

Epigenetic tipping points driven by competition for chromatin-modifiers

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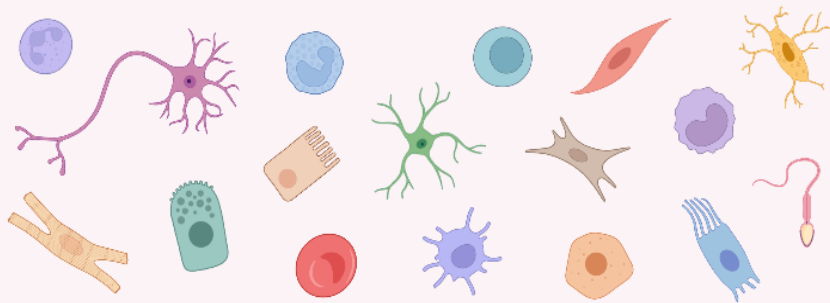


ICREA



EXCELENCIA
MARÍA
DE MAEZTU

On average, there are **over 30 trillion cells** in a single person! It is estimated that there are **>200 types of cells** with different morphologies and functions.



Red blood cell is the most abundant cell type in the human body, accounting for >80% of all cells.



The average lifespan of each type of cell varies greatly. For example:



White blood cells live for ~13 days

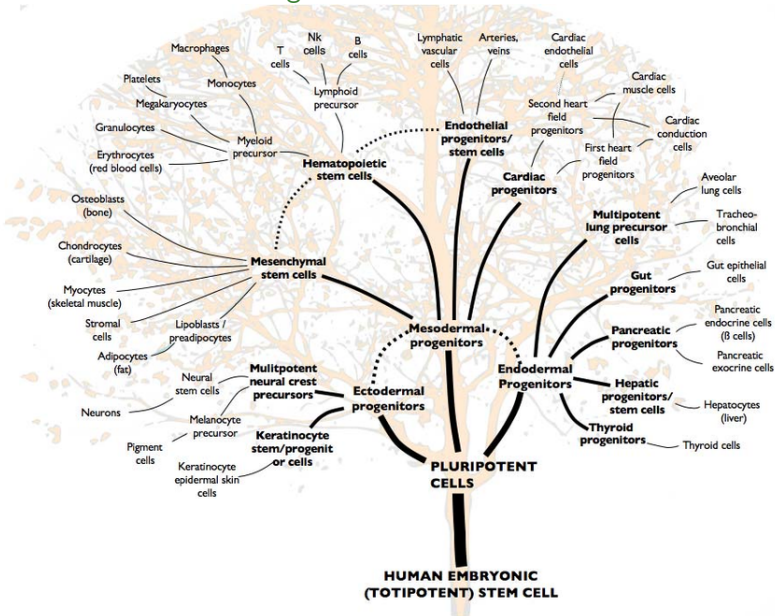


Red blood cells live for ~120 days



Neurons can live as long as the human

All these cells have the same genome





Epigenetic regulation

Many It was years inevitable later, the scent of bitter as
he faced the almonds always reminded firing squad, him
of the fate Colonel Aureliano Buendía was to remember
that distant afternoon of unrequited love

Epigenetic regulation

Many [redacted] years [redacted] later, [redacted] as
he faced the [redacted] firing squad, [redacted]
[redacted] Colonel Aureliano Buendía was to remember
that distant afternoon [redacted]

Epigenetic regulation

It was inevitable, the scent of bitter
almonds always reminded him
of the fate
of unrequited love

Epigenetic regulation

Landscape 1

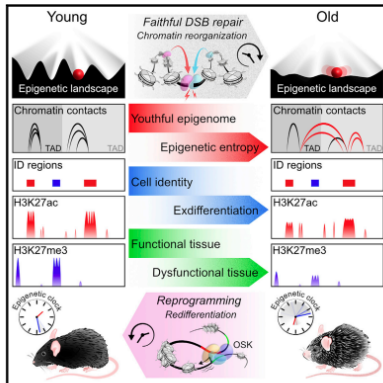


Landscape 2



Loss of epigenetic information as a cause of mammalian aging

Graphical abstract



Authors

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In brief

Aging is characterized by changes in cellular identity and function over time. This process is driven by changes in chromatin factor localization during DNA break repair, which alters the epigenome and advances the epigenetic clock. Expression of a subset of Yamanaka factors, OSK, can reverse these changes and modulate aging.

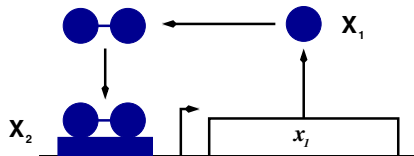
Highlights

- Cellular responses to double-stranded DNA breaks erode the epigenetic landscape
- This loss of epigenetic information accelerates the hallmarks of aging

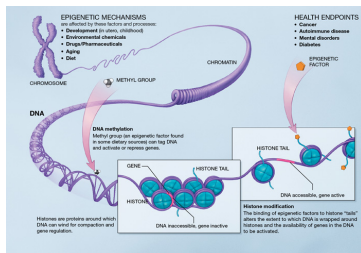
Epigenetic regulation of gene expression

There are several modalities of regulation of gene expression

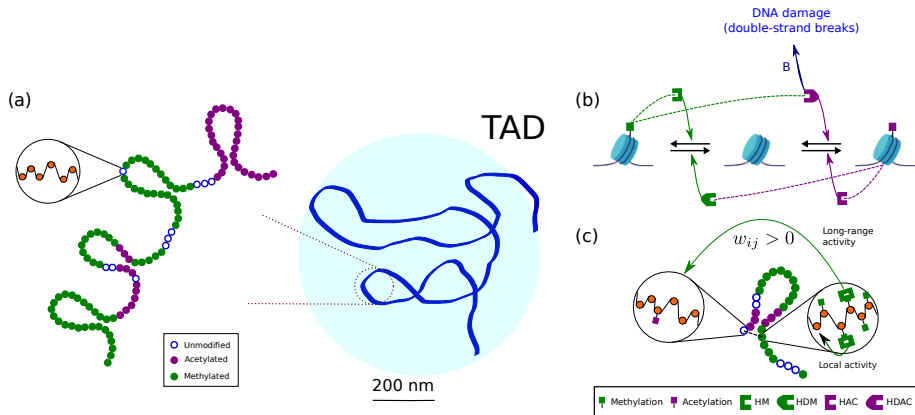
Regulation by transcription factors



Epigenetic regulation. Based on the restriction of access of transcription factors to the gene's promoter region

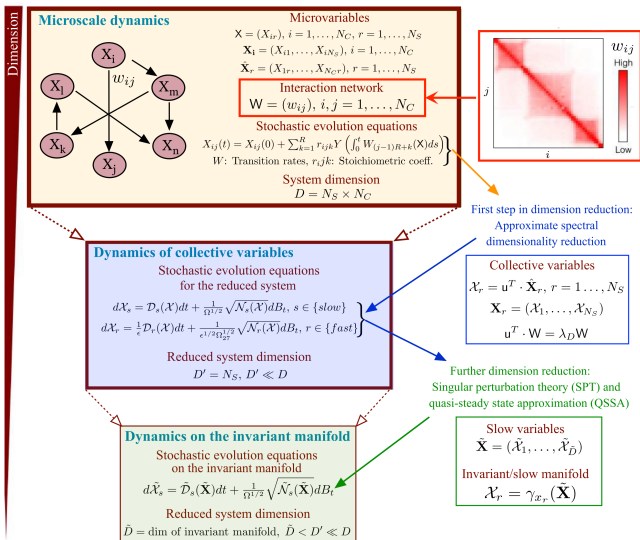


Mathematical model¹

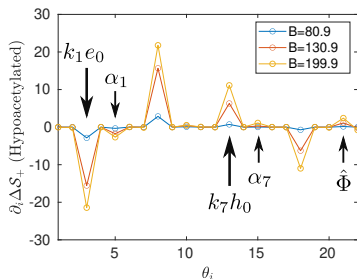
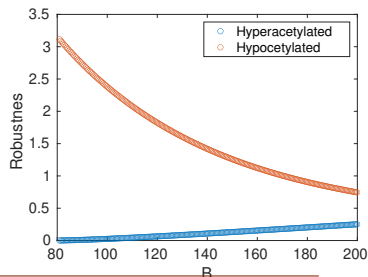
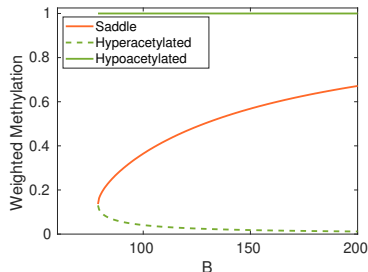
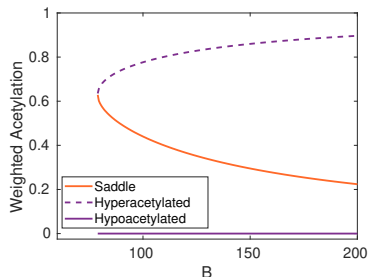


¹Alarcón, Menendez, Sardanyés, Bull. Math. Biol. 88, 57 (2026)

Mathematical model

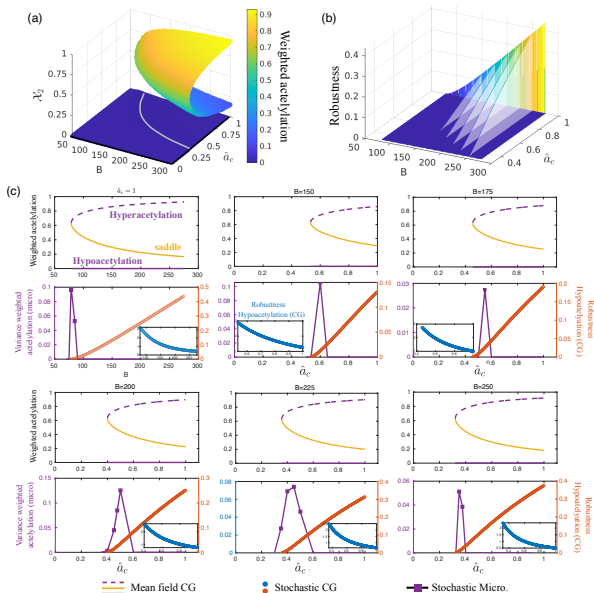


Results: Competition for chromatin modifiers induces tipping points in large-scale epigenetic landscapes²



²Alarcón, Menendez, Sardanyés, Bull. Math. Biol. 88, 57 (2026)
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Results: Metabolic cofactors facilitate tipping points



Conclusions

- Competition for chromatin modifiers (eg sirtuins in response to DNA damage) induces tipping points in large scale epigenetic landscapes
- Metabolic cofactors of epigenetic enzymes are potential biomarkers of impending tipping points