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Comparative Study of Artificial Intelligence Methods in Biohybrid Robot Control

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Abstract: Biohybrid robots, which integrate living biological components such as muscle or neural tissues with artificial mechanical structures, represent a distinct class of systems capable of highly adaptive and biologically inspired movements. Compared to conventional robots, these platforms harness the intrinsic properties of living tissues, including self-repair, high power-to-weight ratios, and natural responsiveness to biochemical and physical stimuli. However, selecting optimal control strategies involves navigating significant trade-offs between stability, learning efficiency, and implementation complexity. Biological actuators are fundamentally constrained by non-linear dynamics and "physiological drift" caused by metabolic fluctuations and fatigue, necessitating controllers that can adapt in real-time to maintain functionality. This paper provides a systematic comparison of AI methods applied to biohybrid control over the past five years, including deep learning, reinforcement learning, hybrid intelligent control, and data-driven adaptive models. The study reveals that hybrid intelligent control currently offers the most practical and balanced solution by embedding AI adaptability within classical stability frameworks. By partitioning the controller into model-based and learning-based components, this paradigm maintains formal safety guarantees while exploiting AI for dynamic compensation. Nevertheless, its implementation remains constrained by high architectural complexity and the difficulty of formally validating the interaction between discrete AI logic and continuous biological feedback. Finally, future research directions such as metabolic-aware control and sustainable intelligent systems are discussed to provide theoretical guidance for advancing robust AI-driven biohybrid robotics.

Keywords: Biohybrid Robot; Artificial Intelligence; Reinforcement Learning; Deep Learning; Intelligent Control; Adaptive Mechanism

1. Introduction

Biohybrid robots, which integrate living biological components such as muscle or neural tissues with artificial mechanical structures, have emerged as a distinct class of systems capable of highly adaptive, flexible, and biologically inspired movements [1,2]. Compared with conventional robots driven purely by electric motors or soft artificial actuators, biohybrid robots can harness intrinsic properties of living tissues, including self-repair, high power-to-weight ratio, and natural responsiveness to biochemical and physical stimuli [3]. These features position biohybrid platforms as promising candidates for applications in soft robotics, micro-scale manipulation, targeted drug delivery, biomedical engineering, and environmental exploration [4].

Biohybrid robots present a unique paradigm by merging cellular intelligence with mechanical robustness.

However, before considering control mechanisms, one must define the core problem space: biological actuators are fundamentally constrained by nonlinear dynamics and history-dependent behaviors. Unlike conventional robotic systems driven by deterministic actuators such as electric motors or pneumatic valves, biohybrid control must manage the intrinsic complexity and inherent variability of living matter. Living tissues are not static; they undergo continuous physiological changes due to growth, remodeling, metabolic fluctuations, and progressive fatigue, necessitating controllers that can adapt in real-time to “drifting” plant dynamics [5].

Furthermore, while conventional actuators can often operate at high loads until mechanical failure, living tissues possess a narrow “health budget” where overstimulation or improper exploration can lead to irreversible cellular damage or tissue failure. Finally, the control of biohybrid systems is complicated by biochemical coupling, where stimuli trigger secondary cascades that influence the robot's state through internal biological variables that are often unobservable with standard sensors. Traditional control theory often fails because these living components undergo continuous physiological drift, which cannot be modeled by static equations. It is specifically to overcome this “biological uncertainty” that artificial intelligence integration becomes not just an enhancement, but a necessity for real-world functionality [6].

The rapid advancement of artificial intelligence (AI) has opened new opportunities to address these complexities in biohybrid robotics [7]. AI-based control methods—ranging from deep learning and reinforcement learning to hybrid intelligent control and data-driven adaptive schemes—have demonstrated the ability to improve motion accuracy, decision-making efficiency, and real-time adaptability in robotic systems more broadly [8]. When integrated with biohybrid platforms, these approaches can enable robots to learn optimal actuation patterns, compensate for tissue fatigue, adapt to changing environments, and exploit rich sensory feedback with minimal manual tuning [9]. At the same time, AI controllers differ markedly in terms of stability, computational cost, data requirements, safety properties, and suitability for specific biohybrid architectures and tasks [10].

Recent reviews on biohybrid robots have primarily focused on actuator materials, fabrication techniques, or high-level system architectures, with relatively limited emphasis on a systematic comparison of AI control strategies themselves [11]. Conversely, surveys of AI-driven control in robotics often treat biohybrid platforms only as niche examples within broader categories such as soft or biomimetic robots, without examining the unique constraints imposed by living tissues. This disconnect makes it difficult for researchers to select suitable AI methods for specific biohybrid configurations or to identify where new control algorithms are most urgently needed [12].

Given this gap, the aim of this review is to provide a comparative analysis of AI-based control strategies applied to biohybrid robots over roughly the past five years, with a primary focus on the control methodology dimension. The discussion is organized around four major categories: (i) deep learning-based control, (ii) reinforcement learning-based control, (iii) hybrid intelligent control that combines AI with conventional or bio-inspired schemes, and (iv) data-driven adaptive control [13]. For each category, representative applications are examined in terms of biological actuator type, system scale, sensing modalities, and control objectives, highlighting strengths, limitations, and suitable usage scenarios in aspects such as real-time actuation, motion precision, environmental adaptability, and multi-task capability. Because biohybrid robots operate at the intersection of fragile living tissues and complex environments, no single metric is sufficient to judge a control strategy; instead, practical design requires balancing accuracy, robustness, sample efficiency (a measure of how little data an AI needs to learn a task, vital for protecting fragile living tissues), and implementation complexity in an application specific manner [14].

Beyond summarizing existing work, this review also identifies open challenges and future directions at the intersection of AI and biohybrid control. Particular attention is given to issues of model generalization under biological variability, integration of predictive and feedback biomimetic control, sample-efficient and safe learning in fragile systems, and the design of cost-effective and sustainable intelligent biohybrid platforms. By providing a structured, control-centered perspective on the current landscape, the study aims to guide the selection and design of AI-driven strategies for biohybrid robots and to support their transition from laboratory prototypes toward robust, ethically grounded real-world applications [15].

2. Materials and Methods

This study adopts a systematic review and comparative analysis methodology to evaluate the application of artificial intelligence control strategies in biohybrid robotic systems. The methodological framework follows the core principles of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a rigorous and standardized approach to data selection and synthesis. The methodological framework was designed to ensure transparency, replicability, and objectivity in data selection, classification, and performance comparison. All selected research publications, datasets, and control frameworks were analyzed based on consistent evaluation metrics focusing on adaptability, stability, responsiveness, and implementation feasibility. The methodological steps described below outline the literature selection process, classification of AI control categories, comparative evaluation criteria, and data synthesis approach.

2.1. Literature Collection and Screening Process

Relevant literature published between 2020 and the present was collected from multiple academic databases, including Web of Science, Scopus, IEEE Xplore, PubMed, and Google Scholar. The search strategy utilized keyword combinations such as "biohybrid robot," "artificial intelligence control," "deep learning actuator control," "reinforcement learning robotic motion," and "hybrid intelligent bioactuation." The database search was conducted and finalized in December, 2025, to capture the most recent advancements.

Inclusion criteria were:

(1) The study involved a biohybrid robotic system incorporating living biological tissues or cells;
(2) Artificial intelligence techniques were applied for actuation, control, adaptation, or decision-making;
(3) Experimental results, simulation data, or performance analysis were provided.

Studies were excluded if they were review articles, conceptual papers without implementation evidence, or studies lacking sufficient detail on control methodology. The selection process followed a structured multi-stage screening approach: (1) Identification of potentially relevant records through systematic database searches; (2) Screening of titles and abstracts to exclude duplicates and studies not meeting the thematic scope; and (3) Eligibility assessment through a comprehensive full-text review. Ultimately, 80 high-quality research articles that strictly met all predefined inclusion criteria were selected for final analysis.

2.2. Classification of AI-Based Control Strategies

The selected studies were categorized into four primary AI control strategy groups to facilitate systematic comparison:

(1) **Deep Learning-Based Control**, which utilizes neural network-based models for pattern recognition and motion prediction.
(2) **Reinforcement Learning Control**, where actuation strategies are optimized through interaction-based learning.
(3) **Hybrid Intelligent Control**, which integrates biologically inspired or rule-based logic with AI-driven adaptation.
(4) **Data-Driven Adaptive Control**, based on statistical modeling and real-time feedback tuning.

Each study was further analyzed according to the biological actuator type (e.g., cardiomyocytes, skeletal muscle, neural tissue), robotic morphology (micro-scale swimmers, soft robotic actuators, macro-scale locomotion platforms), and control architecture. This classification ensured consistent terminology and enabled cross-comparison across studies with different experimental designs [16,17].

2.3. Comparative Evaluation Metrics

To evaluate the performance and feasibility of each AI control strategy, both quantitative and qualitative metrics were examined. Key indicators included motion precision, actuation response time, fatigue compensation capability, environmental adaptability, and stability under continuous operation. When available, numerical data such as trajectory error, energy efficiency, or actuation frequency stability were extracted. For studies lacking explicit performance data, experimental outcomes were compared based on reported behavioral trends, observed adaptability, and operational reliability noted by the original authors. To ensure the rigor of the synthesis, a quality assessment was performed for each study, focusing on the clarity of the experimental setup, the presence of control groups, and the technical validity of the AI implementation. This evaluation framework allowed the identification of behavior patterns and emergent performance differences among AI control approaches.

2.4. Data Synthesis and Interpretation

Following classification and metric-based evaluation, the results were synthesized to identify overarching advantages, limitations, and application suitability of each AI control category. Data synthesis was conducted by cross-tabulating biological actuator types with their corresponding AI architectures to identify performance trends relative to system scale and training data requirements. Interpretation emphasized factors influencing controller robustness, including tissue fatigue, nonlinear biomechanical dynamics, and external environmental disturbances. The synthesized findings were used to construct the comparative discussion and guide conclusions regarding future research needs, focusing on improving generalization, integrating predictive control with feedback regulation, and developing energy-efficient and economically viable biohybrid intelligent systems.

3. Deep Learning-Based Control and Its Applications in Biohybrid Robots

Deep learning-based control leverages multilayer neural network architectures to learn complex, nonlinear mappings between multimodal sensory inputs, biological actuator states, and robot motion outputs in biohybrid systems [18]. In robots powered by cardiomyocytes, skeletal muscle bundles, or optogenetically modulated muscle cells, deep models provide powerful tools for motion prediction, force estimation, and decoding of biological signals, thereby enabling more precise and adaptive closed-loop control than is achievable with purely analytical models [19].

3.1. Surrogate Modeling of Biohybrid Actuators

A central application of deep learning in biohybrid robotics is the construction of surrogate models (simplified mathematical 'stand-ins' that mimic complex biological behaviors to speed up calculations) that approximate the input–output behavior of living actuators under varying stimulation patterns and environmental conditions [20]. Convolutional neural networks and fully connected deep networks have been trained on experimental data to map electrical or optical stimulation parameters, tissue morphology, and environmental variables to resulting deformation, force output, or locomotion speed of muscle-based actuators [21]. Such surrogate models can be embedded within higher-level controllers, used to perform rapid design-space exploration, or integrated into model predictive control schemes to anticipate future actuator responses (**Figure 1**).

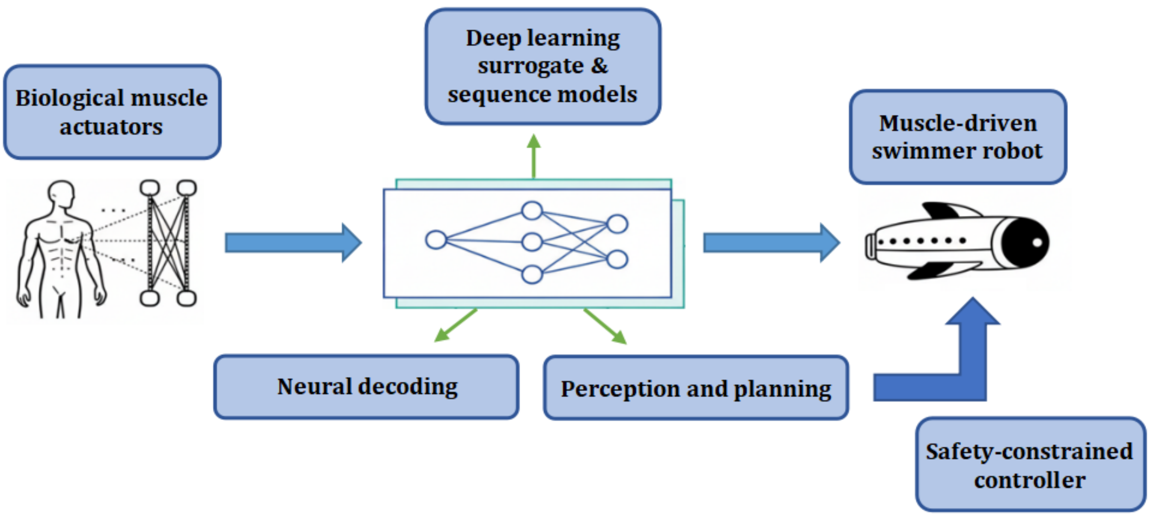

Figure 1. Conceptual schematic of deep learning-based control for muscle-driven biohybrid robots.

Figure 1 illustrates the integration of deep learning-based surrogate and sequence networks to model biological muscle actuators. These internal representations support both neural decoding and perception-planning modules to provide high-level commands. The architecture is exemplified by recent studies utilizing LSTM and GRU networks to capture temporal muscle dynamics, as well as vision-based perception modules that enable closed-loop locomotion in soft biohybrid bodies [22].

In cardiac-tissue-driven soft robots, recurrent architectures such as LSTM and GRU networks have been employed to capture the temporal evolution of contraction cycles and phase relationships between different muscle segments [23]. By learning history-dependent dynamics, these models can compensate for variability arising from growth, remodeling, or short-term fatigue, contributing to more stable rhythms and phase-aligned locomotion in swimmers or walkers driven by spontaneously beating tissues [24]. Similar strategies have been used to approximate the viscoelastic and time-varying properties of skeletal muscle sheets, enabling predictive adjustment of stimulation timing and duty cycles to maintain desired force profiles over extended operation [25].

3.2. Neural Decoding and Perception for Biohybrid Control

Deep learning has also been widely explored for decoding neural activity and complex sensory signals in biohybrid systems that incorporate neural tissues or advanced sensor arrays. For neural-actuated robots, convolutional and recurrent networks have been trained to interpret multi-electrode recordings or calcium imaging data and translate them into control commands or desired motion trajectories, effectively serving as learned interfaces between biological neural circuits and artificial bodies [26]. This capability opens the door to hybrid architectures where biological computation handles high-level decision-making or pattern generation, while deep learning-based decoders and controllers bridge the gap to mechanical actuation.

In addition, deep models have been used to process visual, tactile, and proprioceptive data from sensors integrated into or co-located with biohybrid actuators. For example, in muscle-based crawlers and swimmers, networks trained on video sequences or multimodal sensor streams can infer subtle deformations, contact interactions, and body postures, and use these estimates to predict future locomotion or detect impending failure modes [27]. Such perception modules can either feed into traditional controllers or be combined with learned control policies, forming the perception front-end of end-to-end intelligent control pipelines.

3.3. Sequence Prediction and Long-Horizon Planning

A more recent line of work explores deep sequence models, including encoder–decoder architectures and Transformer-based networks, for predicting long-range actuation sequences and planning complex behaviors in biohybrid robots [28]. These models can learn to generate temporally extended stimulation patterns that achieve desired trajectories or periodic gaits under varying fluid or substrate conditions, which is particularly relevant for micro-scale swimmers and soft-bodied locomotors operating in low-Reynolds-number environments. By capturing long-term dependencies and global temporal structure, sequence models facilitate anticipatory control rather than purely reactive responses, offering improvements in efficiency and robustness [29].

In addition to direct control, deep sequence models have been investigated as components within hierarchical architectures, where they provide high-level motion plans that are executed by lower-level controllers or even reinforcement learning agents. This separation of planning and execution can help mitigate some of the data and safety constraints inherent to working with living tissues, as long-horizon plans can be trained partly in simulation or on simplified models before being transferred to physical biohybrid systems.

3.4. Benefits and Limitations in Biohybrid Contexts

Despite their versatility, deep learning-based controllers face several challenges when applied to biohybrid robots. The requirement for large, high-quality datasets conflicts with the scarcity, noise, and high acquisition cost of experimental measurements from living tissues, often necessitating careful experimental design, data augmentation, or integration with simulation and biophysical modeling. Beyond these computational requirements, the physical interface for data acquisition presents a significant bottleneck for deep learning models. There are two primary modalities for signal collection: (i) exterior electrodes (placed on the skin or in the surrounding liquid) and (ii) integrated or implanted electrodes. While exterior electrodes are non-invasive and avoid immune rejection or the formation of a fibrous capsule, they are highly prone to noise and provide scarce data that is heavily dependent on the individual properties of the biological specimen. Conversely, interior electrodes offer high-fidelity data with minimal noise but introduce significant manufacturing complexity and the risk of encapsulation in biohybrid systems with an active immune response. These hardware constraints must be considered when designing robust

AI-driven perception modules, especially for systems operating in non-sterile, real-world conditions. Furthermore, biological variability and long-term drift in tissue properties mean that models can become outdated, requiring periodic retraining or online adaptation to maintain performance [30].

Another limitation is the difficulty of ensuring safety, interpretability, and formal guarantees when deep networks are deployed in closed-loop control of fragile, living actuators, particularly in medical or assistive scenarios [11,31]. These concerns have motivated the combination of deep learning with more structured approaches, such as model predictive control, Lyapunov-based designs (a mathematical framework used to guarantee that a robot stays stable even during unexpected disturbances), or constrained optimization layers, which can impose stability and safety constraints on learned policies. As a result, deep learning in biohybrid robotics is increasingly viewed not as a standalone solution, but as a powerful component within hybrid architectures that integrate data-driven modeling, classical control theory, and domain knowledge about tissue mechanics and physiology [32].

3.5. Comparative Synthesis and Gaps in Deep Learning Control

Comparing the reviewed deep learning (DL) implementations reveals a clear thematic tension between predictive fidelity and model interpretability. While CNN and RNN-based architectures excel at high-fidelity surrogate modeling—achieving force prediction accuracies far exceeding traditional Hill-type models—they remain largely "black-box" systems [30].

Strengths: DL models are uniquely capable of capturing the complex, history-dependent dynamics of biological actuators without requiring explicit physical equations.

Weaknesses: Most DL approaches lack formal stability guarantees. Their performance is heavily tethered to the quality of training data, making them susceptible to failure when biological specimens undergo significant physiological drift.

Research Gap: There is a critical lack of "physics-informed" neural networks that incorporate biomechanical constraints directly into the learning architecture. Future studies must focus on models that maintain physiological plausibility even when experimental data is noisy or sparse.

4. Reinforcement Learning Control and Its Applications in Biohybrid Robots

Reinforcement learning (RL) enables biohybrid robots to autonomously optimize control strategies through trial-and-error interaction with their environment, guided by task-specific reward signals [33]. This framework is particularly attractive for biohybrid systems because biological tissues exhibit nonlinear, history-dependent, and often poorly modeled responses, including fatigue and morphological adaptation, under repeated stimulation conditions, making traditional model-based controllers difficult to design and tune.

4.1. Model-Free RL for Muscle- and Tissue-Driven Robots

In muscle-driven biohybrid walkers and swimmers, model-free RL algorithms such as proximal policy optimization (PPO), soft actor–critic (SAC), and deep deterministic policy gradient (DDPG) have been used to learn stimulation policies that directly map observed states to control actions [34]. Typical actions include adjusting the amplitude, frequency, phase, or spatial pattern of electrical or optical stimuli delivered to muscle bundles or sheets, with rewards designed to maximize forward displacement, locomotion speed, trajectory tracking accuracy, or energy efficiency. By iteratively exploring and updating policies, RL agents can discover non-intuitive actuation patterns that exploit the intrinsic dynamics of the tissue and the surrounding medium.

RL has also been applied to illumination-controlled optogenetic muscle robots, where agents learn spatiotemporal light stimulation patterns that elicit efficient bending, crawling, or swimming motions. In these systems, the complex coupling between light distribution, muscle activation, and resulting deformation is difficult to capture analytically, making RL an effective tool for discovering robust control strategies that generalize across moderate variations in tissue properties and environmental conditions [35].

4.2. RL in Micro-Scale and Distributed Biohybrid Systems

Micro-scale biohybrid swimmers operating in low-Reynolds-number regimes are especially well suited to RL-based control because they experience strong environmental uncertainty, including Brownian motion, fluctuating fluid properties, and complex boundary interactions [36]. RL controllers can be trained—often initially in simulation—to adapt propulsion direction and actuation timing in response to noisy observations, enabling robust navigation toward targets or along predefined trajectories despite stochastic disturbances (**Figure 2**).

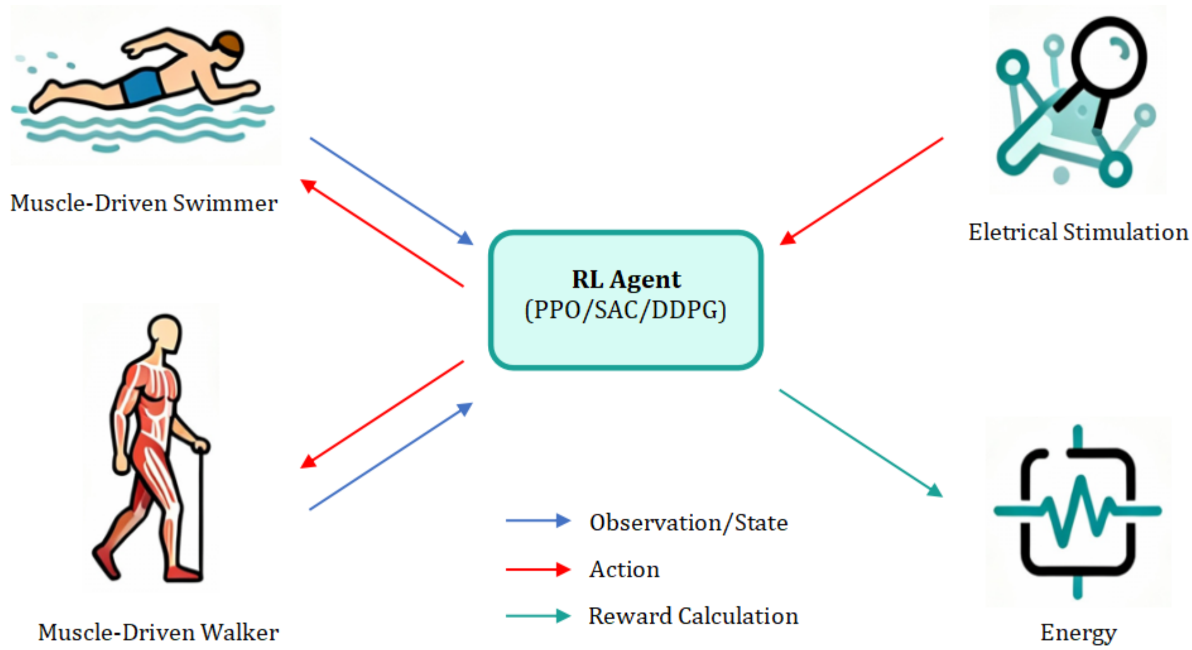

Figure 2. Schematic illustration of model-free reinforcement learning control for muscle- and tissue-driven biohybrid robots.

The RL agent observes the states of biohybrid walkers or swimmers and outputs stimulation commands (electrical or optical) to drive the actuators. Through closed-loop interaction and reward signals based on locomotion speed or energy efficiency, the agent learns robust stimulation policies. This framework has been successfully implemented using PPO and SAC algorithms to discover non-intuitive gaits in optogenetic swimmers and to coordinate complex multi-muscle architectures in voxel-based soft robots [37].

Beyond single-actuator systems, RL has been explored for coordinating many-muscle or distributed actuation architectures that would be intractable to hand-design using conventional methods. In lattice-like or worm-inspired biohybrid robots comprising dozens of individually addressable muscle units, RL agents have been shown to learn control policies that steer the robot toward multiple target locations while implicitly identifying which muscles are most important for each task [38]. Such results suggest a dual role for RL in both control and co-design, helping researchers prioritize actuator placement and configuration before committing to costly fabrication of physical devices.

4.3. Adaptation, Fatigue Compensation, and Co-Design

A notable advantage of RL in biohybrid contexts is its capacity to adapt to changing actuator capabilities, including fatigue, strengthening, or remodeling induced by exercise and use history. By continuously updating policies in response to evolving state–action–reward relationships, RL agents can learn to compensate for progressive weakening or reconfiguration of muscle actuators, maintaining task performance over longer time scales than static controllers [39]. Simulation studies incorporating use-dependent muscle adaptation have reported that agents trained in adaptive environments can achieve higher final rewards and better task performance than agents exposed to non-adaptive models, highlighting the synergy between RL and biological plasticity [40].

RL has also been proposed as a co-design tool for biohybrid robots, where the learning process not only yields a controller but also provides insight into which actuators and morphologies are most critical for a given task [41]. By analyzing the learned activation patterns and sensitivity of performance to different muscles, designers can iteratively refine the layout, stiffness distribution, and actuation capabilities of biohybrid platforms, effectively using RL as a search engine in the high-dimensional space of morphologies and control policies [42].

4.4. Limitations, Safety, and Practical Considerations

Despite its promise, RL-based control in biohybrid robots faces significant practical and conceptual challenges. Most RL algorithms are sample-inefficient, requiring large numbers of interactions to converge on high-quality policies, whereas real biohybrid experiments are slow, expensive, and subject to tissue degradation and ethical constraints [43]. An often-underestimated factor in reinforcement learning is its substantial energy footprint. The high-frequency trial-and-error interactions and deep neural network updates require significant computational power. For mobile biohybrid robots, where power-to-weight ratios are critical, the high energy consumption of RL-based controllers may limit operational longevity compared to more energy-efficient adaptive or hybrid schemes. Exploration—a core element of RL—can easily overstimulate or damage fragile tissues if not properly constrained, and reward design is non-trivial when multiple objectives such as performance, safety, and longevity must be balanced.

To mitigate these issues, recent work emphasizes the use of high-fidelity simulation environments, domain randomization, and sim-to-real transfer techniques to pretrain RL agents before deployment on physical biohybrid systems [44]. In parallel, safety-aware and constrained RL formulations, including shielded policies, safe exploration strategies, and hybrid schemes that combine RL with classical control or model predictive controllers, are being investigated to enforce stability and safety constraints during learning and execution. These developments suggest that, while pure RL may remain difficult to apply directly in many real-world biohybrid scenarios, RL will play an increasingly important role as part of broader hybrid control and design frameworks that integrate domain knowledge, biophysical modeling, and stringent safety considerations [45].

4.5. Comparative Synthesis and Gaps in RL Control

The landscape of reinforcement learning (RL) in biohybrid robotics shows a fundamental trade-off between autonomous gait discovery and tissue integrity [34,45].

Strengths: RL, particularly model-free approaches like PPO or SAC, is unparalleled in discovering counter-intuitive gaits for biohybrid swimmers in complex fluid environments where human-designed controllers often fail.

Weaknesses: These methods suffer from extreme sample inefficiency, requiring thousands of interactions that risk overstimulating fragile cells and exhausting the biological "health budget." While sim-to-real transfer mitigates this, it often fails due to the "reality gap"—the inability of idealized simulations to account for real-world stochasticity.

Research Gap: A significant gap remains in developing "safety-shielded" RL frameworks that prioritize tissue longevity. Future research needs to integrate real-time metabolic feedback into the reward function to truncate exploration before irreversible cellular damage occurs.

5. Hybrid Intelligent Control and Its Applications in Biohybrid Robots

Hybrid intelligent control integrates classical control techniques—such as PID, fuzzy logic, rule-based control, and model predictive control—with machine learning components, aiming to combine the stability and interpretability of traditional methods with the adaptability of AI [46]. This paradigm is particularly attractive for biohybrid robots, where highly nonlinear and time-varying biological processes must be controlled under strict safety and reliability constraints, often in the presence of limited data and partially known dynamics.

5.1. Combining Conventional Control with Learning-Based Modules

A common hybrid strategy is to retain a conventional controller as the core stabilizing element while attaching learning-based modules that provide compensation, adaptation, or high-level decision making [47]. For example, fuzzy-PID controllers combined with neural-network estimators have been employed in cardiomyocyte-driven swimmers to maintain rhythmic beating-driven oscillations while adapting to sudden changes in contraction strength due to biochemical fluctuations or tissue remodeling [48]. In such implementations, the PID or fuzzy logic component enforces baseline stability and desired rhythm, whereas the neural network learns unmodeled dynamics and tunes controller gains or feedforward terms online.

In skeletal muscle-actuated robotic limbs, rule-based or impedance controllers are often used to ensure baseline joint stability and safety, while neural networks approximate the nonlinear force–length and force–velocity relationships of muscle tissues to refine torque commands [49]. This division of labor allows engineers to encode prior knowledge and safety constraints in the classical controller, while the learning component focuses on capturing complex, specimen-specific behaviors that are difficult to express analytically.

5.2. Physics-Informed and Model-Based Hybrid Schemes

Another direction in hybrid intelligent control is the integration of physics-based or biophysical models with data-driven elements, leading to physics-informed or model-augmented controllers. In biohybrid soft robots employing electroactive or muscle-like tissues, finite element or reduced-order models can be used to predict baseline deformation under given loads and stimulation patterns, while machine learning modules compensate for discrepancies due to tissue heterogeneity, fabrication imperfections, or progressive degradation [50]. These hybrid schemes can significantly reduce the amount of experimental data needed for training, as the learning component only needs to approximate residual errors rather than the full system dynamics [51].

Hybrid model predictive control (MPC) frameworks have also been proposed, in which a nominal model—derived from continuum mechanics, muscle contraction theory, or system identification—is combined with a learned correction term or uncertainty estimator [52]. The resulting controller can plan trajectories and stimulation patterns that satisfy constraints on actuator limits, safety margins, and environmental interactions, while adapting online to unmodeled biological variability [53]. Such approaches are particularly relevant for applications that demand both high performance and strong guarantees, such as biohybrid devices intended for biomedical or assistive use.

5.3. Neuromorphic, Bio-Neural, and Closed-Loop Hybrid Architectures

Hybrid intelligent control in biohybrid robots is not limited to combining conventional controllers with machine learning; it can also involve coupling artificial controllers with biological or neuromorphic computation. In neurotechnology-based biohybrid robots, for instance, biological neural circuits can serve as central pattern generators or decision-making modules, while artificial controllers handle signal conditioning, scaling, and actuation mapping. Deep or shallow networks may be used to decode neural activity and feed it into classical controllers, forming a closed-loop system that exploits both biological intelligence and engineered robustness [54].

Neuromorphic hardware and spiking neural networks provide a further avenue for hybrid control, offering energy-efficient and event-driven processing that aligns well with the sparse, time-dependent nature of many biosignals. When combined with traditional control laws or safety layers, these architectures can realize adaptive yet interpretable controllers that operate under tight power and latency constraints, which is important for implantable or mobile biohybrid systems [55].

5.4. Advantages, Limitations, and Design Considerations

Hybrid intelligent control offers several advantages for biohybrid robots, including improved robustness to model uncertainty, enhanced adaptability to biological variability, and better compatibility with safety and interpretability requirements compared to purely data-driven approaches [56]. By explicitly structuring the controller into model-based and learning-based components, designers can more easily analyze stability properties, enforce constraints, and incorporate domain knowledge about tissue mechanics and physiology. This makes hybrid schemes especially suitable for long-term experiments, multi-actuator platforms requiring coordinated control of many biological units, and early-stage translational applications.

However, hybrid controllers are not without limitations. While hybrid schemes offer robustness and interpretability, their performance is often contingent on careful tuning and validation. In soft continuum or deformable robots, fabrication tolerances, hysteresis, and material nonlinearities may still lead to degraded behavior or limited operating workspace, especially when scaling up to many actuators or complex tissue-like materials. The design and tuning of the interaction between classical and learning-based components can be complex, and poor integration may lead to instability, oscillations, or degraded performance [57]. Moreover, developing and validating physics-based or biophysical models that are sufficiently accurate yet computationally tractable remains challenging, particularly for large-scale or highly heterogeneous tissues [58]. Future work in this area is likely to focus on systematic design methodologies, formal analysis tools, and standardized benchmarks that facilitate the principled development and evaluation of hybrid intelligent control architectures for biohybrid robots.

5.5. Comparative Synthesis and Gaps in Hybrid Intelligent Control

Hybrid intelligent strategies attempt to balance the adaptability of AI with the rigor of classical control. A direct comparison shows that hierarchical architectures are currently the most successful implementation of this principle [56].

Strengths: By utilizing AI for high-level perception and classical layers (e.g., MPC or Lyapunov-based designs) for low-level stability, hybrid systems require 50–80% less experimental data than end-to-end DL or RL. This makes them significantly more biocompatible for fragile systems.

Weaknesses: The complexity of these multi-layer architectures leads to "tuning fatigue," where the interaction between discrete AI logic and continuous biological feedback becomes difficult to validate formally.

Research Gap: There is an urgent need for standardized modular interfaces. Current studies are highly customized, making it difficult to "plug-and-play" different AI modules into existing bio-inspired mechanical frameworks.

6. Data-Driven Adaptive Control and Its Applications in Biohybrid Robots

Data-driven adaptive control methods update controller parameters online based on continuous sensing of system performance, without requiring large offline datasets or fully specified models of the underlying dynamics. For biohybrid robots, this paradigm is attractive because it can accommodate gradual changes in tissue properties, environmental fluctuations, and specimen-to-specimen variability using relatively simple computational structures. Compared with deep learning or reinforcement learning, many adaptive controllers can be implemented with modest data and hardware requirements, making them suitable for fragile tissues, time-constrained experiments, and resource-limited platforms [59].

6.1. Adaptive Regulation for Muscle- and Cardiac-Driven Robots

In muscle-based crawlers and walkers, adaptive control schemes such as recursive least squares, model reference adaptive control, and adaptive PID have been employed to compensate for contraction decay and parameter drift over repeated stimulation cycles. By continuously estimating effective gains or time constants from force or kinematic measurements, these controllers can adjust stimulation amplitude and timing to maintain nearly constant step length, gait frequency, or output force, even as muscles fatigue or partially recover [60]. Similar approaches have been applied to cardiomyocyte-driven swimmers, where adaptive frequency tracking and phase-locked loops help synchronize external pacing or control signals with intrinsic beating rhythms under changing biochemical or thermal conditions [61].

For neural-actuated biohybrid systems, adaptive impedance or admittance control can be used to regulate mechanical resistance and interaction forces based on real-time neural activation and motion feedback. In these implementations, controller parameters such as stiffness, damping, or gain matrices are updated online to maintain stable yet responsive behavior when neural firing rates, synaptic strengths, or network connectivity evolve over time. This is particularly important when neural circuits exhibit plasticity or when long-term experiments induce structural or functional changes in the tissue [62].

6.2. Sensor-Based Adaptation and Disturbance Rejection

Data-driven adaptive control also plays a key role in enhancing robustness to external disturbances and unmodeled environmental interactions in biohybrid robots. For soft and micro-scale platforms, adaptive observers and Kalman filter–based estimators can fuse noisy sensor data to produce improved state estimates and automatically tune controller parameters in response to changes in fluid properties, substrate friction, or load conditions. For example, adaptive gain scheduling can be used to maintain stable locomotion across varying viscosities or temperatures by modulating stimulation intensity and timing as a function of estimated environmental state [63].

In addition, relatively simple adaptive rules—such as integral adaptation of control gains based on tracking error statistics—have been shown to significantly improve long-term trajectory tracking and stabilization in systems where only low-bandwidth or intermittent measurements are available [64]. These methods are especially relevant for biohybrid robots that must operate over extended periods with limited sensing and communication capabilities, such as implanted or minimally invasive devices.

6.3. Role within Broader AI Control Architectures

Although data-driven adaptive controllers typically lack the high-level decision-making and long-horizon planning capabilities of RL or the expressive modeling power of deep learning, they offer important complementary strengths within broader AI control architectures. Their simplicity and transparency make them easier to analyze, tune, and validate, which is crucial for safety-critical or regulated applications in which formal guarantees and interpretability are required [65]. Moreover, adaptive elements can be used to stabilize and refine the behavior of more complex AI controllers, for example, by adjusting low-level gains around a policy learned via deep RL or by compensating residual modeling errors left by deep surrogate models.

From a system design perspective, data-driven adaptive control is particularly suited as a baseline or fallback layer that maintains acceptable performance when learning-based components fail, become outdated, or must be disabled for safety reasons [66]. In this sense, adaptive controllers form an essential part of modern biohybrid robotic control stacks, enabling robust long-term operation and graceful degradation, while higher-level AI modules focus on perception, task planning, and policy optimization.

6.4. Comparative Synthesis and Gaps in Data-Driven Adaptive Control

Data-driven adaptive schemes represent the most computationally efficient category, focusing on real-time robustness rather than long-term policy optimization.

Strengths: These methods offer the highest resistance to "drifting" plant dynamics (e.g., tissue remodeling over weeks). They are particularly suited for resource-constrained platforms, such as the environmental sensors proposed for tracking disease vectors [67,68].

Weaknesses: While highly stable, adaptive controllers lack the "intelligence" to perform complex task planning or environmental navigation, limiting their use in high-level autonomous missions.

Research Gap: Future studies should investigate the integration of low-level adaptive control with high-level DL/RL modules. Bridging this gap will enable robots that are both robust to tissue fatigue and capable of complex, mission-driven behaviors in non-sterile, real-world conditions.

7. Comparison of Control Methods

Table 1 summarizes the comparative characteristics of the four major AI-based control paradigms reviewed in this work, with a particular emphasis on their suitability for biohybrid robots. The table highlights how deep learning, reinforcement learning, hybrid intelligent control, and data-driven adaptive control differ in terms of achievable performance, safety and tissue-related risks, data requirements, and typical application scenarios.

Table 1. Comparison of AI-based control strategies for biohybrid robots.

AI Control Strategy	Key Advantages	Main Limitations & Safety Concerns	Data Efficiency/Sample Efficiency	Typical Application Scenarios
Deep learning	High-dimensional perception, accurate surrogate modeling of muscle/neural dynamics, neural signal decoding, trajectory/force prediction, long-range sequence planning	Black-box nature hinders interpretability, requires extensive high-quality datasets, prone to performance degradation when tissue properties drift, difficult to guarantee real-time safety	High data demand (hundreds–thousands of trials), low sample efficiency, periodic retraining needed for biological variability	Neural decoding, muscle surrogate models, perception modules for sensory fusion, sequence-based control in micro-swimmers

Table 1. *Cont.*

AI Control Strategy	Key Advantages	Main Limitations & Safety Concerns	Data Efficiency/Sample Efficiency	Typical Application Scenarios
Reinforcement Learning	Autonomous discovery of complex stimulation patterns, high adaptability to environmental changes, effective for nonlinear dynamics, capable of multi-task learning through reward shaping	Exploration can overstimulate/damage fragile tissues, severe sample inefficiency (thousands of interactions), reward design non-trivial for multi-objective scenarios, safety constraints difficult to enforce during learning	Extremely high interaction demands, impractical for real biohybrid experiments without sim-to-real transfer, current bottleneck in practical deployment	Complex locomotion tasks (primarily simulation-based), adaptive gait learning, co-design and morphology optimization, policy learning with sim-to-real transfer
Hybrid Intelligent	Classical controller enforces baseline stability and safety guarantees, AI components handle adaptation and compensation, improved robustness to biological variability, structure enables formal stability analysis	Complex integration between classical and learning modules, requires domain knowledge of both control theory and AI, tuning interaction between components non-trivial	Moderate data requirements, reduced by ~50–80% compared to pure learning due to structured priors, favorable for resource-constrained biohybrid systems	Safety-critical biomedical applications, multi-actuator coordination, PID/MPC combined with neural adaptation, rule-based control with learning compensation
Data-driven Adaptive	Low computational complexity, real-time feasibility, excellent at compensating fatigue and parameter drift, requires minimal sensing, suitable for long-term experiments, serves as reliable baseline control layer	Limited high-dimensional decision-making capability, lacks long-horizon planning, not suitable for complex perception-heavy tasks, performance plateaus without additional model structure	Low to moderate data requirement, high sample efficiency relative to other AI methods, online learning from minimal experimental data	Long-duration experiments with gradual tissue changes, resource-limited platforms, fatigue compensation in muscle-driven actuators, baseline safety layer in hierarchical architectures

7.1. Quantitative Evidence and Empirical Performance Benchmarks

Experimental evidence supports the efficacy of these AI strategies. For instance, recent deep learning-based surrogate models have achieved force prediction accuracies with R-squared values exceeding 0.95, significantly outperforming traditional Hill-type models in capturing the non-linear dynamics of biological actuators. Furthermore, reinforcement learning-controlled biohybrid swimmers have demonstrated operational speeds of up to 0.85 mm/s (approximately 0.4 body lengths per second), proving that AI can optimize non-intuitive gait patterns that exceed the performance of manually tuned or bio-inspired heuristic controllers. These case studies underscore the practical implications of AI integration, transitioning biohybrid robotics from qualitative observation toward high-precision, data-driven engineering [14].

7.2. Thematic Comparison: Trade-Offs in Autonomy, Safety, and Data Efficiency

The functional integration of AI into biohybrid systems requires balancing several competing objectives, as illustrated in the control logic flowchart (**Figure 3**).

This flowchart illustrates the functional integration between high-level AI decision-making and the biological plant. A dedicated "Policy Shield" incorporating Lyapunov filters and health budget monitoring is highlighted as a critical safety layer that ensures stimulation remains within physiologically safe limits based on real-time sensory feedback [40].

Autonomy vs. Safety: While model-free RL offers the highest degree of autonomy in discovering novel behaviors, it presents the greatest risk to tissue integrity due to its high sample requirements. Conversely, hybrid intelligent control provides a "safety shield" by embedding AI within classical stability frameworks (e.g., Lyapunov-based designs), ensuring that commands remain within the biological "health budget."

Data Efficiency: A critical contrast emerges regarding data requirements. Hybrid and adaptive schemes typically require 50–80% less training data than end-to-end deep learning architectures because they leverage physical priors or error-based adaptation rather than pure correlation [45].

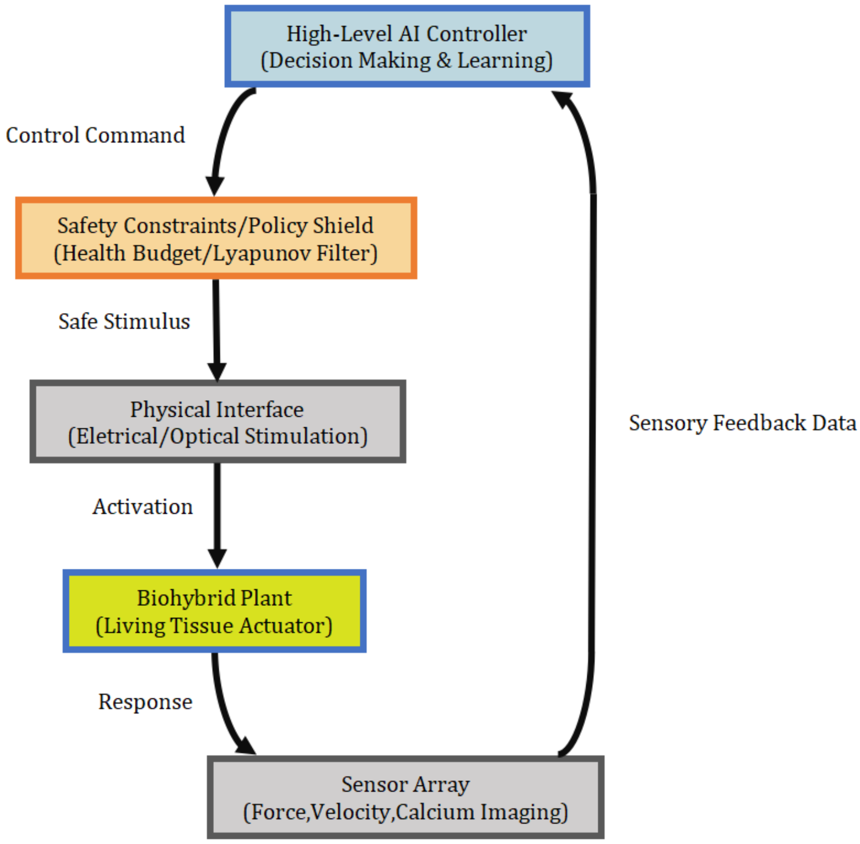

Figure 3. Systemic architecture of the AI-driven closed-loop control interface.

7.3. Identifying the Research Gap: The "Reality Gap" and Specimen Variability

Despite these advancements, a systematic gap remains in handling inter-specimen variability. Most current AI models are optimized for a single biological specimen and fail to generalize when applied to new tissues with different metabolic states. Furthermore, the "reality gap" in sim-to-real transfer remains a significant hurdle; idealized muscle models used in training often fail to account for the stochastic biochemical coupling and physiological drift inherent in living matter. Future research must prioritize "physics-informed" AI that can adapt to these biological uncertainties with minimal recalibration [30].

8. Trade-Offs, Safety, and Data Constraints in AI-Controlled Biohybrid Robots

In AI-controlled biohybrid robots, performance gains and increased autonomy come at the cost of new trade-offs among efficiency, safety, learning capability, and tissue longevity, as well as between data requirements and experimental constraints. This section revisits the previously discussed AI control strategies in the specific context of living actuators and clarifies their respective strengths and limitations. The discussion is organized around three main themes: (i) cross-comparison of different AI control methods and their applicability boundaries in biohybrid settings; (ii) the impact of safety, tissue integrity, and ethical constraints on controller design; and (iii) the tension between sample efficiency and data scarcity, together with practical strategies to mitigate it. Finally, we outline future research directions and governance needs, arguing that the safe and responsible integration of AI into biohybrid systems will require deeper coordination across control theory, machine learning, tissue engineering, and ethics/regulation rather than progress in any single domain in isolation.

8.1. Cross-Comparison of AI Control Strategies in Biohybrid Contexts

The comparative analysis of deep learning, reinforcement learning, hybrid intelligent control, and data-driven adaptive control suggests that their advantages and limitations become particularly pronounced when deployed on living, fragile actuators. Deep learning-based controllers are well-suited for tasks that require high-dimensional perception, surrogate modeling, and accurate prediction of nonlinear biohybrid dynamics, such as decoding neural signals or forecasting muscle contractions under varying stimuli [69]. However, these benefits are often contingent on the availability of relatively large, well-curated datasets and stable experimental conditions, which are difficult to maintain when tissues remodel, fatigue, or degrade over time.

Reinforcement learning, in contrast, directly targets closed-loop performance optimization and long-term adaptation, enabling robots to autonomously discover stimulation patterns that exploit complex fluid–structure–tissue interactions [30]. This makes RL particularly attractive for locomotion and navigation tasks where analytical models are incomplete or unreliable. Yet, the intrinsic sample inefficiency of many RL algorithms clashes with the limited lifetime and ethical constraints of biohybrid systems, and naive exploration can be incompatible with tissue safety.

Hybrid intelligent control provides a compromise by embedding AI components within well-understood classical or physics-based frameworks [70]. In the analyzed studies, such hybrid schemes frequently achieved improved robustness and tracking compared with pure model-based controllers, while avoiding the extreme data demands of end-to-end deep learning or RL. They are especially effective when partial knowledge of the system exists (e.g., approximate muscle mechanics, known constraints), and when safety and interpretability are critical.

Data-driven adaptive control, meanwhile, consistently emerges as a low-complexity yet powerful baseline, particularly for long-term experiments where tissues undergo gradual, rather than abrupt, changes. These controllers excel at compensating parameter drift, fatigue, and environmental variability with modest sensing and computational requirements [71]. However, they generally lack the capability for rich perception, high-dimensional decision making, or multi-task learning, and thus are better viewed as foundational layers rather than complete intelligent control solutions.

Overall, the comparison indicates that no single AI strategy is universally superior [72]. Instead, effective design requires matching the control paradigm to: (i) the biological actuator type and robustness, (ii) the available sensing and data budget, and (iii) the acceptable trade-offs between performance, safety, and implementation complexity.

8.2. Ethical Governance, Tissue Welfare, and Clinical Safety

The integration of living tissues with AI-driven control introduces an ethical dimension that is absent in conventional robotics. While technical safety focuses on preventing mechanical failure, biohybrid systems necessitate a more nuanced exploration of tissue-centric welfare and long-term biological integrity, particularly as these systems move toward real-world applications.

From Technical Safety to Tissue Welfare: Biohybrid robots introduce an additional dimension of risk because their core components—muscle, neural tissue, or organoids—are living and sensitive. Prolonged or aggressive exploration under RL frameworks can lead to overstimulation and irreversible failure. Ethically, this necessitates the development of "health-aware" controllers that treat tissue fatigue not merely as a performance drop, but as a critical ethical boundary. Control frameworks should explicitly encode a "biological health budget," setting strict constraints on stimulation intensity and cumulative load to respect the biological limits of the living actuators [73].

Long-Term Biological Effects and Phenotypic Stability: A major underdeveloped area in current research is the study of long-term biological effects of chronic AI stimulation. As AI-controlled systems move toward in vivo or implantable applications, we must address the potential for unintended phenotypic transformations or accelerated cellular aging caused by high-frequency, non-intuitive control signals. Ensuring the biological stability of the bio-synthetic interface over months or years is not only a technical challenge but a prerequisite for the ethical deployment of biohybrids in clinical settings [9].

Autonomous Risks in Clinical and Sensitive Environments: The deployment of autonomous biohybrid systems in clinical or human-interfacing environments poses unique risks. Unlike deterministic machines, the "living" nature of these robots introduces stochastic behaviors that are difficult to bound analytically. In sensitive environments—such as using biohybrids for environmental surveillance or disease vector control—uncontrolled autonomous exploration could lead to unintended ecological impacts. Future governance frameworks must define the acceptable degree of autonomy for living systems, ensuring that AI decisions remain predictable, transparent, and aligned with human safety protocols [74].

Bridging AI Safety and Bioethics: Emerging tools like shielded policies and Control Barrier Functions (CBFs) offer pathways to embed ethical constraints into learning-based controllers. However, a critical gap remains: most AI safety research is tested on simulated platforms that do not account for irreversible biological damage or the slower time scales of living tissue. Transitioning biohybrid robots from the laboratory to the real world requires a multi-disciplinary effort to bridge the gap between high-level AI safety research and the specific, fragile requirements of bio-synthetic organisms [31].

8.3. Sample Efficiency and Data Limitations in Living Systems

A recurring theme across the surveyed literature is the mismatch between AI methods' data needs and the limited data that biohybrid platforms can realistically provide. Deep learning approaches for surrogate modeling or perception often assume hundreds to thousands of labeled trials or long continuous recordings, while many biohybrid experiments are constrained by tissue lifetime, culture stability, and experimental throughput. Retraining models each time the tissue significantly remodels or degrades further increases the data burden [73].

Reinforcement learning is even more demanding: typical deep RL algorithms require large numbers of episodes to converge, and performance is highly sensitive to exploration strategies. In biohybrid settings, each trial consumes tissue "health budget" due to fatigue, potential micro-damage, and biochemical drift. This makes naive trial-and-error learning untenable for many physical systems and pushes the field toward pretraining in simulation, sim-to-real transfer, and data-efficient RL variants [75].

Several Promising Directions Emerge from the Reviewed Studies and Related Work

Physics-informed and model-augmented learning: By embedding prior knowledge from biomechanics, electrophysiology, or continuum mechanics into neural architectures or loss functions, controllers can learn residual dynamics rather than full-system behavior, dramatically reducing data requirements.

Offline and batch RL: Instead of learning purely from online interaction, controllers can be trained on a fixed dataset of safe, expert-designed, or scripted trajectories, limiting risky exploration on real tissues.

Meta-learning and transfer across specimens: Learning structures that capture common patterns across different biological samples may enable rapid adaptation to new specimens with minimal additional data, partially mitigating inter-sample variability.

Hierarchical and multi-layered designs: When high-level planning is learned from limited demonstrations, while low-level stabilization is handled by adaptive or classical controllers, the data demands of the learning component can be substantially reduced.

These strategies suggest that improving sample efficiency is not solely an algorithmic challenge, but a system-level design problem involving co-optimization of models, controllers, sensing, and experimental protocols [76].

8.4. Strategic Framework for Future Advancement

To transition biohybrid robots from laboratory prototypes to resilient, real-world machines, we propose a systematic progression focused on addressing the most urgent challenges in control theory and biological integration:

8.4.1. Stage 1: Standardization and Health Benchmarking

The immediate priority is to replace qualitative observations with standardized performance metrics to ensure reproducibility across laboratories.

Unified Metrics: Establish a "Bio-Actuator Performance Atlas" that standardizes metrics such as force-to-weight ratios, energy conversion efficiency, and calcium signaling stability [1].

Tissue Health Benchmarks: Define "Safe Operating Envelopes" based on real-time PH levels and lactic acid accumulation to quantify the "biological health budget" for different tissue types [30].

Open-Source Data Platforms: Develop shared datasets for AI training to reduce the need for redundant, high-risk exploration on living specimens, thereby improving sample efficiency [9].

8.4.2. Stage 2: Metabolic-Aware Control and Resilience

The focus moves toward active physiological management through the deep integration of AI and biological feedback loops.

Active Fatigue Compensation: Develop Model Predictive Control (MPC) frameworks that integrate real-time metabolic feedback (e.g., oxygen levels, glucose consumption) directly into the control loop to dynamically adjust stimulation frequency before fatigue occurs [56].

Health-Aware Reward Functions: In Reinforcement Learning (RL), implement reward penalties for "biological stress states," ensuring the AI learns gaits that prioritize tissue longevity rather than just raw speed [74].

Self-Healing Feedback: Integrate AI with bio-synthetic interfaces capable of triggering nutrient delivery or localized temperature control to assist in tissue remodeling and recovery during operation [35].

8.4.3. Stage 3: Generalization and Field Deployment

The final stage aims to achieve robustness across different specimens and uncontrolled, non-sterile environments.

Cross-Specimen Transfer Learning: Utilize Meta-Learning and domain adaptation to allow a control policy trained on "Specimen A" to be rapidly adapted to "Specimen B" with minimal recalibration, accounting for individual variability in muscle fiber density [43].

Deployment in Unstructured Environments: Transition robots to real-world applications such as climate-stressed ecosystems for disease vector control, as proposed in recent environmental surveillance studies. This requires AI that can handle environmental noise (e.g., temperature shifts, variable fluid viscosity) while maintaining biological stability [77].

Autonomous Lifecycle Management: Develop biohybrid systems capable of autonomous "homeostatic rest cycles," where the AI recognizes the need for biological recovery and schedules dormant periods to ensure system integrity over months of operation [78].

8.5. Practical Design Recommendations for Biohybrid Control

Based on the synthesis of trade-offs regarding safety, data efficiency, and biological variability, the following guidelines are proposed for the development of future AI-driven biohybrid systems:

For Safety-Critical Applications: Researchers should prioritize Hybrid Intelligent Control. By embedding neural networks within classical PID or MPC frameworks, systems can leverage AI for adaptation while maintaining formal stability guarantees through the classical control core [45].

For Complex Locomotion and Morphology Co-design: Reinforcement Learning (RL) is recommended, provided it is coupled with high-fidelity simulations and sim-to-real transfer. This mitigates the risk of tissue overstimulation or irreversible damage during the high-entropy exploration phase of learning [79].

For Long-Term Operation and Fatigue Compensation: Data-Driven Adaptive Control serves as the most effective baseline. Its low computational complexity and high sample efficiency make it ideal for resource-limited platforms that must compensate for gradual physiological drift over extended periods [40].

For Perception-Intensive and Neural-Actuated Tasks: Deep Learning decoders (e.g., CNNs or Transformers) are essential for mapping high-dimensional biosignals to control commands. However, these should be integrated with modular architectures to allow for periodic retraining as biological tissues remodel or degrade [80].

9. Conclusions

This review systematically compared four major AI control strategies—deep learning, reinforcement learning, hybrid intelligent control, and data-driven adaptive control—applied to biohybrid robots over roughly the past five years. Across diverse actuator types and morphologies, these methods exhibit distinct strengths in motion precision, environmental adaptability, fatigue compensation, and real-time feasibility. However, their deployment is fundamentally constrained by living tissue fragility, limited experimental throughput, and stringent safety requirements. As a result, no single approach dominates across tasks; achievable performance critically depends on matching the control paradigm to task objectives, sensing and data availability, biological variability, and acceptable trade-offs between accuracy, robustness, and implementation complexity.

For researchers designing AI controllers for biohybrid platforms, the comparative analysis suggests that hybrid intelligent control currently offers the most practical and balanced solution. By embedding learning modules within classical or model-based frameworks, hybrid schemes leverage established stability and safety guarantees while still providing meaningful adaptability to unmodeled biological dynamics. Data-driven adaptive control is particularly suitable for resource-limited and long-duration experiments, where gradual tissue changes must be compensated with minimal computational and data overhead. Deep learning is most advantageous in perception and modeling-intensive settings, such as neural decoding or surrogate modeling of complex muscle dynamics, provided that sufficiently high-quality data can be acquired and maintained. Reinforcement learning holds transformative potential for discovering non-intuitive locomotion strategies and enabling closed-loop co-design of morphology and control, but its severe sample inefficiency and exploration-related safety risks mean that, in practice, RL must be tightly coupled with high-fidelity simulation, sim-to-real transfer pipelines, and explicit safety constraints before being widely deployed on real tissues.

Looking forward, advancing AI-controlled biohybrid robots from laboratory prototypes toward robust and ethically grounded real-world applications will require more than incremental improvements to existing algorithms. Future progress depends on the development of sample-efficient and safety-aware learning frameworks—such as model-based and offline RL, physics-informed neural networks, and uncertainty-aware predictive control—that explicitly account for biological variability and irreversible tissue damage. Multi-layer and modular control architectures, in which high-level AI modules handle perception and task planning while lower-level adaptive or hybrid controllers enforce stability and safety, are likely to form the backbone of next-generation systems. At the same time, the field urgently needs standardized biohybrid benchmarks, shared datasets, and transparent reporting of tissue health, longevity, and ethical considerations. Integrating these technical advances with appropriate governance frameworks for tissue welfare, safe exploration limits, and clinical translation will be essential to realizing AI–biohybrid systems that are not only capable and adaptive, but also reliable, reproducible, and socially responsible.

Author Contributions

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Data Availability Statement

Due to privacy restrictions, this article cannot provide direct access to the underlying dataset.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Kim, M.S.; Kim, Y.H.; Choi, Y.; et al. Biohybrid Actuators in Robotics: Recent Trends and Future Perspectives of Skeletal and Cardiac Muscle Integration. *npj Robot.* **2025**, *3*, 37.
2. Chen, Z.; Chen, J.; Jung, S.; et al. Bioinspired and Biohybrid Soft Robots: Principles and Emerging Technologies. *Matter* **2025**, *8*, 102045.
3. Li, T.; Takeuchi, S. Advancing Biohybrid Robotics: Innovations in Contraction Models, Control Techniques,

and Applications. *Bioeng. Rev.* **2024**, *6*, 25–48.
4. Ahmad, U. Biohybrid Microrobots: A New Frontier in Targeted Drug Delivery and Precision Therapeutics. *J. Biotechnol. Bioeng.* **2025**, *8*, 15–26.
5. Won, P.; Ko, S.H.; Majidi, C.; et al. Biohybrid Actuators for Soft Robotics: Challenges in Scaling Up. *Actuators* **2020**, *9*, 96.
6. Mompó Alepuz, A.; Papageorgiou, D.; Tolu, S. Brain-Inspired Biomimetic Robot Control: A Review. *Front. Neurorobot.* **2024**, *18*, 1395617.
7. Jung, H.; Park, S.; Joe, S.; et al. AI-Driven Control Strategies for Biomimetic Robotics: Trends, Challenges, and Future Directions. *Biomimetics* **2025**, *10*, 460.
8. Sarker, A.; Islam, T.U.; Islam, M.R. A Review on Recent Trends of Bioinspired Soft Robotics: Actuators, Control Methods, Materials Selection, Sensors, Challenges, and Future Prospects. *Adv. Intell. Syst.* **2024**, *7*, 2400414.
9. Bawa, M.; Raman, R. Taking Control: Steering the Future of Biohybrid Robots. *Sci. Robot.* **2024**, *9*, eadr9299.
10. van Laake, L.C.; Overvelde, J.T.B. Bio-Inspired Autonomy in Soft Robots. *Commun. Mater.* **2024**, *5*, 198.
11. Kuplinov, G.N. The Biohybrid Autonomous Robots (BAR): A Feasibility of Implementation. *Front. Robot. AI* **2025**, *12*, 1695262.
12. Wang, X.; Wei, R.; Chen, Z.; et al. Bioinspired Intelligent Soft Robotics: From Multidisciplinary Integration to Next-Generation Intelligence. *Adv. Sci.* **2025**, *12*, e06296.
13. Chen, Z.; Renda, F.; Le Gall, A.; et al. Data-Driven Methods Applied to Soft Robot Modeling and Control: A Review. *IEEE Trans. Robot.* **2024**, *40*, 2241–2256.
14. Drennan, W.C.; Aydin, O.; Emon, B.; et al. A Fast, Muscle-Actuated Biohybrid Swimming Robot. *bioRxiv preprint* **2024**. [CrossRef]
15. Pal, A.; He, T.; Wei, W. Sample-Efficient Model Predictive Control Design of Soft Robotics by Bayesian Optimization. *arXiv preprint* **2022**, *arXiv:2210.08780*. [CrossRef]
16. López-González, A.; Tejada, J.; Rojas, N.; et al. Recent Advances in Neurotechnology-Based Biohybrid Robots. *Soft Matter* **2024**, *20*, 7993–8011.
17. López-González, A.; Tejada, J.C.; López-Romero, J. Review and Proposal for a Classification System of Soft Robots Inspired by Animal Morphology. *Biomimetics* **2023**, *8*, 192.
18. Sapai, S.; Loo, J.Y.; Ding, Z.Y.; et al. A Deep Learning Framework for Soft Robots with Synthetic Data. *Soft Robot.* **2023**, *10*, 1224–1240.
19. De Barrie, D.; Pandya, M.; Pandya, H.; et al. A Deep Learning Method for Vision Based Force Prediction of a Soft Fin Ray Gripper Using Simulation Data. *Front. Robot. AI*. **2021**, *8*, 631371.
20. Zhang, Z.; Jin, Z.; Gu, G. Efficient Pneumatic Actuation Modeling Using Hybrid Physics-Based and Data-Driven Framework. *Cell Rep. Phys. Sci.* **2022**, *3*, 100842.
21. Sun, Z.; Wang, S.; Zhao, Y.; et al. Discriminating Soft Actuators' Thermal Stimuli and Mechanical Deformation by Hydrogel Sensors and Machine Learning. *Adv. Intell. Syst.* **2022**, *4*.
22. Schäfke, H.; Habich, T.L.; Muhmann, C.; et al. Learning-Based Nonlinear Model Predictive Control of Articulated Soft Robots Using Recurrent Neural Networks. *IEEE Robot. Autom. Lett.* **2024**, *9*.
23. Loo, J.Y.; Ding, Z.Y.; Baskaran, V.M.; et al. Robust Multimodal Indirect Sensing for Soft Robots Via Neural Network-Aided Filter-Based Estimation. *Soft Robot.* **2022**, *9*, 591–612.
24. Ni, Y.; Wakimoto, S.; Tian, W.; et al. Length Estimation of Pneumatic Artificial Muscle with Optical Fiber Sensor Using Machine Learning. *Sensors* **2025**, *25*, 2221.
25. Masoud, A.E.; Maas, J. Data-Driven Modeling and Identification of a Bistable Soft-Robot Element Based on Dielectric Elastomer. *Front. Robot. AI* **2025**, *12*, 1546945.
26. Luu, D.K.; Nguyen, A.T.; Jiang, M.; et al. Deep Learning-Based Approaches for Decoding Motor Intent From Peripheral Nerve Signals. *Front. Neurosci.* **2021**, *15*, 667907.
27. Zhang, A.; Truby, R.L.; Chin, L.; et al. Vision-Based Sensing for Electrically-Driven Soft Actuators. *IEEE Robot. Autom. Lett.* **2022**, *7*, 11509–11516.
28. Johnson, J.J.; Yip, M. Motion Planning Using Transformers. *IEEE Robot. Autom. Lett.* **2023**, *8*, 994–1001.
29. Shanghai, N.; Brown, N.B. Advances in Transformers for Robotic Applications: A Review. *arXiv preprint* **2024**, *arXiv:2412.10599*. [CrossRef]
30. Webster-Wood, V.A.; Guix, M.; Xu, N.W.; et al. Biohybrid Robots: Recent Progress, Challenges, and Perspectives. *Bioinspir. Biomim.* **2023**, *18*, 015001.
31. Stiti, C.; Benrabah, M.; Aouaichia, A.; et al. Lyapunov-Based Neural Network Model Predictive Control Using Metaheuristic Optimization Approach. *Sci. Rep.* **2024**, *14*, 18760.
32. Nghiem, T.X.; Drgoňa, J.; Jones, C.; et al. Physics-Informed Machine Learning for Modeling and Control of

Dynamical Systems. *arXiv preprint* **2023**, *arXiv:2306.13867*. [CrossRef]
33. Elguea-Aguinaco, I.; Inziarte-Hidalgo, I.; Bøgh, S.; et al. A Review on Reinforcement Learning for Motion Planning of Robotic Manipulators. *Int. J. Intell. Syst.* 2024, 1636497.
34. Schaffer, S.; Pamu, H.H.; Webster-Wood, V.A. Hitting the Gym: Reinforcement Learning Control of Exercise-Strengthened Biohybrid Robots in Simulation. *arXiv preprint***2024**, *arXiv:2408.16069*. [CrossRef]
35. Kim, Y.; Yang, Y.; Zhang, X.; et al. Remote Control of Muscle-Driven Miniature Robots with Battery-Free Wireless Optoelectronics. *Sci. Robot.* **2023**, *8*, eadd1053.
36. Liu, Y.; Zou, Z.; Pak, O.S.; et al. Learning to Cooperate for Low-Reynolds-Number Swimming: A Model Problem for Gait Coordination. *Sci. Rep.* **2023**, *13*, 9397.
37. Jiao, Y.; Ling, F.; Heydari, S.; et al. Deep Dive into Model-Free Reinforcement Learning for Biological and Robotic Systems: Theory and Practice. *arXiv preprint* **2024**, *arXiv:2405.11457*. [CrossRef]
38. Mozafarinia, H.; Zabetnia, A. Reinforcement Learning for Efficient Locomotion of Bio-Inspired Microswimmers in Low Reynolds Number Fluids. *bioRxiv preprint* **2025**. [CrossRef]
39. Avtges, J.; Ketchum, J.; Schlafly, M.; et al. Real-Time Reinforcement Learning for Dynamic Tasks with a Parallel Soft Robot. *arXiv preprint* **2025**, *arXiv:2509.19525*. [CrossRef]
40. Garg, S.; Goharimanesh, M.; Sajjadi, S.; et al. Autonomous Control of Soft Robots Using Safe Reinforcement Learning and Covariance Matrix Adaptation. *Eng. Appl. Artif. Intell.* **2025**, *153*, 110791.
41. Wang, Y.; Wu, S.; Fu, H.; et al. Curriculum-Based Co-Design of Morphology and Control of Voxel-Based Soft Robots. In Proceedings of the International Conference on Learning Representations, Kigali, Rwanda, 1–5 May 2023.
42. Strgar, L.; Kriegman, S. Accelerated Co-Design of Robots Through Morphological Pretraining. *arXiv preprint* **2025**, *arXiv:2502.10862*. [CrossRef]
43. Tang, C.; Abbatematteo, B.; Hu, J.; et al. Deep Reinforcement Learning for Robotics: A Survey of Real-World Successes. *Annu. Rev. Control Robot. Auton. Syst.* **2025**, *8*, 153–188.
44. Tiboni, G.; Protopapa, A.; Tommasi, T.; et al. Domain Randomization for Robust, Affordable and Effective Closed-Loop Control of Soft Robots. *arXiv preprint* **2024**, *arXiv:2303.04136*. [CrossRef]
45. Brunke, L.; Greeff, M.; Hall, A.W.; et al. Safe Learning in Robotics: From Learning-Based Control to Safe Reinforcement Learning. *Annu. Rev. Control Robot. Auton. Syst.* **2022**, *5*, 411–444.
46. Li, C.; He, S.; Xu, Y.; et al. Model and Control of Hybrid Hard-Soft Robots Using Model Predictive Control. In Proceedings of the 41st Chinese Control Conference, Hefei, China, 25–27 July 2022.
47. Khodaverdian, A.; Gohil, D.; Christofides, P.D. Neural Network Implementation of Model Predictive Control with Stability Guarantees. *Digit. Chem. Eng.* **2025**, *16*, 100262.
48. Han, J.; Shan, X.; Liu, H.; et al. Fuzzy Gain Scheduling PID Control of a Hybrid Robot Based on Dynamic Characteristics. *Mech. Mach. Theory* **2023**, *184*, 105283.
49. Khan, N.A.; Jamwal, P.K.; Hussain, F.; et al. Reinforcement Learning-Driven Path Generation for Ankle Rehabilitation Robot Using Musculoskeletal-Informed Energy Optimization. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2025**, *33*, 1774–1784.
50. Dai, Y.; Deng, Z.; Wang, X.; et al. A Hybrid Controller for a Soft Pneumatic Manipulator Based on Model Predictive Control and Iterative Learning Control. *Sensors* **2023**, *23*, 1272.
51. Shi, L.; Mucchiani, C.; Karydis, K. Online Modeling and Control of Soft Multi-Fingered Grippers via Koopman Operator Theory. *arXiv preprint* **2022**, *arXiv:2206.10707*. [CrossRef]
52. Cangan, B.G.; Navarro, S.E.; Yang, B.; et al. Model-Based Disturbance Estimation for a Fiber-Reinforced Soft Manipulator Using Orientation Sensing. *arXiv preprint* **2022**, *arXiv:2206.11626*. [CrossRef]
53. Licher, J.; Bartholdt, M.; Krauss, H.; et al. Adaptive Model-Predictive Control of a Soft Continuum Robot Using a Physics-Informed Neural Network Based on Cosserat Rod Theory. *arXiv preprint* **2025**, *arXiv:2508.12681*. [CrossRef]
54. Shin, M.; Ha, T.; Lim, J.; et al. Human Motor System-Based Biohybrid Robot-on-a-Chip for Drug Evaluation of Neurodegenerative Disease. *Adv. Sci.* **2024**, *11*, e2305371.
55. Yang, Y.; Bartolozzi, C.; Zhang, H.H.; et al. Neuromorphic Electronics for Robotic Perception, Navigation and Control: A Survey. *Eng. Appl. Artif. Intell.* **2023**, *126*, 106838.
56. Garriga-Casanovas, A.; Shakib, F.; Ferrandy, V.; et al. Hybrid Control of Soft Robotic Manipulator. *Actuators* **2024**, *13*, 242.
57. Wang, L.; Chen, K.; Franco, E. Robust and Adaptive Control of a Soft Continuum Manipulator for Minimally Invasive Surgery. *Robotics* **2024**, *13*, 162.
58. Chen, Z.; Xia, Y.; Liu, J.; et al. Hysteresis-Aware Neural Network Modeling and Whole-Body Reinforcement

Learning Control of Soft Robots. *arXiv preprint* **2025**, *arXiv:2504.13582*. [CrossRef]
59. Yang, Y.; Han, J.; Liu, Z.; et al. Modeling and Adaptive Neural Network Control for a Soft Robotic Arm with Prescribed Motion Constraints. *IEEE/CAA J. Autom. Sin.* **2023**, *10*, 501–511.
60. Mak, Y.X.; Naghibi, H.; Lin, Y.; et al. Adaptive Control of a Soft Pneumatic Actuator Using Experimental Characterization Data. *Front. Robot. AI* **2023**, *10*, 1056118.
61. Lee, K.Y.; Park, S.-J.; Matthews, D.G.; et al. An Autonomously Swimming Biohybrid Fish Designed with Human Cardiac Biophysics. *Science* **2022**, *375*, 639–647.
62. Zhang, Y.; Li, T.; Tao, H.; et al. Research on Adaptive Impedance Control Technology of Upper Limb Rehabilitation Robot Based on Impedance Parameter Prediction. *Front. Bioeng. Biotechnol.* **2024**, *11*, 1332689.
63. Liu, X.; Ikemoto, S.; Yoshimitsu, Y.; et al. Learning Soft Robot Dynamics Using Differentiable Kalman Filters and Spatio-Temporal Embeddings. *arXiv preprint* **2023**, *arXiv:2308.09868*. [CrossRef]
64. Hao, S.; Hu, L.; Liu, P.X. Second-Order Adaptive Integral Terminal Sliding Mode Approach to Tracking Control of Robotic Manipulators. *IET Control Theory Appl.* **2021**, *15*, 2145–2157.
65. Tamang, L.; Bouadjenek, M.R.; Dazeley, R.; et al. Handling Out-of-Distribution Data: A Survey. *IEEE Trans. Knowl. Data Eng.* **2025**, *37*, 5948–5966.
66. Hong, L.; Liu, L.; Peng, Z.; et al. Control of Marine Robots in the Era of Data-Driven Intelligence. *Annu. Rev. Control Robot. Auton. Syst.* **2025**, *9*, 22723–33729.
67. Abbasi, E. The Impact of Climate Change on Travel-Related Vector-Borne Diseases: A Case Study on Dengue Virus Transmission. *Travel Med. Infect. Dis.* **2025**, *65*, 102841.
68. Abbasi, E. The Impact of Climate Change on *Aedes aegypti* Distribution and Dengue Fever Prevalence in Semi-Arid Regions: A Case Study of Tehran Province, Iran. *Sci. Environ. Res.* **2025**, *275*, 121441.
69. Wang, J.; Chortos, A. Control Strategies for Soft Robot Systems. *Adv. Intell. Syst.* **2022**, *4*, 2100165.
70. Sajwan, M.; Singh, S. A Review on the Effectiveness of Machine Learning and Deep Learning Algorithms for Collaborative Robot. *Arch. Comput. Methods Eng.* **2023**, *30*, 3489–3508.
71. Wang, P.; Kershaw, J.; Russell, M.; et al. Data-Driven Process Characterization and Adaptive Control in Robotic Arc Welding. *CIRP Ann. Manuf. Technol.* **2022**, *71*, 45–48.
72. RajaSekhar Reddy, N.V.; Liu, H.; Kim, T.; et al. Biohybrid–AI Marine Sensors for Ocean Health Monitoring under Climate Stress: A Systematic Review. *Synthesis* **2025**, *3*, 12–25.
73. Kasaei, M.; Kouhkiloui Babarahmati, K.; Li, Z.; et al. A Data-Efficient Neural ODE Framework for Optimal Control of Soft Manipulators. *Proc. 7th Conf. Robot Learn.* 2023, *229*, 2700–2713.
74. Abbasi, E. Climate Change and Vector-Borne Disease Transmission: The Role of Insect Behavioral and Physiological Adaptations. *Integr. Org. Biol.* **2025**, *7*, obaf011.
75. Zhao, W.; Peña Queralta, J.; Westerlund, T. Sim-to-Real Transfer in Deep Reinforcement Learning for Robotics: A Survey. In Proceedings of the 2020 IEEE Symposium Series on Computational Intelligence (SSCI), Canberra, Australia, 1–4 December 2020.
76. Banerjee, C.; Nguyen, K.; Fookes, C.; et al. A Survey on Physics-Informed Reinforcement Learning: Review and Open Problems. *Expert Syst. Appl.* **2025**, *287*, 128166.
77. Abbasi, E. Global Expansion of Aedes Mosquitoes and Their Role in the Transboundary Spread of Emerging Arboviral Diseases: A Comprehensive Review. *IJID One Health* **2025**, *6*, 100058.
78. Dulundu, A. The Future of Robotics: Integrating Biological Components in Biohybrid Robotics for Enhanced Functionality and Adaptability. *Next Front. Life Sci. AI* **2024**, *8*, 57.
79. Tapia Sal Paz, B.; Sorrosal, G.; Mancisidor, A.; et al. Reinforcement Learning-Based Control for Robotic Flexible Element Disassembly. *Mathematics* **2025**, *13*, 1120.
80. Radha, H.M.; Hassan, A.K.A. A Survey on Bio-Signal Analysis for Human–Robot Interaction. *Int. J. Electr. Comput. Eng.* **2022**, *12*, 5998–6009.