# **Optimizers manuscript**

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### **Authors**

#### • Jake Crawford

© 0000-0001-6207-0782 · ♥ jjc2718 · ♥ jjc2718

Genomics and Computational Biology Graduate Group, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

• Casey S. Greene 

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Department of Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, CO, USA; Center for Health AI, University of Colorado School of Medicine, Aurora, CO, USA

■ — Correspondence possible via <u>GitHub Issues</u> or email to Casey S. Greene <casey.s.greene@cuanschutz.edu>.

## **Abstract**

## Introduction

Gene expression profiles are widely used to classify samples or patients into relevant groups or categories, both preclinically [1,2] and clinically [3,4]. To extract informative gene features and to perform classification, a diverse array of algorithms exist, and different algorithms perform well across varying datasets and tasks [1]. Even within a given model class, multiple optimization methods can often be applied to find well-performing model parameters or to optimize a model's loss function. One commonly used example is logistic regression. The widely used scikit-learn Python package for machine learning [5] provides two modules for fitting logistic regression classifiers:

LogisticRegression, which uses the liblinear coordinate descent method [6] to find parameters that optimize the logistic loss function, and SGDClassifier, which uses stochastic gradient descent [7] to optimize the same loss function.

Using scikit-learn, we compared the liblinear (coordinate descent) and SGD optimization techniques for prediction of driver mutation status in tumor samples, across a wide variety of genes implicated in cancer initiation and development [8]. We applied LASSO (L1-regularized) logistic regression, and tuned the strength of the regularization to compare model selection between optimizers. We found that across a variety of models (i.e. varying regularization strengths), the training dynamics of the optimizers were considerably different: models fit using liblinear tended to perform best at fairly high regularization strengths (100-1000 nonzero features in the model) and overfit easily with low regularization strengths. On the other hand, models fit using stochastic gradient descent tended to perform best at fairly low regularization strengths (10000+ nonzero features in the model), and overfitting was uncommon.

Our results caution against viewing optimizer choice as a "black box" component of machine learning modeling. The observation that LASSO logistic regression models fit using SGD tended to perform best for low levels of regularization, across diverse driver genes, runs counter to conventional wisdom in machine learning for high-dimensional data which generally states that explicit regularization and/or feature selection is necessary. Comparing optimizers/model implementations directly is rare in applications of machine learning for genomics, and our work shows that this choice can affect generalization and interpretation properties of the model significantly. Based on our results, we recommend considering the appropriate optimization approach carefully based on the goals of each individual analysis.

## Methods

# Results

### **Discussion**

Our results suggest that even for the same model, LASSO logistic regression, optimizer choice can affect model selection and performance. Existing gene expression prediction benchmarks and pipelines typically use a single model implementation (and thus a single optimizer). To our knowledge, the phenomenon we observed with SGD has not been documented in other applications of ML to genomic or transcriptomic data. In the broader machine learning research community, however, similar patterns have been observed for both linear models and deep neural networks (e.g. [9,10]). This is often termed "benign overfitting": the idea that "overfit" models, in the sense that they fit the training data perfectly and perform worse on the test data, can still outperform models that do not fit the training data as well or that have stronger explicit regularization. Benign overfitting has been observed with, and attributed to, optimization using SGD, which is thought to provide a form of implicit regularization [11,12].

We recommend thinking critically about optimizer choice, but this can be challenging for users that are inexperienced with machine learning or unfamiliar with how certain models are fit under the hood. For example, R's glmnet package uses a cyclical coordinate descent algorithm to fit logistic regression models [13], which would presumably behave similarly to liblinear, but this is somewhat opaque in the glmnet documentation itself. LASSO logistic regression is a convex optimization problem, meaning there is a single unique optimum of the loss function in contrast to more complex models such as neural networks, but this optimum can be computationally intensive to find in practice and there is no closed-form solution [14]. Increased transparency and documentation in popular machine learning packages with respect to optimization, especially for models that are challenging to fit, would benefit new and unfamiliar users.

Similar to what we see in our SGD-optimized models, there exist other problems in gene expression analysis where using all available features is better than using a subset. For example, using the full gene set improves correlations between preclinical cancer models and their tissue of origin, as compared to selecting genes based on variability or tissue-specificity [15]. On the other hand, when predicting cell line viability from gene expression profiles, selecting features by Pearson correlation improves performance over using all features, similar to our liblinear classifiers [16]. An avenue of future work for our SGD classifiers would be to interpret the coefficients and compare them systematically to the coefficients found using liblinear. It could be useful to understand if the two optimization methods emphasize the same pathways or functional gene sets, or if there are patterns to which driver mutations perform better with more/fewer nonzero coefficients.

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