Combining Machine Learning and Agent-Based Modeling to Study Biomedical Systems

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Journal/format: Frontiers in Systems Biology, Special Issue on "Combining Mechanistic Modeling with Machine Learning to Study Multiscale Biological Processes"

Running title: Machine Learning & Agent-based Modeling of Biomedical Systems

Author contribution statement (for Frontiers submission system):
NS, CM, and SMP were each actively involved in the design and writing of this review article, from early drafting to final revision stages; the graphical illustrations/figures were created by NS, with input from CM and SMP.

Keywords (Frontiers submission system requires at least 5): agent-based modeling (ABM); machine learning; integrative modeling; rule inference; reinforcement learning; neural network; surrogate model; supervised & unsupervised learning; genetic algorithm; parameter sampling

Abbreviations, acronyms: ABM, agent-based model; AI, artificial intelligence; ANN, artificial neural network; BN, Bayesian network; DNN, deep neural network; DR, diabetic retinopathy; EHR, electronic health record; FCM, fuzzy c-means; GA, genetic algorithm; ML, machine learning; PDE, partial differential equation; RL, reinforcement learning; RWE, real-world evidence; SA, sensitivity analysis;
Machine Learning & Agent-based Modeling of Biomedical Systems

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1. ABSTRACT

Agent-based modeling (ABM) is a well-established computational paradigm for simulating complex systems in terms of the interactions between individual entities that comprise the system’s population. Machine learning (ML) refers to computational approaches whereby algorithms use statistical methods to ‘learn’ from data on their own, i.e. without imposing any a priori model/theory onto a system or its behavior. Biological systems—ranging from molecules, to cells, to entire organisms, to whole populations and even ecosystems—consist of vast numbers of discrete entities, governed by complex webs of interactions that span various spatiotemporal scales and exhibit nonlinearity, stochasticity, and variable degrees of coupling between entities. For these reasons, the macroscopic properties and collective dynamics of biological systems are generally difficult to accurately model or predict via continuum modeling techniques and mean-field formalisms. ABM takes a ‘bottom-up’ approach that obviates common difficulties of other modeling approaches by enabling one to relatively easily create (or at least propose, for testing) a set of well-defined ‘rules’ to be applied to the individual entities (agents) in a system. Evaluating a system and propagating its state over a series of discrete time-steps effectively simulates the system, allowing various observables to be computed and the system’s properties to be analyzed. Because the rules that govern an ABM can be difficult to abstract and formulate from experimental data, at least in an unbiased way, there is a uniquely synergistic opportunity to employ ML to help infer optimal, system-specific ABM rules. Once such rule-sets are devised, running ABM calculations can generate a wealth of data, and ML can be applied in that context too—for example, to generate statistical measures that accurately and meaningfully describe the stochastic outputs of a system and its properties. As an example of synergy in the other direction (from ABM to ML), ABM simulations can generate plausible (realistic) datasets for training ML algorithms (e.g., for regularization, to mitigate overfitting). In these ways, one can envision a variety of synergistic ABM ↔ ML loops. This Review aims to summarize how ABM and ML have been integrated in diverse contexts that span spatial scales including multicellular, or tissue-level scale biology, and human population-level scale epidemiology.
2. INTRODUCTION

2.1 OVERVIEW OF AGENT-BASED MODELING: MOTIVATION, GENERAL APPROACH, AND EXAMPLE APPLICATIONS

Rapid advances in experimental methodologies now enable us to obtain massive quantities of data describing the individual entities in a population, such as single cells within complex, multicellular tissues, or individual patients in large-scale epidemiological systems. Hence, a growing focus of systems biology and biomedical research involves elucidating patterns in large datasets—what are the associations between the discrete, individual entities themselves, and what are the mechanisms by which the behaviors, states and interactions of these autonomous agents contribute to population-wide outcomes? For example, single-cell RNA sequencing (Hwang et al., 2018; Potter, 2018; Kulkarni et al., 2019), single-cell proteomics (Irish et al., 2006; Marx, 2019), and flow cytometry (Wu et al., 2012; Wu et al., 2013; Chen et al., 2019; Argüello et al., 2020) provide snapshots of an individual cell’s state at a single point in time. Yet, understanding the tissue–level and organ–level implications of these single-cell data requires a fundamentally different set of analytical approaches, with the capacity to spatiotemporally integrate potentially disparate data along at least two ‘dimensions’: across entire populations of entities, as well as across multiple scales (cellular → organismal). For instance, using single-cell RNA-Seq one can detect the presence and quantify the amount of RNAs in each of the cells in a tumor, but these data alone cannot illuminate how that particular collection of tumor cells, which undergo different behaviors (e.g., proliferation and migration) as dictated by their unique cellular states, contribute to tissue-level and organ-level outcomes such as angiogenesis and metastasis.

Epidemiological datasets have similarly expanded in recent years (Andreu Perez et al., 2015; Ehrenstein et al., 2017; Saracci, 2018). Many factors have driven this growth, including: (i) improved standardization and systematization of electronic health records (EHRs; Andreu Perez et al., 2015; Booth et al., 2016; Casey et al., 2016; Ponjoan et al., 2019), with concomitantly increased storage, more sophisticated cyberinfrastructure (e.g., cloud computing) and improved data-mining capacities, (ii) adoption of high-resolution, diagnostic medical imaging (Backer et al., 2005; Smith-Bindman et al., 2008; Andreu Perez et al., 2015; Preim et al., 2016), (iii) acquisition of genomic and other ‘omics’ big data, largely via next-generation sequencing (Thomas, 2006; Andreu Perez et al., 2015; Maturana et al., 2016; Chu et al., 2019), (iv) technologies such as wearable patient health sensors (Atallah et al., 2012; Andreu Perez et al., 2015; Guillodo et al., 2020; Perez-Pozuelo et al., 2021), and (v) acquisition of spatial and environmental data from geographical information systems (GIS; Krieger, 2003; Rytkönen, 2004; Andreu Perez et al., 2015)). Despite these many technological advances, without a sound analytical and methodological framework to integrate and then explore these data it remains difficult to understand how, for example, certain lifestyle behaviors or healthcare policies might contribute to the spread of disease in a population of unique individuals. The quantitative determination and forecasting of how individual mechanisms contribute to system-level outcomes (known as "emergent properties") is critical to creating targeted treatments, mitigating disease spread and, ultimately, guiding more informed healthcare policies. As described by Bonabeau (2002), this general type of problem—deciphering the global, collective behavior that emerges in a complex system, composed of a statistically large collection of (locally) interacting, individual components—is particularly amenable to agent-based modeling (ABM).

ABM is now a well-established computational paradigm for simulating a system’s population-level outcomes based on interactions between individual entities in the population. Such an approach or ABM ‘mindset’ (Bonabeau, 2002) is necessarily bottom-up, and the general method has been applied to domains ranging from the dynamics of macroscopic systems, such as global financial markets (Bonabeau, 2002), to the microscopic dynamics of mRNA export from the cellular nucleus (Soheilypour and Mofrad, 2018). ABMs simulate spatially-discrete, autonomous individuals, or ‘agents’, that follow relatively simple probabilistic
'rules' at discrete time-steps. Rules are formulated to describe the discrete, well-defined, individual behaviors that a single agent can enact depending upon (and possibly in response to) both its own state and its local environment. The agents—which can represent proteins, biological cells, individual organisms, or really any definable entity (e.g., individual traders in a stock market)—exhibit specific behaviors over time, and the collection of these behaviors (e.g., patterns of pairwise interactions) gives rise to population-level outcomes in the system/ensemble, such as in embryonic development (Longo et al., 2004; Robertson et al., 2007; Thorne et al., 2007a), blood vessel growth (Peirce et al., 2004; Thorne et al., 2011; Walpole et al., 2015), disease progression within a given organism (Martin et al., 2015; Virgilio et al., 2018), or infectious disease spread among subsets of organisms in a population (Cuevas, 2020; Rockett et al., 2020). As noted in a recent study that developed a "biological lattice-gas cellular automaton" (BIO-LGCA) for the collective behavior of cellular entities in complex multicellular systems (Deutsch et al., 2021), classical, on-lattice ABMs and cellular automata are essentially equivalent approaches.

The discretized nature of ABMs, in time and space, allows them to capture the spatial heterogeneities that are inherent to most complex dynamical systems, biological or otherwise. These heterogeneities, in turn, enable ABMs to be stochastic and, thus, capable of emulating how real biological processes may progress towards potentially different outcomes (i.e., non-deterministic behavior), based on (i) heterogeneity/variation among the agents (i.e., inherent variability stemming from the uniqueness of each individual), or (ii) variability in the environment and the coupling of agents to that potentially dynamic environment (i.e., spatial inhomogeneities). Moreover, ABMs can quantitatively predict numerous outcomes for a dynamical system that may be difficult or impossible to quantify experimentally, at least not with sufficient spatial and temporal resolutions. ABMs can also be leveraged to predict system behaviors in response to a range of different perturbations and initial conditions, allowing for a more comprehensive understanding of biomedical systems than is accessible via experimentation alone. Another key benefit of ABM is that its accuracy as a modeling approach does not suffer from the requirement of average-based assumptions for a system (fully-mixed, mean-field approximations, etc.), in contrast to partial differential equation (PDE)—based approaches or other modeling frameworks that treat a system as a smooth continuum, free of singularities and irregularities. Combined with methodological approaches such as sensitivity analysis (ten Broeke et al., 2014; ten Broeke et al., 2016; Ligmann-Zielinska et al., 2020), these attributes make ABMs particularly useful tools for examining the dependencies of population-level phenomena on the behaviors and interactions of the individuals that comprise the population (e.g., using ABM simulations to map a ‘response surface’, in terms of some underlying set of features/explanatory variables (Willett et al., 2015)).

ABMs have been used extensively to model multicellular processes, such as tissue patterning and morphogenesis (Robertson et al., 2007; Thorne et al., 2007a; Thorne et al., 2007b; Taylor et al., 2017), tumorigenesis (Wang et al., 2007; Gerlee and Anderson, 2008; Zangooei and Habibi, 2017; Oduola and Li, 2018; Warner, 2019), vascularization (Walpole et al., 2015; Walpole et al., 2017; Bora et al., 2019), immune responses (An, 2006; Bailey et al., 2007; Woelke et al., 2011; Xu et al., 2018), and pharmacodynamics (Hunt et al., 2013; Cosgrove et al., 2015; Kim et al., 2015; Ji et al., 2016; Gallaher et al., 2018). In the field of epidemiology, ABMs have also been used to represent human individuals in a population in order to study infectious disease transmission and to create simulations of disease spread in a cohort of individuals over time (Marshall and Galea, 2015; Çağlayan et al., 2018; Tracy et al., 2018; Cuevas, 2020; Rockett et al., 2020); note that in epidemiological, geographic, social, economic and some other settings, the terms ABM and ‘microsimulations’ are often used interchangeably (Heard et al., 2015; Bae et al., 2016; Ballas et al., 2019). While ABMs have been applied widely and fruitfully in biomedical research, they are not without recognized limitations. For example, the rules that govern ABMs can be difficult to abstract and formulate from experimental data alone, at least in a minimally-biased way. In addition, running ABMs can be computationally expensive, and selecting statistical measures that accurately and meaningfully summarize stochastic
outputs can be challenging (ten Broeke et al., 2016). We propose that some of these constraints and limitations may be alleviated by leveraging machine learning (ML) approaches as part of an ABM pipeline.

2.2 What is ML, and Why Might It Be Synergistic With ABM for Biomedical Systems?

Machine learning is a vast set of approaches whereby algorithms use statistical methods to ‘learn’ from data on their own—that is, without being explicitly programmed to do so. In ML, whatever relationships, patterns or other associations that may latently exist in a body of data are gleaned from the data, without requiring an a priori theory or model to specify the details of the possible relationships in advance. Given that, note that some general form for a model must be posited—e.g., we assume datasets can be fit by a linear function, can be represented by a neural network, exist as natural clusters of associations, or so on; how these unavoidable assumptions manifest is known as an ML algorithm’s inductive bias.

Armed with a model, and as put by Alpaydın (2021), "it is not the programmers anymore but the data itself that defines what to do next". How this learning is achieved can be understood by considering ML, most generally, as a way to determine a function that optimally maps a dataset (captured as a set of independent variables, often termed ‘features’) to a set of results/outcomes (dependent variables): that is, we wish to find a function \( F \) that maps the data to the ‘results’, \( \{d\} \rightarrow \{r\} \), where the ‘map’ can be as simple as a linear model (i.e., weighted sum of linear terms) or as complex as a deep neural network (DNN) with many thousands of ‘hyperparameters’ (weights between neurons, activation thresholds, etc.); in the latter case, it is the DNN’s pattern of connectivities and weights that defines the functional map. We generally seek a map that is ‘optimal’ in terms of minimizing the error between predicted outcomes and preexisting outcomes that are already known (as a ‘ground truth’) for a given subset of data (the ‘training set’). The ‘learning’ part of machine learning is essentially the iterative approximation of parameters to optimize a model against an objective function (again, a functional form is assumed in advance, when deciding to model data via one approach or another). This process, in turn, simply means finding a set of weights/parameters that optimizes the map’s fitness, which corresponds to minimizing the model’s prediction error; fundamentally, these ‘weights’ can be as simple as the numerical coefficients of the variable terms in the optimization function (complexity stems from there being myriad such parameters), and minimizing the mean-squared error is mathematically equivalent to maximizing the likelihood of the (normally-distributed) data being observed under our (optimized) linear model. Reaching this point of having optimized the parameters, we are said to have a "trained model"; the second stage of an ML project is generally the "inference stage", wherein a trained model is then utilized to make predictions. This latter stage involves applying the trained model across new/unseen data (i.e., individual data items), which can take the form of either test datasets (while still developing/validating the model) or else real-world data (if the model is being deployed for production purposes, e.g. as part of a computational pipeline for automated tagging of chest X-rays in a clinic).

Numerous useful reviews of ML and deep learning (DL) in the biosciences have appeared in recent years. As but one example, Ching et al. (2018) have thoroughly reviewed the challenges and opportunities posed by applications of ML to big data in the biosciences; while focused on deep learning (LeCun et al., 2015; Goodfellow et al., 2016; Tang et al., 2019), many of the principles of that review apply to ML broadly (e.g., viewing deep networks as analogous to ML’s classic regression methods, but sufficiently generalized so as to allow for nonlinear relationships among features). In the biomedical realm, ML has emerged as a powerful and generalized paradigm for integrating data to classify and predict phenotypes, genetic similarities, and disease states within various biological processes; here, again, numerous reviews are available (Chicco, 2017; Park et al., 2018; Serra et al., 2018; Jones, 2019; Nicholson and Greene, 2020; Su et al., 2020; Peng et al., 2021; Tchito Tchapga et al., 2021).
While that which precisely distinguishes an algorithm as a machine learning algorithm (cf. statistical modeling, for example) is debatable, here we consider ML algorithms as broadly defined by Mitchell’s criterion (Mitchell, 1997): an algorithm is said to ‘learn’ if it improves its performance, $\mathcal{P}$, with respect to a task, $\mathcal{T}$, via execution of some computational processes, $\mathcal{E}$. ML algorithms broadly fall into four main types, depending chiefly on the role of labeled data in the training and learning process (note that the distinctions between some of these types are blurred): Supervised learning, Unsupervised learning, Semi-supervised learning, and Reinforcement learning. (i) Supervised learning algorithms infer relationships between independent and dependent variables by applying a model that was trained against prior data of known type (Bhavsar and Ganatra, 2012; Singh et al., 2016); these ‘ground-truth’ data consist of (accurately) ‘labeled’ samples which can be split in various ways (e.g., into ‘training’, ‘test’ and ‘validation’/‘development’ sets) as part of the model-training regiment. (ii) In unsupervised learning, an ML algorithm autonomously identifies patterns, trends or ‘groupings’ (clusters) in a dataset, with zero human intervention in the form of prior knowledge about the ‘correct’ associations—i.e. only unlabeled data (unannotated by human experts) are available for use (Gentleman and Carey, 2008; Kassambara, 2017). (iii) Semi-supervised learning can be employed when large volumes of data are available but only a small fraction of it is (correctly) labeled—i.e. the training set contains both labeled and unlabeled data, with a preponderance of the latter. Here, we consider "informed ML" (von Rueden et al., 2021), or "expert knowledge–driven" ML, as a form of semi-supervised learning, wherein the modeler may manually adjust model weights based on known behaviors of the system. (iv) In reinforcement learning, the ML process acts via a set of rules (‘policies’) and series of system ‘states’ (akin to ABM), and is rewarded or punished based on the result of a ‘move’; the ML algorithm evolves the system via state transitions so as to maximize rewards in a given environment (Sutton, 1992; Kaelbling et al., 1996; Kulkarni, 2012), and in that way it ‘learns’.

A rich variety of learning algorithms fall within these broader categories, as summarized by the sample inventory of ML approaches in Table 1. While that Table is not comprehensive, each of the ML methods listed there have been widely applied to study and analyze various types of biological systems (proteins, networks, tissues, etc.). Notwithstanding its many major successes, there are a few significant limitations associated with the application of ML to biology. Creating an accurate and robust ML model requires large amounts of experimental data, such as patient data, cellular-scale measurements, ‘omics’ data, etc.; such data may be challenging to obtain for various reasons, including measurement inaccuracies, inherent sparsity of datasets, or other concerns such as paucity of health data stemming from privacy policies. Perhaps most fundamentally vexing for modelers, ML architectures and algorithms generally pursue optimality criteria in a manner that yields "black-box" solutions, and unfortunately the internal mechanisms that may link predictor and outcome variables remain unknown; thus, ML algorithms often do not illuminate the causal mechanisms that underlie system-wide behavior. For these reasons, "explainable AI" has become a highly active research area (Jiménez-Luna et al., 2020; Confalonieri et al., 2021; Vilone and Longo, 2021).

With their respective strengths and limitations, the ABM and ML methodologies can be viewed as complementary approaches for modeling biological systems—particularly for systems and problems wherein the strengths of one type of methodology (ABM or ML) can be leveraged to address specific shortcomings of the other. For example, ML algorithms (e.g. DNNs) are often criticized because their predictions are arrived at in a black-box manner; in addition, most supervised algorithms require large amounts of accurately labeled training data, and overfitting is a common pitfall in many ML approaches. ABMs, on the other hand, (i) are built upon explicit representations/formulations of the precise interactions between system components (these are ‘low-level’, and thus relatively easily formulated), and (ii) can easily generate, via suites of simulations, large quantities of output data. Similarly, while the creation of rules in ABMs is frequently accomplished by manual and subjective curation of the literature, which can lead to a biased or oversimplified abstraction of the true biological complexity, ML approaches such as reinforcement learning
can be used to computationally infer optimal rule-sets for agents and their interactions. Thus, there is a naturally synergistic relationship between these pairs of relative strengths and weaknesses of ABM and ML.

Inspired by this potential synergy, in the remainder of this Review we highlight published studies that have integrated ML with ABMs in the following ways, in order to create more advanced and accurate computational models of biological systems, at both the multicellular and epidemiological scales:

- **Learning ABM Rules via ML**: Reinforcement learning and supervised learning methods can be used to infer and refine agent rules, which are critical inasmuch as these rules are applied at each discrete time step and, thus, largely define the ABM.
- **Surrogate Models of ABMs**: Supervised learning algorithms can be trained to create surrogate models of an ABM, which assist in calibrating the ABM and mitigates the computational costs of having to execute numerous ABMs.
- **Exploring ABMs via ML**: ML methods can help explore the complex, high-dimensional parameter space of an ABM, in terms of sensitivity analysis, model robustness, and so on.

As an overview of the high-level organization of this Review, Figure 1 schematizes how individual studies, reported in the recent literature, have integrated ML into each step of formulating and analyzing an ABM.

### 3. Using ML to Derive and Determine Agent Rules

#### 3.1 Overview and Motivation: Where Do ABM Rules Come From?

An ABM’s ‘rules’ define the autonomous actions that an agent can perform as a function of its state and in response to changes in its local environment. For instance, a cell may undergo apoptosis if it experiences sustained hypoxia, or a healthy individual may be infected with a virus when in close proximity to an infected individual. Note that the words ‘can’ and ‘may’ occur in the previous sentences because an ABM’s rules are defined probabilistically. Rules link cause-and-effect in a manner that is enacted by individual agents/entities (molecules, cells, human individuals, etc.) in the population under consideration. Traditionally, these rules are manually generated by the modeler, who must curate and interpret empirical data describing the system, expert opinions, and/or dogma in the literature. In an ABM, the rule-set is only validated after ABM simulations have been run and predictions are compared to independent experimental data, or to a validation dataset. Hence, a common criticism of the traditional ABM rule-generation process is that there is inherent subjectivity on the part of the model-builder that could introduce bias in the rules, thereby skewing the biological relevance of its downstream results and predictions.

To overcome this potential issue, recent ABMs have begun leveraging ML to computationally determine—in a less ad hoc and heuristic manner—the rules governing agent behaviors based on an agent’s spatial environment at a given time-step. Instead of manually-generated rules, which could be unwittingly biased towards a particular set of predictions that are not statistically representative of the target population or system behavior at large, ML algorithms can learn the rules, parameterizations, and so forth more objectively—by examining experimental data or by applying fundamental mathematical relationships (Figure 2); indeed, this "learn from the data" capacity stems directly from the roots of ML in information theory and statistical learning (Hastie et al., 2009).

#### 3.2 Supervised Learning on Training Datasets to Determine Agent Behavior

Supervised learning algorithms have been leveraged in epidemiological ABMs to define agent behaviors in simulations of the spread of both infectious and non-communicable diseases. One microsimulation (Day et al., 2013) of diabetic retinopathy (DR) in a cohort of individuals used a multivariate logistic regression algorithm to help build the rules that determine when each human agent will advance to the next stage of DR, based on features such as age, gender, duration of diabetes, current tobacco use, and hypertension.
Instead of manually estimating DR stage advancement probabilities from the literature, these rules were computationally learned by training a multivariate logistic regression model on a dataset describing 535 DR patients. The logistic regression algorithm learned a function relating individual patient features to the probability of DR stage advancement, and at the beginning of every simulated year in the ABM this function was used to determine whether each human agent would advance to the next stage of DR. This approach showed that a simulated cohort of 501 patients had no significant differences from an actual live-patient cohort. Moreover, the logistic regression method was useful in identifying key predictors of DR stage advancement (Day et al., 2013). Finally, note that this example illustrates the general principle that regression models are highly applicable to constructing rules when large volumes of patient data are available.

Another study (Alexander Jr et al., 2019) evaluated multiple supervised learning methods to predict, in the context of an ABM platform, individual DR patient responses to pregabalin, a medication that targets the gabapentin receptor and which is used to treat several conditions, including diabetic neuropathy. The study found that ‘ensemble’ methods that combined several instance-based learning methods, including supervised k-nearest neighbors and fuzzy c-means, yielded the highest classification accuracy (Alexander Jr et al., 2019).

Much recent effort in biomedical informatics has focused on developing approaches to automatically and systematically extract and infer statistically rigorous new information—so-called "real-world evidence" (RWE)—from primary data sources such as electronic health records (EHRs). The general aims of such efforts are manifold, including discovery of new uses for drugs already known to be safe and efficacious (an approach known as ‘repurposing’) and, ultimately, to reach high-confidence, clinically-actionable recommendations (e.g., a particular drug for a specific indication), ideally in a personalized, ‘precision medicine’ manner. A potentially synergistic interface can be found between ABMs and RWE-related studies, for example by using raw (low-level), patient-derived data to both develop ABMs (define rule-sets, parameterizations, etc.) and also deploy them for predictive purposes. For instance, real-world data about the spread of COVID-19 in hospitals and other settings have been used to develop and deploy ABMs for use in optimizing policy measures and exploration of other epidemiological questions (Gaudou et al., 2020; Hinch et al., 2021; Park and Sylla, 2021); also broadly notable, recent ABM-based studies of "information diffusion" have been used in the development of advanced community health resources (Lindau et al., 2021) and to examine how "medical innovation" might propagate among specific communities, such as cardiologists (Borracci and Giorgi, 2018).

3.3 Expert Knowledge-driven Supervised Learning Approaches in ABMs

Other studies have demonstrated the utility of ML algorithms in ABM rule generation, even when there is limited available training data. Some studies train supervised learning algorithms on available data and augment the learned functions with expert knowledge. Bayesian networks (BNs), for example, are a common supervised learning algorithm that is paired with expert knowledge. First, the BN is trained on datasets to determine conditional probabilities of a certain event occurring based on predictor values, such as the probability of a sick individual infecting a healthy individual given the physical distance between them. Then, in a type of approach that has been termed "informed ML" (von Rueden et al., 2021), domain experts can subjectively adjust these learned probabilities based on experience and published literature. One study (Abdulkareem et al., 2019) used this approach to determine human agent rules in a previously developed ABM of cholera spread in Kumasi, Ghana. That work (Figure 2) compared four different BNs, trained with varying combinations of survey data and expert opinion support, to define a rule on whether a human agent would decide to use river water based on varying levels of (i) visual pollution, (ii) media influence, (iii) communication with neighbors, and (iv) past experience. The ABM was found to be most accurate when the BNs combined low-level data with expert knowledge; this is somewhat unsurprising, as the available
training data were from a limited number of participants that did not holistically represent the modeled population. Moreover, the study found that a "sequential learning" approach further improved the accuracy of the ABM. Sequential learning refers to training the BN in an ‘online’ manner, simultaneously with the tumor growth – hence, the study incorporated an expert knowledge driven approach to determine human agent water use in the aforementioned cholera–spread ABM: that work trained decision trees on the same training dataset as the earlier study (Abdulkareem et al., 2019) in order to determine whether an agent will use river water based on the same predictor variables. The decision tree scheme differs from the BN approach in that the decision tree does not require expert opinion or sequential learning, and derives (novel) agent rules from scratch by determining a tree-like model/path of how each agent considers the predictor variables to arrive at a decision regarding usage of river water. The decision tree-based approach yielded ABM predictions with different numbers of infected individuals (Augustijn et al., 2020). This discrepancy is predictable because, as outlined in Figure 3, the two different ML integrations led to two fundamentally different rulesets, thus affecting the emergent properties/outcomes of the system. That these different integrations of ML in these two studies yielded different ABM results underscores the importance of testing multiple ML approaches and integration strategies in order to assess which method will yield the highest accuracy ABMs.

Supervised learning approaches that are expert knowledge–driven have also been applied in studies that integrate artificial feed-forward neural networks (ANNs) into ABMs of multicellular systems. As the predecessors of today’s deep neural networks (DNNs), information processing in ANNs is inspired by the hierarchical, multi-layered, densely-interconnected patterns of signaling and information flow between layers of neurons in our brain. In an ANN, each neuron (or ‘hidden unit’) processes input variables, e.g. via a linear summation, and ‘decides’ how to pass this information on to the next neuron (downstream), the decision being based on whether or not the computed numerical values exceed an activation threshold. (The foundations of NNs are treated in the classic text by Haykin (1998).) Ideally, the input variables capture salient features about a system in terms of its dynamics, local environment, and so on; non-numerical information (e.g., categorical data) can be captured as input via a process known as feature encoding. Also, note that both the activation function and the neuron’s input-combining function can range from relatively simple (e.g., weighted linear combination of arguments) to more sophisticated schemes.

As an example, one study incorporated an expert knowledge-based feed-forward ANN to determine cellular behavior based on environmental conditions in an ABM of tumor growth (Gerlee and Anderson, 2007). Within the ABM, each cellular agent encoded an ANN that decided cell phenotype based on inputs describing a cell’s local environment, such as the number of cellular neighbors, local oxygen concentration, glucose concentration, and pH (Gerlee and Anderson, 2007). Each ANN processed these inputs to select one from a limited number of discrete phenotypic responses, such as proliferation, quiescence, movement, or apoptosis. Also, in that work the connection weights and activation thresholds of each neuron were manually set, thus ‘tuning’ the ANN such that overall cellular behavior resembled that of cancer cells (i.e., a certain percentage of cells in the population had each of the output phenotypes), instead of training the ANN on actual cellular data. As cells proliferated, they implicitly passed on their ANN to successive generations. Genetic mutations were incorporated into the simulation model by introducing random fluctuations in the ANN weights and thresholds when passed on to daughter cells (Gerlee and Anderson, 2007). These simulated genetic mutations allowed the authors to study clonal evolution in tumors and the environmental factors that contribute to the emergence of the glycolytic phenotype—a cellular state characterized by...
upregulated glycolysis, and which is known to increase the invasiveness of a tumor (Gerlee and Anderson, 2007; 2008).

The above ANN framework was incorporated into follow-up studies aimed at modeling drug delivery and hypoxia. Those further studies increased the complexity of the cellular ANN by adding growth and inhibitory factors as inputs (Kazmi et al., 2012a; Kazmi et al., 2012b), and also by introducing infusion of a bioreductive drug into the ABM; these studies explored the effects of protein binding on drug transport (Kazmi et al., 2012a; Kazmi et al., 2012b). Other studies used a similar ANN architecture to pinpoint effects of hypoxia on tumor growth (Al-Mamun et al., 2014), and explored the efficacy of a chemotherapeutic agent, maspin, on tumor metastasis (Al-Mamun et al., 2013; Al-Mamun et al., 2016). Overall, this design scheme—i.e., ‘embedding’ ANNs into the agent entities of an ABM—illustrates an intriguing and creative type of synergy that is possible between ML and ABM–based approaches.

3.4 REINFORCEMENT LEARNING TO DETERMINE AGENT BEHAVIOR IN MULTICELLULAR ABMS

Another type of learning algorithm used in multicellular ABMs is reinforcement learning (RL), which learns cellular behaviors as ‘policies’ that maximize a (cumulative) reward based on the surrounding environment and transitions of the system from one ‘state’ to the next (Table 1). The RL approach can be largely viewed as being a type of agent-based Markov decision process (Puterman, 1990). The key elements of this approach are four interrelated concepts: (i) the state that is occupied by an agent at a given instant (e.g., a cell can be ‘quiescent’ versus ‘proliferating’); (ii) the action which an agent can take (e.g., apoptose versus divide); (iii) a probabilistic policy map, specifying the chance (and rewards) of transitions between a given combination of states and actions (call it \( \{s_i, a_i\} \)) to a new state, \( s_{i+1} \) (in other words, the conditional probability of taking action \( a \) and thus adopting state \( s_{i+1} \), while in state \( s_i \)); and (iv) the notion of a reward, value or return (these interrelated quantities can be treated as equivalent for present purposes), which is computed both instantaneously, for incremental state transitions \( i \to i + 1 \), as well as cumulatively (a global reward value, for the entire/completed process; ultimately, RL methods seek to maximize this latter quantity). The reward function can be formulated by the modeler to promote expected cellular behaviors, such as elevated metabolism in the presence of glucose or contact inhibition when surrounded by cells (Kaelbling et al., 1996; Kulkarni, 2012).

Recent studies of multicellular systems (Zangooei and Habibi, 2017; Wang et al., 2018; Hou et al., 2019) have exploited a type of ‘model-free’ RL algorithm known as Q-learning (Table 1) to quantitatively learn which cellular behavior, or action, an agent should take on, based on its surroundings (environmental context). In this approach, state-action pairs (see above) are mapped to a reward space by a quality function, \( Q \), which can be roughly viewed as the expectation value of the reward over a series of state-action pairs (i.e., a series of actions and the successive states that they link). Q-learning seeks state-action policies which are optimal in the sense of maximizing the overall/cumulative reward. As one might imagine, achieving this goal involves both exploration and exploitation in the solution space: (i) roughly speaking, ‘exploration’ means sampling new, potentially distant regions of a system’s universe of possible state-action pairs under the current policy (this can be viewed as a long-term/delayed reward), whereas (ii) ‘exploitation’ means (re)sampling an already characterized and advantageous region of the space (e.g., a local energy minimum); the exploration/exploitation trade-off enters the \( Q \) equation as the (adjustable) learning rate. Intuitively, one can imagine that more exploration occurs relatively early in an RL episode (at which point the solution space, or policy space, has been less mapped-out), whereas the balance might shift towards exploitation in later stages (once the algorithm has learned more productive/rewarding types of actions, corresponding to particular regions of the state-action space).

As an example of the applicability of this type of ML in ABMs, one study developed a 3D hybrid agent-based model of a vascularized tumor, wherein a Q-learning algorithm dynamically determined individual
cell phenotypes based on features of their surrounding environment (Figure 4), such as local oxygen and glucose concentrations, cell division count, and number of healthy and cancerous neighbors (Zangooei and Habibi, 2017). Comparison with predictions from other, validated ODE-based models (Wodarz and Komarova, 2009; Gerlee, 2013) indicated that the ABM could accurately recapitulate cell phenotype selection and angiogenesis behaviors.

Q-learning has also been used to model cell migration behaviors in multicellular systems. Cell migration is an intricate and challenging process to model because a subtle combination of chemotactic gradients, cell substrate interactions, and other factors influence the direction of movement. One study used Q-learning to develop cell migration rules in an ABM of C. elegans embryogenesis (Wang et al., 2018). The study trained a deep-Q network that optimizes individual cell migratory behaviors in the system. Deep-Q networks are a deep-RL approach which integrate deep NNs (e.g., deep convolutional neural nets) with the Q-learning framework to improve the power and efficiency of a basic RL approach (Alpaydin, 2021); this improvement is achieved by virtue of using a DNN, versus a variant of Bellman’s equation from dynamic programming (Eddy, 2004), to represent and optimize the Q-function mentioned above (which, again, underlies the mapping of state-action pairs and probabilistic policies to the reward space). In a similar way, Q-learning also has been used to define cell migration behaviors in leader-follower systems (Hou et al., 2019). In these contexts in particular, RL methods can be seen as a complement to popular ‘swarm intelligence’-based approaches (Table 1), such as the particle-swarm, ant-colony, and dragonfly optimization algorithms (Meraihi et al., 2020; Jin et al., 2021).

4. USING ML TO CALIBRATE MODELS AND REDUCE ABM COMPUTATIONAL COSTS

Typically, ABMs include a variety of parameters that dictate agent behaviors and impact model outcomes. While some of these parameters may be experimentally accessible and well-characterized, such as the time for a cell to divide or the contagious period of an infected individual, often many parameters are unknown and impossible to measure experimentally. For example, the probability of two cells forming an adherens junction or the physical distance over which a virus spreads from individual to individual are parameters that are difficult to accurately measure. Also, certain widely-varying parameters may adopt values that are intrinsically quite broadly distributed. For example, at the molecular level the diffusive properties of proteins and other molecules can vary greatly based on cytosolic crowding, facilitated transport, etc., to such a degree that the distributions of a single parameter (e.g., the translational diffusion coefficient) are quite broadly distributed (greater than an order of magnitude). An acute challenge in ABM development is calibrating such parameter values so that model outputs are statistically similar to experimentally measured values, including their distributions. Parameter calibration typically involves the modeler formulating an appropriate ‘error’ or ‘fitness’ function that compares model outputs with experimental outputs; the calibration algorithm optimizes multiple parameters so as to minimize error or, equivalently, maximize fitness. For example, in an ABM of infectious disease transmission, an error function may be defined as the squared difference between the final fraction of infected individuals in the model versus a real-world example. The parameter calibration algorithm would then seek an ABM parameter combination that minimizes this error function—a daunting computational task, as exhaustive, brute-force "parameter sweeps" rapidly become intractable, even for relatively coarse sampling, because of a combinatorial explosion in the size of the search space (i.e., curse of dimensionality (Donoho, 2000)). ABMs generally have highly multidimensional parameter spaces, making it critical to have an efficient calibration pipeline that can rapidly explore this space and reduce the number of parameter combinations that require evaluation. Genetic algorithms and other "evolutionary algorithms" offer an effective approach for high-dimensionality searches, as has been recognized in the context of ABMs (Calvez and Hutzler, 2005; Stonedahl and Wilensky, 2011).
4.1 Genetic Algorithms

Genetic algorithms (GAs) are a widely used ML approach in parameter calibration and, more generally, in any sort of numerical problem that attempts to identify global optima in vast, multi-dimensional search spaces (Table 1). Inspired by the native biological processes of molecular evolution and natural selection (Holland, 1992), GAs are particularly adept at locating combinations of parameters (as ‘solutions’ or ‘individuals’ in an in silico population) that optimize a fitness function. In general, a GA operates via several distinct stages: (i) initialization of a population of individuals as (randomized) parameter combinations that are encoded as chromosomes (e.g., as bit strings, each chromosome corresponding to one individual), (ii) numerical evaluation of the fitness of each individual in the population at cycle \( n \), (iii) a selection step, wherein parameter combinations/individuals of relatively high fitness are chosen as ‘parents’ based on specific criteria/protocols, thereby biasing the population towards greater overall fitness (the selection protocol’s algorithm and its thresholds can be stochastic to varying degrees, e.g. "tournament selection", "roulette wheel selection" or similar approaches (Zhong et al., 2005)), (iv) the stochastic application of well-defined genetic operators, such as crossover (recombination) and mutation, to a subset of the population, yielding the next generation of individuals as ‘offspring’. That next, \( n+1 \)th set of individuals then becomes generation \( n \), and the steps, from stage (ii) onwards, are iteratively repeated. The GA cycles can terminate after a specific number of iterations/generations, or perhaps once a convergence threshold is reached. At the conclusion of this process, the set of available individuals (with encoded genotypes) represent various solutions to the original problem—that is, the solution is ‘read-out’ from the ‘genetic sequence’ of the final set of chromosomes, representing the ‘fittest’ individuals. As the iterations proceed, with hopeful exploration of new regions of the search space at each stage, the average fitness of a generation approaches more optimal values (e.g., maximal traffic flow, minimal free energy, minimal loss/error function). At that point, the GA can be considered as having converged and identified a parameter combination that optimizes the fitness function.

While GAs can find parameters that optimize multi-objective fitness functions, thus avoiding having to run an ABM for every possible parameter combination, GAs can still be quite computationally expensive. Because of its inherent stochasticity, an ABM must be run multiple times to reach stable values of a single parameter combination (genotype), for a given generation of the iteratively proceeding GA. Thus, as the complexity and computational burden of the ABM increases, traditional GAs become a less computationally feasible option, particularly for calibrating a sophisticated ABM. Nevertheless, note that GAs have been used in tandem with ABMs in areas as diverse as calibrating models of financial and retail markets (Heppenstall et al., 2007; Fabretti, 2013), in parameterizing an ABM "of the functional human brain" (Joyce et al., 2012), and for model refinement and rule-discovery in a ‘high-dimensional’ ABM of systemic inflammation (Cockrell and An, 2021).

One way to increase the efficiency of GAs is to reduce the number of parameters being optimized, thereby reducing the dimensionality of the overall search space of the GA and the number of steps required to achieve convergence. In this context, ML methods can be applied to conduct sensitivity analyses on an ABM and identify the most sensitive/critical parameters to target for calibration. Random forests (RFs), which are composed of an ensemble of decision trees (Table 1), are a popular supervised learning algorithm for conducting sensitivity analysis (Strobl et al., 2007; Strobl et al., 2008; Criminisi et al., 2012). One study (Garg et al., 2019) used RFs to identify sensitive parameters in a multicellular ABM of three different cell populations in vocal fold surgical injury and repair. In that work, the ABM was first run for a variety of input parameter values to generate outputs and create a training dataset that relates input parameter combinations to output values. Then, an RF was trained on this data to classify model outputs based on initial
parameter values. The RF hierarchically orders input parameters by Gini index, which is a measure of variance that relates to the probability of incorrectly classifying an output, were the input parameter randomly chosen from the list of all input parameters (the greater the variance, the greater the degree of misclassification). Viewing the Gini index as a measure of feature importance, a parameter with a higher Gini value can be seen as more disproportionately influencing the outcome (relative to other parameters), as the model is more likely to produce wrong (misclassified) output if that parameter value was randomly chosen. After training the RF, this study selected the top three parameters associated with each cell type in the model for calibration with a GA (Garg et al., 2019). This integrative and multipronged approach reduced the number of parameters required for calibration via the GA, thereby improving the computational efficiency of the overall model calibration process.

4.2 AN OVERVIEW OF SURROGATE MODELS

Supervised learning algorithms that create a more easily evaluated "meta model" or "surrogate model" of an original ABM can also significantly reduce computational burden and make model calibration processes more computationally tractable. As schematized in Figure 5, this approach involves evaluating the ABM on an initial set of parameter combinations by computing the fitness, given an objective function constructed by the modeler. Then, a supervised learning algorithm is trained on this data in order to create a surrogate ML model that can predict ABM outputs for various initial parameter combinations. Finally, parameter-calibration approaches, such as GAs, particle swarm optimization or other methodologies amenable to vast search spaces (Table 1), can be applied to this surrogate model. Often, the surrogate model runs significantly faster than the ABM because the inference stage in an ML pipeline involves simply applying the already-trained model to new data (also, the ML model/function is evaluated for single data items instead of an entire simulation). In order to reduce the run-time of an epidemic model, Pereira et al. (2021) employed this general strategy by training a deep neural network (DNN) on data generated by ABM simulations. Application of the DNN (i.e., inference) was more computationally efficient than executing numerous ABM simulations; and, unlike the ABM, the DNN run-time did not increase as the number of ABM agents increased. This DNN-based surrogate model was then used for parameter calibration (Pereira et al., 2021). Other studies have taken similar approaches, for example by using regression algorithms to train surrogate models of the ABM (Tong et al., 2015; Li et al., 2017; Sai et al., 2019).

A recent microsimulation study (Cevik et al., 2016), tracking the progression of breast cancer in women, used a novel "active learning" approach for parameter calibration. In that work, a surrogate ensemble of ANNs (a ‘bag’ of ANNs, or ‘bagANN’) was trained based on ABM-generated training datasets. Then, the bagANN model was used to predict fitness for untested parameter combinations. Parameter combinations with low predicted fitness were reevaluated by the ABM, and a refined training dataset was developed to further train the bagANN. The bagANN was repeatedly trained on parameter combinations with increasing fitness, until the fitness converged at some maximal value. In this way, the overall computational pipeline essentially consisted of an iterative ‘bouncing’ between the ML (bagANN, in this case) and the ABM stages. This study revealed that an active learning approach could find the optimal parameter combination by evaluating only 2% of the parameter space that had been required to be sampled in a prior study devoted to calibrating the same model (Batina et al., 2013; Cevik et al., 2016).

4.3 ML APPROACHES TO ENABLE CONTINUITY TO EMERGE FROM DISCRETE ABM RULES

Surrogate ML models also present novel opportunities to capture continuous system behaviors via ABMs. ABMs of multicellular interactions can represent cell-cell interactions, such as migration, adhesion and proliferation, that occur over discrete time steps. However, these discrete cell-cell behaviors stem from molecular processes that occur over an effectively continuous time domain, such as the rapid expression of
proteins driven by complex intracellular signaling cascades. Multiscale models attempt to represent phenomena that span intra-cellular and inter-cellular biological scales in a more realistic and accurate manner than is otherwise possible; this is pursued by employing continuous approaches that predict intracellular signaling dynamics, and using these predictions to update the discrete rules describing cell-cell behaviors. However, a key challenge in these multiscale models is the increased computational cost of evaluating a continuum model of reaction kinetics at each discrete time-step of an ABM.

A recent study leveraged the training of surrogate models to improve the computational efficiency of a multiscale model of immune cell interactions in the tumor microenvironment (Cess and Finley, 2020). That work employed an ODE–based mechanistic model in order to predict macrophage phenotype, based on surrounding cytokine concentrations, and an ABM to represent resultant interactions between cells in the tumor. To mitigate the computational burden of evaluating the mechanistic model at each time step, the group trained a neural network on the mechanistic model in order to reduce the model to "a simple input/output system", wherein the inputs were local cytokine concentrations and the outputs were cell phenotype. The NN achieved an accuracy exceeding 98%, and—by revealing that the detailed, intracellular mechanistic model could be reduced to a simple binary model—reduced the overall computational complexity of the hybrid, multi-scale ABM (Cess and Finley, 2020).

5. USING ML TO EXPLORE AN ABM’S PARAMETER SPACE

After model development and calibration, an ABM can be quantitatively explored and used to address various questions via sensitivity analysis (SA). In this general approach, one perturbs the ABM and its independent parameters, while monitoring predicted changes in dependent variables and other relevant outputs (ten Broeke et al., 2016). One goal of exploring parameter space via SA is to determine/assess the optimal values of an intervention; for example, in an ABM of tumorigenesis the modeler could find the optimal dosage and scheduling of a drug agent to minimize tumor size. Another goal of parameter-space exploration is to use ABM simulations to predict real-world responses. In an epidemiological ABM of infectious disease transmission, for example, one can use ABM simulations to predict the timeline of disease spread during an ongoing pandemic. Recent ABMs have leveraged a variety of unique ML approaches to aid in testing a wide range of perturbations and in characterizing stochastic results (Figure 6). Interestingly, our review of the literature reveals that the goal of parameter-space exploration—whether it be optimizing the efficacy of an intervention, training a predictive model on ABM simulation results, or so on—tends to be closely associated with the type of ML algorithm used.

Reinforcement learning methods have been applied to optimization problems in epidemiological and multicellular ABMs, wherein an intervention, such as a drug, is considered an agent and ML is used to find the optimal policy to achieve an output of interest (e.g., minimizing tumor size). A precision medicine, multicellular ABM used deep reinforcement learning (DRL) to find the optimal multi-cytokine therapy dosage for sepsis patients in an ABM of systemic inflammation (Petersen et al., 2019); in that work, the DRL algorithm found the optimal dosage of 12 cytokines to promote patient recovery. RL also has been used, in a multicellular ABM of glioblastoma, to identify an optimal scheduling of Temozolomide treatment for tumor size minimization (Zade et al., 2020). Similarly, RL was also used to optimize radiotherapy treatment of heterogeneous, vascularized tumors (Jalalimanesh et al., 2017a; Jalalimanesh et al., 2017b).

The aforementioned "active learning" approaches have been used to accelerate the parameter space exploration of ABMs. Using the ABM framework PhysiCell (Ghaffarizadeh et al., 2018), a recent study compared GA-based and active learning–based parameter exploration approaches in the context of tumor and immune cell interactions (Ozik et al., 2019). The goal of the parameter space exploration was to optimize six different immune cell parameters, including apoptosis rate, kill rate and attachment rate, in order to
reduce overall tumor cell count. In the GA approach, optimal parameters were found by iteratively selecting parameter combinations that reduced mean tumor cell count. The active learning approach involved training a surrogate RF classifier on the ABM, such that the RF predicts whether a set of input ABM parameters would yield mean tumor cell counts less than a predefined threshold. Then, in a divide-and-conquer-like strategy, the active learning approach selectively samples ‘viable’ parameter subspaces that yield tumor cell counts less than the threshold in order to find a solution (Ozik et al., 2019). That work illustrates the possibilities of integrating ML-guided adaptive sampling strategies with ABM-based approaches.

A combination of supervised and unsupervised learning methods have been leveraged to use ABM simulations to create predictive models. A recent study (Nsoesie et al., 2011) evaluated seven different classification algorithms in terms of their abilities to predict the full epidemic curve (i.e., the graphical representation of population-level disease incidence over time, from the first to last infection), given a partial epidemic curve of only the early, middle, or late stages of disease transmission. The study trained these classification algorithms on simulation data from an influenza ABM that modeled the transmission of influenza virus between human agents. Six different variations of the influenza ABM were used to generate a dataset of partial epidemic curves and their corresponding full epidemic curves. Then, supervised learning algorithms were trained to classify partial epidemic curves into one of the six full-epidemic curve categories. The study found that RF classifiers yielded the highest accuracy, whereas linear discriminant analysis had the lowest accuracy (Nsoesie et al., 2011). Another study (Sheikh-Bahaei and Hunt, 2006) used unsupervised fuzzy c-means (FCM) classification to predict the biliary transport and excretion properties of new drugs, based on similarities to previously simulated drugs in an ABM of the interactions between in silico hepatocyte and drug agents. The study first parametrized biliary transport and excretion properties of experimentally tested drugs in the ABM using a parameter tuning algorithm. Then, the FCM approach was used to cluster and characterize the degree of similarity of a new drug with previously encountered drugs. Based on the degrees of similarity to previously encountered drugs identified by FCM, the biliary transport and excretion properties of the new drug was estimated as a weighted average of that of previously encountered drugs (Sheikh-Bahaei and Hunt, 2006). These examples demonstrate how supervised and unsupervised ML algorithms can be used synergistically with ABMs to predict outcomes for epidemiological and multicellular systems.

Finally, unsupervised ML algorithms have also been used to discover relevant patterns in the results of ABM simulations, such as identifying how differences in single-cell properties in a tumor give rise to distinct tumor spatial organizations. One study (Karolak et al., 2019) co-varied cell radius, cell division age and cell sensitivity to contact inhibition, in a 3D ABM of tumorigenesis, to enable the creation of a simulated library of multicellular tumor organoids. Then, the study ran unsupervised k-medians clustering on this library of multicellular tumor organoids to identify four different classes of tumor organoids. The study found that these four classes of organoids respond differently to drug treatment, and identifying which class a real tumor falls into can guide therapy design (Karolak et al., 2019).

6. DISCUSSION

In this Review, we have summarized how several recent lines of work have incorporated ML in each stage of developing and deploying ABMs of multicellular and/or epidemiological systems—from defining agent behaviors and optimal rule-sets to tuning model parameters and quantitatively exploring a model’s sensitivity and features of its parameter space. Our review of the literature suggests three guiding principles when using ML algorithms in conjunction with ABMs. First, the biological scale of the system (molecular, cellular, organismal, epidemiological, etc.) and the type of data available about the system directly impact the type of ML algorithms (supervised, expert knowledge-driven, unsupervised, reinforcement learning,
etc.) that are applicable to determining agent behaviors. Second, the specific type of ML algorithm used with an ABM strongly impacts the emergent results and veracity of predictions by the ABM; therefore, it is critical to evaluate multiple ML-ABM integration schemes and select the algorithmic approach with highest accuracy and/or similarity to the decision-making structure of the (actual) modeled system. Finally, open-access publication and open-source distribution of validated, clearly-explained and shareable models—which the ABM and related modeling communities can apply, extend, and learn from—is critical in order to advance new techniques and synergistic approaches at the junction of the ML and ABM ecosystems; indeed, this latter point is essentially a call to apply the "FAIR Principles" of scholarly research (Findability, Accessibility, Interoperability and Reusability (Wilkinson et al., 2016)) to the ABM field.

ML is a broad term encompassing a variety of predictive algorithms that each require different levels of data availability for decision making. A chief requirement of supervised learning algorithms, for example, is a large amount of accurately-labeled data for purposes of training and testing. Depending on the biological scale of the modeled system, such datasets may or may not be available, thereby affecting the applicability of supervised learning algorithms to ABM. Many epidemiological systems have extensively used survey data and electronic health records to associate patient features (e.g., age, sex, drug use), with disease states, such as diabetic retinopathy or lung cancer stage. Because of the generally high availability of large epidemiological datasets, many epidemiological ABMs have trained supervised learning algorithms on these data to determine agent rules and behaviors in their models (Day et al., 2013; Alexander Jr et al., 2019; Augustijn et al., 2020). In contrast to epidemiological systems, multicellular systems often lack comprehensive data about the detailed mechanisms that drive complex cellular behaviors. In multicellular systems, a range of cellular behaviors, such as migration, proliferation, apoptosis or necrosis, are contingent upon several dynamic and spatiotemporal cues, such as nutrient availability, local cytokine concentrations and intracellular protein expression levels. Current experimental methodologies are challenged to create datasets that associate these spatiotemporal features of the environment with cellular behaviors across the broad populations of heterogeneous cells that comprise various tissues; thus, training supervised learning algorithms to predict cellular behavior based on environmental features is not currently a routine possibility for those sorts of systems. However, several ABMs have augmented the lack of data in this area with either expert-knowledge–driven machine learning (Gerlee and Anderson, 2007; 2008; Kazmi et al., 2012a; Kazmi et al., 2012b; Al-Mamun et al., 2013; Al-Mamun et al., 2014; Al-Mamun et al., 2016) or RL algorithms (Zangooei and Habibi, 2017; Wang et al., 2018; Hou et al., 2019) to define cellular behaviors within a multicellular ABM. While these recent approaches are not trained on actual experimental datasets, they do enable each cell to autonomously make decisions based on their local environment, thereby realistically modelling cell-to-cell heterogeneity within multicellular systems. These studies illustrate that the limited availability of training data does not necessarily have to be a severe (i.e., prohibitive) constraint in synergistically integrating ML and ABMs.

Much effort in ML is devoted to procuring datasets that suffice for training, particularly in deep learning and classification tasks (whether it be for image recognition, speech processing, etc.). While data accuracy and volume have always been key, the importance of data relevance (to the problem at hand) is being increasingly appreciated as part of a recent "data-centric" shift in AI (Ng, 2022), and ABMs could play a significant role in that context. As described in Goodfellow et al. (2016), one approach to data augmentation is to simply "create fake data and add it to the training set"; for example, for image-related tasks one might obtain ‘fake’ new data from starting images by applying affine transformations, subjecting images to masks or filters, altering intensities, hues, saturation, and so on. We propose that future ML algorithms can leverage ABM’s capacity to efficiently generate large volumes of plausible/reliable simulation data to produce new datasets for ML training workflows.
Different ML algorithms can rely on fundamentally different computational methods and criteria to make decisions. For example, a logistic regression model relies on a weighted linear combination of predictor variables to classify an object, whereas a naive Bayes model uses conditional probabilities in addressing the same task. Depending on the data, the two modeling approaches can make slightly divergent predictions from the same datasets. Thus, when integrated with an ABM, different ML algorithms will impact the accuracy of the ABM in simulating real-world systems and the kinds of predictions the ABM generates. For example, two previously discussed studies took alternative approaches to use ML to define the rule that determines human agent water use in an ABM of cholera spread (Abdulkareem et al., 2019; Augustijn et al., 2020). One study trained Bayesian networks to define agent behaviors, while the other used decision trees to derive the same agent rule. The ABM using the decision tree approach yielded higher predictions for the number of infected individuals; this discrepancy is unsurprising, as the two ABM approaches differ in the fundamental ways in which each agent behaves. Considering how the different integrations of ML in these two studies yield different ABM results shows the importance of testing multiple ML integration strategies to assess the respective accuracies of the methods.

To circumvent the issue of different ML integration strategies yielding different results, several studies have tested a variety of ML integrations within their ABM prior to deriving model predictions (Sheikh-Bahaei and Hunt, 2006; Nsoesie et al., 2011; Alexander Jr et al., 2019; Gaudou et al., 2020; Hinch et al., 2021). These studies suggest that the computational method underlying an ML algorithm should relate to how an (actual) agent could plausibly make decisions in a real-world environment. For example, whether a cell decides to proliferate, migrate or adhere to its neighbors may be a result of combining weighted inputs from signaling cascades, similar to the linear weighted sum found in logistic regression models. Alternatively, when a human decides whether or not to use a particular water source they may (implicitly) evaluate a series of binary questions, similar to the trajectory through a decision tree.

Finally, we note that the intersection of ML and ABM is a nascent and rapidly-growing field, made possible by the increased publication of peer-reviewed, reproducible and shareable ABMs. In order to facilitate the continued growth of this field, it is imperative to publish models that are validated for given biological contexts, well-documented and maintained, transparent and freely available (open-access, open-source), and otherwise readily usable by all researchers in the many ABM-related communities.

**ACKNOWLEDGEMENTS**

We thank Bill Basener, Phil Bourne and Lei Xie for helpful discussions, support, and reading of the manuscript. Portions of this work were supported by NSF CAREER award MCB-1350957 and the UVA School of Data Science. Note that this review provides only a glimpse of ML and ABMs, reflecting our own familiarity with a subset of many potential topics; absence of specific citations reflects only space constraints and not opinions about the significance or merit of earlier work by others.
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Tables 1. This taxonomy of ML algorithms organizes a few popular approaches using a scheme based on Mitchell’s definition of ML. Specifically, we list (i) the type of Task each algorithm can address, (ii) how the algorithm measures the Performance with respect to that task (an "objective function" typically quantifies accuracy), and (iii) the learning process, or Experience, by which an algorithm tunes parameters (generally by optimizing the Performance function) to improve its accuracy for a given task (estimation, classification, etc.). This Table is meant to be viewed flexibly. For instance, though often associated with supervised learning, neural networks span multiple types of ML; as an example, autoencoders are often built via NNs to learn optimal representations/models from unlabeled data by minimizing a "reconstruction error" for generating original/input data from a compressed (latent space) representation, and in that way can be viewed as a form of unsupervised learning.

| Type of ML (category, or "learning style") | Sample algorithms | Task | Performance | Experience |
|-------------------------------------------|------------------|-----|-------------|------------|
| Supervised, including semi-supervised or "expert-knowledge driven" (i.e., at least some labeled data are used) | Linear Regression | Predict a continuous outcome from input parameters/features (numerical estimation) | Sum of squared errors | Iteratively, via gradient descent |
| | Logistic Regression | Predict discrete outcomes (e.g., binary) from input data (classification task) | Logarithmic loss (or 'cross-entropy loss') function | Iteratively, via gradient descent |
| | Naïve Bayes | Predict data labels based on naive prior probability distributions (assumes independent features) | Negative joint likelihood function | For a given problem instance, the class label yielding the largest probability (i.e., a maximum a posteriori [MAP] decision rule) |
| | Decision Trees | Predict the sequence of predictor variables that classify a sample within a particular category (vs others) | Gini index (relates to the relative mean absolute difference); seek a tree that accounts for most of the data, without excessive number of levels | Can alter number of levels, node-splitting functions (e.g., based on Kullback-Leibler div), try ensemble methods (random forests) |
| | Support Vector Machine (SVM) | Computes hyperplane that optimally separates points in a dataset, e.g. for classification or regression tasks | Maximize margin of the decision boundaries ('buffer' between hyperplane and nearby 'support vectors') | Use gradients of a loss function (e.g., hinge loss) to update weights w’s, thus iteratively maximizing margin |
| Unsupervised (only unlabeled data) | k-means clustering (other example families of methods include hierarchical clustering and dimensionality reduction approaches) | For a collection of unlabeled data, creates k ‘natural’ grouping (or sets of associations) between the entities in the set | Gives set of maximal distances between k centroids in unlabeled dataset (maximizes sum of squared between-cluster distances, which is equivalent to minimizing sum of squared distances to centroid within each cluster); equivalently, partitions the dataset into Voronoi cells | Iterate between two stages: (i) assign point x to nearest cluster (lowest distance to mean), (ii) re-compute means, given all pts assigned to each cluster, and (iii) iterates to convergence (no further Δs to point assignments); a greedy algorithm that partitions into k groups |
| Type of ML (category, or "learning style") | Sample algorithms | Task | Performance | Experience |
|------------------------------------------|------------------|-----|-------------|------------|
| Reinforcement learning (either model-based or model-free) | Q-Learning (other RL methods include temporal difference learning, deep-Q networks [DQN], actor/critic framework, associative RL) | Determines a policy (transition probabilities for state/action pairs), that is optimal in sense of maximizing expected cumulative (final) reward, given current state | \( Q \) is the action-value function that is iteratively optimized (policy updates via Bellman equation); in so doing, many parameters can be adjusted (learning rate, discount factor, initialization values \( Q_0 \), etc.); in RL, the performance (and learning) occurs ‘online’/on-the-fly | Classic way is to iteratively improve \( Q \) by updates via the Bellman equation for optimization (via dynamic programming); this recursive principle is that optimal policy at state \( i+1 \) must subsume optimal up to state \( i \). |
| Genetic algorithms (GAs) | Find approximate solutions to an optimization problem, generally occupying an exceedingly high-dimensional parameter space; the solutions, or individuals comprising the population, are encoded as chromosomes (e.g., as binary strings). | A given trial solution/individual is evaluated against an objective function (fitness function); notably, in GAs these functions can have properties that challenge traditional optimization approaches (e.g., discontinuous, non-differentiable, highly non-linear). | A subset of the fittest individuals (chromosomes yielding optimal values against the fitness function) are selected, along with a randomly chosen subset; these parents reproduce via operations like crossover (splicing chromosomes), mutations, etc. (biological evolution). Thus, the population of individuals evolves towards higher fitness, and solutions can be identified (as individual chromosomes). |
| Swarm-based approaches, e.g. particle-swarm optimization, ant-colony optimization, dragonfly optimization | Estimate parameters, in a high-dimensional parameter space, that optimizes a global objective function (e.g., shortest cumulative path between two points, in ant-colony optimization). Sets of parameters are encoded as attributes of individual agents (particles, ants, etc.). | The population of individual entities (ants, agents, etc.) is evaluated against an optimality criterion (fitness function) defined by the modeler. Once a ‘stopping criterion’ is met, a solution to the task can be considered as optimal. | In a given iteration, agents (particles, ants, etc.) are updated (towards other ants, the centroid of a swarm, etc.) based on a combination of terms, one of which is a ‘social learning parameter’ that is, itself, updated; crucially, this social parameter enables global communication amongst entities (e.g., as ant pheromones), and thus the population collectively equilibrates towards higher-fitness regions of the solution space. |
FIGURE 1. This schematic overview of how ML can aid the various stages in the development and application of an ABM also offers representative examples of the various types of synergistic ML-ABM couplings (numbers correspond to literature citations).
Figure 2. Application of ML to define rule sets in epidemiological (left) and multicellular (right) ABMs. In these two illustrative examples, ML-related stages are in red or blue while ABM-related steps are highlighted in yellow. In both contexts, individual agents survey environmental variables at a given time-step of the simulation. These environmental variables form the input for an ML algorithm that outputs a decision for the agent to enact. The left example refers to an ABM developed to simulate cholera spread in Kumasi, Ghana, wherein supervised learning algorithms trained on survey data were used to select the most probable behavior based on environmental variables (Abdulkareem et al., 2019; Augustijn et al., 2020). Several other epidemiological ABMs have leveraged large datasets to train supervised learning algorithms to determine agent behavior (Day et al., 2013; Abdulkareem et al., 2019; Alexander Jr et al., 2019; Augustijn et al., 2020). The right-hand example refers to multicellular ABMs that simulate individual cell behaviors in a tissue selected based on Q-learning (Zangooei and Habibi, 2017) or ANN approaches (Gerlee and Anderson, 2007; 2008; Kazmi et al., 2012a; Kazmi et al., 2012b; Al-Mamun et al., 2013; Al-Mamun et al., 2014; Al-Mamun et al., 2016; Abdulkareem et al., 2019).
FIGURE 3. Contrasting two applications of supervised learning algorithms to define agent rulesets in epidemiological ABMs. Two studies applied ML to define agent rulesets in an ABM developed to simulate cholera spread in Kumasi, Ghana. The first study (top) applied a naive Bayes model to predict water usage of individual agents based on environmental variables (Abdulkareem et al., 2019), while the second study (bottom) trained a decision tree to derive agent behavior based on the same environmental variables (Augustijn et al., 2020). The two ML-ABM integrations predicted different numbers of total infected individuals in the population, illustrating that the ML algorithm used to predict agent behavior can impact the overall trends predicted by an ABM.
FIGURE 4. Application of Q-learning to update cellular states in an ABM of tumorigenesis. An ABM of 3D tumorigenesis (Zangooei and Habibi, 2017) applied Q-learning to find the optimal cell actions (proliferate, migrate, become hypoxic, undergo apoptosis) based on an individual cell’s surrounding environmental variables, including oxygen concentration, glucose concentration, number of healthy cell neighbors, number of cancer cell neighbors.
FIGURE 5. Training surrogate ML models can reduce the computational burden of ABM calibration. Because of the need to repeatedly evaluate potentially complex numerical expressions for multiple agents over several timesteps, parameterizing ABMs can be computationally expensive. Once trained (i.e., as applied in the inference stage), ML models are generally less computationally costly because they entail evaluating a single function to generate a prediction. Several studies (Tong et al., 2015; Cevik et al., 2016; Li et al., 2017; Sai et al., 2019; Pereira et al., 2021) have leveraged this advantage of ML by first evaluating an ABM for a limited range of parameters and then creating a ‘surrogate’ dataset that relates the ABM parameters to final error. Next, a surrogate supervised learning algorithm can be trained on this data and researchers can then use the surrogate model to explore broader regions of the original ABM’s parameter space.
FIGURE 6. Application of ML to parameter space exploration of ABMs. ABMs can be used to generate vast volumes of data and explore how system perturbations affect population-level outcomes in the model. After generating simulation data from an ABM, ML can be used to characterize patterns in the ABM (Karolak et al., 2019). Simultaneously, the data generated by ABMs can be used to train more robust ML algorithms (Sheikh-Bahaei and Hunt, 2006; Nsoesie et al., 2011).