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Epigenetic cell memory: binary or analog?*

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***Abstract*— Epigenetic cell memory is the property enabling multicellular organisms to keep distinct cell types despite sharing the same genotype. DNA methylation and histone modifications play a crucial role in maintaining the long-term memory of gene expression patterns specific to each cell type. Experimental results in semi-synthetic genetic systems show that these modifications silence and reactivate genes in an "all or none" manner, suggesting binary epigenetic memory (only extremal gene expression levels have long-term memory). However, in recent years, continuous and graded variations of gene expression levels have been identified across multiple cell types. Here, by introducing and analyzing a chromatin modification circuit model, we demonstrate that the experimentally observed bimodal probability distributions of gene expression level, used to support the binary memory hypothesis, are also compatible with the analog memory hypothesis, where cells can maintain any initially set gene expression level. Our study shows that intrinsic noise combined with an ultrasensitive response between the level of DNA methylation writer DNMT3A and DNA methylation grade at a gene can explain how analog epigenetic cell memory leads to a bimodal gene expression level distribution. The model can help design experiments to help distinguish between binary and analog memory, thereby offering a tool for interrogating the very essence of epigenetic cell memory.**

I. Introduction

Epigenetic cell memory (ECM) is the property of multicellular organisms to maintain different phenotypes despite sharing a common genetic sequence. This property is primarily influenced by the compaction of DNA chromatin modifiers transiently recruited to a gene influence the fraction of cells that are silenced or active, rather than directly affecting the gene expression level. Overall, these experimental results support the hypothesis of binary epigenetic cell memory (cells can stably maintain only silenced or active gene expression levels). However, in the past years, graded variations in gene expression levels have been observed across various cell types, such as the ones forming the mouse isocortex and hippocampus [9]. This suggests that cells must have a mechanism enabling them to maintain their specific gene expression level and associated identity.

Here, we explore how long-term memory of intermediate gene expression levels can be achieved and how chromatin modifications affect this process. Our goal is to demonstrate that the experimentally observed probability distributions of gene expression level, used to support the binary memory hypothesis, are also compatible with the analog memory hypothesis (cells can maintain any initially set gene expression level). To this end, we first introduce a mathematical model combining histone modifications and DNA methylation, and exploit Gillespie's Stochastic Simulation Algorithm [10] to understand how system's parameters qualitatively affect gene expression memory. Then, we derive a reduced order model recapitulating the mechanisms behind analog memory and use it to determine how experimental results are compatible with analog memory.