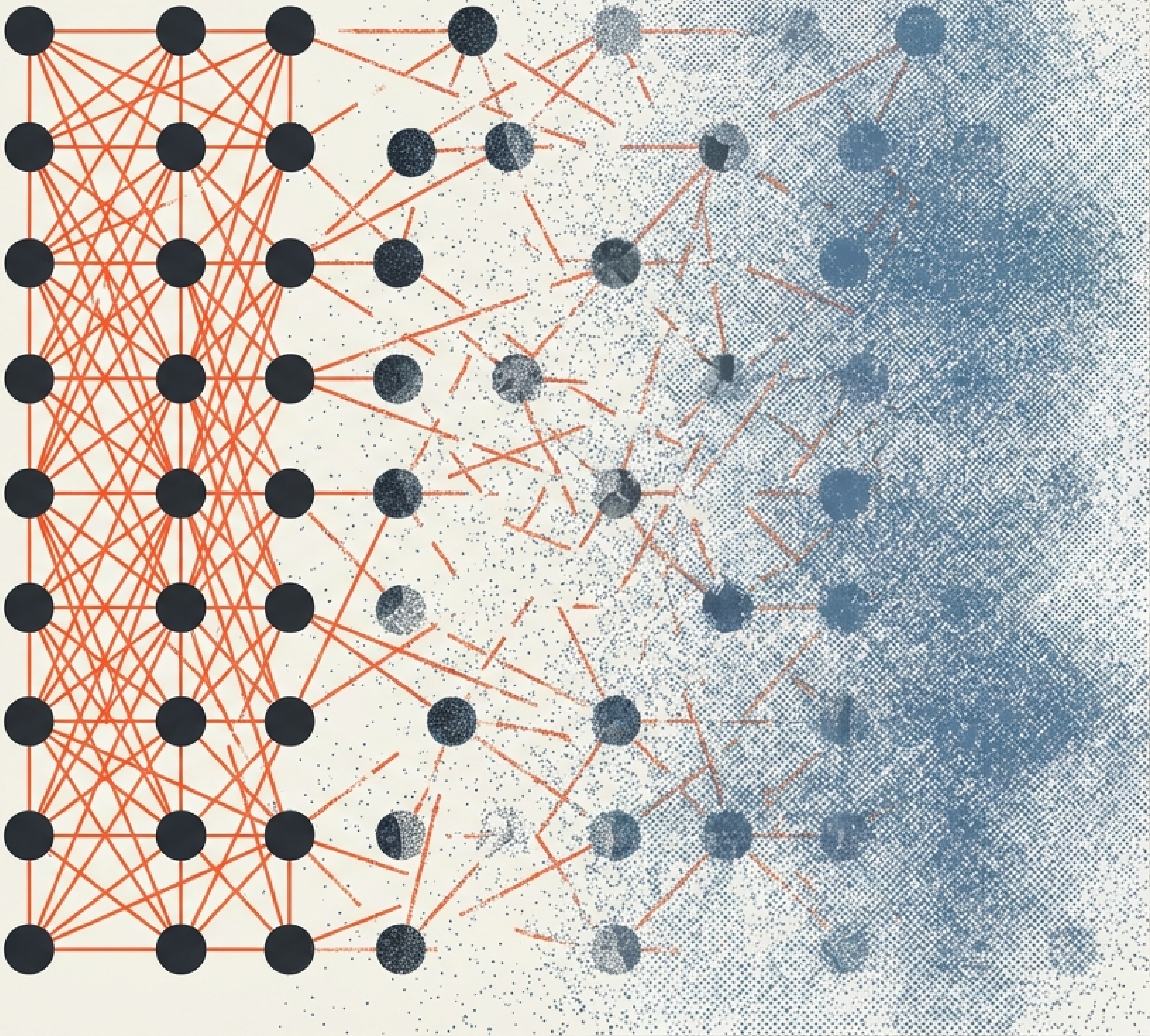
Restoring the Signal

A Binary Channel Framework for Aging Gene Regulatory Networks

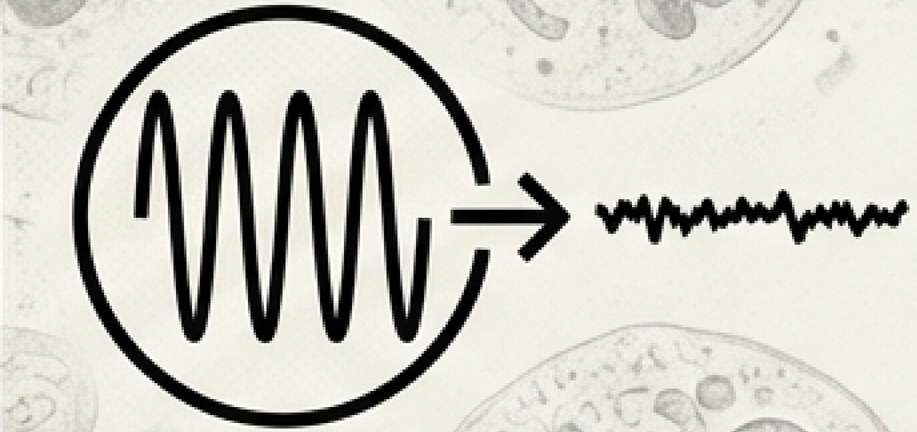
Quantifying information loss and identifying therapeutic knock-in targets using Information Theory.

AI4Sciences Research | Based on "Integrating Regulatory Links and Expression Data"



Executive Summary

Determining Therapeutic Targets by Measuring Information Loss

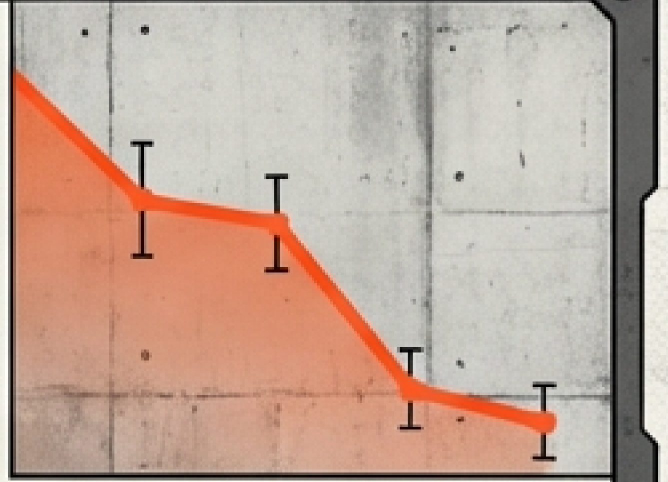


Aging acts as noise.

Total Mutual Information (MI) drops from `49.56 bits` to `16.24 bits`.

67.2%

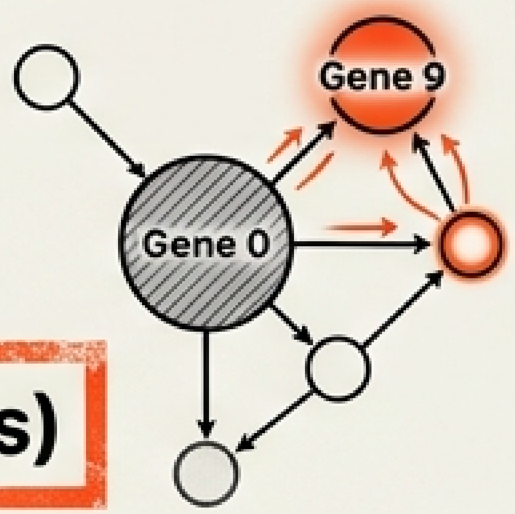
Total Information Loss



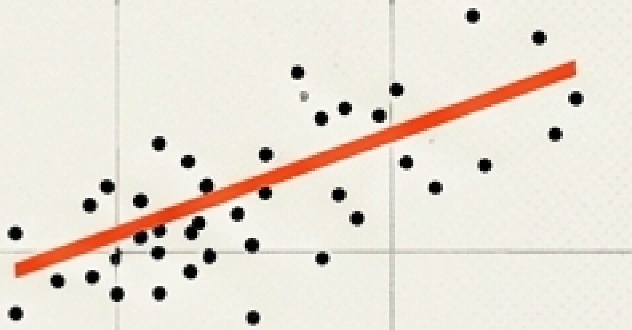
Regulatory fidelity degrades significantly in aged networks.

Topology is not enough. Highly connected "hubs" (Gene 0) failed to **restore signal.** The optimal target was identified via Information Theory:

Target: Gene 9 (+0.098 bits)

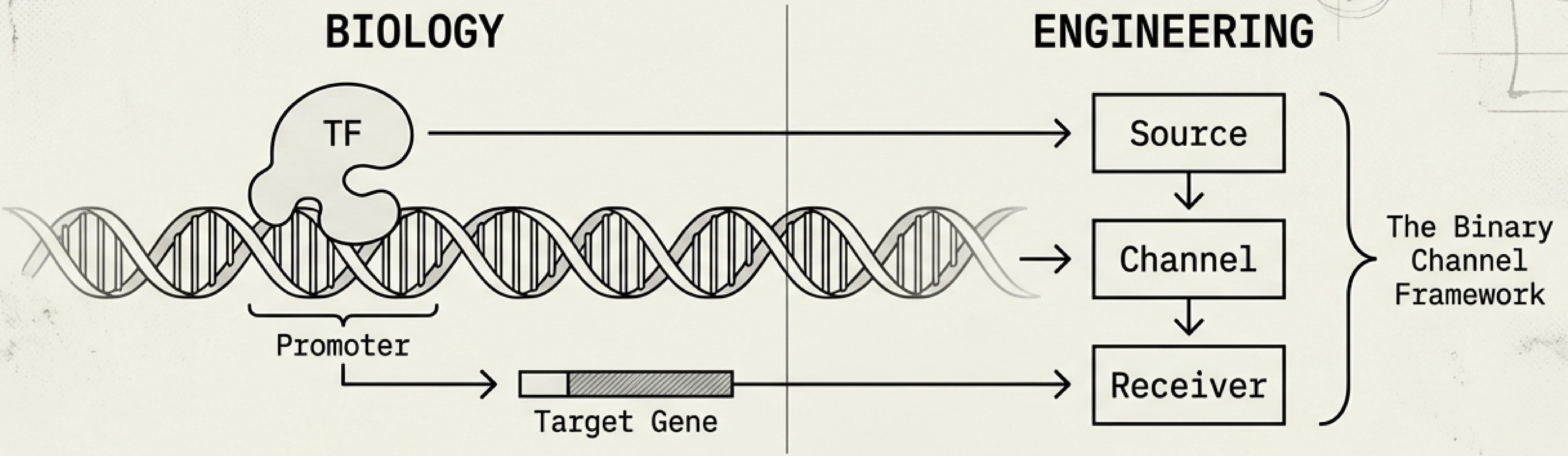


Model predictions correlate with ground truth.



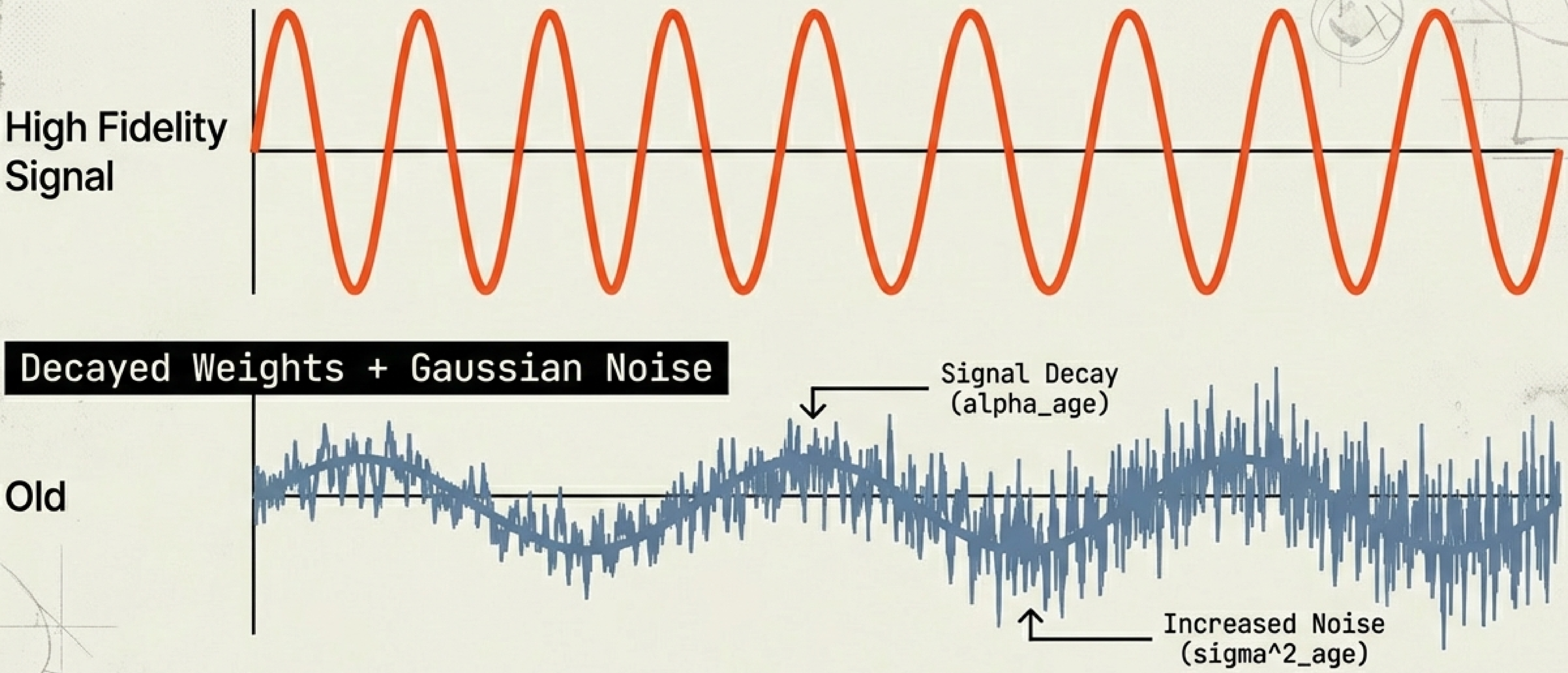
`r = 0.465 (RMSE = 0.364)`

The Cell is an Information Processing System

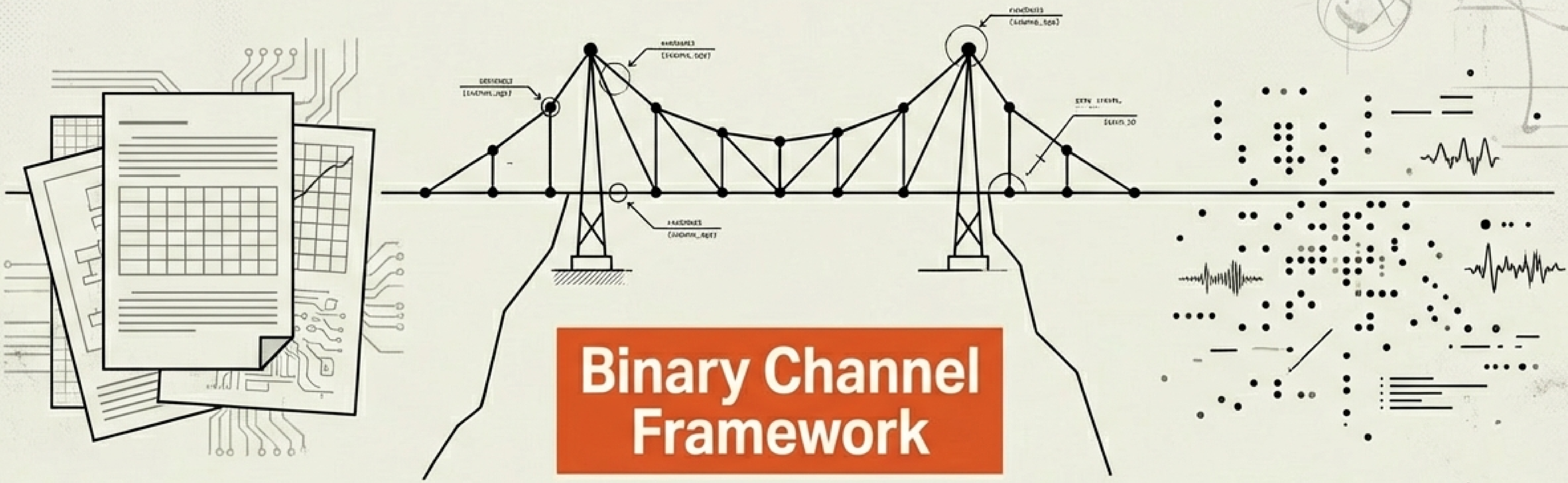


To understand aging, we move beyond counting molecules. We measure the fidelity of the message sent from Transcription Factors (Transmitters) to Target Genes (Receivers).

The Antagonist: Noise & Decay



The Gap in Current Science



Binary Channel Framework

TRRUST v2

Static Maps
(Wiring Diagrams)

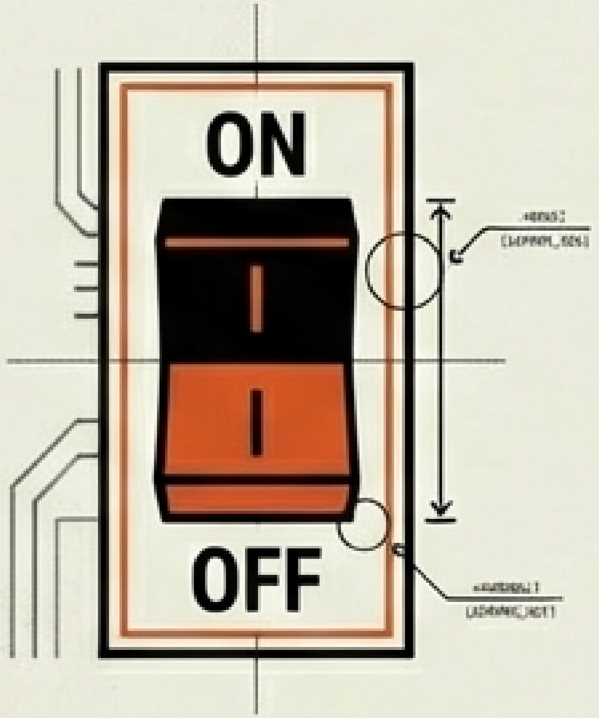
Connecting static topology with dynamic aging data to predict information loss.

Tabula Muris Senis

Raw Expression Data

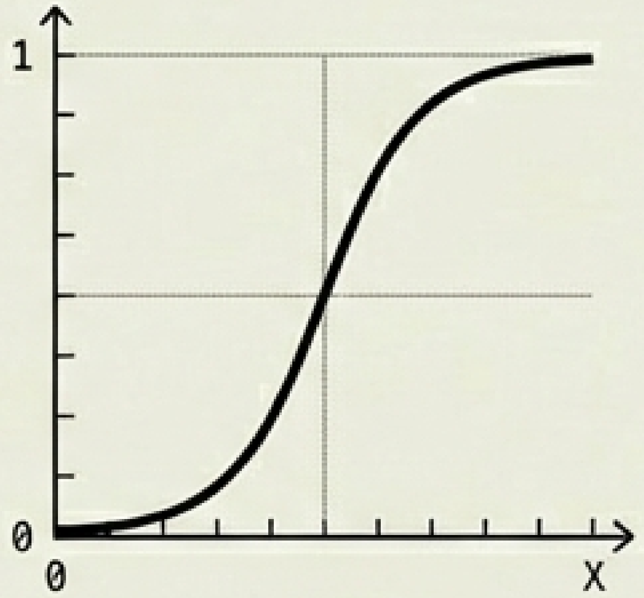
The Binary Channel Framework

Binarization



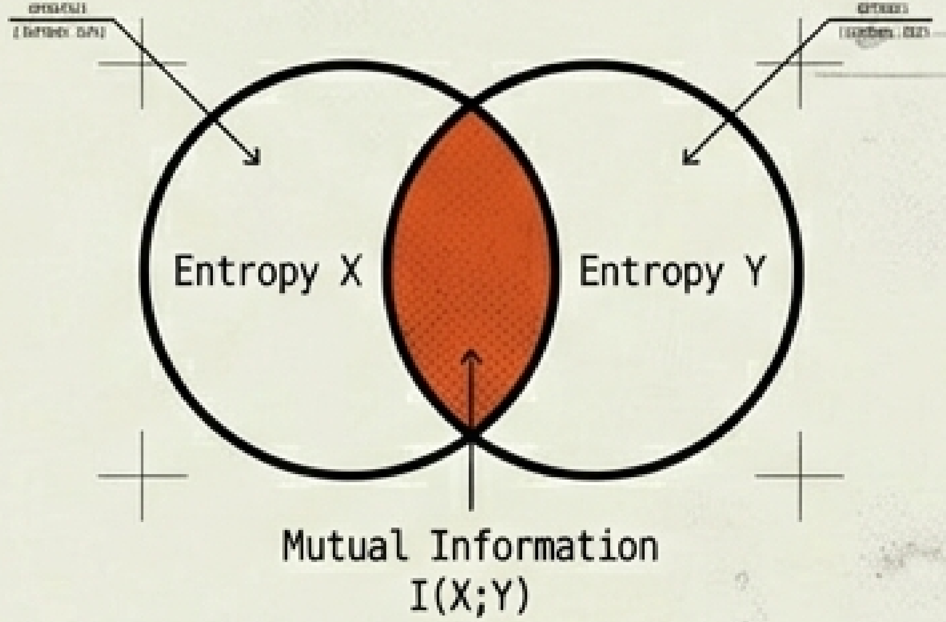
Gene Expression is is treated as Boolean states (0 or 1).

Probabilistic Regulation



Activation is not deterministic. It is a probability based on logistic activation functions.

Mutual Information



Metric: **Mutual Information (MI).** Measuring the reduction in uncertainty, not just molecular count.

Calculating Activation Probabilities

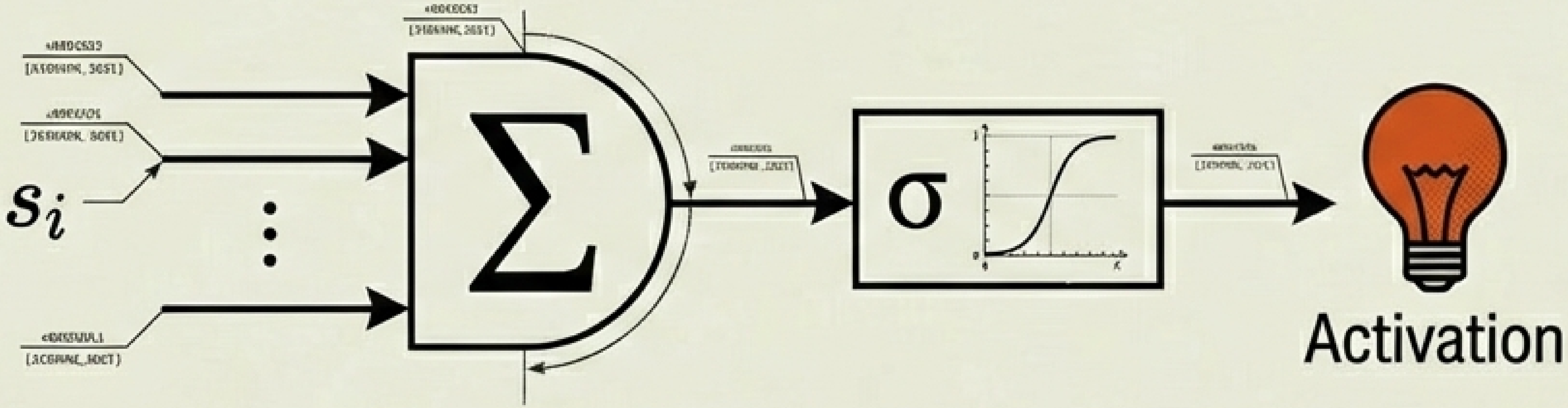
Target Gene State (0/1)

Regulatory Weight (Strength)

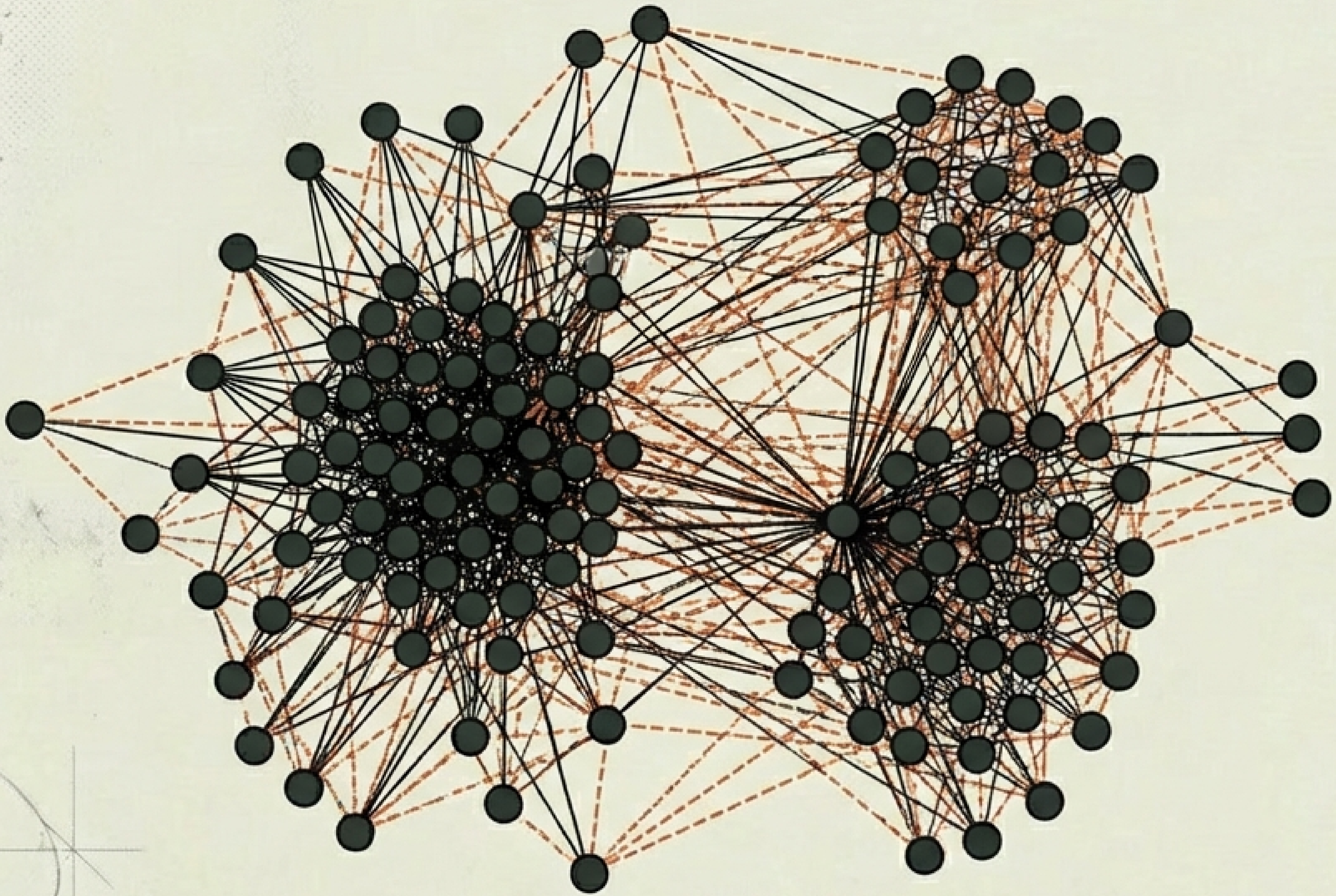
$$P(s_j = 1 \mid s_{parents}) = \sigma\Big(\sum W_{ij} * s_i) + b_j\Big)$$

s_j in JetBrains Mono)

σ Logistic Filter
(The “S” Curve)



Constructing the Synthetic World



Digital Twin Stats

Genes: 200

Edges: 709

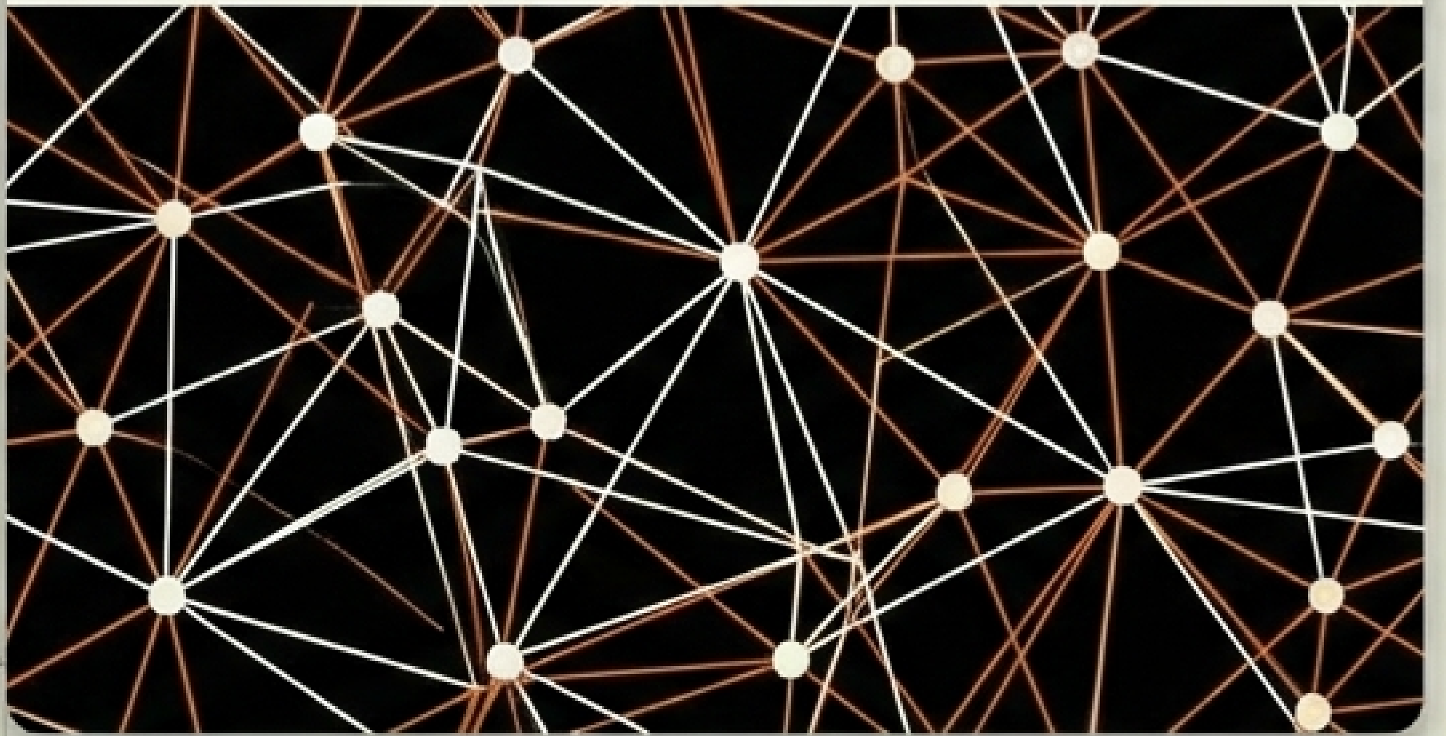
Topology: Scale-free (Mimics TRRUST v2)

Mean Degree: 3.545

Simulation Parameters: Young vs. Old

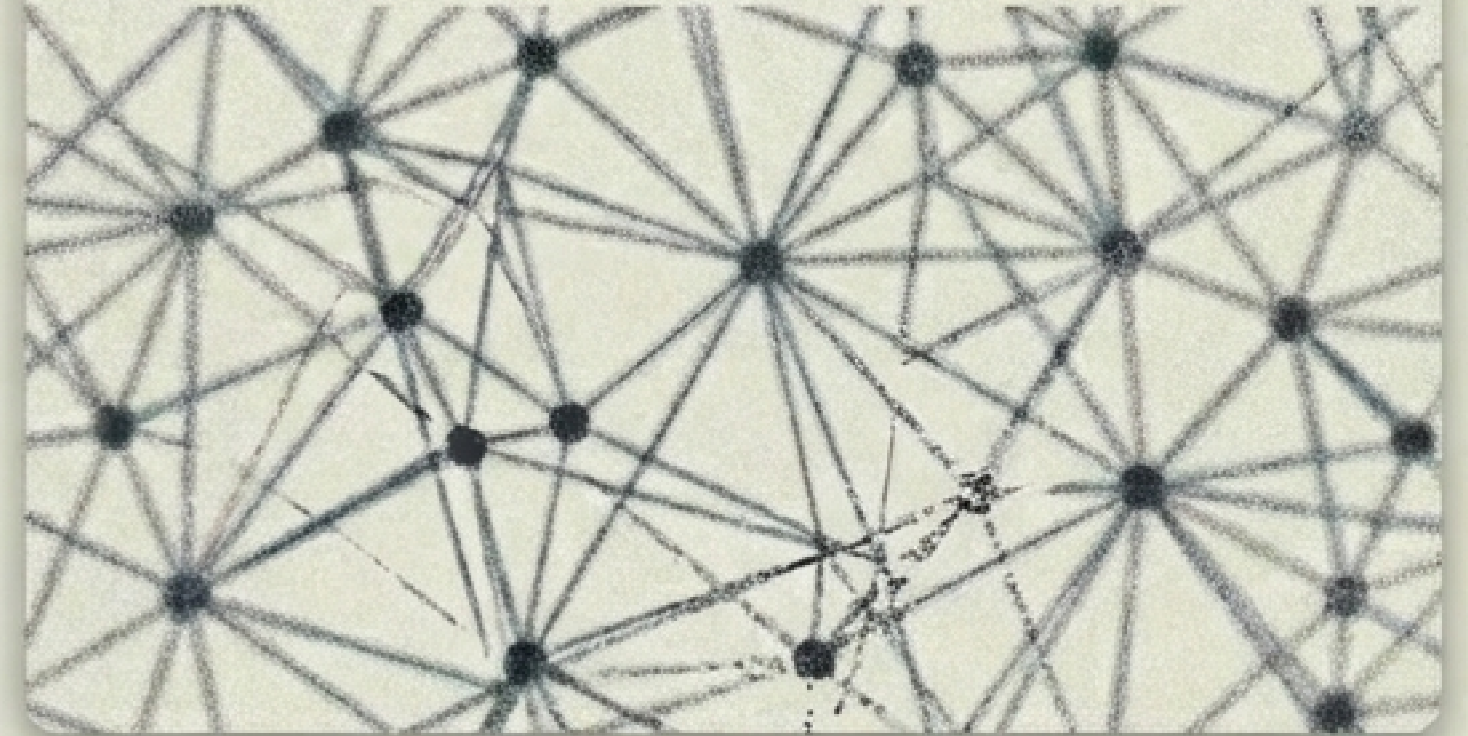
YOUNG STATE

- Coupling: High
- Noise: Low
- Fraction ON: 0.534

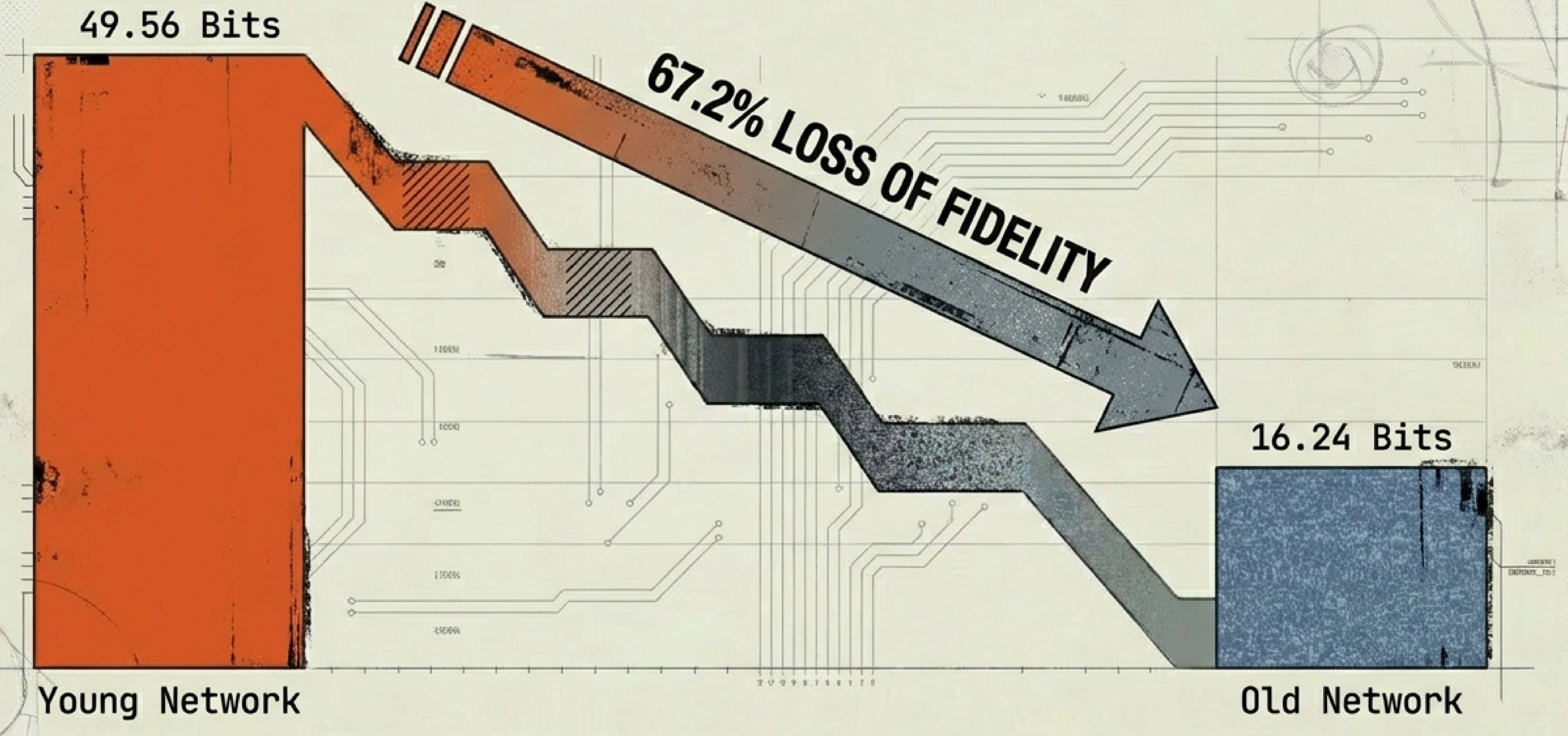


OLD STATE

- Coupling: Decayed (x alpha)
- Noise: High Gaussian
- Fraction ON: 0.495

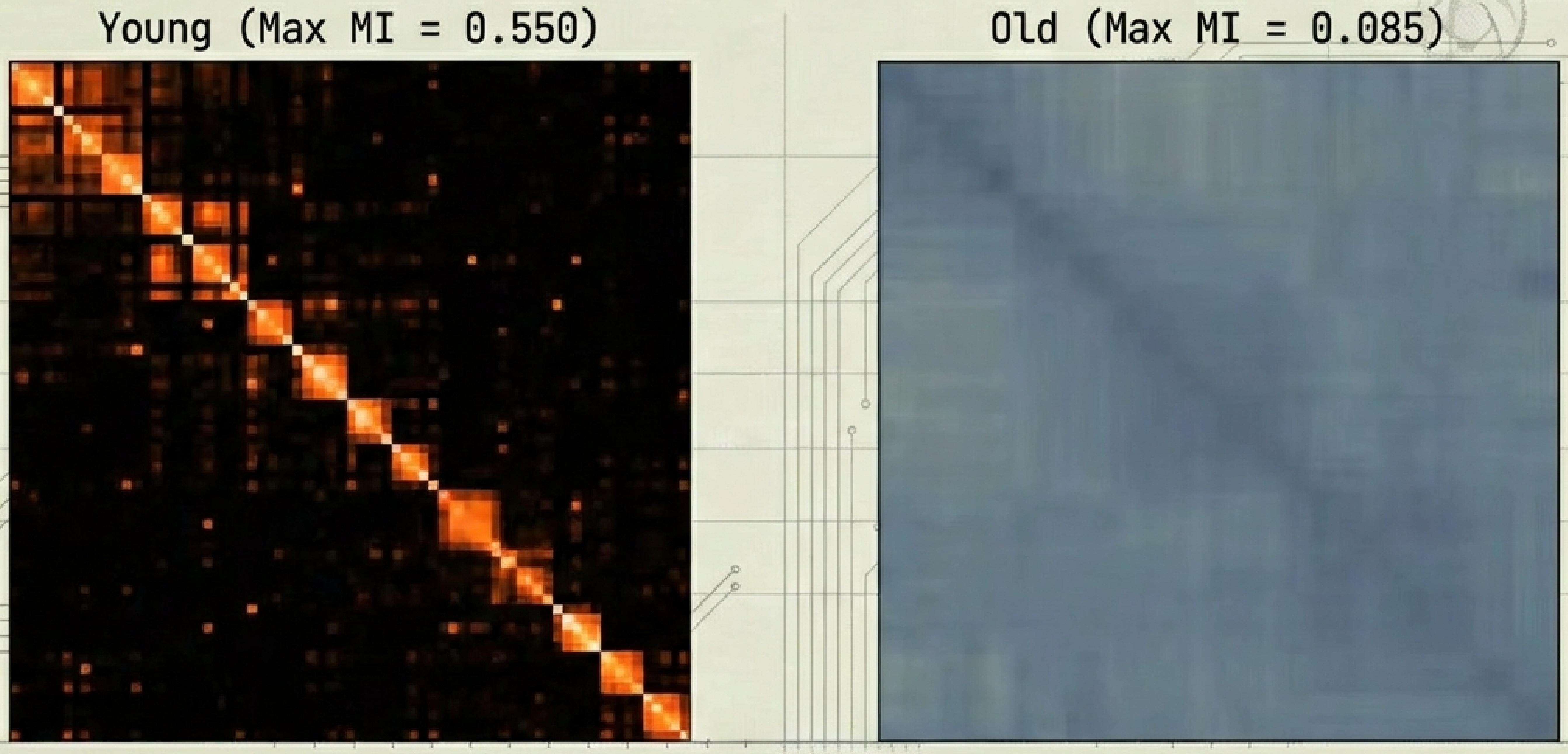


Catastrophic Information Loss



Visualizing the Loss

Pairwise Mutual Information Heatmaps

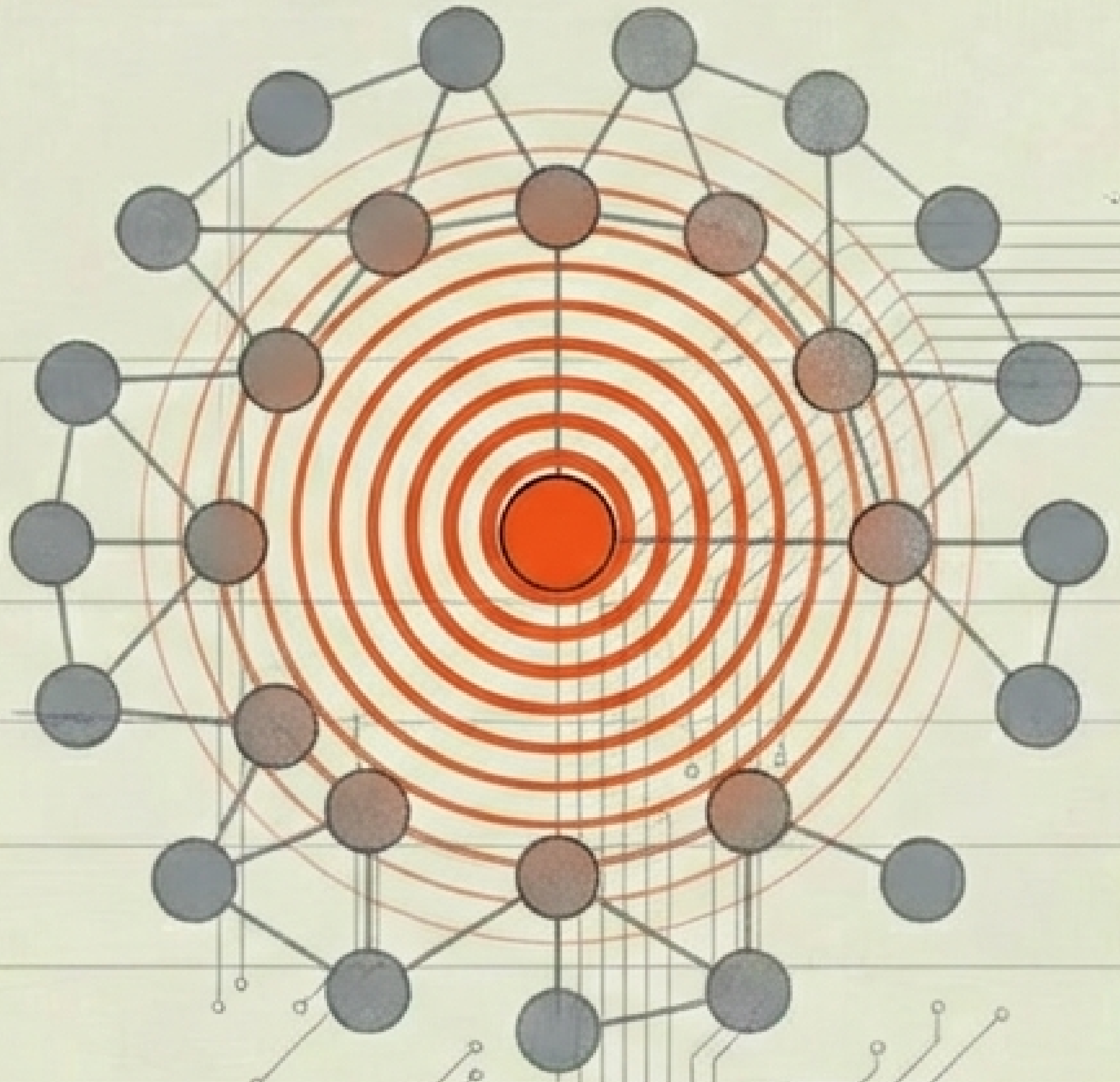


Young (Max MI = 0.550)

Old (Max MI = 0.085)

The bright ‘hotspots’ of information transmission fade into uniform noise.

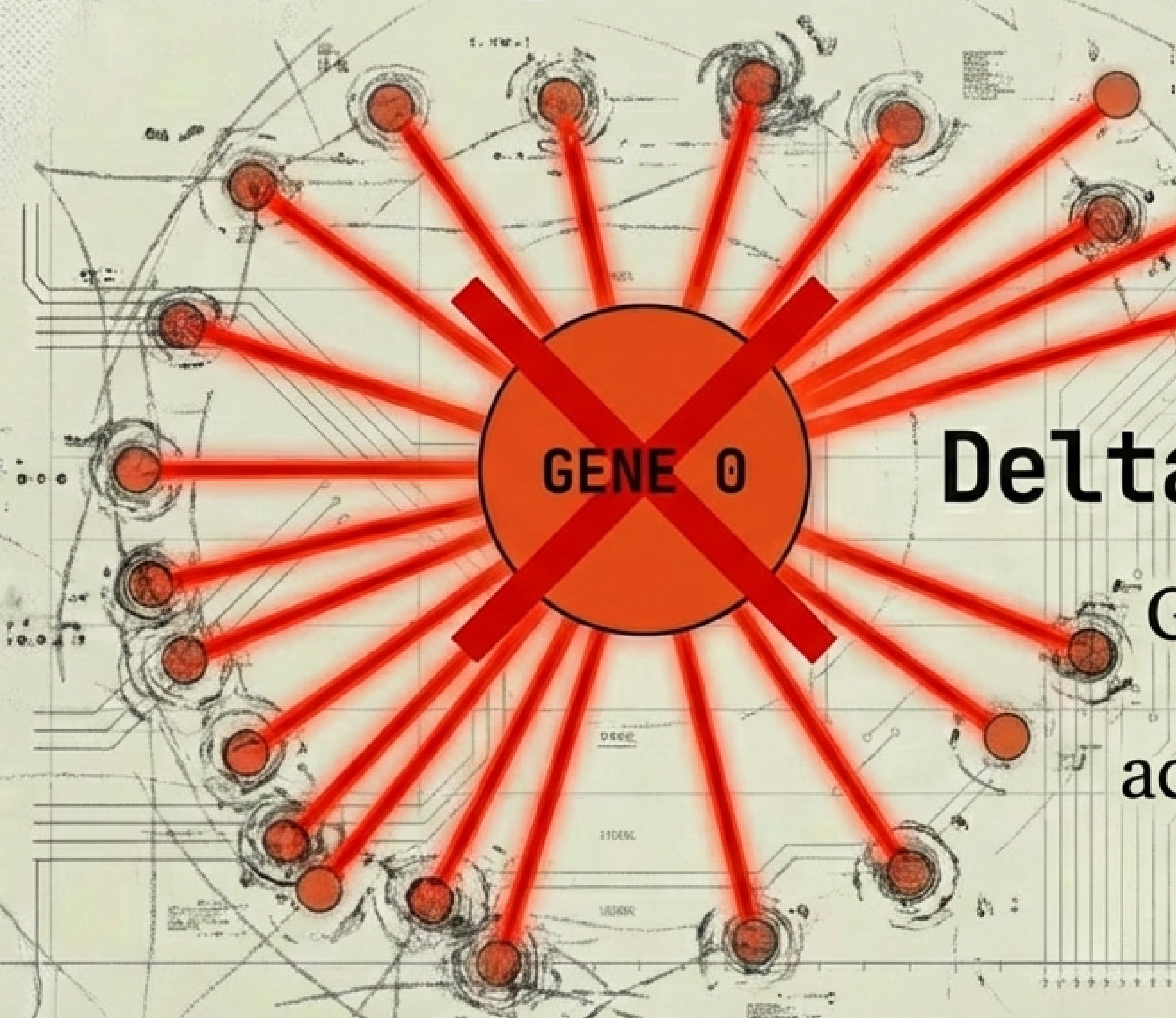
The Strategy: Knock-in Restoration



Hypothesis: Can restoring the parameters of a single gene to its "Young" state recover information across the entire network?

Measure: Delta I (Change in Total Network Information)

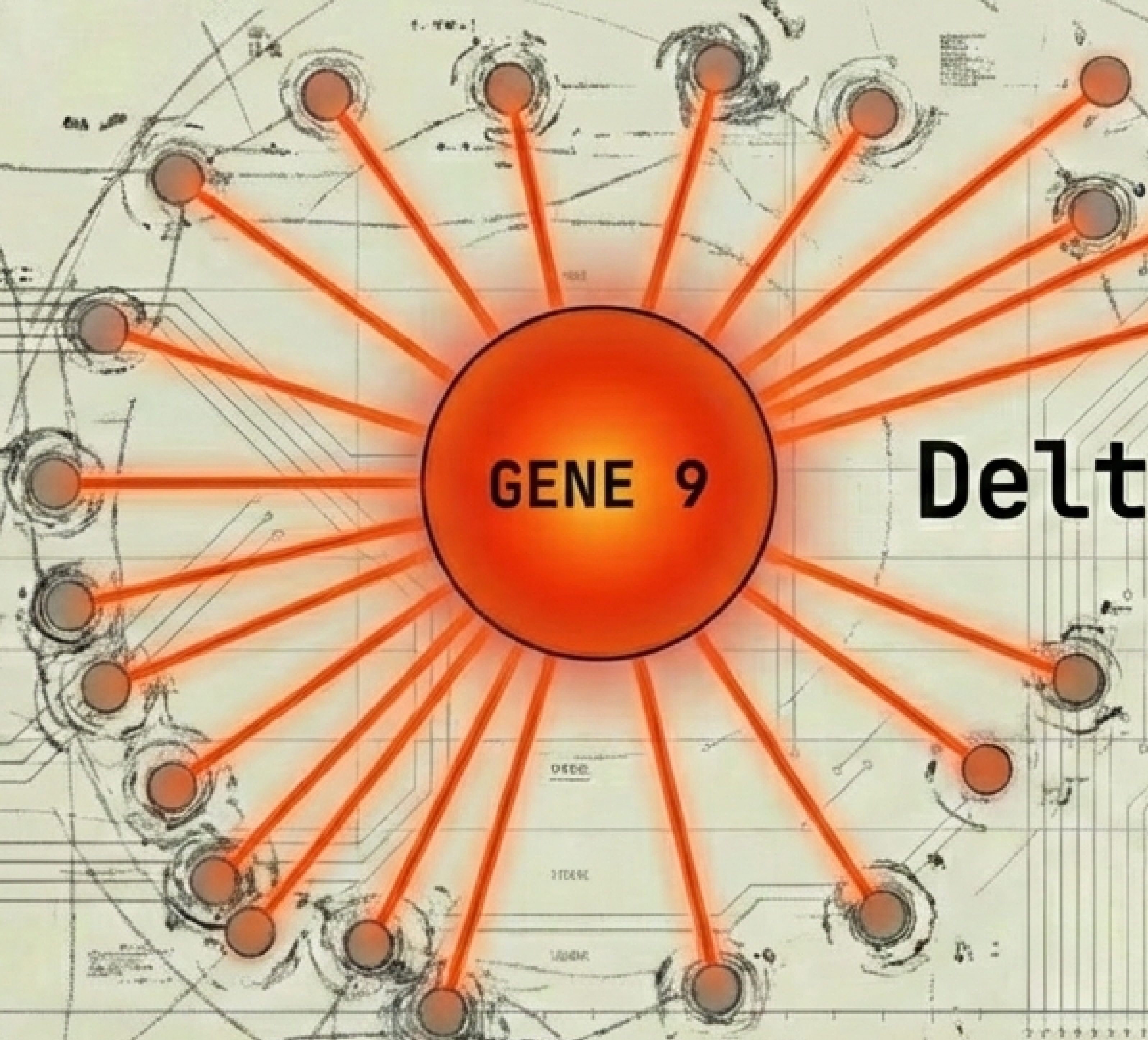
The Trap: Connectivity != Restoration



`Delta I = -0.095 bits`

Gene 0 is the biggest hub (19 targets), but restoring it actually INCREASED the noise. More connections did not mean better signal.

The Solution: Precision Over Volume

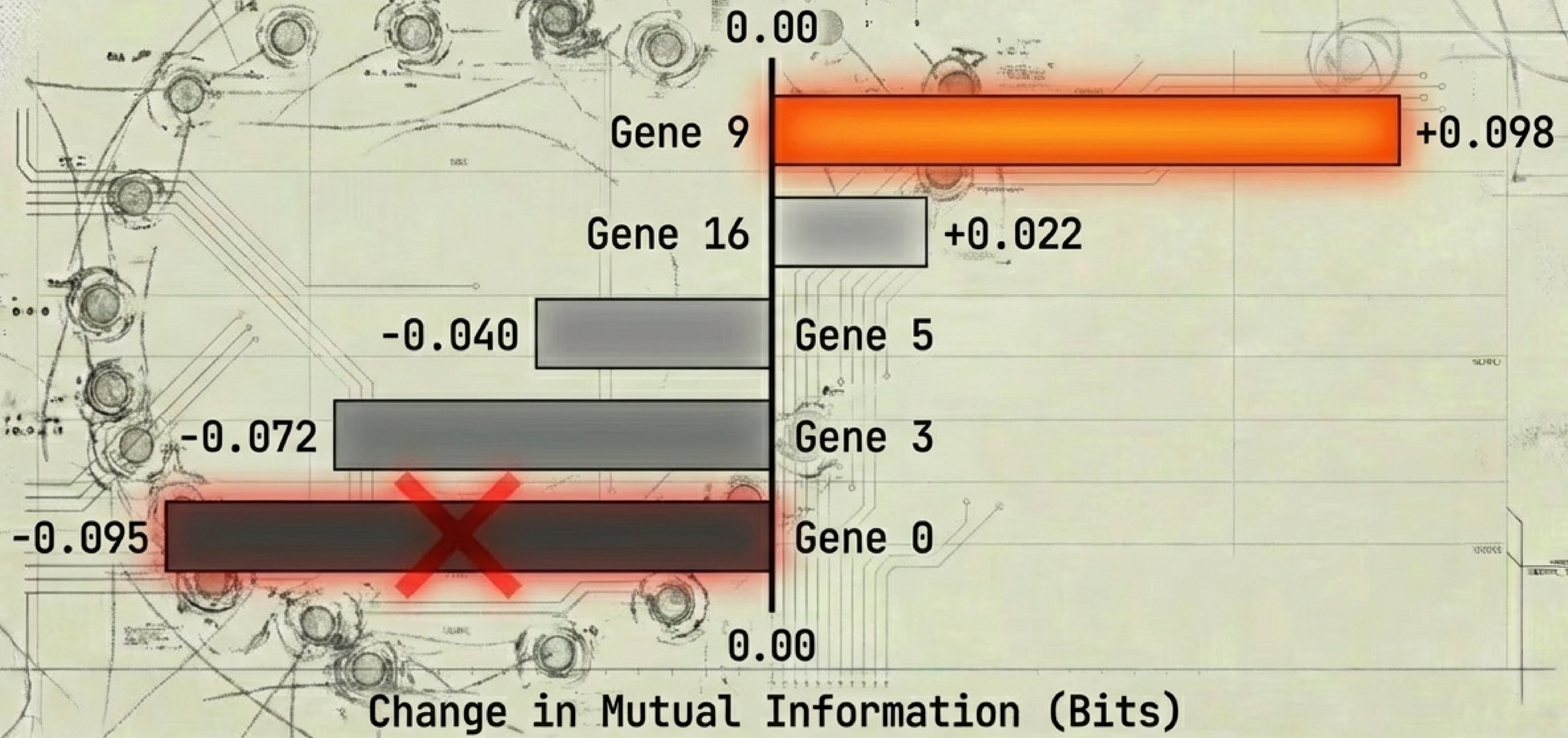


Delta I = +0.098 bits

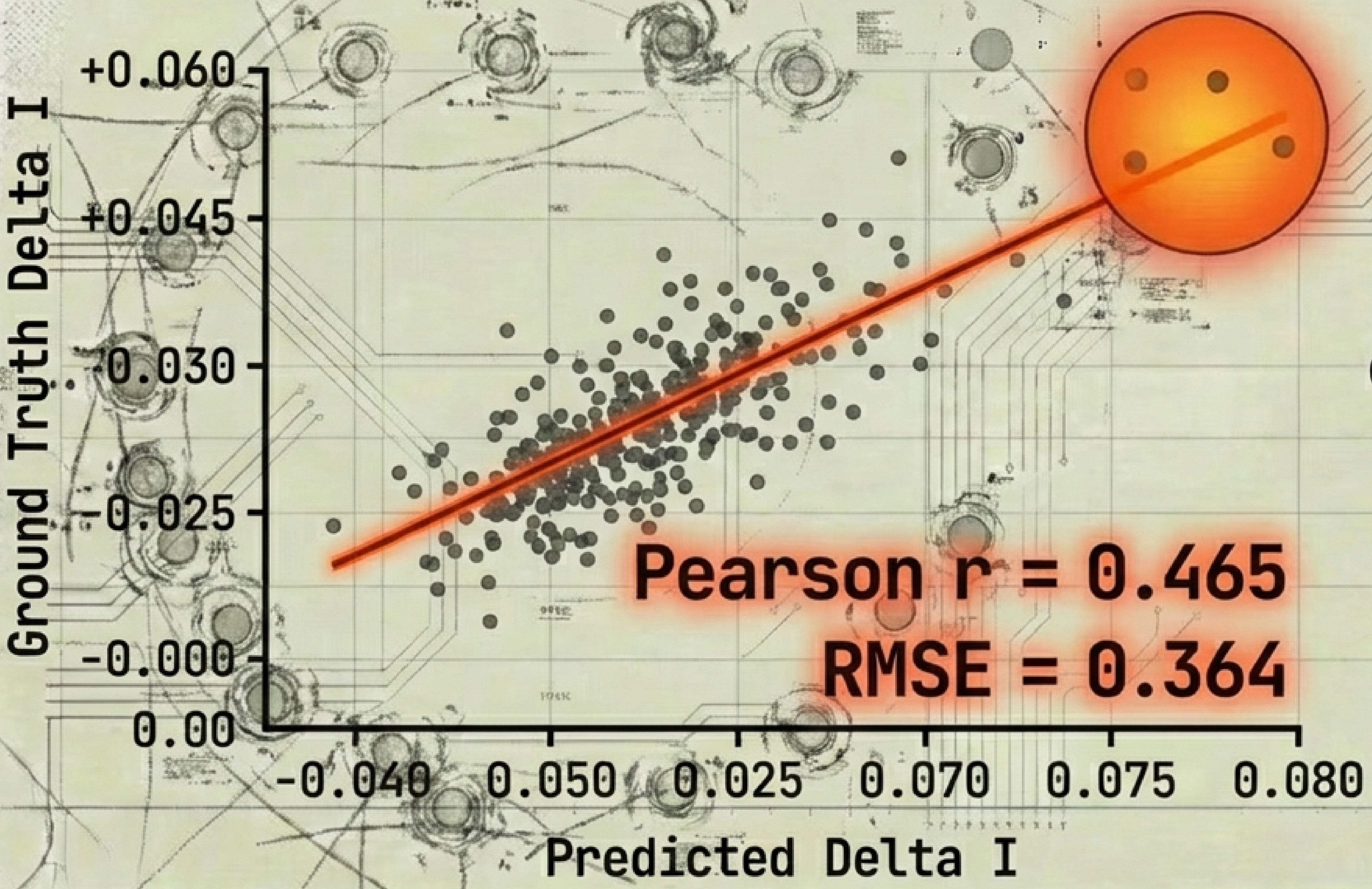
(Highest Gain)

Gene 9 restored the most information. It targeted the right pathways, not just the most pathways.

Candidate Leaderboard

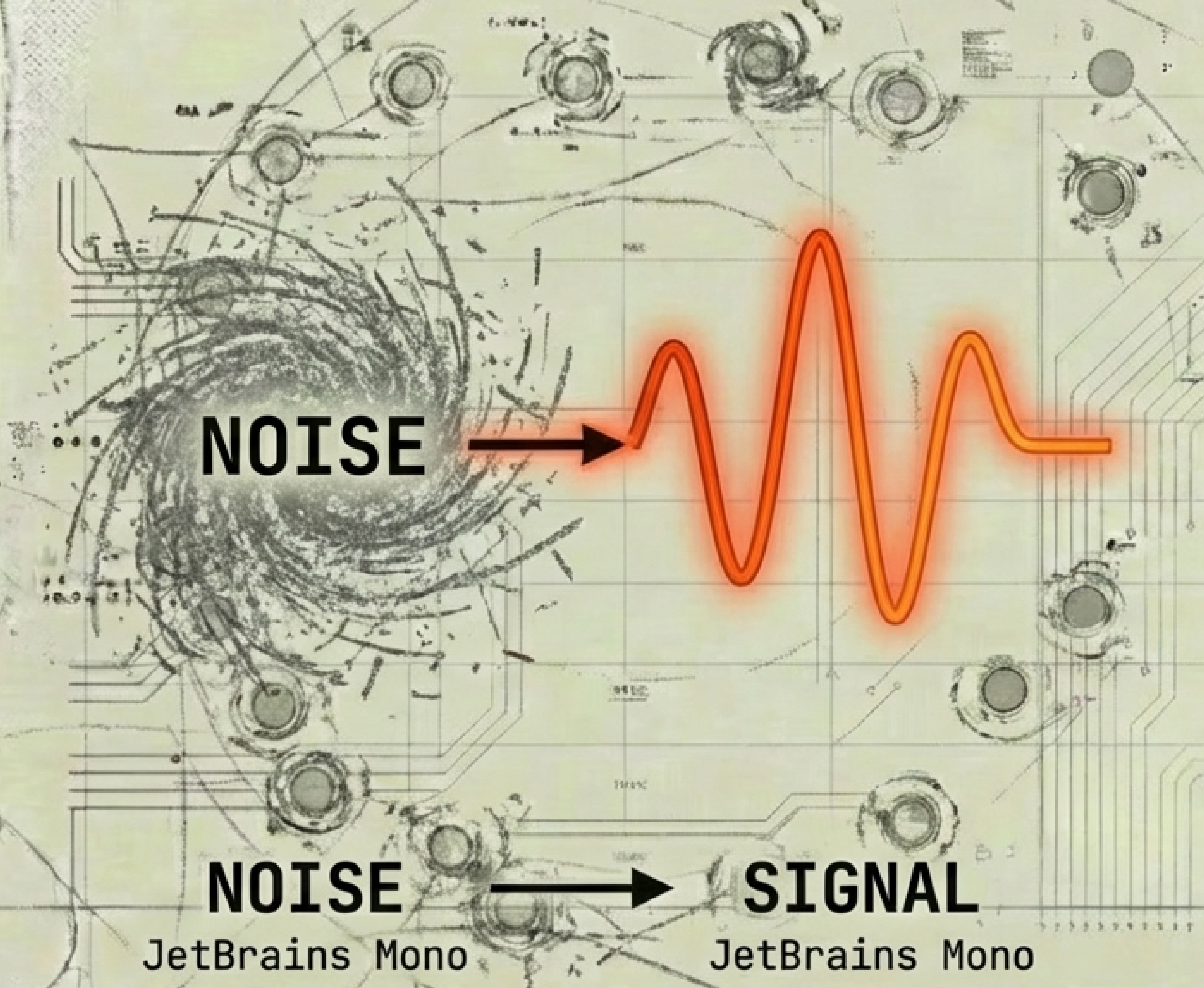


Validation Against Ground Truth



The model correctly identified 2 of the top 3 therapeutic candidates.

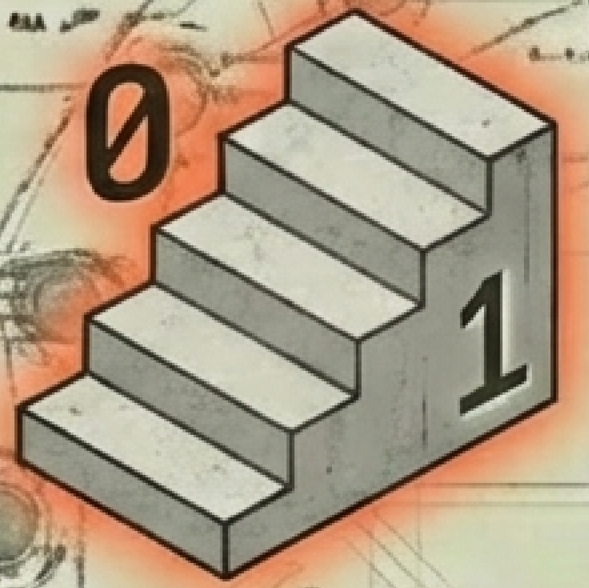
Interpreting the Signal



A correlation of **0.465** is meaningful in high-noise biological systems.

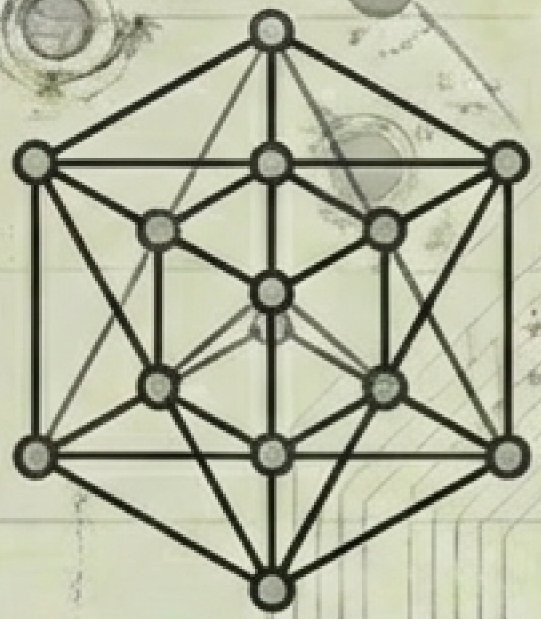
While not perfect, the Binary Channel Framework successfully distinguishes effective targets from ineffective ones, filtering out “false friends” like **Gene 0.**

Limitations of the Framework



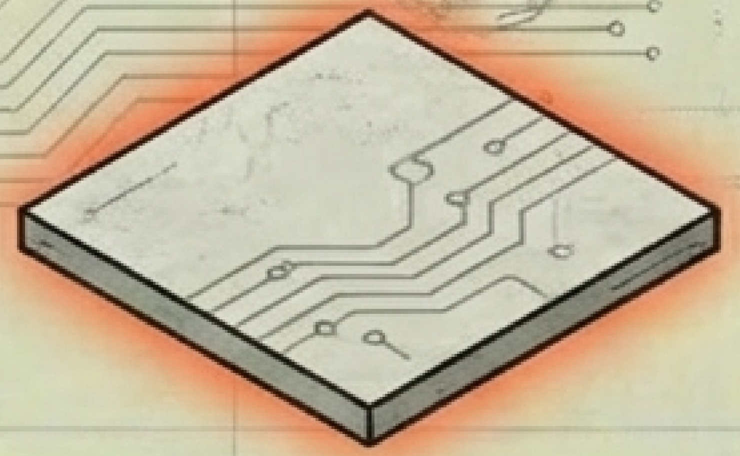
Binary Loss

Real gene expression is graded, not just ON/OFF.



Synthetic Structure

The 200-gene network is a model, potentially missing specific biological motifs.



Uniform Aging

Aging was modeled globally, but real biological decay is heterogeneous.

From Bits to Bedside

Current Frontier

In Silico Prediction

In Vitro Validation

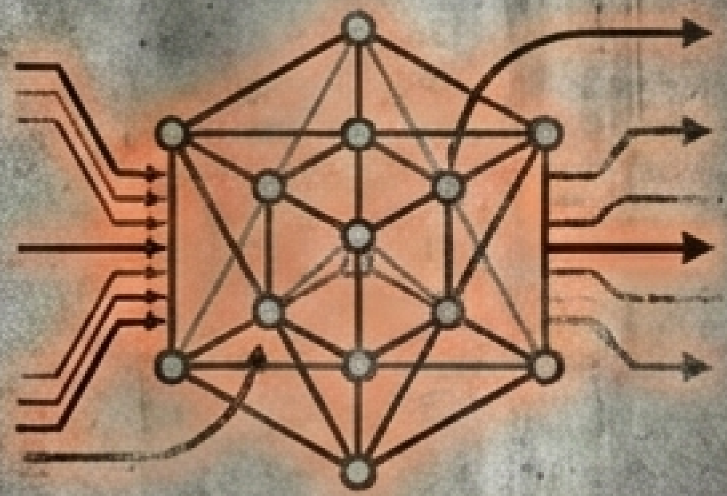
Clinical Therapy

Future work must validate these computational predictions with live-cell experiments and explore multi-gene combinatorial therapies.

Conclusion

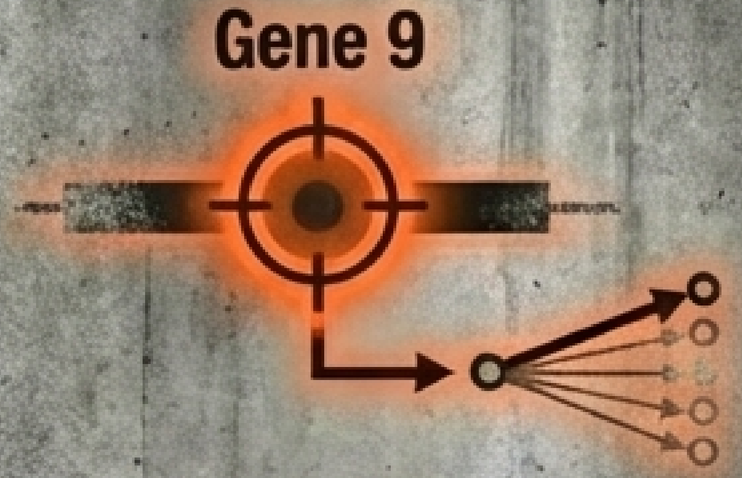
QUANTIFIED

Aging is a 67% loss of information fidelity.



MODELED

Information Theory successfully integrates topology and expression data.



SOLVED

Identified Gene 9 as the optimal target, proving quality of connection > quantity of connection.

References & Data Sources

[1] Han et al. (2018) TRRUST v2: an expanded reference database of human and mouse transcriptional regulatory interactions.

[2] LeFebre et al. (2026) Restoring information in aged gene regulatory networks by single knock-ins. arXiv:2601.04016.

[3] Shannon, C.E. (1948) A *Mathematical Theory of Communication*.

[4] Tabula Muris Consortium (2020). A single-cell transcriptomic atlas characterizes ageing tissues in the mouse.

[5] Tkačik & Bialek (2016) Information processing in living systems.