

Mathematical Framework for Hierarchical Cell Identity Control by Collective Enhancer Dynamics

Anton Grishechkin , Abhirup Mukherjee , and Omer Karin 

Department of Mathematics, *Imperial College London*, London SW7 2AZ, United Kingdom



(Received 8 April 2025; accepted 10 September 2025; published 23 October 2025)

The hierarchical organization of cell identity, characterized by progenitor cells coexpressing multiple transcriptional programs, is a hallmark of animal development with well-documented experimental phenomenology. However, the mechanisms underlying its emergence remain unclear. Here we investigate the origin and regulation of progenitor states using a mechanistic mathematical framework based on transcription factor-enhancer interactions. This framework maps the regulation of cell identity genes to the dynamics of a continuous Modern Hopfield network, governed by an inverse-temperature-like parameter, β , representing epigenetic modifier activity, and an input field, $\mathbf{w}$, reflecting signaling activity. We propose that multilineage-primed progenitor states emerge from the interplay between enhancer competition for epigenetic readers and the activation of overlapping transcriptional programs. Mathematically, these progenitor states correspond to mixed attractor patterns in the network at intermediate β values. We introduce an analytical approach to characterize the identity, stability, and basins of attraction of progenitor states, including their emergence and destabilization at specific β thresholds. Applying this approach, we explain how signaling can instruct differentiation, reconstruct the complex blood progenitor landscape from terminal lineages, and identify potential mechanisms of differentiation dysregulation in cancer. We propose that nonspecific modulation of enhancer competition is a key regulatory axis underlying cell identity transitions.

DOI: [10.1103/dkmq-h4d9](https://doi.org/10.1103/dkmq-h4d9)

I. INTRODUCTION

Animals are composed of a wide range of cell types, each with specialized functions that collectively enable the formation of complex systems such as the brain and immune system. During development, cell types emerge through processes of differentiation, in which progenitor cells progressively adopt distinct identities [1,2]. These processes continue in many adult tissues, including the blood, where stem cells give rise to diverse lineages [3–6], with cells in these lineages further specializing in response to signals [7–10]. Similarly, neural development generates many distinct neuron types through sequential specification [11–18].

At the molecular level, cell type specification is governed by the activation of distinct gene expression programs, mediated by the activation of cell-type-specific enhancers by specialized DNA-binding proteins called transcription factors (TFs) [11,19–24]. Within differentiation hierarchies, progenitor cells frequently coexpress at lower levels the transcriptional programs of their potential progeny, a phenomenon known as multilineage expression, or multilineage priming [2,3,12,25–34]. Multilineage expression is closely tied to differentiation potential, with extracellular signals biasing lineage commitment by modulating the expression of fate-specific programs in progenitor states. For example, erythropoietin amplifies the erythrocyte program in

erythrocyte-primed progenitors, while neural crest progenitor fate potential correlates with the relative expression of target lineage programs [12,35–37]. The ubiquity of multilineage expression suggests that it represents a fundamental mechanism governing lineage commitment.

Multilineage expression is hierarchical because a cell's gene expression program contains within it multiple more restricted subprograms. Each subprogram corresponds to a particular lineage or cell identity. We refer to this aspect as *hierarchical cell identity*. This concept is distinct from cellular potency, which refers to a cell's potential to adopt future identities. Pluripotent embryonic stem cells exemplify this distinction: their pluripotency reflects their potential to adopt the entire range of future identities of the organism, while their hierarchical identity describes their current transcriptional state. Depending on culture conditions, they may restrict expression to the core pluripotency transcriptional program or coexpress various lineage-affiliated programs, with the latter reflecting a hierarchical identity primed towards specific fates [38–42]. Hierarchical identities often reflect progenitor states within differentiation hierarchies, where cells can differentiate into their constituent identities.

Despite their ubiquity, we have limited understanding of how hierarchical identities emerge from the underlying molecular regulatory networks, and how they may facilitate cell state transitions during development and homeostasis. In many systems, including the blood, gene networks are densely interconnected, without clear hierarchy or modularity [43–45], and, across cell types, specification is combinatorial, with TFs frequently overlapping in expression [21,46,47]. Despite this complexity, hierarchical cell identity is a robust phenomena with distinct dynamical features. A particularly

crucial question concerns the origin and control of progenitor states, in both normal development and disease conditions.

We recently introduced a mechanistic model for cell identity dynamics that can bear on the origin and control of progenitor states [48]. The model explains the specification of cell identity through the differential activation of enhancer elements [19–21,48,49], where competition among enhancers for transcriptional regulators stabilizes cellular identities. Mathematically, we capture gene regulatory dynamics using continuous Modern Hopfield networks (MHNs), wherein TF-enhancer interactions drive the “retrieval” of distinct gene expression profiles associated with specific cell types [50,51].

In this model, enhancer competition is governed by an inverse-temperature-like parameter, β . High β values stabilize specific cell-type expression programs associated with distinct enhancer elements, while lower β values allow stabilization of mixed expression programs. Crucially, β is regulated by cellular processes, reflecting epigenetic modifier activity. We hypothesize that cells dynamically adjust β through an annealing-like process to transition between identities, such as from stem to differentiated states, with multilineage-primed progenitors emerging as transient attractors during these transitions. Testing this hypothesis requires understanding the attractor landscape at intermediate β values, which remains uncharacterized.

Here we develop an analytical framework to study MHN properties at intermediate β values and apply it to model differentiation through hierarchical cell identities. Our framework reveals that subsets of cell identities coarsen into progenitor states at specific β thresholds, predictable from the statistical structure of the subset. We leverage this framework to propose a model for the hierarchical control of progenitor state identity, stability, and basins of attraction, which facilitates differentiation transitions and accounts for a wide range of experimental observations on cell identity dynamics, including fundamental aspects of cellular differentiation and their control by signaling pathways.

Model for enhancer-regulated gene expression

Animal cell types are associated with distinct gene expression programs, which emerge from a regulatory mechanism based on the differential activation of enhancer elements [19–21,48,49]. Enhancers facilitate transcription by recruiting molecular machinery that initiates and enables transcription at distant genetic elements. A given genome may encode for hundreds of thousands of potential enhancer elements, yet, in a given cell type, only a small subset of these will be active and facilitate transcription [23].

At the microscopic (single enhancer) level, the activation of enhancer elements is based around regulatory events unique to animals. The process involves the recruitment of coactivator molecules, including the histone acetyltransferases (HATs) CBP/p300, to specific enhancer sites, by TFs [49,52,53]. These HATs function as epigenetic writers, acetylating histone proteins associated with enhancers. Acetylation is turned over by epigenetic erasers, histone deacetylases (HDACs), a process that occurs on a timescale of minutes [49,52]. Histone acetylation results in the recruitment of epigenetic reader molecules, which play an essential role in facilitating

transcription. For genes associated with cell-type specific expression, the bromodomain protein Brd4 is a key regulator, essential for recruiting factors that promote transcriptional elongation—a major rate-limiting step in gene expression [23,54–59], with other epigenetic readers, including Taf1, also implicated in transcriptional control [49]. These processes collectively establish a competitive landscape for enhancer activation, which is the central biological principle our model aims to capture.

At the macroscopic (many enhancer) level, enhancer activities are interconnected through the shared use of TFs and cofactor molecules. Although animal TFs can recognize and bind specific DNA sequences, their interactions are transient, targeting short and degenerate motifs [60]. As a result, a single TF may bind to thousands of enhancer elements across the genome. In contrast, transcriptional cofactors do not recognize specific DNA sequences, and their activity is broadly distributed across multiple enhancers. This coupling of enhancers through cofactors occurs at both the epigenetic writing and reading stages. While HDACs are highly abundant, coactivators such as CBP/p300 are often stoichiometrically limiting compared to TFs, leading to competition between TFs over their recruitment [61,62]. In addition, bromodomain proteins exhibit high mobility, and their rapid redistribution in response to differential enhancer acetylation plays a critical role in modulating enhancer activity [63–72].

To study gene expression dynamics in face of enhancer coupling, we use the framework introduced in Karin [48]. Our analysis considers a set of K enhancers ($i = 1, \dots, K$) regulating the expression of N core TFs, denoted $\mathbf{x} = (x_1, \dots, x_N)$, which can bind any of these enhancers. These enhancers are a subset of all cellular enhancers, as those controlling non-TF genes act as outputs and do not influence model dynamics (see the Supplemental Material [73]). We also include L signaling TFs, $\mathbf{y} = (y_1, \dots, y_L)$, assumed constitutively expressed for simplicity, though the framework can be generalized to cases where signaling also controls TFs that are not constitutively expressed and therefore included in $\mathbf{x}$. The dynamics of the gene regulatory network are

$$\dot{\mathbf{x}} = \mathbf{Q}^T \text{softmax}(\beta \Xi \mathbf{x} + \mathbf{w}) - \mathbf{x}, \quad (1)$$

where $\mathbf{Q}$ has entries $q_{i,j}$ for the contribution of enhancer i to TF x_j transcription, Ξ has entries $\xi_{i,j}$ for the binding affinity of TF x_j to enhancer i , and β controls enhancer competition, reflecting the ratio of HAT to HDAC activity. The softmax function represents a Boltzmann distribution, and time is rescaled. The vector $\mathbf{w} = \beta \mathbf{U} \mathbf{y} + \mathbf{b}$ integrates external signaling and enhancer baseline properties. Here $\mathbf{U}$ has entries $u_{i,j}$ for the binding affinity of signaling TF y_j to enhancer i , and $\mathbf{b}$ has entries b_i for baseline enhancer activation. The full derivation of Eq. (1) is provided in the Supplemental Material [73].

Due to competition over HAT proteins, we do not expect the dynamics to be sensitive to overall recruitment of bromodomain proteins to enhancers (see the Supplemental Material [73]). Importantly, while the derivation was based on p300/CBP-mediated acetylation and Brd4 recruitment, the dynamics described by Eq. (1) are general and capture essential aspects of TF-mediated epigenetic writer recruitment and epigenetic reader competition. They can also be extended to

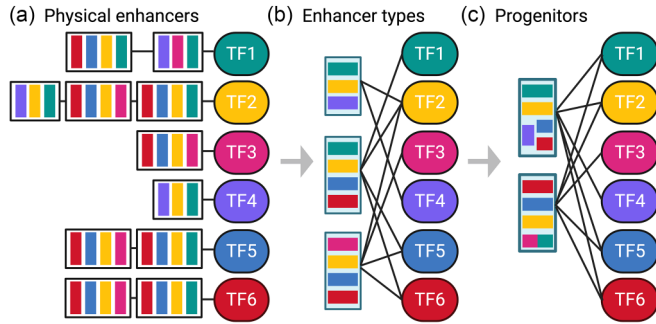


FIG. 1. Scheme of process underlying emergence of hierarchical cell identity. Autoregulatory motifs in cell identity networks are made of enhancers with similar binding profiles that are cobound by the genes they activate. The large white rectangles correspond to physical enhancers, with color bars representing binding motifs for TFs with corresponding colors. (a) Physical enhancers of autoregulatory networks, denoted by white rectangles, are transformed by Eq. (4) into (b) effective “enhancer types” [shaded blue rectangles in (b)], which are mathematical objects corresponding to the rows of Ξ . Through additional applications of the coarse-graining transformation (4) these may be further transformed into progenitor enhancer types, depicted in (c).

account for hysteresis phenomena associated with repressive modifications, including the activity of pioneer factors [48], which, for simplicity of analysis, will not be considered here.

Equation (1) is general, and its role in driving cell identity remains unclear without further simplification. In [48] we simplified it using the experimental observation that across cell types, TFs governing cell identity form dense autoregulatory networks, cobinding to adjacent enhancers [21,24], as shown in Fig. 1(a). These enhancers, sharing similar binding profiles, are coactivated by the same TFs. This allows us to coarse grain them into a single “enhancer type.” Since these enhancers activate the same TFs that bind them, coarse graining correlates the rows of matrices $\mathbf{Q}$ and Ξ . As a result, Eq. (1) can be approximated by a symmetric form:

$$\dot{\mathbf{x}} = \Xi^T \text{softmax}(\beta \Xi \mathbf{x} + \mathbf{w}) - \mathbf{x}. \quad (2)$$

These symmetric dynamics correspond to gradient descent on an energy function:

$$\dot{\mathbf{x}} = -\nabla V(\mathbf{x}, \beta, \Xi, \mathbf{w}), \quad (3)$$

where $V(\mathbf{x}, \beta, \Xi, \mathbf{w}) = -\beta^{-1} \log Z + \frac{1}{2} \mathbf{x}^T \mathbf{x}$, and Z is the softmax denominator in Eq. (2). This formulation is equivalent to continuous MHN models with an input field $\mathbf{w}$ applied to memory patterns (rows of Ξ), connecting it to models in machine learning and neuroscience [50,51,74].

We have previously shown that Eq. (2) recapitulates a key aspect of cell identity specification, namely, at sufficiently large β , each of the observed cell identity profiles is indeed a stable configuration (attractor state) of the gene regulatory network, with its own enhancers differentially activated [48]. As such, the matrix Ξ can be approximated from the observed gene expression profiles of distinct cell types. Through this initialization, Eq. (2) can be used to make parameter-free predictions on the effects of perturbations, including on reprogramming through constitutive expression of TFs, and on

the modulation of β , with the latter appearing to recapitulate observed differentiation hierarchies in numerical simulations [48]. In the subsequent sections, we develop and apply an analytical approach to understand the origin and properties of these states.

II. RESULTS

A. Emergence of hierarchical cell identities in TF-enhancer interaction networks

To understand how hierarchical cell identities emerge from the dynamics of Eq. (2), we observe that as β decreases, competition between enhancers relaxes, supporting the coactivation of enhancers with more distinct binding patterns. The intuition behind our analysis is illustrated in Fig. 1. We first coarse grain the enhancers in autoregulatory motifs into enhancer types, as they are always coactivated in the same cellular context. When β is sufficiently large, competition between enhancer types is strong, and, therefore, enhancer types with distinct binding patterns will uniquely determine cell identity. At lower levels of β , different enhancer types may be coactivated, and, by activating overlapping gene expression programs, they may support each other’s activity. Remarkably, we will show that in this case, different enhancer types coarse grain and act as effective enhancer types that drive an equivalent coarse-grained expression program, resulting in hierarchical cell identity.

To make this quantitatively precise, we show that specific weighted averages of terminal expression programs act as effective attractor programs at intermediate values of β through self-similarity of the dynamics of Eq. (1). The analysis hereafter considers patterns (rows of Ξ) of magnitude unity; a straightforward generalization to patterns of unequal magnitude is provided in the Supplemental Material [73]. To see how progenitor patterns emerge from Eq. (1), consider a subset of indices $\mathcal{L} \subseteq \{1 \dots K\}$ and denote the transformation $\mathbf{Q} \xrightarrow{\mathcal{L}} \mathbf{Q}'$, $\Xi \xrightarrow{\mathcal{L}} \Xi'$, $\mathbf{w} \xrightarrow{\mathcal{L}} \mathbf{w}'$, where $\mathbf{Q}' = \mathbf{Q}_{i \notin \mathcal{L}} \cup \{Q_{\mathcal{L}}^*\}$, $\Xi' = \Xi_{i \notin \mathcal{L}} \cup \{\Xi_{\mathcal{L}}^*\}$, $\mathbf{w}' = \mathbf{w}_{i \notin \mathcal{L}} \cup \{w_{\mathcal{L}}^*\}$, with

$$\begin{aligned} Q_{\mathcal{L}}^* &= \frac{\sum_{i \in \mathcal{L}} Q_i e^{w_i}}{\sum_{i \in \mathcal{L}} e^{w_i}}, \\ \Xi_{\mathcal{L}}^* &= \frac{\sum_{i \in \mathcal{L}} \Xi_i e^{w_i}}{\sum_{i \in \mathcal{L}} e^{w_i}}, \\ w_{\mathcal{L}}^* &= \log \sum_{k \in \mathcal{L}} e^{w_k}, \end{aligned} \quad (4)$$

where Q_i is the i th row of $\mathbf{Q}$, Ξ_i is the i th row of Ξ , and w_i is the i th element of $\mathbf{w}$. We refer to $\Xi_{\mathcal{L}}^*$ as the *progenitor pattern* associated with $\mathcal{L}$. We refer to the transformed dynamics as $g_{\mathcal{L}}(\mathbf{x}, \beta, \mathbf{Q}, \Xi, \mathbf{w})$ and refer to the transformed potential (if it exists) as $V_{\mathcal{L}}(\mathbf{x}, \beta, \Xi, \mathbf{w})$. Note that if the rows Ξ_i , $i \in \mathcal{L}$ are identical, then the transformation leaves the dynamics unchanged; that is, when $\Xi_i = \Xi_k$ for $i, k \in \mathcal{L}$ then $g_{\mathcal{L}}(\mathbf{x}, \beta, \mathbf{Q}, \Xi, \mathbf{w}) = g(\mathbf{x}, \beta, \mathbf{Q}, \Xi, \mathbf{w})$. This observation explains the emergence of symmetric dynamics due to the autoregulatory motif described in the previous section [Figs. 1(a) and 1(b)], and we will therefore assume that the “baseline” dynamics are captured by the symmetric form given by Eq. (2). Note that the transformation preserves symmetry,

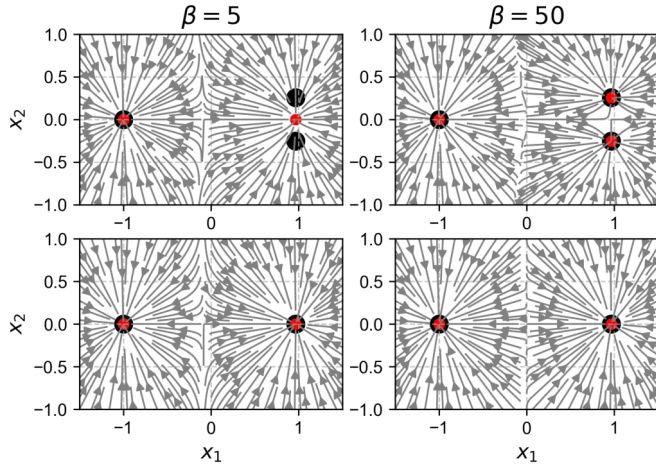


FIG. 2. Coarsening of dynamics. (a) Stream plots, patterns (black) and stable fixed points (red) for the dynamics given by Eq. (2) and parametrized with $\mathbf{w} = \mathbf{0}$ (upper panels) or the dynamics where the two patterns associated with positive x_1 are coarse grained by Eq. (4) (lower panels). Coarse graining is accurate for $\beta = 5$ as it is much smaller than the coalescence threshold of the two rightmost patterns (given by $\beta_{\mathcal{L}} = 15$) and fails for $\beta = 50$.

that is, if $\Xi_i = Q_i$ for all $i \in \mathcal{L}$ then $Q_{\mathcal{L}}^* = \Xi_{\mathcal{L}}^*$. Overall, the transformation given by Eq. (4) coarse-grains the dynamics as the patterns and weights associated with the transformed dynamics are weighted averages of the original patterns.

The coarse graining of a subset of expression patterns into a single progenitor pattern is associated with a β threshold denoted $\beta_{\mathcal{L}}$, which will be referred to as its coalescence threshold. In the case where the patterns are isolated and are of equal angle μ with each other, the progenitor pattern $\Xi_{\mathcal{L}}^*$ is destabilized at a critical $\beta = 2|\mathcal{L}|\mu^{-2}$. More generally, for patterns of unequal angle, the coarse-grained dynamics are similar to the original dynamics up to a correction term,

$$V_{\mathcal{L}}(\mathbf{x}, \beta, \Xi, \mathbf{w}) \approx V(\mathbf{x}, \beta, \Xi', \mathbf{w}') + O(\beta\mu_{\mathcal{L}}^2), \quad (5)$$

where the correction term is at most $\frac{1}{4}\beta\mu_{\mathcal{L}}^2$, with $\mu_{\mathcal{L}}$ being the maximal angle between any two patterns in the subset. The progenitor $\Xi_{\mathcal{L}}^*$ thus has a coalescence threshold which depends on the statistical structure of the associated patterns $\Xi_{i \in \mathcal{L}}$ and is of order $\beta_{\mathcal{L}} \approx 4\mu_{\mathcal{L}}^{-2} \approx \frac{2}{1 - \cos \mu_{\mathcal{L}}}$. The coalescence threshold of a subset $\mathcal{L}$ is thus proportional to the inverse of its diameter by the cosine similarity measure.

From a biological perspective, Eq. (5) implies that at intermediate values of β , subsets of enhancer types activating different transcriptional programs may become effective patterns of the dynamics [Figs. 1(c) and 2], with the transition occurring at larger β for enhancer types with more similar target programs due to their larger coalescence threshold.

Importantly, the coarse-graining transformation can be applied to overlapping pattern subsets, whose coalescence thresholds can be distinct. For example, two overlapping pairs of patterns may be similar $\angle(\Xi_1, \Xi_2) = \mu$, $\angle(\Xi_2, \Xi_3) = \mu$, while the third pair is less similar $\angle(\Xi_1, \Xi_3) = 2\mu$, and the coalescence threshold of the progenitor of Ξ_1, Ξ_3 is much smaller compared with the progenitors of Ξ_1, Ξ_2 and Ξ_2, Ξ_3 . In this case, patterns 1, 2 and patterns 2, 3 may share a stable

progenitor over a broader range of β values compared to patterns 1, 3.

Finally, while the coalescence threshold can capture precisely patterns of stabilization and destabilization of progenitors in strictly hierarchical sets of patterns with strong separation in pattern similarities, in other cases more complex stability properties can emerge. However, by Eq. (4), a subset of patterns $\mathcal{L}$ become coupled through their progenitor $\Xi_{\mathcal{L}}^*$ for values of β smaller than their coalescence threshold.

B. Hierarchical control of cell identity transitions

The analysis so far indicates that different expression patterns, specified by autoregulatory circuits, as well as weighted combinations of expression subsets, act as effective patterns of the dynamics for different values of β . The dependence of the coalescence threshold on the diameter of the subset suggests that lower values of β can support the stable expression of larger subsets of more distinct expression patterns. We now show that the weight vector $\mathbf{w}$, which is modulated by signaling, plays a crucial role in determining which expression patterns achieve this stability.

Under the dynamics of Eq. (2), an increase of w_i (the associated $\mathbf{w}$ entry of pattern i) results in an increase in the basin of attraction of pattern i , at the expense of competing patterns (see the Supplemental Material [73]). Thus, expression patterns associated with larger $\mathbf{w}$ are more likely to be attractors of the dynamics, and therefore, correspond to stable cell types.

While the weight vector entries of terminal (w_i) and progenitor ($w_{\mathcal{L}}^*$) patterns appear mathematically indistinguishable, their biological interpretations are distinct. The weight entries of terminal patterns are directly interpretable within the physical framework of Eq. (1), reflecting a baseline level associated with persistent chromatin and DNA modifications, as well as the binding of signaling TFs upstream of the cell identity network. In contrast, the weight entries of progenitor patterns are log-sum-exp transformations of the weights of their constitutive patterns. This distinction has two important implications for our analysis. The first is that progenitor patterns always have larger weights than their constitutive patterns, with progenitors of larger subsets having larger associated $\mathbf{w}$ entries. The second is that increasing (or decreasing) the associated w_i of a physical enhancer propagates upwards with both (a) increasing (resp. decreasing) the $\mathbf{w}$ entry of its associated progenitor states and (b) increasing (resp. decreasing) the contribution of its associated expression pattern Ξ_i to its progenitors. Crucially, this effect is inherently modular, with other progenitor states remaining unperturbed despite potentially sharing overlapping expression programs. Taken together, these observations imply a form hierarchical control of progenitor states by the input field $\mathbf{w}$.

The modulation of an input field entry w_i thus controls both progenitor identity and the basins of attraction of Ξ_i and its progenitors. While the basin of attraction of Ξ_i increases with w_i , that is, Ξ_i is attractive from a wider range of states, the identities of progenitors associated with Ξ_i become more similar to Ξ_i . Thus, an increase of w_i increases the

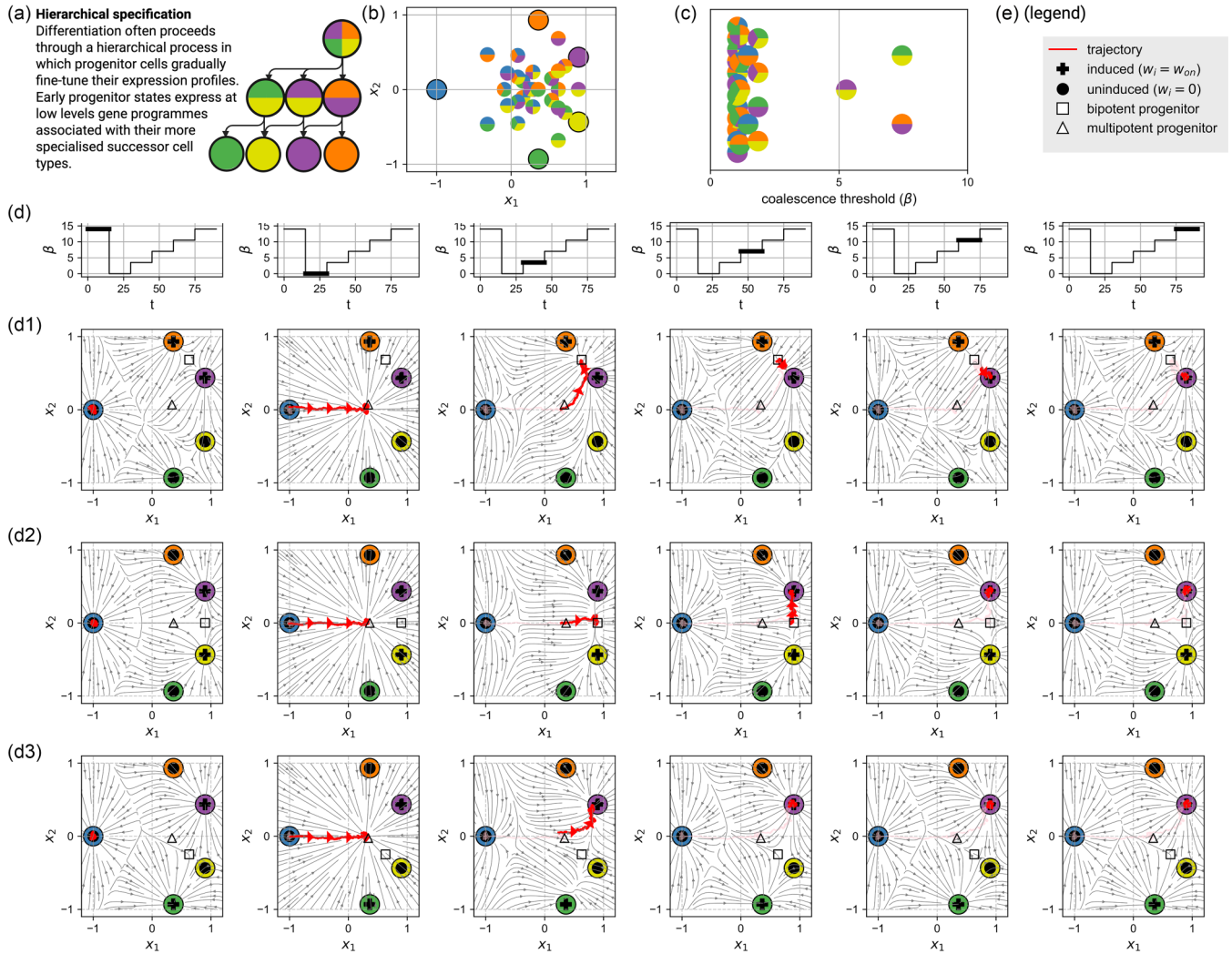


FIG. 3. Hierarchical coarsening of dynamics allows for control of transitions through progenitor states. (a) Differentiation typically involves progenitor states with mixed expression programs (multicolored circles) that gradually resolve into finer identities (monocolor circles). Progenitors with overlapping fate potential may be observed. (b) An example of a system with five patterns (rows of Ξ) depicted as monocolor circles. The progenitor pattern Ξ_L^* [calculated by Eq. (4)] for each nonempty subset $\mathcal{L}$ of the rows of Ξ is plotted as a multicolored circle with colors depicting the relevant associated patterns of $\mathcal{L}$. (c) Coalescence thresholds for all progenitor patterns computed by $\beta_{\mathcal{L}} = \frac{2}{1 - \cos \mu_{\mathcal{L}}}$, where $\mu_{\mathcal{L}}$ is the maximal angle in the subset $\mathcal{L}$. (d) Simulations of annealing (decrease in β followed by gradual increase, see upper subpanel), starting from the blue pattern as an initial condition, with the addition of noise, using the dynamics $d\mathbf{x} = \{\Xi^T \text{softmax}[\beta(t)(\Xi\mathbf{x} + \mathbf{w})] - \mathbf{x}\}dt + \sigma dW$ where dW is an N -dimensional Wiener process, taking $\sigma = 0.03$ and $\mathbf{w}$, here corresponding to signaling, was set as $w_{on} = 0.25$ for induced patterns (cross) and otherwise (circle) set to zero. Bipotent progenitors for co-induced states were drawn as empty squares while multipotent progenitors associated with all five patterns were depicted as empty triangles. Simulation lines are drawn in red with red arrows capturing direction of progression.

likelihood that a progenitor of Ξ_i will be within its basin of attraction. Our analysis similarly extends to progenitor states, as an increase in w_i leads to an increase in the basins of attraction of all progenitor patterns, due to an increase in their associated weights, and increases their similarity compared with competing patterns that do not incorporate Ξ_i . These observations capture, mathematically, established experimental observations on how differentiation signals guide differentiation towards specific cell types by increasing the relative representation of their expression programs in progenitor states [35].

The observation on how $\mathbf{w}$ controls progenitor identity and basins of attraction suggests that an annealing mechanism,

whereby β is decreased, and then slowly increased, can be used to transition between attractor states (Fig. 3). Namely, modulation of $\mathbf{w}$, such as by signaling, can control the end states of the annealing process. In the presence of noise or variability in parameters, an increase in w_i can increase the rate at which pattern Ξ_i is formed. A feedback controller that adjusts w_i according to the production rate of different patterns can therefore control the fractions of patterns produced. In a biological context, such a controller could operate through a mechanism where the production of a cell type Ξ_i decreases the activity of an intercellular signaling ligand that activates its associated enhancers, resulting in population-level negative feedback. Overall, this framework demonstrates

how $\mathbf{w}$ modulation can orchestrate control on the production of cellular populations.

C. Properties of hierarchical differentiation

We now apply the analytical framework to develop specific predictions regarding hierarchical differentiation. As introduced, systems like the blood, intestinal epithelium, and neural crest emerge from multilineage-primed progenitors that progressively specify into increasingly restricted progenitors [Fig. 3(a)]. Although often depicted as tree-like structures analogous to evolutionary phylogeny, fate convergence in hierarchical differentiation is common, where a single cell type arises through multiple differentiation trajectories [6,37,75]. This is well studied in the blood, where numerous progenitor cell types exhibit overlapping fate potentials [4]. The origin and nature of these progenitor states and overlapping differentiation pathways are the focus of this section.

To illustrate how complex differentiation landscapes arise within our framework, we examine a simple illustrative example [Fig. 3(b)] with two variables, x_1, x_2 , and five expression programs $\Xi_1, \dots, \Xi_5$, represented as monocolored circles corresponding to the expression programs of distinct differentiated cell types. Using the transformation in Eq. (4), we plotted all 26 possible progenitor states as pie charts, taking a baseline state of $\mathbf{w} = 0$. For each progenitor state, we computed its coalescence threshold [Fig. 3(c)], and examined dynamical differentiation trajectories during annealing in the presence of different signaling conditions [Fig. 3(d)].

During annealing [Fig. 3(d)], dynamical trajectories, initialized at the leftmost blue pattern (the “stem” state), transition through a bifurcating landscape before differentiating. In the examples plotted in Fig. 3(d), differentiation concluded in the purple pattern. Differentiation followed distinct pathways depending on which cell types were co-induced ($w_i = w_{\text{on}}$). When the purple pattern was co-induced with the orange (d1) or yellow (d2) patterns, differentiation proceeded through bipotent progenitors (purple-orange for d1, purple-yellow for d2), with the purple-orange progenitor resolving at higher β . In contrast, when the green pattern was co-induced (d3), the system bypassed the bipotent progenitor entirely. These differences arise from variations in the coalescence thresholds of progenitor states: the purple-orange progenitor has the highest threshold, the purple-yellow slightly lower, and the purple-green progenitor has a threshold comparable to that of the multipotent progenitor (a mixture of all cell types). This example illustrates that progenitors with larger and more distinct coalescence thresholds are more likely to be observed during the annealing process.

Figure 3 demonstrates the key predictions on differentiation through annealing: (a) differentiation through hierarchical cell identities reflects changes in β that facilitate transitions between stem and differentiated states; (b) progenitor states with larger coalescence thresholds, compared to competing states, are more likely to be observed, as they act as attractor states across a broader range of β values during the annealing process; and (c) among competing progenitor states with similar coalescence thresholds, those that encompass a

wider range of patterns are more likely to be observed due to their larger associated $\mathbf{w}$ entries.

D. Emergence of hierarchical state transitions in haematopoiesis

We now apply the framework to study the origin of progenitor states in blood formation. Blood formation, or haematopoiesis, occurs through the differentiation of a stem population capable of generating all blood lineages. This process follows a well-defined hierarchical structure, starting with stem cells transitioning into multipotent progenitors, which then differentiate into more restricted cell types, ultimately giving rise to one of 11 major lineages. The potential of blood progenitors and their differentiation trajectories have been extensively characterized using various experimental approaches, including *in vitro* culture assays, transplantation studies, single-cell gene expression and chromatin analysis, and fate mapping [4,76]. Blood progenitor states can exhibit self-renewal and longevity, suggesting they represent stable attractors within the gene regulatory network. In addition, after acquiring their initial differentiated identity, many blood cell types undergo additional specialization, such as during tissue migration or in response to immune challenges. Haematopoiesis is therefore a central model system for studying hierarchical cell specification.

A central question in haematopoiesis concerns the origin and nature of blood progenitor states. These states exhibit low-level expression of transcriptional programs associated with their successor cell types [3,6,25–27,31–33] and are responsive to differentiation signals. Importantly, different progenitors can possess partially overlapping fate potentials, leading to deviations from a strict tree structure and enabling alternative differentiation routes to the same terminal fate [4,6]. While, in theory, a vast number of progenitor states could exist (on the order of 2^{11}), far fewer have been observed. This discrepancy raises the question of why these specific sets of progenitors and differentiation trajectories are favoured.

To investigate the origin of progenitor states in haematopoiesis using our analytical framework, we initialized Eq. (2) with mouse TF expression profiles from the 11 major blood lineages. Previous numerical simulations in a balanced differentiation setting (that is, annealing with noise, using a computed weight vector $\mathbf{w}$ that provides uniform lineage production) demonstrated that the model recapitulates known blood differentiation trajectories, including overlapping pathways [48] [Fig. 4(a)]. Here we extend this work by developing a method to infer progenitor states within our analytical framework.

As an initial approach to generate a differentiation tree based on the coalescence threshold concept, we applied complete-linkage clustering [78] to lineage-specific TF expression profiles [Fig. 4(b)]. Complete-linkage clustering produces a dendrogram where clusters are agglomerated hierarchically by iteratively merging the pair of clusters that would yield the smallest maximum diameter among all possible cluster pairs. When cosine similarity is used as the distance, this diameter corresponds to the coalescence threshold, enabling the algorithm to produce a candidate differentiation tree where clusters represent putative progenitor states.

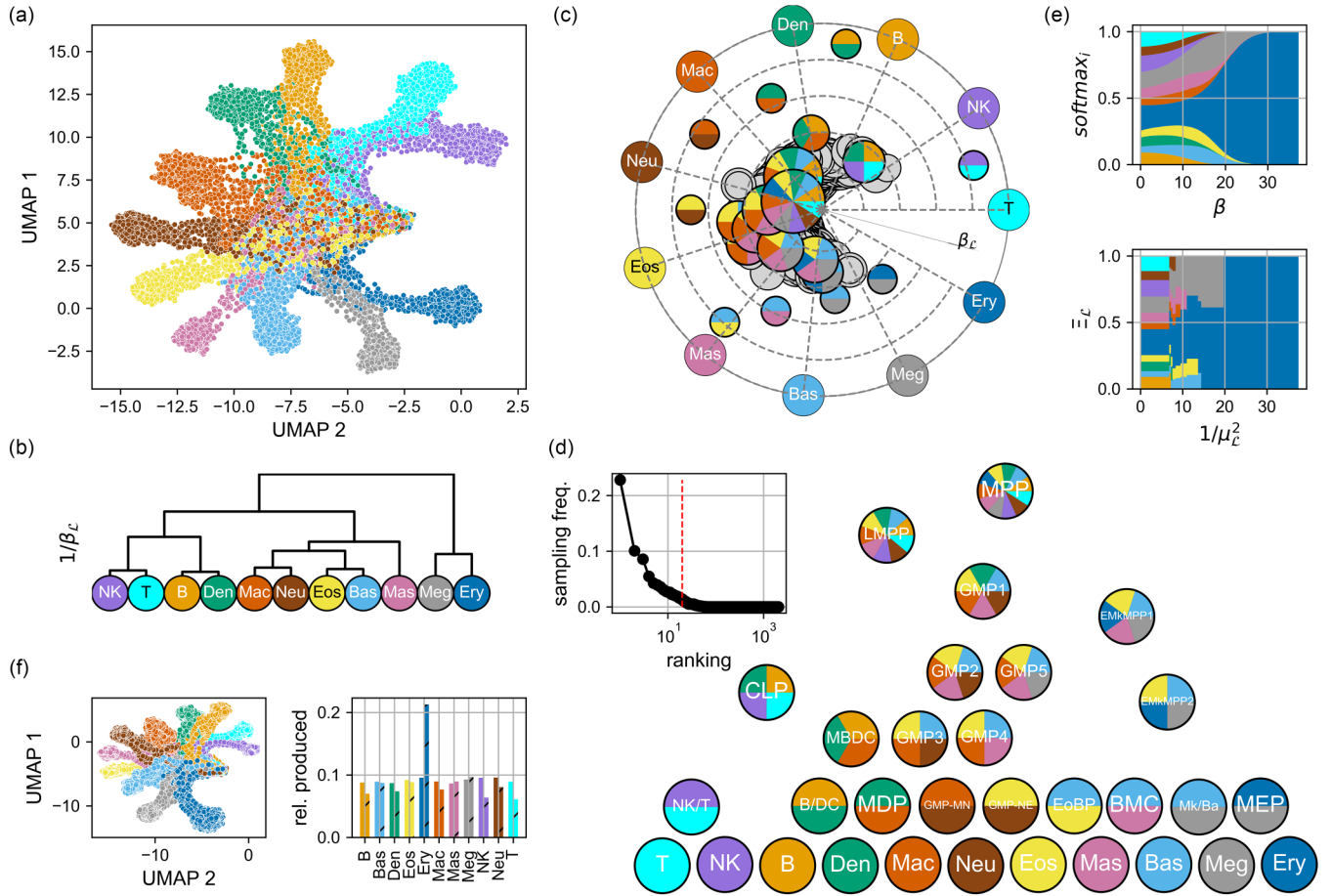


FIG. 4. Hierarchical regulation of cell identity in blood formation. (a) Simulations of annealing, taking TF expression patterns of haematopoietic lineages, with $\mathbf{w}$ set by a proportional negative feedback controller with an error proportional to the imbalance of blood cell production. In all simulations the noisy version of Eq. (2) was used (see the Supplemental Material [73] and Fig. 3), setting $\sigma = 0.05$. Annealing trajectories were plotted using Uniform Manifold Approximation and Projection (UMAP) and colored by terminal cell type. (b) Dendrogram of the TF expression patterns of haematopoietic lineages produced by complete-linkage clustering. (c) All 2036 possible progenitor states were plotted at a radius proportional to their corresponding coalescence threshold, computed as in Fig. 3(c). The top 20 sampled progenitor states in D were colored, with other progenitor states depicted in gray. (d) The 20/2036 most frequently sampled progenitor states following the application of the probabilistic sampling method to haematopoietic lineages. Progenitor states (multicolored circles) were colored according to their constituent patterns (monocolored circles). (Inset) Frequency of sampling of each progenitor states after 10^6 iterations, with dashed red line corresponding to the 20th most frequently sampled progenitor. (e, upper) Average contribution of different blood lineage expression programs to $\mathbf{x}(t)$ during annealing trajectories from (a) that result in erythrocyte production, given by $\text{softmax}(\beta \Xi \mathbf{x} + \mathbf{w})$. (e, lower) At each coalescence threshold the largest progenitor state that is associated with an erythrocyte lineage is selected and plotted according to the relative contributions of each blood lineage to its expression profile, given by the transformation Eq. (4). (f, right) The relative production of different blood cell types, with the parameters inferred in (a) (blank) and with the $\mathbf{w}$ entry of erythrocytes increased by 10% (hatched), demonstrating how signaling can increase the relative production of different cell types in the annealing procedure. (f, left) Corresponding UMAP plot for annealing dynamics with enhanced erythrocyte production. For all simulations and analysis, the matrix Ξ was initialized from the averaged mouse gene expression profiles of 11 major blood lineages from Haemopedia [77], initialized as in Karin [48].

Application of complete-linkage clustering to lineage-specific TF expression profiles generated a dendrogram [Fig. 4(b)] that successfully recapitulates many established progenitor states. However, this approach is inherently limited by its tree structure constraint, which cannot accommodate progenitors with overlapping fate potential. In addition, analytical closed-form expressions for basins of attraction for an arbitrary Ξ as a function of β and $\mathbf{w}$ are not available, motivating the development of alternative approaches to hierarchy construction under specific signaling environments.

To overcome these challenges, we developed a sampling-based method for comprehensive enumeration of progenitor states, enabling prediction under arbitrary signaling environments. We first computed coalescence thresholds for all 2036 possible progenitor states [Fig. 4(c)]. We then implemented a heuristic sampling procedure to assess progenitor emergence likelihood in differentiation trajectories where several (*a priori* unknown) cell types may be co-induced. Intuitively, we sampled across different annealing stages and selected progenitors that remained potentially stable—neither bifurcating themselves nor descending from states that failed to bifurcate,

with bifurcation points estimated by the coalescence thresholds. Specifically, for each iteration, we (1) randomly selected a target cell type i (e.g., neutrophil); (2) uniformly sampled a threshold $\beta_0 \leq \max_{i \in \mathcal{L}} \beta_{\mathcal{L}}$; (3) retained only i -containing progenitors with thresholds larger than β_0 and no ancestors in this subset; and (4) uniformly sampled from this progenitor subset. Progenitor states sampled more frequently under this procedure are predicted to be more likely to be observed during differentiation.

Using only terminal blood expression profiles, our method reconstructed many observed progenitors of the haematopoietic hierarchy, including known progenitors with overlapping lineage potential [Fig. 4(d); cf. [4,76,79,80]]. Of the 2036 possible states, 1973 were never sampled across 10^6 iterations, while the top 20 progenitors [Fig. 4(d), inset] included experimentally observed bipotent progenitors for T/NK cells [81], B cells/dendritic cells [82], dendritic cells/macrophages [83,84], macrophages/neutrophils [31,84], neutrophils/eosinophils [85–87], eosinophils/basophils [88], basophils/mast cells [89], and megakaryocytes/erythrocytes [90–92]. The method also identified established multipotent progenitors, such as the eosinophil/megakaryocyte/erythroid/mast cell/basophil progenitor (EMkMPP) [93,94], the granulocyte/macrophage progenitor (GMP) [31,87,95], the common lymphoid progenitor (CLP) [96], and lymphoid-primed multipotent progenitors (LMPPs) [97].

Crucially, the analysis also explains overlapping differentiation pathways revealed by fate mapping and single-cell studies. These include monocyte differentiation through joint potential with either neutrophils or dendritic cells [6,84]; dendritic cell differentiation through joint potential with lymphoid and myeloid lineages [98,99]; and basophil fate aligning either with megakaryocyte/erythrocyte or granulocyte/macrophage trajectories [94,100]. Beyond these established states, our analysis further predicts the existence of a macrophage/B cell/dendritic cell progenitor (MBDC), which has been hypothesized [79] but, to our knowledge, not yet experimentally demonstrated. Furthermore, the model predicts a range of accessible GMP-like progenitors associated with subsets of restricted but overlapping fate potentials. Such heterogeneity within the GMP compartment has been implicated experimentally [31,87,100], but its full resolution may require detailed analysis of gene expression states coupled with fate-mapping and perturbation studies. Overall, the reconstruction of these hierarchical states from terminal lineage data alone suggests that they may emerge during blood differentiation from an annealing-like process captured by Eq. (2).

Finally, we used blood as a model system to illustrate how signaling can regulate the relative production of terminal lineages by biasing progenitor states, thereby explaining observed effects such as erythropoietin's influence on blood differentiation. As presented in Fig. 4(a), we examine the dynamics of annealing in the presence of noise, where we define $\mathbf{w}$ through negative feedback, simulating the body's regulatory mechanisms that balance cellular production, such as negative feedback through homeostatic mechanisms [101–103]. This results in a balanced differentiation landscape, where all fates are proportionally represented through a bifurcating process. The identity of progenitor states and their coalescence

thresholds are captured by the coarse-graining transformation [Fig. 4(e)]. We then increased the $\mathbf{w}$ entry corresponding to the erythrocyte fate, simulating the biological effect of erythropoietin [Fig. 4(f)]. This adjustment both increased the erythrocyte production rate and increased the relative contribution of the erythrocyte expression profile to its associated progenitor states, effectively recapitulating the known effects of erythropoietin on red blood cell production [35,104] [Fig. 4(f)]. Our modeling framework therefore recapitulates how signaling can bias the relative production of a specific cell type in a complex differentiation landscape through biasing its progenitors, an effect that appears to be a common feature in developing tissues [12,105,106].

E. Pathways to dysregulation in cancer and implications for differentiation therapy

Our theoretical framework provides a basis for analyzing dysregulation of cell identity in cancer, a hallmark of which is profound disruption of cell identity often driven by differentiation failures [107]. This is particularly evident in blood cancers, where malignant states are associated with impaired progenitor maturation [108]. Below we propose possible mechanisms for such differentiation failures based on our model.

Central to our findings is the dynamical landscape's dependence on β : progenitor states are stabilized at fixed β values, while differentiation requires an increase in β to drive cell fate bifurcations. Consequently, differentiation failures emerge from two distinct dysregulations: (i) persistent maintenance of β below the critical threshold or (ii) elevation of the β threshold required for bifurcation.

Mechanistically, dysregulation of β originates from perturbations in epigenetic control systems. Specifically, imbalances between HAT and HDAC activities, or mutations disrupting regulatory mechanisms governing the annealing-associated decrease in β , can prevent the required β modulation during differentiation. Our model therefore predicts that differentiation failures can emerge in cases where HAT activity is inhibited, reducing β , or HDAC activity is augmented, suppressing β elevation. These predictions align with experimental observations of differentiation defects under these perturbation conditions [109–119].

Consistent with the prediction that augmenting HDAC activity suppresses differentiation, broad HDAC inhibition conversely induces differentiation in cancers characterized by maturation arrest and in multipotent progenitors [111,112,119–124]. Our model attributes these effects to heightened sensitivity in enhancer competition due to larger β following HDAC inhibitor treatment.

In addition to the dysregulation of epigenetic processes, many cancers are driven by mutations that modulate the activity of TFs governing cell identity [125]. These mutations often involve deletions or regulatory changes caused by chromosomal translocations. Notable examples in blood cancers include Pu.1 and Gata2, which are strongly and differentially expressed in myeloid lineages [126–128], and Pax5, which is uniquely expressed in B cells [129,130]. Similarly, certain TFs are highly expressed in stem cells compared to differentiated lineages, and their dysregulation can lead to

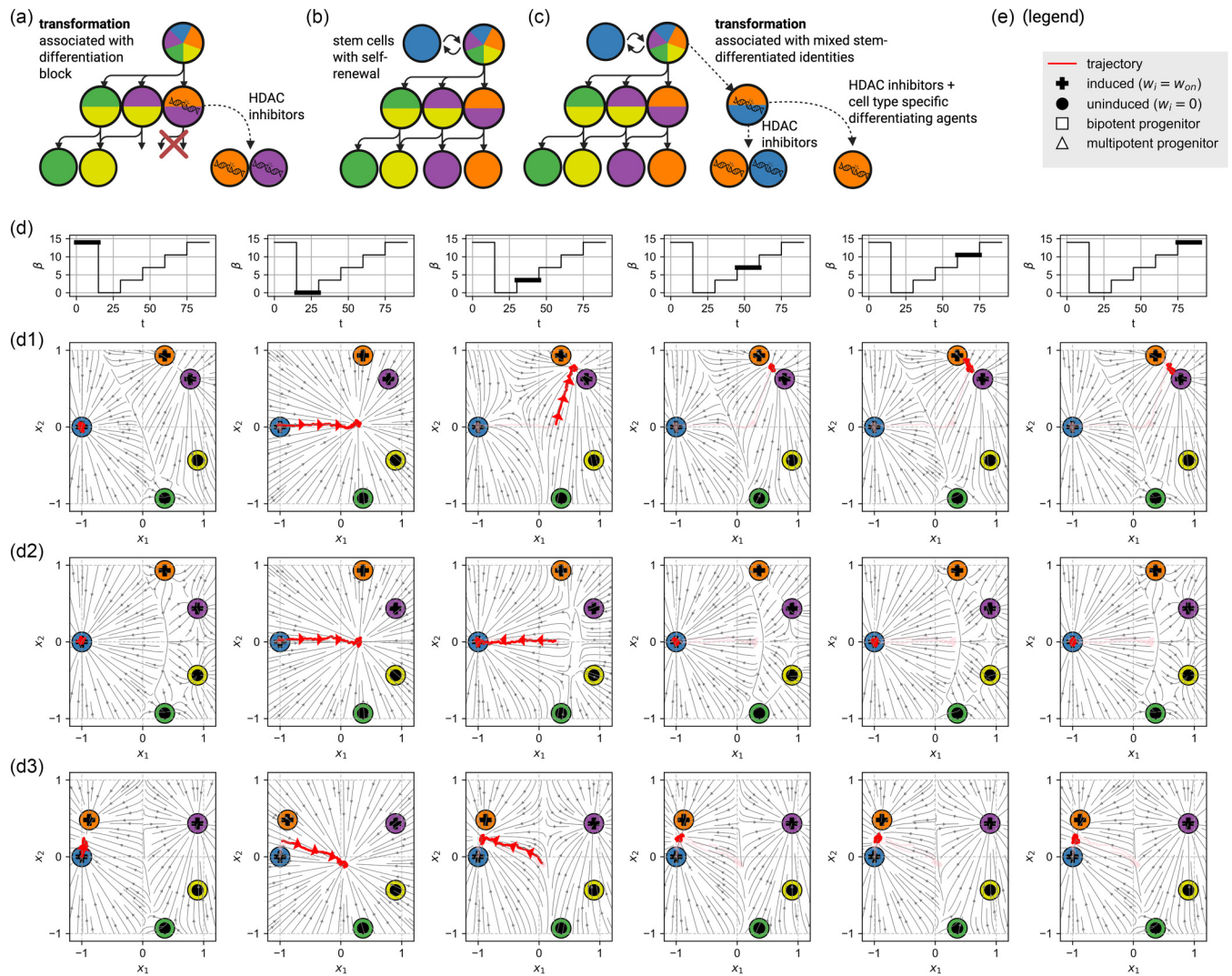


FIG. 5. Dysregulation of differentiation following mutation with application to differentiation therapy. (a) Differentiation may be inhibited in mutants where the coalescence threshold is increased, resulting in failure to resolve cell identity following annealing. Treatment with HDAC inhibitors, which increases β , can restore differentiation by overcoming the increase in coalescence threshold. (b) Stem cells can self-renew following annealing when their own w entry is large enough. (c) Specific mutations that increase the coalescence threshold between differentiated and stem states can result in the stabilization of a mixed differentiated-stem identity following annealing. In this case, treatment with HDAC inhibitors may be insufficient as the identity may resolve into a stem identity rather than a differentiated identity, and supplementation with an agent that increases the relevant w entries of the differentiated identity may be needed. (d1) Illustration of mutant corresponding to case (a), (d2) Illustration of self-renewing stem populations as in (b), (d3) Illustration of mutant corresponding to case (c). All simulations were performed as in Fig. 3, here setting $w_{on} = 0.75$. Simulation lines are drawn in red with red arrows capturing direction of progression.

the aberrant stabilization of a mixed stem-differentiated state. For instance, Lmo2 and Tal1, which are strongly expressed in haematopoietic stem cells but downregulated in lymphocytes, can drive lymphoblastic leukaemias when misexpressed [131–133]. Erg, another key TF, is typically downregulated during stem cell differentiation, but its upregulation promotes a mixed stem/differentiated state in both myeloid [134,135] and lymphoblastic leukaemias [134,136]. Since mixed stem-differentiated identities appear to play a central role in blood cancer persistence [137–139], understanding their origin is of great clinical importance.

Our analysis suggests that the mechanisms underlying transformation following TF dysregulation may involve

changes in the coalescence threshold of progenitor states (Fig. 5). The deletion of a TF, or its activation under an inappropriate transcriptional context, leads effectively to a modulation of the rows of Ξ , changing the coalescence thresholds of the different progenitor states. If two or more states become more similar to each other, a new progenitor state may be observed, or may fail to resolve following annealing [Fig. 5(a), d1], leading potentially to dysregulation. This perspective provides a straightforward explanation for the effectiveness of HDAC inhibitors in differentiation therapy for some blood cancers [111,112,121,140,141], as they may help restore normal differentiation by increasing β further to facilitate differentiation.

Mutational changes in coalescence thresholds may also stabilize hybrid stem-differentiated identities [Figs. 5(b)–5(c), d3]. In our model, self-renewing stem cells (e.g., haematopoietic, embryonic) correspond to distinct Ξ rows governed by specific transcriptional programs. Self-renewal rates depend on $\mathbf{w}$ vector entries linked to stem programs [Fig. 5(b), d2]. Mutations can stabilize mixed stem-differentiated states if they increase their coalescence threshold [Fig. 5(c), d3].

By our model, mixed stem-differentiated states are more likely to resist HDAC inhibitor monotherapy. Increased β can revert such progenitors to therapy-persistent self-renewing stem cells instead of terminally differentiated cells. This prediction aligns with experimental evidence that HDAC inhibitors may, under certain conditions, amplify stem core transcriptional programs and enhance their self-renewal [142–144]. The model consequently supports combination therapy with cell-type-specific differentiating agents that increase relevant $\mathbf{w}$ entries which can bias differentiation away from stem identities [145,146].

III. DISCUSSION

In this study, we developed a mathematical framework to explain the mechanistic basis of progenitor states and hierarchical differentiation landscapes in animal gene regulatory networks. We demonstrate that hierarchical cell identities, in which cells coexpress multiple transcriptional programs, represent a fundamental outcome of epigenetic write, erase, read mechanisms controlling animal gene expression. Our framework provides an analytical basis to examine key aspects of these mixed states: their identity, stability, and basins of attraction. The model also explains how these states enable signaling-sensitive transitions through progenitor biasing.

Our cell identity model mathematically maps to continuous MHNs, utilizing a pattern input field $\mathbf{w}$ [50,51,74,147–149]. In the broader Hopfield network literature, fixed points representing mixtures of memory patterns, known as spurious states, were historically viewed as artifacts that hinder accurate pattern retrieval. MHNs mitigate these states by tuning a high inverse-temperature parameter β [51,150]. However, at lower β , spurious states emerge, and their properties remain underexplored. Our framework characterizes these states, proposing they enable robust transitions between memory patterns via β annealing, with broad implications for fields like neuroscience and machine learning due to the generality of MHNs. Finally, while our formalization was based on enhancer-based gene regulation, our analysis may apply to any cellular process that can be captured by Eq. (1).

A specific mathematical analogy exists between our hierarchical cell identity specification model and generative diffusion models which are broadly used in machine learning. Recent work shows that reverse diffusion in these models is equivalent to continuous MHNs, with training examples encoded in the rows of Ξ , and β modulated through an annealing-like process [74]. In diffusion models, large datasets drive a shift from memorization to generalization, generating novel outputs. Emerging evidence suggests spurious states may facilitate this shift [149]. Similarly, in cellular

differentiation, signal-sensitive mixtures of “primitive” identities (rows of Ξ) could produce novel cell types, providing a mathematical parallel to generalization in diffusion models.

From a biological perspective, our model proposes that non-specific competition among enhancers for transcriptional regulators is a key driver of cell identity determination and hierarchical state transitions. Drawing on experimental evidence [61,62,65–67,70,151,152], we investigated two primary competitive processes: (i) TF-mediated competition for the recruitment of HAT molecules, resulting in differential enhancer acetylation, and (ii) acetylation-dependent redistribution of epigenetic readers, such as Brd4, which drives enhancer-specific transcription. These processes collectively explain the dynamics captured in Eq. (1). A key insight of our model is that nonspecific repressive interactions, arising from competition for transcriptional resources, may underpin cell differentiation. This contrasts with traditional models, which often rely on specific repressive interactions mediated by TFs to silence alternative lineages. While specific repression may play a role in certain contexts, our analysis suggests that nonspecific mechanisms are sufficient to account for differentiation dynamics.

To gain analytical tractability, we simplified the model by omitting dynamic regulation of repressive enhancer chromatin. Enhancers often face repression via mechanisms inhibiting TF binding, which may induce hysteresis requiring pioneer TF activity to restore access [153,154]. Such dynamics can be incorporated in the model, as shown in [48]. In differentiation hierarchies, epigenetic repression typically emerges as cells acquire differentiated identities, while stem cells and early progenitors maintain open chromatin [155–157]. Thus, Eq. (1) is suitable for modeling differentiation in open chromatin contexts, and incorporating repressive dynamics would be important for studying dedifferentiation or reprogramming.

The observation that dedifferentiation may require overcoming hysteretic repression could explain the epigenetic mechanisms driving this process. While HDAC inhibition promotes differentiation and HAT inhibition can block it, whether HAT inhibition alone induces dedifferentiation remains unclear [158–160]. In the presence of hysteresis, dedifferentiation likely requires robust activation of competing enhancers, which HAT inhibition may impede by reducing TF expression [49]. Thus, dedifferentiation via reduced β may necessitate both relaxed enhancer competition (e.g., through HAT inhibition) and transcriptional amplification to counter repression.

An additional mechanism for driving differentiation and dedifferentiation, interpretable within our model, may be through the expression of Myc proteins. Myc proteins are important regulators of differentiation across various cell types, transitioning from high to low expression levels across many differentiation hierarchies. They exhibit antidifferentiation effects that may be independent of their proproliferation functions [161–163]. Myc binds promiscuously to regulatory sites, amplifying transcription and sequestering coactivators like HATs [164,165]. In our framework, Myc-driven coactivator sequestration reduces β , while transcriptional amplification may overcome hysteretic repression, facilitating dedifferentiation [166].

While our discussion has focused on hierarchical differentiation from progenitor states, our findings also carry important implications for direct reprogramming between specified cell types (transdifferentiation). Direct reprogramming is typically achieved through the constitutive overexpression of specific TFs, and we have previously demonstrated that our model can quantitatively account for the outcomes of various established reprogramming protocols [48]. In our framework, constitutive TF overexpression effectively corresponds to modulation of $\mathbf{w}$, which in turn alters the basins of attraction associated with different cell types. A sufficiently large relative increase in the $\mathbf{w}$ entry corresponding to a given cell type expands its basin of attraction to subsume those of competing fates, thereby driving reprogramming toward that identity. By contrast, a more modest increase in $\mathbf{w}$ may only permit reprogramming toward transcriptionally related cell types, as these require a smaller shift of the separatrix between attraction basins. In addition, changes in β may interact with this process by altering the underlying transcriptional state of the cell. A strong decrease in β , by broadening the range of accessible expression states, can facilitate reprogramming into more transcriptionally distinct cell identities, potentially explaining the role of Myc expression in promoting reprogramming [167,168]. Together, we propose that direct reprogramming outcomes can be systematically understood as shifts in the geometry of attraction basins governed by $\mathbf{w}$ and β .

Unlike classical gene regulatory models that presuppose hierarchical or modular network architectures [169–171], our framework reveals hierarchy as an emergent property arising from fundamental enhancer dynamics. By modeling the interplay of enhancer cooperation and competition, we can explain the emergence and control of hierarchical cell identities without imposing any *a priori* hierarchical structure on the transcriptional regulatory network. Our analysis demonstrates that enhancer competition enables a highly modular control of differentiation, even in the absence of modularity at the level of the transcriptional network. Signaling pathways that activate a specific transcriptional program through its enhancers will selectively perturb the associated progenitor states without impacting other states. This finding is unexpected, given that TFs are widely shared across different cell types, resulting in densely interconnected regulatory networks at the TF level. Modularity emerges only when regulation is examined through the lens of enhancer-TF interactions. Our findings

highlight that incorporating enhancer structure—whether implicitly through symmetry considerations, as in this study, or explicitly—is crucial for accurately modeling the regulation of cell identity.

The dynamics of differentiation in our model exhibit both similarities and differences compared to Waddington’s classic epigenetic landscape picture of cellular differentiation [1,147,172]. As in the Waddingtonian picture, differentiation in our model proceeds in a hierarchical manner through a series of bifurcations, from multipotent to ever more restricted progenitors. The modeling framework presented here makes the concept of potency quantitatively precise, in that we show that a differentiation signal for fate i , which modulates w_i , will perturb all progenitors associated with this fate towards it, while other progenitors will not be affected. Our analysis thus unifies the experimental observations on hierarchical differentiation, multilineage expression, and differentiation potency, into a single mathematical framework. In contrast to the classical Waddingtonian picture, however, our hierarchical picture does not entail a tree-like differentiation landscape. Rather, analysis suggests that differentiation landscapes may be much more flexible, with multiple possible trajectories to the same target fate. Moreover, the trajectories taken may themselves change according to signaling, which can lead to changes in the basins of attraction of the progenitor states. These flexible and non-tree-like dynamics are in line with experimental knowledge on complex differentiation dynamics in systems such as blood formation and the neural crest [4,37]. While our analysis proposes flexible differential landscapes, these landscapes are nevertheless constrained by the statistical structure of the target states and can be quantitatively predicted through the coalescence threshold measure.

ACKNOWLEDGMENT

A.G. is supported by a Roth Fellowship at Imperial College London. We thank the reviewers for their valuable comments and suggestions.

DATA AVAILABILITY

The data that support the findings of this article are openly available [77].

-
- [1] C. Waddington, *The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology* (Allen and Unwin, London, 1957).
 - [2] J. A. Briggs, C. Weinreb, D. E. Wagner, S. Megason, L. Peshkin, M. W. Kirschner, and A. M. Klein, The dynamics of gene expression in vertebrate embryogenesis at single-cell resolution, *Science* **360**, eaar5780 (2018).
 - [3] R. Månsson, A. Hultquist, S. Luc, L. Yang, K. Anderson, S. Kharazi, S. Al-Hashmi, K. Liuba, L. Thorén, J. Adolfsson *et al.*, Molecular evidence for hierarchical transcriptional lineage priming in fetal and adult stem cells and multipotent progenitors, *Immunity* **26**, 407 (2007).
 - [4] R. Ceredig, A. G. Rolink, and G. Brown, Models of haematopoiesis: Seeing the wood for the trees, *Nat. Rev. Immunol.* **9**, 293 (2009).
 - [5] E. Dzierzak and A. Bigas, Blood development: Hematopoietic stem cell dependence and independence, *Cell Stem Cell* **22**, 639 (2018).
 - [6] C. Weinreb, A. Rodriguez-Fraticelli, F. D. Camargo, and A. M. Klein, Lineage tracing on transcriptional landscapes links state to fate during differentiation, *Science* **367**, eaaw3381 (2020).
 - [7] D. Allman and S. Pillai, Peripheral B cell subsets, *Curr. Opin. Immunol.* **20**, 149 (2008).

- [8] J. A. Bluestone, C. R. Mackay, J. J. O'shea, and B. Stockinger, The functional plasticity of T cell subsets, *Nat. Rev. Immunol.* **9**, 811 (2009).
- [9] M. Williams, A. Mildner, and S. Yona, Developmental and functional heterogeneity of monocytes, *Immunity* **49**, 595 (2018).
- [10] I. Ballesteros, A. Rubio-Ponce, M. Genua, E. Lusito, I. Kwok, G. Fernández-Calvo, T. E. Khoyratty, E. van Grinsven, S. González-Hernández, J. Á. Nicolás-Ávila *et al.*, Co-option of neutrophil fates by tissue environments, *Cell* **183**, 1282 (2020).
- [11] S. Blankvoort, M. P. Witter, J. Noonan, J. Cotney, and C. Kentros, Marked diversity of unique cortical enhancers enables neuron-specific tools by enhancer-driven gene expression, *Curr. Biol.* **28**, 2103 (2018).
- [12] R. Soldatov, M. Kaucka, M. E. Kastriti, J. Petersen, T. Chontorotzea, L. Englmaier, N. Akkuratova, Y. Yang, M. Häring, V. Dyachuk *et al.*, Spatiotemporal structure of cell fate decisions in murine neural crest, *Science* **364**, eaas9536 (2019).
- [13] Z. Li, W. A. Tyler, E. Zeldich, G. Santpere Baró, M. Okamoto, T. Gao, M. Li, N. Sestan, and T. F. Haydar, Transcriptional priming as a conserved mechanism of lineage diversification in the developing mouse and human neocortex, *Sci. Adv.* **6**, eabd2068 (2020).
- [14] N. Sharma, K. Flaherty, K. Lezgiyeva, D. E. Wagner, A. M. Klein, and D. D. Ginty, The emergence of transcriptional identity in somatosensory neurons, *Nature (London)* **577**, 392 (2020).
- [15] L. Faure, Y. Wang, M. E. Kastriti, P. Fontanet, K. K. Cheung, C. Petitpré, H. Wu, L. L. Sun, K. Runge, L. Croci *et al.*, Single cell rna sequencing identifies early diversity of sensory neurons forming via bi-potential intermediates, *Nat. Commun.* **11**, 4175 (2020).
- [16] M. E. Kastriti, L. Faure, D. Von Ahsen, T. G. Boudierlique, J. Boström, T. Solovieva, C. Jackson, M. Bronner, D. Meijer, S. Hadjab *et al.*, Schwann cell precursors represent a neural crest-like state with biased multipotency, *EMBO J.* **41**, e108780 (2022).
- [17] A. Laddach, S. H. Chng, R. Lasrado, F. Prohazky, M. Shapiro, A. Erickson, M. Sampedro Castaneda, A. V. Artemov, A. C. Bon-Frauches, E.-M. Amaniti *et al.*, A branching model of lineage differentiation underpinning the neurogenic potential of enteric glia, *Nat. Commun.* **14**, 5904 (2023).
- [18] C. Li, J. Gehring, and M. E. Bronner, Spatiotemporal dynamics of the developing zebrafish enteric nervous system at the whole-organ level, *Dev. Cell* **60**, 613 (2024).
- [19] M. P. Creighton, A. W. Cheng, G. G. Welstead, T. Kooistra, B. W. Carey, E. J. Steine, J. Hanna, M. A. Lodato, G. M. Frampton, P. A. Sharp *et al.*, Histone h3k27ac separates active from poised enhancers and predicts developmental state, *Proc. Natl. Acad. Sci. USA* **107**, 21931 (2010).
- [20] W. A. Whyte, D. A. Orlando, D. Hnisz, B. J. Abraham, C. Y. Lin, M. H. Kagey, P. B. Rahl, T. I. Lee, and R. A. Young, Master transcription factors and mediator establish super-enhancers at key cell identity genes, *Cell* **153**, 307 (2013).
- [21] D. Hnisz, B. J. Abraham, T. I. Lee, A. Lau, V. Saint-André, A. A. Sigova, H. A. Hoke, and R. A. Young, Super-enhancers in the control of cell identity and disease, *Cell* **155**, 934 (2013).
- [22] D. Lara-Astiaso, A. Weiner, E. Lorenzo-Vivas, I. Zaretzky, D. A. Jaitin, E. David, H. Keren-Shaul, A. Mildner, D. Winter, S. Jung *et al.*, Chromatin state dynamics during blood formation, *Science* **345**, 943 (2014).
- [23] S. Heinz, C. E. Romanoski, C. Benner, and C. K. Glass, The selection and function of cell type-specific enhancers, *Nat. Rev. Mol. Cell Biol.* **16**, 144 (2015).
- [24] V. Saint-André, A. J. Federation, C. Y. Lin, B. J. Abraham, J. Reddy, T. I. Lee, J. E. Bradner, and R. A. Young, Models of human core transcriptional regulatory circuitries, *Genome Res.* **26**, 385 (2016).
- [25] M. Hu, D. Krause, M. Greaves, S. Sharkis, M. Dexter, C. Heyworth, and T. Enver, Multilineage gene expression precedes commitment in the hemopoietic system, *Genes Dev.* **11**, 774 (1997).
- [26] T. Miyamoto, H. Iwasaki, B. Reizis, M. Ye, T. Graf, I. L. Weissman, and K. Akashi, Myeloid or lymphoid promiscuity as a critical step in hematopoietic lineage commitment, *Dev. Cell* **3**, 137 (2002).
- [27] E. M. Mercer, Y. C. Lin, C. Benner, S. Jhunjunwala, J. Dutkowski, M. Flores, M. Sigvardsson, T. Ideker, C. K. Glass, and C. Murre, Multilineage priming of enhancer repertoires precedes commitment to the B and myeloid cell lineages in hematopoietic progenitors, *Immunity* **35**, 413 (2011).
- [28] E. W. Brunskill, J.-S. Park, E. Chung, F. Chen, B. Magella, and S. S. Potter, Single cell dissection of early kidney development: Multilineage priming, *Development* **141**, 3093 (2014).
- [29] Y. Ohnishi, W. Huber, A. Tsumura, M. Kang, P. Xenopoulos, K. Kurimoto, A. K. Oleś, M. J. Araújo-Bravo, M. Saitou, A.-K. Hadjantonakis *et al.*, Cell-to-cell expression variability followed by signal reinforcement progressively segregates early mouse lineages, *Nat. Cell Biol.* **16**, 27 (2014).
- [30] T.-H. Kim, F. Li, I. Ferreira-Neira, L.-L. Ho, A. Luyten, K. Nalapareddy, H. Long, M. Verzi, and R. A. Shivdasani, Broadly permissive intestinal chromatin underlies lateral inhibition and cell plasticity, *Nature (London)* **506**, 511 (2014).
- [31] A. Olsson, M. Venkatasubramanian, V. K. Chaudhri, B. J. Aronow, N. Salomonis, H. Singh, and H. L. Grimes, Single-cell analysis of mixed-lineage states leading to a binary cell fate choice, *Nature (London)* **537**, 698 (2016).
- [32] S. Zheng, E. Papalex, A. Butler, W. Stephenson, and R. Satija, Molecular transitions in early progenitors during human cord blood hematopoiesis, *Mol. Syst. Biol.* **14**, e8041 (2018).
- [33] E. W. Martin, J. Krietsch, R. E. Reggiardo, R. Sousae, D. H. Kim, and E. C. Forsberg, Chromatin accessibility maps provide evidence of multilineage gene priming in hematopoietic stem cells, *Epigenet. Chromatin* **14**, 2 (2021).
- [34] P. N. Singh, S. Madha, A. B. Leiter, and R. A. Shivdasani, Cell and chromatin transitions in intestinal stem cell regeneration, *Genes Dev.* **36**, 684 (2022).
- [35] A. Grover, E. Mancini, S. Moore, A. J. Mead, D. Atkinson, K. D. Rasmussen, D. O'Carroll, S. E. W. Jacobsen, and C. Nerlov, Erythropoietin guides multipotent hematopoietic progenitor cells toward an erythroid fate, *J. Exp. Med.* **211**, 181 (2014).
- [36] J. S. Herman, n. Sagar, and D. Gruen, Fateid infers cell fate bias in multipotent progenitors from single-cell RNA-seq data, *Nat. Methods* **15**, 379 (2018).

- [37] A. G. Erickson, P. Kameneva, and I. Adameyko, The transcriptional portraits of the neural crest at the individual cell level, *Semin Cell Dev Biol.* **138**, 68 (2023).
- [38] H. Marks, T. Kalkan, R. Menafrá, S. Denisssov, K. Jones, H. Hofemeister, J. Nichols, A. Kranz, A. F. Stewart, A. Smith *et al.*, The transcriptional and epigenomic foundations of ground state pluripotency, *Cell* **149**, 590 (2012).
- [39] D. C. Factor, O. Corradin, G. E. Zentner, A. Saiakhova, L. Song, J. G. Chenoweth, R. D. McKay, G. E. Crawford, P. C. Scacheri, and P. J. Tesar, Epigenomic comparison reveals activation of “seed” enhancers during transition from naive to primed pluripotency, *Cell Stem. Cell* **14**, 854 (2014).
- [40] E. Abranches, A. M. Guedes, M. Moravec, H. Maamar, P. Svoboda, A. Raj, and D. Henrique, Stochastic NANOG fluctuations allow mouse embryonic stem cells to explore pluripotency, *Development* **141**, 2770 (2014).
- [41] A. M. Klein, L. Mazutis, I. Akartuna, N. Tallapragada, A. Veres, V. Li, L. Peshkin, D. A. Weitz, and M. W. Kirschner, Droplet barcoding for single-cell transcriptomics applied to embryonic stem cells, *Cell* **161**, 1187 (2015).
- [42] A. A. Kolodziejczyk, J. K. Kim, J. C. Tsang, T. Ilicic, J. Henriksson, K. N. Natarajan, A. C. Tuck, X. Gao, M. Bühler, P. Liu *et al.*, Single cell RNA-sequencing of pluripotent states unlocks modular transcriptional variation, *Cell Stem. Cell* **17**, 471 (2015).
- [43] N. Novershtern, A. Subramanian, L. N. Lawton, R. H. Mak, W. N. Haining, M. E. McConkey, N. Habib, N. Yosef, C. Y. Chang, T. Shay *et al.*, Densely interconnected transcriptional circuits control cell states in human hematopoiesis, *Cell* **144**, 296 (2011).
- [44] F. K. Hamey, S. Nestorowa, S. J. Kinston, D. G. Kent, N. K. Wilson, and B. Göttgens, Reconstructing blood stem cell regulatory network models from single-cell molecular profiles, *Proc. Natl. Acad. Sci. USA* **114**, 5822 (2017).
- [45] K. E. Trevers, H.-C. Lu, Y. Yang, A. P. Thiery, A. C. Strobl, C. Anderson, B. Pálkovášová, N. M. de Oliveira, I. M. de Almeida, M. A. Khan *et al.*, A gene regulatory network for neural induction, *eLife* **12**, e73189 (2023).
- [46] D. Arendt, J. M. Musser, C. V. Baker, A. Bergman, C. Cepko, D. H. Erwin, M. Pavlicev, G. Schlosser, S. Widder, M. D. Laubichler *et al.*, The origin and evolution of cell types, *Nat. Rev. Genet.* **17**, 744 (2016).
- [47] M. B. Reilly, C. Cros, E. Varol, E. Yemini, and O. Hobert, Unique homeobox codes delineate all the neuron classes of *C. elegans*, *Nature (London)* **584**, 595 (2020).
- [48] O. Karin, Enhancernet: A predictive model of cell identity dynamics through enhancer selection, *Development* **151**, dev202997 (2024).
- [49] T. Narita, S. Ito, Y. Higashijima, W. K. Chu, K. Neumann, J. Walter, S. Satpathy, T. Liebner, W. B. Hamilton, E. Maskey *et al.*, Enhancers are activated by p300/CBP activity-dependent PIC assembly, RNAPII recruitment, and pause release, *Mol. Cell* **81**, 2166 (2021).
- [50] D. Krotov and J. Hopfield, Large associative memory problem in neurobiology and machine learning, *arXiv:2008.06996*.
- [51] H. Ramsauer, B. Schäfl, J. Lehner, P. Seidl, M. Widrich, T. Adler, L. Gruber, M. Holzleitner, M. Pavlović, G. K. Sandve *et al.*, Hopfield networks is [sic] all you need, *arXiv:2008.02217*.
- [52] B. T. Weinert, T. Narita, S. Satpathy, B. Srinivasan, B. K. Hansen, C. Schölz, W. B. Hamilton, B. E. Zucconi, W. W. Wang, W. R. Liu *et al.*, Time-resolved analysis reveals rapid dynamics and broad scope of the CBP/p300 acetylome, *Cell* **174**, 231 (2018).
- [53] J. J. Ferrie, J. P. Karr, T. G. Graham, G. M. Dailey, G. Zhang, R. Tjian, and X. Darzacq, P300 is an obligate integrator of combinatorial transcription factor inputs, *Mol. Cell* **84**, 234 (2024).
- [54] B. Chapuy, M. R. McKeown, C. Y. Lin, S. Monti, M. G. Roemer, J. Qi, P. B. Rahl, H. H. Sun, K. T. Yeda, J. G. Doench *et al.*, Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma, *Cancer Cell* **24**, 777 (2013).
- [55] J. Lovén, H. A. Hoke, C. Y. Lin, A. Lau, D. A. Orlando, C. R. Vakoc, J. E. Bradner, T. I. Lee, and R. A. Young, Selective inhibition of tumor oncogenes by disruption of super-enhancers, *Cell* **153**, 320 (2013).
- [56] L. Liu, Y. Xu, M. He, M. Zhang, F. Cui, L. Lu, M. Yao, W. Tian, C. Benda, Q. Zhuang *et al.*, Transcriptional pause release is a rate-limiting step for somatic cell reprogramming, *Cell Stem. Cell* **15**, 574 (2014).
- [57] T. Kanno, Y. Kanno, G. LeRoy, E. Campos, H.-W. Sun, S. R. Brooks, G. Vahedi, T. D. Heightman, B. A. Garcia, D. Reinberg *et al.*, BRD4 assists elongation of both coding and enhancer RNAs by interacting with acetylated histones, *Nat. Struct. Mol. Biol.* **21**, 1047 (2014).
- [58] G. E. Winter, A. Mayer, D. L. Buckley, M. A. Erb, J. E. Roderick, S. Vittori, J. M. Reyes, J. di Iulio, A. Souza, C. J. Ott *et al.*, Bet bromodomain proteins function as master transcription elongation factors independent of CDK9 recruitment, *Mol. Cell* **67**, 5 (2017).
- [59] E. Altendorfer, Y. Mochalova, and A. Mayer, Brd4: A general regulator of transcription elongation, *Transcription* **13**, 70 (2022).
- [60] J. J. Ferrie, J. P. Karr, R. Tjian, and X. Darzacq, “Structure”-function relationships in eukaryotic transcription factors: The role of intrinsically disordered regions in gene regulation, *Mol. Cell* **82**, 3970 (2022).
- [61] M. A. Gillespie, C. G. Pali, D. Sanchez-Taltavull, P. Shannon, W. J. Longabaugh, D. J. Downes, K. Sivaraman, H. M. Espinoza, J. R. Hughes, N. D. Price *et al.*, Absolute quantification of transcription factors reveals principles of gene regulation in erythropoiesis, *Mol. Cell* **78**, 960 (2020).
- [62] H. Polansky and H. Schwab, Dynamics of sequestering the limiting p300/CBP, viral cis-regulatory elements, and disease, *J. Biosci.* **45**, 79 (2020).
- [63] A. Dey, F. Chitsaz, A. Abbasi, T. Misteli, and K. Ozato, The double bromodomain protein BRD4 binds to acetylated chromatin during interphase and mitosis, *Proc. Natl. Acad. Sci. USA* **100**, 8758 (2003).
- [64] N. Hah, C. G. Danko, L. Core, J. J. Waterfall, A. Siepel, J. T. Lis, and W. L. Kraus, A rapid, extensive, and transient transcriptional response to estrogen signaling in breast cancer cells, *Cell* **145**, 622 (2011).
- [65] S. E. Step, H.-W. Lim, J. M. Marinis, A. Prokesch, D. J. Steger, S.-H. You, K.-J. Won, and M. A. Lazar, Anti-diabetic rosiglitazone remodels the adipocyte transcriptome by redistributing transcription to PPAR γ -driven enhancers, *Genes Dev.* **28**, 1018 (2014).

- [66] J. D. Brown, C. Y. Lin, Q. Duan, G. Griffin, A. J. Federation, R. M. Paranal, S. Bair, G. Newton, A. H. Lichtman, A. L. Kung *et al.*, NF- κ B directs dynamic super enhancer formation in inflammation and atherogenesis, *Mol. Cell* **56**, 219 (2014).
- [67] S. F. Schmidt, B. D. Larsen, A. Loft, R. Nielsen, J. G. S. Madsen, and S. Mandrup, Acute tnf-induced repression of cell identity genes is mediated by NF κ B-directed redistribution of cofactors from super-enhancers, *Genome Res.* **25**, 1281 (2015).
- [68] J.-E. Lee, Y.-K. Park, S. Park, Y. Jang, N. Waring, A. Dey, K. Ozato, B. Lai, W. Peng, and K. Ge, BRD4 binds to active enhancers to control cell identity gene induction in adipogenesis and myogenesis, *Nat. Commun.* **8**, 2217 (2017).
- [69] V. K. Mishra, F. Wegwitz, R. L. Kosinsky, M. Sen, R. Baumgartner, T. Wulff, J. T. Siveke, H.-U. Schildhaus, Z. Najafova, V. Kari *et al.*, Histone deacetylase class-I inhibition promotes epithelial gene expression in pancreatic cancer cells in a BRD4-and MYC-dependent manner, *Nucl. Acids Res.* **45**, 6334 (2017).
- [70] I. J. Marié, H.-M. Chang, and D. E. Levy, HDAC stimulates gene expression through BRD4 availability in response to ifn and in interferonopathies, *J. Exp. Med.* **215**, 3194 (2018).
- [71] J. D. Brown, Z. B. Feldman, S. P. Doherty, J. M. Reyes, P. B. Rahl, C. Y. Lin, Q. Sheng, Q. Duan, A. J. Federation, A. L. Kung *et al.*, BET bromodomain proteins regulate enhancer function during adipogenesis, *Proc. Natl. Acad. Sci. USA* **115**, 2144 (2018).
- [72] M. J. Slaughter, E. K. Shanle, A. Khan, K. F. Chua, T. Hong, L. D. Boxer, C. D. Allis, S. Z. Josefowicz, B. A. Garcia, S. B. Rothbart *et al.*, HDAC inhibition results in widespread alteration of the histone acetylation landscape and BRD4 targeting to gene bodies, *Cell Rep.* **34**, 108638 (2021).
- [73] See Supplemental Material at <http://link.aps.org/supplemental/10.1103/dkmq-h4d9> for further model and simulation details.
- [74] L. Ambrogioni, In search of dispersed memories: Generative diffusion models are associative memory networks, *arXiv:2309.17290*.
- [75] A. G. Erickson, S. Isaev, A. Artemov, J. He, B. Semsch, A. Murtazina, J. Sun, K. Mangold, A. Chalou, J. Frisen *et al.*, Unbiased profiling of multipotency landscapes reveals spatial modulators of clonal fate biases (2024), doi:10.1101/2024.11.15.623687.
- [76] E. Laurenti and B. Göttgens, From haematopoietic stem cells to complex differentiation landscapes, *Nature (London)* **553**, 418 (2018).
- [77] J. Choi, T. M. Baldwin, M. Wong, J. E. Bolden, K. A. Fairfax, E. C. Lucas, R. Cole, C. Biben, C. Morgan, K. A. Ramsay *et al.*, Haemopedia RNA-seq: A database of gene expression during haematopoiesis in mice and humans, *Nucl. Acids Res.* **47**, D780 (2019).
- [78] D. Defays, An efficient algorithm for a complete link method, *Comput. J.* **20**, 364 (1977).
- [79] G. Brown and I. Sanchez-Garcia, Is lineage decision-making restricted during tumoral reprogramming of haematopoietic stem cells?, *Oncotarget* **6**, 43326 (2015).
- [80] S. E. W. Jacobsen and C. Nerlov, Haematopoiesis in the era of advanced single-cell technologies, *Nat. Cell Biol.* **21**, 2 (2019).
- [81] A. M. Michie, J. R. Carlyle, T. M. Schmitt, B. Ljutic, S. K. Cho, Q. Fong, and J. C. Zuniga-Pflucker, Clonal characterization of a bipotent T cell and NK cell progenitor in the mouse fetal thymus, *J. Immunol.* **164**, 1730 (2000).
- [82] D. Izon, K. Rudd, W. DeMuth, W. S. Pear, C. Clendenin, R. C. Lindsley, and D. Allman, A common pathway for dendritic cell and early B cell development, *J. Immunol.* **167**, 1387 (2001).
- [83] D. K. Fogg, C. Sibon, C. Miled, S. Jung, P. Aucouturier, D. R. Littman, A. Cumano, and F. Geissmann, A clonogenic bone marrow progenitor specific for macrophages and dendritic cells, *Science* **311**, 83 (2006).
- [84] A. Yáñez, S. G. Coetzee, A. Olsson, D. E. Muench, B. P. Berman, D. J. Hazelett, N. Salomonis, H. L. Grimes, and H. S. Goodridge, Granulocyte-monocyte progenitors and monocyte-dendritic cell progenitors independently produce functionally distinct monocytes, *Immunity* **47**, 890 (2017).
- [85] D. Metcalf, S. Mifsud, and L. Di Rago, Stem cell factor can stimulate the formation of eosinophils by two types of murine eosinophil progenitor cells, *Stem Cells* **20**, 460 (2002).
- [86] K. Kim, S. M. Hwang, S. M. Kim, S. W. Park, Y. Jung, and I. Y. Chung, Terminally differentiating eosinophils express neutrophil primary granule proteins as well as eosinophil-specific granule proteins in a temporal manner, *Immune Netw.* **17**, 410 (2017).
- [87] I. Kwok, E. Becht, Y. Xia, M. Ng, Y. C. Teh, L. Tan, M. Evrard, J. L. Li, H. T. Tran, Y. Tan *et al.*, Combinatorial single-cell analyses of granulocyte-monocyte progenitor heterogeneity reveals an early uni-potent neutrophil progenitor, *Immunity* **53**, 303 (2020).
- [88] J. A. Denburg, S. Telizyn, H. Messner, B. Lim, N. Jamal, S. Ackerman, G. Gleich, and J. Bienenstock, Heterogeneity of human peripheral blood eosinophil-type colonies: Evidence for a common basophil-eosinophil progenitor, *Blood* **66**, 312 (1985).
- [89] Y. Arinobu, H. Iwasaki, M. F. Gurish, S. Mizuno, H. Shigematsu, H. Ozawa, D. G. Tenen, F. K. Austen, and K. Akashi, Identification of Bipotent Basophil/Mast Cell Progenitors in Adult Murine Hematopoiesis, *Blood* **106**, 633 (2005).
- [90] N. Debili, L. Coulombel, L. Croisille, A. Katz, J. Guichard, J. Breton-Gorius, and W. Vainchenker, Characterization of a bipotent erythro-megakaryocytic progenitor in human bone marrow, *Blood* **88**, 1284 (1996).
- [91] A. M. Vannucchi, F. Paoletti, S. Linari, C. Cellai, R. Caporale, P. R. Ferrini, M. Sanchez, G. Migliaccio, and A. R. Migliaccio, Identification and characterization of a bipotent (erythroid and megakaryocytic) cell precursor from the spleen of phenylhydrazine-treated mice, *Blood* **95**, 2559 (2000).
- [92] E. C. Forsberg, T. Serwold, S. Kogan, I. L. Weissman, and E. Passegué, New evidence supporting megakaryocyte-erythrocyte potential of Flk2/Flt3+ multipotent hematopoietic progenitors, *Cell* **126**, 415 (2006).
- [93] R. Drissen, N. Buza-Vidas, P. Woll, S. Thongjuea, A. Gambardella, A. Giustacchini, E. Mancini, A. Zriwil, M. Lutteropp, A. Grover *et al.*, Distinct myeloid progenitor-differentiation pathways identified through single-cell RNA sequencing, *Nat. Immunol.* **17**, 666 (2016).
- [94] B. K. Tusi, S. L. Wolock, C. Weinreb, Y. Hwang, D. Hidalgo, R. Zilionis, A. Waisman, J. R. Huh, A. M. Klein, and M. Socolovsky, Population snapshots predict early haematopoietic and erythroid hierarchies, *Nature (London)* **555**, 54 (2018).

- [95] K. Akashi, D. Traver, T. Miyamoto, and I. L. Weissman, A clonogenic common myeloid progenitor that gives rise to all myeloid lineages, *Nature (London)* **404**, 193 (2000).
- [96] A. Galy, M. Travis, D. Cen, and B. Chen, Human T, B, natural killer, and dendritic cells arise from a common bone marrow progenitor cell subset, *Immunity* **3**, 459 (1995).
- [97] A. Giladi, F. Paul, Y. Herzog, Y. Lubling, A. Weiner, I. Yofe, D. Jaitin, N. Cabezas-Wallscheid, R. Dress, F. Ginhoux *et al.*, Single-cell characterization of haematopoietic progenitors and their trajectories in homeostasis and perturbed haematopoiesis, *Nat. Cell Biol.* **20**, 836 (2018).
- [98] P. Sathe, D. Vremec, L. Wu, L. Corcoran, and K. Shortman, Convergent differentiation: Myeloid and lymphoid pathways to murine plasmacytoid dendritic cells, *Blood* **121**, 11 (2013).
- [99] M. Kanayama, Y. Izumi, N. Onai, T. Akashi, Y. Hiraoka, and T. Ohteki, Diverse developmental pathways of lymphoid conventional dendritic cells with distinct tissue distribution and function, *Sci. Adv.* **11**, eadt4909 (2025).
- [100] S. Pan, H. Tang, B. Yao, G. Tian, B. Sun, Y. Hu, Y. Chen, J. Li, X. Xu, C. Zhang *et al.*, Decoding the ontogeny of myeloid lineage diversity by cross-species and developmental analyses of hematopoietic progenitor atlases, *Cell Rep.* **44**, 115406 (2025).
- [101] N. B. Becker, M. Günther, C. Li, A. Jolly, and T. Höfer, Stem cell homeostasis by integral feedback through the niche, *J. Theor. Biol.* **481**, 100 (2019).
- [102] A. Stanoev and A. Koseska, Robust cell identity specifications through transitions in the collective state of growing developmental systems, *Curr. Opin. Syst. Biol.* **31**, 100437 (2022).
- [103] B. D. Simons and O. Karin, Tuning of plasma cell lifespan by competition explains the longevity and heterogeneity of antibody persistence, *Immunity* **57**, 600 (2024).
- [104] A. S. Eisele, J. Cosgrove, A. Magniez, E. Tubeuf, S. T. Bento, C. Conrad, F. Cayrac, T. Tak, A.-M. Lyne, J. Urbanus *et al.*, Erythropoietin directly remodels the clonal composition of murine hematopoietic multipotent progenitor cells, *eLife* **11**, e66922 (2022).
- [105] M. X. Moreau, Y. Saillour, A. W. Cwetsch, A. Pierani, and F. Causeret, Single-cell transcriptomics of the early developing mouse cerebral cortex disentangle the spatial and temporal components of neuronal fate acquisition, *Development* **148**, dev197962 (2021).
- [106] A. Nusser, Sagar, J. B. Swann, B. Krauth, D. Diekhoff, L. Calderon, C. Happe, D. Gruen, and T. Boehm, Developmental dynamics of two bipotent thymic epithelial progenitor types, *Nature (London)* **606**, 165 (2022).
- [107] D. Hanahan, Hallmarks of cancer: New dimensions, *Cancer Disc.* **12**, 31 (2022).
- [108] J. A. B. Bispo, P. S. Pinheiro, and E. K. Kobetz, Epidemiology and etiology of leukemia and lymphoma, *Cold Spring Harbor Perspect. Med.* **10**, a034819 (2020).
- [109] R. Eckner, T.-P. Yao, E. Oldread, and D. M. Livingston, Interaction and functional collaboration of p300/CBP and bHLH proteins in muscle and B-cell differentiation, *Genes Dev.* **10**, 2478 (1996).
- [110] Y. Shi and C. Mello, A CBP/p300 homolog specifies multiple differentiation pathways in *Caenorhabditis elegans*, *Genes Dev.* **12**, 943 (1998).
- [111] P. A. Marks, V. M. Richon, and R. A. Rifkind, Histone deacetylase inhibitors: Inducers of differentiation or apoptosis of transformed cells, *J. Natl. Cancer Inst.* **92**, 1210 (2000).
- [112] M. Göttlicher, S. Minucci, P. Zhu, O. H. Krämer, A. Schimpf, S. Giavara, J. P. Sleeman, F. L. Coco, C. Nervi, P. G. Pelicci *et al.*, Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells, *EMBO J.* **20**, 6969 (2001).
- [113] A. Poleskaya, I. Naguibneva, L. Fritsch, A. Duquet, S. Ait-Si-Ali, P. Robin, A. Vervisch, L. Pritchard, P. Cole, and A. Harel-Bellan, CBP/p300 and muscle differentiation: No hat, no muscle, *EMBO J.* **20**, 6816 (2001).
- [114] N. Kang-Decker, C. Tong, F. Boussouar, D. J. Baker, W. Xu, A. A. Leontovich, W. R. Taylor, P. K. Brindle, and J. M. Van Deursen, Loss of CBP causes T cell lymphomagenesis in synergy with p27^{Kip1} insufficiency, *Cancer Cell* **5**, 177 (2004).
- [115] N. G. Iyer, H. Özdag, and C. Caldas, P300/CBP and cancer, *Oncogene* **23**, 4225 (2004).
- [116] L. Tou, Q. Liu, and R. A. Shivdasani, Regulation of mammalian epithelial differentiation and intestine development by class I histone deacetylases, *Mol. Cell. Biol.* **24**, 3132 (2004).
- [117] L. Pasqualucci, D. Dominguez-Sola, A. Chiarenza, G. Fabbri, A. Grunn, V. Trifonov, L. H. Kasper, S. Lerach, H. Tang, J. Ma *et al.*, Inactivating mutations of acetyltransferase genes in B-cell lymphoma, *Nature (London)* **471**, 189 (2011).
- [118] A. J. van Voorden, R. Keijser, G. J. Veenboer, S. A. Lopes Cardozo, D. Diek, J. A. Vlaardingerbroek, M. van Dijk, C. Ris-Stalpers, A. M. van Pelt, and G. B. Afink, EP300 facilitates human trophoblast stem cell differentiation, *Proc. Natl. Acad. Sci. USA* **120**, e2217405120 (2023).
- [119] P. Likasitwatanakul, Z. Li, P. Doan, S. Spisak, A. K. Raghawan, Q. Liu, P. Liow, S. Lee, D. Chen, P. Bala, P. Sahgal *et al.*, Chemical perturbations impacting histone acetylation govern colorectal cancer differentiation, *Gastroenterology* (2025).
- [120] J. Hsieh, K. Nakashima, T. Kuwabara, E. Mejia, and F. H. Gage, Histone deacetylase inhibition-mediated neuronal differentiation of multipotent adult neural progenitor cells, *Proc. Natl. Acad. Sci. USA* **101**, 16659 (2004).
- [121] E. San José-Enériz, N. Gimenez-Camino, X. Agirre, and F. Prosper, HDAC inhibitors in acute myeloid leukemia, *Cancers* **11**, 1794 (2019).
- [122] S. Ego, Y. Aubert, M. Doepner, A. Anderson, A. Maldonado-Lopez, G. Pacella, J. Lee, E. K. Ko, J. Zou, Y. Lan *et al.*, Lsd1 inhibition promotes epithelial differentiation through derepression of fate-determining transcription factors, *Cell Rep.* **28**, 1981 (2019).
- [123] J. N. Anastas, B. M. Zee, J. H. Kalin, M. Kim, R. Guo, S. Alexandrescu, M. A. Blanco, S. Giera, S. M. Gillespie, J. Das *et al.*, Re-programing chromatin with a bifunctional LSD1/HDAC inhibitor induces therapeutic differentiation in dipg, *Cancer Cell* **36**, 528 (2019).
- [124] J. Xie, Z. Wang, W. Fan, Y. Liu, F. Liu, X. Wan, M. Liu, X. Wang, D. Zeng, Y. Wang *et al.*, Targeting cancer cell plasticity by HDAC inhibition to reverse EBV-induced dedifferentiation in nasopharyngeal carcinoma, *Signal Transduct. Target Ther.* **6**, 333 (2021).
- [125] J. I. Sive and B. Göttgens, Transcriptional network control of normal and leukaemic haematopoiesis, *Exp. Cell Res.* **329**, 255 (2014).

- [126] F. Rosenbauer, K. Wagner, J. L. Kutok, H. Iwasaki, M. M. Le Beau, Y. Okuno, K. Akashi, S. Fiering, and D. G. Tenen, Acute myeloid leukemia induced by graded reduction of a lineage-specific transcription factor, PU.1, *Nat. Genet.* **36**, 624 (2004).
- [127] C. N. Hahn, C.-E. Chong, C. L. Carmichael, E. J. Wilkins, P. J. Brautigan, X.-C. Li, M. Babic, M. Lin, A. Carmagnac, Y. K. Lee *et al.*, Heritable *GATA2* mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia, *Nat. Genet.* **43**, 1012 (2011).
- [128] B. Will, T. O. Vogler, S. Narayanagari, B. Bartholdy, T. I. Todorova, M. da Silva Ferreira, J. Chen, Y. Yu, J. Mayer, L. Barreyro *et al.*, Minimal PU.1 reduction induces a preleukemic state and promotes development of acute myeloid leukemia, *Nat. Med.* **21**, 1172 (2015).
- [129] I. Mikkola, B. Heavey, M. Horcher, and M. Busslinger, Reversion of B cell commitment upon loss of PAX5 expression, *Science* **297**, 110 (2002).
- [130] C. Cobaleda, W. Jochum, and M. Busslinger, Conversion of mature B cells into T cells by dedifferentiation to uncommitted progenitors, *Nature (London)* **449**, 473 (2007).
- [131] M. P. McCormack, L. F. Young, S. Vasudevan, C. A. de Graaf, R. Codrington, T. H. Rabbitts, S. M. Jane, and D. J. Curtis, The *Lmo2* oncogene initiates leukemia in mice by inducing thymocyte self-renewal, *Science* **327**, 879 (2010).
- [132] S. M. Cleveland, S. Smith, R. Tripathi, E. M. Mathias, C. Goodings, N. Elliott, D. Peng, W. El-Rifai, D. Yi, X. Chen *et al.*, *Lmo2* induces hematopoietic stem cell-like features in T-cell progenitor cells prior to leukemia, *Stem Cells* **31**, 882 (2013).
- [133] T. Sanda and W. Z. Leong, TAL1 as a master oncogenic transcription factor in T-cell acute lymphoblastic leukemia, *Exp. Hematol.* **53**, 7 (2017).
- [134] C. L. Carmichael, D. Metcalf, K. J. Henley, E. A. Kruse, L. Di Rago, S. Mifsud, W. S. Alexander, and B. T. Kile, Hematopoietic overexpression of the transcription factor ERG induces lymphoid and erythro-megakaryocytic leukemia, *Proc. Natl. Acad. Sci. USA* **109**, 15437 (2012).
- [135] E. Diffner, D. Beck, E. Gudgin, J. A. Thoms, K. Knezevic, C. Pridans, S. Foster, D. Goode, W. K. Lim, L. Boelen *et al.*, Activity of a heptad of transcription factors is associated with stem cell programs and clinical outcome in acute myeloid leukemia, *Blood* **121**, 2289 (2013).
- [136] J. A. Thoms, Y. Birger, S. Foster, K. Knezevic, Y. Kirschenbaum, V. Chandrakanthan, G. Jonquieres, D. Spensberger, J. W. Wong, S. H. Oram *et al.*, Erg promotes T-acute lymphoblastic leukemia and is transcriptionally regulated in leukemic cells by a stem cell enhancer, *Blood* **117**, 7079 (2011).
- [137] P. van Galen, V. Hovestadt, M. H. Wadsworth II, T. K. Hughes, G. K. Griffin, S. Battaglia, J. A. Verga, J. Stephansky, T. J. Pastika, J. L. Story *et al.*, Single-cell RNA-seq reveals aml hierarchies relevant to disease progression and immunity, *Cell* **176**, 1265 (2019).
- [138] P. Anand, A. Guillaumet-Adkins, V. Dimitrova, H. Yun, Y. Drier, N. Sotudeh, A. Rogers, M. M. Ouseph, M. Nair, S. Potdar *et al.*, Single-cell RNA-seq reveals developmental plasticity with coexisting oncogenic states and immune evasion programs in ETP-ALL, *Blood* **137**, 2463 (2021).
- [139] C. A. Peretz, V. E. Kennedy, A. Walia, C. L. Delley, A. Koh, E. Tran, I. C. Clark, C. E. Hayford, C. D'Amato, Y. Xue *et al.*, Multiomic single cell sequencing identifies stemlike nature of mixed phenotype acute leukemia, *Nat. Commun.* **15**, 8191 (2024).
- [140] M. Bots, I. Verbrugge, B. P. Martin, J. M. Salmon, M. Ghisi, A. Baker, K. Stanley, J. Shortt, G. J. Ossenkoppele, J. Zuber *et al.*, Differentiation therapy for the treatment of t(8;21) acute myeloid leukemia using histone deacetylase inhibitors, *Blood* **123**, 1341 (2014).
- [141] P. Wang, Z. Wang, and J. Liu, Role of HDACs in normal and malignant hematopoiesis, *Mol. Cancer* **19**, 1 (2020).
- [142] K. Hayashi, S. M. C. de Sousa Lopes, F. Tang, and M. A. Surani, Dynamic equilibrium and heterogeneity of mouse pluripotent stem cells with distinct functional and epigenetic states, *Cell Stem Cell* **3**, 391 (2008).
- [143] C. B. Ware, L. Wang, B. H. Mecham, L. Shen, A. M. Nelson, M. Bar, D. A. Lamba, D. S. Dauphin, B. Buckingham, B. Askari *et al.*, Histone deacetylase inhibition elicits an evolutionarily conserved self-renewal program in embryonic stem cells, *Cell Stem Cell* **4**, 359 (2009).
- [144] B. G. Debeb, L. Lacerda, W. Xu, R. Larson, T. Solley, R. Atkinson, E. P. Sulman, N. T. Ueno, S. Krishnamurthy, J. M. Reuben *et al.*, Histone deacetylase inhibitors stimulate dedifferentiation of human breast cancer cells through WNT/ β -catenin signaling, *Stem Cells* **30**, 2366 (2012).
- [145] C. K. Hahn, K. N. Ross, I. M. Warrington, R. Mazitschek, C. M. Kanegai, R. D. Wright, A. L. Kung, T. R. Golub, and K. Stegmaier, Expression-based screening identifies the combination of histone deacetylase inhibitors and retinoids for neuroblastoma differentiation, *Proc. Natl. Acad. Sci. USA* **105**, 9751 (2008).
- [146] M. Leiva, S. Moretti, H. Soilihi, I. Pallavicini, L. Peres, C. Mercurio, R. Dal Zuffo, S. Minucci, and H. de Thé, Valproic acid induces differentiation and transient tumor regression, but spares leukemia-initiating activity in mouse models of APL, *Leukemia* **26**, 1630 (2012).
- [147] N. E. Boukacem, A. Leary, R. Thériault, F. Gottlieb, M. Mani, and P. François, Waddington landscape for prototype learning in generalized Hopfield networks, *Phys. Rev. Res.* **6**, 033098 (2024).
- [148] M. Yampolskaya and P. Mehta, Hopfield networks as models of emergent function in biology, *arXiv:2506.13076*.
- [149] B. Pham, G. Raya, M. Negri, M. J. Zaki, L. Ambrogioni, and D. Krotov, Memorization to generalization: Emergence of diffusion models from associative memory, *arXiv:2505.21777*.
- [150] C. Lucibello and M. Mézard, Exponential capacity of dense associative memories, *Phys. Rev. Lett.* **132**, 077301 (2024).
- [151] M. J. Guertin, X. Zhang, S. A. Coonrod, and G. L. Hager, Transient estrogen receptor binding and p300 redistribution support a squelching mechanism for estradiol-repressed genes, *Mol. Endocrinol.* **28**, 1522 (2014).
- [152] A. S. Portuguese, I. Grbesa, M. Tal, R. Deitch, D. Raz, L. Kliker, R. Weismann, M. Schwartz, O. Loza, L. Cohen *et al.*, Ep300 sequestration to functionally distinct glucocorticoid receptor binding loci underlie rapid gene activation and repression, *Nucl. Acids Res.* **50**, 6702 (2022).
- [153] N. P. Blackledge and R. J. Klose, The molecular principles of gene regulation by polycomb repressive complexes, *Nat. Rev. Mol. Cell Biol.* **22**, 815 (2021).

- [154] A. Balsalobre and J. Drouin, Pioneer factors as master regulators of the epigenome and cell fate, *Nat. Rev. Mol. Cell Biol.* **23**, 449 (2022).
- [155] T. Chen and S. Y. Dent, Chromatin modifiers and remodellers: Regulators of cellular differentiation, *Nat. Rev. Genet.* **15**, 93 (2014).
- [156] G. N. Aughey, A. Estacio Gomez, J. Thomson, H. Yin, and T. D. Southall, CATaDa reveals global remodelling of chromatin accessibility during stem cell differentiation in vivo, *eLife* **7**, e32341 (2018).
- [157] G. S. Gulati, S. S. Sikandar, D. J. Wesche, A. Manjunath, A. Bharadwaj, M. J. Berger, F. Ilagan, A. H. Kuo, R. W. Hsieh, S. Cai *et al.*, Single-cell transcriptional diversity is a hallmark of developmental potential, *Science* **367**, 405 (2020).
- [158] L. Zhang, C. Sheng, F. Zhou, K. Zhu, S. Wang, Q. Liu, M. Yuan, Z. Xu, Y. Liu, J. Lu *et al.*, CBP/p300 HAT maintains the gene network critical for β cell identity and functional maturity, *Cell Death Dis.* **12**, 476 (2021).
- [159] Z. Zhong, N. Harmston, K. C. Wood, B. Madan, and D. M. Virshup, A p300/GATA6 axis determines differentiation and Wnt dependency in pancreatic cancer models, *J. Clin. Invest.* **132**, e156305 (2022).
- [160] S. D. Whedon and P. A. Cole, Kats off: Biomedical insights from lysine acetyltransferase inhibitors, *Curr. Opin. Chem. Biol.* **72**, 102255 (2023).
- [161] K. M. Ryan and G. D. Birnie, Cell-cycle progression is not essential for c-Myc to block differentiation, *Oncogene* **14**, 2835 (1997).
- [162] J. Leon, N. Ferrandiz, J. C. Acosta, and M. D. Delgado, Inhibition of cell differentiation: A critical mechanism for Mmyc-mediated carcinogenesis?, *Cell Cycle* **8**, 1148 (2009).
- [163] C. Bahr, L. Von Paleske, V. V. Uslu, S. Remeseiro, N. Takayama, S. W. Ng, A. Murison, K. Langenfeld, M. Petretich, R. Scognamiglio *et al.*, A Myc enhancer cluster regulates normal and leukaemic haematopoietic stem cell hierarchies, *Nature (London)* **553**, 515 (2018).
- [164] A. Sabò and B. Amati, Genome recognition by Myc, *Cold Spring Harbor Perspec. Med.* **4**, a014191 (2014).
- [165] F. Faiola, X. Liu, S. Lo, S. Pan, K. Zhang, E. Lymar, A. Farina, and E. Martinez, Dual regulation of c-Myc by p300 via acetylation-dependent control of myc protein turnover and coactivation of Myc-induced transcription, *Mol. Cell. Biol.* **25**, 10220 (2005).
- [166] M. Bernabé-Rubio, S. Ali, P. G. Bhosale, G. Goss, S. A. Mobasser, R. Tapia-Rojas, T. Zhu, T. Hiratsuka, M. Battilocchi, I. M. Tomás *et al.*, Myc-dependent dedifferentiation of GATA6+ epidermal cells resembles reversal of terminal differentiation, *Nat. Cell Biol.* **25**, 1426 (2023).
- [167] M. Nakagawa, N. Takizawa, M. Narita, T. Ichisaka, and S. Yamanaka, Promotion of direct reprogramming by transformation-deficient Myc, *Proc. Natl. Acad. Sci. USA* **107**, 14152 (2010).
- [168] M. Francesconi, B. Di Stefano, C. Berenguer, L. de Andrés-Aguayo, M. Plana-Carmona, M. Mendez-Lago, A. Guillaumet-Adkins, G. Rodriguez-Esteban, M. Gut, I. G. Gut *et al.*, Single cell RNA-seq identifies the origins of heterogeneity in efficient cell transdifferentiation and reprogramming, *eLife* **8**, e41627 (2019).
- [169] H. Bolouri and E. H. Davidson, Modeling transcriptional regulatory networks, *BioEssays* **24**, 1118 (2002).
- [170] P. Betancur, M. Bronner-Fraser, and T. Sauka-Spengler, Assembling neural crest regulatory circuits into a gene regulatory network, *Annu. Rev. Cell Dev. Biol.* **26**, 581 (2010).
- [171] I. S. Peter and E. H. Davidson, Evolution of gene regulatory networks controlling body plan development, *Cell* **144**, 970 (2011).
- [172] R. A. Nimmo, G. E. May, and T. Enver, Primed and ready: Understanding lineage commitment through single cell analysis, *Trends Cell Biol.* **25**, 459 (2015).