

Numerical Optimization and Emerging Computational Approaches in Biological Mathematical Modeling: A Narrative Review

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ABSTRACT

Mathematical modeling is a technique that is increasingly the preferred choice for the current era of biology, where the researcher catches a glimpse of the underlying biological processes using precise, quantitative modeling approaches. This paper provides a current update on the progress that is unfolding within the realm of numerical optimization for biological modeling, and the new computer-based approaches that are transforming the landscape for the better. It provides a perspective on the history of the development of biological modeling approaches that evolved sequentially, initially through very elementary, deterministic approaches, progressively advancing to increasingly complex approaches that are stochastic and multi-scale, the current advances that are emerging using new approaches for the improvement of model parameter estimation, comparison, and forecasting, the connection between machine learning and biological modeling, the development of new hybrid modeling approaches, and the challenges that emerge forth with large-scale biological data.

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1. Introduction

Biological systems are characterised by complexity, including nonlinear dynamics, hierarchical structure, and nonequilibrium phenomena. Examples range from the behavior of single cells at the molecular level, through populations and ecosystems, and the dynamics of their hierarchical structure also defy intuitive biological logic, requiring the use of mathematical modeling for a better understanding (Alon, 2019).

Over the last two decades, the biological modeling community has undergone a paradigm shift. This shift results from tremendous growth in computing power and the enormous volume of biological data. Biotechnologies such as high-throughput sequencing, imaging, and omics technologies have not only created challenges for the biological community but also provided opportunities for modellers. Though analytical approaches are very useful for their qualitative analysis, the complexity of current biological systems demands the use of numerical optimization tools (Alon, 2019).

This paper will explore the current state of affairs regarding mathematical modeling within the biological sciences, paying specific attention to new advances made within the realm of numerical optimization. We will also explore how new approaches that seek to combine new understandings of biological systems with advances made within the data sciences can help fill the gap between current mathematical modeling practices and new approaches made possible by machine learning (Lubin & Dunning, 2015).

2. Foundations of Mathematical Modeling in Biology

2.1 Classical Modeling Frameworks

The Michaelis-Menten equation provides a similarly illuminating example of enzymatic reaction kinetics.

PDEs generalize these ideas for spatially distributed systems, for example, modeling developmental biological patterns, tumor growth and invasion, and the spread of epidemics. Reaction diffusion systems, inspired by the model of morphogenesis developed by Alan Turing, illustrate how local interaction and diffusion can give rise to complex spatial

patterns found in nature.

Stochastic model approaches recognize the inevitability of random events underlying biological processes, especially in the case of small numbers of molecules or individuals. The Gillespie algorithm, for the stochastic simulation of chemical reactions at the molecular level, is a central technique of systems biology approaches, whereas stochastic differential equations offer a conceptual basis for stochastic extensions of continuous-time models (Deb et al., 2002).

2.2 The Parameter Estimation Challenge

One of the core challenges faced by mathematical biologists is parameter estimation: identifying the model parameters that fit the data. This inverse problem is usually ill-posed. It contains challenges of identifiability, over parameterization, and noisy data. Biologically, data is usually sparse, noisy, and often only measured for a limited number of parameters (Ghusinga et al., 2016).

Conventional parameter estimation strategies involved least squares fitting and the maximum likelihood approach, which were solved using gradient-based optimization algorithms. Nevertheless, these traditional numerical approaches come with their own challenges, especially in high-dimensional parameter spaces, the presence of local minima, and model complexity. The nonlinear and stiff nature of biological models also adds complexity when analyzing the optimization problem (Al-jilawi & Hadi, 2025; Ghusinga et al., 2016).

3. Advances in Numerical Optimization

3.1 Global Optimization Methods

Global optimisation algorithms have revolutionised parameter estimation for biological modelling by enabling escape from local minima and systematic exploration of the entire parameter space. Genetic algorithms, also known as evolutionary algorithms, are inspired by natural selection. They work with populations of potential solutions that undergo selection, crossover, or mutation. Such algorithms performed well on discontinuous or multi-modal objective functions.

Simulated annealing is a technique inspired by metallurgy, where the optimisation algorithm can accept worse solutions with a probability that decreases over time, much like the cooling of metal. This stochastic technique allows the algorithm to escape local optima and has various uses, ranging from predicting protein structure to modelling niches.

Particle swarm optimization is inspired by the behavior of flocks of birds or schools of fish, where each particle changes its position according to its own knowledge and that of the neighboring particles. Particle swarms have exhibited remarkable efficiency for traversing the complex fitness topography typical of biological systems (Gillespie, 1977; Kaelbling et al., 1996).

3.1.1 Lotka-Volterra Predator Model

System of Ordinary Differential Equations (ODEs)

$$\begin{aligned}\frac{dN}{dt} &= \alpha N - \beta NP \\ \frac{dP}{dt} &= \delta NP - \gamma P\end{aligned}$$

Where:

- $N(t)$ = Prey Population at time t
- $P(t)$ = Predator Population at time t
- α = Prey growth rate (birth rate)
- β = Predation rate (interaction coefficient)
- δ = Predator growth efficiency (conversion rate)
- γ = Predator death rate

3.2 Bayesian Optimization and Uncertainty Quantification

There has been growing interest in Bayesian parameter estimation, which provides a sound framework for combining prior knowledge with new data. Markov Chain Monte Carlo (MCMC) analysis, using the Metropolis-Hastings algorithm and Hamiltonian Monte Carlo, allows for the sampling of posterior distributions when these cannot be calculated analytically (Karniadakis et al., 2021).

Advances have been made in the area of Sequential Monte Carlo (SMC) that make it computationally efficient for

large-scale problems, and the use of Approximate Bayesian Computation (ABC) allows it to handle cases when the evaluation of the likelihood function, or computing the likelihood, is impossible. ABC has also been used for population genetics, the study of epidemics, and systems biology (Kennedy & Eberhart, 1995).

Gaussian processes have been identified as useful surrogates for optimisation, enabling efficient exploration of expensive objective functions. By modeling the objective function probabilistically, Bayesian optimization can leverage this model to make informed choices on where to evaluate the objective function, thus significantly reducing the number of function evaluations (Ashyraliyev et al., 2009).

3.3 Multi-Objective Optimization

Biological systems usually consist of several conflicting objectives that need to be optimised. Multi-objective optimization techniques, including the Non-dominated Sorting Genetic Algorithm (NSGA-II), help to identify the optimal trade-offs among several conflicting objectives. This technique has been employed for various applications, ranging from the design of metabolic networks, drug therapy, and evolutionary ecology (van Mourik et al., 2014).

The idea of Pareto optimality takes into consideration the fact that maximizing one objective function sometimes results in minimizing the other. This is because of the limitations posed by biological systems. It provides better understandings of the feasible solutions based on the Pareto front (Marjoram et al., 2003; Murray, 2002).

3.3.1 Pareto Dominance

Solution θ^1 dominates θ^2 if:

$$J_i(\theta^{(1)}) \leq J_i(\theta^{(2)}) \quad \forall i \in \{1, \dots, m\}$$

And

$$\exists j : J_j(\theta^{(1)}) < J_j(\theta^{(2)})$$

Hypervolume Indicator

$$HV(A) = \Lambda(\cup_{a \in A} [a, r])$$

Where:

- A = set of non-dominated solutions
- r = reference point
- Λ = Lebesgue measure (volume)

3.3.2 Weighted Sum Method

$$J_{total}(\theta) = \sum_{i=1}^m w_i J_i(\theta)$$

Where $\sum_{i=1}^m w_i = 1$ and $w_i \geq 0$

4. Emerging Approaches in Biological Modeling

4.1 Hybrid Mechanistic-Machine Learning Models

The integration of mechanistic modeling with machine learning is undoubtedly one of the most promising areas of current research in the biological sciences. On the one hand, mechanistic modeling encodes biological knowledge by using equations that are mathematically derived on the basis of the underlying principles. Machine learning, on the other hand, is great at finding patterns in high-dimensional data, even when there isn't a clear mechanical framework (Orth et al., 2010).

Universal differential equations are one way to combine neural networks with systems of differential equations that try to find unknown terms or closure relations. This approach of combining neural networks with differential equation systems has previously shown promise in finding laws from data, improving approximations for systems that aren't fully understood, and speeding up simulations that take a lot of computing power using neural networks (Rackauckas et al., 2020; Raue et al., 2009).

4.2 Agent-Based and Multi-Scale Modeling

Agent-based Models (ABMs) model biological systems using autonomous agents, the interaction of which results in the emergence of system-level dynamics. The model, which is ideal for modeling biological phenomena that entail spatial

variability, agent variability, and discrete events, can also be used for the study of the immune system, tumor growth, tissue formation, and disease spread (Williams & Rasmussen, 2006).

The problem of modeling at various scales, ranging from the molecular level, cells, tissues, and organisms, among others, has led to the emergence of multi-scale modeling. Such modeling integrates various models developed at distinct scales of study. For instance, the model for signaling within cells can help predict the behavior of cells during tissue modeling, and the forces generated by tissue mechanics can affect gene expression. Software developed for modeling includes CompuCell3D and PhysiCell.

4.2.1 Objective Function (Cost Function)

Mean Squared Error (MSE)

$$J(\theta) = \frac{1}{n} \sum_{i=1}^n [(N_{obs,i} - N_{sim,i}(\theta))^2 + (P_{obs,i} - P_{sim,i}(\theta))^2]$$

Where:

- $\theta = [\alpha, \beta, \delta, \gamma]$ = parameter vector
- $N_{obs,i}$, $P_{obs,i}$ = observed data at time t_i
- $N_{sim,i}(\theta)$, $P_{sim,i}(\theta)$ = simulated data with parameters θ
- n = number of observation points

Alternative: Weighted MSE

$$J(\theta) = \frac{1}{n} \sum_{i=1}^n [w_N (N_{obs,i} - N_{sim,i}(\theta))^2 + w_P (P_{obs,i} - P_{sim,i}(\theta))^2]$$

Where w_N and w_P are weights for prey and predator populations.

4.3 Data-Driven Model Discovery

Sparse identification of nonlinear dynamics (SINDy) and other equivalent approaches offer a new paradigm for the construction of models, where the dynamics are automatically learned from time series data. Such approaches make use of the idea of sparse regression to derive reduced models out of a library of candidate model building blocks. For biological systems, the paradigm has been applied for learning structure for gene regulatory networks, metabolic pathway graphs, and interaction networks of various species (Williams & Rasmussen, 2006).

For equation discovery, the following challenges are especially prevalent in the biological sciences, where the presence of measurement noise is a problem, the data is irregularly sampled, and the underlying dynamics could include latent variables: Recent advances that have incorporated ensemble learning, symbolic regression, and Bayes-based approaches have helped deal with these challenges.

4.4 Optimal Experimental Design

Optimization methods are progressively used not only for the estimation of parameters, but also for the design of biological experiments. Optimal experimental design aims at determining the experimental settings, the time points, and the observables that maximize the information about the parameters or that allow a discrimination between hypotheses. This new approach will certainly make biological experiments more efficient.

Fisher information matrices and other concepts within the realm of information theory serve as the mathematical building blocks for assessing the informational value of experimental design strategies.

5. Applications across Biological Domains

5.1 Systems Biology and Metabolic Engineering

Genome-scale metabolic models, which include thousands of processes and metabolites, are used to predict cellular phenotype, therapeutic targets, and metabolic engineering. Constraint-based optimization strategies, such as flux balance analysis, have made it possible for large-scale modeling of metabolism without kinetic parameters.

In recent advances, the integration of omics data with metabolic models helped build context-specific models that express the metabolism of different cell types, diseases, or environmental situations. The use of machine learning approaches along with constraint-based models is attempting to enhance the prediction of fluxes and provide regulatory

principles for metabolic control.

5.2 Epidemiological Modeling

The COVID-19 pandemic brought a new level of awareness about the relevance of mathematical modeling for epidemiology. Compartmental, network, and agent-based modeling have helped unfold the dynamics of disease spreading, explore results of intervention measures, and make predictions about the spreading of the epidemic. Contemporary mathematical modeling of epidemiology, on the other hand, is characterized by increasing inclusion of space, age structure, behavior, and data assimilation.

Optimization is a very important tool for the calibration of epidemiological models to surveillance data, as well as for optimizing intervention strategies, which not only meet public health goals but also take into account economic and social factors. The implementation of real-time forecasting tools, much like weather forecasting, is a current topic of active investigation that brings together model-based and statistical approaches.

5.3 Pharmacology and Personalized Medicine

Pharmacokinetic/pharmacodynamic (PK-PD) modeling applies mathematical representations of drug absorption, distribution, metabolism, excretion, and effects. Such modeling aids drug development to predict optimal dosing strategies, characterization of drug/drug interactions, and the population that will probably benefit from treatment. Contemporary advances that incorporated quantitative systems pharmacology allowed the use of biological pathway representations together with the usual PK-PD modeling for mechanism-based predictions of drug action (Toni et al., 2009; Villaverde et al., 2016).

5.4 Ecology and Conservation Biology

Ecological modeling: It deals with various questions, ranging from population dynamics, community assembly, and other ecosystem processes. Optimization methods have been used for various applications, including wildlife management, conservation, and sustainable resource exploitation. Individual-based modeling incorporates demographic stochasticity and individual variability, and metacommunities model ecological spatial processes.

This is because climate change has raised the need for predictive models of ecological systems that can predict the distribution of species, phenological changes, and transformations of ecosystems under new climate conditions. It is promising to use process-based models of ecology along with machine learning that is trained on large datasets of biodiversity (Voit, 2017).

6. Convergence Criteria

6.1 Gradient-Based Methods

$$\|\nabla J(\theta_k)\| < \varepsilon_g$$

Where ε_g is a small threshold (e.g., 10^{-6}).

Parameter Change

$$\|\theta_{k+1} - \theta_k\| < \varepsilon_\theta$$

Objective Function Change

$$|J(\theta_{k+1}) - J(\theta_k)| < \varepsilon_f$$

Relative Change

$$\frac{|J(\theta_{k+1}) - J(\theta_k)|}{|J(\theta_k)|} < \varepsilon_{rel}$$

6.2 Uncertainty Quantification and Validation

Uncertainty propagation throughout the modeling chain, from parameter estimation through prediction, is still a current issue. Biological prediction tasks often contribute to critical decision-making in the medical, public health, and conservation fields, so it is very important that uncertainty be reported openly and thoroughly. Uncertainty propagation through complex nonlinear modeling is not a plain error bar problem (Vernon et al., 2018).

Model validation, especially that of predictive models, demands careful attention to experimental design and statistical technique. The difference between model fitting and new, prospective observation is critical, but often not well defined (Wilensky & Rand, 2015; Wilkinson, 2018).

Gradient Descent:

iteration	alpha	beta	delta	gamma	error
1.000000	0.001000	4.613931	22.982782	0.001000	1841.811661
2.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
3.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
4.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
5.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
6.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
7.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
8.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
9.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
10.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
11.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
12.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
13.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
14.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
15.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
16.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
17.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
18.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
19.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032
20.000000	0.001000	276152239568.161499	276501634167.628113	519506672624.490356	4492.275032

Simulated Annealing:

iteration	alpha	beta	delta	gamma	error
1.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
2.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
3.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
4.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
5.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
6.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
7.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
8.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
9.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
10.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
11.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
12.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
13.000000	0.300000	0.015000	0.008000	0.400000	1841.811661
14.000000	0.300000	0.015000	0.008000	0.400000	1841.811661

	15.000000		0.300000		0.015000		0.008000		0.400000		1841.811661	
	16.000000		0.300000		0.015000		0.008000		0.400000		1841.811661	
	17.000000		0.300000		0.015000		0.008000		0.400000		1841.811661	
	18.000000		0.300000		0.015000		0.008000		0.400000		1841.811661	
	19.000000		0.300000		0.015000		0.008000		0.400000		1841.811661	
	20.000000		0.300000		0.015000		0.008000		0.400000		1841.811661	
+-----+-----+-----+-----+-----+												

PSO:

iteration	alpha	beta	delta	gamma	error
1.000000	0.693052	0.022557	0.017827	0.375999	1562.793434
2.000000	0.642149	0.029898	0.009425	0.338675	645.947263
3.000000	0.610348	0.026901	0.009613	0.384687	201.262238
4.000000	0.585408	0.025527	0.008641	0.413526	54.616642
5.000000	0.580655	0.025555	0.008586	0.422197	42.529457
6.000000	0.579461	0.023708	0.008827	0.426612	37.835144
7.000000	0.578443	0.023990	0.008789	0.428655	36.059082
8.000000	0.567744	0.023878	0.008861	0.435660	34.243578
9.000000	0.567611	0.023708	0.008872	0.435971	33.681461
10.000000	0.566291	0.023570	0.008884	0.437209	33.308611
11.000000	0.566092	0.023531	0.008892	0.437327	33.204035
12.000000	0.551946	0.022318	0.009150	0.449558	30.706356
13.000000	0.548739	0.022155	0.009216	0.453211	30.411451
14.000000	0.548574	0.022195	0.009194	0.452581	30.158798
15.000000	0.548574	0.022195	0.009194	0.452581	30.158798
16.000000	0.548224	0.022331	0.009202	0.452076	30.099943
17.000000	0.547154	0.022220	0.009241	0.453049	29.977477
18.000000	0.547058	0.022210	0.009239	0.453208	29.953262
19.000000	0.542004	0.022103	0.009293	0.456646	29.681805
20.000000	0.533605	0.021383	0.009462	0.464656	29.000174

Nelder-Mead:

iteration	alpha	beta	delta	gamma	error
1.000000	0.311250	0.015562	0.008300	0.360000	1638.202558
2.000000	0.278438	0.015984	0.008525	0.370000	1575.883443
3.000000	0.292266	0.016723	0.008919	0.347500	1561.578355
4.000000	0.292266	0.016723	0.008919	0.347500	1561.578355
5.000000	0.292266	0.016723	0.008919	0.347500	1561.578355
6.000000	0.292266	0.016723	0.008919	0.347500	1561.578355
7.000000	0.273711	0.015816	0.009011	0.385190	1549.123727
8.000000	0.273711	0.015816	0.009011	0.385190	1549.123727
9.000000	0.273711	0.015816	0.009011	0.385190	1549.123727
10.000000	0.277874	0.016874	0.009273	0.365608	1543.997965
11.000000	0.277874	0.016874	0.009273	0.365608	1543.997965
12.000000	0.277874	0.016874	0.009273	0.365608	1543.997965
13.000000	0.263842	0.015516	0.009884	0.402679	1529.535718
14.000000	0.263842	0.015516	0.009884	0.402679	1529.535718
15.000000	0.263842	0.015516	0.009884	0.402679	1529.535718
16.000000	0.263842	0.015516	0.009884	0.402679	1529.535718
17.000000	0.238580	0.014408	0.010283	0.435214	1522.929565
18.000000	0.241860	0.015316	0.010227	0.430145	1522.188591

| 19.000000 | 0.241860 | 0.015316 | 0.010227 | 0.430145 | 1522.188591 |
 | 20.000000 | 0.218048 | 0.012605 | 0.011638 | 0.492737 | 1511.144334 |
 21 000000 | 0.115673 | 0.006160 | 0.022260 | 0.913062 | 1485.753768

7. Conclusion

In light of the findings presented in this research, it can be concluded that significant advancements in mathematical modeling and numerical optimization techniques have substantially contributed to deepening our understanding of complex biological systems, particularly those characterized by nonlinearity and uncertainty. The results clearly demonstrate that traditional optimization methods, such as stepwise regression, suffer from instability and high sensitivity to initial value selection, which in some cases leads to parameter divergence rather than convergence towards an optimal solution. In contrast, global optimization algorithms, particularly particle swarm optimization (PSO), have proven more efficient in exploring parameter spaces and achieving more realistic values with a significantly lower error function, making them a suitable choice for such nonlinear biological models. Simulated annealing and the Nelder-Mead method also showed relatively limited improvement but remained less effective than PSO. These results underscore that the choice of optimization algorithm is not merely a technical matter but a crucial element in the reliability of the model and its biological interpretation. Furthermore, the research highlights the importance of integrating Bayesian statistical methods and machine learning with traditional mechanical models to address noise, data scarcity, and uncertainty, particularly in modern applications such as personalized medicine, epidemiology, and environmental science. Overall, this work reflects the strong trend in the future of biological modeling toward hybrid and intelligent approaches capable of leveraging big data without compromising a deep biological understanding of the systems under study.

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