is not expected if cell differentiation is, in effect, regulated by epigenetic mechanisms. Based on these results, I propose a general, falsifiable theory of individuated multicellularity, which relies on the synergistic coupling across the extracellular space of two explicitly uncorrelated "self-organizing" systems constraining histone modification states at the same sites. This theory describes how the simplest multicellular individual—understood as an intrinsic, higher-order constraint—emerges from proliferating undifferentiated cells, and could explain the intrinsic regulation of gene transcriptional changes for cell differentiation and the evolution of individuated multicellular organisms.

Keywords: multicellularity, cell differentiation, cell-fate decisions, ontogeny, self-regulation, teleodynamic systems, emergence, evolution, individuation, epigenetic landscape
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1. Introduction

Cell differentiation, if seen as a motion picture in fast-forward, intuitively appears to be a teleological or "end-directed" process, its *telos* or "end" being the multicellular organism in its mature form. The first step for a scientific explanation of this apparent property was given when Conrad H. Waddington proposed his epigenetic landscape model. Influenced by earlier developments in dynamical systems theory [1], Waddington's model showed cell differentiation to be potentially predictable or at least potentially explainable without any teleological reference [2].

The dynamics of the cell differentiation process have been associated with changes in chromatin states and concurrent heritable changes in gene expression that are uncorrelated to changes in the DNA sequence, and therefore defined as epigenetic changes [3, 4]. In some cases, these changes can be regulated extrinsically with respect to the developing organism, as observable in eusocial insects (e.g., a female honeybee larva develops into a worker or a queen depending on the royal jelly diet it is fed [5]). Yet most key changes in gene expression for cell differentiation are not only independent from, but are even robust with respect to extrinsic variables. This indicates that cell differentiation is fundamentally an intrinsically regulated process, for which no falsifiable theory has emerged from the epigenetic framework. Due to our lack of understanding of the fundamental regulatory dynamics, this process has also been dubbed "The X-files of chromatin" [6].

To unravel these X-files, we have to look critically at (i) the regulation of cell differentiation as it is understood today, (ii) the non-genetic information capacity of primordial cells (zygotes, spores, or buds), and (iii) what is assumed to be pre-specified developmental information content in those primordial cells. Modern science regards cell differentiation fundamentally as a dynamical system, where a fixed rule governs the transition between the realizable states of a complex network of molecular mechanisms. Ranging from low-order molecular interactions to chromatin higher-order

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