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Metaheuristic Optimization in Biological Sciences: A Narrative Critical Review of Bioinformatics, Ecology, and Systems Biology

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Abstract

Biological optimization tasks require search procedures that match their representation, objectives and constraints. This narrative critical review connects sequence alignment, protein modeling, gene-expression feature selection, phylogenetic inference, conservation planning and systems biology through those methodological requirements. It distinguishes search quality from biological validity and identifies the evidence needed for fair comparisons. Documented examples include genetic alignment, Lamarckian docking, likelihood-based tree inference, spatial conservation scoring and cooperative network-model inference. The numerical performance and bibliometric compilations lack traceable source mappings and common evaluation records, so they are excluded from the validated synthesis. No systematic-review population, pooled hybrid advantage or universal algorithm ranking is established. The review develops a research agenda centered on identifiability, independent biological validation, matched computational budgets and transparent data and code.

Keywords: Metaheuristics, Computational biology, Bioinformatics, Conservation planning, Systems biology, Validation, Reproducibility.

1 | Introduction

Biological optimization spans sequence alignment, structural modeling, feature selection, phylogenetic inference, conservation planning and dynamic model calibration. These tasks differ in representation,

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objective, constraints and observational uncertainty. A general search architecture must therefore be adapted to the biological question rather than justified only by its metaphor or by performance on synthetic objective functions [1], [2]. This review examines those connections and the requirements for interpreting comparative claims.

Large search spaces are common but do not alone establish an NP-hardness result or the failure of all deterministic methods. Wang and Jiang analyze the complexity of multiple sequence alignment under sum-of-pairs scoring [3]. For n labeled taxa, the number of unrooted binary tree topologies is $(2n - 5)!!$; it is approximately 2.22×10^{20} for $n = 20$ and 2.84×10^{74} for $n = 50$. These counts explain the challenge of enumeration, but they do not quantify the runtime of a particular phylogenetic search or replace a formal complexity analysis.

A metaheuristic guides candidate generation, evaluation and selection without generally certifying a global optimum in a finite run [1]. The relevant biological contribution depends on what is optimized and how the candidate is represented. Improving a sequence score, an energy function, a classification loss or a conservation penalty are distinct achievements, each conditional on its model and validation protocol.

Evolutionary, swarm and trajectory-based methods offer different search mechanisms. Differential evolution forms trial vectors from population differences [4]; particle swarm optimization uses individual and social search information [5]; ant-system methods construct combinatorial candidates [6]; simulated annealing uses temperature-dependent acceptance [7]. Inspiration-based families overlap conceptually and should not be treated as mutually exclusive mathematical classes.

Parallel evaluation may help when independent candidate evaluations dominate the runtime, but synchronization, memory and model-evaluation costs can limit the gain. Multi-objective methods such as NSGA-II maintain non-dominated candidate sets [8]. In biology, cost, accuracy, parsimony and ecological representation may conflict; the resulting trade-offs remain conditional on the validity of their objectives and constraints.

The review connects molecular, organismal and ecological decisions through their formulation and evidence requirements. Its cross-domain perspective is useful for transferring representations and validation principles. It does not establish the first comprehensive systematic review, a complete census of applications or a universally effective optimizer. A verified corpus and a common evaluation design would be required for those stronger claims.

The questions are how biological problem structure affects representation and search, what a hybrid component contributes, and what evidence supports a comparison. Particular attention is given to separating a documented algorithmic mechanism from an unverified numerical compilation. Hybridization is treated as a design choice requiring validation rather than a default source of superiority.

Section 2 examines representations and multi-objective formulations. Section 3 specifies the narrative evidence boundary. Section 4 considers six biological application domains, Section 5 examines comparative interpretation, and Section 6 discusses bibliometric requirements. Sections 7 and 8 identify limitations and research priorities, followed by the conclusion.

2 | Theoretical Background

2.1 | Classification of Metaheuristic Algorithms in Biological Contexts

A useful classification records both the update mechanism and the biological representation. *Table 1* provides a descriptive taxonomy of familiar algorithm names and potential application contexts. Its listed examples are schematic associations, not a measured prevalence distribution or evidence that every listed application has been demonstrated by the originating algorithm paper.

Table 1. Descriptive algorithm taxonomy.

Algorithm	Abbreviation	Category	Year	Biological/Physical Inspiration	Typical Application in Biology
Genetic Algorithm	GA	Evolutionary	1975	Darwinian natural selection and genetics	MSA, phylogenetics, feature selection, reserve design
Simulated Annealing	SA	Physics-based	1983	Thermodynamic annealing of metals	Protein folding, molecular docking, phylogenetics
Particle Swarm Optimization	PSO	Swarm Intelligence	1995	Social behavior of bird flocking and fish schooling	Gene selection, parameter estimation, neural network training
Ant Colony Optimization	ACO	Swarm Intelligence	1996	Pheromone trail-following in ant colonies	MSA, DNA motif finding, pathway analysis
Differential Evolution	DE	Evolutionary	1997	Differential mutation of vector populations	ODE parameter estimation, energy minimization, systems biology
Artificial Bee Colony	ABC	Swarm Intelligence	2005	Foraging behavior of honey bee colonies	Protein structure prediction, gene clustering
Firefly Algorithm	FA	Swarm Intelligence	2009	Bioluminescent signaling in fireflies	Feature selection, classification, clustering
Cuckoo Search	CS	Swarm Intelligence	2009	Brood parasitism in cuckoo birds; Lévy flights	Gene regulatory network inference, biomarker discovery
Bat Algorithm	BA	Swarm Intelligence	2010	Echolocation behavior of microbats	Molecular docking, drug design
Grey Wolf Optimizer	GWO	Swarm Intelligence	2014	Leadership hierarchy and hunting strategy of grey wolves	Species distribution modeling, feature selection, ecological optimization
Whale Optimization Algorithm	WOA	Swarm Intelligence	2016	Bubble-net hunting strategy of humpback whales	Medical image segmentation, EEG signal classification

Note: Introduction-year labels follow the named canonical formulations; application labels are illustrative rather than quantitative evidence of usage or effectiveness.

Evolutionary search uses variation and selection on an encoded candidate. Binary strings can represent selected features or planning units; real-valued vectors can represent kinetic parameters; structured objects can represent alignments or trees. Differential evolution combines difference-based mutation with recombination rather than replacing recombination altogether [4]. Its continuous representation explains a modeling fit, not general superiority in systems biology.

Particle swarm optimization requires a specified position, velocity and boundary rule [5]. Ant-system construction requires a graph, feasible moves and pheromone updates [6]. Discrete transfer functions or domain-specific construction rules change these mechanisms and must be described. The biological setting does not automatically make a swarm method more appropriate than local search, mathematical programming or a specialized inferential procedure.

Simulated annealing provides a trajectory-based search mechanism [7]. Asymptotic convergence statements depend on explicit assumptions about cooling and reachability and do not certify the quality of a practical finite run. Its documented use in Marxan conservation planning illustrates a link between spatial decisions and a defined score [9].

2.2|Encoding Schemes for Biological Optimization Problems

Representation determines which candidates and moves are admissible. Four recurring forms are binary selection, continuous parameters, permutations and hierarchical structures. These are modeling choices rather than guarantees of effectiveness.

Binary encoding assigns a selection indicator to each feature or planning unit. With p candidate features there are 2 raised to p possible subsets. A search procedure still needs a feasible-subset rule, an evaluation design

and constraints on subset size. Feature selection must occur inside the training procedure to avoid using held-out biological outcomes during model selection [10].

Real-valued encoding is appropriate for continuous kinetic or model parameters. Differential evolution and particle swarm optimization operate in this space [4], [5]. Bounds, identifiability, observation error and numerical integration tolerance remain properties of the biological calibration problem and cannot be delegated to the optimizer.

Permutation encoding is useful when the decision is an ordering, such as a schedule or scaffold sequence. Variation should preserve a valid permutation or use an explicit repair. A permutation is not a general substitute for a phylogenetic tree or a gapped alignment; those objects require representations that preserve their own structure.

A tree representation can encode topology and branch information separately. Rearrangement operators define admissible topological moves, and continuous branch parameters can be optimized conditionally. The likelihood model and the uncertainty attached to phylogenetic inference are separate from the choice of search operator [11].

2.3 | Multi-Objective Optimization in Biology

Multi-objective biological decisions can balance predictive performance with parsimony or biodiversity representation with cost. The objectives should remain interpretable, and hard requirements should not be relaxed silently through arbitrary penalties. NSGA-II is one documented non-dominated search architecture [8]; it is not a universal biological standard or evidence that every reported front is globally Pareto-optimal.

A non-dominated candidate cannot be improved in one stated objective without worsening another within the compared candidate set. This finite-set property does not imply that no better feasible solution exists elsewhere. A reported frontier should therefore be described as an approximation and evaluated for feasibility, diversity and sensitivity to objective scaling.

3. | Narrative Review Method and Evidence Boundary

This article is a narrative critical review. It uses identifiable methodological and biological sources to compare formulations and validation requirements. It does not claim a registered systematic-review protocol, a completed PRISMA selection process or a validated meta-analysis.

3.1 | Literature Scope

The scope includes sequence analysis, protein modeling, feature selection, phylogenetics, conservation planning and systems biology. Foundational algorithm papers and selected domain examples provide conceptual connections. The numerical search compilation in *Table 2* lacks the database exports, exact full queries, screening decisions and included-study identifiers needed to establish a reproducible systematic search. Its counts are not used to define the evidence population.

Table 2. Unverified search-count compilation.

Database	Search Query (Abbreviated)	Initial Results	After Duplicate Removal	After Title/Abstract Screening	After Full-Text Assessment	Final Included
PubMed	("metaheuristic" OR "genetic algorithm" OR "particle swarm" OR "differential evolution" OR "ant colony") AND ("bioinformatics" OR "gene expression" OR "protein structure" OR "phylogenetic" OR "ecological modeling" OR "systems biology")	1,842	1,653	612	198	156

Table 2. Continued.

Database	Search Query (Abbreviated)	Initial Results	After Duplicate Removal	After Title/Abstract Screening	After Full-Text Assessment	Final Included
Scopus	TITLE-ABS-KEY(metaheuristic* OR "evolutionary algorithm" OR "swarm intelligence") AND TITLE-ABS-KEY(bioinformatics OR "computational biology" OR ecology OR "systems biology")	2,376	1,891	743	231	187
Web of Science	TS=("optimization algorithm*" OR "metaheuristic*") AND TS=("biological" OR "bioinformatics" OR "protein" OR "gene" OR "ecological" OR "phylogen*")	1,956	1,287	524	168	139
IEEE Xplore	("metaheuristic" OR "bio-inspired optimization") AND ("bioinformatics" OR "computational biology" OR "biomedical")	987	764	289	87	72
Total (after cross-database deduplication)		7,161	4,218	1,437	489	347

Note: The reported database and screening counts have not been linked to identifiable records and are excluded from quantitative synthesis.

3.2 | Evidence Selection

A relevant source must identify a biological decision or explain a search or validation principle used in that decision. Methodological reviews are useful for context but do not substitute for primary performance data. Synthetic-function benchmarks cannot establish superiority on biological applications. A complete domain evidence extraction would need task identities, objective definitions, datasets, algorithms, budgets and source locations for every reported quantity.

3.3 | Quality Criteria

The quality criteria concern problem formulation, representation, feasibility, matched comparisons, independent validation and reproducibility. No measured inter-rater agreement or independently completed quality-scoring exercise is asserted. Such claims require reviewer identities, a defined rubric and the underlying study-level assessments.

3.4 | Synthesis Boundary

The synthesis is qualitative. *Tables 3-10* preserve a numerical compilation whose source mappings, common evaluation conditions and generating records remain unverified. Their numbers are not treated as pooled effects, reproducible benchmark results or statistical evidence of an optimizer advantage. *Table 11* likewise lacks a traceable bibliometric corpus. These limits apply to every comparative interpretation in the article.

4 | Applications in Biological Sciences

The six domains below are compared through their decisions, representations and validation requirements. Identifiable sources establish methodological connections. The accompanying numerical compilations remain outside the validated synthesis.

4.1|Sequence Analysis and Alignment

Multiple sequence alignment optimizes a stated scoring rule over gapped biological sequences. Complexity depends on the formulation; the sum-of-pairs problem is analyzed by Wang and Jiang [3]. A higher score is not automatically a more accurate reconstruction of evolutionary homology, so biological benchmark accuracy and objective value should be reported separately.

SAGA is a documented genetic-algorithm approach to sequence alignment [12]. Its relevance is the use of domain-specific variation on alignments. This establishes an algorithmic connection, not the numerical values attributed to it in *Table 3*. Later methods require their own verified representations and benchmark protocols.

BAliBASE 3.0 provides reference alignments for evaluation [13]. Sum-of-pairs and total-column accuracy measures assess different aspects of agreement with a reference. Version identity, sequence subsets and scoring conventions must be held fixed in a comparison. Source dates in *Table 3* precede the benchmark version for some rows; without a documented later reimplementation those rows cannot be read as results from the original cited studies.

Table 3. Unverified alignment-performance compilation.

Algorithm	BAliBASE Category	SP Score	TC Score	Computation Time (s)	Improvement over ClustalW (%)
GA-MSA (SAGA)	RV11 (equidistant)	0.891	0.724	342	+5.2
PSO-MSA	RV11 (equidistant)	0.884	0.708	287	+4.4
ACO-MSA	RV11 (equidistant)	0.872	0.695	518	+2.9
ABC-MSA	RV11 (equidistant)	0.897	0.741	276	+5.9
Hybrid GA-PSO-MSA	RV11 (equidistant)	0.912	0.768	415	+7.6
DE-MSA	RV11 (equidistant)	0.905	0.752	198	+6.8
GWO-MSA	RV11 (equidistant)	0.908	0.759	231	+7.1
ClustalW (baseline)	RV11 (equidistant)	0.847	0.672	12	

Note: Numerical entries and attribution strings are retained as reported and do not establish a common BAliBASE 3.0 comparison.

The trade-off between alignment quality and computational cost is meaningful only under a matched protocol. An algorithm published before a benchmark can be reimplemented on it later, but the reimplementation, code, settings and measurements must be identified. Chronological inconsistency cannot be resolved by assigning an unsourced score to the originating paper.

Other sequence tasks, such as motif discovery or primer selection, require their own objectives and validation. Alignment, motif enrichment and primer specificity are not interchangeable outcomes. A credible comparison should state which biological property is measured and avoid transferring accuracy figures between distinct tasks.

4.2|Protein Structure Prediction and Folding

Protein structure modeling involves structural representations and objectives whose relationship to biological conformation must be justified. Energy minimization and agreement with an experimental reference are distinct measures. A lower value from one energy function is not directly comparable with a value from another, and cannot alone certify a more accurate structure.

Simplified search models can test conformational operators, while realistic structure prediction introduces richer physical and learned constraints. Modern learned structure prediction, exemplified by AlphaFold [14], answers a different modeling question from a generic optimizer benchmark. Search may support refinement or sampling, but the contribution requires controlled evaluation rather than a universal energy-minimization claim.

A structural benchmark comparison must identify targets, versions, templates, training information and scoring procedures. *Table 4* attributes later CASP targets to papers with earlier dates and mixes different targets. It therefore cannot support a common comparative ranking without a documented reimplementation and target-level extraction.

Table 4. Unverified protein-performance compilation.

Algorithm	Protein Target	GDT-TS Score	RMSD (Å)	Energy (Kcal/Mol)	Iterations ($\times 10^3$)
GA-Fragment Assembly	CASP11-T0837	42.8	8.72	−287.4	500
DE-Rosetta Refinement	CASP11-T0837	48.3	7.14	−312.6	250
PSO-Torsion Angle Opt.	CASP11-T0837	39.6	9.51	−264.8	800
ABC-Conformational Search	CASP11-T0837	44.1	8.24	−295.7	350
SA-Monte Carlo	CASP11-T0837	46.5	7.68	−303.1	1,200
Hybrid DE-SA	CASP12-T0886	56.2	5.43	−348.9	400
GA-Neural Network Hybrid	CASP13-T0950	61.7	4.82	−372.3	300
WOA-Rosetta Refinement	CASP14-T1024	52.4	6.15	−331.5	450

Note: Target identities, source attribution and common evaluation conditions require validation; entries are excluded from comparative conclusions.

The structure literature cannot be summarized by treating energy, RMSD and GDT-TS as interchangeable or by ranking values from different targets. A hybrid method should identify the source of learned constraints and isolate the contribution of search under a common starting model and budget. The numerical compilation does not currently establish that differential evolution or any hybrid is consistently superior.

AutoDock4 documents a docking architecture with a Lamarckian genetic search and local optimization [15]. Molecular docking predicts binding poses under a scoring model and is distinct from de novo protein folding. A source on GPU acceleration or gradient-based local search should not be relabeled as evidence for differential evolution.

4.3|Gene Expression Analysis and Feature Selection

Gene-expression feature selection faces a large number of candidate variables relative to biological samples. The statistical task is to identify predictive and stable features while evaluating generalization outside model selection. Feature-selection frameworks and their biological roles are reviewed by Saeys et al. [10]. Compactness, prediction and functional interpretation are separate objectives.

A binary feature selector explores 2 raised to p subsets for p candidate genes. This count motivates restricted search but does not prove that a particular optimizer is necessary or dominant. Preprocessing, feature selection, hyperparameter tuning and classifier fitting must be performed within the training folds, with independent data reserved for final assessment.

The dataset names and dimensions in *Table 5* do not, by themselves, define a comparable experiment. Different preprocessing, train–test splits and selected sample subsets can yield different results under the same dataset label. Each row requires an identifiable primary source or a released common reimplementation before its accuracy, AUC or feature-reduction value can be compared.

Table 5. Unverified gene-expression performance compilation.

Algorithm	Dataset (Genes × Samples)	Selected Features	Classification Accuracy (%)	AUC-ROC	Reduction Ratio (%)
Binary GA-SVM	Leukemia (7,129 × 72)	23	97.2	0.981	99.68
Binary PSO-KNN	Leukemia (7,129 × 72)	31	95.8	0.969	99.57
MOBPSO-SVM	Leukemia (7,129 × 72)	18	98.6	0.993	99.75
DE-Random Forest	Colon (2,000 × 62)	12	93.5	0.952	99.40
ABC-SVM	Colon (2,000 × 62)	15	91.9	0.938	99.25
GWO-SVM	Colon (2,000 × 62)	14	94.4	0.961	99.30
Cuckoo Search-KNN	Lymphoma (4,026 × 62)	27	96.8	0.978	99.33
FA-Random Forest	Lymphoma (4,026 × 62)	34	95.2	0.964	99.16
SIW-APSO-ELM	Breast Cancer (24,481 × 97)	42	96.9	0.982	99.83
Hybrid GA-PSO-SVM	Breast Cancer (24,481 × 97)	35	97.8	0.989	99.86

Note: Dataset versions, source rows, feature selection and validation protocols are unresolved; numerical entries are not pooled or ranked.

The displayed feature-reduction percentages describe the retained subset relative to the stated feature count. They do not establish preserved out-of-sample performance or biological relevance. Classifier choice and nested selection can affect the result as much as the optimizer. External cohorts, stability analyses and biological validation address questions that a high internal classification score cannot answer.

Claims that selected genes identify disease pathways require traceable gene identifiers, an enrichment background and a documented analysis. A predictive signature can be useful without constituting a causal mechanism. The review does not infer clinical efficacy or pathway confirmation from unverified optimization tables.

4.4 | Phylogenetic Tree Construction

Maximum-likelihood phylogenetic inference optimizes the likelihood of aligned observations under a substitution model [11]. The topology count $(2n - 5)!!$ is approximately 2.84×10^{74} for 50 labeled taxa. Search avoids exhaustive enumeration, while inference still depends on the alignment, substitution model, branch treatment and uncertainty analysis.

Topology search may use stochastic variation, local rearrangements or their combination. Algorithm families should be compared through the moves they implement and their stopping rules. A genetic label does not confer a statistical interpretation on a tree, and a high likelihood does not establish that the inferred topology is the biological truth.

Table 6 lacks row-level source mappings, sequence alignments, substitution models and matched runtime measurements. Its log-likelihoods, tree lengths and distances cannot establish an algorithm order. A Robinson–Foulds comparison also requires a defined reference tree and compatible taxa.

Table 6. Unverified phylogenetic-performance compilation.

Algorithm	Dataset (Taxa)	Log-Likelihood	Tree Length	Robinson-Foulds Distance	Time (Min)
GA-ML (GARLI)	rbcL-55 (55)	−17,432.7	4.218	4	48
PSO-Tree Search	rbcL-55 (55)	−17,489.3	4.247	8	72
ACO-Phylogeny	rbcL-55 (55)	−17,456.1	4.231	6	93
SA-Tree Search	rbcL-55 (55)	−17,441.2	4.223	4	67
DE-Tree Optimization	rbcL-55 (55)	−17,438.5	4.219	4	55
GA-ML (GARLI)	Zilla-500 (500)	−87,623.4	18.742	32	847
Hybrid GA-SA	Zilla-500 (500)	−87,591.8	18.698	26	1,124
RAxML (non-metaheuristic baseline)	rbcL-55 (55)	−17,430.1	4.215	2	15

Note: Source datasets, models, reference trees and runtime protocols must be established before interpretation.

Comparative phylogenetic evaluation should state the optimization target, starting trees, branch optimization and total likelihood evaluations. The same likelihood scale is needed for a numerical comparison. A

topological distance is descriptive relative to a chosen reference, not a certificate of causal evolutionary accuracy. Numerical entries in *Table 6* remain outside the validated synthesis.

4.5 | Ecological Modeling and Conservation Biology

Ecological optimization includes model calibration and spatial planning, with uncertainty in observations, future environments and management priorities. The search layer evaluates a stated model; biological validity and policy consequences require separate evidence. The conservation-planning example below illustrates that distinction.

The official Marxan manual describes selection of planning units using a score containing planning cost, a spatial boundary term and penalties for unmet representation targets [9]. Penalty weights and the boundary modifier encode priorities. A low combined score should be accompanied by explicit target attainment and spatial interpretation; it cannot be compared across incompatible penalties or study regions.

Species-distribution modeling requires independent spatial evaluation and attention to sampling bias. Tuning a predictive model through a metaheuristic may improve a selected score, but it does not by itself establish habitat realism or conservation benefit. Table 7 lacks the extraction and validation records needed to verify its ecological performance claims.

Table 7. Unverified ecological-performance compilation.

Algorithm	Ecological Problem	Study Area / Dataset	Objective Function Value	Species Coverage (%)	Area Efficiency (%)
SA (Marxan)	Marine reserve selection	Great Barrier Reef, Australia	1,247 (cost units)	92.4	33.2
GA-Reserve Design	Terrestrial reserve network	Cerrado Biome, Brazil	3,812 (cost units)	88.7	28.6
NSGA-II Reserve	Multi-objective reserve selection	Pacific Northwest, USA	Pareto front (15 solutions)	85.3–96.1	22.4–41.7
ACO-Corridor Design	Wildlife corridor optimization	Western Ghats, India	87.3 (connectivity index)	79.2	18.5
GWO-BPNN (GNNA)	Species distribution modeling	23 species, global	AUC = 0.912		
PSO-MaxEnt Tuning	SDM hyperparameter optimization	European birds (127 species)	AUC = 0.897		
DE-Population Viability	PVA parameter estimation	Iberian lynx, Spain	MSE = 0.0031		

Note: Study areas, source results and metric definitions are not reconciled; entries do not support cross-region optimizer rankings.

Multi-objective planning can expose feasible alternatives balancing representation, cost and connectivity [8]. The returned set is an approximation, and final decisions depend on priorities and model uncertainty. A Pareto presentation is useful when these trade-offs are explicit, but does not remove the need for ecological constraints or establish complete global optimality.

4.6 | Systems Biology and Gene Regulatory Networks

Systems biology combines mechanistic models and observations to examine biological dynamics. Parameter calibration and network-topology inference are related but distinct inverse problems. A favorable fitted score must be assessed together with identifiability, observation assumptions and predictive behavior.

For n genes, a directed signed graph without self-edges has $n(n-1)$ potential edges and 3 raised to $n(n-1)$ signed configurations when activation, repression and absence are separate states. GRN inference requires more than choosing among these configurations. Model assumptions, perturbation data, noise and identifiability affect which interactions can be supported [16]. DREAM-related benchmark work illustrates the need for explicitly defined inference and evaluation tasks [17].

Table 8 does not identify the particular network, simulations, train–test information or generating implementation for each result. Precision, recall and their derived F1 measure must refer to the same edge set and averaging convention. Numerical agreement within a row cannot establish biological or computational provenance.

Table 8. Unverified gene-network performance compilation.

Algorithm	Network Size (Nodes/Edges)	Precision	Recall	F1-Score	AUROC
GA-Boolean Network	DREAM4-10 (10 / 15)	0.687	0.613	0.648	0.791
DE-S-System	DREAM4-10 (10 / 15)	0.724	0.667	0.694	0.832
PSO-DBN	DREAM4-10 (10 / 15)	0.698	0.640	0.668	0.808
CS-ODE Model	DREAM4-10 (10 / 15)	0.712	0.653	0.681	0.819
Hybrid DE-PSO	DREAM4-10 (10 / 15)	0.756	0.693	0.723	0.857
GA-Boolean Network	DREAM4-100 (100 / 176)	0.423	0.381	0.401	0.694
DE-S-System	DREAM4-100 (100 / 176)	0.487	0.432	0.458	0.738
Hybrid DE-PSO	DREAM4-100 (100 / 176)	0.512	0.458	0.483	0.761
NSGA-II-GRN	DREAM4-100 (100 / 176)	0.498	0.467	0.482	0.752

Note: Network identities, source mappings and evaluation conventions require validation before comparative interpretation.

Different network and parameter representations produce different search problems. Kimura and colleagues describe cooperative coevolution for S-system network inference [18]; this should not be relabeled as generic DE superiority. The present numerical compilation does not establish that a DE–PSO hybrid has the best performance across identifiable DREAM networks.

Dynamic-model calibration can contain weakly identified parameter combinations, as illustrated by work on sloppy sensitivities in systems biology [19]. Search may find several parameter vectors with similar fit, but optimizer diversity is not a confidence interval. Independent predictions, sensitivity analysis and an appropriate inferential framework are needed to interpret those solutions.

Metabolic optimization includes problems that can be expressed through mathematical programming and problems involving discrete interventions. These cases require their own formulations. A metaheuristic should be justified by the resulting decision structure, rather than assumed necessary for every biological model or every flux analysis.

5 | Interpretation of Comparative Numerical Compilations

5.1 | Cross-Domain Comparability

Table 9 retains cross-domain labels, gaps and p-values whose study-level evidence has not been established. No complete common algorithm-by-instance score matrix or effect-size extraction is available. These entries cannot identify the best algorithm in a domain or support a pooled cross-domain conclusion.

Table 9. Unverified cross-domain ranking compilation.

Biological Domain	Problem Type	Best Algorithm	Second Best	Solution Quality Gap (%)	Statistical Significance (p-Value)
Sequence Analysis	Multiple Sequence Alignment	Hybrid GA-PSO	DE-MSA	1.2	0.034
Protein Structure	Ab initio folding	Hybrid DE-SA	GA-Fragment Assembly	3.8	0.012
Protein Structure	Molecular docking	Lamarckian GA	DE-Docking	1.5	0.047
Gene Expression	Feature selection (microarray)	Hybrid GA-PSO-SVM	MOBPSO-SVM	0.8	0.089
Gene Expression	Feature selection (RNA-seq)	GWO-SVM	DE-Random Forest	1.4	0.028
Phylogenetics	ML tree search	GA-ML (GARLI)	Hybrid GA-SA	0.3	0.156
Ecological Modeling	Reserve selection	SA (Marxan)	NSGA-II	2.1	0.019
Ecological Modeling	Species distribution	GWO-BPNN	PSO-MaxEnt	1.7	0.031
Systems Biology	GRN inference	Hybrid DE-PSO	DE-S-System	2.4	0.008
Systems Biology	ODE parameter estimation	Adaptive DE (SHADE)	jDE	1.1	0.042

Note: Best-algorithm labels, gaps and p-values are unvalidated reporting and are excluded from the review conclusions.

Cross-domain transfer should concern representations and mechanisms, not a pooled league table of incompatible scores. Alignment accuracy, protein-structure error, classification performance and conservation cost have different meanings and evaluation units. Any quantitative synthesis must specify which comparable effects are combined and how uncertainty, dependence and study quality are treated.

5.2 | Hybrid Metaheuristic Approaches in Biology

Hybridization combines components that perform different mathematical roles. A classifier can evaluate a feature subset, a local search can refine a candidate, and a surrogate can approximate an expensive objective. These are distinct forms of combination. Their benefit must be measured with matched evaluation budgets and suitable ablations.

A feature-selector–classifier pipeline searches for subsets whose prediction performance is assessed by a classifier. The classifier is an evaluator, not necessarily a second optimizer. A valid nested evaluation must isolate final assessment data from every selection or tuning step [10].

Combining two search rules creates a hybrid whose order, state exchange, control parameters and acceptance mechanism must be specified. Merely assigning labels such as GA–SA or DE–PSO does not determine an executable algorithm. Local and global evaluation costs should be counted together.

A learned surrogate or initialization model can guide search, but the final candidate should be checked through the stated underlying evaluator. *Table 10* does not provide traceable primary comparisons or matched budgets for its reported gains and speedups. It is not evidence that deep-learning hybrids dominate biological optimization.

Table 10. Unverified hybrid-performance compilation.

Hybrid Method	Application Domain	Accuracy/Quality Improvement (%)	Computation Speedup
GA-SVM	Microarray cancer classification	+3.4 (vs. GA-KNN)	1.2×
PSO-Random Forest	RNA-seq feature selection	+2.8 (vs. PSO-SVM)	1.5×
DE-Neural Network	ODE parameter estimation	+8.2 (vs. standalone DE)	3.4×
GA-SA (GARLI)	Phylogenetic ML tree search	+0.6 (log-likelihood)	0.7× (slower)
GWO-BPNN	Species distribution modeling	+4.7 (AUC vs. BPNN alone)	0.9×
DE-PSO-S-System	Gene regulatory network inference	+5.3 (F1 vs. DE alone)	0.8× (slower)
DL-guided GA-MSA	Multiple sequence alignment	+3.1 (SP score vs. GA-MSA)	2.8×
AlphaFold2 + DE Refinement	Protein structure refinement	+1.2 (GDT-TS)	0.6× (slower)

Note: Reported gains, speedups and attribution labels require primary source extraction and are not accepted as comparative evidence.

A claim that a transformer-guided alignment optimizer improves accuracy and convergence requires an identifiable paper, an explicit sequence representation and evaluation records. Biological contact prediction, alignment scoring and conformational sampling should not be conflated. No gain is inferred from the unsupported values in *Table 10*.

5.3 | Scalability Analysis Across Problem Sizes

Scalability must be evaluated on a stated implementation and biological task. Population size and representation dimension account for only part of the cost; objective evaluation, constraints, synchronization and data access can dominate.

For a basic vector-population implementation, updating candidates may take cost proportional to population size times dimension. This excludes the cost of evaluating biological objectives and does not establish how many iterations are needed for a target solution quality.

Swarm and evolutionary methods require comparable accounting of update, evaluation and memory costs. No dimension threshold establishes a universal speed advantage of one family over another. Scaling claims should be measured with task identities, hardware and achieved solution quality.

Trajectory-based search can use inexpensive local changes when the objective admits incremental updates. Parallel candidate evaluation or multiple trajectories may help, but the attainable gain depends on synchronization and the model. A generic search label is insufficient to assert scalability to a specific number of planning units.

5.4 | Conditions for Statistical Comparison

Friedman testing ranks the same algorithms within each independent problem instance; it requires a complete matched design. *Table 9* supplies only best and second-best labels, not such a score matrix. The previously reported omnibus statistic cannot be reproduced from that table and is not asserted as a validated result.

The five reported average ranks, 1.85, 2.15, 2.60, 3.25 and 3.80, sum to 13.65, whereas valid complete ranks for five algorithms must sum to 15, including averaged ties. They therefore cannot establish the stated Friedman or Nemenyi inference. For illustration of the method only, the usual Nemenyi convention with five algorithms, ten independent instances and $q = 2.728$ gives a critical difference of about 1.93; this is not a reconstructed test result for the unverified compilation.

6 | Bibliometric Evidence Requirements

A bibliometric growth claim requires database versions, exact queries, dates, record identities and a reproducible deduplication procedure. The reported publication-count trajectory is not linked to such a corpus and is excluded from the conclusions. Arithmetic consistency of a growth rate alone would not validate the records or explain the cause of a trend.

The relation between a technological development and publication activity is an empirical question. Chronological coincidence with sequencing advances or learned protein prediction does not identify a causal mechanism. A trend analysis would need a defined corpus and an explicit analytic design rather than an unsupported account of methodological inflection points.

Table 11 retains journal counts and impact-factor labels whose records, counting rule and reporting year are unverified. The table does not establish journal rank, bibliometric coverage or current journal metrics.

Table 11. Unverified journal-count and metric compilation.

Rank	Journal	Publication Count	Impact Factor (2024)	Primary Domain
1	BMC Bioinformatics	142	2.9	Bioinformatics, gene expression
2	Bioinformatics (Oxford)	118	4.4	Sequence analysis, structure prediction
3	PLOS Computational Biology	97	3.8	Systems biology, network inference
4	IEEE/ACM Transactions on Computational Biology and Bioinformatics	86	3.6	Algorithm development, feature selection
5	Journal of Computational Biology	73	1.4	Phylogenetics, sequence alignment
6	Briefings in Bioinformatics	64	6.8	Reviews, multi-omics integration
7	Scientific Reports	58	3.8	Diverse biological applications
8	Ecological Modelling	52	2.6	Species distribution, conservation
9	Biological Conservation	41	4.9	Reserve design, spatial conservation
10	Proteins: Structure, Function, and Bioinformatics	38	2.9	Protein structure prediction, docking

Note: No ranking or journal-metric conclusion is drawn from these entries.

Country shares require a documented rule for full or fractional affiliation counting and treatment of multi-country papers. Citation-impact comparisons require a fixed date, citation source and normalization convention. No geographic share or country ranking is asserted from the unsupported compilation.

Interdisciplinary collaboration may be useful, but a causal or quantitative citation advantage requires a defined disciplinary coding and adjustment for relevant confounding factors. The review does not infer such an advantage without the underlying authorship and citation records.

7 | Challenges and Limitations

The principal limitation of this review is the evidence status of its quantitative compilations. It offers a narrative methodological analysis, while the search population, extracted performance values, inferential calculations and bibliometric records remain unverified.

Scaling to larger biological tasks increases representation and objective-evaluation costs. Weakly identified models and correlated observations can also limit what is scientifically learnable, independently of runtime. Dimensionality reduction or parallelization should therefore be evaluated against both computational and biological requirements.

An optimized point solution does not automatically identify a biological mechanism or quantify uncertainty. Repeated optimizer runs describe computational variation; posterior or confidence statements require a separate justified statistical model. Interpretability should be assessed through identifiable features, structures, constraints and domain evidence.

Feature-selection evaluation must include selection inside the training folds and reserve independent biological samples for final assessment [10]. A high internal accuracy can be compatible with selection bias or population-specific effects. External validation, stability and biological interpretation should be measured rather than inferred from a compact gene set.

Benchmarks such as BAliBASE provide task-specific reference information [12]. A benchmark name does not ensure equivalent datasets, versions, score definitions, tuning budgets or hardware. Cross-study comparisons need a traceable mapping of these elements before differences can be attributed to an optimizer.

Reproducibility requires objective definitions, parameters, independent seeds, data versions and code or executable descriptions. No percentage of inadequately reported studies is estimated without a coded corpus.

Adaptive methods still require configuration and cannot be described as parameter-free simply because some parameters are updated during search.

Algorithmic novelty should be assessed through operators, state, acceptance rules and information flow. Metaphors can aid explanation but do not establish a new mechanism. Domain-specific representation, principled constraint handling or a reproducible biological insight may provide a stronger contribution than another renamed optimizer.

8 | Future Research Directions

Future research should prioritize biological validity and reproducible comparison. The proposals below describe questions and design directions, not experimentally established improvements.

Learned models can initialize or approximate expensive search evaluations. Their training information and generalization must be separated from final assessment. Candidate improvements should be checked through the underlying biological objective, and any hybrid advantage should be isolated under a matched budget.

Single-cell optimization may involve clustering, feature selection or experimental design, each with different units and dependence structures. Large data volume does not by itself justify a metaheuristic. The decision, objective and validation should be specified before transferring a generic search method.

Guide-RNA selection can be formulated with multiple efficacy, specificity and feasibility criteria, but off-target prediction and experimental editing outcomes are distinct quantities. A proposed Pareto search would require validated predictive models, explicit biological constraints and independent evaluation before practical recommendations.

Patient-specific optimization is conditional on response models and clinical constraints. A computational optimum is not a validated treatment recommendation. Clinical safety, outcome evaluation and appropriate study governance remain separate requirements.

Quantum-inspired classical algorithms should be assessed through their implemented operators and matched comparisons. A quantum vocabulary does not establish quantum hardware use, a computational speedup or tractability of an otherwise hard biological problem. Any claimed advantage requires a precise computational and evidential basis.

Distributed or federated search may avoid centralizing raw data, but privacy does not follow automatically from exchanging model or population statistics. A proposed system needs an explicit threat model, information-sharing protocol and validation under data heterogeneity. No privacy guarantee is asserted in this review.

9 | Conclusion

This narrative review connects six biological domains through their representations, search mechanisms and evidence requirements. Identifiable sources support examples such as genetic sequence alignment, Lamarckian docking, likelihood-based phylogenetics, spatial conservation planning and cooperative network-model inference. It does not certify a systematic-review population or a common cross-domain benchmark.

Algorithm suitability depends on the objective, constraints, representation and evaluation cost. Hybridization can combine useful mathematical roles, but its superiority cannot be inferred from the unverified numerical compilations. The review establishes no universal ranking of differential evolution, swarm methods or hybrid optimizers.

The critical methodological issues are source traceability, independent biological validation, identifiability, matched budgets and reproducibility. They should be resolved before quantitative comparative claims are used to select an algorithm or support a biological conclusion.

Promising directions include transparent learned-evaluator hybrids, domain-specific benchmarks and uncertainty-aware decisions. Their value will depend on reproducible experiments and meaningful biological endpoints rather than novelty of terminology.

Future studies should publish their formulation, instance identities, data versions, configuration, raw outputs and analytic scripts, and separate search quality from biological validity. This would allow a quantitative synthesis grounded in comparable observations rather than unsupported aggregate claims.

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Data Availability

All data are included in the text.

Conflict of Interest

The author declares that he does not have any conflict of interest.

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