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**Perspectives**

# When cells think: a neuro-symbolic view of epigenetic regulation

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## Abstract

Traditionally viewed as a set of switches regulating gene expression, epigenetic mechanisms may also operate as an information-processing system with symbolic and subsymbolic features. In this framework, gene-specific DNA methylation and other localized epigenetic marks act as symbolic 'on/off' signals, while repetitive and noncoding DNA elements form a substrate for probabilistic, distributed responses to environmental stimuli. This hybrid perspective parallels machine-learning approaches, where symbolic representations are combined with subsymbolic methods (e.g. neural networks) to achieve robust learning and adaptation. Here, we propose that epigenetic regulation integrates these two dimensions (i.e. symbolic control and subsymbolic redundancy) to enable cells to adapt to complex environmental challenges, maintain heritable memory of past exposures, and evolve. In this manuscript, we introduce the concept of epigenetic intelligence, clarifying the synergy between discrete, 'symbolic' epigenetic switches (e.g. gene-specific DNA methylation) and the more 'subsymbolic', distributed features of the genome (e.g. repetitive elements methylation). This approach appears to be novel, as existing literature has not explicitly framed epigenetic regulation within a neuro-symbolic artificial intelligence perspective.

**Keywords:** repetitive elements; neuro-symbolic AI; cellular adaptation

## Introduction

Over the past two decades, epigenetics has transformed our understanding of how cells adapt to environmental stimuli without altering the underlying DNA sequence [1]. Traditionally viewed as a set of molecular switches that regulate gene expression, epigenetic mechanisms, particularly DNA methylation and histone modifications, are now seen as dynamic contributors to cellular memory and plasticity. Yet, a deeper conceptual framework may be needed to explain the 'intelligence' with which these systems operate.

In parallel, advances in artificial intelligence (AI) have led to the rise of neuro-symbolic systems, which integrate logical, symbolic reasoning with the adaptability of neural networks [2]. These hybrid AI models exhibit robust learning, long-term memory, and plasticity qualities that resonate strikingly with biological regulation. Here, we propose that epigenetic mechanisms can be understood through a similar lens. By viewing the genome as a hybrid symbolic–subsymbolic system, we introduce the concept of 'epigenetic intelligence' (EI), a framework that positions gene regulation in analogy to computational process shaped by both rule-based and probabilistic information layers. We adopt a broad definition of EI that encompasses both the analogy with cognitive architectures and the application of computational intelligence tools (e.g. machine learning and statistical modelling) to study epigenetic regulation. This framing aligns with earlier proposals that ascribe logic-like behaviour or decision-making capacity to cellular systems. For instance, Richardson [3] described epigenetic processes as mechanisms for extracting deep correlations from environmental inputs, while Ramanathan and Broach [4] questioned whether cells can 'think' by integrating multiple signals to produce context-appropriate responses.

A more extensive elaboration of this conceptual framework has been explored in a preprint currently available online [5].

## A hybrid model of epigenetic control

Epigenetic regulation encompasses a broad spectrum of mechanisms that operate at multiple scales, from fine-grained chemical modifications on DNA and histones to large-scale chromatin architecture. Within this complexity, two primary categories of regulation can be conceptually distinguished [6].

The first is localized, discrete, and deterministic. DNA methylation at promoter CpG sites serves as a molecular switch,

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turning gene expression on or off in a stable and inheritable manner [7]. Histone modifications further modulate gene accessibility, and topological structures such as topologically associating domains (TADs) organize the genome into functionally distinct regions. These features correspond to the symbolic dimension of computation, rule-based, interpretable, and hierarchically structured. They resemble logic gates in AI systems, offering precise and persistent control over gene expression.

The second category is redundant, distributed, and probabilistic. Repetitive DNA elements, including Long Interspersed Nuclear Elements (LINEs), Short Interspersed Nuclear Elements (SINEs), and endogenous retroviruses, form a dense, interconnected network throughout the genome [8]. These sequences were once considered genomic 'dark matter', or even 'junk DNA', but are now recognized for their regulatory potential. Transposable elements can mobilize in response to stress or developmental cues, reshaping gene networks. Noncoding RNAs also participate in fine-tuning transcriptional responses. This ensemble forms a subsymbolic regulatory layer, analogous to the distributed, weight-based adjustments of nodes in neural networks, supported by flexibility, redundancy, and context-sensitive modulation. Unlike discrete epigenetic marks, these mechanisms act collectively and stochastically, generating plasticity and robustness through diversity.

The integration of symbolic and subsymbolic layers allows the genome to maintain both stability and dynamic adaptability. It can preserve core regulatory programs, fixed through evolution, while remaining responsive to novel environmental inputs. This hybrid architecture mirrors the strengths of neuro-symbolic AI systems: interpretability coupled with learning capacity.

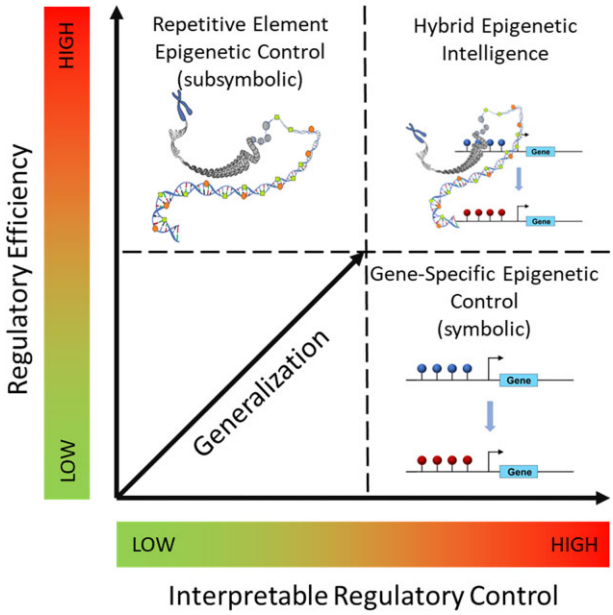


**Figure 1.** A conceptual model of EI as a hybrid regulatory system. Symbolic (gene-specific) and subsymbolic (repetitive element-based) epigenetic controls exhibit complementary properties. Symbolic regulation enables interpretable and stable gene control via discrete marks such as CpG methylation, while subsymbolic elements offer distributed, probabilistic responsiveness through repetitive sequences and transposon activity. Their integration, shown in the upper right quadrant, defines EI—a framework that balances regulatory efficiency and interpretability to enhance adaptive generalization in complex environments.

## Learning, memory, and feedback

Epigenetic systems exhibit multiple features that align with the concept of biological learning. Environmental exposures, ranging from nutrition and toxins to psychosocial stressors, can induce stable epigenetic modifications that endure across cell generations, encoding a molecular memory of past experiences. These changes influence developmental trajectories, immune responses, and even behavioural phenotypes.

This adaptive process is dynamic and iterative. Cells continuously update their epigenetic landscape in response to internal and external signals, analogous to how artificial neural networks adjust weights based on new input. Feedback mechanisms are crucial: when the activity of transposable elements disrupts genome integrity, repressive complexes such as the Krüppel-associated box domain zinc finger proteins (KRAB-ZFPs) can restore chromatin compaction [9]. Alternatively, if transposable elements activate beneficial gene programs, chromatin remodellers like p300 may stabilize their open conformation [10]. These loops resemble reinforcement learning strategies, where beneficial outcomes reinforce the epigenetic configuration.

Such memory is not merely individual but can span generations. Transgenerational epigenetic inheritance suggests that some acquired epigenetic states are passed on to offspring, forming a cumulative record of ancestral exposures. This property highlights the long-term learning potential of the epigenome and positions it as a central player in evolutionary adaptation.

## Theoretical foundations: epigenetics meets learning theory

Concepts from statistical learning theory provide a valuable framework for understanding the computational logic underlying EI. Key principles, such as the bias–variance trade-off, the Vapnik–Chervonenkis dimension, probably approximately correct learning, and the information bottleneck theorem, all find meaningful parallels in biological regulation [11, 12].

Symbolic epigenetic elements, such as methylation marks at CpG islands, impose a high-bias structure, providing consistent, rule-based regulation that favours generalization over flexibility. In contrast, the subsymbolic network of repetitive elements introduces variance, enabling fine-grained, context-aware responses (Fig. 1). This trade-off reflects the balance between overfitting and underfitting in machine-learning models, where a system must generalize well without becoming too rigid or too noisy [13]. To clarify their biological significance, we draw specific analogies; for example, CpG methylation patterns can be seen as high-bias elements, encoding stable, generalizable gene silencing. In contrast, the activity of transposable elements introduces regulatory variance, enabling the system to respond adaptively to environmental inputs. These dynamics reflect the classical machine-learning balance between overfitting and generalization, interpreted here as biological plasticity versus stability.

Bayesian principles offer a compelling unification of these perspectives. In a Bayesian neuro-symbolic model, prior knowledge encoded in symbolic rules is updated through probabilistic inference based on new data. Similarly, epigenetic regulation combines stable, inherited patterns with plastic adjustments driven by experience [14]. This integration allows cells to weigh historical stability against current demands, optimizing their regulatory output in uncertain environments. This conceptual mapping is supported by biological evidence. Regulatory proteins such as KRAB-ZFPs and p300 mediate dynamic responses to environmental stimuli by repressing or activating specific genomic

loci, including transposable elements that can influence gene regulation. These feedback mechanisms adjust the epigenetic landscape based on previous and current conditions, in a way that resembles how Bayesian systems update prior knowledge in light of new data. Such probabilistic adaptation, while not literal inference, illustrates how cells weigh prior configurations with environmental signals to optimize gene expression under uncertainty. Moreover, we have expanded the framework to explicitly incorporate multiscale chromatin architecture. Structures such as TADs and enhancer–promoter loops play a key role in shaping gene regulation. TADs contribute to symbolic control by establishing stable, physical boundaries that constrain regulatory interactions in a rule-like manner. In contrast, enhancer–promoter loops enable subsymbolic flexibility through transient, context-dependent contacts that fine-tune gene expression. Together, these 3D features integrate structural stability with dynamic adaptability, supporting the proposed dual-layer model and linking genome topology with principles from learning theory. However, the classification of transposable elements as subsymbolic is not absolute: many exhibit enhancer-like behaviour with precise spatiotemporal regulation [15]. Our model accounts for this by viewing the symbolic/subsymbolic divide as a continuum rather than a strict dichotomy.

The genome, in this light, can be seen as a learning system, one that encodes, updates, and refines regulatory logic through hybrid symbolic and subsymbolic operations. Rather than viewing epigenetics as a passive readout of environmental effects, the EI framework proposes it as an active and integrative mechanism, capable of learning, reasoning, and adapting.

This work aligns with the original cybernetic view of organisms as adaptive control systems. We frame EI as an intrinsic mechanism for minimizing uncertainty and maintaining homeostasis in dynamic environments. By linking symbolic priors (bias) with stochastic adaptation (variance), the proposed model mirrors optimal stochastic control as a bias–variance trade-off system, essential for autonomous regulation in complex living systems [16].

### Broader implications and future directions

Reframing epigenetic regulation as a form of biological intelligence has broad implications. It enriches our understanding of genome function, offers a new paradigm for studying environmental adaptation, and suggests a biomimetic roadmap for developing AI systems.

In medicine, EI could inform personalized risk prediction based on the adaptability of an individual's epigenetic profile. In synthetic biology, designing gene circuits with symbolic and subsymbolic components may yield more robust, learning-capable organisms.

Finally, this perspective invites deeper exploration of the parallels between cellular cognition and machine learning [17, 18]. Just as neuro-symbolic AI systems bridge logic and data, cells appear to bridge inherited rules and learned responses. The same natural principles that underpin adaptation in biological systems are now being rediscovered and implemented in AI.

## Conclusion

The genome may not only encode life, but it may compute it. EI presents a framework in which biological systems exhibit learning, memory, and decision-making through a hybrid symbolic–subsymbolic architecture. By aligning epigenetic regulation with principles from cybernetics, AI, and statistical learning, we open a new avenue for understanding how life adapts and how machines might follow.

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## Author contributions

Elia Mario Biganzoli (Conceptualization [equal], Funding acquisition [equal], Writing—original draft [equal]) and Valentina Bollati (Conceptualization [equal], Funding acquisition [equal], Writing—original draft [equal])

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## Data availability

Not applicable.

## References

1. Bird A. DNA methylation patterns and epigenetic memory. *Genes Dev* 2002;**16**:6–21.
2. D'Avila Garcez AS, Lamb LC, Gabbay DM. *Neural-Symbolic Cognitive Reasoning*. Berlin/Heidelberg: Springer Berlin Heidelberg, 2009. https://doi.org/10.1007/978-3-540-73246-4
3. Richardson K. Heritability lost; intelligence found: intelligence is integral to the adaptation and survival of all organisms faced with changing environments. *EMBO Rep* 2012;**13**:591–5.
4. Ramanathan S, Broach JR. Do cells think? *Cell Mol Life Sci* 2007;**64**:1801–04.
5. Biganzoli E, Bollati V. Epigenetic intelligence (EI): the neuro-symbolic conceptual framework for biological adaptation. Zenodo. https://doi.org/10.5281/ZENODO.15014910
6. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet* 2016;**17**:487–500.
7. Smith ZD, Meissner A. DNA methylation: roles in mammalian development. *Nat Rev Genet* 2013;**14**:204–20.
8. De Koning APJ, Gu W, Castoe TA *et al.* Repetitive elements may comprise over two-thirds of the human genome. *PLoS Genet* 2011;**7**:e1002384.
9. Kosuge M, Ito J, Hamada M. Landscape of evolutionary arms races between transposable elements and KRAB-ZFP family. *Sci Rep* 2024;**14**:23358.
10. Kikuchi M, Morita S, Wakamori M *et al.* Epigenetic mechanisms to propagate histone acetylation by p300/CBP. *Nat Commun* 2023;**14**:4103.

11. Vapnik VN, Vapnik VN. *Statistical Learning Theory*. New York/Weinheim: Wiley, 1998.
12. Valiant LG. A theory of the learnable. *Commun ACM* 1984;**27**:1134–42.
13. d'Avila Garcez AS, Lamb LC, Gabbay DM. *Neural-Symbolic Cognitive Reasoning*. Berlin/Heidelberg: Springer Berlin Heidelberg, 2009. https://doi.org/10.1007/978-3-540-73246-4
14. Rashid S, Taubenfeld G, Bar-Joseph Z. Genome-wide epigenetic modifications as a shared memory consensus problem. arXiv, https://doi.org/10.48550/ARXIV.2005.06502, 13 May 2020, preprint: not peer reviewed.
15. Chuong EB, Elde NC, Feschotte C. Regulatory activities of transposable elements: from conflicts to benefits. *Nat Rev Genet* 2017;**18**:71–86.
16. Wiener N. *Cybernetics or Control and Communication in the Animal and the Machine*. Cambridge, MA: The MIT Press, 2019. https://doi.org/10.7551/mitpress/11810.001.0001
17. Levin M. The computational boundary of a "self": developmental bioelectricity drives multicellularity and scale-free cognition. *Front Psychol* 2019;**10**:2688.
18. Baluška F, Levin M. On having no head: cognition throughout biological systems. *Front Psychol* 2016;**7**:902.



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