Selene: a PyTorch-based deep learning library for sequence data

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To enable the application of deep learning in biology, we present Selene (https://selene.flatironinstitute.org/), a PyTorch-based deep learning library for fast and easy development, training, and application of deep learning model architectures for any biological sequence data. We demonstrate on DNA sequences how Selene allows researchers to easily train a published architecture on new data, develop and evaluate a new architecture, and use a trained model to answer biological questions of interest.

Deep learning describes a set of machine learning techniques that use stacked neural networks to extract complicated patterns from high-dimensional data. These techniques are widely used for image classification and natural language processing, and have led to very promising advances in the biomedical domain, including genomics and chemical synthesis. In regulatory genomics, networks trained on high-throughput sequencing data (for example, ChIP-seq), or 'sequence-based models', have become the de facto standard for predicting the regulatory and disease impact of mutations. While deep-learning-related publications are often accompanied by the associated pre-trained models, a key challenge in both developing new deep learning architectures and training existing architectures on new data is the lack of a comprehensive, generalizable, and user-friendly deep learning library for biology.

Beyond regulatory genomics, sequence-level deep learning models have broad promise in a wide range of research areas, including recent advances on prediction of disease risk of missense mutations in proteins and potential applications to, for example, predicting target site accessibility in genome editing. We must enable the adoption and active development of deep-learning-based methods in biomedical sciences. For example, a biomedical scientist interested in a publication of a model capable of predicting the disease-associated effect of mutations should be able to train a similar model on their own ChIP-seq data focused on their disease of interest. A bioinformatician interested in developing new model architectures should be able to experiment with different architectures and evaluate all of them on the same data. Currently, this requires advanced knowledge specific to deep learning, substantial new code development, and associated time investment far beyond what most biomedical scientists are able to commit.

Here we present Selene, a framework for developing sequence-level deep learning networks that provides biomedical scientists with comprehensive support for model training, evaluation, and application across a broad range of biological questions. Sequence-level data refers to any type of biological sequence such as DNA, RNA, or protein sequences and their measured properties (for example, binding of transcription factors or RNA-binding proteins, or DNase sensitivity). Selene contains modules for (1) data sampling and training for model development (Fig. 1a) and (2) prediction and visualization for analyses using the trained model (Fig. 1b,c). With Selene, researchers can run model development and analysis workflows out-of-the-box. For more advanced use cases, Selene provides templates for extending modules within each workflow so that users can adapt the library to their particular research questions.

There has been recent work to make deep learning in biology more accessible: DragoNN is a toolkit for teaching deep learning in regulatory genomics; pysster is a Python package for training convolutional neural networks on biological sequence data; and Kipoi is a framework to archive, use, and build on published predictive models in genomics. These resources constitute the nascent software ecosystem for sequence-level deep learning. Selene is our contribution to this ecosystem. Selene supports general model development not constrained to a particular architecture (in contrast to pysster) or task (in contrast to DragoNN) and is designed for users with different levels of computational experience. Users are supported in tasks ranging from simply applying an existing model, to retraining it on new data (tasks also supported by Kipoi), to developing new model architectures (a task that is challenging to do with any other tool). The models developed using Selene can be shared and used through the Kipoi framework.

To demonstrate Selene’s capabilities for developing and evaluating sequence-level deep learning models, we use it to (1) train a published architecture on new data; (2) develop, train, and evaluate a new model (improving a published model); and (3) apply a trained model to data and visualize the resulting predictions in the case studies that follow.

In the first case study, a researcher wants to use the DeepSEA model architecture as a starting point and train the model on different data. Selene is completely general and a user can easily use or specify any model of their choice using modules in PyTorch.

Suppose a cancer researcher is interested in modeling the regulatory elements of the transcription factor GATA1, specifically focusing on proerythroblasts in bone marrow. This is a tissue-specific genomic feature that DeepSEA does not predict. The researcher downloads peak data from Cistrome and a reference genome FASTA file. Once a researcher formats the data to match the documented inputs and fills out the necessary training parameters (for example, batch size or learning rate), they can use Selene to train the DeepSEA architecture on their data with no new lines of Python code. In this example, they find that the model obtains an area under the curve (AUC) of 0.942 on this feature (Fig. 2a).

Selene automatically generates training, testing, and validation samples from the provided input data. The samples generated for each partition can be saved and used in subsequent model development so that comparisons can be made across models with different

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architectures and/or parameters. Further, Selene automatically evaluates the model on the test set after training and, in this case, generates figures to visualize the model’s performance as receiver operating characteristic and average precision curves.

Now that the researcher has a trained model, they can use Selene to apply in silico mutagenesis—converting every position in the sequence to every other possible base (DNA and RNA) or amino acid (protein sequences)—to a set of GATA1 sequences drawn from the test set and examine the consequences of these ‘mutations’. Selene supports visualization of the outputs of in silico mutagenesis as a heat map and/or motif plot. By visualizing the log-fold change for these sequences in a heat map, the researcher can see that the model detects disruptions in binding at the GATA motif (Fig. 2b).

We provide the code and results for this example in Selene’s GitHub repository (https://github.com/FunctionLab/selene; see case 1 in the ‘manuscript’ folder).

In another use case, a researcher may want to develop and train a new model architecture. For example, a bioinformatician might want to modify a published model architecture to see how that affects performance. First, the researcher uses modules in PyTorch to specify the model architecture they are interested in evaluating; in this case study, they try to enhance the DeepSEA architecture with batch normalization and three additional convolutional layers. The researcher specifies parameters for training and the paths to the model architecture and data in a configuration file and passes this as input to the library’s command-line interface (CLI). Training is automatically completed by Selene; afterward,
Selene's modeling capability extends far beyond the case studies described here. The library can be applied to not only DNA but also RNA and protein sequences, and not only chromatin data but any current genome-, transcriptome-, or even proteome-wide measurements. We developed Selene to increase the accessibility of deep learning in biology and facilitate the creation of reproducible workflows and results. Furthermore, Selene is open-source software that will continue to be updated and expanded on the basis of community and user feedback.

Online content
Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41592-019-0360-8.
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Author contributions
K.M.C and J.Z. conceived the Selene library. K.M.C and E.M.C. designed, implemented, and documented Selene. K.M.C performed the analyses described in the manuscript. O.G.T. supervised the project. K.M.C., E.M.C., and O.G.T wrote the manuscript.

Competing interests
The authors declare no competing interests.

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Methods

Overview of Selene. Selene consists of two components: a Python library for developing sequence-level neural networks, and a command-line interface (CLI) for prototypical use cases of the library (that is, training a new model, evaluating an existing model, and analyzing sequence data and variants with a trained model). We herein refer to these components as the software development kit (SDK) and the CLI, respectively. All functionality provided by the CLI is also available to the user through the SDK. Rather than supplanting the SDK, the CLI is intended to maximize code reuse and minimize user time spent learning SDK by heavily reducing the configuration tasks left to the user (for example, when GPU usage is specified, the CLI ensures all appropriate computations are performed on the GPU). When appropriate, the SDK does deliver functionality beyond that of the CLI. For instance, the SDK includes several data visualization methods that would be too unwieldy as executables run from the command line.

Thorough documentation for the SDK is available at https://selene.flatironinstitute.org, and tutorials for both the CLI and SDK can be found on the GitHub page (https://github.com/FunctionLab/selene). Notably, one tutorial demonstrates how to use Selene to train a deep neural network regression model (https://github.com/FunctionLab/selene/blob/master/tutorials/regression_mp swagger/get_regression_mp swagger_example.ipynb). This tutorial illustrates Selene’s use outside of the models of transcriptional regulation shown in the case studies.

Selene software development kit. The Selene SDK, formally known as seleneSdk, is an extensible Python package intended to ease the development of new programs that leverage sequence-level models through code reuse. The Selene CLI is built entirely on the functionality provided by the SDK, but it is probable that users will use the SDK outside this context. For example, after training a new sequence-level model with the CLI one could use the SDK in conjunction with a Python-based web application framework (e.g., Flask, Django) to build a web server so that other researchers can submit sequences or variants and get the trained model’s predictions as output.

Leveraging the SDK in a user’s Python project is no different from using any other Python module. That is, one only needs to import the seleneSdk module or any of its members and supply them with the correct parameters. The runtime behavior of each component of seleneSdk, as well as the required parameters for all members of seleneSdk, is described in detail in the online documentation (https://selene.flatironinstitute.org/overview/overview.html).

Selene CLI. The Selene CLI is a usable program to be run from the command line by the user. It encapsulates the configuration, execution, and logging of Selene’s most common use cases. These use cases are embodied by the CLI’s three commands: train, evaluate, and analyze. These commands are used to train new models, evaluate the performance of trained models, and analyze model predictions (perform in silico mutagenesis or variant effect prediction), respectively. Each command configures its specific runtime environment with a combination of command line arguments and parameters drawn from user-provided configuration files. The flexibility of these configuration files allows them to leverage user-developed code as well, and further extends the usability of the CLI. We provide a step-by-step tutorial that describes the CLI configuration file format and shows some example configuration keys and values (https://github.com/FunctionLab/selene/blob/master/tutorials/getting_started_with_selene/getting_started_with_selene.ipynb). Examples of CLI configuration code files are available at https://github.com/FunctionLab/selene/tree/master/config_examples. Finally, comprehensive documentation detailing all possible configurations supported by Selene can be found on Selene’s documentation website (https://selene.flatironinstitute.org/overview/cli.html). Users can reference any of these resources when creating their own configuration files.

Model architectures. DeepSEA architecture used in case 1 (from the supplementary note in the DeepSEA publication): (1) Convolutional layer (320 kernels; window size, 8; step size, 1) (2) Pooling layer (window size, 4; step size, 4) (3) Convolutional layer (480 kernels; window size, 8; step size, 1) (4) Pooling layer (window size, 4; step size, 4) (5) Convolutional layer (480 kernels; window size, 8; step size, 1) (6) Pooling layer (window size, 4; step size, 4) (7) Convolutional layer (960 kernels; window size, 8; step size, 1) (8) Convolutional layer (960 kernels; window size, 8; step size, 1) (9) Fully connected layer (919 genomic features) (10) Sigmoid output layer

Dropout proportion (proportion of outputs randomly set to 0): • Layer 5: 20% • Layer 8: 50%

Batch normalization applied after layers 2, 5, and 8 and before dropout.

Both architectures use the binary cross-entropy loss function and stochastic gradient descent optimizer (momentum, 0.9; weight decay, 10−4).

Reproducing the case studies. Below, we have described the steps taken for each of the case studies. The code required to reproduce each case study is included in the GitHub repository (https://github.com/FunctionLab/selene/tree/master/manuscript) and was run with Selene version 0.2.0. We have also created Zenodo records for each case that contain all the input data, data processing scripts and output files generated from Selene:

• Case 1: https://doi.org/10.5281/zenodo.1442433
• Case 2: https://doi.org/10.5281/zenodo.1442437
• Case 3: https://doi.org/10.5281/zenodo.1445555

Case 1: Training a state-of-the-art architecture on a different dataset. Steps to train DeepSEA on new data.

1. Download the data from Cistrome. In this case, we are only working with one specific genomic feature. Cistrome ID 33545, measurements from GSM970258.

2. Format the data. We use tools from Samtools18 (specifically, tabix19 and bgzip from HTSlib, https://www.htslib.org/). Create a .bed file of chromosome, start, and end and the genomic feature name (useful when there is more than one feature). Sort this file and compress it into a .gz file. Tabix index this file.

Specific commands:

(i) Only use the columns [chr, start, end]:

\[
\text{cut} -f 1-3 <\text{peaks-file}> > <\text{coordinates-file}>
\]

Note: Eventually, we will add support for parsing BED files with strand specific features and/or continuous values that quantify these features.

(ii) Add the genomic feature name as the fourth column of the file:

\[
\text{sed} -i \text{"s/\$/\t\text{feature-name}/\"} <\text{coordinates-file}>
\]

(iii) Sort the file by [chr, start, end]:

\[
\text{sort} -k1V -k2n -k3n <\text{coordinates-file}> > <\text{sorted-coordinates-file}>
\]

(iv) Compress the file:

\[
\text{bgzip} <\text{sorted-coordinates-file}>\text{-}f <\text{gz-file}>
\]

(v) Tabix index the file:

\[
\text{tabix} -p \text{bed} <\text{sorted-coordinates-file}>,\text{gz}
\]

3. Create a file of distinct features that the model will predict, where each feature is a single line in the file. This can easily be created from the .bed file in step 2 by running cut -f 4 <coordinates-file> | sort -u > <distinct-features>

4. Download the GRCh38/hg38 FASTA file. We downloaded the reference sequences GRCh37/hg19 and GRCh38/hg38 used in our analyses from ENCODE15.

5. Specify the model architecture, loss and optimizer as a Python file. An example of this is available for DeepSEA at https://github.com/FunctionLab/selene/blob/master/models/deepsea.py.

6. Fill out the configuration file with the appropriate file paths and training parameters. We recommend starting from one of the example training files in the GitHub tutorials (for example, https://github.com/FunctionLab/selene/blob/master/tutorials/evaluating_with_selene/evaluating_with_selene.ipynb) or in the config_examples directory (https://github.com/FunctionLab/selene/tree/master/config_examples). You can also review the documentation for the configuration parameters on Selene’s website10.

7. Run Selene.

Steps to apply and visualize the results of in silico mutagenesis.

1. Collect sequences you want to visualize as a FASTA file. For this particular case, we provide a script to do so (https://github.com/FunctionLab/selene/blob/master/manuscript/case1/data/get_test_regions.py).

2. Fill out the configuration file with the appropriate file paths (for example, the path to the FASTA file and the trained model weights file).

3. Run Selene. You will get the raw predictions and the log, fold change scores as output files.


Brief Communication

(4) Follow one of the Jupyter notebook tutorials for in silico mutagenesis (https://github.com/FunctionLab/selene/blob/master/tutorials) to generate visualizations for the sequences. We have done this at https://github.com/FunctionLab/selene/blob/master/manuscript/case1/3_visualize_ism_outputs.ipynb.

Case 2: developing a new architecture and making model comparisons. Steps to train ‘deeper DeepSEA’ on the same exact data as DeepSEA.

(1) Download the code and data bundle from the DeepSEA website (http://deepsea.princeton.edu/media/code/deepsea_train_bundle.v0.9.tar.gz). You should now have a data directory containing all the .mat files. This is the directory used in the original training.

(2) Fill out the configuration file for Selene’s MultiFileSampler (https://selene.flatironinstitute.org/record/2214970/files/DeepSEA_data.targz). This is a python file for specifying the directories in the standalone version of DeepSEA (http://deepsea.princeton.edu/media/code/deepsea.v0.9.tar.gz).

(3) Run Selene.

(5) Follow the script provided for this case to analyze the variant predictions (https://github.com/FunctionLab/selene/blob/master/manuscript/case3/2_variant_groups_comparison.sh).

Statistical analysis. Details of the statistical test used for case study 3 are specified in the associated text and figure legend (Fig. 3b).

Case 3: applying a new model to variants.

(1) Download the single-nucleotide polymorphisms from the International Genomics of Alzheimer’s Project. (https://www.niagads.org/igap-age-onset-survival-analyses-p-value-only).

(2) Group the variants into those with P values below 0.05 (significant) and those with P values above 0.50 (non-significant).

(3) Fill out the configuration file with the paths to the two variant files and the trained model weights file from case 2.

(4) Run Selene.

(5) Follow the script provided for this case to analyze the variant predictions (https://github.com/FunctionLab/selene/blob/master/manuscript/case3/2_variant_groups_comparison.sh).

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Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection: No software was used to collect data in this study (that is, no data was collected).

Data analysis: Project homepage: https://selene.flatironinstitute.org
               GitHub: https://github.com/FunctionLab/selene
               Archived version: https://github.com/FunctionLab/selene/archive/0.2.0.tar.gz

Additional software used:
               Samtools (version 1.9). Specifically, tabix and bgzip in the HTSlib (version 1.9) package.

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Data sources

Cistrome
Cistrome file ID: 33545, measurements from GSM970258 (Xu et al., 2012)
http://dc2.cistrome.org/api/downloads/eyJpZCI6IjMzNTQ1In0%3A1fujCu%3ArNvWLCNoET6o9Sdki8fEv13uRu4b/

ENCODEx and Roadmap Epigenomics chromatin profiles
Files listed in https://media.nature.com/original/nature-assets/nmeth/journal/v12/n10/extref/nmeth.3547-S2.xlsx

IGAP age at onset survival
https://www.niagads.org/datasets/ng00058 (p-values only file)

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