# Mathematical Model for Controllability of Dynamic Genome Networks

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Chromosome arrangement in the nucleus is highly structured during interphase, the non-dividing portion of the cell cycle. For example, localization of chromosome segments near the nuclear center tends to be associated with euchromatin, gene-rich regions of the genome and high levels of transcription. In contrast, peripheral localization near the nuclear envelope is correlated with heterochromatin, gene-poor regions and reduced transcription. An exception is the vicinity of nuclear pores, where genes are much more actively transcribed in peripheral environments rich in pre-mRNA processing machinery. During differentiation, up-regulated genes migrate into activating nuclear compartments, which are often filled with 'transcription factories', while down-regulated genes move into repressing nuclear compartments.

Although the non-random structure of the interphase genome is widely accepted, and is understood in some detail, it is much less clear how dynamic nuclear geometry relates to genome function. Exquisite nuclear organization is thought to contribute to the highly coordinated expression of genes needed for the proper control of cell function and differentiation; yet testable models of this control have been lacking.

Over the past few years, a new mathematical framework for understanding the self-organizing feedback between structural and functional nuclear organization has emerged from work spearheaded by Indika Rajapakse, a joint postdoctoral fellow with Mark Groudine in the Basic Sciences Division and Charles Kooperberg in the Program of Biostatistics and Biomathematics in the Public Health Sciences Division. Given his background in electrical engineering and mathematics, Dr. Rajapakse has been the driving force behind the mathematical formalization of nuclear structure and function in terms of the spatial (chromosomal proximity) network and the functional (gene co-regulatory) network. Both types of genomic network are state-dependent and dynamic. This means that their collective properties depend on the states of their constituent elements – called nodes in graph theory – and that the pattern of network connectivity (*i.e.,* the 'graph') changes over time, resulting in fluid emergent properties.

In the most recent contribution to their theoretical push forward, Rajapakse and Groudine, in collaboration with Mehran Mesbahi (Department of Aeronautics & Astronautics, University of

Washington), adapt their new framework of interacting state-dependent networks to explain distinct phases of genomic reorganization during cell differentiation. In particular, they focus on network controllability – the ability of external signals or master regulators, such as MyoD, to steer the evolution of genomic networks through their respective state spaces. The authors demonstrate how network entropy (or graph disorder) is positively related to controllability, for example during the differentiation of muscle cells: more disordered networks are more controllable because they have a larger scope of possible behaviors. During cell specialization, entropy of genomic networks first increases during a period of maximal controllability. Subsequently, the interacting genomic networks become more ordered, which stabilizes the cell phenotype. Rajapakse and colleagues also show us how to pinpoint 'driver nodes', which have maximal influence on steering cellular organization. Identification of driver nodes in real genomic networks could eventually contribute to technologies that may allow us to reprogram differentiated cells into pluripotent cells, or to redirect cancer cells along new trajectories that avoid further pathology.

Rajapakse I, Groudine M, Mesbahi M. 2011. Dynamics and control of state-dependent networks for probing genomic organization.*Proc Natl Acad Sci USA* 108:17257-17262.

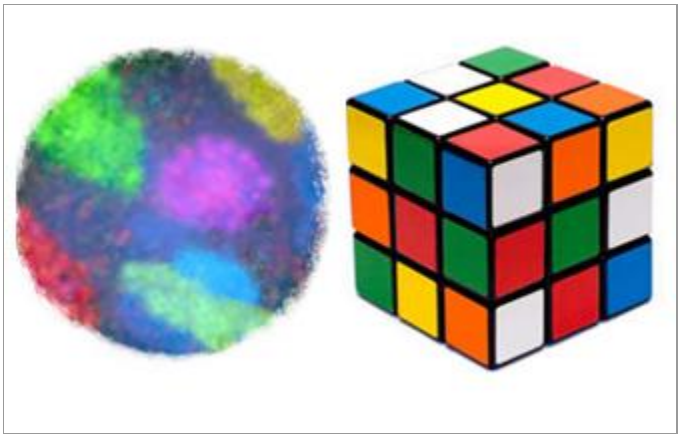

*Image design by ME Arnegard*

Schematic interphase nucleus (left) showing chromosome territories in different colors; territories are visualized by spectral karyotyping (or multicolor DNA FISH). Right: An overly simplistic model of a proximity network of dynamic genome organization resembles a Rubik's cube of sorts. Here, genes are represented by the smaller blocks (or network nodes) that make up the larger cube (or nucleus). However, unlike Rubik's cube, each block can also rotate in any direction about its geometric center. In the simplest state-dependent network described by Rajapakse et al., interactions only occur between blocks that are next to each other, and the type of interaction is determined by opposing face colors of adjacent genes. Chromosomal geometry evolves with changes in the configuration of the metaphorical, nuclear Rubik's cube depicted here. In turn, changes in network structure cause profound changes in cell function through reciprocal interactions with a second network: the gene regulatory network (not shown). Rather than the all-or-none interactions among genes in this heuristic chromosomal proximity network, the authors actually modeled the spatial nuclear network much more realistically using diffusion equations.