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Mechanisms and Machines: On the Continued Relevance of Mathematical Modeling in Biological Sciences

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Abstract

Mathematical modeling has long provided mechanistic insight and predictive power across biological scales, from the structure and dynamics of biomolecules to neural activity and even up to population dynamics and epidemics. With the rise of machine learning and large-scale data, its continued relevance is sometimes questioned. We argue that mathematical models remain indispensable: they support interpretability, causal insight, and principled generalization beyond what is commonly attainable with purely data-driven methods. At the same time, modern machine learning increasingly embeds mathematical structure, through geometric and graph-based learning, topological data analysis, and physics-informed networks, showing that progress in data-driven approaches often relies on theoretical foundations rather than replacing them.

What is "already known":

- Mathematical modeling remains indispensable in biology, providing causal insight, interpretability, and principled generalization beyond purely data-driven approaches.
- Modern biological systems exhibit multiscale, nonlinear, and higher-order structure that cannot be faithfully captured by pairwise or Euclidean models alone.
- Network, hypergraph, and simplicial-complex frameworks enable more accurate representations of biological interactions across molecular, cellular, and population scales.

What this article adds:

- Geometric and topological data analysis reveal robust global structure in high-dimensional biological data, including cycles, bottlenecks, and multiscale organization.
- Structure-aware machine learning integrates mechanism, geometry, and topology, yielding models that are more interpretable, data-efficient, and biologically meaningful.
- The future of biological inference lies in integration, where mechanistic models and machine learning form a unified mathematical framework rather than competing paradigms.

1. Introduction

Biological systems are characterized by multiscale organization, nonlinear interactions, and adaptive dynamics [1]. Understanding such complexity has always required more than observation: it demands conceptual frameworks capable of explaining how system-level behavior emerges from underlying mechanisms. Mathematical modeling has historically served this role. From enzyme kinetics and neural networks to population dynamics and evolutionary game theory, mechanistic models have allowed biologists to formalize hypotheses, derive predictions, and identify unifying principles that are not accessible through observation alone.

The landscape of biological research, however, is undergoing a profound shift. High-throughput sequencing, imaging, and multi-omics technologies now produce data at a scale that was unimaginable a generation ago. These advances have accelerated the rise of machine learning (ML) and deep learning (DL), which excel at identifying structure in high-dimensional and complex datasets. Their success has prompted a recurring question: in an AI-dominated era, what remains of the role of traditional mathematical modeling?

This question reflects a deeper tension between two modes of scientific inquiry. Mechanistic models provide causal understanding, interpretability, and principled generalizability, qualities essential for reasoning about biological systems beyond the available data. Data-driven models, by contrast, offer strong predictive power and the ability to directly exploit complex empirical patterns. Yet they often operate as black boxes, lacking the explanatory depth needed to reveal why a biological system behaves as it does. This manuscript argues that mathematical modeling remains essential, not despite the rise of AI, but because of it. Mechanistic models supply the structure, constraints, and theoretical insight necessary for meaningful biological interpretation, while modern ML provides powerful tools for parameter estimation, pattern discovery, and model refinement. Rather than competing paradigms, they are complementary components of a coherent scientific strategy. The future of biological inquiry lies in their integration, through theory-guided learning, physicsinformed networks, hybrid dynamical systems, and AI-accelerated mechanistic modeling. While biological research continues to advance through increasingly specialized problems and methods, there remains a pressing need to transcend this fragmentation through more abstract and integrative frameworks [2-4]. Unlike mathematics, which encompasses diverse subjects unified by a single methodological foundation: rigorous proof, biology addresses a single subject: life. Mathematical modeling offers a unifying language capable of integrating knowledge across scales, methodologies, and levels of biological organization, enabling principled connections between data, theory, and mechanism across the living world.

Guided by this integrative perspective, the manuscript is organized around complementary mathematical frameworks that connect biological mechanism, interaction, and data. We begin with From Observation to Mechanism: Early Mathematical Biology, which introduces the transition from descriptive accounts to mechanistic modeling, and continue with Foundations of Mechanistic Modeling in Biological Systems, surveying key dynamical systems approaches such as enzyme kinetics, population dynamics, electrophysiology and excitable media, epidemiological models, pattern formation, and reaction–diffusion and chemotaxis. The focus then shifts to Modeling Biological Interactions: Graphs and Beyond, addressing network-based and higher-order representations, followed by Mathematical Data Science, which examines the geometric and topological structure of biological data and the necessity of combining multiple analytical paradigms. These themes converge in Bridging Paradigms: StructureAware ML, highlighting how modern learning approaches can be enriched by mechanistic, geometric, and topological insights. We conclude by synthesizing these developments, emphasizing mathematical modeling as a unifying framework for integrating theory, data, and computation in contemporary biology.

2. From Observation to Mechanism: Early Mathematical Biology

Early biology was largely descriptive, centered on cataloguing organisms and documenting morphological variation. Darwin's observations of the Gal´apagos finches [5] exemplify how qualitative natural history provided the first empirical clues about adaptation and divergence. A decisive shift toward quantitative reasoning began with Gregor Mendel's

experiments on pea plants, which introduced probabilistic laws of inheritance and established a mathematical foundation for understanding genetic transmission. This development was reinforced by the early statistical analyses of heritable traits conducted by Galton and Pearson, marking a transition from purely qualitative description to mechanism-based inference [6]. Together, these advances laid the groundwork for formal mathematical frameworks in evolution and ecology, setting the stage for the dynamical and mechanistic modeling that would define modern mathematical biology.

3. Foundations of Mechanistic Modeling in Biological Systems

Mechanistic modeling has long served as a cornerstone of biological theory, providing a rigorous way to explain how complex behaviors emerge from underlying molecular, cellular, and ecological interactions. Unlike purely descriptive approaches, mechanistic models encode hypotheses about causal structure, regulatory logic, and dynamic rules. Their strength lies not only in prediction but also in clarifying organizing principles, identifying key variables, and revealing patterns that generalize across scales. Below, a set of classical examples illustrates how mathematical formalisms have shaped biological understanding for more than a century:

Enzyme Kinetics

The Michaelis–Menten formulation models catalytic reactions using ordinary differential equations (ODEs), clarifying how substrate concentration, reaction rates, and enzyme saturation interact to determine metabolic fluxes [7]. The model remains a cornerstone of biochemical kinetics because it links measurable parameters to the underlying molecular mechanisms.

Population Dynamics

Models such as the logistic equation and Lotka–Volterra systems capture growth, competition, and predator–prey interactions, revealing how feedback shapes ecological equilibria, stability, and oscillatory behavior [1]. They formalize ecological theory and provide powerful tools for analyzing stability and bifurcations in interacting populations.

Population Genetics

The Wright–Fisher model is a foundational stochastic framework in population genetics that represents genetic drift as a discrete-time Markov process in finite populations. By linking microscopic reproductive events to macro-scopic evolutionary patterns, the model established a rigorous foundation for analyzing neutrality, selection, mutation, and fixation, and continues to inform modern theoretical and computational approaches to evolutionary dynamics [8, 9].

Electrophysiology and Excitable media

The Hodgkin–Huxley model provided the first quantitative account of membrane excitability, describing how ionic conductances generate action potentials. Reduced models, such as the Fitz Hugh–Nagumo equations, capture the essential dynamics of excitability using a fast activator and slow recovery variable [10]. Remarkably, this mathematical structure unifies diverse biological phenomena: the same class of reaction–diffusion and excitable-media equations explains cardiac wave propagation, spiral-wave dynamics, self-organization in Dictyostelium discoideum aggregation [1, 11], and even pseudopodium formation during amoeboid locomotion [12]. The shared dynamical formulation demonstrates how seemingly disparate systems, from heartbeat generation to collective cell signaling, are governed by similar nonlinear mechanisms.

Epidemiological Models

Compartmental models such as the SIR and SEIR systems use ordinary differential equations to track **S**usceptible, **I**nfectious, and **R**ecovered populations [1]. These models illuminate threshold effects, herd immunity, and the role of contact structure in outbreak dynamics, providing critical tools for public health.

Pattern Formation and Turing-Type Models

Turing's reaction–diffusion framework showed how chemical interactions, governed by nonlinear coupled differential equations and diffusion, can spontaneously generate spatial patterns. [13]. Modern extensions explain pigmentation patterns, morphogen gradients, limb development, and a variety of biological self-organization phenomena, for example, see [14] and the references therein.

Chemotaxis Modeling

The Keller–Segel equations describe how cell populations migrate up chemical gradients through coupled reaction–diffusion and taxis terms [15, 16]. This framework explains aggregation, wave formation, and pattern dynamics in bacterial and amoeboid populations. Complementary modeling efforts at single-cell resolution extend this continuum picture [17-19]. These mechanistic descriptions illustrate how celllevel chemotactic responses give rise to populationlevel patterns in these models. Such frameworks are broadly applicable beyond the model organisms, informing studies of directed cell migration in cancer metastasis, wound healing, immune responses, and developmental processes [20].

Together, these examples showcase how mathematical structures, ODEs, PDEs, stochastic processes, and dynamical-systems theory, allow researchers to analyze equilibria, feedback loops, robustness, bifurcations, and emergent behavior far beyond what direct observation alone can provide.

A defining strength of mechanistic models is interpretability: each parameter corresponds to a measurable biological quantity, and each term encodes a specific hypothesis about interactions. This correspondence makes such models invaluable as explanatory scaffolds, tools for designing experiments, identifying missing mechanisms, and discerning which variables are essential. Even simplified models reveal relationships that remain valid across systems or contexts, contributing to their power and generalizability. However, mechanistic modeling also faces challenges. Biological systems involve highdimensional interactions, multiscale dynamics, and context-dependent behaviors. Necessary simplifications can obscure the heterogeneity and stochasticity revealed by modern high-resolution data. These limitations have motivated an increasing interest in integrating richer datasets, network representations, and computational tools into biological modeling. This growing intersection naturally leads to the next theme: how biological interactions can be represented beyond traditional equations, most notably through graph-based and network-oriented models, which provide a bridge between classical theory and modern data-driven approaches.

4. Modeling Biological Interactions: Graphs and Beyond

Representing biological interactions through directed and undirected graphs, a collection of vertices and (directed/undirected) edges between them, has a long and influential tradition across the life sciences. From protein–protein interaction networks to neural circuits, graphs have served as a foundational abstraction for describing how biological entities influence one another [21]. Early network models often adopted unweighted representations to simplify computation and analysis: nodes denote biological entities, edges encode the presence of an interaction, and edge directions specify the flow of influence. Protein– protein interaction networks capture the physical and functional cooperation of proteins [22]; gene regulatory networks (GRNs) and transcriptional regulatory networks (TRNs) encode directed regulatory control among genes and transcription factors [23] and metabolic networks reflect enzymatic reaction pathways and flux constraints [24]. Some networks also carry signs on their edges to encode positive or negative influences [25]. A prominent example arises in neural networks, where directed synaptic connections specify the direction of information flow, and the edge sign distinguishes excitatory from inhibitory interactions among neurons [26].

Although early network models were largely unweighted, modern datasets increasingly incorporate edge weights to quantify interaction strength, frequency, affinity, similarity, or other biologically meaningful features. The choice of weighting scheme depends strongly on the biological system, the data modality, and the experimental technology [27]. Contemporary high-throughput methods, including single-cell sequencing, multi-omics integration, largescale connectomics, and high-resolution imaging, now generate extremely large, high-dimensional, and often noisy datasets, containing millions of interactions and terabytes of spatial or temporal information, see for instance [28]. The complexity and multiscale organization of these datasets exceed the capabilities of traditional heuristic or descriptive tools, motivating the need for mathematically principled frameworks that can uncover robust patterns and mechanisms across diverse biological contexts. Crucially, the structure of a biological network and its topology, motifs and connectivity patterns, has a direct

and predictive relationship with its function, dynamics, robustness, and information-processing capability. This principle underlies much of modern systems biology, neuroscience, and network science [21, 29, 30].

At the same time, classical graph-based modeling imposes a pairwise view of biological interactions: edges represent binary relationships between two entities. While extremely successful, this abstraction captures only a subset of the underlying complexity. Many biological processes are intrinsically higherorder, involving coordinated interactions among multiple components. For example, in chemical and metabolic reactions, a set of educts jointly produces a set of products; such transformations cannot be faithfully represented by simple pairwise edges. Graph models obscure the true combinatorial structure of these processes and may misrepresent stoichiometry, conservation laws, or functional dependencies. These limitations have motivated the development of more expressive mathematical frameworks, such as hypergraphs, simplicial complexes, and higher-order networks, that more accurately capture the multi-way nature of biological interactions [31, 32]. A hypergraph generalizes the notion of a graph by allowing edges, called *hyperedges*, to connect any number of vertices; when exactly two vertices are involved, a hyperedge reduces to an ordinary edge. Hyperedges can be represented in different ways; a commonly used visualization is via (colored) regions that include the vertices they connect. For example, in Figure 1 (left), the hypergraph consists of four hyperedges: A is a singleton hyperedge containing the single vertex v_3; B connects the vertices v_1,v_4,v_5,v_6, and v_8; C connects v_1,v_2, and v_6; and D is a standard edge connecting the two vertices v_2 and v_7. Moreover, hypergraphs may be directed or undirected. For example, chemical reactions are naturally modeled by directed hyperedges that map a set of educts to a set of products. By contrast, simplicial complexes are higher-dimensional generalizations of graphs, consisting of collections of sets called *simplices* that are closed under taking subsets. A 0-simplex corresponds to a vertex, a 1-simplex to an edge together with its two vertices, a 2-simplex to a filled triangle together with its three edges and three vertices, and higher-dimensional simplices are defined analogously. For instance, in Figure 1 (right), we see a simplicial complex containing a 3-dimensional simplex colored in red, a 2-dimensional simplex colored in green, 12 edges (1-simplices), and 8 vertices (0- simplices). Simplicial complexes have increasingly been used to model diverse biological networks, spanning molecular interactions to neural connectivity, see for instance [33, 34].

Together, these differences motivate a central question in applied network science: when does incorporating higher-order interactions into data models provide genuine advantages over pairwise representations?

5.Mathematical Data Science

Shape of Data: From Linear Regression to Topological Data Analysis

Classical statistical tools such as linear regression offer some of the earliest and most influential frameworks for uncovering relationships in data. Linear regression can be viewed as a basic form of shape analysis: it characterizes how one variable depends on another by fitting the best straight line to the data, and naturally extends to multiple variables and higher-dimensional hyperplanes. Because of its simplicity, interpretability, and analytical power, linear regression has become a foundational tool in biology [35]. But what if the data do not align along a straight line, but instead trace a circle?

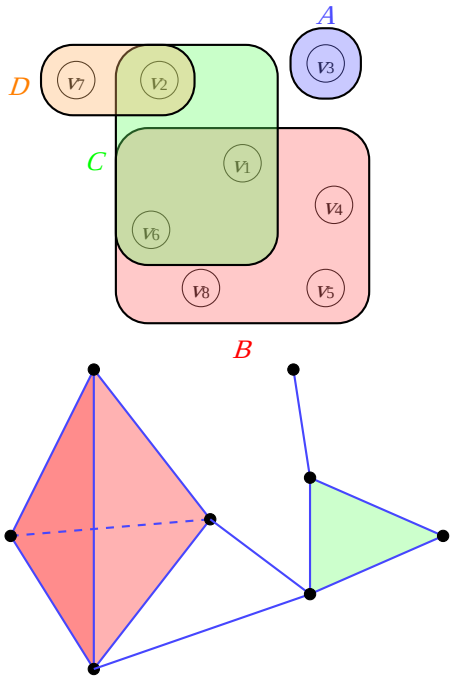

Figure 1. Comparison of a hypergraph (up) and a simplicial complex (down). The green hyperedge C connects three vertices but does not imply any pairwise edges among them. By contrast, the green 2-simplex encodes a three-way interaction together with all its faces, i.e., the three edges and three vertices.

Or what if the points lie scattered on the surface of a sphere? How can we systematically identify the underlying shape in such cases? Modern biological datasets rarely conform to the simple geometry of a line or hyperplane. Highdimensional measurements in areas such as single-cell transcriptomics, protein conformational ensembles, ecological networks, or neural activity often reveal curved, branched, or multi-scale structure [36, 37]. In these situations, the central question shifts from fitting a linear model to understanding the *shape of the data itself*. Topology is an area of mathematics that studies properties of shapes that remain invariant under continuous deformations, such as stretching or bending, but not tearing or gluing.

Topological data analysis (TDA) builds on these ideas and provides a mathematically rigorous framework for extracting robust and noise-stable features from high-dimensional and incomplete datasets [38-40]. It provides a principled way to compress data while preserving its topological features. At its core, TDA consists of two complementary tasks:

- **Visualization:** constructing *simplicial complexes* based on similarity or proximity relations among data points;
- **Analysis:** quantifying topological features via homology, in particular persistent homology, which tracks the evolution of connected components, loops, and higher-dimensional holes across scales.

For instance, consider a dataset represented by blue points, as shown in Figure 2. Our goal is to understand the "shape" of the data and its "persistent" features. One common approach is to place balls (colored in orange) around each data point and gradually increase their radius. Whenever two balls intersect, we draw an edge between the corresponding points; when three balls intersect, we fill in a triangle, and so on. In this way, we construct a simplicial complex that serves as a representation of the underlying shape of the data.

We then analyze the topology of this shape by asking, for example, how many holes it has in different dimensions. In topology, zero-dimensional holes correspond to connected components, one-dimensional holes correspond to cycles that cannot be continuously shrunk to a point, two-dimensional holes correspond to voids, and higher-dimensional holes are defined analogously.

In Figure 2, as the radius increases from α_1 to α_3, the number of connected components decreases from 11 to 2 and eventually to 1, while only at α_3 does a prominent cycle appear that passes through most of the points and cannot be contracted to a point.

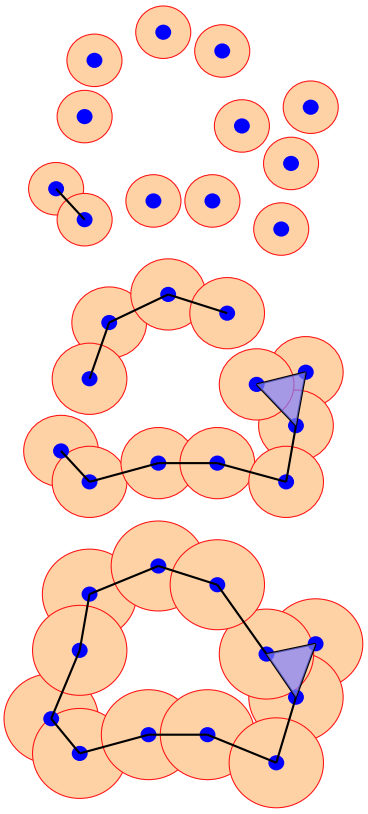

Figure 2. Simplicial structures generated by expanding local neighborhoods at increasing radii: (up) balls with radius $\alpha_1 > 0$, (middle) balls with radius $\alpha_2 > \alpha_1$, and (down) balls with radius $\alpha_3 > \alpha_2 > \alpha_1$.

A fundamental question, then, is how to choose the "right" radius to describe the shape of the data. The answer is that there is no single correct radius. Instead, one considers a range of radii and tracks how topological features appear and disappear. Features that persist over a long range of radii are interpreted as meaningful structural characteristics of the data. For a comprehensive overview of the theory and computation of persistent homology see [41].

Together, these methods generalize the simplest geometric assumption underlying linear regression, from a line or hyperplane to simplicial complexes and spaces with rich topological structure. In this way, TDA advances the idea of modeling biological phenomena by directly learning the shape of the data. Recent surveys show that TDA has become a powerful tool for uncovering organizational principles across multiple biological scales, particularly in contexts where data exhibit branching, multiscale, or heterogeneous structure. Applications of TDA in biology span a wide range of domains, characterizing protein

conformational and folding landscapes, quantifying spatial organization in tissues, and detecting structured patterns in molecular, cellular, and neural networks [42, 43]. While the success of these methods depends on factors such as sampling density, metric choice, and parameter selection, these studies collectively demonstrate that topological approaches often provide robustness to noise, interpretability, and the ability to detect global features that may be difficult to capture with classical statistical or geometric techniques.

5.2. From Clustering Coefficient to Geometric Data Analysis

One of the most fundamental tasks in biological network analysis and network science in general is to detect *clusters*, densely interconnected groups of nodes, and *bottlenecks*, sparse bridges that constrain flow between such groups, as shown in Figure 3. In biological networks, clusters often correspond to functional modules such as protein complexes in protein–protein interaction (PPI) networks, co-regulated gene sets in gene regulatory or co-expression networks, or metabolic pathways in metabolic networks. Bottlenecks, in turn, can appear as hub metabolites linking pathways, key regulatory genes connecting otherwise separate modules, or connector hubs between brain regions in neural networks, where their disruption may have disproportionate functional impact.

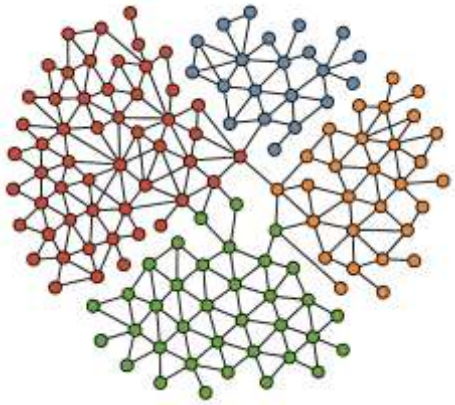

Figure 3: Community detection in a simple graph with four different communities

Traditionally, one of the simplest and most widely used tools for quantifying local network density is the *clustering coefficient*. In its local form, the clustering coefficient of a node measures the fraction of possible triangles among its neighbors that are actually present, providing a basic but powerful summary of how "cliquish" a node's neighborhood is. However, the existence of more complex cluster structures, such as overlapping, hierarchical, and dynamic communities, has motivated the development of more sophisticated community detection methods that go beyond purely local, node-based measures. Classical approaches such as the Girvan–Newman algorithm, modularity maximization, spectral methods, and stochastic block models are among the most widely used tools for community detection [44,45]. Which method performs best depends strongly on the network itself, and no universal approach works well across all network types.

Clusters appear across many kinds of biological data and often reveal meaningful functional organization. In protein–protein interaction networks communities represent functional groups of proteins working together. Gene co-expression networks exhibit regulatory modules, and metabolic networks often contain clusters corresponding to shared biochemical pathways. Community detection methods therefore help researchers uncover functional modules in protein interaction data, metabolic networks, and gene co-expression datasets, see for instance [46-48]. These studies support the view that clusters frequently reflect functional modules and contribute to the robustness of biological processes. These methods have also been used to uncover drug-gene and gene-disease modules in large bipartite networks [49]. Here, a bipartite graph is a graph whose vertices can be divided into two disjoint sets, with edges occurring only between vertices in different sets.

However, the analysis of today's large-scale, noisy, and heterogeneous datasets requires even more sophisticated methods, methods that can handle higher-order interactions, high dimensionality, and diverse data modalities. In recent years, fundamental tools from pure mathematics have become increasingly influential, often surpassing traditional approaches. Geometric methods, in particular, have enriched community detection and network analysis by importing ideas from differential geometry into the study of graphs and hypergraphs. By treating a network as a metric space and assigning curvature values to (hyper)edges, these approaches introduce measures on connections rather than solely on vertices, reflecting a conceptual shift from vertex-based to edgebased network descriptors. (Hyper)edges with positive curvature tend to lie within well-connected regions (dense communities), whereas strongly negative

curvature often highlights bottlenecks or intermodular bridges [50-52].

In biological networks, such geometric tools have been used to analyze robustness, differentiate cancer networks, and identify functional and structural communities as well as critical bottlenecks [53-58]. Together, these developments extend the classical clustering-coefficient perspective into a genuinely geometric data analysis of networks, in which clusters, bottlenecks, and functional modules are interpreted through curvature, flows, and higher-order structure. This geometric viewpoint provides a richer language for connecting network architecture with biological function.

5.3. None of These Methods Alone Is Enough

Modern datasets are no longer well described by linear or low-dimensional Euclidean models: they exhibit curvature, branching, cycles, and higher-order interactions. Topology and geometry together provide the mathematical language needed to capture this complexity. Topology uncovers global, robust patterns such as connectivity, loops, and multi-scale organizations, while geometry quantifies structure, distances, curvature, and dynamical flows. Alone, each view is incomplete; combined, they yield a unified framework that reveals both the shape and the mechanics of complex data. As data become increasingly nonlinear and relational, this topological–geometric perspective is not only essential for building interpretable and structurally faithful models, but also represents one of the most active and rapidly evolving areas of modern data science, deeply rooted in diverse branches of pure mathematics.

An important example comes from dimensionreduction methods: techniques that take highdimensional data, such as thousands of gene expression measurements, protein interaction profiles, or imaging pixels, and map them into a lowerdimensional 2-d or 3-d spaces while preserving what is deemed the “most important” structure. What counts as important varies across methods: some emphasize cluster separation, others preserve geodesic distances. Linear techniques such as Principal Component Analysis (PCA) project high-dimensional data onto orthogonal directions capturing maximal variance. As a result, they cannot fully capture the complexity of data lying on curved manifolds, whereas geometric approaches such as diffusion maps recover local nonlinear structure but may miss global loops or holes. Modern methods therefore increasingly integrate both geometric information and topological constraints to faithfully capture the underlying shape of complex datasets. For comparisons of such approaches in biological data, see [59, 60].

Developing an integrated viewpoint that connects mathematical areas traditionally considered separate is becoming ever more necessary. Interested readers can have a look at the related contributions of the second author in [61- 66].

6. Bridging Paradigms:

Structure-Aware Machine Learning

6.1. Machine Learning and Deep Learning in Modern Biological Inference

ML and DL have become central tools in biological data analysis, enabling the extraction of patterns from highdimensional, noisy, and heterogeneous datasets such as genomics, imaging, single-cell profiles, and molecular dynamics simulations. These methods excel in settings where explicit mechanistic laws are difficult to formulate and are widely used for tasks such as classification, representation learning, pattern discovery, and prediction. Their strength lies in their ability to approximate complex functions directly from data, uncover latent structure, and integrate diverse data modalities [67]. DL, a subfield of ML, employs multilayered neural networks to learn hierarchical representations of data, enabling models to approximate complex functions and decision rules. By leveraging large volumes of (often unstructured) data, DL systems iteratively refine their internal parameters to improve accuracy and adaptability. The overarching goal is to automatically extract increasingly abstract features from raw inputs, thereby reducing the need for manual feature engineering. With the expansion of computational resources and biological datasets, DL has become a major driver of modern computational biology and artificial intelligence, powering applications ranging from protein structure prediction to imagebased phenotyping. However, despite their impressive empirical performance, standard ML/DL models often lack explicit notions of biological mechanism, geometry, or topology, which can limit interpretability and hinder generalization across biological conditions. This recognition has motivated recent efforts to incorporate structural priors into learning architectures, paving the way for methods that blend mechanistic insight with data-driven flexibility.

6.2. Integrating Topology and Geometry into Deep Learning

Traditional ML assumes that data lies in Euclidean vector spaces and can be represented by feature vectors. However, many real-world datasets, such as molecular graphs, 3-d meshes, or complex social networks, do not naturally fit this paradigm. This has driven growing interest in incorporating geometric and topological structure into learning pipelines to more faithfully capture the intrinsic organization of such data. Beyond improving data representation, topology offers tools for understanding and shaping the behavior of deep models themselves, revealing how information flows through neural networks and guiding the design of architectures with meaningful structural constraints (see, for instance, the position paper [68] for an overview of developments and open problems, and [69] for recent progress on one of the key challenges in this direction). Topological methods have already shown practical impact, for example, persistent homology has powered leading results in the D3R Grand Challenges, a premier international competition in computer-aided drug design [70]. Topological DL therefore emerges not merely as an enhancement of existing tools, but as a principled framework for building learning systems that respect the inherent structure of the world.

Parallel to the rise of topological methods, geometric DL develops models that explicitly respect and exploit the geometric structure of non-Euclidean data. Many modern datasets consist of structured objects such as sets, graphs, matrices, manifolds, or data governed by symmetry groups, and geometric DL provides a unified framework for encoding these structures directly into neural architectures. Crucially, many prediction tasks come with built-in geometric constraints: for example, when predicting the structural properties of molecules, the output should not depend on the molecule's global rotation, meaning the model must be rotation-invariant. In such settings, it is essential that learning algorithms respect the fundamental geometric and symmetry properties of the data. By enforcing appropriate invariances, equivariances, and geometric constraints, geometric DL (see, for instance, [71]) aligns model computations with the underlying symmetries and local/global geometry of the data, often yielding architectures that are more data-efficient, more interpretable, and endowed with stronger inductive biases and theoretical guaranties. These methods have demonstrated substantial impact across the biological sciences, including molecular modeling [72], biochemistry [73], and biomedical imaging [74]. For a broader overview of topological and geometric DL, we refer the reader to [75, 76].

A well-known example of structure-aware DL is AlphaFold [77], whose developers were awarded the 2024 Nobel Prize in Chemistry for their contributions to protein structure prediction. By explicitly incorporating evolutionary information together with physical and geometric constraints into its architecture, AlphaFold addressed long-standing limitations of computational structure prediction, which had struggled to achieve near-atomic accuracy. Its geometry-aware design enabled reliable structure inference even in the absence of close homologous templates. More broadly, AlphaFold illustrates how ML models can substantially benefit from respecting the intrinsic structure of biological data. Alongside developments in topological and geometric DL, this example reinforces the central theme of this section: incorporating topology and geometry provides a principled pathway toward models capable of capturing the complexity of biological systems.

7. Conclusion

Mathematical modeling remains central to biological inquiry, even as data-driven approaches increasingly shape modern research. Rather than replacing mechanistic reasoning, ML expands its scope when guided by mathematical structure. This work has emphasized three core insights. First, mechanistic models provide indispensable causal understanding, interpretability, and principled generalization beyond observed data. Second, contemporary applications of ML in biology increasingly benefit from incorporating geometric, topological, or physical structure, rather than operating purely as unconstrained black-box predictors. Third, biological systems are inherently multiscale and higherorder, demanding representations that extend beyond pairwise interactions and classical Euclidean assumptions.

Taken together, these perspectives suggest that different modeling paradigms capture complementary aspects of biological systems. Meaningful biological understanding increasingly emerges from the principled integration of mechanistic models, network-based representations, geometric and topological data analysis, and structure-aware learning. Mathematical modeling thus continues to serve as a unifying

language connecting biological mechanism, data, and computation across scales.

8. Declarations

8.1. Acknowledgments

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8.2. *Authors' Contributions*

Both authors contributed equally to all aspects of this work, including conceptualization, methodology, formal analysis, investigation, visualization, writing (original draft and review & editing), supervision, and project administration.

8.3. *Declaration of Interest*

The authors declare no competing interests.

8.4. *Ethical Considerations*

All ethical principles were adhered in conducting and writing this article.

8.5. *Transparency of Data*

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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8.7. Using Artificial Intelligent chatbots Not Used.

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