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Concept Paper

Artificial Intelligence for Mapping Cellular and Neural Circuit State Transitions in Human Disease: Toward Multiscale Disease Modeling

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Abstract

Understanding human disease requires frameworks that can connect molecular and cellular perturbations to systems-level dysfunction and clinical phenotype across time. Recent advances in single-cell and spatial profiling have revealed that cellular identity is dynamic and distributed across continuous state landscapes, while developments in electrophysiology, neuroimaging, and circuit analysis have underscored the importance of distributed neural dynamics in health and disease. In parallel, artificial intelligence (AI) has emerged as a powerful approach for analyzing high-dimensional, multimodal biomedical data and reconstructing biological relationships that are difficult to resolve using conventional methods alone. In this narrative review, we examine how AI-based methods can be used to map cellular and neural circuit state transitions in human disease and how these approaches may be integrated to support multiscale models of disease progression. We discuss current strategies for characterizing cellular state landscapes, including single-cell, spatial, trajectory-based, graph-based, and multimodal approaches, and we review AI-driven methods for decoding neural circuit dynamics from electrophysiological, imaging, and large-scale functional datasets. We further highlight bidirectional interactions linking cellular states, synaptic and microcircuit remodeling, circuit-level dysfunction, and behavioral or clinical outcomes, emphasizing disease progression as a sequence of coupled transitions across molecular, cellular, synaptic, and network scales. Finally, we discuss the implications of AI-integrated multiscale medicine for biomarker discovery, disease trajectory modeling, therapeutic window identification, and adaptive precision intervention, while addressing challenges related to causality, interpretability, validation, ethics, and clinical translation. Together, these developments support a shift from static classifications of disease toward dynamic, multiscale, and clinically relevant models that better reflect the evolving behavior of biological systems.

Keywords: artificial intelligence; cellular state transitions; neural circuit dynamics; multiscale disease modeling; single-cell omics; multimodal integration; disease trajectory modeling; precision medicine

1. Introduction

Understanding the mechanisms underlying human disease remains a central challenge in biomedical science. Traditional approaches have largely relied on reductionist and static models, in which biological systems are decomposed into discrete components such as genes, proteins, or cell types. While these frameworks have provided important mechanistic insights, they often do not fully capture the dynamic and multiscale nature of disease progression, which involves coordinated changes across molecular, cellular, tissue, and system-level processes [1,2]. Increasing evidence suggests that many diseases evolve through temporally structured transitions rather than fixed pathological states, indicating that static representations may be insufficient to explain disease initiation, progression, and therapeutic response.

Recent experimental and computational studies indicate that cellular identity is not fixed, but instead exists along continuous and context-dependent state spaces. Technologies such as single-cell

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transcriptomics, spatial transcriptomics, and lineage tracing have revealed that cells transition between functional states in response to developmental signals, environmental cues, and pathological perturbations [3–6]. These findings have led to a conceptual shift in which disease processes are increasingly interpreted as trajectories through cellular state space, rather than static deviations from a normal baseline. This perspective emphasizes the importance of identifying not only cellular compositions but also the dynamic pathways that connect cellular states over time.

In parallel, a growing body of work highlights the importance of neural circuits as fundamental units of brain function and dysfunction. Neural activity arises from coordinated interactions within distributed networks of neurons and glial cells, and disruptions at the circuit level have been associated with a range of neurological and psychiatric conditions, including neurodegenerative disorders, epilepsy, and mood disorders [7–10]. However, cellular and circuit-level processes are frequently investigated in isolation, limiting our ability to understand how molecular and cellular alterations propagate to system-level dysfunction. Bridging this gap remains a key challenge in contemporary neuroscience and systems medicine.

Artificial intelligence (AI) has emerged as a powerful set of computational approaches for analyzing complex, high-dimensional biological data. Machine learning and deep learning methods have demonstrated the ability to extract meaningful patterns from diverse datasets, including single-cell omics, spatial profiling, electrophysiological recordings, and neuroimaging data [11–14]. Importantly, these approaches enable the integration of heterogeneous data types and support the reconstruction of dynamic biological processes across multiple scales. As such, AI provides a potential framework for linking cellular state dynamics with higher-order functional organization.

Despite these advances, existing reviews have largely focused on either cellular-level analyses, such as single-cell omics and trajectory inference, or circuit-level investigations, including neural decoding and brain imaging, often treating these domains as distinct areas of study. There remains a relative lack of integrative frameworks that explicitly connect cellular state transitions with neural circuit dynamics, particularly in the context of AI-driven analysis [11,15–17]. This gap limits the development of comprehensive models capable of explaining how local cellular changes contribute to system-level dysfunction and clinical phenotypes.

In this narrative review, we aim to address this gap by synthesizing current advances in AI-driven cellular state mapping and neural circuit analysis within a unified conceptual framework. Specifically, we examine how AI-based methods can be used to map cellular and neural circuit state transitions in human disease, and how these approaches can be integrated to support multiscale models of disease progression. We discuss methodologies for modeling cellular state landscapes, approaches for decoding neural circuit dynamics, and emerging strategies for linking these levels across biological scales. By doing so, this review provides a conceptual foundation for future work aimed at developing integrative, AI-enabled models of human disease.

The importance of this review lies in its focus on connecting previously fragmented domains into a coherent framework. By integrating cellular and circuit-level perspectives and highlighting the role of AI as an enabling technology, this work outlines a path toward more comprehensive and predictive models of disease. Such models may ultimately support improved diagnostic strategies, more precise therapeutic interventions, and a deeper understanding of the dynamic processes that underlie human health and disease.

2. Cellular State Landscapes in Human Disease

2.1. Technologies Enabling Cellular State Profiling

Advances in single-cell and spatial profiling technologies have substantially refined our understanding of cellular organization in both healthy and diseased tissues. Techniques such as single-cell RNA sequencing (scRNA-seq) enable the measurement of gene expression at the resolution of individual cells, revealing extensive cellular heterogeneity and identifying previously unrecognized subpopulations within complex tissues [18–21]. These approaches have demonstrated

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that cellular populations previously considered homogeneous often consist of diverse functional states with distinct molecular profiles.

Complementary methods, including spatial transcriptomics and multiplexed imaging technologies, preserve the spatial context of gene expression, allowing the mapping of cellular states within intact tissue architectures [22–25]. This spatial information is particularly important in disease contexts, where cellular behavior is influenced by local microenvironments, gradients of signaling molecules, and cell–cell interactions. Together, these technologies provide a multidimensional view of tissue organization by integrating molecular identity with spatial and contextual information.

2.2. Cellular State Continuums and Landscape Frameworks

Traditional biological models have classified cells into discrete types defined by stable molecular markers. However, accumulating experimental evidence indicates that cellular identity is more accurately represented as a continuum of states, rather than fixed categories. Cells can transition between functional states in response to developmental programs, environmental signals, and pathological perturbations [26–29].

Lineage tracing and trajectory-based analyses further support this view, suggesting that cellular populations are organized along continuous developmental and functional pathways. These observations have led to the concept of cellular state landscapes, in which cells occupy positions within a high-dimensional space defined by transcriptional, epigenetic, and functional features.

Within this framework, biological processes such as differentiation, activation, and stress adaptation can be interpreted as movements through state space. This perspective allows for the identification of intermediate and transitional states that may not be captured by traditional classification systems but may play critical roles in disease initiation and progression.

2.3. Disease as a Perturbation of Cellular State Landscapes

In disease contexts, cellular state landscapes are often altered, reflecting shifts in population distributions and transitions between functional states. Rather than representing a single abnormal state, many diseases involve dynamic and progressive changes across multiple cellular states.

For example, tumor progression has been associated with transitions between proliferative, invasive, and therapy-resistant cellular states, with evidence suggesting that cancer cells can dynamically adapt to environmental pressures and therapeutic interventions [30–33]. Similarly, in inflammatory and immune-mediated conditions, immune cells transition between activation states that influence tissue damage and repair processes.

In neurological disorders, both neuronal and glial populations exhibit progressive changes in gene expression and functional properties that may precede overt pathology. Disease-associated cellular states, particularly among microglia and astrocytes, have been implicated in neurodegenerative processes and may contribute to circuit-level dysfunction [34–37]. These observations support the interpretation of disease as a trajectory through a perturbed cellular state landscape.

2.4. Dynamics, Quantification, and Transition Modeling

Cellular state transitions are often nonlinear and context-dependent, reflecting the influence of multiple interacting factors, including microenvironmental signals, immune interactions, metabolic conditions, and systemic inputs [28,38,39]. These dynamics can give rise to complex transition patterns, including branching trajectories, reversible states, and critical transition points.

Quantitatively, cellular states are often represented within high-dimensional feature spaces derived from gene expression or multimodal data. Dimensionality reduction techniques, such as principal component analysis and manifold learning approaches, are commonly used to project these data into lower-dimensional representations that preserve key structural relationships. Methods such

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as pseudotime analysis attempt to order cells along inferred trajectories, providing a temporal framework for studying state transitions.

In addition, probabilistic and graph-based models have been used to describe cellular state transitions as networks, where nodes represent states and edges represent transition probabilities. These approaches allow for the identification of stable states, transitional intermediates, and potential tipping points within cellular systems. However, it is important to recognize that these models are often based on snapshot data and rely on assumptions regarding temporal relationships, which may not fully capture underlying biological dynamics.

The progression from cellular heterogeneity to disease-perturbed cellular states is illustrated schematically in **Figure 1**.

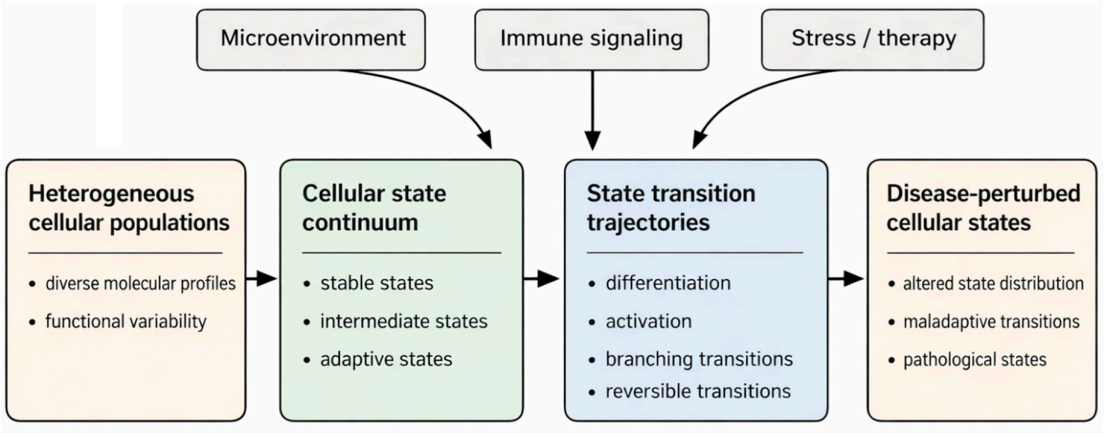

Figure 1. Cellular state landscapes and disease-related state transitions. Cellular populations can be understood as heterogeneous systems distributed across a continuum of functional states rather than fixed cell types. Cells move through transition trajectories that may include differentiation, activation, branching, and reversible changes. In disease, these trajectories become perturbed, resulting in altered state distributions and maladaptive cellular states. These transitions are shaped by contextual influences including the microenvironment, immune signaling, and stress-related or therapeutic perturbations.

2.5. Limitations and Challenges in Cellular State Mapping

Despite significant advances, several limitations remain in current approaches to cellular state mapping. Many single-cell and spatial profiling techniques capture static snapshots of dynamic biological processes, making it challenging to directly infer temporal relationships and causal mechanisms [6,40,41]. Trajectory inference methods, while informative, often rely on computational assumptions that may not reflect true biological progression.

Technical challenges, including batch effects, variability in data quality, and limitations in spatial resolution, can also affect the interpretation of results. Additionally, integrating multimodal datasets across platforms and scales remains a complex task, requiring robust computational frameworks and standardized methodologies.

Another important challenge lies in translating cellular state information into functional and clinical insights. While changes in gene expression can indicate shifts in cellular states, linking these changes to functional outcomes and disease phenotypes requires further experimental validation.

Addressing these limitations will be essential for advancing the field and for enabling more accurate and predictive models of disease based on cellular state landscapes.

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3. Artificial Intelligence for Cellular State Mapping

3.1. Computational Challenges in Cellular State Analysis

The analysis of cellular state landscapes presents substantial computational challenges due to the high dimensionality, sparsity, and heterogeneity of single-cell and spatial datasets. Modern profiling technologies generate measurements across thousands of molecular features per cell, often spanning large and diverse cellular populations. These datasets are further complicated by technical variability, batch effects, and incomplete sampling of biological states [42–44].

In addition, cellular state transitions are inherently dynamic, whereas most experimental measurements represent static snapshots. Reconstructing trajectories and inferring relationships between cellular states therefore requires computational approaches capable of extracting structure from high-dimensional, partially observed data. These challenges have motivated the increasing application of artificial intelligence (AI) and machine learning methods in the analysis of cellular systems.

3.2. Machine Learning for Representation and Feature Extraction

Machine learning approaches have been widely applied to identify latent structures within high-dimensional single-cell datasets. Dimensionality reduction techniques, such as principal component analysis and nonlinear manifold learning methods, are commonly used to project gene expression data into lower-dimensional spaces that preserve meaningful relationships between cells [45–47].

More recently, deep learning approaches, including autoencoders and variational autoencoders, have been employed to learn compact and denoised representations of cellular states. These models are capable of capturing nonlinear relationships within the data and have been used to improve clustering, visualization, and characterization of cellular populations [48–50].

Such representations facilitate the identification of cellular subpopulations, gradients of variation, and rare or transient states. However, the biological interpretability of learned features remains an ongoing challenge, as latent representations do not always correspond directly to well-defined molecular or functional variables.

3.3. Trajectory Inference and Modeling of State Transitions

A central objective in cellular state analysis is the reconstruction of developmental and disease-related trajectories. Trajectory inference algorithms aim to order cells along pseudotemporal axes, providing a computational framework for studying dynamic processes such as differentiation, activation, and disease progression [28,51–53].

These methods typically rely on assumptions of continuity between cellular states and use graph-based, probabilistic, or geometric approaches to model transitions. Because many datasets are cross-sectional, temporal relationships must be inferred indirectly, often through the structure of the data manifold.

While trajectory inference has provided valuable insights into cellular dynamics, several limitations should be considered. Pseudotime does not necessarily correspond to real biological time, and inferred trajectories may be sensitive to preprocessing steps, sampling density, and modeling assumptions. Consequently, trajectory-based findings are most robust when supported by complementary experimental approaches, such as lineage tracing or time-resolved measurements.

3.4. Graph-Based and Network Modeling Approaches

Graph-based methods have emerged as a powerful framework for modeling relationships between cellular states. In these approaches, cells are represented as nodes within a graph, and edges represent similarities or inferred transitions between states. This structure enables the analysis of both local and global relationships within cellular populations [54–57].

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Graph neural networks (GNNs) extend this framework by enabling the learning of representations that incorporate both node-level features and network topology. These models have been applied to tasks such as cell classification, trajectory inference, and the integration of spatial and molecular data.

Network-based approaches also support the analysis of interactions between cells and their microenvironments, facilitating the identification of signaling pathways and regulatory relationships that influence state transitions. However, the construction of biologically meaningful graphs remains nontrivial, as outcomes may depend on the choice of similarity metrics, neighborhood definitions, and graph structure.

3.5. Multimodal Integration and Inference of Cellular State Transitions

A major strength of contemporary AI-based approaches lies in their capacity to integrate multimodal datasets, including transcriptomic, epigenomic, proteomic, and spatial measurements, into unified analytical frameworks. Because cellular states are shaped by multiple layers of regulation, analyses based on a single modality may provide only partial representations of underlying biological processes. Integrative computational models therefore aim to construct joint representations of cellular identity that capture complementary information across data types [58–61].

In practice, multimodal integration involves several computational tasks, including cross-modal alignment of cells measured in different assays, joint embedding of heterogeneous datasets into shared latent spaces, imputation of missing modalities, and inference of regulatory relationships linking molecular layers [55,58,60,62]. Deep learning architectures, matrix factorization approaches, and graph-based integration frameworks have increasingly been applied to these problems, particularly in studies seeking to connect transcriptional states with chromatin accessibility, protein expression, or spatial organization.

These approaches are particularly relevant for studying cellular state transitions, as they can improve the resolution of intermediate states and help distinguish transient from more stable phenotypic changes. Multimodal models may also support the inference of lineage relationships, differentiation pathways, and activation programs by incorporating complementary regulatory information. In disease contexts, this can facilitate the identification of transition-associated programs that may not be apparent from transcriptomic data alone [38,59,62,63].

At the same time, multimodal integration remains technically and conceptually challenging. Different data modalities vary in scale, resolution, sparsity, and noise characteristics, and many datasets do not measure all features within the same cells. As a result, integrated models rely on assumptions regarding correspondence between modalities and require careful normalization and alignment strategies. These factors can influence downstream biological interpretation, and AI-derived inferences are most informative when supported by independent experimental validation. A summary of major technologies, data modalities, and AI approaches used to map cellular and circuit state transitions is provided in **Table 1**.

Table 1. Technologies and AI methods for mapping cellular and circuit state transitions.

Domain	Data modality	Method / AI approach	Primary analytical purpose	What it can reveal	Main limitations	References
Cellular state profiling	Single-cell RNA sequencing (scRNA-seq)	Dimensionality reduction, deep latent	Representation of cellular heterogeneity and state structure	Cellular subpopulations, rare states, gradients of cellular	Sparsity, batch effects, snapshot nature of	[64,65]

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		embedding, autoencoders, variational autoencoders		variation, latent state organization	data, limited direct temporal information	
Cellular state profiling	Single-cell ATAC-seq / epigenomic profiling	Multimodal integration, latent variable models, matrix factorization, deep generative models	Characterization of chromatin-defined cell states and regulatory landscapes	Regulatory programs, chromatin accessibility dynamics, epigenetic constraints on state transitions	Sparse signal, noisy data, integration challenges with transcriptomic modalities	[66,67]
Cellular state profiling	Single-cell proteomic / multimodal assays	Joint embedding, multimodal deep learning, probabilistic integration	Integration of protein and transcript features for refined cellular state definition	Concordance or divergence between transcriptional and protein states, functional phenotype refinement	Limited feature depth, cross-platform variability, incomplete multimodal correspondence	[68,69]
Spatial state mapping	Spatial transcriptomics	Graph-based integration, spatially aware deep learning, neighborhood modeling	Mapping cellular states within tissue architecture	Spatial organization of states, tissue niches, local cellular interactions, state–environment relationships	Resolution limits, mixed spots in some platforms, complex spatial normalization	[57,70]

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Spatial state mapping	Multiplexed imaging / spatial proteomics	Graph neural networks, image-based feature extraction, spatial clustering	Identification of state distributions and cell–cell interactions in situ	Tissue microenvironment structure, signaling neighborhoods, spatial coupling of phenotypes	Imaging noise, segmentation errors, limited multiplexing in some platforms	[54,71]
Trajectory reconstruction	Cross-sectional single-cell datasets	Trajectory inference, pseudotime modeling, diffusion-based methods, graph trajectory models	Reconstruction of developmental or disease-related state transitions	Differentiation pathways, branching trajectories, transitional intermediates, candidate progression routes	Pseudotime may not reflect true biological time, sensitivity to preprocessing and sampling density	[51,52]
Lineage and transition modeling	Lineage tracing + omics integration	Probabilistic lineage inference, graph modeling, multimodal temporal alignment	Reconstruction of lineage relationships and directional transitions	Cell fate relationships, clonal dynamics, validation of inferred trajectories	Experimental complexity, incomplete lineage capture, integration difficulty across modalities	[27,51]
Cellular interaction modeling	Single-cell + spatial neighborhood data	Graph neural networks, cell–cell interaction inference, network learning	Modeling relationships among cells and their microenvironments	Local signaling structure, interaction networks, microenvironmental regulation of state transitions	Dependency on graph construction choices, uncertainty in inferred interactions	[54,72]
Neural populatio	Calcium imaging	Supervised learning, deep	Decoding behavioral or cognitive	Population-level activity patterns,	Indirect measurement of	[73]

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n decoding		neural networks, temporal decoding models	variables from neural activity	behavioral state prediction, stimulus representation	activity, temporal resolution constraints, signal preprocessing dependencies	
Neural population decoding	Electrophysiological recordings	Supervised decoding, recurrent neural networks, state-space models	Mapping neural firing patterns to behavior, cognition, or circuit states	High-temporal-resolution representations of neural dynamics, transitions between functional states	Limited sampling of full networks, variability across sessions and individuals	[74,75]
Brain-wide functional analysis	fMRI	Machine learning classifiers, representation learning, connectivity modeling	Identification of large-scale functional signatures and disease-associated patterns	Functional connectivity structure, distributed network states, disease classification signals	Indirect hemodynamic signal, limited temporal resolution, susceptibility to confounds	[76,77]
Brain-wide functional analysis	EEG / MEG	Time-series classification, spectral feature learning, deep temporal models	Characterization of neural dynamics across time and disease states	Oscillatory signatures, transient network states, seizure-related or disease-related patterns	Noise sensitivity, source localization ambiguity, inter-subject variability	[78,79]
Circuit modeling	Neural population time series / multimodal neural data	Recurrent neural networks, dynamical systems models,	Simulation and prediction of circuit	Temporal state transitions, network stability, responses to	Limited biological interpretability, possible mismatch	[74,80]

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		latent state models	dynamics over time	perturbation, hidden dynamic structure	between model structure and circuit biology	
Closed-loop circuit analysis	Real-time neural recordings	Adaptive decoding, reinforcement learning, closed-loop control algorithms	Real-time detection of circuit states and adaptive intervention	Online state estimation, seizure detection, adaptive stimulation targets, responsive modulation	Generalizability, safety, interpretability, dependence on real-time signal quality	[81,82]
Multiscale integration	Single-cell, spatial, synaptic, circuit, and clinical datasets	Multimodal deep learning, shared latent space models, cross-modal alignment, integrative graph frameworks	Linking biological information across scales	Relationships between cellular state transitions, tissue organization, circuit dynamics, and clinical outcomes	Heterogeneous data structures, temporal misalignment, incomplete sampling, limited causal interpretability	[58,83]

Taken together, AI-based approaches have expanded the analytical capacity of cellular state research from descriptive profiling toward more integrative and predictive modeling. By enabling the reconstruction of cellular trajectories, the identification of latent structures, and the integration of multimodal data, these methods provide new insights into the organization and dynamics of cellular systems.

However, an important next step lies in extending these approaches beyond cellular-level analysis to incorporate higher-order functional organization. In particular, linking cellular state transitions to neural circuit dynamics represents a critical and relatively underexplored direction. Understanding how molecular and cellular changes propagate to network-level dysfunction is essential for developing comprehensive models of disease, especially in the context of neurological and psychiatric disorders. The following section therefore examines neural circuits as dynamic systems and considers how AI-based approaches can be applied to decode circuit-level organization and dysfunction.

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4. Neural Circuits as Dynamic Disease Networks

4.1. Organization and Functional Principles of Neural Circuits

In parallel with advances in cellular biology, substantial progress has been made in understanding the organization and function of neural circuits. Neural circuits consist of interconnected networks of neurons and glial cells, whose coordinated activity underlies perception, cognition, and behavior. Rather than acting as isolated units, individual neurons participate in distributed networks, where information is encoded through patterns of connectivity and activity across populations of cells [75,84,85].

Circuit function is shaped by multiple interacting factors, including synaptic connectivity, intrinsic cellular properties, neuromodulatory signaling, and interactions with non-neuronal cell types such as astrocytes and microglia. These components collectively determine how information is processed and transmitted within the nervous system. Importantly, neural circuits are dynamic and adaptable, exhibiting plasticity in response to experience, environmental changes, and physiological conditions.

4.2. Experimental Mapping of Circuit Structure and Dynamics

Technological developments have enabled increasingly detailed characterization of neural circuit structure and activity. Connectomic approaches, including high-resolution anatomical reconstruction and viral tracing methods, have provided insights into the organization of neural networks across scales [86–89]. These structural data define the connectivity patterns that constrain circuit function.

Functional measurements, including in vivo calcium imaging, electrophysiological recordings, and neuroimaging approaches such as functional MRI, allow the observation of neural activity across populations of cells and brain regions [75,84,90]. These studies indicate that neural circuits exhibit complex, time-dependent patterns of activity, often involving coordinated dynamics across distributed regions.

Together, structural and functional approaches provide complementary perspectives on neural circuits. However, integrating these data to obtain a unified understanding of circuit organization and dynamics remains a significant challenge, particularly in the context of large-scale datasets.

4.3. Neural Circuit Dysfunction and Disease Signatures

Disruptions in neural circuit organization and activity have been implicated in a wide range of neurological and psychiatric disorders. Many conditions are increasingly understood not solely as disorders of individual cell types, but as disturbances of network-level function that affect information processing across distributed systems.

For example, in Parkinson's disease, degeneration of dopaminergic neurons alters activity patterns within basal ganglia circuits, leading to motor dysfunction [91–93]. In mood disorders such as depression, dysregulation of limbic and prefrontal networks has been associated with altered emotional processing and cognitive control [94–96]. In epilepsy, abnormal synchronization of neuronal populations results in recurrent seizure activity, reflecting pathological network dynamics [97,98].

In neurodegenerative diseases, circuit dysfunction often emerges prior to widespread neuronal loss, suggesting that early alterations in network activity may contribute to disease progression [99–101]. These observations support the concept of circuit-level disease signatures, in which specific patterns of connectivity and activity are associated with distinct disease states.

4.4. Dynamic Circuit States, Cellular Interactions, and Challenges

Neural circuits can be understood as dynamic systems that transition between functional states over time. These circuit states are characterized by coordinated patterns of activity across neuronal

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populations and may reflect distinct modes of information processing. Transitions between such states can occur over multiple timescales and are influenced by both intrinsic cellular properties and external inputs [102,103].

Importantly, circuit dynamics are closely linked to underlying cellular and molecular processes. Changes in neuronal excitability, synaptic strength, and cellular stress responses can alter network activity, while glial cells—including astrocytes and microglia—actively modulate synaptic transmission, metabolic support, and inflammatory signaling [104–108]. These interactions highlight the bidirectional relationship between cellular states and circuit-level function.

Despite advances in experimental and analytical approaches, several challenges remain. Neural circuits operate across multiple spatial and temporal scales, and their behavior cannot be fully captured by any single measurement modality. Integrating structural connectivity, functional activity, and cellular-level information remains complex, and many datasets provide only partial views of circuit dynamics.

Furthermore, linking circuit-level observations to underlying biological mechanisms continues to be a major challenge. Understanding how changes in cellular states propagate to network dysfunction requires integrative frameworks capable of connecting molecular, cellular, and systems-level processes.

Taken together, these considerations suggest that neural circuits should be viewed as dynamic, multiscale systems that evolve over time and are shaped by interactions across biological levels. Characterizing circuit state transitions, and understanding how they relate to underlying cellular processes, remains essential for developing integrative models of disease. The complexity and scale of neural circuit data, however, present significant analytical challenges, particularly in capturing nonlinear and time-dependent relationships across distributed networks.

5. AI-Driven Neural Circuit Decoding

5.1. Decoding, Classification, and Prediction of Neural Activity

Artificial intelligence has been increasingly applied to the analysis of neural circuit data, particularly in tasks involving the decoding, classification, and prediction of neural activity patterns. Machine learning algorithms can process high-dimensional datasets generated by electrophysiological recordings, calcium imaging, and related techniques, enabling the identification of relationships between neural activity and behavioral or cognitive variables [73,109,110].

Decoding approaches aim to infer external or internal variables—such as sensory stimuli, motor outputs, or cognitive states—from patterns of neural activity. These methods are often implemented using supervised learning models trained on labeled datasets. In parallel, classification tasks involve distinguishing between discrete conditions, such as behavioral states or disease categories, based on neural data. Predictive modeling extends these approaches by attempting to forecast future neural states, behavioral outcomes, or transitions between functional states [110,111].

Recent work has employed deep learning architectures to capture complex and nonlinear relationships within neural population activity, improving performance in decoding and prediction tasks [73,111]. These approaches have contributed to a more detailed understanding of how information is represented across neural circuits. However, model performance is influenced by data quality, sampling density, and inter-individual variability, and high predictive accuracy does not necessarily imply mechanistic interpretability.

5.2. AI Analysis of Brain Imaging and Large-Scale Circuit Data

AI-based methods have been widely used to analyze large-scale neural datasets derived from brain imaging modalities such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). These techniques capture activity across distributed brain regions and generate complex, time-resolved datasets that require advanced computational approaches for analysis [112,113].

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Machine learning models have been applied to identify patterns of functional connectivity, characterize network organization, and classify disease states based on imaging data [113–115]. For example, AI approaches have been used to distinguish patient populations from healthy controls, identify biomarkers associated with neurological and psychiatric disorders, and stratify individuals based on disease subtypes or progression trajectories.

In addition to classification, predictive models have been developed to estimate disease progression, treatment response, and transitions between clinical states [112]. Unsupervised and representation learning methods have further enabled the identification of latent structures within imaging data, revealing patterns of network organization that may not be captured by conventional analyses.

Despite these advances, challenges remain in terms of reproducibility, generalizability across datasets, and sensitivity to confounding factors such as demographic variability and acquisition protocols. These limitations highlight the need for careful validation and standardization in AI-based analyses of large-scale neural data.

5.3. Brain–Machine Interfaces, Closed-Loop Systems, and Modeling of Circuit Dynamics

Artificial intelligence plays a central role in the development of brain–machine interfaces (BMIs), which aim to decode neural signals in real time and translate them into control outputs for external devices. Machine learning algorithms are used to map neural activity to motor commands or communication signals, enabling applications such as prosthetic control and assistive technologies for individuals with neurological impairments [82,116].

Beyond open-loop decoding, there is increasing interest in closed-loop systems, in which AI models continuously monitor neural activity and adapt system outputs in real time. Such approaches have been explored in contexts including adaptive neurostimulation, seizure detection and intervention, and modulation of pathological circuit activity [82,117]. These systems represent an important step toward dynamic interaction with neural circuits, where interventions are informed by ongoing circuit states.

AI methods are also increasingly used for the computational modeling of neural circuit dynamics. Approaches such as recurrent neural networks and dynamical systems models have been employed to simulate patterns of neural activity, characterize network stability, and predict responses to perturbations [118]. These models can provide insights into how circuit-level dynamics emerge from underlying interactions and may support hypothesis generation for experimental studies.

However, several challenges remain. Many AI models function as high-dimensional systems that are difficult to interpret, raising questions about their biological relevance. In addition, translating model outputs into mechanistic insights about neural circuits requires careful integration with experimental data and domain knowledge. Generalizability across individuals and conditions remains a further limitation, particularly in clinical applications. Addressing these challenges will be essential for advancing the use of AI in neural circuit research.

The relationship between cellular and circuit-level analytical streams, and their convergence within AI-enabled multiscale modeling, is illustrated schematically in Figure 2.

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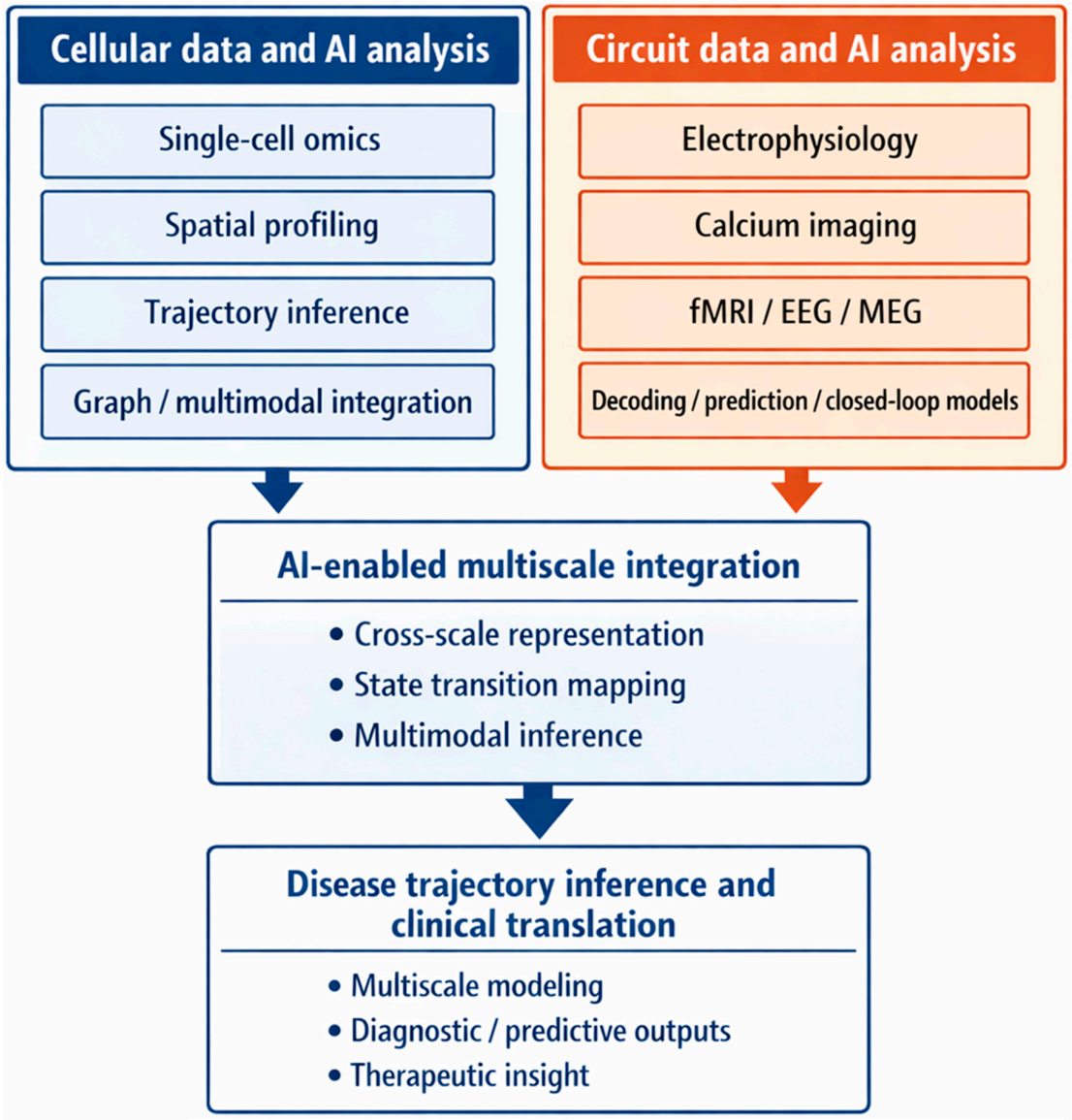

Figure 2. AI approaches for mapping cellular and circuit state transitions across biological scales. AI methods are increasingly used to analyze both cellular and circuit-level data across biological scales. On the cellular side, approaches including single-cell omics, spatial profiling, trajectory inference, and graph-based or multimodal integration support the characterization of cellular heterogeneity and state transitions. On the circuit side, electrophysiology, calcium imaging, and large-scale neuroimaging can be analyzed using AI-based decoding, prediction, and closed-loop models to characterize neural dynamics and dysfunction. These analytical streams can be integrated within AI-enabled multiscale frameworks to support disease trajectory inference and clinically relevant diagnostic, predictive, and therapeutic insights.

6. Linking Cellular States and Neural Circuits

6.1. Cellular–Circuit Interactions Across Scales

A major challenge in biomedical research is understanding how processes at the cellular level relate to circuit-level function across space and time. Increasing evidence suggests that these levels are closely interconnected and evolve through coupled dynamics, in which cellular states and circuit activity influence one another over time [119–121]. In this view, biological systems are not static but

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are characterized by continuous transitions, where changes at one level can propagate across scales and shape system-level behavior.

Neural activity has been shown to regulate stem-cell behavior, including proliferation, differentiation, and integration into existing circuits. Activity-dependent signaling mechanisms—mediated through neurotransmitter release, calcium dynamics, and downstream transcriptional programs—link circuit activity to cellular state transitions [122–126]. Conversely, changes in cellular states, including neuronal stress responses, alterations in excitability, and synaptic remodeling, can influence network dynamics and shift circuits between functional states.

Between the cellular and circuit levels, synapses and local microcircuits represent critical intermediate scales. Synaptic strength, plasticity mechanisms, and local connectivity patterns determine how signals are transmitted and transformed within networks. Changes at this mesoscopic level can amplify or buffer cellular perturbations, shaping how local alterations propagate into larger-scale circuit dynamics [120,125,127,128]. Thus, understanding disease-related processes requires considering not only individual cells and global circuits but also the intermediate structures that link them.

Glial cells play a central role in mediating these multiscale interactions. Astrocytes regulate synaptic transmission and metabolic support, while microglia contribute to immune surveillance, synaptic remodeling, and inflammatory signaling [104,121,129]. Transitions in glial states—such as reactive astrocytosis or microglial activation—can influence both synaptic function and network-level activity, thereby coupling cellular responses to circuit behavior.

In addition, neuroimmune signaling represents an important interface between cellular and circuit processes. Cytokines and other signaling molecules can modulate neuronal excitability and synaptic function, while neural activity can influence immune responses within the central nervous system [130,131]. These interactions contribute to a dynamic system in which cellular states, synaptic processes, and circuit activity are tightly interdependent and evolve over time.

6.2. Toward Integrative Multiscale Models of Disease

The bidirectional and temporally coupled interactions between cellular states and neural circuits highlight the need for integrative models that capture disease processes across multiple biological scales. Within such models, disease progression can be conceptualized as a sequence of linked transitions, in which cellular state changes, synaptic remodeling, and circuit-level dynamics co-evolve over time.

Alterations at the cellular level—such as changes in gene expression, metabolic state, or immune activation—can influence synaptic function and local microcircuit organization, which in turn affect large-scale network activity. These circuit-level changes can feed back to modulate cellular behavior, creating dynamic loops that shape disease trajectories [93,119,132,133]. This framework suggests that disease is not confined to a single level of organization but emerges from coupled state transitions across molecular, cellular, and network scales.

A schematic overview of coupled multiscale disease progression from cellular perturbation to circuit dysfunction and clinical phenotype is provided in **Figure 3**.

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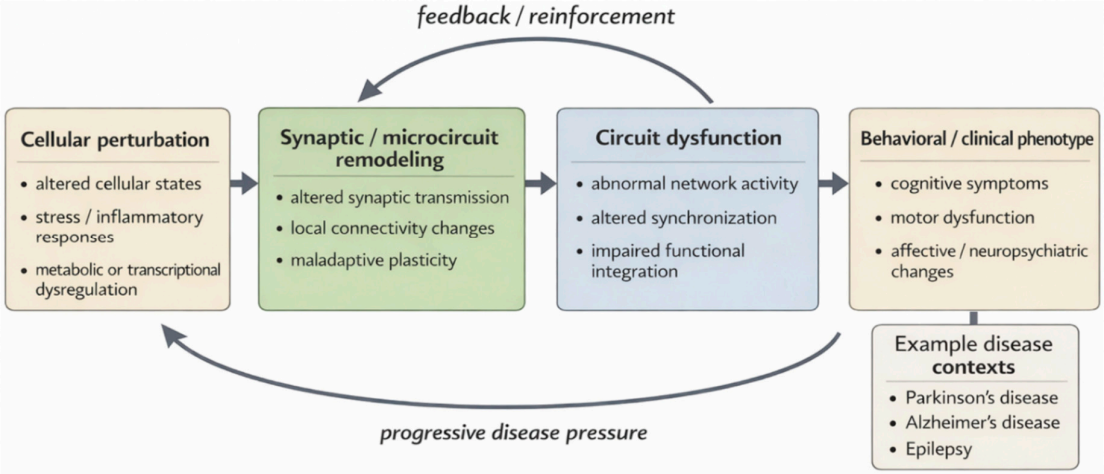

Figure 3. Coupled multiscale disease progression from cellular perturbation to circuit dysfunction and clinical phenotype. Disease progression can be understood as a multiscale process in which perturbations at the cellular level propagate through synaptic and microcircuit remodeling to produce circuit-level dysfunction and, ultimately, behavioral or clinical manifestations. Cellular perturbations may include altered cellular states, inflammatory responses, and metabolic or transcriptional dysregulation. These changes can reshape synaptic transmission and local connectivity, contributing to abnormal network activity, impaired synchronization, and disrupted circuit integration. Feedback relationships across scales may further reinforce disease progression over time. Representative disease contexts include Parkinson's disease, Alzheimer's disease, and epilepsy.

These multiscale interactions can be illustrated in specific disease contexts. In Parkinson's disease, degeneration of dopaminergic neurons is associated with shifts in cellular states, including altered metabolic and stress responses, which propagate to changes in synaptic transmission and basal ganglia circuit dynamics, ultimately leading to motor dysfunction. Similarly, in Alzheimer's disease, transitions in glial states—particularly microglial activation and astrocytic reactivity—are associated with synaptic alterations and progressive disruption of large-scale network activity, contributing to cognitive decline [92,93,134,135]. These examples highlight how cellular, synaptic, and circuit-level processes are interconnected and evolve together over the course of disease progression.

Such multiscale interactions are particularly relevant in conditions including neurodegenerative diseases, epilepsy, and neuroinflammatory disorders, where progressive changes in cellular states are closely linked to alterations in circuit dynamics [135–137]. In these contexts, early cellular perturbations may lead to subtle changes in synaptic and network activity that precede overt clinical symptoms, while later-stage disease may involve reinforcing feedback between cellular dysfunction and circuit instability.

Artificial intelligence provides a potential framework for integrating data across these scales and modeling their interactions. By combining information from single-cell profiling, spatial mapping, synaptic and circuit-level measurements, and longitudinal data, AI-based approaches may enable the reconstruction of disease trajectories that span multiple levels of biological organization [83,132,138,139]. Such models may support the identification of key transition points and the prediction of how perturbations at one scale influence outcomes at another. Representative examples of how cellular state changes propagate through synaptic and circuit-level dysfunction to clinical phenotypes across disease contexts are summarized in **Table 2**.

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Table 2. Cellular states, synaptic/microcircuit changes, circuit dysfunction, and clinical outcomes across disease contexts.

Disease context	Cellular state changes	Synaptic / microcircuit alterations	Circuit-level dysfunction	Behavioral / clinical consequence	Relevance to multiscale modeling	References
Parkinson's disease	Degeneration of dopaminergic neurons; altered neuronal stress-response and metabolic states; reactive astrocytic and microglial changes	Altered nigrostriatal and corticostriatal synaptic transmission; disturbed inhibitory–excitatory balance within basal ganglia microcircuits	Abnormal basal ganglia network activity, disrupted oscillatory dynamics, and impaired motor circuit coordination	Bradykinesia, rigidity, tremor, and progressive motor dysfunction	Illustrates how neuronal state changes propagate through synaptic and microcircuit disruption to large-scale motor circuit abnormalities and clinical symptoms	[134,140]
Alzheimer's disease	Neuronal stress and degeneration; microglial activation;	Synaptic loss, impaired synaptic plasticity, and disruption of local hippocamp	Progressive disruption of large-scale network connectivity and reduced	Memory impairment, cognitive decline, and progressive loss of executive function	Demonstrates how glial and neuronal state transitions interact with synaptic	[141,142]

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	astrocytic reactivity; altered inflammatory and homeostatic cellular states	al and cortical microcircuits	functional integration across memory-related circuits		degeneration and network disorganization during disease progression	
Epilepsy	Altered neuronal excitability states; reactive astrocytes and microglia; inflammatory and metabolic shifts in local tissue environments	Enhanced excitatory transmission, impaired inhibitory control, maladaptive synaptic remodeling, and destabilized local microcircuits	Pathological hypersynchrony, recurrent seizure-generating network states, and impaired circuit stability	Recurrent seizures, cognitive impairment, and variable neuropsychiatric symptoms	Highlights how cellular and inflammatory state changes can reduce network stability and drive recurrent pathological circuit transitions	[143,144]
Depression	Altered neuronal and glial functional states; stress-associated transcriptional changes;	Reduced synaptic plasticity, altered local connectivity within limbic and prefrontal microcircuits, and	Dysregulated limbic–prefrontal circuit activity and altered functional connectivity in mood-related networks	Persistent low mood, anhedonia, cognitive slowing, and affective dysregulation	Supports a model in which stress-related cellular changes scale upward to synaptic	[145,146]

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	impaired cellular resilience; neuroimmune dysregulation	disturbed neuromodulatory balance			and circuit dysfunction underlying behavioral symptoms	
Neuroinflammatory disorders	Immune cell activation; reactive microglial and astrocytic states; altered neuronal homeostasis under inflammatory conditions	Cytokine-driven modulation of synaptic transmission, impaired synaptic stability, and disrupted local circuit interactions	Abnormal network activity, reduced circuit adaptability, and impaired functional integration across affected regions	Cognitive impairment, sensory or motor dysfunction, fatigue, and neurobehavioral abnormalities	Emphasizes the role of immune–neural coupling in linking inflammatory cellular states to synaptic and circuit-level dysfunction	[147,148]
Traumatic brain injury / injury-related disorders	Neuronal stress responses; glial activation; altered repair-associated and inflamma	Synaptic disruption, loss of local connectivity, maladaptive plasticity, and unstable microcircui	Impaired network communication, abnormal circuit reconfiguration, and altered activity	Cognitive deficits, sensory–motor impairments, mood changes, and persistent neurologic	Illustrates how acute cellular injury responses can evolve into persistent multiscale	[149,150]

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	tory cellular programs	t reorganization	propagation	al dysfunction	dysfunction affecting circuit organization and behavior	
Neurodegenerative disorders broadly	Progressive neuronal vulnerability states; glial activation; metabolic and proteostatic dysregulation	Synaptic weakening or loss, impaired local plasticity, and deterioration of microcircuit integrity	Large-scale circuit disconnection, reduced adaptability, and abnormal functional dynamics	Cognitive, motor, and behavioral decline depending on the affected systems	Provides a general framework for understanding disease progression as coupled transitions across cellular, synaptic, and network scales	[77,151]

However, significant challenges remain. Multiscale datasets are heterogeneous and often difficult to align, and causal relationships between cellular, synaptic, and circuit-level processes are not always clearly defined. In addition, interpreting model outputs in biologically meaningful ways requires careful integration with experimental evidence. Addressing these challenges will be essential for advancing multiscale models of disease and for translating these approaches into clinical applications.

7. Toward AI-Integrated Multiscale Medicine

7.1. Multiscale Organization of Disease and the Need for Integration

The integration of cellular and circuit-level analyses points toward the development of multiscale models of disease, in which biological processes are understood across interconnected levels of organization. Increasing evidence suggests that disease does not arise from isolated perturbations at a single level, but rather from coordinated changes that propagate across molecular, cellular, tissue, and systems-level processes [152–155].

Within this framework, disease can be conceptualized as a process that unfolds across multiple interacting domains, including cellular state landscapes, tissue and microenvironment organization,

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neural circuit dynamics, and behavioral or clinical outcomes. These levels are not independent; instead, they are linked through dynamic interactions and feedback mechanisms [153,154,156,157]. Changes in cellular states may alter tissue organization and local signaling environments, which in turn influence circuit-level activity and ultimately affect behavior and clinical presentation.

Importantly, these multiscale interactions unfold over time, suggesting that disease may be more accurately described as a trajectory through interconnected state spaces rather than as a sequence of independent events. Capturing these temporal relationships across scales remains a key challenge for current models.

7.2. Artificial Intelligence as a Framework for Multiscale Integration

Artificial intelligence provides a computational framework for integrating heterogeneous datasets and identifying patterns that span multiple biological scales. Machine learning and deep learning approaches are particularly well suited to handling high-dimensional, multimodal data and have been increasingly applied to problems involving data integration, representation learning, and predictive modeling [156,158–160].

In the context of multiscale medicine, AI-based approaches can be used to combine information from single-cell and spatial profiling, synaptic and circuit-level measurements, and clinical datasets [156,157,159]. By constructing joint representations of these data, AI models may enable the identification of relationships between cellular state transitions, tissue organization, and circuit dynamics. Such models can support the inference of disease trajectories, linking early molecular and cellular changes to later functional and clinical outcomes.

AI methods may also facilitate the identification of multiscale biomarkers, defined as features that integrate information across levels of biological organization. These biomarkers have the potential to provide more robust indicators of disease state and progression compared to single-modality measures.

While these approaches are effective in identifying patterns and associations across scales, it is important to distinguish between predictive performance and causal understanding. Many AI models capture correlations within data without explicitly resolving the underlying biological mechanisms, highlighting the need for integration with experimental and mechanistic studies.

7.3. Implications for Diagnosis, Prediction, and Therapeutic Strategies

AI-integrated multiscale approaches have the potential to influence several areas of biomedical research and clinical practice. One important application lies in the development of more precise diagnostic tools based on multiscale signatures that reflect coordinated changes across cellular, circuit, and behavioral levels [157,161,162]. Such approaches may improve early detection and enable more accurate differentiation between disease subtypes.

Predictive modeling represents another promising direction. By integrating longitudinal data across multiple scales, AI-based models may enable the prediction of disease progression, including transitions between clinical states and responses to therapeutic interventions [156,158,161,163]. These models may provide insight into the timing and sequence of disease-related changes, supporting more informed and adaptive clinical decision-making.

In addition, multiscale frameworks may inform the development of targeted therapeutic strategies that act across different levels of biological organization. Interventions may be designed to modulate molecular pathways, cellular states, synaptic function, or circuit dynamics, either individually or in combination [164–167]. Understanding how these levels interact may improve the design of therapeutic approaches that account for feedback between scales.

A schematic translational roadmap for AI-integrated multiscale medicine is shown in **Figure 4**.

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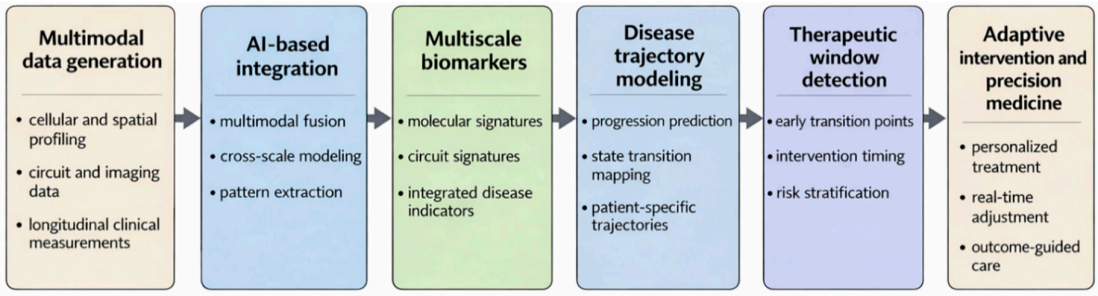

Figure 4. Translational roadmap for AI-integrated multiscale medicine. Future applications of AI-integrated multiscale medicine may be conceptualized as a translational pipeline beginning with multimodal data generation across cellular, circuit, and clinical domains. These data can be integrated using AI-based methods to derive multiscale biomarkers and model disease trajectories over time. Such models may support the identification of therapeutic windows and enable adaptive, personalized interventions informed by patient-specific disease dynamics. This flowchart summarizes a potential translational path from multiscale data integration to precision medicine.

Despite these opportunities, several challenges remain. Multiscale datasets are often heterogeneous, incomplete, and collected across different temporal and spatial resolutions, complicating their integration into unified models. Aligning cellular, circuit, and clinical data requires careful consideration of scale mismatches and temporal dynamics. In addition, translating computational findings into clinically actionable insights remains a significant hurdle, particularly given issues related to model interpretability, reproducibility, and validation across patient populations. Addressing these challenges will be essential for realizing the full potential of AI-integrated multiscale medicine.

8. Future Directions

Future developments in this field are likely to be driven by continued advances in both data generation and computational methodologies, enabling more comprehensive and temporally resolved representations of biological systems. Emerging technologies in single-cell and spatial profiling, high-resolution connectomics, and large-scale neural recording are expanding the ability to capture biological processes across multiple levels of organization. At the same time, improvements in artificial intelligence and computational modeling are providing new tools for integrating these datasets and extracting meaningful patterns from increasingly complex and high-dimensional data [161,168–170].

One promising direction involves the development of digital twins of biological systems, in which computational models are used to simulate individual disease trajectories based on patient-specific data. Such models may incorporate information across molecular, cellular, synaptic, circuit, and clinical levels, enabling the exploration of how perturbations at one scale influence outcomes at others. In parallel, AI-based approaches may support real-time analysis of neural activity, enabling adaptive and responsive interventions informed by ongoing circuit dynamics. A major future objective will be the ability to identify and model critical state transitions across these interconnected levels, including transition points that may represent opportunities for earlier or more effective therapeutic intervention [171–173].

The integration of longitudinal and multimodal datasets represents another critical area of progress. By combining data collected over time and across multiple modalities, it may become possible to construct more accurate models of disease progression that capture both temporal dynamics and multiscale interactions. Such approaches could support earlier detection of disease-related changes, improved prediction of clinical trajectories, and more precise identification of intervention windows. In this context, personalized modeling of disease may enable strategies

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tailored to individual patients, taking into account variability in genetic, cellular, and circuit-level factors [174–176].

Despite these opportunities, several challenges remain. Multiscale datasets are often heterogeneous, incomplete, and collected across different temporal and spatial resolutions, complicating their integration into unified models [177–179]. Data standardization and harmonization across platforms and institutions will be necessary to enable robust and reproducible analyses. Model validation is also critical, particularly in ensuring that computational predictions are reliable and generalizable across diverse patient populations [169,180–182]. Issues related to interpretability remain central, as complex AI models must be linked to biologically meaningful mechanisms to support scientific understanding and clinical trust. In addition, ethical considerations—including data privacy, algorithmic bias, and equitable access to emerging technologies—must be carefully addressed as these approaches move toward clinical implementation. Key challenges, emerging opportunities, and future priorities for AI-integrated multiscale medicine are summarized in **Table 3**.

Table 3. Challenges, opportunities, and future priorities for AI-integrated multiscale medicine.

Challenge	**Significance**	**Current limitations**	**Future opportunities**	**Potential clinical implications**	**References**
Data heterogeneity across modalities	Multiscale disease modeling depends on integrating molecular, cellular, circuit, imaging, and clinical datasets that differ substantially in format, scale, and resolution	Data are generated using different platforms, preprocessing pipelines, feature spaces, and quality standards, limiting comparability and joint analysis	Development of harmonized preprocessing workflows, cross-platform integration methods, and shared multimodal data standards	More robust biomarker discovery, improved generalizability of predictive models, and stronger cross-study reproducibility	[183]
Temporal misalignment across biological scales	Disease progression unfolds over time, but cellular, synaptic, circuit, and clinical data	Cross-sectional designs and uneven sampling make it difficult to	Longitudinal multimodal study designs, time-aware computational models, and	Earlier detection of disease transitions, better prediction of progression,	[158,184]

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	are often collected at different and nonaligned timepoints	reconstruct temporal relationships and state transitions across scales	improved temporal alignment strategies	and improved identification of therapeutic windows	
Limited causal inference	Predictive associations across scales are informative, but mechanistic understanding requires distinguishing correlation from causation	Many AI models infer statistical relationships from observational data without resolving directional or mechanistic dependencies	Integration of AI with perturbation experiments, causal inference frameworks, and mechanistically informed modeling	More reliable target identification and greater confidence in intervention strategies	[185,186]
Model interpretability	Scientific and clinical adoption depends on understanding how model outputs relate to biological mechanisms and disease processes	Complex deep learning models may achieve strong performance while remaining difficult to interpret biologically	Development of interpretable AI methods, biologically constrained architectures, and explanation tools linked to experimental validation	Improved clinician trust, clearer biological insight, and stronger translational potential	[187,188]
Incomplete multiscale coverage	Disease processes often span levels that are incompletely sampled, leaving	Many studies capture only one or two biological levels, limiting the	Expanded multimodal datasets spanning multiple scales,	More complete disease modeling and better linkage between mechanistic	[157,189]

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	important gaps between molecular, cellular, synaptic, circuit, and clinical domains	construction of integrated disease models	including synaptic, microcircuit, and longitudinal clinical measurements	biology and patient outcomes	
External validation and reproducibility	Models that perform well in one dataset or institution may not generalize to independent cohorts or real-world settings	Independent validation is often limited, and results may be sensitive to site-specific protocols, cohort composition, and analytic choices	Multi-center validation studies, benchmark datasets, transparent reporting practices, and reproducible computational pipelines	Greater reliability of AI tools in biomedical research and stronger readiness for clinical deployment	[190,191]
Generalizability across patient populations	Multiscale AI models must perform across diverse individuals, disease stages, and healthcare environments	Many models are trained on restricted cohorts that do not adequately represent biological, demographic, or clinical diversity	Inclusion of more diverse patient populations, stratified evaluation, and federated or distributed learning approaches	Fairer and more broadly applicable models for diagnosis, prognosis, and therapeutic guidance	[192,193]
Clinical workflow integration	Even accurate models have limited value if they do not align with clinical	Model outputs are often not presented in formats that	Development of clinician-facing decision-support	Greater adoption in practice, improved decision	[194,195]

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	workflows, decision timing, and interpretability needs	support routine clinical use or time-sensitive decision-making	systems, workflow-aware interfaces, and prospective implementation studies	support, and more effective patient management	
Standardization of multimodal data infrastructure	Scalable multiscale medicine requires interoperable data ecosystems across research and healthcare settings	Fragmented databases, inconsistent metadata, and lack of shared ontologies hinder integration, reuse, and comparison across studies	Shared repositories, interoperable metadata standards, and common data models across modalities and institutions	Faster model development, stronger collaboration, and improved reproducibility across settings	[196,197]
Ethical, legal, and privacy considerations	Multiscale AI models often rely on sensitive, longitudinal, and potentially identifiable datasets, raising governance and trust concerns	Risks include insufficient consent frameworks, privacy breaches, data misuse, and limited clarity around governance responsibilities	Privacy-preserving learning, transparent governance structures, and ethically informed data-sharing frameworks	More responsible implementation, stronger public trust, and safer clinical adoption	[198,199]

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Algorithmic bias and equity	Unequal representation in training data can produce systematic underperformance for certain populations	Bias may arise from cohort selection, measurement variability, social determinants of health, and healthcare system disparities	Bias auditing, fairness-aware modeling, representative datasets, and continuous monitoring after deployment	Reduced inequities in AI-supported diagnosis, prognosis, and treatment recommendations	[200,201]
Prospective clinical translation	Clinical value depends on demonstrating benefit in real-world patient care rather than only retrospective performance	Many AI models remain proof-of-concept and lack prospective evaluation in clinically relevant environments	Prospective clinical studies, adaptive evaluation frameworks, and integration with patient outcome analyses	Stronger evidence for clinical utility and improved translation from computational modeling to therapeutic benefit	[202,203]

Addressing these challenges will require coordinated efforts across experimental, computational, and clinical disciplines, as well as the development of shared infrastructures for data integration and model evaluation. Prospective validation in clinically relevant settings will be essential to determine whether these models can improve decision-making and patient outcomes in real-world practice. As these efforts progress, they may contribute to a shift toward more predictive, dynamic, and personalized approaches to understanding and treating human disease, grounded in the ability to map and modulate biological state transitions across scales.

Conclusions

Artificial intelligence is providing new tools for understanding the dynamic and multiscale nature of human disease. By enabling the integration of cellular state mapping and neural circuit analysis, AI-based approaches support a shift from static representations of pathology toward models that capture how disease emerges, evolves, and propagates across biological systems over time. In this context, disease can be conceptualized not as a fixed condition, but as a trajectory through interconnected cellular and circuit state spaces, shaped by continuous interactions across molecular, cellular, synaptic, and network levels.

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Advances in single-cell and spatial profiling have revealed the complexity and plasticity of cellular state landscapes, while developments in circuit-level recording and analysis have underscored the importance of distributed network dynamics in shaping function and dysfunction. Artificial intelligence provides a unifying analytical framework capable of integrating these domains, enabling the analysis of high-dimensional, multimodal datasets and supporting the reconstruction of disease-related transitions across scales. These approaches offer new insights into how localized cellular changes may influence circuit behavior, and how alterations in network dynamics may, in turn, modulate cellular processes.

This review proposes a conceptual framework in which cellular and neural circuit state transitions are viewed as interconnected components of disease progression across scales. Within this framework, disease is understood as a sequence of coupled transitions spanning multiple levels of organization, rather than as a collection of isolated abnormalities. Such a perspective may facilitate the identification of critical transition points, improve the prediction of disease trajectories, and inform the development of therapeutic strategies that account for interactions between cellular and circuit-level processes.

At the same time, it is important to recognize that current AI-based methods primarily capture patterns and associations within complex datasets, and that linking these findings to underlying biological mechanisms remains an ongoing challenge. Continued progress will depend on advances in data generation, computational modeling, and experimental validation, as well as on the development of frameworks capable of reliably integrating information across scales and over time. Addressing challenges related to data heterogeneity, model interpretability, and clinical translation will be essential for realizing the full potential of these approaches.

As these methodologies mature, they have the potential to redefine how disease is conceptualized, shifting from static classifications toward dynamic, multiscale models that capture the evolving behavior of biological systems.

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