# Transform the Information Landscape

## Applying Waddington Landscape to Information Theory of Aging and Epigenetic Rejeuvanation

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***Abstract.*** The Information Theory of Aging (ITOA) provides a framework for understanding aging and rejuvenation through changes in epigenetic information. This paper demonstrates that the Waddington landscape — a 3D topology representing cells' trajectories during changes in cell identity — serves as a mechanistic model of epigenetic information. It explains how aging-driven cellular functional decline and reprogramming-induced rejuvenation can be understood through transformations of the Waddington landscape. The paper offers insights into the representation of epigenetic information and how it may be manipulated to restore younger cellular states.

## 1. Introduction

Almost all metazoans experience aging, the process of progressive functional and homeostatic decline that leads to death. Researches document that transient expression of the reprogramming factors Sox2, Oct4, Klf4 (SOK) can reset the cellular epigenetic landscape, reverse epigenetic aging, and rejuvenate metabolic performance, known as partial reprogramming-induced epigenetic rejuvenation [1, 2, 3, 4]. This yield epigenetics rejuvenation a promising research direction for potential reversal of aging. The Information Theory of Aging (ITOA) suggests that aging is caused by the loss of epigenetic information over time, though the memory of the original information remains [5, 6]. SOK can tap into this memory and restore youthful epigenetic states via epigenetic modifiers, leading to rejuvenation [5]. This paper discusses ITOA with Waddington landscape to explain the aging process and epigenetic rejuvenation.

## 2. Aging and Epigenetic Information

### 2.1. Life as information

Information can be understood as the extent to which a given informational relation alters or enhances existing knowledge [7]. The developmental and aging processes of an organism reflect a four-dimensional pattern of information that guides the dynamic evolution of phenotypes through three-dimensional space and time.

The central dogma of biology states that DNA is transcribed into RNA, which is then translated into proteins that perform functions shaping phenotypes. However, an organism's DNA sequence remains almost unchanged throughout its lifespan. Epigenetics studies the molecules and mechanisms that can sustain different gene activity states without altering the DNA sequence [8]. Examples of epigenetic regulation include DNA

methylation, histone modification, chromatin remodeling, non-coding RNA (ncRNA) regulation, and RNA modification [9]. Therefore, it is epigenetic regulation that controls the dynamics of DNA expression, determining the spatiotemporal order of the information of life.

Given the important role of epigenetics in the temporal development of phenotypes, it is not surprising that reprogramming-induced epigenetic rejuvenation is the only in vivo method capable of resetting both the transcriptome and DNA methylome to facilitate long-term functional recovery [5]. Currently, it is the only method capable of achieving this reset.

Before moving on to discuss the representation of such information, I would like to address the recurring question of where the information is resided in the following section.

### 2.2. Location of epigenetic information

As reviewed by Cohen et al., biological aging exhibits the following features: (1) networks of interacting elements, including key metabolism pathways such as mTOR, Sirtuins, and AMPK [10]; (2) feedback/feedforward loops, exemplified by senescence-associated secretory phenotypes from paracrine signaling [11, 12]; (3) multi-scale or modular hierarchical structure, such as the propagation of dysfunctional aged cells across tissues [13, 14]; (4) nonlinear dynamics, such as the accelerating decline in multiple systems at the end of life [15]. These hallmarks illustrate biological aging as a complex system [16].

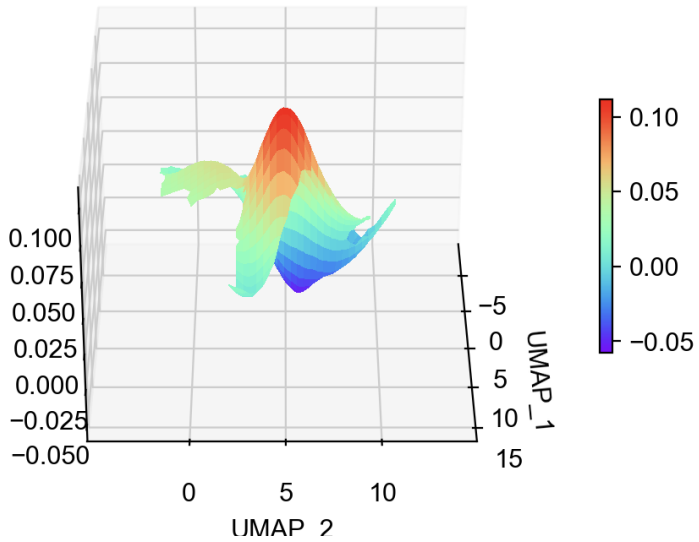
The act of digging down into the location of information is prone to losing sight of the whole complex system: starting at the organism level to determine where information resides in the tissue, then narrowing to the tissue level to locate information within cells, further examining in on the cellular level to explore molecular information, and ultimately studying atomic interactions. A characteristic of a complex system is that its emergent properties cannot be directly or additively inferred from its component parts [16]. Even if a clear source of the information of aging is found, the aged biological mechanics of the organism would be a deteriorating receiver to receive and process such information, which would not only undermines the causal link between the information source and the aging phenotypes, but the entropy of the information source itself can also be increased.

Thus, given the regulating role of epigenetic information in the aging process illustrated in the previous section, a more direct and practical question to ask in aging theory is, how can we represent and manipulate the epigenetic information?

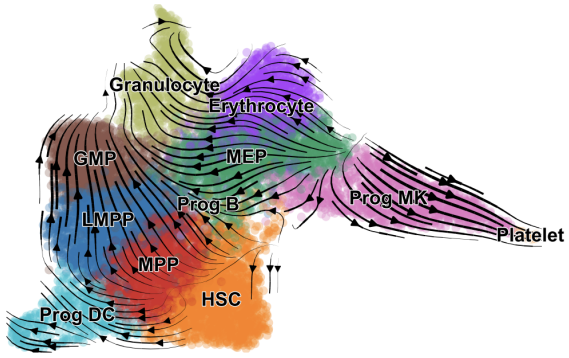
## 3. Represent Epigenetic Information with Waddington Landscape

The Waddington landscape is a model that describes how cells travel their trajectories with the change in cellular identities. One classical example is the stem cell differentiation. In this 3D model, a stem cell starts at a high point and rolls down, gradually losing its potential and following specific pathways to differentiate into particular cell types [17]. More than just a metaphor as originally proposed in 1957, the Waddington landscape has been shown to have solid mathematical meaning through quasi-stability and vector field analysis of biological differentiation processes [18, 19].

Methods have been adopted to construct Waddington landscape, such as transcriptome signaling entropy or Hopfield neural networks, to reflect the differential pattern of the cells [20, 21]. Here I used field decomposition of the Uniform Manifold Approximation and Projection for Dimension Reduction (UMAP) embedding of RNA velocity vectors, incorporating epigenetic regulation of chromatin opening or closing status, to construct the Waddington landscape of 11,605 human hematopoietic progenitor stem cells (HPSCs) (**Fig.1**) [22, 23]. Essentially, the greater the magnitude of the velocity vector in the dimensional decomposition vector fields, the steeper the landscape gradients on the z-axis. The UMAP embedding of the RNA velocity vector field matches the known differentiation pathways of HPSCs [23].




**(a)** Waddington Landscape

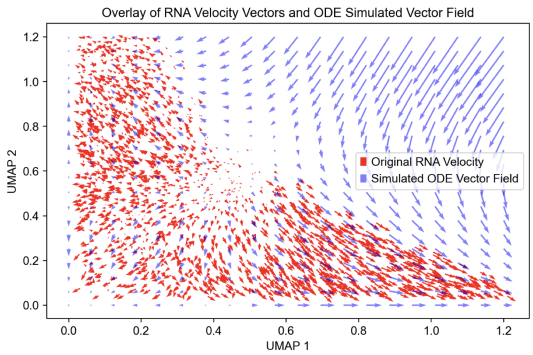



**(b)** UMAP Projection

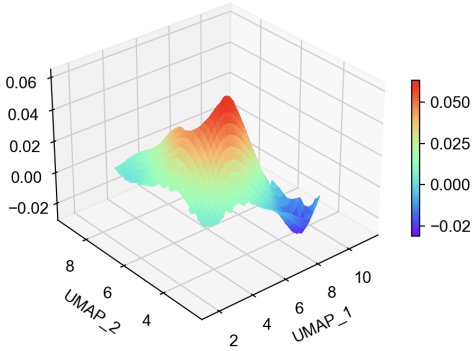
**Figure 1**: Computations of HSPC Differentiation from RNA Velocity Data

The top part of the landscape describes HPSC differentiation into erythroid and myeloid lineages, regulated by transcription factors Pou1 and GATA5, as described in a mathematical model [24]. The corresponding portion of the UMAP velocity vector field fits this mathematical model with parameters in a meaningful range, and the landscape reflects differentiation trajectories of bidirectional attractors from an unstable equilibrium point (**Fig.2**) [24]. This illustrates the cellular differentiation process separating into two

attractor sites corresponding to distinct phenotypes (erythroid and myeloid lineages). This demonstrates that the Waddington landscape can serve as a mechanistic model for the differentiation stages of an organism's development.




**(a)** ODE Fitting with the RNA Velocity data




**(b)** Waddington Sub-Landscape

**Figure 2**: Computations of Myeloid and Ethyroid Lineage Differentiation

The Waddington landscape can be extended to include the aging stage of exdifferentiation, which refers to the process that aged cells lose its somatic identity and cannot perform the correct function [25, 26, 5]. Reflecting on the landscape is the erosion of the attractor topology that has originally held the cells in the correct somatic landscape, and the cells traveled down to a region with ambiguous identity (**Fig.3**). The proposed mechanism is that events of DNA double-strain break, viral infection, physical and other damages induce the relocalization of chromatin modifying proteins (RCM) to try to fix the issues [6, 27, 28, 4, 29]. After the RCM, the chromatin modifying protein' positions remain without returning to the original states, therefore introducing noises to the original epigenetic information, leading to the blurring of landscape [27, 5]. This aligns with the evolutionary aging theory of antagonistic pleiotropy, which suggests that when epigenetic noise occurs, it benefits cells in the short term by recruiting chromatin factors to repair DNA damage and keep the cells alive. However, in the long term, these actions are detrimental and drive aging due to the loss of epigenetic information [30, 5, 6]. Thus, the Waddington landscape can represent epigenetic information, given its alignment with the mechanisms and phenotypes of biological aging.

## 4. Transformation of Epigenetic Information Landscape

### 4.1. The reprogramming process assesses the memory of the epigenetic landscape and transforms it

Without correcting mutations in DNA sequence, the biological age reset in zygote formation and the normal lifespans of cloned mammals from somatic nuclear transfer suggest that aged cells possess the memory of youthful epigenetic information [31]. As mentioned above, such memory is encompassed in the complex system of biological aging.

Recent studies suggest that partial reprogramming induced by Sox2, Oct4 and Klf4 (SOK) rewrite the epigenetic landscape in vivo and improve cellular metabolic per-

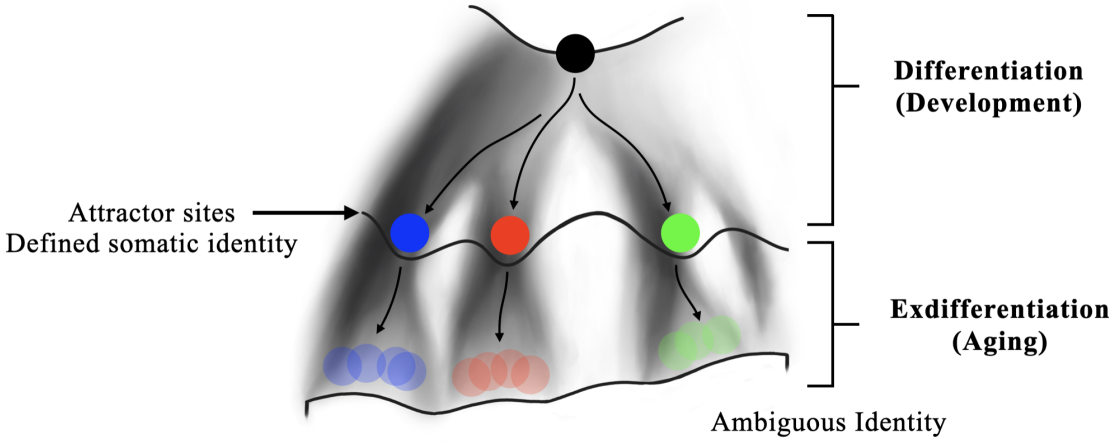
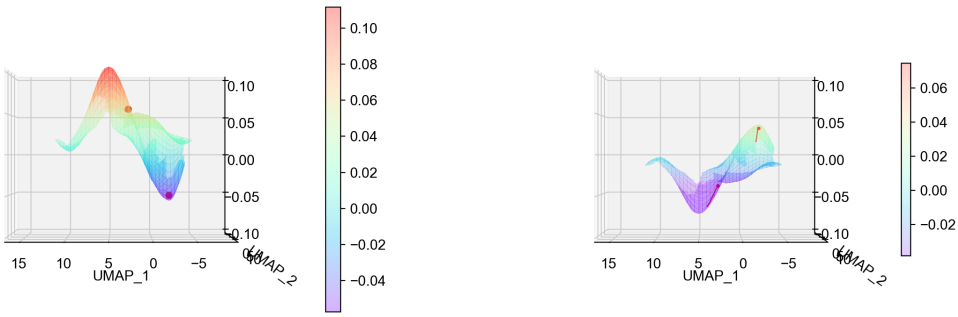



**Figure 3**: Complete Waddington Landscape of Development and Aging

formance [1, 2, 3, 4, 32]. In other words, SOK acquires access to the memory of epigenetic information and transforms the landscape to rejuvenate the cells.

L. Camillo and R. Quinlan proposed that during partial reprogramming, the Waddington landscape is flipped and flattened [33]. In the untransformed landscape, stem cells are the maxima. However, during reprogramming, the cells move toward the stem cell states following the reverse landscape gradient; flipping the maxima into minima and vice versa (**Fig.4**). Taking a mathematical perspective on the landscape which I have computed, the RNA velocity vector reversed its direction from moving away from the progenitors to toward the progenitors. The landscape derived from the vector field decomposition will thus also be inverted [22]. Additionally, the observation that reprogramming generates both cancer cells with much higher eAge than the organism and iPSC with much lower eAge implies the landscape is flattened [34]. When SOK is applied to cells, it calls out the memory of epigenetic information, and transforms the epigenetic landscape by reversing and flipping it.




**(a)** Normal Development

**(b)** During Reprogramming

**Figure 4**: The reverse and flattening of HSPC differentiation Waddington landscape. The red dotes represent the epigenetic status of two cells. (b) shows the trajectories of cells traversing through the landscape.

Thus, the aged exdifferentiated cells would travel down to the younger attractor site with defined somatic identity. The cells that are already in the attractor site, if given enough time and conditions, would travel out of the attractor influence toward its progenitor state and transiently enter a zone of epigenetic instability and ambiguous identity, as observed [32]. As the reprogramming ended, the Waddington landscape is restored. The previously-old cells would still stay at their position due to attractor influence, and the young cells would slide back to the attractor stage (**Fig.5**).

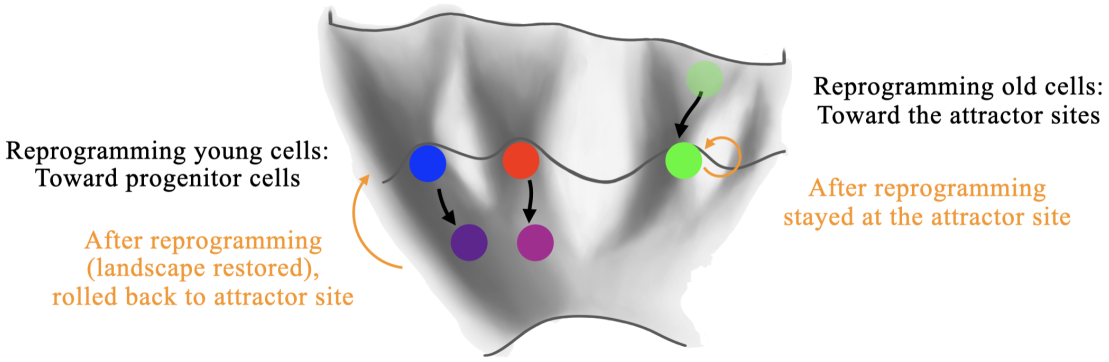



**Figure 5**: Complete Waddington Landscape of Development and Aging

The flattened nature allows cells to surpass barriers easier and traverse faster, which makes reprogramming an effective, and in-turn, sensitive method to move cells across epigenetic landscape, illustrated by experiments with mature lung epithelial cells where partial reprogramming created an unnatural progenitor state [35]. This shows transformation of epigenetic information can make cells settle into a different local minima that does not align with its original differentiation trajectory, making transdifferentiation possible.

### 4.2. The access and transformation of epigenetic information by non-reprogramming biological features

Experimental observations validate factors or biological features besides reprogramming factors to have access of and capacity to transform epigenetic information in different ways.

**1) Reinforcing attractor landscape to enhance cellular identity preservation.** For example, active transcription-associated chromatin marks such as DOT1L-catalyzed H3K79 methylation and FACT-mediated histone turnover act to maintain somatic gene expression profile while inhibiting reprogramming [36]. Another example is metformin, an activator of longevity pathway AMPL and increased lifespan in mice [37]. 100 M concentration of metformin is sufficient to alleviate several aging markers in human cells, but only 10 M significantly reduces reprogramming efficiency [38, 39, 40]. As the treatment fosters genetic stability by making grooves deeper in the Waddington landscape, when the landscape is flipped during reprogramming, those deeper grooves now become higher barriers for cells to cross [33]. This explains why some longitudinal-promoting treatments can oppose reprogramming-induced rejuvenation.

**2) Carving horizontal new paths.** Reprogramming research in C. elegans achieves the direct transdifferentiation in vivo, in which one tissue is directly turned into another from a different germ layer lineage [41]. The transcription factors utilized create a new path on the landscape which leads the cells to traverse across without traveling toward their corresponding progenitors.

**3) Carving vertical new paths.** Sodium butyrate and alpha-ketoglutarate are shown to increase reprogramming efficiency while preserving identity [42]. Also, an alternative reprogramming method, 7F reprogramming with seven factors Jdp2-Jhdm1b-Mkk6-Glis1-Nanog-Essrb-Sall4, activates another reprogramming pathway different from the OSK-method, and is suggested to have potential in decoupling rejuvenation and dedifferentiation [43, 44]. Those factors may carve a path straight down in the reprogramming landscape to rejuvenate the cells without the risk of acquiring undefined identity. Finding such factors would be an important target of rejuvenation studies to mitigate the safety risk of cellular identity obfuscation.

**4) Forming new attractor sites.** Mutations in oncogenic DNA sequences can create new attractor sites in originally unstable locations on the landscape. For example, during the differentiation of megakaryocyte-erythroid progenitors (MEP) into defined megakaryocyte cell types, cells travel down from local maxima to attractor sites of defined cell identity, following the potential gradient of the epigenetic landscape. However, mutations in oncogenic DNA sequences alter the landscape and create new attractor sites (correspond to leukemia) on the potential gradient between MEP and the defined blood cell types. This causes leukemia cells to stably self-replicate with a functionless cellular identity [45].

## 5. Concluding marks

This paper illustrates that the Waddington landscape can mechanistically represent the epigenetic information that instructs the dynamics of development and the aging process. SOK reprogramming factors achieve rejuvenation by accessing the memories of epigenetic information, reversing, and flattening the landscape, allowing cells to travel to a younger state. Other biological entities can also transform the landscape in various ways to achieve different effects, such as stabilizing cell identities, transdifferentiation, and cancer formation.

Though this paper mainly describes aging mechanisms at the cellular level, developing effective aging interventions requires understanding the information theory of aging from a comprehensive, systematic perspective. At the tissue level, it has been found that adult mouse organs are composed of mosaics of cells spanning various ages [46]. Exploring how the heterogeneity of epigenetic information in tissue cells contributes to the entropy of tissue-level epigenetic information and how this entropy influences tissue aging would be an interesting avenue for further research. At the organismal level, intra-organ positive feedback and feedforward loops sustain and stabilize phenotypic states, and circulating factors in the blood can induce body-wide phenotypic changes [47]. Instead of focusing on a single molecular pathway, examining network interactions and the representation of epigenetic information from a comprehensive, systematic perspective could be a key research focus in the study of aging.

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