

Simulation assisted machine learning

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Predicting how a proposed cancer treatment will affect a given tumor can be cast as a machine learning problem, but the complexity of biological systems, the number of potentially relevant genomic and clinical features, and the lack of very large scale patient data repositories make this a unique challenge. “Pure data” approaches to this problem are underpowered to detect combinatorially complex interactions and are bound to uncover false correlations despite statistical precautions taken (1). To investigate this setting, we propose a method to integrate simulations, a strong form of prior knowledge, into machine learning, a combination which to date has been largely unexplored. The results of multiple simulations (under various uncertainty scenarios) are used to compute

similarity measures between every pair of samples: sample pairs are given a high similarity score if they behave similarly under a wide range of simulation parameters. These similarity values, rather than the original high dimensional feature data, are used to train kernelized machine learning algorithms such as support vector machines, thus handling the curse-of-dimensionality that typically affects genomic machine learning. Using four synthetic datasets of complex systems—three biological models and one network flow optimization model—we demonstrate that when the number of training samples is small compared to the number of features, the simulation kernel approach dominates over no-prior-knowledge methods. In addition to biology and medicine, this approach should be applicable to other disciplines, such as weather forecasting, financial markets, and agricultural management, where predictive models are sought and informative yet approximate simulations are available. The Python SimKern software, the models (in MATLAB, Octave, and R), and the datasets are made freely available at <https://github.com/davidcraft/SimKern>.

There are two general approaches to predicting the behavior of complex systems, simulation and machine learning (ML). Simulation is the preferred method if the dynamics of the system being studied are known in sufficient detail that one can simulate its behavior with high fidelity and map the system behavior to the output to be predicted. ML is valuable when the system defies accurate simulation but enough training data exists to train a general black-box machine learner, which could be anything from a linear regression or classification model to a neural network. In this work, we propose a technique to

combine simulation and ML in order to leverage the best aspects of both and produce a system that is superior to either technique alone.

Our motivation is personalized medicine: how do we assign the right drug or drug combination to cancer patients? Across cultures and history, physicians prescribe medicines and interventions based on how the patient is predicted to respond. Currently these choices are made based on established patient-classification protocols, physician judgment, clinical trial eligibility, and occasionally limited genomic profiling of the patient. All of these approaches, in one way or another, attempt to partition patients into groups based on some notion of similarity.

Genomics is especially relevant for computing the similarity between two cancer patients since cancer is associated with alterations to the DNA, which in turn causes the dysregulation of cellular behavior (2). Bioinformatic analysis has revealed that there is heterogeneity both within a patient tumor and across tumors; no two tumors are the same genomically (3, 4). Although in a small fraction of cases specific genetic conditions are used to guide therapy choices, for example breast (commonly amplified gene: HER2), melanoma (BRAF mutation), lung (EML4-ALK fusion), and head-and-neck (HPV status for radiation dose de-escalation (5)), there remains a large variability in patient responses to these and other treatments, likely due to the fact that patients will usually have tens or hundreds of mutations and gene copy number variations, not to mention a distinct germline genetic state (6), human leukocyte antigen type (7), tumor epigenetic DNA modifications, microbiome, and comorbidity set. Even amidst this heterogeneity, the notion of patient similarity—although currently not deeply understood due to the complexities of cancer biology—is appealing both conceptually and for its value in the ML setting, as we will see.

Simulating a drug is a task that far exceeds our current scientific capacity: it enters

the patient, either intravenously or orally, and winds its way to the cancer cells, where it either influences the cancer cell via receptors on the cell membrane or penetrates into the cell and affects signaling pathways, cell metabolism, DNA repair, apoptosis, or some combination of these and other modules. Nevertheless, a vast amount of knowledge of cellular processes, residing in molecular biology textbooks and millions of scientific papers, has been accrued over the past century and it seems worthwhile to attempt to use that information, if unclear how. Most research efforts in the personalized medicine realm take a pure data ML approach. Given the complexity of patient biology and cancer, this approach will require vast amounts of high quality patient data that is suitably standardized for algorithmic processing. With this drug sensitivity prediction problem as our backdrop, we develop a method to combine approximate simulations with ML and demonstrate using *in silico* experiments that a judicious combination can yield better predictions than either technique alone. The basic idea is a division of labor: coarse and approximate simulations are used to compute similarity measures, and these similarity measures are then used by the ML algorithm to build a predictive model.

Our method is centered on kernelized ML. Rather than feature vectors (a list of attributes for each sample), kernelized learning requires only a similarity score between pairs of samples. For training one needs the outcome of each training sample and a measurement of the similarity between all pairs of training samples. For predicting the outcome of a new sample (a sample could be a patient but we use the term sample to invoke a more general ML context), one needs to provide the similarity of that sample to each training sample. It is well known in ML that good similarity measures, which come from expert domain knowledge, result in better ML performance (8). We assume we can simulate the behavior of each sample based on its known individual characteristics (i.e. features). We also assume that we do not know exactly how to simulate the systems, so rather than

a single simulation we have a family of plausible simulations. Two samples are given a high similarity score if they behave similarly across a wide range of simulations (see Supplementary information).

To demonstrate the simulation-based kernel ML method, we create datasets by simulation which provides us with a known ground truth and the ability to generate arbitrarily large datasets. For each of these datasets, we also create a separate approximate simulation model family. A member of this family is a simulation which takes as input a feature vector and produces an output which is used in computing similarity to other samples. Thus there are two simulations built for each dataset: the first is used to generate the dataset initially, which represents the real world ground truth data, and the second, which we call SimKern, is the simulation family that represents our approximate ideas about how to simulate the data. In a real world application, one would build only the SimKern simulation family since the ground truth data would already exist. We investigate four models: radiation impact on cells, flowering time in plants, a Boolean cancer model, and a network flow optimization problem. Full details of the datasets and simulations are given in the Supplementary information with brief descriptions below.

The **radiation cancer cell death model** is a set of ordinary differential equations (ODEs) which represents a simplified view of the biochemical processes that happen after a cancer cell is hit by radiation. The core of the model involves the DNA damage response regulated by the phosphorylation of ATM and subsequent p53 tetramerization (9). We have added cell cycle arrest terms, a DNA repair process, and apoptosis modules in order to capture the idea that cellular response to DNA damage involves the combined dynamics of these various processes. The model has 34 ODEs. The output from the model is one of four classes: apoptosis, cell cycle arrest, cell cycling, and other (e.g., heading towards mitotic catastrophe). A population of distinct cell types is formed by varying 33 of the

ODE rate constants and the mutation status of six genes (ARF, BAX, SIAH, Reprimo, p53, and APAF1), for a feature vector length of 39. The SimKern simulation uses the same underlying model as the original ODE model with two key differences: 87 of the ODE parameters are marked as uncertain and given Gaussian probability distributions around their true values, and the simulation outputs the time dynamics of the ODEs rather than a classification.

The **flowering time model** is a set of six ODEs that simulate the gene regulatory network governing time to flowering of the Arabidopsis plant (10) and yields a regression problem. 19 mutants are modeled and experimentally validated by the authors. We use those 19 mutational states as well as 34 additional perturbations on the rate parameters to create a varied ground truth sample set. The output of the model is the time to flowering which, following the authors, we take to be the time at which the protein AP1 exceeds a particular threshold. For the SimKern model we assume the same model but with uncertainty about the rate parameters. The SimKern simulation output is the time dynamics of the six ODEs.

The **Boolean cancer model** is a discrete dynamical system of cancer cellular states (11). There are no rate parameters since this is a Boolean model. We use the initial state vector (the on/off status of the 32 nodes in the network) as well as mutations of five of the genes (p53, AKT1, AKT2, NICD, and TGF β) to create a varied sample population with 37 features. In the SimKern simulation, we use a reduced version of the model provided in the original publication. It is unclear how to map the initial conditions from the full model to the initial conditions of the modularly-reduced model, so for all of the modules we randomly choose the mapping, which gives rise to the uncertainty for the SimKern simulations. The output from the SimKern model is the same classification as from the ground truth model.

The **network flow model** is an optimization problem rather than a simulation. It falls into a subclass of linear optimization models called network flows which are used a wide range of applications including production scheduling and transportation logistics (12). An optimal solution is a path of flow along arcs of a directed graph that minimizes the total arc cost along the path. Slight changes in arc costs, which represent the features in this model, can lead to changes in the routing of the optimal flow. The network is designed in layers and is such that the flow will pass through exactly one of the three arcs in the final layer, which gives us a classification problem (see Figure S2). For the ground truth dataset, we choose 12 out of the 80 arc costs to be variable from one sample to the next. We build two separate SimKern models: the closer model perturbs 23 arc costs including the 12 costs that were varied to make the ground truth dataset resulting in a higher quality kernel and the harder model varies 21 additional arc costs resulting in a lower quality kernel.

For each model we begin by generating a dataset of n samples using the ground truth simulation. This produces an $n \times p$ feature matrix X and a response vector y of length n . Figure 1 shows a schematic of the data processing steps after a dataset is created. We compare standard feature-based ML algorithms (orange/top: linear support vector machine (SVM), radial basis function (RBF) SVM, and random forest (RF)) with simulation kernel based methods (green/bottom: kernelized SVM and kernelized RF). We also include results for 1-nearest neighbor (NN) and kernelized 1-nearest neighbor (SimKern NN). As NN-type algorithms are arguably the simplest non-trivial ML algorithms, including these algorithms allows us to understand the distinct contributions of ML algorithm sophistication and simulation-based kernels. The details of partitioning the data into training, validation, and test datasets are given in the supporting information document. Briefly, since we can generate as many samples as we wish, we train the models

and tune the hyperparameters on training and validation datasets which are distinct from the final testing set which we use to generate the plots of classification accuracy and R^2 . For each model, we generate a plot that shows model performance versus training dataset size for the various ML algorithms. The general theme that emerges, see Figure 2, is that for small training dataset sizes, the methods using the SimKern kernel outperform the Standard ML methods. For larger training sizes, however, the uninformed methods either approach the kernelized methods or exceed them, depending on the quality of the kernel.

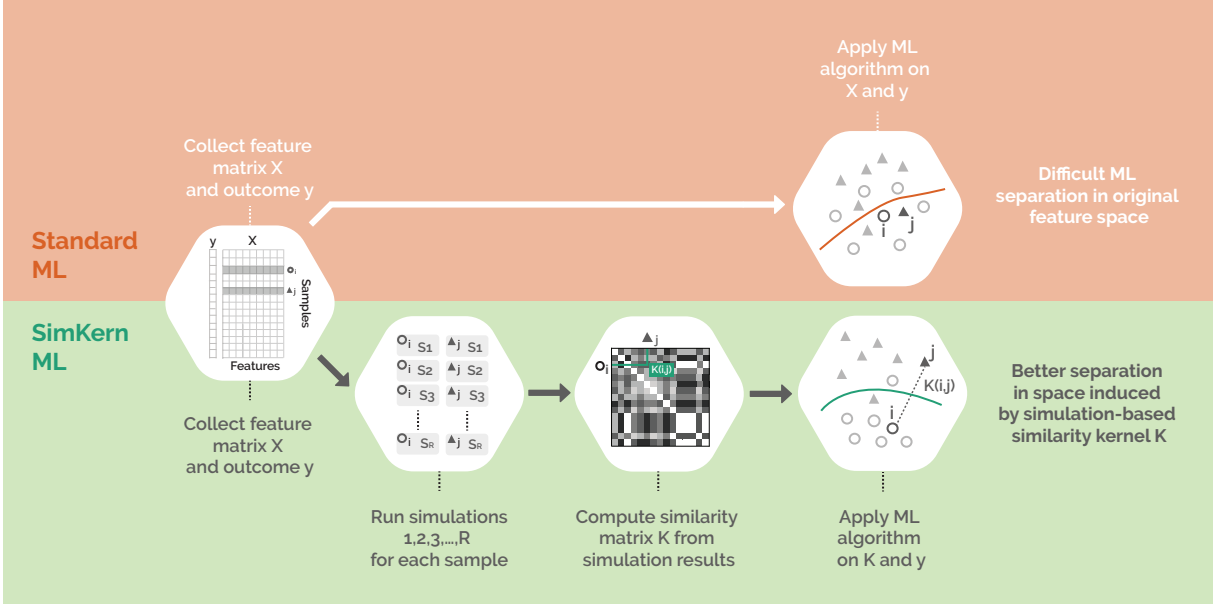


Figure 1: Workflow comparison of standard machine learning (ML) and SimKern ML. The feature matrix X and outcome data y are given (in this paper, we generate such “ground truth” datasets by simulating complex systems, a step which is not shown in this figure). Traditional feature-based ML is depicted in the upper orange part. SimKern, the simulation-based method, pre-processes the dataset by sending each sample through a number of approximate simulations. Each sample pair is given a similarity score based on how closely they behave under the various simulations. This information is stored in a kernel matrix K , where $K(i, j)$ measures the similarity between samples i and j . Note that $K(i, i) = 1$ and $0 \leq K(i, j) \leq 1$. Useful SimKern simulations yield a kernel K that improves the downstream machine learning performance.

For the radiation model, we examine the results for two kernels which represent different levels of expert knowledge. Both cases utilize the same SimKern simulation but the higher quality kernel uses the dynamics of only the compartments of the ODE set that are used in the classification of the samples in the initial ground truth simulation. The lower quality kernel uses all ODE equations, therefore not emphasizing the most important ones (13). For small training sizes (up to 50 samples), the SVM with the SimKern kernel dominates but we can attribute most of the performance gain to the similarity kernel itself given that the NN algorithm using the same similarity kernel also dominates over the no-prior-knowledge methods for all training sizes shown. The summary line plots for the radiation model, lower left of Figure 2, indicate that the Standard ML algorithms have not been saturated by 500 samples.

The results of the flowering time model clearly show the trend of decreasing variance in predictive performance with increasing training sizes (Figure S3). SimKern learning is strongly dominant up to 75 training samples, after which the two learning styles converge to $R^2 \approx 1$ (Figure 2, lower right). We call kernels that can learn a dataset to high accuracy with enough data *sufficient*. In contrast, the Boolean cancer model kernel is based on a model reduction with additional uncertainty and produces what we call a *biased* kernel. For the Boolean model, the SimKern approach produces an accuracy that initially dominates but quickly plateaus to around 85% and is overtaken by no-prior-knowledge methods when more training data is available, Figure S4. The fact that the kernel learning barely improves with additional data implies that the feature space induced by the simulation kernel is simple enough to be learned by a small amount of samples (14).

The Boolean model is a discrete simulation, and the network flow model is essentially discrete since its output is which of the three exit arcs the optimal flow passes through. For these models, RF is the dominant Standard ML method, which is likely related to

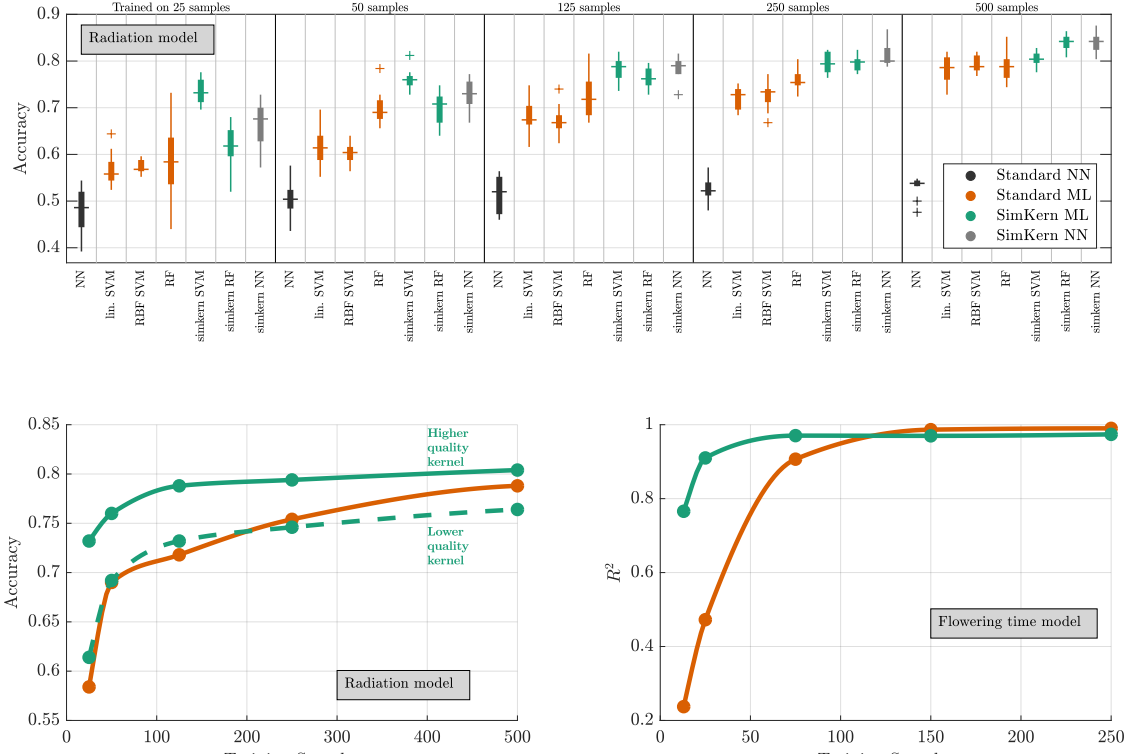


Figure 2: Machine learning results for the radiation model and the flowering time model. The upper box-whisker plot offers a detailed comparison of machine learning approaches for the radiation model dataset with the higher quality kernel. On all sample training sizes, the SimKern learning approaches (green and light gray) dominate but especially for small training set sizes. The lower figures are derived from the detailed box plots by selecting the single best algorithms from the orange (no-prior-knowledge) and the green (prior knowledge in the form of the simulation-derived similarity kernel). The lower quality kernel in the bottom left radiation plot arises by using all of the differential equation results to compute the similarity score rather than just the differential equations for the compartments used to classify the samples. In the lower right panel we plot the coefficient of determination, R^2 , versus training sample size for the flowering time model, again showing superiority of the SimKern (prior knowledge, in green) approach. Detailed results for the other models are in the Supplementary information.

the discrete characteristics of the underlying models. In a real world setting, the quality of the kernel will make or break the success of the SimKern approach. For the network flow problem we use two separate kernels: the higher quality kernel, Figure S5, dominates

throughout but even the lower quality and clearly biased kernel, Figure S6, is still useful in the very small training set size range. The quality of a simulation-generated kernel also depends on the number of trials R that are used to compute the kernel. Figure S7 displays both the kernel convergence and the improved learning accuracy from the further converged kernel, for the higher quality kernel network flow case.

We introduce simulation as a pre-processing step in a machine learning pipeline, in particular as a way to include detailed expert knowledge. One can consider simulation as a technique which regularizes data or as a specialized feature extraction method. In either view, the SimKern methodology offers a decomposition of an overall ML task into two steps: similarity computation followed by predictive modeling using the pairwise similarities. This decomposition highlights that to improve the performance of a ML model one can direct efforts into determining better similarity scores between all samples. This is in contrast to the more commonly heard call for “more data” to achieve better ML results. Of course, more samples are always desirable but here we show that, particularly in limited data settings, sizable performance gains can come from high quality similarity scores. We note again that it is not required that the simulations used to compute similarity scores have as outputs that which we are trying to predict in the ML, e.g., the class that the sample belongs to. All that is required for the SimKern approach is that samples with comparable simulation outputs are scored with high similarity.

The decomposition also points out the individual contributions made by the simulations and the machine learning step. The simulation-based kernel structures the space in which the samples live (or more technically, the dual of the space (15)), and ML finds the patterns in this simplified space. We see that, in order to improve machine learning performance, we can either improve the kernel or increase the number of samples to better populate the space. For the cases shown here, custom similarity measures show large

improvements especially in limited data settings (up to a 20% increase in classification accuracy and a 2.5 fold increase in R^2 , depending on the case and the amount of training data used). One could also use the output of the simulations as features for machine learning rather than the additional kernelization step that we employed. Using the simulation outputs directly is related to the field of model output statistics from weather forecasting, where low level data from primary simulations are used as inputs to a multiple regression model which outputs human-friendly weather predictions (16). However, in our case, we opted for kernelizing the simulation outputs to highlight the fundamental concept of similarity and because a similarity computation is natural when the output of the simulations is a set of time varying entities. Using whatever means one has available, be they computational, experimental, or theoretical, if one can compute good similarity scores, one has gone a long way towards better predictive modeling.

It remains to be seen which techniques will be the most fruitful as we make our way towards personalized cancer medicine. Direct testing of chemotherapeutic agents on biopsied patient tissues is a straightforward and promising “hardware-based” approach (17). In the machine learning realm, expert feature selection may turn out to be more feasible than the simulation-based kernel methods described in this report. A key question is: can we make simulation-based kernels that—although almost certainly biased—will still be useful (see e.g. Figure S4). Progress in detailed biological simulation, such as the full simulation of the cell cycle of the bacterium *Mycoplasma genitalium* (18) and integrated cancer signaling pathways for predicting proliferation and cell death (19) offer some encouragement, but cancer influences human biology at all levels, from organ systems to minute phosphorylations and mutations that control gene regulation and immune system recognition. It is thus by no means clear if we are close to simulations that can be useful in this context. However, the magnitude of the problem—both in economic terms and for

the number of future patients at stake—suggests pressing forward on all fronts that display conceptual promise.

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