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AI-Enhanced Design-to-Manufacturing Framework for Biohybrid Production: RAG-Guided Constraint Specification and Validation-Driven Process Optimization

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Abstract

This paper presents an AI-enhanced framework integrating computational design with manufacturing systems for biohybrid machine production. The framework employs retrieval-augmented generation (RAG) for automated constraint specification, evolutionary algorithms for morphology generation, and machine learning surrogates, accelerating rapid design optimization. Bidirectional design-simulation integration enables quality control findings to systematically update computational models, reducing production iterations. Validation demonstrated 48% convergence to expert-validated designs, while constraint-guided design reduced trial-and-error iterations. The framework aims to transform ad-hoc expert judgment into a systematic production methodology toward systematic production engineering.

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1. Introduction

Biohybrid machines combine living cells with engineered structures to achieve actuation, sensing, and adaptation that conventional rigid robots struggle to match [1]. Skeletal muscle actuators offer compliant force generation at small scales suited to minimally invasive medical devices [2]. The BioMeld project developed a steerable biohybrid catheter actuated by skeletal muscle tissue as a proof of concept. Translating such concepts into manufacturable devices remains difficult. Development still depends on iterative trial and error, where designers fabricate candidate structures, test them, and revise based on observed outcomes.

This artisanal process limits reproducibility and scalability. Each design cycle consumes biological materials, fabrication time, and expert attention. Computational design tools promise relief, yet most operate in isolation from the manufacturing systems that realize physical devices. Predictions that ignore fabrication constraints generate designs that cannot be built. Manufacturing data rarely feeds back to improve computational models. Digital twin research has demonstrated the value of integrating design, manufacturing, and feedback within a single information loop [3]. Biohybrid production presents distinct challenges that arise from living components, distributed fabrication, and long bio-fabrication lead times.

This paper presents an AI-enhanced framework that integrates computational design with manufacturing for biohybrid machine production. The framework organizes design into four stages. Retrieval-augmented generation translates natural language requirements into formal constraint

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specifications. Evolutionary algorithms generate candidate morphologies [4, 5]. Multi-level simulation refines and optimizes designs. Experimental validation confirms predictions and updates the framework. The central contribution lies in bidirectional design-manufacturing integration, where design specifications inform fabrication planning, and quality control findings systematically update computational models.

The framework addresses the production-engineering challenge directly. It connects computational design outputs to a distributed manufacturing cell [6], routes fabrication quality decisions back to design constraints, and accumulates validated knowledge across projects. Validation on a biohybrid catheter demonstrated that constraint-guided design reduces trial-and-error iterations, and that manufacturing feedback prevents recurring fabrication failures.

The remainder of this paper proceeds as follows. Section 2 reviews related work in biohybrid design automation and design-manufacturing integration. Section 3 describes the framework architecture. Section 4 details the design-manufacturing integration loop. Section 5 reports validation results. Section 6 concludes.

2. Related work

Evolutionary computation has long generated morphologies for soft-bodied robots. Compositional pattern-producing networks encode body structure through compact generative representations [7]. NeuroEvolution of Augmenting Topologies evolves both network weights and topology [8]. Building on these methods, researchers evolved soft robots with multiple materials and showed that generative encodings produce more complex morphologies than direct encodings [9]. Later work co-optimized morphology and control within embodied machines [10]. These methods explore design spaces beyond human intuition. They target locomotion in simulated environments rather than manufacturable medical devices.

Recent work within the BioMeld project applied neuroevolution to biohybrid medical devices. Tsompanas and Balaz outlined an evolutionary morphology generator for a modular biohybrid catheter [4]. Alcaraz-Herrera and colleagues developed neuroevolution methods for soft medical device design [5], optimized the HyperNEAT substrate for soft actuators [11], and applied cooperative coevolution to morphology generation [12]. This body of work establishes that evolutionary algorithms can generate viable biohybrid morphologies. It does not address how generated designs connect to manufacturing.

Digital twin research integrates design, production, and feedback within unified information loops [3]. These approaches mature in conventional manufacturing, where geometry and material behavior remain stable and predictable. Biohybrid production differs in three respects. Living components introduce biological variability. Fabrication spans distributed specialized partners. Muscle tissue culture imposes long lead times. A bio-intelligent manufacturing cell for biohybrid machine fabrication has been demonstrated [6], yet its coupling to upstream computational design remained limited.

No existing framework closes the loop between AI-driven biohybrid design and physical manufacturing. Retrieval-augmented generation, which grounds language model outputs in retrieved knowledge [13], has seen little application to engineering constraint specification. This paper addresses both gaps.

3. Framework architecture

The framework organizes biohybrid machine design into four sequential stages connected by feedback loops (Fig. 1). Each stage transforms its inputs through combined computational and human processes. Computational tools execute routine high-volume tasks such as constraint formalization, morphology generation, and simulation. Human experts make the high-value judgments such as requirement prioritization, candidate selection, and validation interpretation. This division preserves expert authority where it matters while automating laborious steps.

Stage 1 (Problem Definition). The first stage converts natural language requirements into formal constraint specifications. A retrieval-augmented generation system [13] searches a library of twenty validated design templates and retrieves relevant precedents. A large language model then translates requirements into a machine-readable specification covering 313 parameters across seven categories: geometric, functional, physical, operational, manufacturing, regulatory, and environmental. A confidence score governs the workflow. High-confidence retrievals at or above 0.85 proceed automatically. Low-confidence cases below 0.65 trigger expert clarification. The stage produces three outputs: a machine-readable constraint specification, a human-readable template summary, and initialization recommendations for the next stage.

Stage 2 (Ideation). The second stage generates candidate morphologies through evolutionary search. Compositional pattern-producing networks encode body geometry [7], and NeuroEvolution of Augmenting Topologies evolves their structure [8]. Constraint specifications from Stage 1 configure the search by selecting coordinate systems, activation functions, and penalty weights. The search produces a population of 50 to 150 candidates that span the feasible design space. Project work established that this approach generates viable biohybrid morphologies [4, 5]. Experts then review the population and select three to eight candidates based on fitness, manufacturability, and design diversity.

Stage 3 (Digital Prototyping). The third stage refines selected candidates through a multi-level simulation hierarchy that matches computational cost to design phase. Voxelyze soft-body simulation screens all candidates rapidly, at approximately 100 times the speed of finite element analysis. COMSOL and Abaqus then provide high-fidelity predictions for the one to three strongest candidates. Machine learning surrogates, trained on finite element results, predict performance at more than 10,000 times the speed of direct simulation. Parametric optimization varies geometry, materials, and actuation patterns to maximize performance while respecting constraints. The stage outputs optimized specifications, performance predictions, manufacturing specifications, and validation protocols.

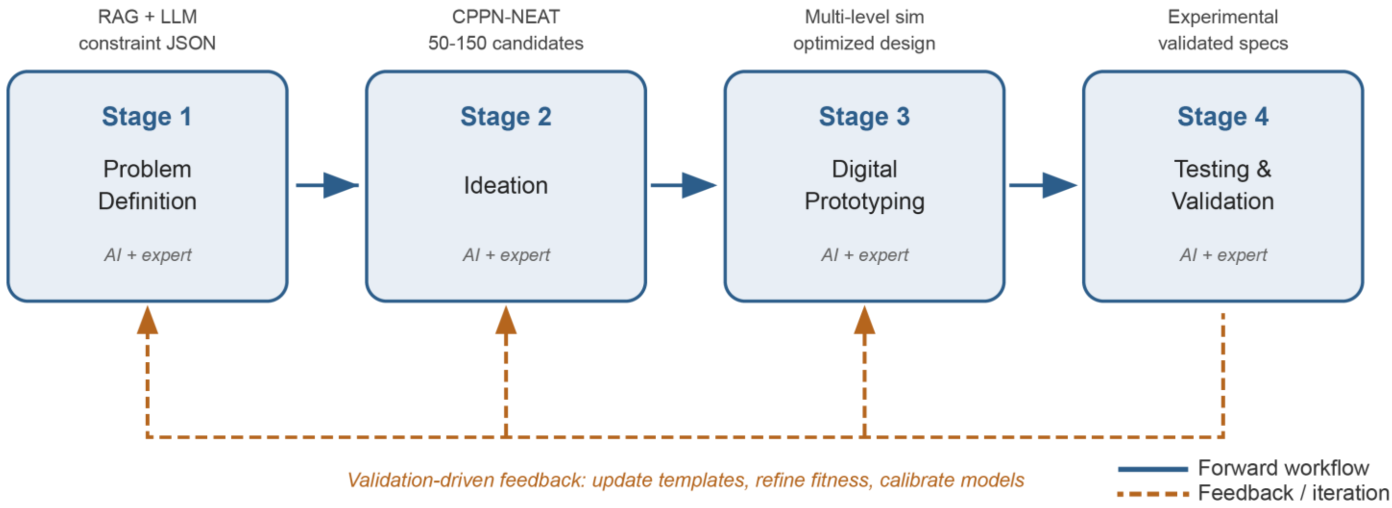

Fig. 1. Four-stage human-in-the-loop framework. The forward workflow (blue) proceeds from problem definition to validation. Validation-driven feedback (orange) updates earlier stages. Each stage combines AI automation with expert judgment.

Stage 4 (Testing and Validation). The fourth stage validates predictions experimentally and updates the framework. Experts design validation strategies that balance informativeness against resource constraints. Measured results calibrate simulation models and train machine learning predictors. Validation findings update framework knowledge through four channels: constraint template refinements, fitness function adjustments, simulation calibrations, and documented failure modes. These updates flow back to earlier stages, which closes the design loop and strengthens subsequent projects.

4. Design-manufacturing integration

The framework's distinguishing feature is bidirectional integration between design and manufacturing (Fig. 2). A forward path translates computational designs into fabrication instructions. A reverse path routes manufacturing outcomes back into computational models. Most design automation tools provide only the forward direction, which leaves fabrication knowledge stranded on the factory floor. The reverse path closes this gap.

Forward path. Stage 3 produces manufacturing specifications that include CAD models, bills of materials, process parameters, and dimensional tolerances. These specifications feed production planning tools that generate process flow charts and scheduling. Fabrication then proceeds across a distributed manufacturing cell composed of four specialized partners [6]. The partners perform catheter skeleton fabrication, flexible electronics integration, bioreactor preparation, and muscle tissue culture. Total production spans 19.5 working days. Muscle tissue bio-fabrication forms the critical path at 17 working days, which reflects the biological lead time that distinguishes biohybrid production from conventional manufacturing.

Quality control as a decision layer. Quality control nodes punctuate the production sequence. At each node, inspection results drive one of four decisions. An accept decision advances the component to the next operation. A reject decision scraps the component. A rework decision returns it to a prior operation. A redesign decision signals that the failure stems from the design itself rather than the fabrication. Redesign decisions activate the reverse path.

Reverse path. Manufacturing findings update the framework through several channels. When fabrication reveals systematic design limits, the framework records new constraints, adjusts fitness functions, and recalibrates simulation models. Four examples from catheter development illustrate the mechanism. First, force transmission degraded by 25 to 35 percent in features below 2 mm, which led to a minimum feature size constraint of 2 mm in Stage 1. Second, observed assembly tolerances informed alignment constraint ranges. Third, measured material properties, such as a validated polydimethylsiloxane stiffness range of 0.1 to 0.45 MPa, updated simulation inputs in Stage 3. Fourth, recurring fabrication failures, such as anchor detachment, became documented failure modes and fitness penalties in Stage 2. Each update prevents the corresponding failure from recurring in later designs.

Closing the loop. This bidirectional structure converts isolated fabrication experience into reusable design knowledge. Conventional workflows discard such experience after each project. The framework instead accumulates it, so that constraints, models, and penalties improve with every validated device. Fabrication limits enter Stage 1 as constraints, which lets designs respect production capabilities from the outset rather than failing at fabrication. The integration remains demonstrated at component level. System-level validation across multiple complete projects represents the next step for adopters.

4. **Validation and results**

Validation followed a component-level strategy. Each computational capability was tested against experimental data rather than against the complete workflow. This approach established quantified accuracy for the individual tools that the framework integrates.

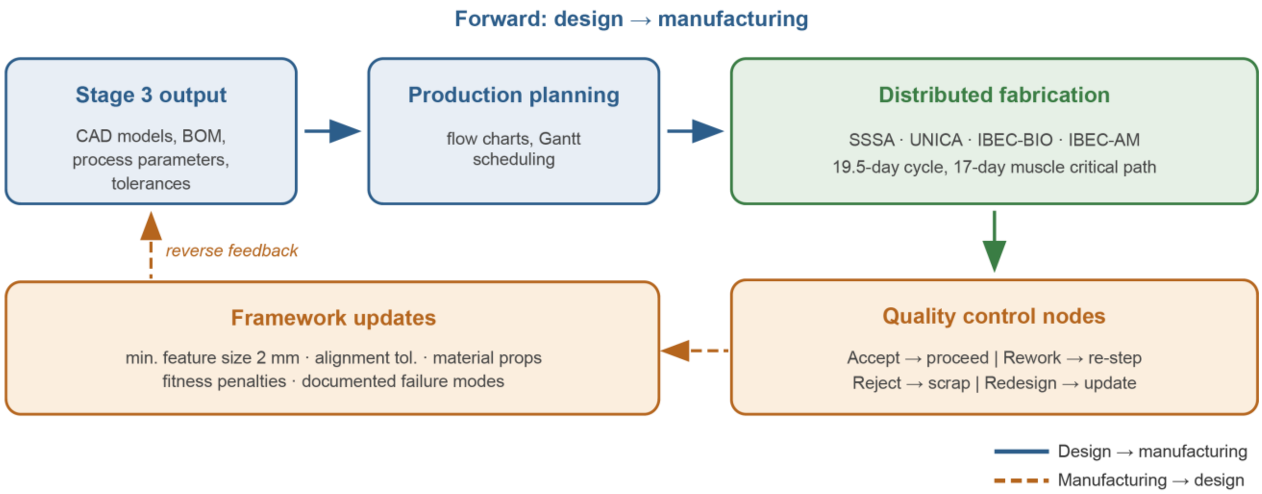

Fig. 2. Bidirectional design-manufacturing integration. The forward path (blue) converts Stage 3 outputs into production plans for distributed fabrication. Quality control decisions route findings through the reverse path (orange) to update framework constraints, fitness functions, and models. SSSA, UNICA, IBEC-BIO, IBEC-AM, represent acronyms of research groups involved in the BioMeld project (SSSA - Scuola Superiore Sant'Anna; UNICA - Università degli Studi di Cagliari; Institute for Bioengineering of Catalonia - IBEC).

Morphology generation. Autonomous evolutionary search, built on the neuroevolution methods developed for biohybrid morphology design [4, 5], rediscovered expert design practice without explicit guidance. Among the top-performing evolved morphologies, 48 percent (12 of 25) independently adopted the ring-like architecture that laboratory experts favor. The remaining morphologies revealed mechanically viable alternatives, such as thin films and bulk masses, that lie beyond conventional fabrication practice. This outcome shows that constraint-guided search both converges toward validated regions and explores beyond them. A systematic study of 486 evolutionary runs further examined whether the activation-function selection strategy affects search outcomes. Solution quality proved insensitive to this choice, which indicates that the method does not require careful tuning of this hyperparameter.

Simulation hierarchy. The multi-level simulation hierarchy delivers complementary speed and fidelity (Fig. 3). Voxelyze provides rapid comparative ranking at approximately 100 times the speed of finite element analysis, though it does not yield quantitative force predictions. Finite element analysis in COMSOL and Abaqus serves as the high-fidelity reference. Machine learning surrogates trained on finite element results reproduce predictions at more than 10,000 times the speed of direct simulation. A Random Forest surrogate for structural response achieved near-perfect agreement with COMSOL. A long short-term memory model reconstructed muscle force time-series with an R-squared of 0.9956. Surrogate accuracy holds within the trained domain and requires an upfront investment of roughly 10,000 finite element runs.

Manufacturing feedback. Validation also confirmed the reverse path. Fabrication of miniaturized variants exposed the scale-dependent force loss that became the 2 mm feature size constraint. Once encoded, this constraint prevented the same failure in subsequent designs. The mechanism converted a single fabrication failure into permanent framework knowledge.

Scope. These results establish component-level capability. System-level validation, which would measure the complete four-stage workflow across several independent projects, remains future work. The current evidence supports confidence-based deployment, where high-accuracy predictions guide computational design and lower-confidence regimes trigger targeted experimental verification.

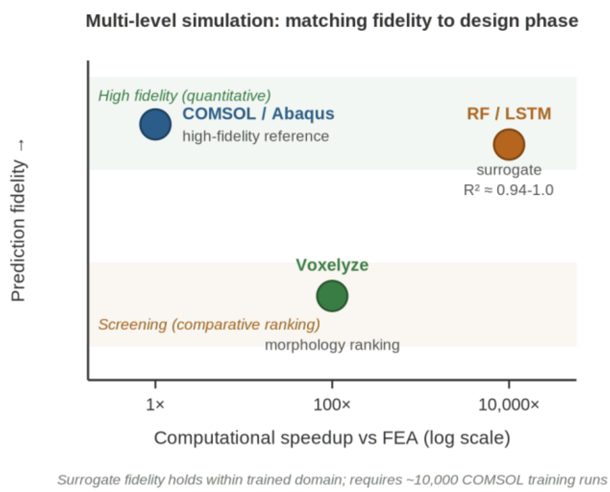

Fig. 3. Speed-fidelity trade-off across simulation levels. Voxelyze screens rapidly at low quantitative fidelity, finite element analysis anchors high fidelity at reference speed, and trained surrogates combine high speed with high fidelity within their trained domain.

6. Conclusion and outlook

This paper presented an AI-enhanced framework that integrates computational design with manufacturing for biohybrid machine production. The framework couples retrieval-augmented constraint specification, evolutionary morphology generation, and multi-level simulation within a four-stage workflow. Its central contribution is the bidirectional design-manufacturing loop, which converts quality control findings into reusable design knowledge.

Component-level validation established the capability of each computational tool. Evolutionary search rediscovered expert designs and identified viable alternatives. Machine learning surrogates reproduced finite element predictions at a fraction of the cost. Manufacturing feedback prevented recurring fabrication failures through encoded constraints. Together these results advance biohybrid development from artisanal trial and error toward systematic production engineering.

The framework remains validated at component level. System-level validation across several independent design projects is the natural next step, and it would quantify the reduction in design iterations that the framework targets. Near-term adoption can extend the template library beyond its current twenty entries, lower the entry barrier through guided interfaces, and broaden the approach to biohybrid machines beyond the catheter. The framework provides the infrastructure. Its value will grow as practitioners apply it, encounter new challenges, and contribute their solutions to the shared knowledge base.

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