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Integrating Gene Regulatory Network Dynamics with Heterogeneous Stem Cell Regeneration

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Abstract. Stem cell regeneration is crucial for development and maintaining tissue homeostasis in self-renewing tissues. The dynamics of gene regulatory networks (GRNs) play a vital role in regulating stem cell renewal and differentiation. However, integrating the quantitative dynamics of GRNs at the single-cell level with population-level stem cell regeneration poses significant challenges. This study presents a computational framework that links GRN dynamics to stem cell regeneration through an inheritance function. This function captures epigenetic state transitions during cell division in heterogeneous stem cell populations. Our model derives this function using a hybrid approach that integrates cross-cell-cycle GRN dynamics, effectively connecting cellular-level GRN structures with population-level regeneration processes. By incorporating GRN structure directly into stem cell regeneration dynamics, this framework simulates cross-cell-cycle gene regulation using individual-cell-based models. The scheme is adaptable to various GRNs, providing insights into the relationship between gene regulatory dynamics and stem cell regeneration. Additionally, we propose a future perspective that integrates single-cell ribonucleic acid sequencing data, GRN analysis, and cell regeneration dynamics using AI-driven tools to enhance the precision of regenerative studies.

AMS subject classifications: 92-10, 92C42

Key words: Cell plasticity, inheritance function, gene regulatory network, cell division, stem cell regeneration.

1 Introduction

Biological processes such as immune responses and cancer evolution are inherently multiscale dynamics that occur at molecular, cellular, and tissue levels [10, 12, 38]. Stem cell

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regeneration is crucial in linking molecular and tissue-level development, thereby maintaining tissue homeostasis [8, 40, 50]. The intricate interplay between gene expression regulation and cell population dynamics is essential for sustaining dynamic equilibrium during stem cell regeneration. However, gene regulation and population evolution dynamics operate on different scales and are typically described by separate mathematical models. It is imperative to bridge the gap between these scales of dynamics.

Cell division is central to stem cell regeneration as it connects molecular and population-level dynamics. At the molecular level, gene regulation networks governing cell cycling dictate cell growth, differentiation, and division decisions. The dynamics occurring within a cell at the molecular level determine the signals that trigger cell division [9]. At the population level, these cell divisions directly influence the evolutionary dynamics of different cell types. Furthermore, variability in the epigenetic state of cells during deoxyribonucleic acid (DNA) replication and mitosis may lead to transitions between cell types post-division, which is vital for maintaining tissue homeostasis and promoting development [43, 44].

The evolution of gene expression in a single cell is often mathematically described using a set of ordinary differential equations

$$\frac{\mathrm{d}\boldsymbol{X}}{\mathrm{d}t} = \boldsymbol{F}(\boldsymbol{X}) - \boldsymbol{K}\boldsymbol{X}, \tag{1.1}$$

where $\boldsymbol{X} = (X_1, X_2, \cdots, X_n)$ represents the transcription level (messenger ribonucleic acid (mRNA) concentration) or protein concentration of multiple genes. The nonlinear function $\boldsymbol{F} = (F_1, F_2, \cdots, F_n)$ describes the rates of transcription or protein production and can be specified based on the gene regulatory network, $\boldsymbol{K} = \mathrm{diag}(k_1, k_2, \cdots, k_n)$ represents the rates of mRNA (or protein) degradation and dilution. Differential equations of the form (1.1), which can be extended to include delays or stochastic fluctuations, have been effectively used to study the dynamics of gene regulatory networks [25, 30, 52]. However, cell division is not accounted for in the differential equation model (1.1), making it unsuitable for long-term processes related to cell proliferation and differentiation.

Extending the differential equation (1.1) to include cell divisions and population dynamics is challenging. However, a top-down approach using the Euler coordinate model can be employed to describe the dynamics of stem cell regeneration while considering cell proliferation and differentiation. Recent studies [28, 29] established a mathematical model for stem cell regeneration that integrates cell division, cell heterogeneity, and the random transition of epigenetic states. This model builds upon the classical G0 cell cycle model proposed by Burns and Tannock [4], introducing a variable $\boldsymbol{x}$ – typically a high-dimensional vector – to represent the epigenetic state of a cell.

In this framework, the rates of cell proliferation, differentiation, senescence, and apoptosis are assumed to depend on the epigenetic state of the cell. Let $Q(t, \boldsymbol{x})$ denote the number of cells possessing the epigenetic state $\boldsymbol{x}$. The evolution of $Q(t, \boldsymbol{x})$ is governed by the following differential-integral equation [28, 29]: