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Epigenetic Climate Change: Using Entropy and Artificial Intelligence to Predict Cellular State Transitions in Cancer

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Abstract

Traditional frameworks view cancer progression through genetic mutation and clonal selection. However, emerging long-read epigenomic studies reveal that stochastic epigenetic alterations introduce an underappreciated evolutionary layer governing cellular adaptation. Nanopore methylome analyses of acute myeloid leukemia (AML) demonstrate that extensive hypermethylation in CpG-poor regions and heightened epigenetic entropy accompany relapse and transcription factor network rewiring. This perspective article introduces "Epigenetic Climate Change," a framework positioning methylation entropy as a cellular climate indicator and artificial intelligence as a predictive forecasting engine. We propose the Epigenetic Climate Index (ECI) to operationalize system stability, integrating nanopore methylomics and graph-based machine learning to forecast disease trajectories—such as drug resistance and relapse—before irreversible clinical transitions occur.

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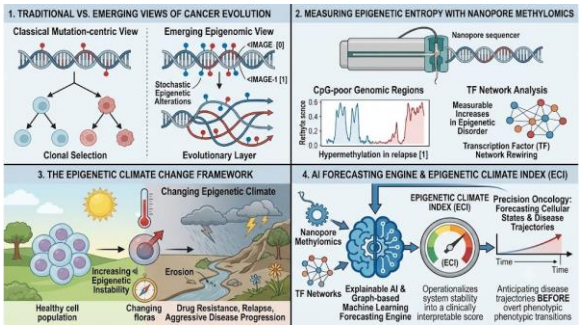
Graphical abstract



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1. Introduction

The modern understanding of cancer has largely been shaped by the somatic mutation theory and the clonal evolution model, which together propose that successive genetic alterations generate cellular diversity upon which selection pressures act [12]. Under this framework, chemotherapy eliminates sensitive clones while resistant variants survive and expand to cause clinical relapse [13]. This paradigm has underpinned cancer diagnostics, prognostics, and therapeutic development for several decades. Nevertheless, accumulating evidence suggests that genetic alterations alone cannot fully account for the extent of therapeutic resistance and disease recurrence observed clinically [10].

Many cancers exhibit substantial phenotypic plasticity despite relatively stable mutational landscapes [14]. Epigenetic mechanisms—including DNA methylation, histone modifications, chromatin remodeling, and transcription factor regulation—provide an additional layer of adaptive capacity that can rapidly and reversibly alter cellular behavior without changing the underlying DNA sequence [15,16]. DNA methylation in particular represents a stable, heritable epigenetic modification that plays critical roles in transcriptional regulation and chromatin architecture [17]. The reversibility of epigenetic modifications makes them especially attractive both as biomarkers of disease state and as therapeutic targets [18].

Recent long-read nanopore methylome studies have revealed extensive methylation remodeling during AML relapse. Hypermethylation was observed

predominantly within CpG-poor genomic regions rather than at classical CpG islands, and many of these methylation events were associated with transcription factor regulatory networks linked to chemoresistance [1]. These findings suggest that cancer cells may continuously explore alternative epigenetic configurations until a treatment-resistant state is achieved. When viewed through the lens of information theory, such stochastic exploration of methylation states can be quantified as increasing epigenetic entropy—a measure of regulatory uncertainty and disorder [19,20].

This observation motivates a new conceptual framework: cancer progression may more closely resemble the dynamics of a complex adaptive system than deterministic genetic evolution. In this model, increasing epigenetic entropy functions as an indicator of instability, signaling that a cell population is approaching a critical transition. Just as environmental climate science uses thermodynamic and statistical measures to forecast ecosystem state transitions, epigenomics may deploy analogous entropy-based measures—supported by AI forecasting engines—to predict cellular state transitions before they manifest clinically [21,22].

The present perspective/hypothesis article is structured as follows. We first examine the conceptual analogy between environmental instability and epigenetic instability, drawing on published evidence linking environmental stressors to epigenetic remodeling. We then review the theoretical and experimental basis for methylation entropy as a measure of cellular instability. We next introduce the Epigenetic Climate Change framework and the proposed Epigenetic Climate Index. Finally, we outline a computational pipeline

integrating nanopore methylomics and AI to forecast future cellular epigenetic states, and we discuss clinical implications for precision oncology in AML and beyond.

2. Environmental Perturbations and Epigenetic Plasticity

Epigenetic mechanisms are exquisitely sensitive to environmental signals, functioning as molecular interfaces between external exposures and the genome [23]. This sensitivity is conserved across kingdoms of life, from Arabidopsis thaliana to humans, and has been proposed as a mechanism enabling rapid phenotypic adaptation to environmental change [24,25]. Several classes of environmental stressors have well-documented associations with DNA methylation remodeling, providing a biological rationale for conceptualizing environmental and epigenetic instability as analogous phenomena.

Psychosocial stress represents one of the most extensively studied environmental modulators of the epigenome. Chronic psychosocial stress activates the hypothalamic-pituitary-adrenal (HPA) axis, culminating in systemic glucocorticoid secretion. Glucocorticoids activate the glucocorticoid receptor, which induces both immediate transcriptional changes and lasting epigenetic modifications across many target tissues [26]. Critically, cumulative lifetime stress has been shown to predict accelerated epigenetic aging as measured by epigenetic clock algorithms, an effect that appears to be mediated in part through glucocorticoid signaling at CpG sites within glucocorticoid response elements [27]. These findings suggest that psychosocial stressors do not merely transiently

perturb gene expression but can leave lasting imprints on the methylome with consequences for disease susceptibility.

Atmospheric pollutants constitute another well-characterized class of epigenetic disruptors. Long-term exposure to nitrogen dioxide (NO2) and nitrogen oxides (NOx) has been associated with global somatic hypomethylation in blood-derived DNA, with particular effects observed at the shores and shelves of CpG islands and within gene bodies [28]. Functional analysis of exposure-associated differentially methylated sites revealed enrichment of immune regulatory pathways, suggesting that pollution-induced methylation changes may modulate inflammatory programs relevant to carcinogenesis. Temperature and relative humidity have also been associated with differential methylation at specific genes controlling coagulation, inflammation, cortisol signaling, and DNA repair [29], supporting the concept that ambient meteorological conditions can influence epigenome composition.

Cigarette smoking induces some of the most reproducible epigenome-wide methylation signatures observed in human populations, particularly at sites associated with aryl hydrocarbon receptor signaling, inflammation, and xenobiotic metabolism [30]. Dietary composition represents a further modulator: caloric restriction, specific fatty acids, and micronutrients interact with the epigenome through metabolic intermediates that serve as cofactors for methyltransferases and demethylases [31]. Notably, long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs) have been shown to modulate DNA methylation fidelity in breast adipose tissue, with high-dose supplementation reducing methylation heterogeneity in a

manner distinct from low-dose effects [32].

Beyond direct somatic effects, environmentally induced epigenetic changes may be transmitted transgenerationally through germline methylation marks that escape epigenetic reprogramming [33]. Paternal diet from weaning to puberty has been shown to induce sperm DNA methylation changes inherited by subsequent generations, with associated phenotypic consequences including altered growth and fertility [34]. In plant systems, experimental demethylation has revealed that DNA methylation modulates adaptive responses to moisture regimes, with demethylated individuals showing patterns of adaptation to drought not apparent in naturally methylated counterparts [35]. These findings collectively indicate that the epigenome is a dynamic, environmentally sensitive regulatory system capable of encoding organismal experience across both somatic and germline timescales.

An important conceptual clarification is required at this point. The analogy proposed in this framework between environmental instability and epigenetic instability does not imply that specific environmental temperatures directly cause proportional increases in methylation entropy across biological systems. Instead, both environmental climate instability and epigenetic instability represent manifestations of increasing system disorder, where external perturbations disrupt homeostatic regulatory programs and expand the variance of system states [36]. This conceptual parallel provides an intuitive and scientifically grounded framework for understanding how chronic exposure to disruptive signals—whether meteorological or biochemical—can

progressively destabilize regulatory architectures and increase the probability of state transitions.

3. Methylation Entropy as a Measure of Cellular Instability

Entropy, as formalized by Shannon in 1948 [19], provides a mathematical measure of uncertainty or disorder within a system. In its application to DNA methylation, entropy quantifies the heterogeneity of methylation states observed across a population of cells or across genomic regions within a single cell. A locus where all cells are uniformly methylated or uniformly unmethylated carries low entropy; a locus where methylation states are distributed stochastically across cells carries high entropy. The quantification of methylation entropy thus captures information about the regularity and predictability of epigenetic programs beyond what is conveyed by mean methylation levels alone.

A foundational application of Shannon entropy to methylation data was the development of quantitative differentially methylated region (QDMR) analysis, which adapts Shannon entropy to quantify methylation differences across multiple samples and identify differentially methylated regions from genome-wide profiles [37]. Applied to MeDIP-chip and reduced-representation bisulfite sequencing data, this approach identified thousands of tissue-specific differentially methylated regions enriched for cell differentiation-associated genes, demonstrating that entropy-based metrics can reveal biologically meaningful epigenetic heterogeneity at genome scale.

A comprehensive analysis of methylation entropy across 49 human

tissue datasets and 42 mouse embryo methylation datasets demonstrated that methylation entropy is associated with specific DNA binding motifs, regulatory DNA elements, and CpG density, and that its contribution to tissue- and time-specific patterns of development is comparable to that of mean methylation levels [38]. Critically, methylation entropy was directly related to gene expression variability in development, suggesting a functional role for epigenetic entropy in developmental plasticity. These findings establish entropy as an informative, independently meaningful dimension of the methylome with relevance to cellular state transitions.

Network-level approaches have extended the concept of entropy from individual loci to cellular regulatory architectures. Increased entropy of signal transduction networks has been demonstrated in cancer compared to normal tissues, and network entropy has been shown to correlate with stem cell pluripotency and dedifferentiation [39]. A related framework of signaling entropy, computed from gene expression data mapped to protein-protein interaction networks, has provided a systems-level measure of cellular plasticity with prognostic relevance across cancer types [40]. These studies support the interpretation that entropy at multiple scales—from individual CpGs to regulatory networks—reflects the degree of epigenetic and transcriptional constraint operating within a cell population.

From an information thermodynamics perspective, DNA methylation patterns can be modeled as a binary language constrained by thermodynamic principles analogous to those governing communication systems [41]. Under this framework,

the ability of methylation marks to encode regulatory information is bounded by thermodynamic noise, and the distinction between functional regulatory signals and stochastic background becomes a quantitative rather than binary question. This thermodynamic perspective reinforces the interpretation that increasing methylation entropy represents a transition from regulatory precision toward stochastic exploration of state space—a transition with direct relevance to cancer cell plasticity.

Spatial correlations between adjacent CpG sites provide an additional dimension for entropy analysis. An information-theoretic framework incorporating spatial CpG correlations enables identification of genomic loci under strong epigenetic control—characterized by bipolar methylation patterns—from those undergoing stochastic remodeling [42]. Application to mouse brain methylome data revealed that incorporating spatial structure substantially improves the identification of cell-type-specific methylation markers, suggesting that entropy analyses that account for regional methylation context may offer superior biological resolution compared to site-level approaches.

A clinically significant recent advance is the demonstration that fragment-level methylation entropy, measured from cell-free DNA (cfDNA), constitutes a robust biomarker for cancer detection. Integration of methylation entropy with methylation levels and cfDNA fragmentation features into a multimodal model achieved an area under the curve of 0.979 for multi-cancer detection in a prospective clinical cohort, with tissue-of-origin classification accuracy of 92.3% across seven cancer types [43]. These findings validate

methylation entropy as a clinically actionable signal and establish the principle that entropy captures cancer-associated epigenetic heterogeneity that complements conventional methylation level measurements. Similarly, the Methylation Pattern Consistency Index (MPCI), a novel metric capturing consistent methylation patterns across sequencing reads, has demonstrated superior performance over existing methylation heterogeneity metrics for distinguishing closely related cell types and detecting cancer-derived cfDNA at low abundance [44].

4. Epigenetic Remodeling in Leukemia Relapse: Experimental Evidence

AML represents one of the most intensively studied hematological malignancies from an epigenetic perspective, owing to the high frequency of mutations in DNA methylation modifier genes including DNMT3A, TET2, IDH1, IDH2, EZH2, and ASXL1 [45]. Pan-cancer analyses have demonstrated that mutations in these genes produce genome-wide promoter methylation landscapes that are significantly distinct from those of tumors without such mutations, with differentially methylated regions (DMRs) exerting downstream effects on gene expression through both methylation-dependent and transcription factor-mediated mechanisms [46].

The most direct experimental evidence supporting the Epigenetic Climate Change framework derives from high-resolution nanopore methylome profiling of AML samples at diagnosis and relapse [1]. This study revealed that relapse-associated methylation changes are characterized not by targeted promoter hypermethylation at

specific oncogenic loci, but by widespread, stochastic hypermethylation preferentially accumulating within CpG-poor genomic regions. This pattern of random hypermethylation is mechanistically distinct from the classical model of epigenetic silencing and suggests that cancer cells under chemotherapeutic pressure do not execute a directed epigenetic program but rather undergo progressive regulatory entropy as the epigenome explores an expanded state space.

Critically, many of the relapse-associated methylation changes in this study overlapped with transcription factor binding sites, implicating TF network rewiring as a downstream consequence of methylation entropy accumulation [1]. Transcription factors whose binding is sensitive to CpG methylation within their recognition motifs can be selectively displaced or recruited by methylation state changes, thereby propagating local methylation perturbations into global transcriptional network rearrangements. This mechanistic chain—from stochastic methylation events to TF displacement to network rewiring to chemoresistance phenotype—provides a biologically coherent pathway through which entropy increase drives therapeutic resistance.

The epigenetic landscape of AML is further shaped by intratumoral heterogeneity that single-cell multi-omics technologies are beginning to resolve [47]. Single-cell methylation analyses have revealed that leukemic stem cells maintain distinct epigenetic states from bulk blast populations, and that minimal residual disease may be maintained by epigenetically distinct cellular subpopulations that persist after cytotoxic therapy. These

findings indicate that relapse may arise not solely from mutation-driven clonal selection but from the epigenetic selection of pre-existing cellular states that confer chemotolerance—a process that increased methylation entropy may predict by signaling the expansion of accessible state space within the tumor.

Supporting this interpretation, the concept of cancer attractor states—stable configurations of gene regulatory networks toward which cellular dynamics converge—provides a systems biology framework for understanding how epigenetic exploration generates clinically relevant state transitions [48]. Cancer cells under therapeutic pressure can be conceptualized as dynamic systems traversing an epigenetic landscape, with most explored states being nonviable but rare configurations conferring survival advantages being selectively retained. The discovery that increased methylation entropy accompanies relapse is therefore consistent with a model in which entropy quantifies the breadth of epigenetic exploration occurring prior to attractor state discovery.

5. The Epigenetic Climate Change Framework

Building on the evidence reviewed above, we propose the Epigenetic Climate Change framework as an organizing conceptual model for understanding and predicting cancer epigenetic evolution. This framework draws an explicit structural analogy between environmental climate dynamics and cellular epigenetic dynamics, using the analogy not as a literary device but as a rigorous conceptual scaffold that maps well-characterized features of complex adaptive systems onto the epigenome.

5.1 The Conceptual Analogy

Stable ecosystems are characterized by relatively predictable environmental conditions that maintain self-reinforcing ecological relationships. Analogously, healthy cellular systems maintain tightly regulated gene expression programs enforced by stable epigenetic states, where methylation patterns at regulatory elements reinforce specific transcriptional identities [15]. As in ecology, stability is maintained by negative feedback mechanisms: transcription factor networks regulated by their own methylation-sensitive binding reinforce particular cellular identities and suppress alternative regulatory programs [16].

Environmental disturbances—whether acute events such as storms or chronic conditions such as progressive warming—increase system variability and can push ecosystems toward tipping points beyond which alternative stable states are established [49]. Analogously, biological stressors including chemotherapy, chronic inflammation, genotoxic exposures, and altered metabolic states can perturb cellular regulatory mechanisms, progressively increasing methylation variability across the population. The critical transition from a chemotherapy-sensitive to a chemotherapy-resistant state may represent the cellular equivalent of an ecological regime shift: a nonlinear transition driven by accumulating instability rather than a gradual proportional response.

Under this framework, methylation entropy becomes analogous to climate variability: a summary statistic that captures the degree of disorder in the regulatory system and provides information about the proximity of critical transitions. Just as increasing

climate variability can signal ecosystem instability even when mean temperature changes are modest, increasing methylation entropy may signal epigenetic instability even when mean methylation levels appear relatively stable. This distinction is important because therapeutic resistance may be driven by the expansion of epigenetic variance—creating opportunities for rare favorable configurations—rather than by directional mean methylation changes.

5.2 Proposed Epigenetic Climate Index

To operationalize this framework for clinical and research applications, we propose a novel composite metric termed the Epigenetic Climate Index (ECI). Conceptually, the ECI would integrate multiple dimensions of epigenetic system stability into a single interpretable score. Building on prior work integrating network entropy, signaling entropy, and methylation heterogeneity as measures of cellular state [39,40,44], the ECI would be computed as a weighted linear combination of component scores:

$$\mathbf{ECI = w_1(Methylation\ Entropy\ Score) + w_2(TF\ Instability\ Score) + w_3(Network\ Disruption\ Score) + w_4(Pathway\ Variability\ Score)}$$

where the component weights (w1 through w4) would be determined empirically through training on longitudinal patient datasets linking epigenomic profiles to clinical outcomes. Each component would be normalized to a common scale before aggregation, and the resulting ECI would be scaled to a 0–100 range to facilitate clinical interpretation. The ECI differs conceptually from individual CpG-level biomarkers in

capturing systemic epigenetic stability rather than isolated molecular events. This systems-level characterization aligns with the emerging understanding that chemoresistance emerges from network-level regulatory reorganization rather than from changes at specific genomic loci [1,40]. Validation of the ECI would require longitudinal epigenomic profiling of patient cohorts through treatment cycles, linking ECI trajectories to clinical outcomes including time to relapse, response duration, and overall survival.

Table 1. **Network Disruption:** The breakdown of normal cellular signaling and interaction networks.

ECI Range	Epigenetic State	Clinical Interpretation
0–20	Stable State	Low regulatory entropy; stable epigenetic program
20–40	Mild Perturbation	Emerging heterogeneity; low-level stochastic remodeling
40–60	Adaptive State	Moderate entropy; expanded regulatory plasticity
60–80	High Plasticity	High entropy; active exploration of alternative states
80–100	Relapse-Prone State	Critical instability; imminent transition risk

6. Artificial Intelligence as a Biological Forecasting Engine

The application of AI to epigenomic data has expanded rapidly over the past decade, encompassing classification of tumor subtypes from methylation profiles, prediction of clinical outcomes, identification of epigenetic biomarkers, and integration of multi-omics datasets [18,50,51]. Brain tumor classification

from DNA methylation profiles, pioneered by the reference cohort established for CNS tumor taxonomy, demonstrated that machine learning could outperform conventional histopathological classification by capturing genome-wide methylation patterns that encode tumor identity more precisely than morphological features alone [52]. These successes established the principle that AI can learn biologically meaningful patterns from high-dimensional methylation data that exceed human analytical capacity.

Machine learning approaches applicable to epigenomic data include conventional supervised methods (random forests, support vector machines, gradient boosting), deep learning architectures (convolutional neural networks, recurrent networks, transformers), and graph-based models that capture relational structure within molecular networks [53,54,55]. Convolutional neural networks have demonstrated particular utility in learning from sequential genomic data, capturing local and long-range patterns in DNA methylation and histone modification profiles with high accuracy [55,56]. Graph neural networks offer complementary strengths for modeling the relational structure of transcription factor networks and gene regulatory graphs, enabling prediction of network-level consequences of localized methylation changes [57].

The cancer epigenomics literature has documented numerous applications of these methods to clinical prediction tasks. AI-driven multi-cancer early detection (MCED) systems integrating methylation profiles—including GRAIL's Galleri and CancerSEEK—have demonstrated clinically relevant sensitivity and specificity for cancer detection from blood-derived cfDNA

[58]. Deep learning applied to AML datasets has enabled refined risk stratification, classification of epigenetic subtypes, and prediction of therapeutic response to novel agents including menin and LSD1 inhibitors [47,59]. A systematic analysis of AI applications in leukemia research, encompassing 2,338 peer-reviewed publications, documents the substantial methodological diversification of this field and highlights emerging directions including multi-omics integration and longitudinal disease monitoring [60].

The conceptually transformative advance proposed here is a shift from AI-based classification—asking which state a cell currently occupies—to AI-based forecasting: predicting which state a cell population is evolving toward. This distinction maps precisely onto the difference between current-state weather observation and weather forecasting. Meteorologists do not predict the behavior of individual air molecules; they identify large-scale patterns in thermodynamic variables that determine future atmospheric states [21]. Analogously, an AI forecasting system applied to the epigenome need not model individual methylation events but can instead learn predictive associations between methylation entropy trajectories, TF network dynamics, and chromatin accessibility changes on one hand, and future cellular state transitions on the other.

Methodological precedents for forecasting future cellular states exist in the trajectory inference and RNA velocity literature. Pseudotime trajectory inference algorithms reconstruct developmental and disease progression pathways from single-cell transcriptomic data, enabling inference of the ordering of cellular states along differentiation or

disease trajectories [61]. RNA velocity extends this approach by leveraging the ratio of spliced to unspliced transcripts to infer the instantaneous direction of transcriptional change, effectively predicting near-future gene expression states from current transcriptomic snapshots [62,63]. The extension of these principles to the methylome—predicting future methylation states from current entropy trajectories—represents the conceptual core of the Digital Epigenetic Weather Forecasting system proposed here.

Explainability is a critical requirement for clinical AI systems. The black-box nature of many deep learning models has impeded clinical adoption, as predictions without mechanistic rationale cannot be validated or interrogated by clinicians [58,64]. Explainable AI (XAI) frameworks, including SHAP (SHapley Additive exPlanations), attention mechanisms, and agentic audit loops, provide tools for identifying which features drive model predictions and flagging cases where prediction confidence is low [65]. An agentic AI framework incorporating entropy-based triage and feature match rate quantification has been proposed for CNS tumor classification, enabling the system to autonomously assess diagnostic confidence and escalate uncertain cases for human review [65]. Analogous architectures would be essential for an ECI-based forecasting system deployed in clinical oncology.

7. Proposed Computational Pipeline for Epigenetic Forecasting

The computational realization of the Epigenetic Climate Change framework would require integration of multiple methodological components spanning long-read sequencing, bioinformatics, network biology, and machine learning. We outline a proposed

pipeline structure below, noting that each component draws on established methodologies while their integration into a unified forecasting architecture represents a novel contribution.

7.1 Nanopore Methylome Acquisition

Oxford Nanopore Technology (ONT) long-read sequencing enables simultaneous detection of base sequence and DNA methylation at single-molecule resolution without bisulfite conversion, preserving native DNA integrity and enabling phased methylation analysis across extended genomic regions [1]. Base-calling and methylation calling from raw electrical signal data (Fast5/POD5 format) are performed using Dorado or equivalent tools, yielding per-read methylation probability scores at individual CpG dinucleotides. Long reads spanning hundreds to thousands of base pairs enable fragment-level methylation haplotype analysis, capturing the co-methylation structure of CpG clusters that short-read bisulfite sequencing cannot resolve [44].

7.2 Entropy Computation and Feature Engineering

Shannon methylation entropy would be computed at individual CpG loci and across regulatory regions using the formulation $H = -\Sigma_i\ p_i\ \log_2\ p_i$, where p_i represents the probability of observing each distinct methylation state across reads covering the locus [19,37]. Spatial CpG correlations would be incorporated to distinguish loci under strong epigenetic control—characterized by bimodal methylation—from those undergoing stochastic remodeling [42]. Transcription factor methylation burden would be computed by integrating methylation levels at TF binding sites derived from curated databases with TF expression data,

yielding a quantitative measure of TF regulatory disruption. Network connectivity scores would be derived from graph-theoretic analysis of TF co-regulatory networks, quantifying the fragmentation and rewiring of regulatory modules associated with elevated methylation entropy.

7.3 Graph-Based Machine Learning and State Forecasting

The relational structure of TF regulatory networks is naturally represented as a graph, where nodes correspond to regulatory genes and edges represent co-regulatory relationships modulated by methylation [46]. Graph neural networks (GNNs) operating on these regulatory graphs can learn to predict network-level state transitions from node-level methylation features, capturing emergent properties of the regulatory system that are inaccessible to feature-independent classifiers [57]. Temporal graph neural networks, which extend GNNs to incorporate longitudinal data, have demonstrated improved disease prediction accuracy on clinical datasets by modeling the dynamics of biomarker trajectories rather than static snapshots [66].

The forecasting objective would be formulated as: given the current ECI and its rate of change computed from serial methylome measurements, predict the probability distribution over future cellular states at a specified clinical timepoint. This formulation parallels short-range and medium-range weather forecasting, in which ensemble models initialized with current atmospheric state generate probabilistic forecasts of future conditions [21]. Transformer-based architectures pre-trained on large methylome corpora (methylome foundation models) may offer particular advantages for this task by

capturing long-range dependencies in methylation state trajectories that recurrent networks may miss [67].

7.4 Explainability and Clinical Integration

All model predictions would be accompanied by SHAP-derived feature importance attributions identifying which methylation regions, TF binding sites, and network modules contribute most strongly to the forecast [64]. Low-confidence predictions—identified by entropy-based triage of prediction distributions—would be flagged for additional data collection or clinical review [65]. Integration with clinical metadata including treatment history, cytogenetic risk stratification, and MRD status would enable the forecasting model to contextualize epigenetic trajectories within the broader clinical picture, supporting individualized therapeutic decision-making.

8. Clinical Implications in AML and Precision Oncology

AML represents an ideal initial clinical context for the Epigenetic Climate Change framework given the central role of epigenetic dysregulation in its pathogenesis, the high rate of relapse following standard chemotherapy, and the emerging availability of epigenetically targeted therapies [47,59]. Current risk stratification in AML relies primarily on cytogenetic and molecular genetic features, with ELN (European LeukemiaNet) guidelines classifying patients into favorable, intermediate, and adverse risk categories based on recurrent chromosomal abnormalities and gene mutations [10]. While powerful, this framework does not capture epigenetic heterogeneity within cytogenetic risk groups, which may

partly explain the variability in outcomes observed among patients assigned to the same genetic risk category.

An ECI-based monitoring system could complement genetic risk stratification by tracking epigenetic system stability through induction chemotherapy, consolidation, and post-treatment surveillance. Rising ECI values during morphological remission—indicating increasing methylation entropy despite apparent disease control—could identify patients at elevated risk of epigenetic relapse before cytological or molecular evidence of disease recurrence emerges. This prospective identification of high-risk trajectories would create a clinical window for pre-emptive intervention: intensification of consolidation therapy, early transition to allogeneic transplantation, or initiation of epigenetically targeted agents such as hypomethylating agents, menin inhibitors, or LSD1 inhibitors [47].

The broader framework of AI-assisted dynamic treatment planning aligns with emerging concepts in systems oncology [22,68]. A Global Biomarker and Vulnerability Score integrating multi-scale tumor-host data—including epigenomic, immune, metabolic, and physiological indicators—has been proposed as a basis for adaptive, AI-assisted treatment strategies in metastatic disease [68]. The ECI could constitute the epigenomic component of such a composite vulnerability score, linking methylation entropy trajectories to overall disease stability assessments updated in real time from longitudinal liquid biopsy data. Dynamic network biomarker theory, which identifies disease tipping points by monitoring increased fluctuations and correlations within biomolecular networks, has achieved greater than

80% accuracy in predicting tumor progression in experimental settings and provides a statistical framework for tipping-point detection that the ECI framework could instantiate for the epigenome specifically [66].

Beyond AML, the Epigenetic Climate Change framework has potential applicability across cancer types characterized by epigenetic plasticity and non-genetic resistance mechanisms. Glioblastoma, for which MGMT promoter methylation status is a critical predictive biomarker, represents a candidate context: radiomics-based models integrating imaging features with molecular biomarkers have demonstrated clinical utility for non-invasive MGMT prediction [69], and the addition of methylome entropy measures could refine tumor epigenetic state characterization beyond binary promoter methylation status. Breast cancer, where cfDNA methylation entropy has demonstrated feasibility as a cancer detection biomarker [32], and colorectal cancer, where methylation-based MCED tests have achieved high sensitivity [43], are further settings where entropy-based forecasting could add clinical value.

9. Limitations and Future Directions

Several limitations of the proposed framework warrant explicit acknowledgment. First, the Epigenetic Climate Index remains a proposed metric without prospective clinical validation. Its clinical utility depends on the demonstration that ECI scores computed from accessible clinical samples (bone marrow aspirates, peripheral blood, cfDNA) are technically reproducible, biologically interpretable, and predictive of clinical outcomes in prospective cohorts. The optimal weighting of component scores, the most informative genomic regions for

entropy computation, and the clinical thresholds defining actionable ECI ranges all require empirical determination through carefully designed longitudinal studies.

Second, the proposed analogy between environmental instability and epigenetic instability, while conceptually productive, should not be interpreted as implying that specific environmental stressors predictably increase methylation entropy in a dosimetric fashion. The relationship between environmental exposures and epigenetic variance is likely to be highly context-dependent, varying with cell type, genetic background, developmental stage, and the specific exposure in question [25,36]. Future studies specifically designed to measure the effect of defined environmental perturbations on population-level methylation entropy—rather than mean methylation levels—would strengthen the empirical foundation of this conceptual analogy.

Third, the computational pipeline proposed here requires substantial methodological development before clinical implementation. Nanopore methylome profiling at sufficient depth for reliable entropy estimation across regulatory regions requires sequencing coverage that may not be routinely achievable from clinical specimens without technical optimization [1]. Computational tools for robust entropy calculation, TF network mapping, and GNN-based forecasting from methylation data are at varying stages of development and validation [37,42,57]. Standardization of data processing pipelines and entropy calculation methodologies across laboratories will be essential for multi-center clinical studies.

Fourth, interpretability challenges inherent to complex AI models remain

a significant barrier to clinical deployment [58,64]. Explainable AI approaches can identify which features drive predictions, but translating feature-level explanations into biologically actionable insights requires domain expertise and careful clinical annotation. The development of curated biological knowledge bases linking epigenetic features to known regulatory mechanisms will be essential for transforming AI-generated forecasts into clinically interpretable guidance.

Looking forward, several technological developments have the potential to substantially accelerate progress in this field. Longitudinal nanopore methylome monitoring from liquid biopsy—exploiting the sensitivity of cfDNA methylation entropy for cancer detection—could enable non-invasive serial ECI computation without requiring repeated bone marrow sampling [43]. Single-cell methylation profiling would extend entropy analysis to the intratumoral heterogeneity level, enabling identification of high-entropy cellular subpopulations that may represent the reservoir from which resistant states emerge [47]. Transformer-based methylome foundation models, analogous to large language models for protein sequence analysis, could capture long-range dependencies in methylation state trajectories and generalize across cancer types and therapeutic contexts [67]. Digital epigenetic twin systems—computational representations of individual patient epigenomes updated in real time from clinical measurements—represent an aspirational long-term goal that would enable truly individualized epigenetic forecasting aligned with the principles of precision medicine.

10. Conclusions

This perspective article has introduced the Epigenetic Climate Change framework, proposing that methylation entropy functions as a cellular climate indicator analogous to thermodynamic disorder in environmental systems, and that AI can serve as a forecasting engine predicting future cellular epigenetic states before their clinical manifestation. The framework is grounded in established biological evidence linking environmental perturbations to epigenetic remodeling, in information-theoretic approaches to quantifying methylation heterogeneity, and in experimental nanopore methylome data demonstrating that AML relapse is accompanied by increasing stochastic methylation and TF network rewiring [1,19,38,39].

The central conceptual advance proposed here is a shift from epigenomic characterization of existing disease states toward forecasting of future disease trajectories. Just as climate science seeks to forecast ecosystem transitions before catastrophic events occur, precision oncology may develop the capacity to forecast cellular epigenetic transitions before therapeutic resistance emerges. The proposed Epigenetic Climate Index represents one operational instantiation of this forecasting ambition: a composite systems-level metric designed to summarize epigenetic system stability in a clinically interpretable and actionable form [39,40,44].

Realizing this vision will require coordinated advances in long-read sequencing technology, entropy-based bioinformatics, regulatory network modeling, and clinical AI—alongside prospective clinical studies designed to validate ECI measurements against longitudinal

clinical outcomes. The ultimate objective is not merely to detect resistant disease after it has emerged, but to identify and intercept the epigenetic trajectory leading toward resistance itself. The future of cancer epigenomics may therefore lie not in describing the present methylome, but in forecasting the future epigenome.

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