Concept Paper

Pseudogenes and the Hidden Dimension of Biological Time

Abdulmohsen H. Alrohaimi *

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Pseudogenes and the Hidden Dimension of Biological Time

Abdulmohsen H. Alrohaimi

School of Pharmacy, Shaqra University, Shaqra, Saudi Arabia; alrohaimi@su.edu.sa

Abstract

Pseudogenes have traditionally been interpreted as nonfunctional remnants of protein-coding genes and therefore occupy a marginal position in genomic interpretation. This project proposes a novel conceptual perspective in which pseudogenes are reconsidered as potential components of a latent genomic layer associated with biological time and regulatory history. Rather than contributing primarily through immediate gene expression, certain pseudogenes may reflect accumulated biological trajectories and long-term regulatory constraints within genomic systems. By reframing pseudogenes through a temporal lens, this work explores the possibility that non-executing genomic elements may encode traces of past regulatory states that shape future biological responses. The project aims to develop a conceptual framework that integrates genomic persistence, biological memory, and temporal constraint in understanding genome organization and disease trajectories.

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Introduction

Modern genomics has achieved unprecedented resolution in describing molecular states. Advances in sequencing, chromatin profiling, and single-cell technologies now enable detailed mapping of transcriptional activity, regulatory architecture, and cellular heterogeneity across tissues and conditions. Yet despite this progress, a persistent conceptual limitation remains: current frameworks struggle to represent biological history, temporal directionality, and irreversibility within largely static models of gene regulation [1–3].

This limitation becomes evident when addressing phenomena that resist explanation by instantaneous molecular states alone. Genetically similar individuals frequently follow divergent disease trajectories. Chronic conditions tend to emerge through ordered sequences rather than as isolated events. Late-stage interventions often fail despite successful engagement of molecular targets implicated in early disease onset. These observations suggest that biological systems retain information about past states in ways that constrain future possibilities, yet such temporal constraints are not explicitly encoded in prevailing genomic models [2,3].

Long-term regulatory persistence has been extensively discussed in the context of epigenetic memory, chromatin organization, and regulatory network stability [1,4]. However, these approaches primarily focus on mechanisms that sustain active or repressible states, offering limited insight into how non-executing genomic elements may contribute to the accumulation of biological history. As a result, the genomic representation of time remains implicit rather than structural [4,5].

This Perspective argues that addressing this gap requires reframing how certain genomic elements are interpreted—not by assigning them new functions, but by reconsidering the frameworks through which biological relevance is defined. In particular, it asks whether elements historically classified as marginal may have been overlooked not because of inactivity, but because their potential roles are poorly captured by execution-centric models of genome function.

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The Problem of Biological Time

Biological systems are not defined solely by their current molecular states, but by the paths through which those states were reached. Development, adaptation, aging, and disease unfold over extended periods, during which prior events leave persistent constraints on future responses. Yet most genomic analyses remain optimized for capturing snapshots rather than trajectories, emphasizing instantaneous regulation over historical accumulation [2,3].

This mismatch is particularly evident in long-horizon biology, where relevant dynamics precede overt phenotypes. Repeated exposures, unresolved stress, and iterative repair can accumulate into durable regulatory consequences even when short-term homeostasis appears restored. In such settings, what matters is not only whether a regulatory program is "on" or "off," but whether the system's future options have been progressively narrowed [3].

Aging biology illustrates this limitation with particular clarity. Chronological time alone poorly predicts functional decline, disease susceptibility, or resilience. Instead, outcomes reflect how systems have responded to repeated challenges and how those responses have been retained. Epigenetic persistence provides compelling examples of long-term retention, including durable regulatory changes following metabolic or inflammatory history [6,7]. Yet persistence alone does not fully explain how biological systems acquire directionality—why late interventions often encounter constraints that are not captured by a target's modifiability or by a cell's current molecular profile [2,3].

Irreversibility in biology rarely arises from a single catastrophic event. More often, it emerges as a systems-level property: the progressive restriction of accessible regulatory configurations as history accumulates. By the time dysfunction becomes clinically apparent, alternative trajectories may already be inaccessible even if local molecular targets remain technically alterable. This reframes a central question for genomics: not only which state is present, but which states remain reachable.

Why Current Frameworks Fall Short

Contemporary genomic frameworks have been highly effective at explaining how regulatory states are established and maintained. Epigenetic modifications, chromatin architecture, and regulatory network dynamics provide robust accounts of stability and responsiveness [1,5]. However, these models are primarily designed to describe state persistence rather than the accumulation of historical constraint across extended biological time [3,4].

Epigenetic memory is commonly framed as heritable activation or repression across cell divisions. While this captures continuity, it offers limited language for encoding path dependence—how repeated exposures progressively reshape which future regulatory states remain accessible [3,6,7]. Similarly, systems-level descriptions emphasize robustness, buffering, and return to equilibrium. These concepts are powerful when systems rebound, but less informative when systems transition into progressively constrained configurations in which return is incomplete, delayed, or unavailable [2].

A second limitation arises from an execution-centric definition of relevance. Biological importance is commonly inferred from measurable outputs—transcripts, proteins, or phenotypes—within finite observational windows. Genomic elements that do not obviously participate in immediate execution are therefore difficult to integrate, regardless of their long-term retention or contextual informativeness. In practice, inactivity can become conflated with irrelevance [4].

These limitations do not imply that current models are incorrect. Rather, they suggest incompleteness for questions that unfold across time. Existing frameworks describe how regulatory states operate; they less directly describe how biological history becomes embedded as constraint.

Reframing Pseudogenes Through a Temporal Lens

Pseudogenes entered genomic nomenclature largely as evolutionary remnants—copies of protein-coding genes presumed to have lost functional relevance. This classification shaped how they

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were investigated and, in many contexts, how they were ignored. Yet a growing literature indicates that pseudogene-derived transcripts can participate in regulatory interactions in specific settings, particularly in cancer biology [8].

The central question here is not whether individual pseudogenes exert local regulatory effects—many genomic elements do—but whether pseudogenes represent a class of material that is systematically poorly captured by execution-centric models. By definition, pseudogenes are weakly coupled to protein output. If genome function is interpreted primarily through execution—what is translated and what rapidly alters phenotype—then elements not designed for execution will be structurally undervalued.

A temporal reframing suggests a different possibility: pseudogenes may be informative not because they execute, but because they persist. Their long-term retention, regulatory connectivity, and potential participation in RNA-mediated or chromatin-mediated interactions raise the possibility that some pseudogene activity is better interpreted as reflecting history—what a system has been exposed to and what it has repeatedly traversed—rather than immediate output.

This is a conservative reframing. It does not claim that pseudogenes constitute a dominant regulatory layer or a universal mechanism. It suggests only that the conceptual category of "non-executing" elements may include components whose relevance is expressed primarily over time.

Latency Without Activation

A key conceptual distinction follows: latency is not simply silence, nor is it synonymous with readiness for activation. Latency can be defined as conditional accessibility—a state in which information is retained in a form that is not currently executed, yet remains capable of shaping future regulatory landscapes under specific contexts. Importantly, such influence may occur without a discrete activation event or a return to an earlier baseline.

Epigenetic memory provides an instructive analogy. In metabolic and inflammatory settings, systems can retain durable marks that alter subsequent responses long after the initiating exposure has resolved.[6,7] These observations demonstrate that biological systems can store history as altered future responsiveness. Extending this conceptual space suggests that other genomic components—particularly those not tied to immediate protein execution—may participate in structuring long-term constraints on what remains reachable.

From this view, latent elements need not be interpreted as "waiting to become active." Their role may be to stabilize constraints, bias trajectories, or retain traces of prior regulatory routes. The central point is not activation, but directionality: history is not merely remembered; it shapes which futures remain available.

Implications for Genomics and Intervention

Treating biological time as an explicit organizing dimension reshapes how genomic data are interpreted. Rather than asking only what differs between two states, the more informative question becomes whether those differences encode where a system has been and which paths have become less accessible. This aligns with growing interest in longitudinal and trajectory-aware single-cell analyses, but the conceptual shift extends beyond any single method.

In translational contexts, this framing offers one explanation for a recurring pattern: late interventions can fail despite correct target engagement. Such failures may reflect system-level constraints that are not visible in state snapshots. If pseudogene-associated signals or other non-executing elements correlate with historical constraint, they could help operationalize how far along a trajectory a system has progressed—even when conventional markers appear modifiable.

These implications remain hypotheses for future work rather than conclusions. The present contribution is the conceptual reframing that renders such hypotheses intelligible.

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What this Perspective Does Not Claim

This Perspective does not claim that pseudogenes are primary drivers of biological memory, nor that they provide a universal mechanism of irreversibility. It does not propose a specific molecular pathway, a disease-specific model, or a deterministic mapping between pseudogene activity and outcome. It does not replace epigenetic frameworks; rather, it highlights a conceptual gap that epigenetics alone does not fully formalize: the explicit representation of time-embedded constraint in genomic interpretation.

The argument is deliberately modest. Some genomic elements may be systematically undervalued because prevailing models privilege execution over retention. Reconsidering such elements through a temporal lens may clarify dimensions of biological organization that snapshot-based approaches struggle to capture.

Conclusion

Genomics has become increasingly defined by resolution—finer maps of chromatin, more precise catalogs of transcripts, and deeper characterization of cellular states. Yet biological systems are governed not only by what is present, but by what has been traversed and what remains possible. The next conceptual advance may arise not from observing finer detail, but from integrating biological time as an explicit dimension of genome function. Re-examining pseudogenes through this lens does not promise a single mechanism; it offers a disciplined way to ask a missing question: how does biological history become embedded as constraint?

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