UiO : Universitetet i Oslo

Machine Learning in Computational Biology: Overview

IN-BIOS5000/IN-BIOS9000

Milena Pavlović
Biomedical Informatics Research Group
Department of Informatics

milenpa@student.matnat.uio.no

Disclaimer

I am a machine learning researcher, not a biologist:
you are the experts there!

Learning aims

- Key points should be the intuition and high-level understanding of what machine learning is, types of problems it can help solving
- Machine learning is not a black box: every choice we make has a meaning
- Overall understanding that there is a data representation component and a machine learning algorithm
- High-level understanding of machine learning workflow, comparison and uncertainty related to it

Sequencing technologies provide data which can be examined for biological properties

CDR3	V gene	J gene	Species
CAAAERNTGELFF	TRBV28*01	TRBJ2-2*01	HomoSapiens
CAAGVENTGELFF	TRBV5-6*01	TRBJ2-2*01	HomoSapiens
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Motifs and data from VDJdb (Bagaev et al. 2020)

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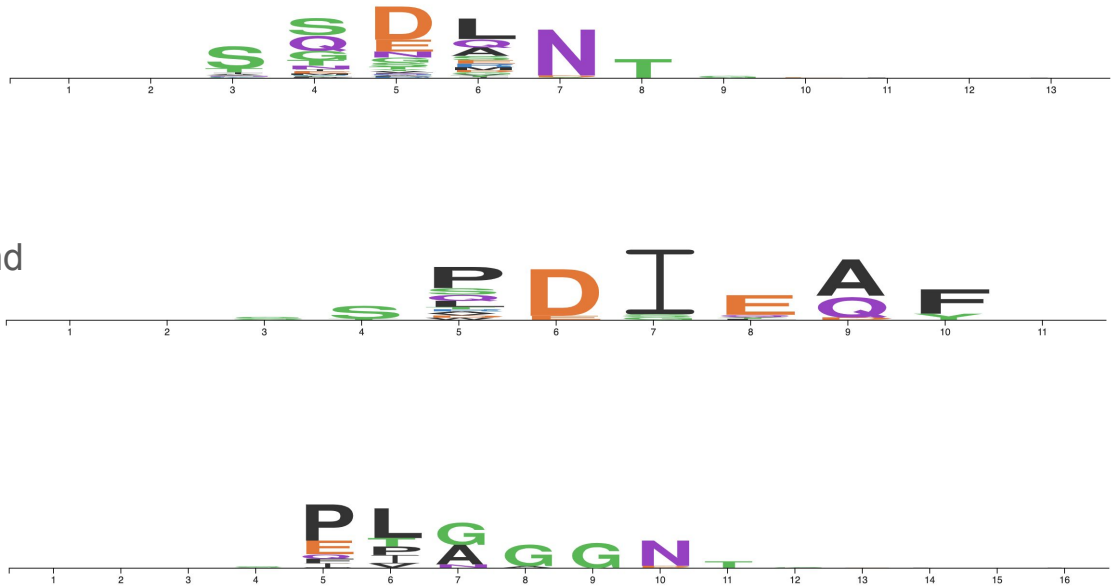
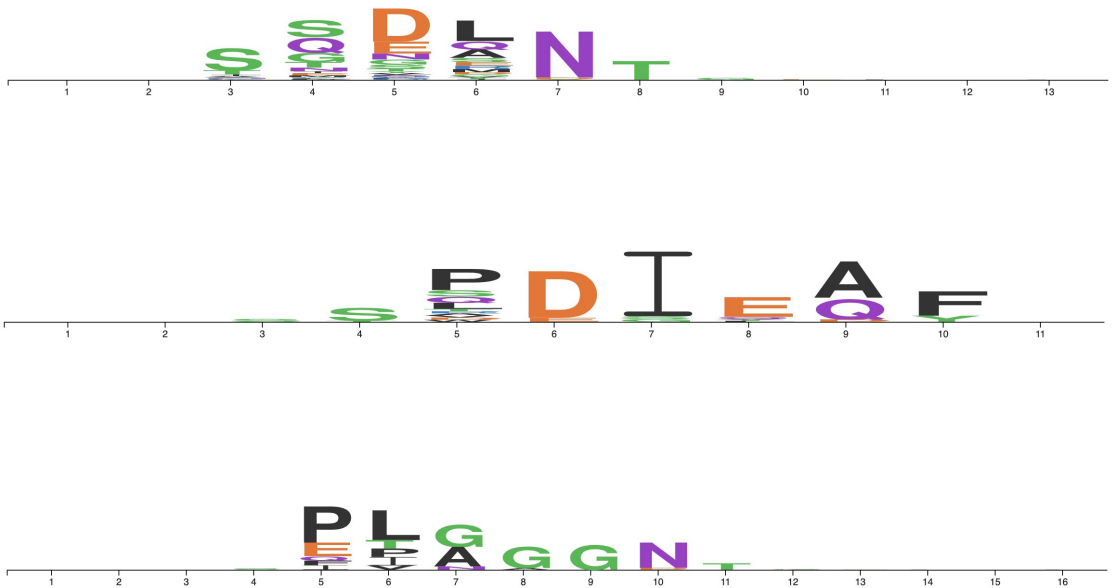
discover motifs and remove genetic background →



Motifs and data from VDJdb (Bagaev et al. 2020)

Sequencing technologies provide data which can be examined for biological properties

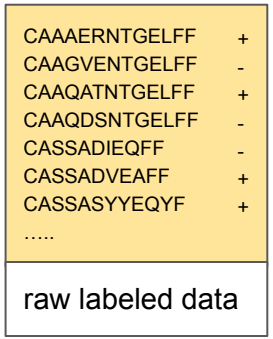
- One way to approach an analysis: make a position weight matrix showing product multinomial distribution of amino acids
- But what if we want to predict if a sequence is specific to a virus or not?



Motifs and data from VDJdb (Bagaev et al. 2020)

Machine learning is a powerful approach to discovering patterns in (biological) data

- A set of methods that allow for making inferences about the data
- Example: will the receptor bind to the virus or not? - we can fit a logistic regression model on receptor data and then predict binding for new receptors



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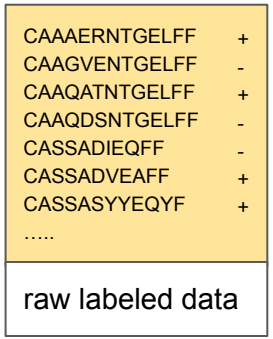

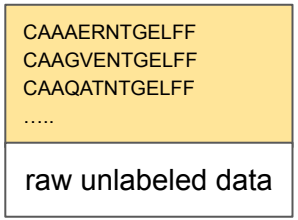

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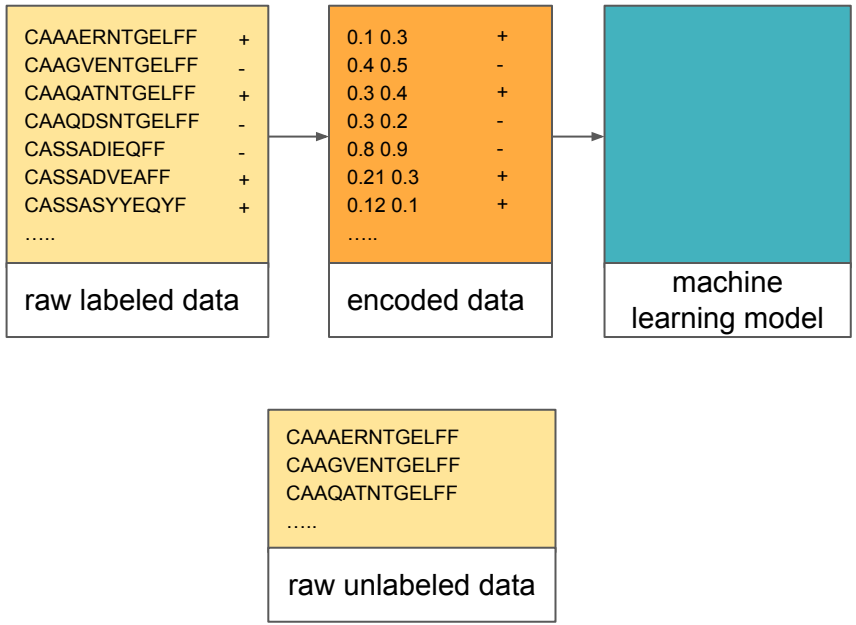

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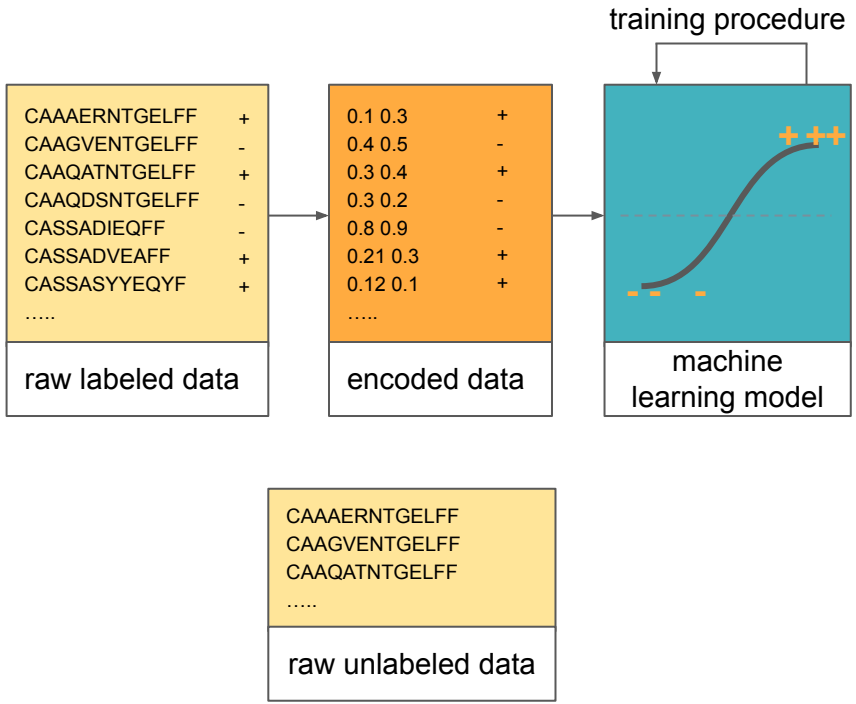

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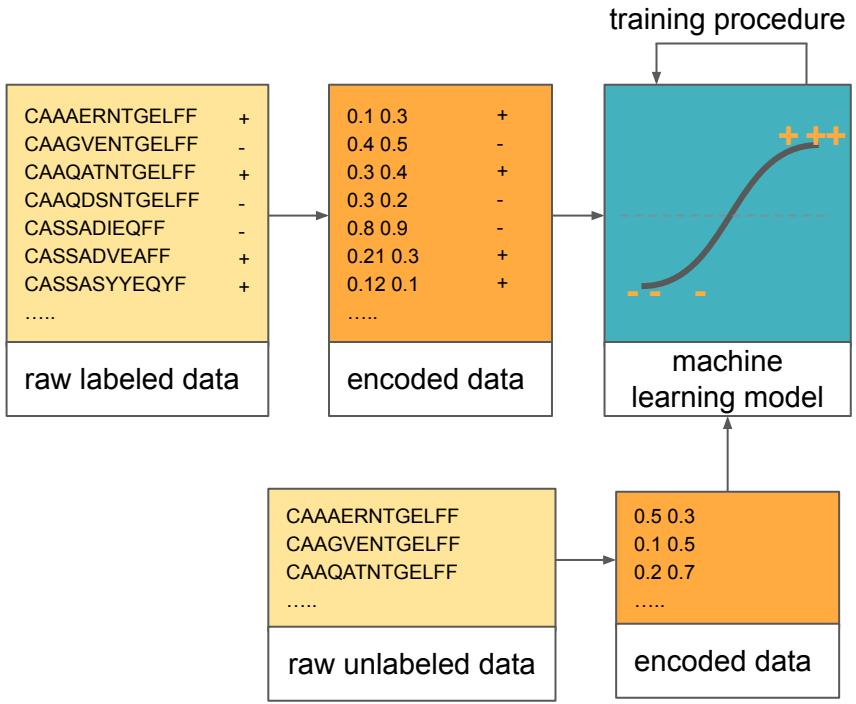

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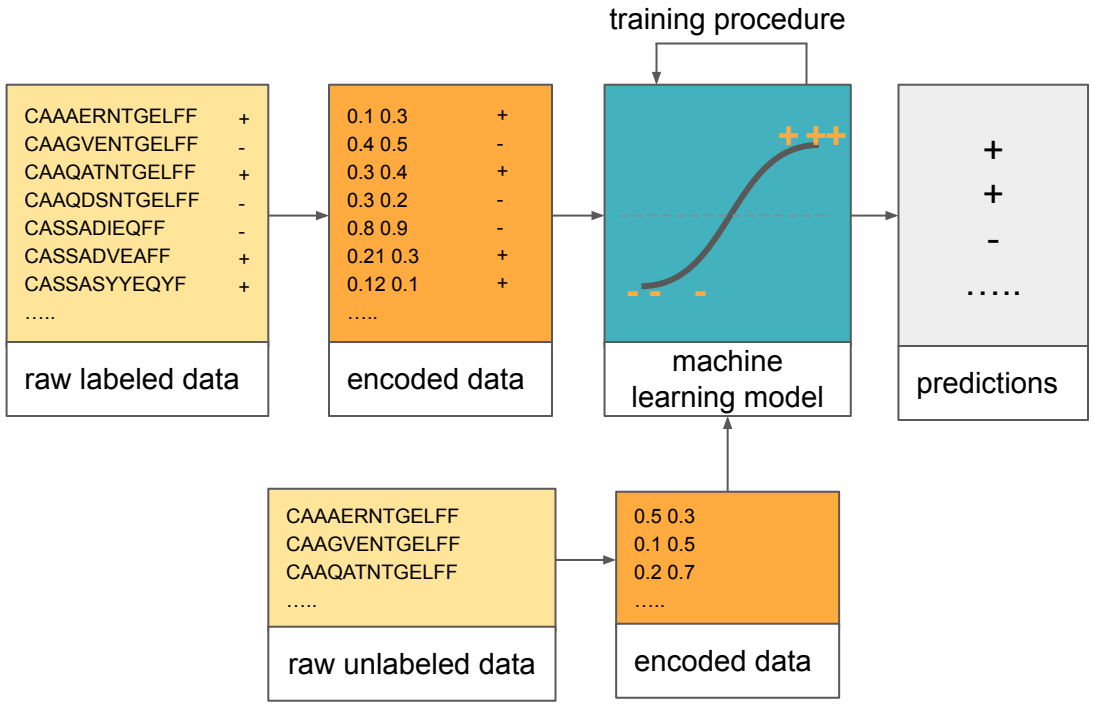
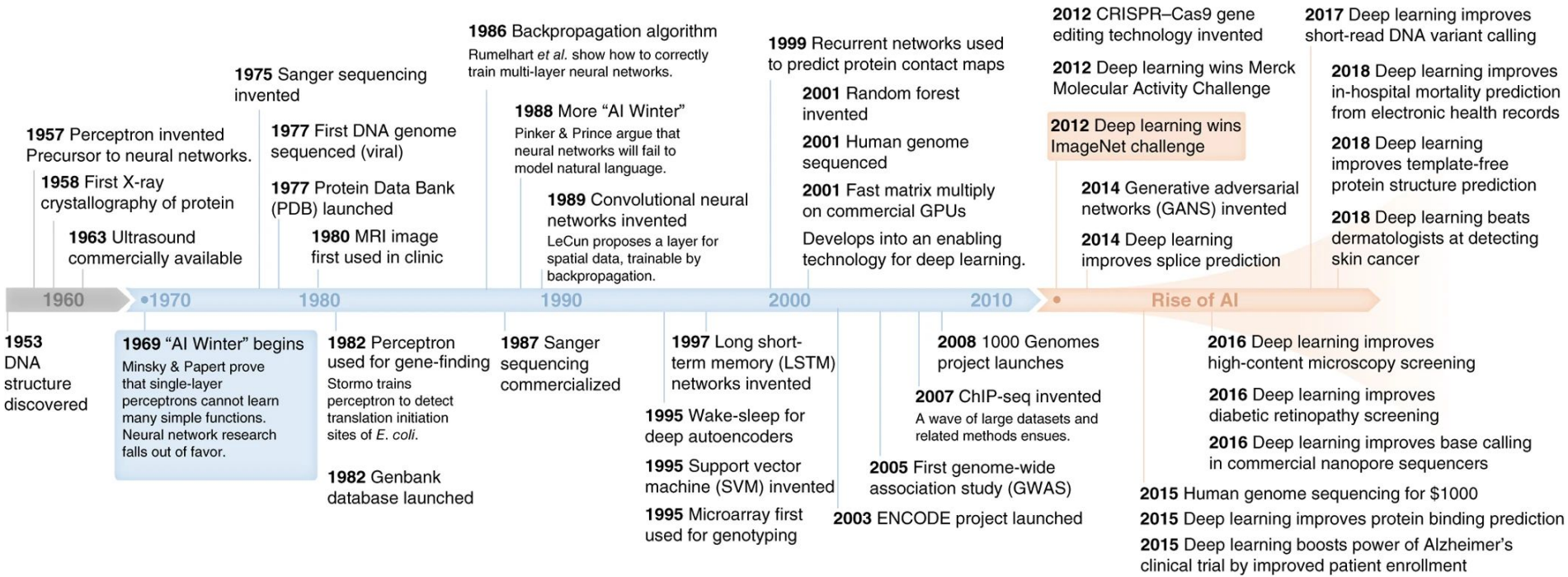
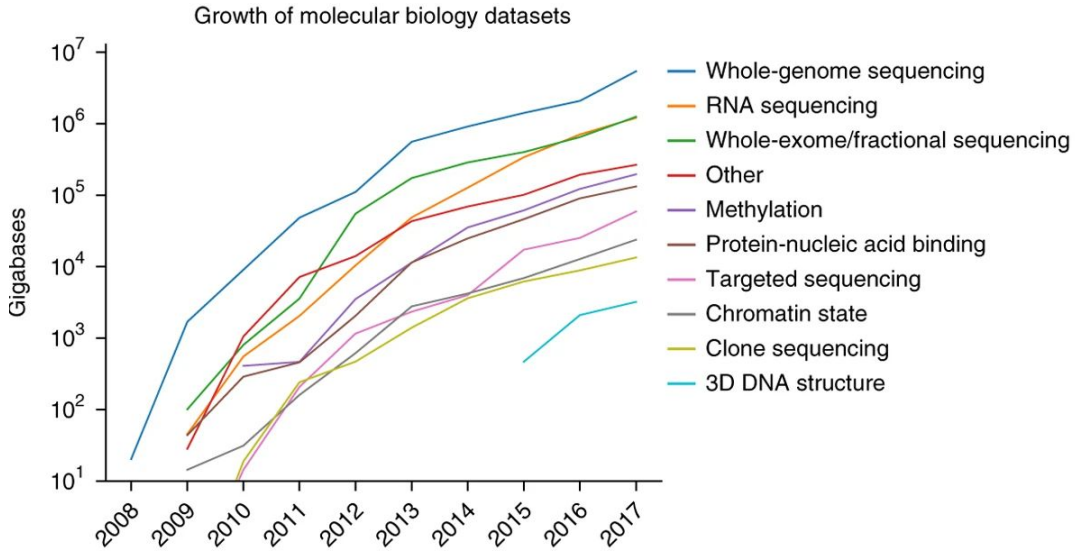


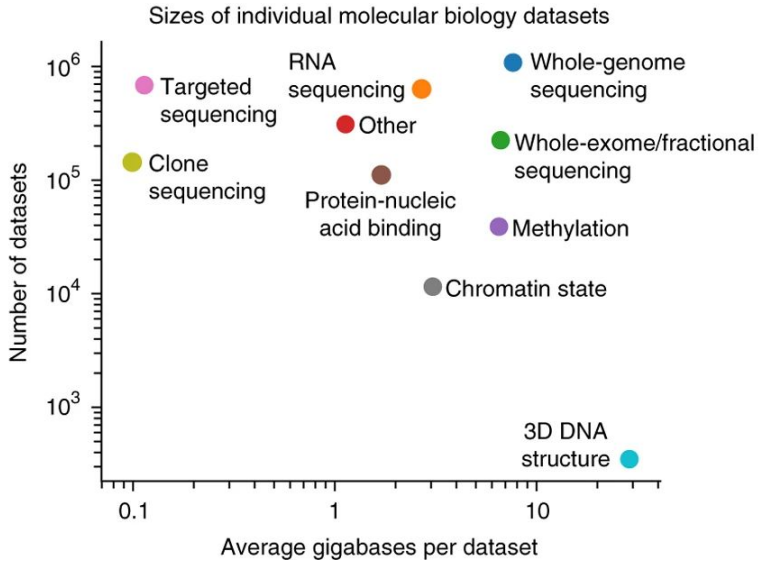
ML and computational biology development timeline



Wainberg et al. 2018

Data availability increased significantly in the recent years





Wainberg et al. 2018

A variety of research questions in computational biology can be tackled with machine learning

- Machine learning can be used for analysis of genomic data:
  - transcription factor binding
  - antigen binding
  - translation initiation site discovery
  - splicing prediction
  - single-cell RNA-seq clustering
- And also for obtaining genomic data:
  - variant calling

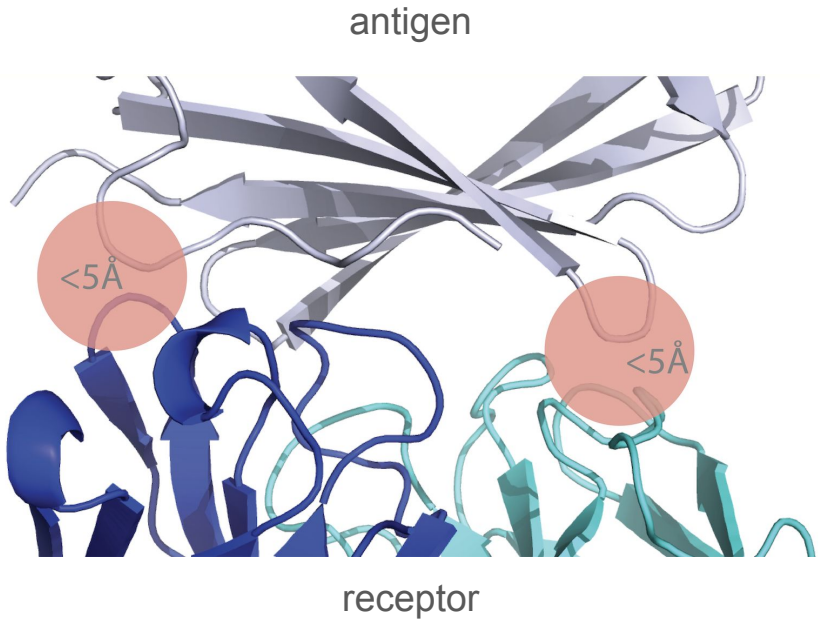
A variety of research questions in computational biology can be tackled with machine learning

Example: antigen binding prediction

Immune receptors (proteins) bind to antigens (e.g., parts of viruses) to help eliminate them

Given a set of receptors known to bind a given antigen, can we predict for the new receptor if it will bind to the antigen?

Classification problem!



Akbar et al. 2019

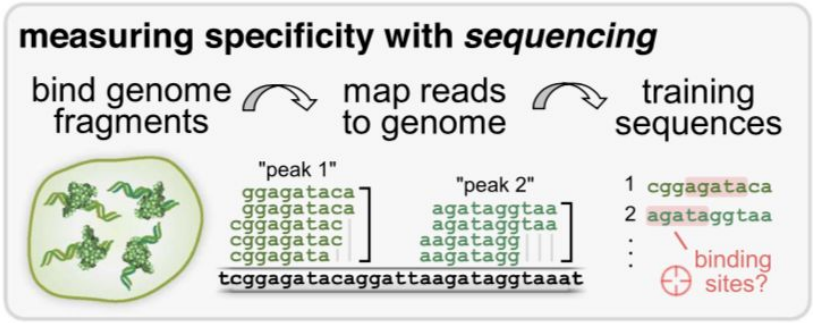
A variety of research questions in computational biology can be tackled with machine learning

Transcription factor binding prediction:

Transcription factors are proteins which bind to certain sites in DNA and regulate transcription of genes

Given a set of DNA sequences for which we know if they will bind or not, how can we predict if a transcription factor will bind to a new DNA sequence?

Classification problem!



Leung et al. 2016

Published: 27 July 2015

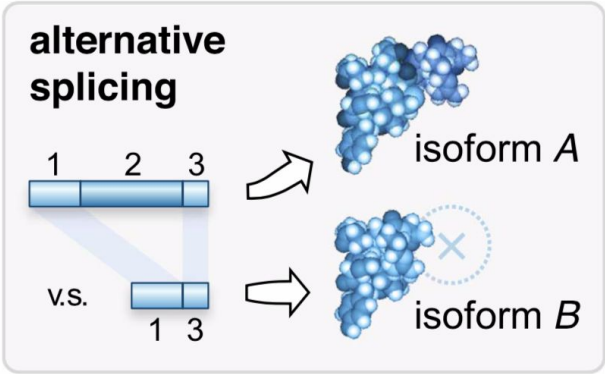
Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning

Babak Alipanahi, Andrew Delong, Matthew T Weirauch & Brendan J Frey

Nature Biotechnology **33**, 831–838(2015) | Cite this article

A variety of research questions in computational biology can be tackled with machine learning

- Splicing: processing of precursor RNA that creates messenger RNA by removing non-coding regions (introns) and connects gene-coding regions (exons) together
- Predicting how often exons will be included in the transcripts is a regression problem



Leung et al. 2016

RESEARCH ARTICLE

The human splicing code reveals new insights into the genetic determinants of disease

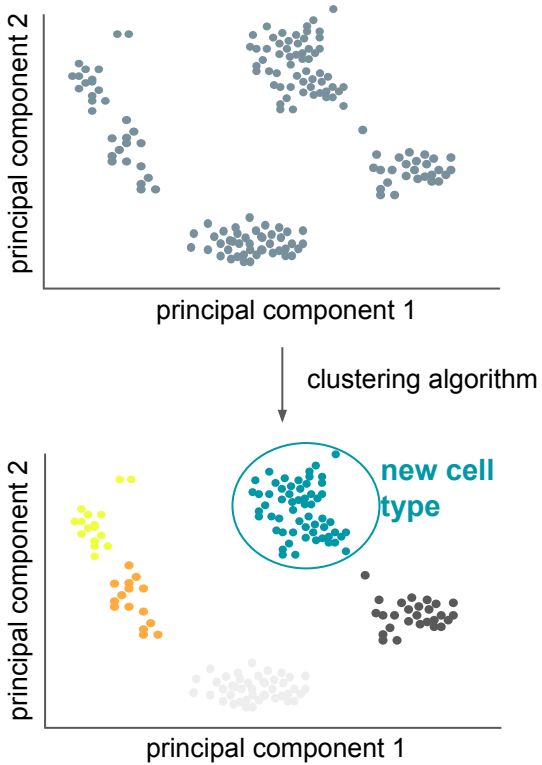
Hui Y. Xiong[1,2,3,*], Babak Alipanahi[1,2,3,*], Leo J. Lee[1,2,3,*], Hannes Bretschneider[1,3,4], Daniele Merico[5,6,7], Ryan K. C. Yuen[5,6,7], Yimin Hua[8], Serge Gueroussov[2,7], Hamed S. Najafabadi[1,2,3], Timothy R. Hughes[2,3,7], Quaid Morris[1,2,3,7], Yoseph Barash[1,2,9], Adrian R. Krainer[8], Nebojsa Jojic[10], Stephen W. Scherer[3,5,6,7], Benjamin J. Blencowe[2,5,7], Brendan J. Frey[1,2,3,4,5,7,10,†]

A variety of research questions in computational biology can be tackled with machine learning

Single-cell RNA-seq clustering for identification of cell types:

A dimensionality reduction technique is applied to normalized count data

Clustering the data (using e.g., k-means algorithm) can reveal new cell types



Review Article | Published: 07 January 2019

Challenges in unsupervised clustering of single-cell RNA-seq data

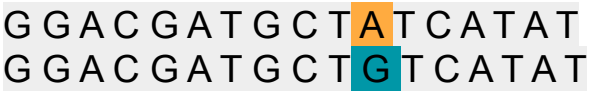
Vladimir Yu Kiselev, Tallulah S. Andrews & Martin Hemberg ✉

Nature Reviews Genetics **20**, 273–282(2019) | Cite this article

A variety of research questions in computational biology can be tackled with machine learning

Variant calling: finding genetic variants from sequence reads

From a pileup of the reference and read data around each candidate variant, ML models could determine the probabilities for each of the three diploid genotypes



Published: 24 September 2018

A universal SNP and small-indel variant caller using deep neural networks

Ryan Poplin, Pi-Chuan Chang, David Alexander, Scott Schwartz, Thomas Colthurst, Alexander Ku, Dan Newburger, Jojo Dijamco, Nam Nguyen, Pegah T Afshar, Sam S Gross, Lizzie Dorfman, Cory Y McLean & Mark A DePristo

Nature Biotechnology **36**, 983–987(2018) | Cite this article

Article | Open Access | Published: 01 March 2019

A multi-task convolutional deep neural network for variant calling in single molecule sequencing

Ruibang Luo, Fritz J. Sedlazeck, Tak-Wah Lam & Michael C. Schatz

Nature Communications **10**, Article number: 998 (2019) | Cite this article

A variety of research questions in computational biology can be tackled with machine learning

DeepGOPlus: improved protein function prediction from sequence
Maxat Kulmanov, Robert Hoehndorf ✉

Bioinformatics, Volume 36, Issue 2, 15 January 2020, Pages 422–429, https://doi.org/10.1093/bioinformatics/btz595

Sequence alignment using machine learning for accurate template-based protein structure prediction
Shuichiro Makigaki ✉, Takashi Ishida ✉

Bioinformatics, Volume 36, Issue 1, 1 January 2020, Pages 104–111, https://doi.org/10.1093/bioinformatics/btz483

Learned protein embeddings for machine learning FREE
Kevin K Yang, Zachary Wu, Claire N Bedbrook, Frances H Arnold ✉

Bioinformatics, Volume 34, Issue 15, 01 August 2018, Pages 2642–2648, https://doi.org/10.1093/bioinformatics/bty178

Graph neural representational learning of RNA secondary structures for predicting RNA-protein interactions
Zichao Yan, William L Hamilton ✉, Mathieu Blanchette ✉

Bioinformatics, Volume 36, Issue Supplement_1, July 2020, Pages i276–i284, https://doi.org/10.1093/bioinformatics/btaa456

Article | Published: 06 July 2020

Deep learning decodes the principles of differential gene expression

Shinya Tasaki ✉, Chris Gaiteri, Sara Mostafavi & Yanling Wang

Nature Machine Intelligence **2**, 376–386(2020) | Cite this article

Article | Open Access | Published: 11 May 2020

Deep learning enables accurate clustering with batch effect removal in single-cell RNA-seq analysis

Xiangjie Li, Kui Wang, Yafei Lyu, Huize Pan, Jingxiao Zhang, Dwight Stambolian, Katalin Susztak, Muredach P. Reilly, Gang Hu ✉ & Mingyao Li ✉

Nature Communications **11**, Article number: 2338 (2020) | Cite this article

QDeep: distance-based protein model quality estimation by residue-level ensemble error classifications using stacked deep residual neural networks
Md Hossain Shuvo, Sutanu Bhattacharya ✉, Debswapna Bhattacharya ✉

Bioinformatics, Volume 36, Issue Supplement_1, July 2020, Pages i285–i291, https://doi.org/10.1093/bioinformatics/btaa455

Computational biology poses unique challenges for machine learning

- ❏ Dimensionality & dataset size
- ❏ Signal and noise in the data
- ❏ Unknown ground truth and weakly labeled datasets
- ❏ Selection bias

Keep in the data generation process in mind!

Machine learning in computational biology - outline

- Introduction to machine learning:
  - What is machine learning, types of problems, assumptions, workflow, generalization
- Machine learning models and algorithms:
  - Discriminative vs generative models, supervised models (logistic and linear regression, kNN, neural networks), unsupervised models (dimensionality reduction, clustering)
- Data representation:
  - Considerations and examples, one-hot encoding, feature engineering, representation learning
- Model comparison and uncertainty:
  - Model assessment, model selection, uncertainty, cross-validation
- Transparency and reproducibility

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References

Wainberg M, Merico D, Delong A, Frey BJ. Deep learning in biomedicine. *Nature Biotechnology*. 2018;36(9):829-838. doi:10.1038/nbt.4233

Bagaev DV, Vroomans RMA, Samir J, et al. VDJdb in 2019: database extension, new analysis infrastructure and a T-cell receptor motif compendium. *Nucleic Acids Res*. 2020;48(D1):D1057-D1062. doi:10.1093/nar/gkz874

Akbar R, Robert PA, Pavlović M, et al. A compact vocabulary of paratope-epitope interactions enables predictability of antibody-antigen binding. *bioRxiv*. Published online November 30, 2019:759498. doi:10.1101/759498

Leung MKK, Delong A, Alipanahi B, Frey BJ. Machine Learning in Genomic Medicine: A Review of Computational Problems and Data Sets. *Proceedings of the IEEE*. 2016;104(1):176-197. doi:10.1109/JPROC.2015.2494198