# Ten Quick Tips for Deep Learning in Biology

*This manuscript (permalink) was automatically generated from Benjamin-Lee/deep-rules@785dd4a on January 2, 2019.*

## Authors


- **Benjamin D. Lee**
  0000-0002-7133-8397 · Benjamin-Lee
  School of Engineering and Applied Sciences, Harvard University; Department of Genetics, Harvard Medical School; Lab41, In-Q-Tel


## Introduction

Deep learning (DL), a subfield of machine learning (ML) implementing artificial neural networks with many layers, is increasingly used for the analysis of biological data [1]. Despite its growing popularity, DL itself remains an active area of research. Its everchanging complexity and lack of current beginner resources focused on biological applications pose large barriers of entry to newcomers who wish to utilize state-of-the-art DL in their research. Biological insight garnered from DL has been well-documented in the scientific literature, with applications ranging from predicting protein-drug binding kinetics [2] to identifying the lab-of-origin of synthetic DNA [3]. However, few resources articulate DL best practices to the scientific community. Most instructional literature focuses on ML broadly, rather than DL specifically, further limiting accessibility and reproducibility [4]. To address this issue, we solicited input from a diverse community of researchers, who wrote this manuscript collaboratively using the GitHub version control platform [5] and Manubot [6].

In the course of our discussions, several themes became clear: the importance of understanding and applying ML fundamentals as a baseline for utilizing DL, the necessity for extensive model comparisons and careful evaluation, and the need for critical thought in interpreting results generated by means of DL, among others. Ultmately, the tips we established range from high-level guidance to the implementation of best practices, and it is our hope that they will provide actionable, DL-specific advice for both new and experienced DL practitioners alike who would like to employ DL in biological research. By increasing the accessibility of DL techniques to biology, we aim to improve the overall quality and reproducibility of DL in the literature, enabling these powerful methods to be properly utilized to generate new scientific insights.

# Tip 1: Concepts that apply to machine learning also apply to deep learning

Deep learning is a distinct subfield of machine learning, but it is still a subfield. Deep learning has proven to be an extremely powerful paradigm capable of outperforming “traditional” machine learning approaches, but it is not immune to the many limitations inherent to machine learning. Many best practices for machine learning apply to deep learning as well. For instance, deep supervised learning models should be trained, tuned, and tested on non-overlapping datasets. Those developing deep learning models should select data that are relevant to the problem at hand; non-salient data can hamper performance or lead to spurious conclusions. Furthermore, investigators should begin by thoroughly inspecting their data. When coupled with imprudence, data that is biased, skewed, or of low quality will produce models of dubious performance and limited generalizability. Biases in testing data can also unduly influence measures of model performance. For example, many conventional metrics for classification (e.g. area under the receiver operating characteristic curve or AUROC) have limited utility in cases of extreme class imbalance. As such, model performance should be evaluated with a carefully-picked panel of relevant metrics that make minimal assumptions about the composition of the testing data [7]. Extreme cases warrant testing the robustness of the model and metrics on simulated data for which the ground truth is known. Said simulations can be used to verify the correctness of the model’s implementation as well. Like all computational methods, deep learning should be leveraged in a systematic manner that is reproducible and rigorously tested.

## Tip 2: Use traditional methods to establish performance baselines

## Tip 3: Understand the complexities of training deep neural networks

## Tip 4: Know your data and your question

## Tip 5: Choose an appropriate neural network architecture and data representation

## Tip 6: Expect to tune hyperparameters extensively and systematically

Deep neural networks have the ability to approximate arbitrary continuous functions, as long as the neural network contains enough hidden nodes [8]. However, this flexibility makes the training process somewhat challenging. Users should expect to systematically evaluate the impact of numerous hyperparameters when they aim to apply deep neural networks to new data or challenges.

Neural network architectures also have their own odd nuances that affect hyperparameter portability. For example, in variational autoencoders (VAEs) there are two elements that are being optimized, reconstruction and distribution loss [9]. In common implementations, the relative weights of each are a function of the number of input features (more increase the importance of reconstruction loss) and the number of features in the latent space (more increase the importance of the distribution loss). Users who apply a VAE architecture to a new dataset with more input features, even without changing any hyperparameters, alter the relative weights of the components of the loss function.

This flexibility also makes it difficult to evaluate the extent to which neural network methods are well-suited to solving a task. Hu and Greene [10] discuss a Continental Breakfast Included (CBI) effect by which unequal hyperparameter tuning skews the evaluation of methods, especially those with performance that varies substantially with modest changes to hyperparameters. The implication of CBI on methods developers is discussed more in Rule 2 (`TODO: cgreene tie these together`). The implication of CBI on users of deep neural networks

is that attaining performance numbers that match those reported in publications is likely to require an input of human and compute time for hyperparameter optimization.

## Tip 7: Address deep neural networks' increased tendency to overfit the dataset

## Tip 8: Do not necessarily consider a DL model as a black box

## Tip 9: Interpret predictions in the correct manner

## Tip 10: Don't share models trained on sensitive data

One of the greatest opportunities for deep learning in biology is the ability for deep learning techniques to incorporate representation learning to extract information that can not readily be captured by traditional methods [11]. The abundance of features for each training example means that the representation learning of the deep learning models can capture information-rich abstractions of data during the training process. Therefore with both deep learning and traditional machine learning models (*e.g. k*-nearest neighbors models, which learn by memorizing the full training data), it is imperative not to share models trained on sensitive data. Applying deep learning to images of cats from the internet does not pose significant ethical, legal, or privacy problems; this is not the case when dealing with classified, confidential, trade secret, or other types of biological data that cannot be shared. For example, adversarial training techniques such as model inversion attacks can be used to exploit model predictions to recover recognizable images of people's faces used for training [12]. These risks are even more significant in deep learning compared to traditional machine learning techniques due to the greater representational capacity of the models. This is achieved by the large number of model weights, even in a relatively small project, that allow deep learning to model high-dimensional non-linear relationships among data. It is this enhanced modeling capacity that allows the model to learn more robust and nuanced features of specific data, leading to the danger of revealing the underlying sensitive data. When training deep learning models on sensitive data, be sure not to share the model weights directly, and use privacy preserving techniques [13] such as differential privacy [14,15] and homomorphic encryption [16,17] to protect sensitive data.

## Conclusion

# References


1. **Opportunities and obstacles for deep learning in biology and medicine**
Travers Ching, Daniel S. Himmelstein, Brett K. Beaulieu-Jones, Alexandr A. Kalinin, Brian T. Do, Gregory P. Way, Enrico Ferrero, Paul-Michael Agapow, Michael Zietz, Michael M. Hoffman, … Casey S. Greene
*Journal of The Royal Society Interface* (2018-04) https://doi.org/gddkhn
DOI: 10.1098/rsif.2017.0387 · PMID: 29618526 · PMCID: PMC5938574

2. **VAMPnets for deep learning of molecular kinetics**
Andreas Mardt, Luca Pasquali, Hao Wu, Frank Noé
*Nature Communications* (2018-01-02) https://doi.org/gcvf62
DOI: 10.1038/s41467-017-02388-1 · PMID: 29295994 · PMCID: PMC5750224

3. **Deep learning to predict the lab-of-origin of engineered DNA**
Alec A. K. Nielsen, Christopher A. Voigt
*Nature Communications* (2018-08-07) https://doi.org/gd27sw
DOI: 10.1038/s41467-018-05378-z · PMID: 30087331 · PMCID: PMC6081423

4. **Ten quick tips for machine learning in computational biology**
Davide Chicco
*BioData Mining* (2017-12) https://doi.org/gdb9wr
DOI: 10.1186/s13040-017-0155-3 · PMID: 29234465 · PMCID: PMC5721660

5. **Ten Quick Tips for Deep Learning in Biology. Contribute to Benjamin-Lee/deep-rules development by creating an account on GitHub**
Benjamin Lee
(2019-01-02) https://github.com/Benjamin-Lee/deep-rules

6. **Open collaborative writing with Manubot**
Daniel S. Himmelstein, David R. Slochower, Venkat S. Malladi, Casey S. Greene, Anthony Gitter
(2018-12-31) https://greenelab.github.io/meta-review/

7. **Comparison of Deep Learning With Multiple Machine Learning Methods and Metrics Using Diverse Drug Discovery Data Sets**
Alexandru Korotcov, Valery Tkachenko, Daniel P. Russo, Sean Ekins
*Molecular Pharmaceutics* (2017-11-13) https://doi.org/gcj4p2
DOI: 10.1021/acs.molpharmaceut.7b00578 · PMID: 29096442 · PMCID: PMC5741413

8. **Approximation capabilities of multilayer feedforward networks**
Kurt Hornik

*Neural Networks* (1991) https://doi.org/dzwxkd
DOI: 10.1016/0893-6080(91)90009-t

9. **Auto-Encoding Variational Bayes**
Diederik P Kingma, Max Welling
*arXiv* (2013-12-20) https://arxiv.org/abs/1312.6114v10

10. **Parameter tuning is a key part of dimensionality reduction via deep variational autoencoders for single cell RNA transcriptomics**
Qiwen Hu, Casey S Greene
*Cold Spring Harbor Laboratory* (2018-08-05) https://doi.org/gdxxjf
DOI: 10.1101/385534

11. **Convolutional Networks on Graphs for Learning Molecular Fingerprints**
David Duvenaud, Dougal Maclaurin, Jorge Aguilera-Iparraguirre, Rafael Gómez-Bombarelli, Timothy Hirzel, Alán Aspuru-Guzik, Ryan P. Adams
*arXiv* (2015-09-30) https://arxiv.org/abs/1509.09292v2

12. **Model Inversion Attacks that Exploit Confidence Information and Basic Countermeasures**
Matt Fredrikson, Somesh Jha, Thomas Ristenpart
*Proceedings of the 22nd ACM SIGSAC Conference on Computer and Communications Security - CCS '15* (2015) https://doi.org/cwdm
DOI: 10.1145/2810103.2813677

13. **A generic framework for privacy preserving deep learning**
Theo Ryffel, Andrew Trask, Morten Dahl, Bobby Wagner, Jason Mancuso, Daniel Rueckert, Jonathan Passerat-Palmbach
*arXiv* (2018-11-09) https://arxiv.org/abs/1811.04017v2

14. **Deep Learning with Differential Privacy**
Martin Abadi, Andy Chu, Ian Goodfellow, H. Brendan McMahan, Ilya Mironov, Kunal Talwar, Li Zhang
*Proceedings of the 2016 ACM SIGSAC Conference on Computer and Communications Security - CCS'16* (2016) https://doi.org/gcrnp3
DOI: 10.1145/2976749.2978318

15. **Privacy-Preserving Distributed Deep Learning for Clinical Data**
Brett K. Beaulieu-Jones, William Yuan, Samuel G. Finlayson, Zhiwei Steven Wu
*arXiv* (2018-12-04) https://arxiv.org/abs/1812.01484v1

16. **SIG-DB: Leveraging homomorphic encryption to securely interrogate privately held genomic databases**

Alexander J. Titus, Audrey Flower, Patrick Hagerty, Paul Gamble, Charlie Lewis, Todd Stavish, Kevin P. O'Connell, Greg Shipley, Stephanie M. Rogers
*PLOS Computational Biology* (2018-09-04) https://doi.org/gd6xd5
DOI: 10.1371/journal.pcbi.1006454 · PMID: 30180163 · PMCID: PMC6138421

17. **The AlexNet Moment for Homomorphic Encryption: HCNN, the First Homomorphic CNN on Encrypted Data with GPUs**
Ahmad Al Badawi, Jin Chao, Jie Lin, Chan Fook Mun, Sim Jun Jie, Benjamin Hong Meng Tan, Xiao Nan, Khin Mi Mi Aung, Vijay Ramaseshan Chandrasekhar
*arXiv* (2018-11-02) https://arxiv.org/abs/1811.00778v1