

PIN1-p53 bifurcation dictates opposite cell fate decisions in Alzheimer's disease and glioblastoma via distinct energy landscape topologies

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Abstract

Although Alzheimer's disease (AD) and glioblastoma (GBM) share common aging-related risk factors, they lead to opposite cellular fates—neurodegeneration versus uncontrolled proliferation. The system-level mechanisms driving this striking divergence remain elusive. Here, we integrated single-cell and single-nucleus transcriptomic data from AD (84 donors) and GBM (18 samples) to comparatively map the energy landscape of cell fate decisions in these two diseases. By computing a PIN1-p53 Bifurcation Index and CellEnergy landscape, we reveal that AD and GBM diverge at a critical Bifurcation Point. AD cells descend from a Health Peak into a deep AD Valley, characterized by a senescent profile with PIN1 downregulation and p53 activation. In contrast, GBM cells settle on a flat, low-energy GBM Plateau, exhibiting a proliferative profile driven by PIN1 overexpression and p53 suppression. We further identified pioneer gene candidates at the Bifurcation Point, with MDM2 and PIN1 upregulated in AD, and BBC3 in GBM. Interpreted within the Hyper Solution Landscape (HSL) framework, these findings provide a biological explanation for the path-dependent nature of cell fate decisions and provide a mechanistic framework linking the PIN1-p53 axis to the inverse comorbidity between AD and cancer, suggesting that the PIN1-p53 axis acts as a critical decision node.

Keywords: Alzheimer's disease; Glioblastoma; Hyper Solution Landscape; PIN1-p53 Bifurcation; CellEnergy; Cell fate decision; Single-cell RNA-seq

Introduction

Alzheimer's disease (AD) and glioblastoma (GBM) represent two devastating age-related brain disorders with seemingly opposite clinical trajectories (Caniceiro et al., 2026). AD is characterized by progressive neuronal loss and cognitive decline (Scheltens et al., 2021), whereas GBM is defined by uncontrolled cellular proliferation and malignant growth (Pouyan et al., 2025). Strikingly, epidemiological studies have consistently reported an inverse comorbidity between AD and cancer: patients with AD have a significantly decreased incidence of cancer, and vice versa (Zheng et al., 2025; Driver et al., 2012; Catalá-López et al., 2014). Despite their divergent clinical outcomes, AD and GBM share common upstream risk factors, including aging, metabolic dysregulation, and insulin resistance (Marcello et al., 2026; Zabłocka et al., 2021; Affuso et al., 2024). This raises a fundamental biological question: how can shared risk factors drive cells toward such strikingly opposite fates?

The PIN1-p53 axis has emerged as a critical molecular hub in determining these opposite fate decisions (Lanni et al., 2021; Seo et al., 2020). PIN1 is a prolyl isomerase that regulates cell cycle progression and protein stability (Yeh & Means, 2007; Wu et al., 2026), while p53 is the

prototypical tumor suppressor controlling apoptosis and senescence (Papazoglu & Mills, 2007). In AD, PIN1 is typically downregulated and p53 is chronically activated, driving neurons toward senescence and degeneration (Lanni et al., 2021; Najafizadeh et al., 2025). In contrast, GBM cells exhibit PIN1 overexpression and p53 suppression, allowing them to bypass apoptosis and sustain rapid proliferation (Zabłocka et al., 2021). Despite the established roles of PIN1 and p53 in both diseases, the system-level dynamics of how this axis dictates divergent cell fate decisions remain poorly understood.

The Waddington landscape metaphor provides a conceptual framework for understanding cell fate decisions, where cells are envisioned as balls rolling down a hilly terrain toward distinct valleys representing stable cell states (Sáez et al., 2022; Ferrell, 2012). In this study, we define the high-plasticity healthy state as the Health Peak, the critical decision node as the Bifurcation Point, and the two terminal valleys as the AD Valley and GBM Plateau. However, traditional dynamical models face a fundamental limitation: parameter dependency, as different parameter sets can lead to distinct landscapes with varying predictions (Zhang et al., 2026; Han et al., 2025). To address this limitation, we turned to the concept of the Hyper Solution Landscape (HSL), recently proposed by Zhang et al. (2026). This framework posits that cells with identical initial states can diverge into opposite fates depending on the specific paths they take. By applying this concept to our single-cell data, we aim to interpret the divergent AD and GBM landscapes. Concomitantly, we integrated the concept of CellEnergy, calculated based on Gene Local Network Energy (GLNE) (Long et al., 2025; Zhu et al., 2024), with the HSL framework to quantify the overall stability and plasticity of cells within their regulatory networks.

To address these gaps, we integrated single-nucleus transcriptomic data of L2/3 IT neurons from AD (84 donors) and single-cell transcriptomic data from GBM (18 samples) to construct a comparative energy landscape of cell fate decisions. We computed a PIN1-p53 Bifurcation Index to quantify the balance of this axis and further identified the Bifurcation Point (where the index equals 0). Additionally, we calculated the CellEnergy landscape for both diseases to capture their distinct energy topologies. By applying the core concept of the HSL framework to real-world single-cell data, we reveal that AD and GBM diverge at a critical Bifurcation Point. AD cells descend from a Health Peak into a deep AD Valley, whereas GBM cells settle on a flat GBM Plateau. This provides a unified mechanistic explanation for how shared aging-related risk factors can drive opposite cell fates, offering new insights into the long-observed inverse comorbidity between AD and cancer.

Method

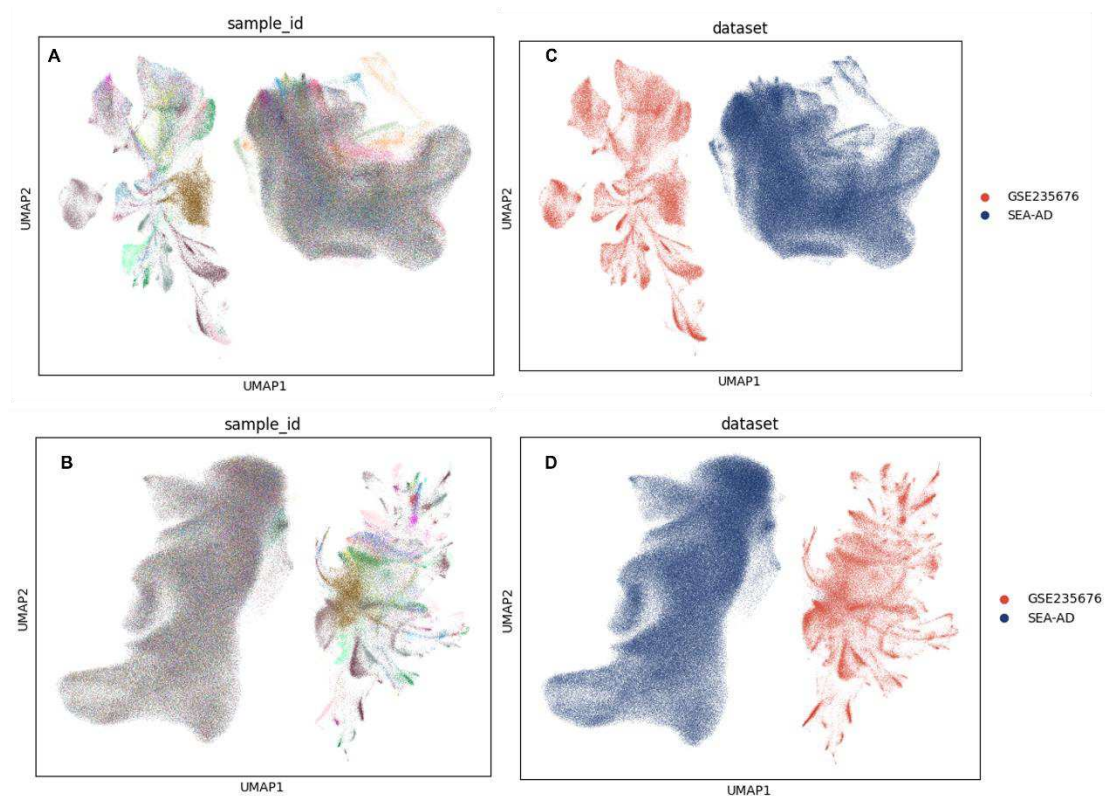
1. Data acquisition and preprocessing

The AD single-nucleus RNA-seq data (L2/3 IT neurons, 289,940 cells from 84 donors) were

obtained from the SEA-AD consortium (<https://portal.brain-map.org/explore/seattle-alzheimers-disease>). The L2/3 IT neurons were selected because they are highly vulnerable to AD pathology and represent a critical cell type in the disease progression (Lin et al., 2025; Gabitto et al., 2024). The GBM scRNA-seq data (18 samples) were obtained from the GEO database (accession: GSE235676). For the GBM dataset, we retained the entire cellular composition (including both malignant and non-malignant cells) to capture the full heterogeneity of the tumor microenvironment, rather than performing a specific malignant cell pre-selection.

To integrate the datasets, the expression matrix was normalized to 10,000 counts per cell (`sc.pp.normalize_total, target_sum=1e4`) and log-transformed (`sc.pp.log1p`). Highly variable genes (HVGs) were selected using `sc.pp.highly_variable_genes (n_top_genes=2000)` with `batch_key="sample_id"`. Since the data source is completely confounded with the disease type (AD vs. GBM), we deliberately used `sample_id` (instead of dataset source) as the batch key for ComBat (`sc.pp.combat`) to remove technical batch effects while preserving the true biological differences. Dimensionality reduction was performed using PCA, followed by UMAP visualization. Cell clustering was performed using the Leiden algorithm (`resolution = 0.5`).

Batch effect correction and validation. To integrate the datasets, we applied ComBat using `sample_id` as the batch key (AD: Donor ID; GBM: GSM ID). Since the data source (SEA-AD vs. GSE235676) is completely confounded with the disease type (AD vs. GBM), we deliberately avoided using the dataset source as the batch key to prevent over-correction that would erase true biological differences. To validate this approach, we generated UMAP embeddings before and after ComBat correction (Supplementary Figure S1). Before correction, cells clustered primarily by `sample_id`, indicating severe technical batch effects. After correction, cells from different samples were well mixed, confirming the successful removal of technical noise. Importantly, AD and GBM cells remained clearly separated on the UMAP after correction (Supplementary Figure S1D), demonstrating that the biological divergence between diseases was preserved. The corrected expression matrix was used for all downstream analyses.



Supplementary Figure S1. Validation of ComBat batch correction using sample_id.

(A, B) UMAP embeddings colored by sample_id (A) and dataset (B) before ComBat correction, showing severe sample-level batch effects.

(C, D) UMAP embeddings colored by sample_id (C) and dataset (D) after ComBat correction. After correction, cells from different samples are well mixed, while AD (blue) and GBM (red) remain clearly separated, confirming the removal of technical noise and the preservation of biological divergence.

2. Bifurcation Index calculation

To quantify the balance between the PIN1 and p53 pathways, we defined the PIN1-axis gene set (PIN1, MYC, CCND1) and the p53-axis gene set (TP53, BAX, BBC3). PIN1 was selected as the core regulator given its established role in cell cycle progression and protein stability (Lu & Zhou, 2007). MYC is a direct transcriptional target of PIN1 (Lu & Zhou, 2007), while CCND1 (encoding cyclin D1) is directly bound and stabilized by PIN1 (Liou et al., 2002; Ryo et al., 2003). For the p53-axis, TP53 was chosen as the central tumor suppressor, and BAX and BBC3 (PUMA) were included as they are canonical p53 transcriptional targets that execute the apoptotic program (Fischer, 2017; Vogt et al., 2018). The pathway activity scores were calculated as the mean expression of the corresponding genes. The Bifurcation Index was

defined as:

$$\text{Bifurcation Index} = P_{axis} - S_{axis}$$

where P_{axis} and S_{axis} represent the mean expression of the PIN1-axis and p53-axis genes, respectively. Positive values indicate a PIN1-dominant state, while negative values indicate a p53-dominant state. The Bifurcation Index was defined as the difference between the PIN1-axis and p53-axis activity scores ($P_{axis} - S_{axis}$). This approach of using a composite score to quantify a directional cellular state is conceptually similar to the ‘immune resistance score’ defined by Jerby-Arnon et al. (2018), which integrated multiple gene program scores to characterize a specific cellular phenotype.

3. CellEnergy and trajectory inference

CellEnergy calculation: CellEnergy was calculated using Gene Local Network Energy (GLNE) as previously described (Long et al., 2025). Briefly, the expression matrix was binarized (1 for expressed, 0 for unexpressed). A gene-gene correlation matrix (W) was constructed using Pearson correlation, with diagonal elements set to 0. For each gene i in cell n , the GLNE was calculated as:

$$E_i^n = -0.5 \times g_i^n \times \sum_{j \in N(i)} W_{ij} g_j^n$$

where g_i^n is the binary expression state of gene i in cell n . The total CellEnergy of cell n was defined as the sum of GLNE across all genes:

$$E_n = \sum_{i=1}^M E_i^n$$

Here, the gene sets used for GLNE calculation were the same PIN1-axis and p53-axis gene sets defined above.

Inferred pseudo-time construction: Because true temporal information is absent in cross-sectional single-cell data, we constructed an inferred pseudo-time axis based on the continuous Bifurcation Index. This feature-based approach is well-suited for pathway-specific trajectory analysis, where cells are ordered according to their progression along a defined biological axis (e.g., PIN1-p53 balance) rather than global transcriptomic distances (Trapnell et al., 2014; Street et al., 2018). The Bifurcation Index was sorted from low to high to represent the continuous decision axis of the PIN1-p53 network. CellEnergy was plotted along this axis and smoothed using a sliding window approach to reduce single-cell noise (Qiu et al., 2017).

The Bifurcation Point was defined at a bifurcation index of 0. To mathematically locate this

point from the energy landscape, we calculated the energy change rate ($|dE/dx|$), where E is the CellEnergy and x is the Bifurcation Index. In dynamical systems, the maximum value of $|dE/dx|$ represents the steepest 'cliff' in the energy landscape, corresponding to the most unstable transition state where cells undergo the most rapid fate transition (Jin et al., 2018; Zhu et al., 2024). This derivative was calculated using `np.gradient` on the smoothed energy curve. The point of maximum $|dE/dx|$ coincided exactly with the Bifurcation Point for both AD and GBM.

Landscape-Flux phase space: To quantify cell accumulation and identify the attractors, we constructed a phase space based on the landscape-flux theory (Wang, 2015; Zhu et al., 2024). The Bifurcation Index was used as the x-axis representing the decision position, and CellEnergy was used as the y-axis representing the potential. Kernel Density Estimation (KDE) was performed using a Gaussian kernel (`scipy.stats.gaussian_kde`) to estimate the probability density of cells within this phase space. The density peaks, representing the most frequent cell states (attractors), were visualized to reveal the distinct landscapes of AD and GBM.

4. Statistical analysis

Patient-level differences in the Bifurcation Index between AD (n=84) and GBM (n=18) were assessed using the non-parametric Mann-Whitney U test. The exact P-value for this comparison was 0.003051. P-values < 0.05 were considered statistically significant. FDR correction (Benjamini-Hochberg method) was applied where multiple comparisons were involved.

To rule out potential biases caused by the unbalanced sample size (AD n=84 vs. GBM n=18), a downsampling validation was performed. The AD cohort was randomly reduced to 18 donors (matched to the GBM cohort) in a single random downsampling run (Supplementary Figure S3). The robustness of the energy landscape was confirmed by the persistence of the deep AD Valley in the downsampled cohort.

Pioneer gene identification: Cells at the Bifurcation Point ($|bifurcation\ index| < 0.1$) were selected to calculate the log2 fold change (log2FC) between AD and GBM:

$$\log_2 FC = \log_2 \left(\frac{Mean_{AD} + 1}{Mean_{GBM} + 1} \right)$$

A pseudocount of +1 was used to avoid division by zero. Genes with $|\log_2 FC| > 0.5$ were defined as pioneer gene candidates. The threshold of $|\log_2 FC| > 0.5$ was chosen to capture genes with biologically meaningful expression differences, consistent with previous single-cell studies (Jiang et al., 2025; Hao et al., 2024). As noted in recent methodological reviews, a 0.5 cutoff paired with stringent adjusted p-values is particularly appropriate for dosage-sensitive genes such as transcription factors and signaling regulators (Long et al., 2026).

5. Cell fate state definition and visualization

Cell fate states were defined based on the 10th and 90th percentiles of the Bifurcation Index. Cells below the 10th percentile were classified as 'AD Valley', cells above the 90th percentile as 'GBM Plateau', and the remaining cells (intermediate 80%) as 'Bifurcation Point'. The 10th and 90th percentiles were chosen to capture the extreme terminal phenotypes (fully senescent vs. fully proliferative), while minimizing the inclusion of undifferentiated intermediate states. This quantile-based discretization strategy is consistent with previous single-cell studies that use similar approaches to define distinct cellular states based on continuous scores (Malagoli Tagliazucchi et al., 2023; Hao et al., 2024; Xu et al., 2025).

Note on terminal state selection: For gene expression analysis at the terminal states (Figure 3D), we selected cells with the lowest 5% CellEnergy to represent the energy-minimum terminal states (AD Valley and GBM Plateau). This energy-based threshold is conceptually distinct from the fate state definition (which is based on the Bifurcation Index) but reflects the same terminal biological outcomes.

Visualizations were generated using matplotlib and seaborn in python. The Sankey diagram was constructed using plotly. All analyses were performed in python 3.9 using scanpy and related libraries.

Table 1. Overview of the analytical workflow and key parameters.

Stage	Step	Method / Description	Tools / Parameters	Output
1. Data Curation	Data acquisition	AD: L2/3 IT neurons (84 donors, 289,940 cells); GBM: bulk tumor tissue (18 samples).	SEA-AD consortium (https://portal.brain-map.org) & GEO (GSE235676)	Integrated single-cell dataset
	Preprocessing	Normalization and log-transformation; highly variable gene selection.	sc.pp.normalize_total (1e4), sc.pp.log1p, sc.pp.highly_variable_genes (2000 HVGs, batch_key=sample_id)	Normalized expression matrix
	Batch correction	ComBat correction using individual sample IDs (avoiding dataset source as the key to prevent over-correction).	sc.pp.combat (key=sample_id), validated by UMAP (Supplementary Fig S5)	Batch-corrected expression matrix
	Dimensionality reduction	Principal Component Analysis and UMAP visualization; Leiden clustering.	PCA, UMAP, Leiden (resolution = 0.5)	UMAP embeddings (Fig 1A)

2. Metric Calculation	Bifurcation Index	Defined as the difference between PIN1-axis and p53-axis activity scores (P_axis - S_axis).	PIN1-axis: PIN1, MYC, CCND1; p53-axis: TP53, BAX, BBC3	Bifurcation Index (Fig 1B)
	CellEnergy (GLNE)	Gene Local Network Energy computed by summing local network interactions.	scipy.stats.gaussian_kde, Pearson correlation matrix (Fig 2A)	CellEnergy landscape (Fig 2A)
3. Landscape & Trajectory	Bifurcation Point identification	Mathematically defined as the maximum energy change rate ($ dE/dx $).	np.gradient, smoothed energy curve	Bifurcation Point (index=0) (Fig 3D, 3F)
	Inferred pseudo-time	Sorted cells by Bifurcation Index (low to high) as the decision axis; smoothed energy.	Sliding window approach	Energy trajectories (Fig 3A, 3C)
	Landscape-Flux phase space	Density peaks (attractors) quantified in the (Bifurcation Index, CellEnergy) space.	Gaussian KDE	Attractor distribution (Fig 2C)
4. Molecular Drivers	Pioneer gene identification	Log2 fold change (AD vs. GBM) calculated at the Bifurcation Point.	$ \log_2FC > 0.5$, pseudocount +1	MDM2, PIN1, BBC3 (Fig 3E, Fig 3B)
5. Fate Outcomes	Fate state composition	Cells defined by 10th/90th percentiles of Bifurcation Index.	AD Valley (<10%), GBM Plateau (>90%), Bifurcation Point (intermediate 80%)	Sankey diagram (Fig 3G), composition (Fig 1E)
6. Theoretical Model	HSL framework integration	Applied the Hyper Solution Landscape concept to interpret opposite fate decisions.	Conceptual model (Fig 4A, 4B)	Unified mechanism for AD-GBM inverse comorbidity

Supplementary Table S1. Summary of gene sets and parameter settings.

Gene Set / Parameter	Genes	Rationale / Reference
PIN1-axis	PIN1, MYC, CCND1	PIN1 regulates cell cycle and protein stability (Lu & Zhou, 2007); MYC and

		CCND1 are downstream targets (Liou et al., 2002).
p53-axis	TP53, BAX, BBC3	TP53 is the central tumor suppressor; BAX and BBC3 are canonical apoptotic effectors (Fischer, 2017).
Bifurcation Index	P_axis - S_axis	Directional pathway scoring concept (Jerby-Arnon et al., 2018).
Fate State Thresholds	10th / 90th percentiles	Quantile-based discretization for extreme phenotypes (Malagoli Tagliazucchi et al., 2023).
Pioneer Gene Cutoff	$ \log_2FC > 0.5$	Standard single-cell differential expression threshold (Hao et al., 2024).

Results

1. AD and GBM exhibit distinct bifurcation landscapes

To investigate the differences in cell fate decisions between Alzheimer's disease (AD) and glioblastoma (GBM), we first performed dimensionality reduction and visualization on the integrated single-cell dataset. AD and GBM cells formed distinct clusters on the UMAP, indicating that the true disease heterogeneity was preserved after ComBat batch correction (Figure 1A). We then projected the PIN1-p53 bifurcation index onto the UMAP (Figure 1B). GBM regions exhibited a prominent red shift (PIN1-dominant), whereas AD regions were biased towards blue (p53-dominant).

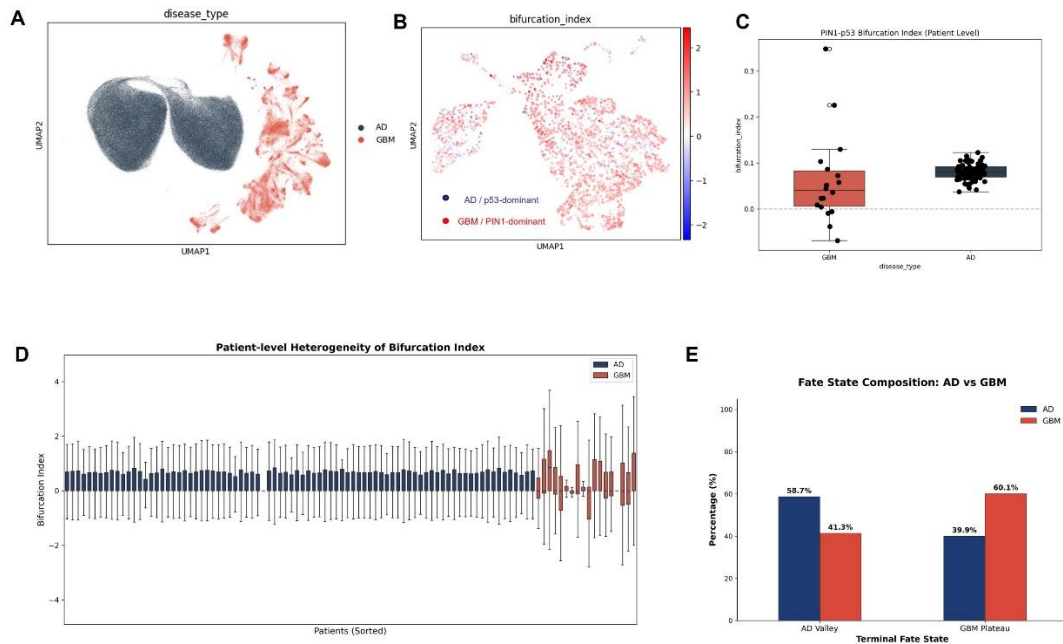


Figure 1. AD and GBM exhibit distinct bifurcation landscapes.

(A) UMAP visualization of integrated single-cell transcriptomic data colored by disease type (AD, blue; GBM, red). AD and GBM cells form distinct clusters, indicating that the true disease heterogeneity was preserved after ComBat batch correction using sample_id.

(B) UMAP projection of the PIN1-p53 Bifurcation Index. Red indicates positive values (PIN1-dominant), whereas blue indicates negative values (p53-dominant). GBM regions exhibit a prominent red shift, while AD regions are biased towards blue.

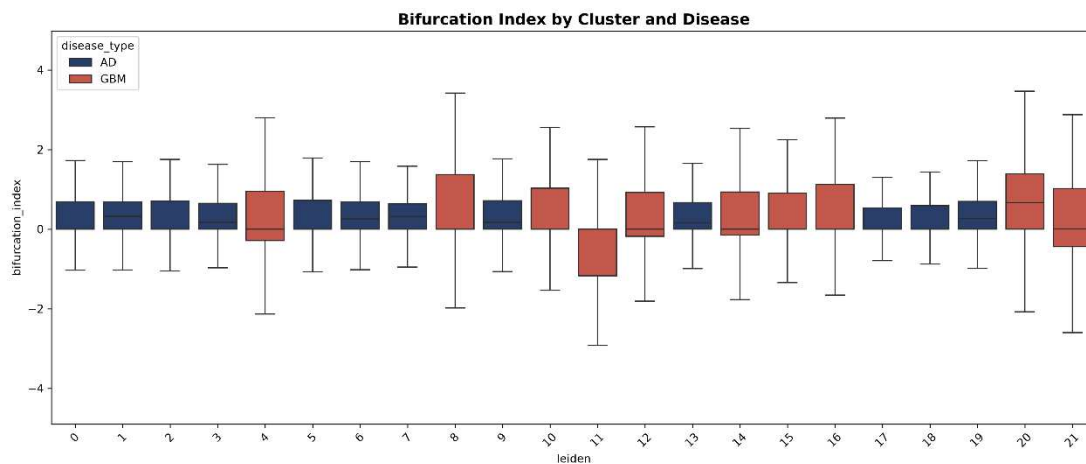
(C) Patient-level boxplot comparing the Bifurcation Index between AD (n=84) and GBM (n=18). A statistically significant difference was observed (Mann-Whitney U test, $P = 0.003051$).

(D) Patient-level heterogeneity of the Bifurcation Index. AD patients exhibit a highly uniform distribution, whereas GBM patients display substantial inter-tumoral heterogeneity.

(E) Fate state composition of terminal states. The AD Valley is predominantly enriched with AD cells (58.7%), whereas the GBM Plateau is predominantly composed of GBM cells (60.1%). The presence of GBM cells within the AD Valley (41.3%) likely reflects non-malignant cells (e.g., microglia/macrophages) in the tumor microenvironment that intrinsically exhibit a p53-dominant, senescent-like profile. This confirms that despite sharing a common Bifurcation Point, AD and GBM diverge into distinct terminal fates.

At the patient level, the bifurcation index differed significantly between AD (n=84) and GBM (n=18) (Mann-Whitney U test, $P=0.003051$; Figure 1C). Notably, AD patients exhibited a highly uniform distribution, while GBM patients displayed substantial inter-tumoral heterogeneity (Figure 1D). This suggests that GBM comprises multiple molecular subtypes

with varying degrees of PIN1-p53 imbalance. To dissect the cellular composition of the terminal states, we calculated the column-wise proportions (Figure 1E). The AD Valley was predominantly composed of AD cells (58.7%), whereas the GBM Plateau was predominantly composed of GBM cells (60.1%). Notably, the GBM cells present within the AD Valley (41.3%) are likely attributed to non-malignant cells in the tumor microenvironment that also exhibit a p53-dominant profile. This confirms that despite sharing a common Bifurcation Point, AD and GBM diverge into distinct terminal fates. To further dissect this heterogeneity, we analyzed the bifurcation index across Leiden clusters (Supplementary Figure S1). While AD clusters displayed consistently uniform bifurcation indices, specific GBM clusters (e.g., clusters 8, 11, and 20) exhibited extreme values, confirming that the inter-tumoral heterogeneity is driven by specific malignant subpopulations.



Supplementary Figure S2. Bifurcation Index across Leiden clusters.

Boxplot showing the Bifurcation Index distribution across different Leiden clusters for AD and GBM. While AD clusters display consistently uniform indices, specific GBM clusters (e.g., clusters 8, 11, and 20) exhibit extreme values, confirming that inter-tumoral heterogeneity is driven by specific malignant subpopulations.

2. Energy landscape reveals a deep valley in AD versus a flat plateau in GBM

To understand the physical principles underlying these fate decisions, we computed the CellEnergy (GLNE) (Long, C., Li, H., et al., 2025) for all cells. CellEnergy is a quantitative metric that assigns a single energy value to each cell by summing the local network energy of all genes, based on a gene-gene interaction network constructed from single-cell expression data. Briefly, we first binarized the expression matrix, constructed a gene-gene correlation network, and computed the GLNE for each gene. The sum of GLNE values across all genes defines the CellEnergy of a cell, which reflects its overall stability and plasticity within the gene regulatory network. Our landscape analysis is structured around three key features: the Health Peak (high-energy plasticity), the Bifurcation Point (bifurcation index = 0, where cell fates

diverge), and the terminal states. The terminal states are defined as the AD Valley (a steep, deep energy minimum representing senescence) and the GBM Plateau (a flat, low-energy landscape without a sharp minimum, representing proliferation).

The distribution of CellEnergy was markedly different between the two diseases (Figure 2A). CellEnergy was calculated as previously described (Long et al., 2025). Briefly, the gene expression matrix was binarized (1 for expressed, 0 for unexpressed) using a threshold of >0. A gene-gene correlation matrix (W) was computed using pearson correlation, and the diagonal elements were set to 0. For each gene i in cell n , the Gene Local Network Energy (GLNE) was calculated as: $E_i^n = -0.5 \times g_i^n \times \sum_{j \in N(i)} W_{ij} g_j^n$, where g_i^n is the binary expression state of gene i in cell n . The total CellEnergy of cell n was defined as the sum of GLNE across all genes: $E_n = \sum_{i=1}^M E_i^n$. AD cells exhibited a broad energy distribution, whereas GBM cells were tightly concentrated at extremely low energy levels. We further constructed the energy landscape by plotting CellEnergy against the bifurcation index (Figure 2B). The AD trajectory descends from the Health Peak into a sharp, deep **AD Valley** (minimum energy = -22625.24 at bifurcation index = 0.3971), while the GBM trajectory remains on a low-energy flat **GBM Plateau** (minimum energy = -34071.81 at bifurcation index = 0).

To quantify the cell distribution within this landscape, we generated the Landscape-Flux phase space (Figure 2C) (Zhu et al., 2024). Strikingly, cells from both AD and GBM predominantly accumulate at the **Bifurcation Point** (bifurcation index = 0). However, their energy levels at this point differed drastically: AD cells transiently reside at a relatively high energy level (= -10630.22) before sliding into the deeper AD Valley, whereas GBM cells immediately reach their terminal GBM Plateau at an extremely low energy level (= -35832.56).

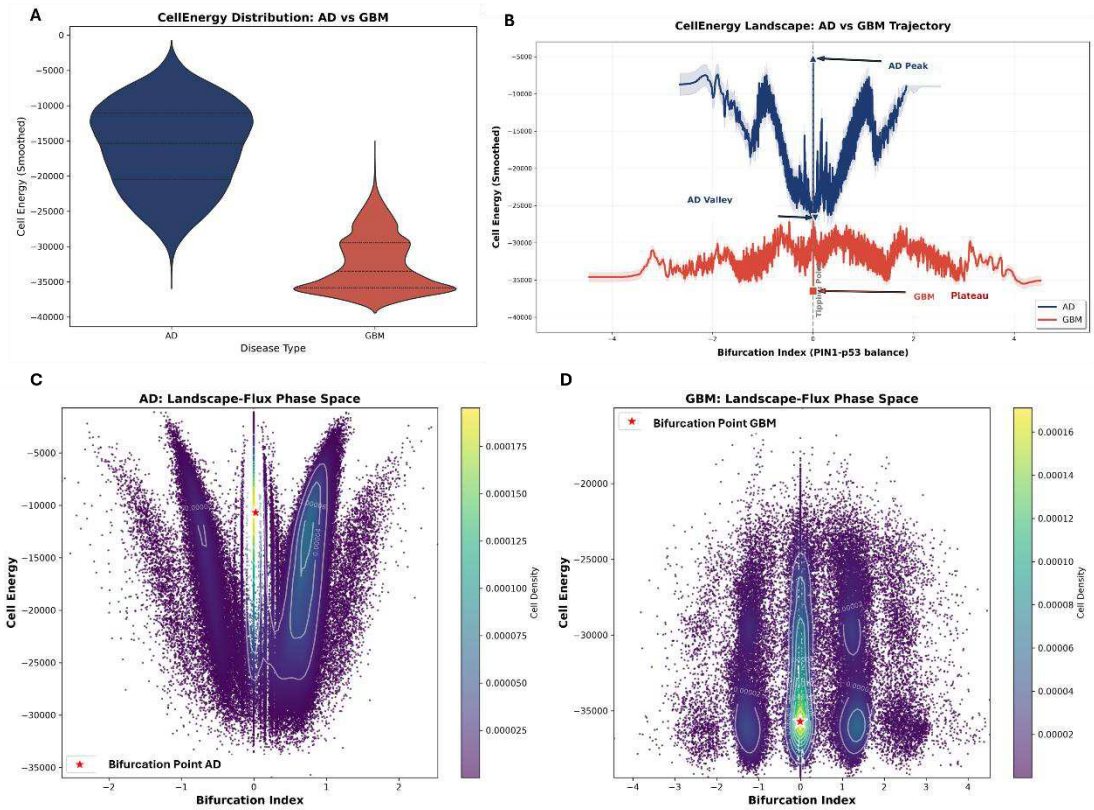


Figure 2. CellEnergy landscape reveals a deep valley in AD versus a flat plateau in GBM.

(A) Violin plot showing the distribution of CellEnergy (GLNE) in AD and GBM. AD cells exhibit a broad energy distribution, whereas GBM cells are tightly concentrated at extremely low energy levels.

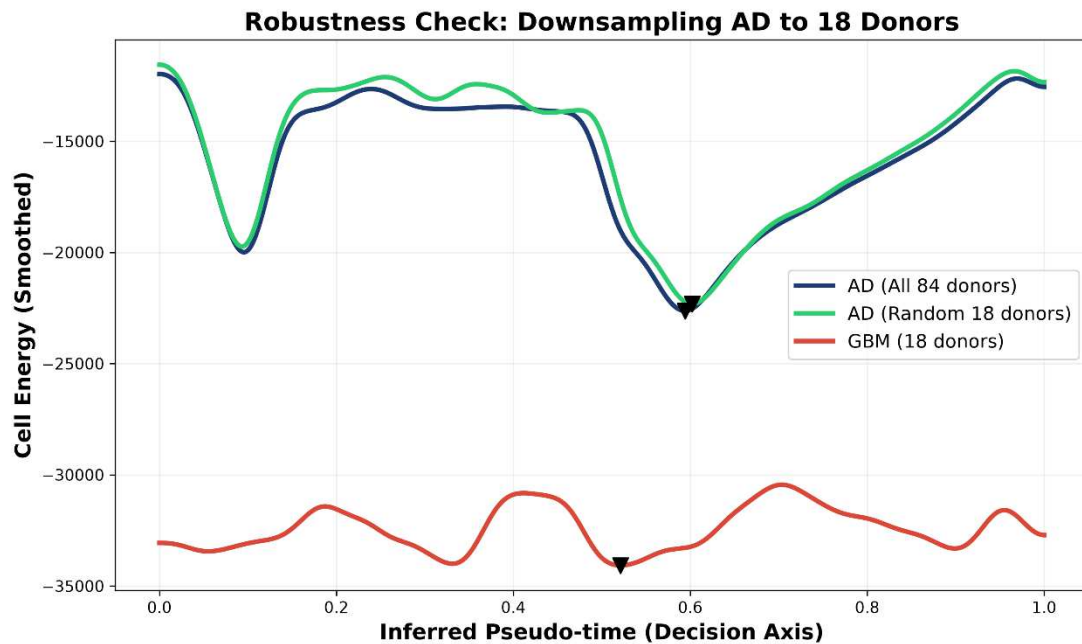
(B) CellEnergy landscape plotted against the Bifurcation Index. The AD trajectory descends from the Health Peak into a sharp, deep AD Valley (minimum energy = -22625.24 at bifurcation index = 0.3971). In contrast, the GBM trajectory remains on a low-energy flat GBM Plateau (minimum energy = -34071.81 at bifurcation index = 0.00).

(C) Landscape-Flux phase space for AD. The red star indicates the highest cell density (Bifurcation State), showing that AD cells transiently reside at a relatively high energy level before sliding into the deeper AD Valley.

(D) Landscape-Flux phase space for GBM. The red star indicates the Bifurcation State at an extremely low energy level, confirming that GBM cells immediately reach their terminal GBM Plateau without further descent.

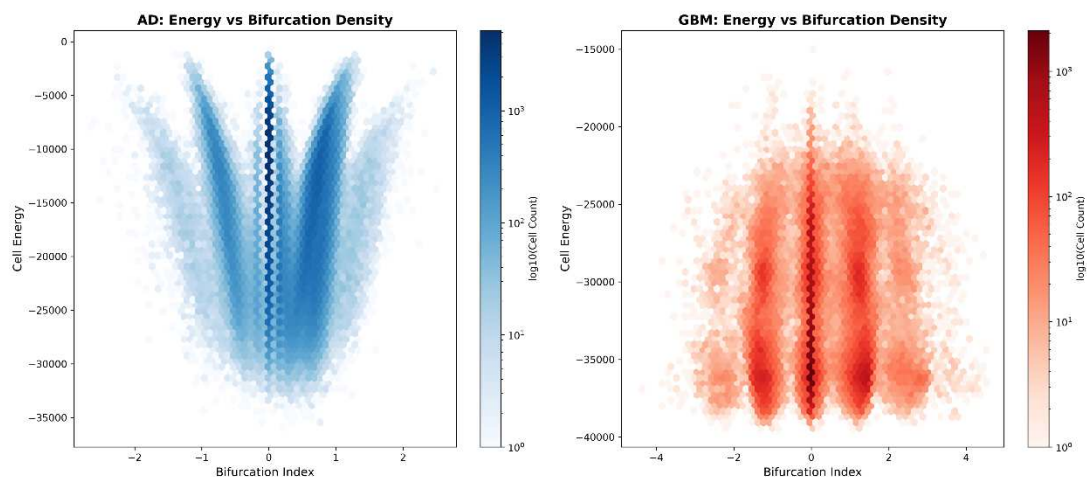
To rule out potential biases caused by the unbalanced sample size (AD $n=84$ vs. GBM $n=18$), we performed a rigorous downsampling validation (Supplementary Figure S3). Even when randomly reducing the AD cohort to 18 donors, the deep AD Valley persisted. In contrast, the GBM Plateau remained flat. To validate that these landscape topologies were not artifacts of kernel density estimation, we visualized the raw cell distribution using hexagonal density plots

(Supplementary Figure S4). The prominent vertical band at the Bifurcation Point confirms that the majority of cells in both diseases reside here.



Supplementary Figure S3. Downsampling validation of the energy landscape.

To rule out potential biases caused by unbalanced sample sizes (AD $n=84$ vs. GBM $n=18$), the AD cohort was randomly downsampled to 18 donors. The deep AD Valley persisted, whereas the GBM Plateau remained flat, confirming the robustness of the landscape topologies independent of sample size.



Supplementary Figure S4. Hexagonal density plots of energy versus bifurcation.

Hexagonal density plots showing the raw cell distribution in the phase space. The prominent vertical band at a bifurcation index of 0 confirms that the majority of cells reside in the Bifurcation State. The U-shaped distribution in AD versus the low-energy concentration in GBM reinforces the distinct phase space topologies of the two diseases.

3. Inferred pseudo-time trajectories reveal the dynamic transition at the Bifurcation Point

To capture the dynamic evolutionary process from the initial decision state to the terminal fate, we first constructed inferred pseudo-time trajectories for AD and GBM (Figure 3A, 3C). Methodologically, we sorted the cells according to their bifurcation index (representing the continuous decision axis of the PIN1-p53 network) and plotted the smoothed CellEnergy along this axis using a sliding window approach. This analysis reveals distinct dynamic behaviors between the two diseases: in AD, the energy drops precipitously as cells approach the Bifurcation Point, forming a sharp and deep AD Valley downstream. In contrast, GBM cells cross the Bifurcation Point smoothly with minimal energy fluctuation, settling into a stable GBM Plateau without further descent.

To quantitatively locate this critical cell fate decision point from a physical perspective, we calculated the energy change rate ($|dE/dx|$) (Figure 3D, 3F). This mathematically defined as the maximum value of the first derivative of the smoothed energy curve, representing the steepest 'cliff' in the energy landscape where cells undergo the most rapid transition. As shown in Figure 3D and 3F, this point of maximum energy change coincides exactly with the Bifurcation Point (bifurcation index = 0) for both AD and GBM, confirming that the bifurcation node serves as the physical tipping point where cell fates diverge.

To characterize the molecular signatures of the terminal states, we next examined the gene expression profiles at the terminal energy valley (Figure 3B). We extracted the cells with the lowest 5% CellEnergy (defined as the terminal energy valley) and calculated the mean expression of target genes (PIN1, TP53, MYC, CCND1, BAX, BBC3, CDKN1A, MDM2) after normalization (target_sum = 1e4) and log-transformation (log1p). At this terminal state, GBM cells exhibited a globally quiescent transcriptional profile (all genes near zero), reflecting a "lying flat" state. In contrast, AD valley cells showed significant upregulation of PIN1, MDM2, and BAX, indicating a state of active transcriptional stress or "self-rescue" attempts.

To identify the molecular drivers determining the fate decision before terminal locking, we shifted our analysis to the Bifurcation Point (Figure 3E). We selected cells at the Bifurcation Point (bifurcation index = 0, $|index| < 0.1$) and calculated the log2 fold change (log2FC) as $\log_2 \left(\frac{Mean_{AD}+1}{Mean_{GBM}+1} \right)$, where +1 was used as a pseudocount to avoid division by zero. Genes with $|\log_2FC| > 0.5$ were defined as pioneer gene candidates. MDM2 (log2FC = +0.74) and PIN1 (log2FC = +0.62) were identified as the top pioneer genes in AD, suggesting that AD cells attempt to "self-rescue" by upregulating PIN1 and MDM2 at the decision node. Conversely, BBC3 was identified as a pioneer gene candidate in GBM (log2FC = -0.56), revealing a transient apoptotic pressure that GBM cells ultimately evade. Collectively, these findings establish a coherent trajectory from the Bifurcation Point to the distinct terminal states, driven by opposite molecular programs.

Finally, to quantify the macroscopic outcome of these molecular drivers, we constructed a Sankey diagram based on the cell fate state assignments (Figure 3G). The diagram visually summarizes the opposite trajectories: the vast majority of AD cells (originating from the left) flow through the Bifurcation Point and terminate in the AD Valley (Senescent State), whereas GBM cells predominantly transition into the GBM Plateau (Proliferative State). This data-driven visualization quantitatively confirms that the distinct molecular programs at the Bifurcation Point ultimately drive opposite fate decisions in AD and GBM.

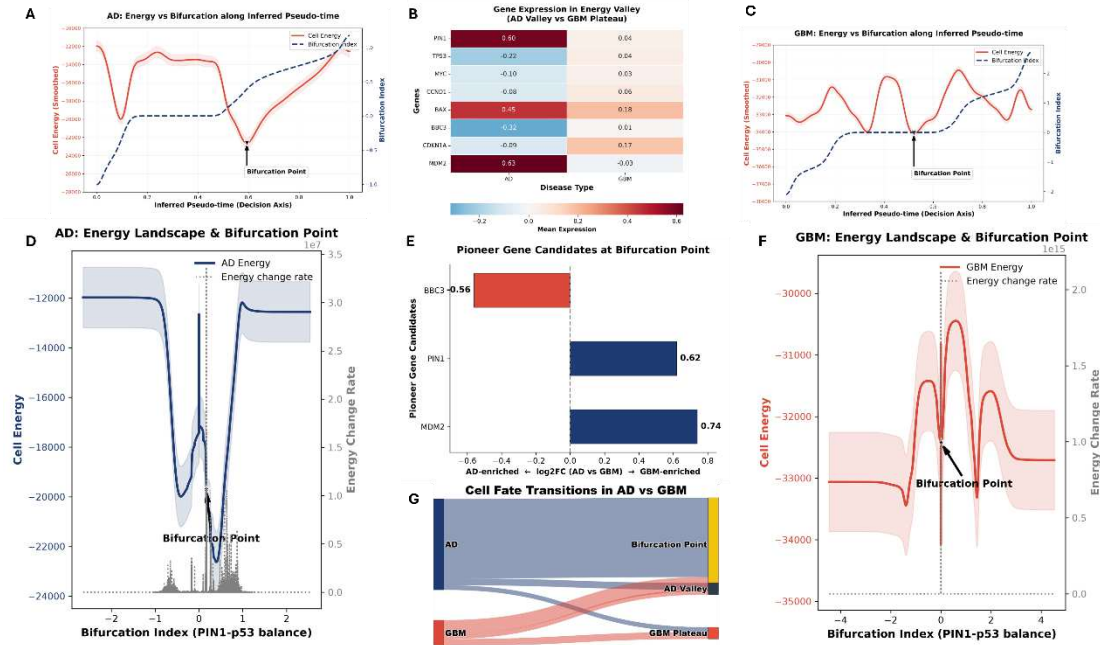


Figure 3. Inferred pseudo-time trajectories, energy landscape, and molecular drivers of cell fate decisions.

(A, C) Inferred pseudo-time trajectories for AD (A) and GBM (C). The energy drops precipitously as cells approach the Bifurcation Point in AD, forming a distinct AD Valley. In contrast, GBM cells cross the Bifurcation Point smoothly, settling into the GBM Plateau.

(B) Gene expression profiles at the terminal energy valley (AD Valley vs GBM Plateau). AD valley cells show significant upregulation of PIN1, MDM2, and BAX, whereas GBM valley cells exhibit a globally quiescent transcriptional profile.

(D, F) Energy change rate ($|dE/dx|$) identifying the Bifurcation Point (index = 0) for AD (D) and GBM (F). The maximum $|dE/dx|$ coincides exactly with the Bifurcation Point.

(E) Pioneer gene candidates at the Bifurcation Point. MDM2 ($\log_2FC = +0.74$) and PIN1 ($\log_2FC = +0.62$) are the top pioneer genes in AD, while BBC3 ($\log_2FC = -0.56$) is identified in GBM.

(G) Sankey diagram summarizing cell fate transitions. The Bifurcation Point serves as a transitional hub, with cells subsequently diverging into their respective terminal states (AD

Valley vs. GBM Plateau).

Discussion

The HSL framework explains the opposite fate decisions in AD and GBM

In this study, the term 'landscape topology' refers to the structural features of the energy landscape, including the number and types of attractors (Health Peak, AD Valley, GBM Plateau), the bifurcation node, and the connectivity (flux direction) between them. In this study, we reveal a striking topological divergence in the energy landscapes of AD and GBM: AD cells descend from a Health Peak into a deep AD Valley, whereas GBM cells settle on a flat, low-energy GBM Plateau. To interpret these findings, we employed the Hyper Solution Landscape (HSL) framework (Zhang et al., 2026), which posits that cells with identical initial states can diverge into opposite fates depending on the specific paths they take. Our conceptual landscape model (Figure 4A) illustrates this principle: healthy cells reach a critical Bifurcation Point, after which AD cells dive into a deep AD Valley, while GBM cells remain on a flat GBM Plateau. Our study extends the HSL concept from theoretical ODE models to real-world single-cell transcriptomic data, providing a biological interpretation of its core 'route-dependent fate decision' principle.

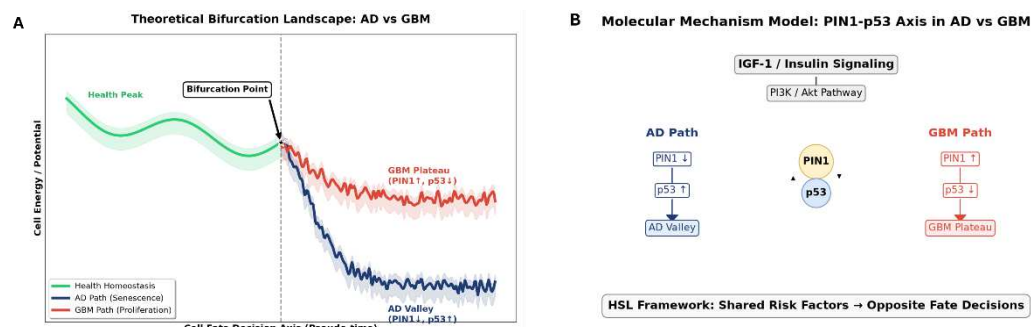


Figure 4. The HSL framework explains the opposite fate decisions in AD and GBM.

(A) Theoretical bifurcation landscape. Healthy cells (Health Peak) reach a critical Bifurcation Point, after which AD cells (blue) dive into a deep AD Valley, while GBM cells (red) remain on a flat GBM Plateau.

(B) Molecular mechanism model of the PIN1-p53 axis. IGF-1/Insulin signaling activates the PI3K/Akt pathway, which differentially regulates PIN1 and p53. In AD, PIN1 is downregulated and p53 is upregulated, driving cells towards the AD Valley. In GBM, PIN1 is overexpressed and p53 is suppressed, driving cells towards the GBM Plateau.

Mechanistic divergence: the PIN1-p53 axis and the metabolic paradox

Mechanistically, this divergence is driven by the opposite regulation of the PIN1-p53 axis (Figure 4B). IGF-1/Insulin signaling activates the PI3K/Akt pathway, which differentially

regulates PIN1 and p53. In AD, PIN1 is downregulated and p53 is upregulated, driving cells towards a senescent state. In GBM, PIN1 is overexpressed and p53 is suppressed, driving cells towards a proliferative state. This molecular divergence perfectly explains the transcriptomic profiles observed at the **Bifurcation Point** (Figure 3D, 3E), where AD cells attempted "self-rescue" via MDM2/PIN1 upregulation, whereas GBM cells exhibited a distinct pioneer gene signature (e.g., BBC3).

This molecular divergence further translates into an apparent metabolic paradox. While GBM cells reside in a low-energy GBM Plateau, they exhibit a highly proliferative phenotype. This paradox can be resolved by metabolic reprogramming, specifically the Warburg effect. Unlike AD neurons, which rely heavily on mitochondrial oxidative phosphorylation (OXPHOS) and are highly vulnerable to energy depletion, GBM cells shift their metabolism to aerobic glycolysis. Although this produces ATP less efficiently, it provides abundant biosynthetic precursors (such as nucleotides and lipids) to sustain rapid proliferation (Demetrius & Simon, 2013; Area et al., 2019; Dymova et al., 2021). Thus, the low-energy GBM Plateau represents a stable proliferative niche, whereas the deep AD Valley acts as an irreversible senescent trap for post-mitotic neurons (Long et al., 2025; Zhu et al., 2024). Topologically, the flat GBM Plateau reflects a highly stable proliferative niche where cells are no longer constrained by energy barriers, whereas the steep AD Valley acts as an irreversible "energy trap" where high plasticity is abruptly lost.

Cross-disease implications: shared risk factors but opposite outcomes

The opposite fate decisions observed in AD and GBM resonate with the epidemiological phenomenon of the inverse comorbidity between Alzheimer's disease and cancer. Epidemiological studies have consistently reported that AD patients have a decreased incidence of cancer, and vice versa (Zheng et al., 2025; Driver et al., 2012). Our findings provide a single-cell resolution mechanism for this long-observed clinical phenomenon: both diseases share common upstream risk factors (such as aging, metabolic dysregulation, and insulin resistance) (Caniceiro, et al., 2026; Zabłocka et al., 2021), yet they diverge at the PIN1-p53 decision node, driving cells toward opposite terminal states. This supports the hypothesis that shared aging-related pathways can drive divergent disease outcomes (Lanni et al., 2021). Consequently, therapeutic strategies targeting the PIN1-p53 axis must be carefully evaluated, as interventions designed to suppress PIN1 in cancer might inadvertently push neurons toward the AD Valley.

Theoretical elevation: from pioneer genes to energy landscape

Our findings provide empirical support for the concept of "transition state nucleation" and "pioneer genes" proposed in recent physical biology studies (Zhu et al., 2024). The transition state, defined mathematically as the point of maximum energy change rate ($|dE/dx|$), coincides exactly with the Bifurcation Point in our landscape. At this critical juncture, we identified MDM2 and PIN1 as pioneer gene candidates in AD, and BBC3 in GBM, which act as

“nucleation seeds” that bias the subsequent fate trajectory. Specifically, MDM2 and PIN1 upregulation in AD reflects an active “self-rescue” program through p53 inhibition (Barrio et al., 2021) and stabilization of pro-survival proteins (Liou et al., 2003), while BBC3 upregulation in GBM represents a transient apoptotic pressure that is ultimately evaded (Strasser et al., 2011; Yu et al., 2001).

These molecular events are physically manifested in the energy landscape. The concept of CellEnergy provides a quantitative framework for understanding these fate decisions, where high energy indicates a state of high plasticity (like the Health Peak) and low energy represents a stable, terminally differentiated or senescent state (like the AD Valley or GBM Plateau) (Long et al., 2026; Zhu et al., 2024). Our results reveal that AD cells maintain a high-energy Bifurcation State before abruptly collapsing into the deep AD Valley, consistent with a loss of plasticity during senescence (Demetrius & Simon, 2013). In contrast, GBM cells undergo a direct, smooth transition into a low-energy state driven by metabolic reprogramming—the Warburg effect—where aerobic glycolysis supports rapid proliferation despite reduced ATP yield (Dymova et al., 2021; Cortes Ballen et al., 2024). Thus, the low-energy GBM Plateau represents a stable proliferative niche, whereas the deep AD Valley acts as an irreversible senescent trap for post-mitotic neurons (Zhu et al., 2024). Together, these findings suggest that pioneer genes at the Bifurcation Point determine the direction of fate divergence, while CellEnergy quantifies the physical stability of the resulting terminal states.

Limitations

A potential limitation of our study is that the AD and GBM datasets originate from different studies, introducing a confounding factor between disease type and data source (AD from SEA-AD, GBM from GSE235676). However, by using sample_id (instead of dataset source) as the batch key in ComBat, we minimized technical noise at the individual level while preserving the biological divergence between diseases. The robustness of this approach is further supported by the downsampling validation (Supplementary Figure S2). Additionally, a limitation of this study is the unbalanced sample size between the AD (n=84) and GBM (n=18) cohorts. To mitigate this, we performed downsampling validation: even when randomly reducing the AD cohort to 18 donors, the deep AD Valley persisted, whereas the GBM Plateau remained flat. Future studies with larger GBM cohorts and experimental validation (e.g., lineage tracing or gene knockout) are warranted to further validate the generalizability of the HSL framework.

Finally, a limitation of this study is the cellular heterogeneity mismatch between the AD and GBM datasets. The AD dataset consists exclusively of L2/3 IT neurons, whereas the GBM dataset includes the bulk tumor tissue, comprising both malignant cells and diverse stromal/immune cells in the tumor microenvironment. Consequently, the divergence in PIN1-p53 bifurcation observed here may partially reflect differences in cellular composition rather than disease-specific programs. Future studies should perform cell-type-specific comparisons

(e.g., comparing malignant GBM cells directly to AD neurons) to further validate the specificity of the PIN1-p53 axis and to dissect the contribution of non-malignant cells in the GBM microenvironment.

Conclusion

In conclusion, our study establishes that the PIN1-p53 axis acts as a critical decision node at the Bifurcation Point, driving opposite fate decisions in AD and GBM through distinct energy landscape topologies. These findings bridge the gap between physical biology and clinical epidemiology, offering a unified framework to understand the inverse comorbidity between AD and cancer.

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