Analog Epigenetic Cell Memory: Biology and Engineering

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The goal of this project is to uncover the molecular underpinnings of *analog* epigenetic cell memory and use this knowledge to establish engineering capabilities for creating autonomous and reconfigurable multi-cellular systems with graded cell-types. We recently discovered that cells keep long-term memory of a wide range of gene expression states through graded DNA methylation, which persists in time at the initially set grade. This is surprising given the current belief that DNA methylation occurs in an “all or none” fashion, making long-term memory an exclusive attribute of active and repressed gene states. This project combines stochastic models of chromatin modification with experiments in engineered mammalian cell lines in order to achieve three objectives. The first objective is to unveil the molecular determinants of analog epigenetic cell memory through a “build-to-understand” approach using our chromosomally integrated reporter system in mammalian cells. The second objective is to establish the engineering capabilities required to precisely modulate analog memory. To achieve this, we propose a hierarchical design in which a “hard” genetic circuit rewires the chromatin modification network to make DNA methylation grade respond to the output of a “soft” genetic circuit that encodes a user-defined gene expression program. The third objective is to establish the engineering foundations required to create multi-cellular systems with user-defined, persistent, yet reconfigurable, spatial gradients of gene expression, in response to transient environmental stimuli. To this end, we will augment the soft circuits with cell-cell communication modules that link the circuit state of one cell to that of nearby cells. This project, if successful, will open new research avenues in the study of cellular differentiation, tissue engineering, and organoids generation. Tools for precise modulation of long-term analog cell memory will impact current DoD-relevant technologies, including the synthesis of complex living materials, the design of interactive biomaterials that store increasingly sophisticated information with minimal power requirement, and next-generation biosensors that record intensity and duration of environmental stimuli. The outcomes of this project will also set the basis to new future technologies of potential DoD interest, such as the creation of human memory organoids for regenerative medicine and performance enhancement.