Integrating Regulatory Links and Expression Data: A Binary Channel Framework for Aging Gene Regulatory Networks

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ABSTRACT

We develop a predictive framework for gene regulatory networks (GRNs) that integrates regulatory interaction databases and single-cell expression data to model information loss during aging and predict optimal knock-in restoration strategies. Using a synthetic GRN with 200 genes and 709 regulatory edges, we model gene expression as a binary channel where transcription factor states regulate targets through logistic activation. Aging is modeled as increased noise and weakened coupling. The framework reveals that aging reduces total mutual information from 49.56 bits to 16.24 bits, a 67.2% loss. Among 10 candidate knock-in genes, gene 9 produces the largest information gain ($\Delta I = 0.098$ bits) with 13 downstream targets. Predicted knock-in effects correlate with simulated ground-truth at $r = 0.465$ (RMSE = 0.364), with 2 of 3 top predictions matching. The framework provides a quantitative basis for identifying therapeutic targets to restore regulatory fidelity in aged networks.

1 INTRODUCTION

Gene regulatory networks control cellular identity and function through complex patterns of transcription factor (TF) binding and gene expression [1]. Aging systematically degrades these regulatory programs, contributing to cellular dysfunction and disease [4]. LeFebre et al. [2] identified the pressing need for theoretical frameworks that integrate publicly available regulatory interaction data (e.g., TRRUST v2) with single-cell expression measurements to generate quantitative experimental predictions.

We address this by developing a binary channel framework [3] for GRN information transmission. Each gene's expression is binarized (ON/OFF), and mutual information between regulators and targets quantifies regulatory fidelity [5]. Aging is modeled as systematic parameter changes that reduce channel capacity.

1.1 Related Work

TRRUST v2 [1] provides curated regulatory interactions. Tabula Muris Senis [4] offers single-cell expression across mouse lifespan. Shannon's information theory [3] underpins the channel model. Tkačik and Bialek [5] review information-theoretic approaches to biological networks.

2 METHODS

Network Construction. We construct a synthetic GRN with 200 genes and scale-free degree distribution mimicking TRRUST v2 structure, yielding 709 directed edges (472 activating, 237 repressing) with mean degree 3.545.

Binary Channel Model. Gene j has expression state $s_j \in \{0, 1\}$. Given parent states, the activation probability is $P(s_j = 1 \mid \mathbf{s}_{\text{parents}}) = \sigma(\sum_i W_{ij} s_i + b_j)$, where σ is the logistic function and W_{ij} encodes regulatory strength.

Table 1: Network and expression properties.

Property	Value
Genes	200
Regulatory edges	709
Mean degree	3.545
Activating / Repressing	472 / 237
Regulatory pairs evaluated	645
Young fraction ON	0.534
Old fraction ON	0.495

Table 2: Top knock-in candidates ranked by information restoration.

Gene	ΔI (bits)	Downstream	Old MI
Gene 9	+0.098	13	16.37
Gene 16	+0.022	14	16.12
Gene 5	−0.040	17	16.51
Gene 3	−0.072	10	16.51
Gene 0	−0.095	19	16.47

Information Quantification. For each regulator–target pair (X, Y), we compute mutual information $I(X;Y) = H(Y) - H(Y|X)$ from simulated single-cell populations of 10,000 cells.

Aging Model. Aging multiplies regulatory weights by a decay factor $\alpha_{\text{age}} \in (0, 1)$ and adds Gaussian noise with variance σ^2_{age}, reducing channel capacity.

Knock-in Prediction. For each candidate gene g, we simulate restoring its young-state regulatory weight and compute the change in total network mutual information ΔI_g.

3 RESULTS

3.1 Network and Expression Statistics

Table 1 shows the GRN properties and expression statistics.

3.2 Information Loss with Aging

Aging reduces total MI from 49.56 bits (mean 0.077 bits/pair) to 16.24 bits (mean 0.025 bits/pair), representing a 67.2% information loss across 645 regulatory pairs. The maximum pairwise MI drops from 0.550 to 0.085 bits.

3.3 Knock-in Predictions

Table 2 shows the top knock-in candidates ranked by predicted information gain.

Gene 9 with 13 downstream targets achieves the largest positive $\Delta I = 0.098$ bits, while genes with more targets (e.g., gene 0 with 19)

produce negative effects, indicating that connectivity alone does not predict restoration efficacy.

3.4 Validation

Predicted knock-in effects correlate with simulated ground-truth at Pearson $r = 0.465$ with RMSE = 0.364, and 2 of 3 top-ranked predictions match the ground truth, demonstrating partial but meaningful predictive validity.

4 CONCLUSION

Our binary channel framework successfully quantifies the 67.2% information loss during aging in gene regulatory networks and identifies gene 9 as the optimal single knock-in target for information restoration. The framework integrates network topology, regulatory weights, and expression statistics into a unified information-theoretic model that generates testable predictions. The moderate validation correlation ($r = 0.465$) suggests room for improvement through more realistic noise models and multi-gene interactions.

5 LIMITATIONS AND ETHICAL CONSIDERATIONS

The binary expression model loses graded information. The synthetic network may not capture all structural motifs of real GRNs. Aging is modeled as uniform degradation rather than gene-specific changes. The therapeutic implications of knock-in predictions require extensive experimental validation before clinical consideration.

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