# A Framework for Adaptive Intervention via Digital Twins of Gene Regulatory Networks

Autrio Das 2022112007
Aryaman Bahl 2022113010

October 25, 2025

**Abstract**

This project proposes a novel framework for cancer therapy by conceptualizing a cancer-associated Gene Regulatory Network (GRN) as a controllable engineering system. We aim to build a dynamic digital twin of a patient's GRN, continuously updated with real-time data such as DNA methylation (DNAm). By applying principles from control theory, this *in silico* model will be used to simulate and optimize adaptive intervention strategies. The ultimate goal is to identify minimal "actuator" gene sets capable of steering the cancer network from a malignant state back towards a healthy, stable state, paving the way for personalized, predictive, and robust therapeutic interventions.

## 1 Introduction

Traditional approaches to cancer modeling often rely on static snapshots, failing to capture the dynamic, adaptive, and heterogeneous nature of the disease [1]. This research moves beyond these limitations by embracing the digital twin (DT) paradigm—a persistent virtual representation of a patient's molecular machinery that co-exists with the patient, continuously recalibrating based on new data [2].

The central thesis is the conceptualization of the epigenetic network as a controllable robotic system. In this analogy, the GRN is the system, its state is defined by gene expression levels, "sensors" are molecular assays (e.g., RNA-seq, DNAm data), and "actuators" are therapeutic interventions (e.g., drugs targeting specific genes). This framework recasts clinical challenges like drug resistance as classic engineering problems of disturbance rejection [3]. By focusing on the reversibility of epigenetic alterations like DNAm, we can leverage control theory to design adaptive strategies that robustly steer the network towards a desired healthy state [4]. This *in silico* crucible for therapeutic simulation could dramatically accelerate and de-risk the development of novel, personalized treatments [5].

## 2 Objectives and Motivation

The primary motivation is to shift cancer treatment from a reactive to a proactive and adaptive model:

- To build a dynamic, state-space model of a breast cancer GRN from DNAm and gene expression data.
- To identify a minimal set of "driver nodes" (actuators) that have maximal control over the network state.
- To design and simulate robust control strategies (e.g., feedback control, optimal control) to steer the cancer network towards a healthy state.
- To validate the model's ability to predict network response to simulated interventions and disturbances (e.g., drug resistance).

## 3 Materials and Methods

The framework will be developed using publicly available breast cancer datasets (e.g., TCGA) providing paired DNA methylation (RRBS) and gene expression (RNA-seq) data for both tumor and normal tissues.

The initial step involves Differentially Methylated Region (DMR) analysis to identify significant methylation differences. This epigenetic signal will then be correlated with gene expression data to establish functional links, based on the premise that promoter hypermethylation typically leads to gene repression (negative correlation). This analysis will inform the structure and parameters of the GRN digital twin.

## 4 Initial Results

Data acquisition and preprocessing are underway. Initial statistical analyses will focus on identifying significant DMRs and correlating them with gene expression to build the foundational network model. Figures and plots demonstrating these correlations and the initial network topology are pending.

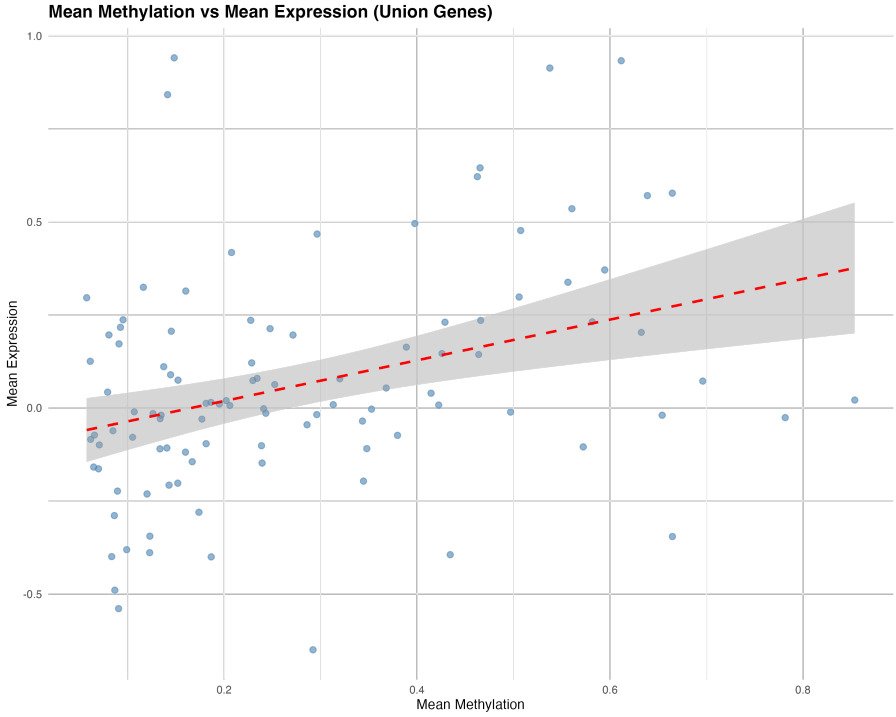


Figure 1: Correlation analysis between mean promoter methylation ($\beta$-values) and mean gene expression (RNA-seq normalized counts) for union genes. The positive correlation (red dashed line with 95% confidence interval shown in gray) indicates that higher methylation is associated with increased gene expression in this dataset, contrary to the typical inverse relationship observed in promoter regions. This may suggest the analyzed regions include gene body methylation or enhancer elements where positive correlations are known to occur.

## 5 Conclusion

This research aims to provide a proof-of-concept for a new paradigm in cancer therapy. By integrating digital twin technology with control theory, we hope to create a powerful simulation tool for designing personalized, adaptive interventions that can robustly manage the complex dynamics of cancer.

## References


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