Bridging mechanism and data: Hybrid modeling approaches for cancer and aging research

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Bridging mechanism and data: Hybrid modeling approaches for cancer and aging research

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Systems biology continues to face the challenge of uniting causal explanation and interpretability with the drive for greater predictive power and scalability. Mechanistic models based on ordinary differential equations (ODEs) provide interpretability and causal grounding in systems biology, yet they often suffer from parameter uncertainty, limited scalability, and computational costs. Machine learning (ML) approaches offer strong predictive performance by learning from high-dimensional, noisy biological data, but this data-driven strength comes at the cost of limited transparency and limited generalizability. Hybrid approaches that integrate mechanistic modeling with ML are emerging as a powerful new paradigm: data-driven modules reduce dimensionality and noise, encode multimodal and longitudinal data, and serve as surrogates for expensive mechanistic submodels, while mechanistic constraints guide ML toward biologically meaningful solutions. This synergy opens the door to uncertainty-aware, generalizable, and computationally tractable models with enhanced predictive power. Applications in cancer and aging research illustrate the promise of hybrid models in predicting treatment success, charting aging trajectories, and designing preventive strategies. Hybrid mechanistic–ML frameworks are not merely incremental improvements but represent a step towards personalized digital twins of biological systems, adaptive, interpretable, and predictive tools for precision medicine and geroscience.

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Introduction

Systems biology has long sought to integrate diverse biological processes into coherent explanatory frameworks, traditionally relying on mathematical and statistical modeling to capture cellular regulation, metabolic fluxes, and signaling dynamics. Early systems biology was built on a foundation of pathway diagrams, mass–balance equations, and rule-based or stochastic models that provided mechanistic insight but were limited by data availability and computational constraints [1–3]. As high-throughput technologies matured, the field turned increasingly to quantitative dynamical models, primarily ordinary differential equations (ODEs), to encode causal hypotheses and predict system behavior [4]. These mechanistic models offer interpretability and biological grounding, yet they often struggle with parameter uncertainty, latent variables, limited scalability, and high computational cost when extended to multi-omic or organism-level processes. With the growing dimensionality and heterogeneity of biological datasets, purely mechanistic approaches face increasing practical challenges, creating a natural opening for machine learning (ML) methods to handle noise, reduce dimensionality, and learn structure where mechanistic knowledge is incomplete or uncertain.

Over the past several years, ML has become increasingly popular in systems biology, offering powerful tools for extracting nonlinear patterns from high-dimensional, noisy data. Although ML provides strong predictive performance and can exploit modern multi-omics datasets, its data-driven strength comes at the cost of

transparency, limited generalizability, and challenges in biological interpretability.

These complementary strengths and weaknesses have prompted the development of modeling frameworks that connect mechanistic with ML methods. As these combined approaches continue to evolve, the terminology describing them has broadened. The term *hybrid modeling* has been used in various ways across the computational biology literature, including to describe multiscale models that combine different mathematical descriptions, such as continuous and discrete, or stochastic and deterministic frameworks. For the purpose of this review, we use *hybrid modeling* to refer specifically to the general class of approaches that combine mechanistic models with machine learning (ML) or artificial intelligence (AI) methods, without committing to any specific sub-paradigm. This encompasses modular combinations of mechanistic models and ML [5], *scientific machine learning* (SciML), which embeds differential-equation structure directly into differentiable ML architectures [6], and *mechanistic learning*, which emphasizes learning unknown mechanisms or dynamical laws from data under explicit biological constraints [7]. Our focus is on the conceptual and practical principles underlying this integration, regardless of whether the implementation aligns more closely with traditional hybrid models, SciML, or mechanistic learning frameworks.

In the sections that follow, we review recent methodological advances and discuss emerging applications in cancer and aging, outlining the opportunities and remaining challenges that will determine the impact of hybrid models in the life and clinical sciences.

Bridging data complexity and biological mechanism

Although the increased availability of high-throughput technologies has resulted in a surge of biological data available for ML purposes [8], several important challenges and limitations remain. Biological data are highly uncertain, due to inherent biological variability, measurement errors, and incomplete data, including missing values and data scarcity [9]. Furthermore, limitations in reproducibility and quality control remain [10]. Biological data is complex and highly dimensional, while the number of samples is often limited due to high costs or limited resources [11]. This issue, often referred to as *the curse of dimensionality*, reflects the sparsity of high-dimensional biological data, and ML algorithms tend to overfit such data [12], resulting in poor generalization. A promising approach towards a more holistic understanding of complex biological systems is multi-omics integration, which captures complementary molecular layers. However, this remains challenging due to difficulties in integrating and normalising data from different experimental modalities and omics platforms [13]. Furthermore, deep learning is promising for multi-omics analysis, but interpretability and explainability remain limited [14]. Finally, no single computational strategy is universally suitable, and specialized architectures are required to capture spatial, temporal, and multiscale dependencies in biological data.

Hybrid models offer a unified framework that capitalizes on the complementary strengths of mechanistic ODE models and ML, combining them in ways that can partially compensate for the limitations each paradigm faces when used in isolation (see Table 1). Mechanistic ODE models have the advantage of causal grounding of underlying biological processes in the model formulation. This enables the model to be interpretable, at least for moderately large models, and helps elucidate the underlying biological mechanisms it describes. ML models can detect nonlinear dependencies, reduce high-dimensional data to informative latent spaces, and approximate complex dynamics without fully specified equations. Although mechanistic models can be used to test hypotheses against data, distinguishing between alternative models becomes challenging when different mechanisms provide equally good fits [15]. For instance, in tumor growth modeling, different assumptions about nutrient-limited versus immune-mediated growth inhibition can produce indistinguishable fits to bulk tumor volume data. This model selection challenge is not unique to mechanistic approaches; in ML, different architectures, hyperparameter settings, or feature subsets can yield comparable predictive performance while capturing different underlying patterns. However, for mechanistic models the competing alternatives correspond to different causal hypotheses about biological mechanisms, so the inability to distinguish between them has direct implications for biological interpretation, whereas for ML models the ambiguity typically lies in the learned representation rather than in competing mechanistic explanations. Further, parameter estimation is often hampered by limited identifiability, arising both from structural non-identifiability, where different parameter combinations yield identical model outputs, and from practical non-identifiability, where parameters cannot be reliably estimated from sparse or noisy data, particularly in large models [16]. Disease-focused mechanistic models remain difficult to parameterize, constrained by pathway-specific assumptions, and limited in scalability as models are expanded to incorporate additional biological detail [17,18]. As these models grow in size alongside increasing data availability, computational demands rise substantially, leading to high solver costs and practical limits on model complexity [6,19,20]. At the same time, ML methods do not elucidate underlying biological mechanisms in the same way as mechanistic models [6]. Further, ML models have a tendency for overfitting and poor generalization to out-of-sample scenarios [21], which can be

Table 1

Relevant terms and their definitions.

Term	Definition
Mechanistic models	Mathematical models that explicitly encode biological processes and causal relationships, typically using differential equations or rule-based formulations grounded in known biophysical or biochemical mechanisms.
Machine learning (ML)	A class of data-driven computational methods that learn patterns, representations, or predictive functions directly from data, often excelling in high-dimensional and noisy settings but without explicit mechanistic interpretation.
Ordinary differential equation (ODE)	A mathematical equation describing the temporal evolution of system variables as deterministic functions of their current state, widely used to model biological dynamics such as signaling, metabolism, or population processes.
Hybrid modeling	Defined broadly as the general class of methods that combine machine learning methods with mechanistic models.
Scientific machine learning (SciML)	A class of methods that embed scientific structure, such as differential equations, conservation laws, or physical constraints, directly into machine learning architectures to improve generalization and interpretability.
Mechanistic learning	A modeling framework terminology that emphasizes learning unknown mechanisms or dynamical laws from data under explicit biological constraints.
Physics-Informed Neural Networks (PINNs)	Neural networks trained under constraints derived from known differential equations or physical laws, ensuring that learned solutions satisfy mechanistic consistency while fitting observational data.
Biologically informed neural networks (BINNs)	A type of neural architecture that incorporate biological prior knowledge, such as known pathways or interaction networks, by restricting connectivity or parameterization to biologically plausible structures.
Neural ODEs	An integration strategy that embeds learnable neural components directly into differential equation frameworks, allowing for the inference of unknown or uncertain dynamics from data while preserving known reaction structure.
ML surrogates	Machine learning models trained to approximate computationally expensive mechanistic simulations, providing fast and differentiable substitutes for numerical solvers or high-dimensional submodules, while dramatically reduces simulation cost while maintaining biological meaning.
Bayesian neural network (BNN)	A probabilistic neural network that represents model parameters as probability distributions rather than point estimates, enabling principled uncertainty quantification in predictions and inference.
Digital twin (personalized digital twin)	Computational models that integrate mechanistic and data-driven components to simulate and predict the behavior of an individual biological system, continuously updated using patient-specific data.
Multi-omics	The integrated analysis of multiple molecular data layers - such as genomics, transcriptomics, proteomics, metabolomics, and epigenomics—to capture biological systems across scales.
Stochastic differential equation (SDE)	A differential equation that includes stochastic terms to model random fluctuations and intrinsic variability, commonly used to represent noise and uncertainty in biological dynamics.
Probabilistic ODE	A framework in which the ordinary differential equation itself remains deterministic, but uncertainty is placed over its components, such as model parameters, functional forms, or numerical solutions, using probability distributions, enabling quantification of epistemic uncertainty distinct from the intrinsic stochasticity modeled by SDEs.
Latent variable	A quantity that influences the observed behavior of a biological system but is not directly measured, such as unobserved intermediate species, hidden cell states, or unmeasured regulatory interactions, and must therefore be inferred indirectly from available data.
Scalability	The capacity of a model to be expanded in biological detail, incorporating additional species, reactions, compartments, or pathways, while remaining computationally tractable for simulation, parameter estimation, and inference.
Hierarchical design	A modeling framework, such as hierarchical Bayesian models, that learns shared population−level parameters while simultaneously estimating individual-level deviations, allowing information from the full cohort to inform patient-specific predictions even when individual data are sparse.
Federated design	

(*continued on next page*)

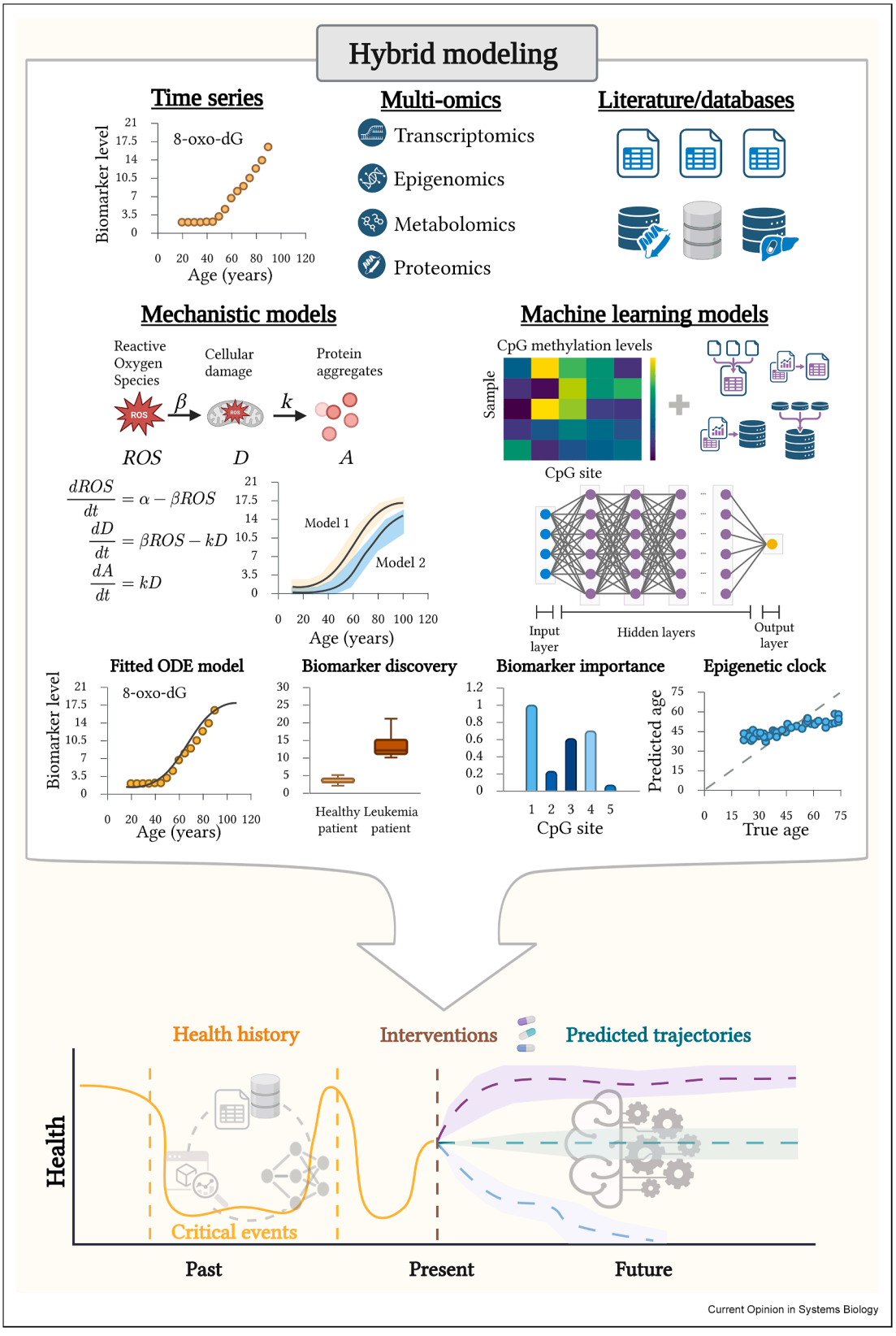
Table 1 (*continued*)

Term	Definition
	A distributed learning architecture where models are trained across multiple clinical sites without pooling raw patient data; each site trains on its local data and only model updates are shared, preserving privacy while enabling the model to learn from larger and more diverse populations.

especially problematic in a context with limited data. In addition, ML models typically cannot leverage the same tools for uncertainty quantification as classical statistical methods provide [9,22]. By combining the two paradigms, hybrid models can partially mitigate specific limitations of each. Mechanistic constraints serve as a form of inductive bias within the hybrid framework, restricting learned dynamics to biologically plausible regimes and thereby reducing the effective number of free parameters that must be estimated from data, which improves generalization from limited samples [21,23]. Mechanistic model components can also generate synthetic training data through simulation, augmenting sparse experimental datasets and enabling ML components to learn in data regimes that would otherwise be insufficient [24]. In Bayesian hybrid frameworks, prior knowledge about biological parameters is encoded as informative priors, enabling principled inference even when observations are scarce [25,26]. It is important to note, however, that these strategies alleviate rather than eliminate data limitations. Hybrid models do not resolve the fundamental challenge of data sparsity in biological research, but they provide principled ways to make more effective use of the data that are available.

A broad range of integration strategies have emerged to combine mechanistic structure with ML flexibility [18]. ML surrogates can replace computationally expensive mechanistic modules, dramatically reducing simulation cost while retaining biological meaning [24]. Neural ODEs and Universal Differential Equations (UDEs) [27], allow the modeler to retain known mechanistic terms in the differential equation while replacing only the unknown or uncertain components with neural network approximations. In this sense, the known reaction structure is explicitly encoded and preserved by construction, the neural network does not learn or replace it but rather fills in the gaps where mechanistic knowledge is missing. However, the learned components may not be unique, as multiple solutions can provide equally good fits to the data. Mechanistic priors can be incorporated into neural architectures through physics-informed neural networks (PINNs) [23], biologically informed neural networks (BINNs) [28], structural regularization, or constraint-based losses, ensuring biological and physical consistency. BINNs restrict connectivity to known gene interactions or signaling pathways, yielding interpretable predictions and enables identification of biologically relevant drivers [28,29], whereas PINNs constrain learning to biologically feasible manifolds and can improve modeling of longitudinal data by reducing the amount of patient information required [30]. PINNs and BINNs are sensitive to the formulation and weighting of multicomponent loss functions, specifically, the balance between the data-fitting term and the mechanistic constraint term. If the mechanistic penalty is weighted too heavily, the model may underfit the data; if too lightly, the learned solution may violate known biological constraints. This loss-balancing problem is non-trivial and often requires careful tuning or adaptive weighting strategies and remains an active area of research [31]. Hybrid inference methods increasingly rely on Bayesian neural networks and probabilistic ODEs to quantify uncertainty, which is essential in noisy and incomplete biological settings [25,26,32]. Complementing these approaches, dimensionality-reduction techniques, including autoencoders [33], variational latent-variable models [34,35], and reduced-order modeling [36], compress high-dimensional data into latent states that mechanistic models can evolve over time. Beyond these data-driven compression techniques, mathematically rigorous dimensionality reduction based on invariant manifolds offers a complementary perspective. Recent work on spectral submanifolds has demonstrated that exact, low-dimensional invariant structures can be identified in high-dimensional dynamical systems, yielding reduced-order models with formal guarantees [37]. In the hybrid modeling context, such techniques could provide principled reduced coordinates for large-scale ODE systems on which data-driven components operate, potentially offering better generalization than purely statistical compression. However, their application to noisy, partially observed biological systems remains largely unexplored and represents a promising direction for future work.

Fig. 1



Overview of data sources and modeling approaches that are integrated in hybrid modeling. Systems biology collects and uses data from various sources. Time series data captures dynamic behavior of a biological system, e.g. change in biomarker levels over time. Multi-omics data consist of

Together, these methodological advances provide a flexible and expanding toolkit for integrating mechanistic knowledge with data-driven components in a way that is computationally efficient, uncertainty-aware, and biologically interpretable. By uniting causal structure with the adaptability of modern ML, they offer a modeling paradigm capable of absorbing uncertainty, integrating multimodal data, and producing predictive, scalable, and mechanistically meaningful representations of complex biological systems.

Hybrid modeling approaches in cancer and aging

Cancer and aging are two of the most complex and consequential biological processes, each shaped by high-dimensional data and nonlinear mechanisms that no single modeling approach can capture. Their combination of rich datasets and incomplete causal understanding makes them ideal high-impact domains for hybrid ML—mechanistic models, especially as a strategy to overcome time-dependent gaps and latent variables. These two fields offer a significant opportunity for hybrid modeling to deliver transformative advances in prognosis, prevention, and personalized therapy.

Cancer is a highly complex and heterogeneous medical condition, shaped by intricate, non-linear mechanisms, many of which are still largely unknown. In addition, the disease is characterized by high intra- and intertumor heterogeneity and interpatient variability, which underlie strong differences in treatment response [38,39]. Owing to this, precision medicine is an essential but challenging medical advancement. Although ML, in combination with high-throughput techniques, has revolutionised cancer research, many predictive models lack biological grounding and offer limited interpretability. For instance, deep learning models for drug response prediction in cancer have achieved competitive accuracy but provided limited insight into the biological mechanisms underlying predicted sensitivities [40]. Notable efforts toward interpretable, biologically grounded analysis exist, such as IntOGen, which integrates multiple signals to identify cancer driver genes and pathways in a mechanistically interpretable manner [41], but achieving both strong predictive performance and full biological interpretability simultaneously remains an open challenge. Moreover, the heterogeneity of clinical oncology data, in combination with the inherent heterogeneity of oncological conditions, limits the generalizability of data-driven approaches, both across patient cohorts, where differences in demographics and treatment protocols hinder transferability, and across cancer types, where distinct molecular profiles prevent patterns from generalizing. Even within a single cancer type, intra-tumor heterogeneity and clonal evolution can erode the reliability of patient-level predictions over time. These shortcomings reinforce the need for hybrid model approaches in oncology [17] and recent work reflects a steady expansion of such methods in the field [7,18]. A biologically interpretable model, P-Net, was developed to stratify prostate cancer based on genomic profiles [42]. Unlike standard deep neural networks, P-Net achieves interpretability through its architecture: the network layers are structured to mirror the hierarchy of known biological pathways, with input nodes corresponding to genes, intermediate layers representing pathways and biological processes, and the output encoding clinical predictions. This design allows the contribution of each gene and pathway to the prediction to be traced through the network, enabling the identification of both established and novel genes that drive prostate cancer progression. This form of architecturally embedded interpretability differs from that offered by BINNs [28], which achieve interpretability by constraining network connectivity to known molecular interaction networks, thereby identifying which known interactions are most influential for a given prediction. Both approaches move beyond post-hoc explanation methods (such as SHAP values or attention maps) by building biological knowledge directly into the model structure, but they do so at different levels of biological organization: P-Net at the pathway hierarchy level, and BINNs at the molecular interaction level. Recently, a framework for latent neural stochastic differential equations (SDEs) has been developed for clinical time series, providing the expected treatment response and associated uncertainty. The model naturally handles irregular sampling, a

molecular data collected from different omes, to gain a holistic understanding of biological systems. Literature consists of published research, and biological databases contain certain data types, e.g. protein structures and genomic sequences. Hybrid models combines the strengths of mechanistic and machine learning modeling approaches. Mechanistic models provide causally grounded representations of biological processes and enable uncertainty quantification of parameters and predictions, as well as model selection between competing mechanistic hypotheses; the example illustrates an ODE describing cellular damage driven by reactive oxygen species (ROS), fitted to time-series data to recover biomarker trajectories. These trajectories may differ systematically between healthy individuals and cancer patients, reflecting disease-specific alterations in underlying biological mechanisms. Machine-learning models capture nonlinear patterns in high-dimensional data; shown here is a neural network predicting biological age from CpG methylation profiles, with influential CpG sites identified as key contributors to the prediction. Textual information from the literature and database resources can further inform model structure, parameterization, and biomarker selection. The aforementioned data types and modeling approaches are integrated into a unified framework, to enable biologically grounded personalized health predictions, with associated uncertainties, of intervention outcomes based on accumulated data. Created in BioRender. P, A. (2026) https://BioRender.com/erpfo5v.

common challenge with clinical oncology data, and captures variability in patients' responses to the same treatment, accounting for patient covariates [43]. As a further example, imaging-calibrated mechanistic models of tumor growth have been coupled with machine learning-based calibration to predict patient-specific responses to radiation therapy in glioblastoma, demonstrating how hybrid frameworks can directly inform treatment planning by integrating patient imaging data with biophysical models of tumor dynamics [44]. Similarly, mechanistic models of intracellular signaling have been combined with deep neural networks for drug response prediction in cancer cell lines, showing that the hybrid approach outperformed both purely mechanistic and purely data-driven models while providing insight into which signaling mechanisms mediate drug sensitivity [45].

Aging is a prototypical example of a multiscale, heterogeneous biological process in which molecular damage, altered gene regulation, mitochondrial dysfunction, immune remodeling, and organ-level functional decline interact over decades. These dynamics are nonlinear, adaptive, and strongly context-dependent, making aging an ideal yet demanding target for hybrid frameworks. By adaptive, we mean that aging involves not simply passive deterioration but active regulatory responses, such as compensatory stress-response upregulation, immune remodeling driven by chronic inflammation, or metabolic reprogramming following mitochondrial decline, whereby the system continuously adjusts its behavior rather than following a fixed trajectory. However, hybrid models are underused in the aging field, likely due to a lack of mechanistic understanding of long-term processes, limiting the availability of mechanistic models, resulting in only a few examples where hybrids between data-driven models and mechanistic constraints exist. In vascular and neurological aging, hybrid stroke-risk models have been embedded into digital twin frameworks by integrating multi-level cardiovascular and haemodynamic simulators that encode known physiology with ML-based risk classifiers trained on patient registry data. This hybrid architecture enables personalized risk prediction and allows clinicians to simulate the effect of specific interventions, such as blood pressure management or anticoagulation therapy, on individual stroke risk [46]. On the predictive side, a hybrid statistical—machine-learning system has been developed to assess dementia risk by integrating feature-selection pipelines with ensemble classifiers trained on longitudinal data from older adults, highlighting how structured clinical data can support early detection in aging populations [47]. Hybrid approaches are also slowly being utilized for biological-age estimation and aging biomarkers. For biological-age estimation, causality-enriched epigenetic clocks have decomposed CpG methylation sites into those reflecting biological damage and those reflecting adaptive responses, and this causal partitioning improved prediction of mortality and age-related disease risk compared to conventional epigenetic clocks that treat all methylation changes as equivalent aging markers [48].

Hybrid models offer significant opportunities in both oncology and aging by combining multimodal patient data with mechanistic insight to produce predictive, interpretable, and personalized representations of disease and physiological change (Fig. 1). In cancer, hybrid frameworks can integrate patient-specific omics, imaging, and clinical markers with mechanistic models of tumor growth and treatment response, enabling in-silico prediction of tumor evolution, therapy resistance, and optimal intervention strategies. These mechanistic components provide clinically meaningful interpretability while ML-driven modules allow adaptive updating of treatment plans as new patient data accumulate. A similar promise extends to aging, where hybrid models can fuse longitudinal omics, lifestyle factors, and clinical trajectories with mechanistic descriptions of key pathways, such as senescence, inflammation, or metabolic regulation, to simulate individual aging trajectories and evaluate potential interventions including caloric restriction, exercise, senolytics, or geroprotective drugs. Building scalable and reproducible hybrid frameworks, supported by efficient computational simulators, will further enable drug discovery for age-related diseases, the development of personalized aging clocks, and the in-silico exploration of trade-offs across aging pathways. Collectively, such approaches have the potential to shift oncology and geroscience from largely descriptive or retrospective analyses toward predictive, mechanistically grounded systems capable of guiding personalized prevention and treatment.

Roads ahead: toward generalizable, mechanistically grounded, and clinically useful hybrid models

Realizing the potential of hybrid modeling will rely on reconciling the need for maintaining generalizability while preserving mechanistic grounding, and enabling hybrid systems to support precision medicine and preventive strategies under real-world data constraints. Addressing the first objective will require approaches that more tightly couple mechanistic structure with data-driven components, such as embedding biochemical constraints, conservation laws, or structural priors directly into neural architectures, and using uncertainty-aware inference to prevent overconfident extrapolation beyond the training domain.

Advances in latent-variable modeling and operator learning may allow ML components to propose candidate mechanisms or interactions for experimental testing, strengthening the feedback loop between data-driven discovery and mechanistic refinement.

Variational autoencoders and related generative models can learn low-dimensional representations of complex biological data that, when coupled with mechanistic ODE models, may reveal previously unrecognized regulatory interactions. For example, scGen used a variational autoencoder to learn a latent space of single-cell transcriptomic states, highlighting coordinated gene programs that suggest candidate regulatory modules for mechanistic investigation [49]. Operator learning methods, such as DeepONet [50], learn mappings between function spaces, for instance, from initial conditions or parameters to solution trajectories, and could, in a hybrid context, identify which mechanistic structures best explain observed biological data, effectively proposing candidate mechanisms for experimental validation. Identifiability-aware model design will also be essential, ensuring that mechanistic cores are constrained to what the data can realistically support, while ML components fill structural gaps only where needed. This also raises the question of scalability: how large mechanistic models can we build if ML absorbs the data-driven burden, or whether fundamental computational bottlenecks will persist at larger scales.

The second objective, translating hybrid systems into precision medicine and preventive care, requires models that can operate reliably in clinical environments characterized by missing data, heterogeneous modalities, and limited longitudinal sampling. Personalized digital twins represent a promising direction [51–53], providing continuously updated hybrid models that assimilate omics, clinical markers, and physiologic data to simulate individual trajectories and evaluate intervention strategies. Hybrid frameworks that learn across populations yet make individualized predictions, for example, through hierarchical or federated designs, may help overcome data scarcity at the level of a single patient. For clinical adoption, hybrid models will need to produce transparent, uncertainty-aware outputs aligned with actionable clinical endpoints such as treatment optimization, risk stratification, or preventive strategy selection.

Hybrid models clearly offer advantages in predictive power and personalization, often extrapolating more reliably than black-box ML by constraining learning to plausible dynamical regimes [21,23,27,31,54]. Yet, unlocking their full potential will require methodological advances, including end-to-end uncertainty propagation [9,55,56], stiff-solver–robust training [20,57], identifiability-aware experimental design [58,59], biologically consistent multimodal fusion [60], and the development of modular modeling standards [61]. Ethical questions will also grow in importance [62]. Predictive aging trajectories, personalized treatment advice, and AI-driven decision support raise concerns about privacy, psychological impact, autonomy, and accountability, especially as hybrid models become more personalized and clinically influential.

Together, these challenges and opportunities define the frontier of hybrid modeling. Whether the field remains primarily exploratory or advances into a mature translational technology will depend on our ability to build hybrid systems that are not only mechanistically credible and data-efficient, but also clinically reliable, ethically grounded, and capable of supporting real-world decision-making in precision oncology, geroscience, and beyond.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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* of special interest
** of outstanding interest

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A comprehensive overview of uncertainty quantification (UQ) methodologies and their current limitations in biological and healthcare modelling, highlighting a critical gap in the systematic incorporation of uncertainty analyses into mechanistic and data-driven models. They show that, despite the increasing use of computational models for clinical decision support and digital twin applications, UQ remains underdeveloped and poorly integrated in biological contexts, limiting the credibility and translational potential of model-based predictions. By framing UQ as an essential component for reliable inference in noisy, heterogeneous biological systems and outlining methodological opportunities to address this, the review underscores the need for robust probabilistic frameworks in hybrid modelling.

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This paper highlights the importance of embedding biological knowledge directly into neural network architectures to overcome limitations of conventional machine learning. They argue that biologically informed neural networks (BINNs) improve interpretability and fidelity by constraining learned representations to reflect known pathways, interactions, or mechanistic structure. Such approaches help bridge the gap between predictive performance and causal understanding, making them particularly valuable in complex systems biology problems where purely data-driven models fall short. This perspective underscores the growing importance of hybrid methods that integrate domain knowledge with flexible learning.

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A systematic review of biologically informed deep learning models applied to cancer, highlighting key strategies for encoding complex oncology data and interpreting model predictions. The review categorizes approaches that integrate biological knowledge—such as pathways, interaction networks, or mechanistic constraints—into deep learning architectures to improve both performance and interpretability. It identifies recurring trends in how models incorporate prior knowledge and assesses their ability to produce biologically meaningful insights from multi-omics and clinical data. By synthesizing these developments, the authors delineate opportunities and challenges in applying biologically informed deep learning to cancer research.

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This paper introduces a reduced-order modelling framework based on shallow recurrent decoder networks that accurately reconstruct high-dimensional dynamical states from sparse and limited measurements. The approach achieves stable and efficient dimensionality reduction while retaining predictive accuracy across nonlinear and chaotic systems, outperforming conventional encoder–decoder architectures. These results demonstrate that lightweight recurrent decoders can serve as effective data-driven surrogates for complex dynamical systems, enabling substantial computational savings without sacrificing fidelity.

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The paper introduces causality-enriched epigenetic clocks, DamAge and AdaptAge, which separately track detrimental and adaptive methylation changes, respectively, and show that these clocks correlate with adverse outcomes and beneficial adaptations. These results provide a causally informed framework for ageing biomarkers that can improve the interpretation of biological age and the assessment of interventions.

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A comprehensive roadmap for developing human body digital twins, integrating advances in sensors, computational models, data assimilation, and personalized simulation. They highlight key challenges like including multimodal data integration, real-time updating, and scalability, as well as opportunities for clinical translation in disease monitoring, treatment planning, and preventive health. By synthesizing technological, computational, and ethical considerations, the article provides a strategic framework for advancing digital twin technologies toward impactful biomedical applications.

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This paper highlights the role of digital twins in P4 medicine, predictive, preventive, personalized, and participatory healthcare, emphasizing how integrated, multi-scale patient models can transform clinical practice. They discuss how digital twins can unify diverse data types with mechanistic and statistical modelling to support individualized diagnosis, treatment planning, and disease prevention. By outlining key conceptual foundations and implementation challenges, the paper positions digital twins as a unifying paradigm for modern, data-driven healthcare.

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This paper provides a review of the evolution of systems biology and systems medicine, tracing the shift from traditional mechanistic models toward frameworks that explicitly incorporate uncertainty quantification. They highlight advances in mathematical modelling, data integration, and probabilistic approaches that enable more robust inference and prediction in complex biological and clinical systems. By examining how uncertainty is characterised and propagated across modelling workflows, the authors underscore its importance for reliable decision support in biomedical engineering and translational research.

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