arboretum Documentation

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Inferring a gene regulatory network (GRN) from gene expression data is a computationally expensive task, exacerbated by increasing data sizes due to advances in high-throughput gene profiling technology.

Quick Start

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The *Arboretum* software library addresses this issue by providing a computational strategy that allows executing the class of GRN inference algorithms exemplified by GENIE3[1] on hardware ranging from a single computer to a multi-node compute cluster. This class of GRN inference algorithms is defined by a series of steps, one for each target gene in the network, where the most important candidates from a set of regulators are determined from a regression model to predict a target gene's expression profile.

Members of the above class of GRN inference algorithms are attractive from a computational point of view because they are parallelizable by nature. In arboretum, we specify the parallelizable computation as a dask graph[2], a data structure that represents the task schedule of a computation. A dask scheduler assigns the tasks in a dask graph to the available computational resources. Arboretum uses the dask distributed scheduler to spread out the computational tasks over multiple processes running on one or multiple machines.

Arboretum currently supports 2 GRN inference algorithms:

1. **GRNBoost2**: a novel and fast GRN inference algorithm using Stochastic Gradient Boosting Machine[3] (SGBM) regression with early-stopping regularization.
2. **GENIE3**: the classic GRN inference algorithm using Random Forest (RF) or ExtraTrees (ET) regression.

```
# import python modules
import pandas as pd
from arboretum.utils import load_tf_names
from arboretum.algo import grnboost2

# load the data
ex_matrix = pd.read_csv(<ex_path>, sep='\t')
```

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[1] Huynh-Thu VA, Irrthum A, Wehenkel L, Geurts P (2010) Inferring Regulatory Networks from Expression Data Using Tree-Based Methods. PLoS ONE

[2] Rocklin, M. (2015). Dask: parallel computation with blocked algorithms and task scheduling. In Proceedings of the 14th Python in Science Conference (pp. 130-136).

[3] Friedman, J. H. (2002). Stochastic gradient boosting. Computational Statistics & Data Analysis, 38(4), 367-378.

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```
tf_names = load_tf_names(<tf_path>)

# infer the gene regulatory network
network = grnboost2(expression_data=ex_matrix,
                    tf_names=tf_names)

network.head()
```

TF	target	importance
G109	G1406	151.648784
G16	G1440	136.741815
G188	G938	124.707570
G10	G1312	124.195566
G48	G1419	121.488200

Check out more examples.

CHAPTER 1

License

BSD 3-Clause License

CHAPTER 2

References

2.1 Installation Guide

Caution: Python Environment

It is highly recommended to prepare a Python environment with the Anaconda or Miniconda distribution and install Arboretum's dependencies using the conda package manager.

- NumPy
- SciPy
- scikit-learn
- pandas
- dask
- distributed

This avoids complexities in ensuring that libraries like NumPy and SciPy link against an optimized implementation of linear algebra routines.

2.1.1 Install using pip

The arboretum package is available from PyPI (Python Package Index), a repository of software for the Python programming language.

Using pip, installing the arboretum package is straightforward:

```
$ pip install arboretum
```

Note: You can use pip to install arboretum in an Anaconda environment.

2.1.2 Install from source

Installing Arboretum from source is possible using following steps:

1. clone the Github repository using the git tool:

```
$ git clone https://github.com/tmoerman/arboretum.git
$ cd arboretum
```

2. build Arboretum using the provided script:

```
$ ./pypi_build.sh
```

3. install the freshly built Arboretum package using pip:

```
$ pip install dist/*
```

2.2 User Guide

2.2.1 Modules overview

Arboretum consists of multiple python modules:

arboretum.algo

- Intended for **typical users**.
- Access point for launching GRNBoost2 or GENIE3 on local or distributed hardware.

arboretum.core

- Intended for **advanced users**.
- Contains the low-level building blocks of the Arboretum framework.

arboretum.utils

- Contains small utility functions.

2.2.2 Dependencies Overview

Arboretum uses well-established libraries from the Python ecosystem. Arboretum avoids being a proverbial "batteries-included" library, as such an approach often entails unnecessary complexity and maintenance. Arboretum aims at doing only one thing, and doing it well.

Concretely, the user will be exposed to one or more of following dependencies:

- Pandas or NumPy: the user is expected to provide the input data in an expected

format. Pandas and NumPy are well equipped with functions for data preprocessing. * Dask.distributed: to run Arboretum on a cluster, the user is responsible for setting up a network of a scheduler and workers. * scikit-learn: relevant for advanced users only. Arboretum can run "DIY" inference where the user provides their own parameters for the Random Forest or Gradient Boosting regressors.

2.2.3 Input / Output

Arboretum accepts as input:

- an expression matrix (rows = observations, columns = genes)
- (optionally) a list of gene names in the expression matrix
- (optionally) a list of transcription factors (a.k.a. TFs)

Arboretum returns as output:

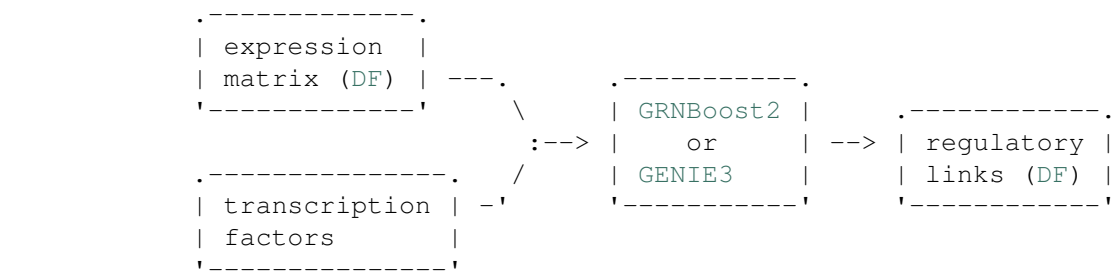
- a Pandas DataFrame (DF) with columns `['TF', 'target', 'importance']`

Tip: As data for following code snippets, you can use the data for network 1 from the DREAM5 challenge (included in the resources folder of the Github repository):

- `<ex_path>` = net1_expression_data.tsv
- `<tf_path>` = net1_transcription_factors.tsv

Expression matrix as a Pandas `DataFrame`

The input can be specified in a number of ways. Arguably the most straightforward way is to specify the expression matrix as a Pandas DataFrame, which also contains the gene names as the column header.



In the following code snippet, we launch network inference with grnboost2 by specifying the `expression_data` as a DataFrame.

Listing 1: *Expression matrix as a Pandas DataFrame*

```
import pandas as pd

from arboretum.utils import load_tf_names
from arboretum.algo import grnboost2

# ex_matrix is a DataFrame with gene names as column names
ex_matrix = pd.read_csv(<ex_path>, sep='\t')
```

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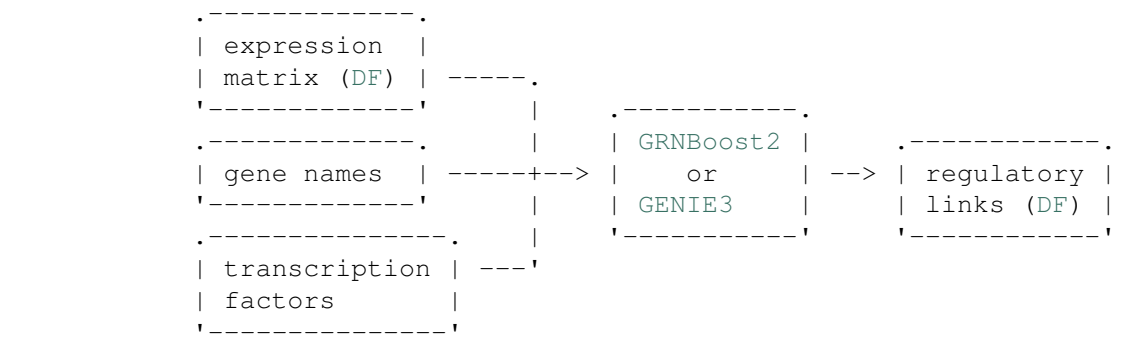
```
# tf_names is read using a utility function included in Arboretum
tf_names = load_tf_names(<tf_path>)

network = grnboost2(expression_data=ex_matrix,
                    tf_names=tf_names)
```

Expression matrix as a NumPy `ndarray`

Arboretum also supports specifying the expression matrix as a Numpy ndarray (in our case: a 2-dimensional matrix). In this case, the gene names must be specified explicitly.



Caution: You must specify the gene names in the same order as their corresponding columns of the NumPy matrix. **Getting this right is the user's responsibility.**

Listing 2: *Expression matrix as a NumPy ndarray*

```
import numpy as np

from arboretum.utils import load_tf_names
from arboretum.algo import grnboost2

# ex_matrix is a numpy ndarray, which has no notion of column names
ex_matrix = np.genfromtxt(<ex_path>, delimiter='\t', skip_header=1)

# we read the gene names from the first line of the file
with open(<ex_path>) as file:
    gene_names = [gene.strip() for gene in file.readline().split('\t')]

# sanity check to verify the ndarray's nr of columns equals the length of the gene_
↪names list
assert ex_matrix.shape[1] == len(gene_names)

# tf_names is read using a utility function included in Arboretum
tf_names = load_tf_names(<tf_path>)

network = grnboost2(expression_data=ex_matrix,
                    gene_names=gene_names,  # specify the gene_names
                    tf_names=tf_names)
```

2.2.4 Running with a custom Dask Client

Arboretum uses Dask.distributed to parallelize its workloads. When the user doesn't specify a dask distributed Client explicitly, Arboretum will create a LocalCluster and a Client pointing to it.

Alternatively, you can create and configure your own Client instance and pass it on to Arboretum. Situations where this is useful include:

- inferring multiple networks from different datasets
- inferring multiple networks using different parameters from the same dataset
- the user requires custom configuration for the LocalCluster (memory limit, nr of processes, etc.)

Following snippet illustrates running the gene regulatory network inference multiple times, with different initialization seed values. We create one Client and pass it to the different inference steps.

Listing 3: *Running with a custom Dask Client*

```
import pandas as pd

from arboretum.utils import load_tf_names
from arboretum.algo import grnboost2
from distributed import LocalCluster, Client

# create custom LocalCluster and Client instances
local_cluster = LocalCluster(n_workers=10,
                             threads_per_worker=1,
                             memory_limit=8e9)
custom_client = Client(local_cluster)

# load the data
ex_matrix = pd.read_csv(<ex_path>, sep='\t')
tf_names = load_tf_names(<tf_path>)

# run GRN inference multiple times
network_666 = grnboost2(expression_data=ex_matrix,
                        tf_names=tf_names,
                        client=custom_client,  # specify the custom client
                        seed=666)

network_777 = grnboost2(expression_data=ex_matrix,
                        tf_names=tf_names,
                        client=custom_client,  # specify the custom client
                        seed=777)

# close the Client and LocalCluster after use
client.close()
local_cluster.close()
```

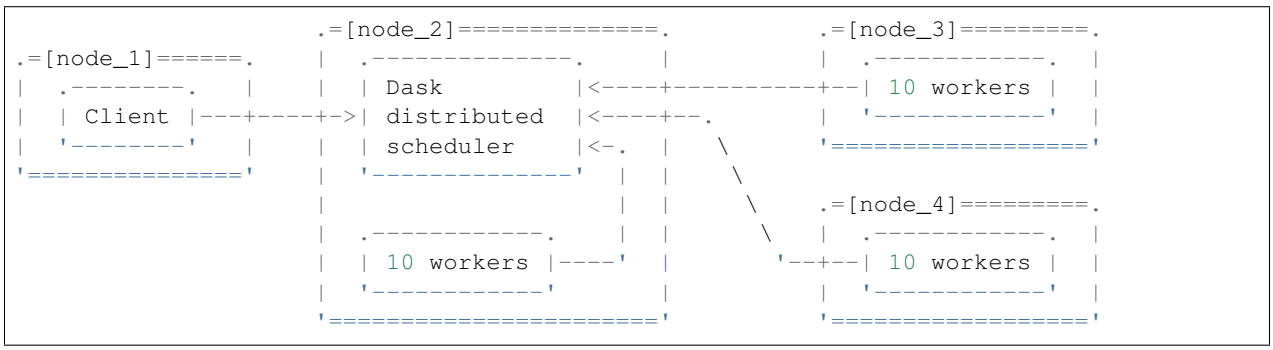
2.2.5 Running with a Dask distributed scheduler

Arboretum was designed to run gene regulatory network inference in a distributed setting. In distributed mode, some effort by the user or a systems administrator is required to set up a dask.distributed `scheduler` and some `workers`.

Tip: Please refer to the Dask distributed network setup documentation for instructions on how to set up a Dask

distributed cluster.

Following diagram illustrates a possible topology of a Dask distributed cluster.



- `node_1` runs a Python script, console or a Jupyter notebook server, a Client instance is configured with the TCP address of the distributed scheduler, running on `node_2`
- `node_2` runs a distributed scheduler and 10 workers pointing to the scheduler
- `node_3` runs 10 distributed workers pointing to the scheduler
- `node_4` runs 10 distributed workers pointing to the scheduler

With a small modification to the code, we can infer a regulatory network using all workers connected to the distributed scheduler. We specify a Client that is connected to the Dask distributed scheduler and pass it as an argument to the inference function.

Listing 4: *Running with a Dask distributed scheduler*

```
import pandas as pd

from arboretum.utils import load_tf_names
from arboretum.algo import grnboost2
from distributed import Client

ex_matrix = pd.read_csv(<ex_path>, sep='\t')
tf_names = load_tf_names(<tf_path>)

scheduler_address = 'tcp://10.118.224.134:8786'  # example address of the remote␣
↪scheduler
cluster_client = Client(scheduler_address)       # create a custom Client

network = grnboost2(expression_data=ex_matrix,
                    tf_names=tf_names,
                    client=cluster_client)  # specify Client connected to the remote␣
↪scheduler
```

2.3 Examples

matrix:

notebook local notebook distributed

script local script distributed

2.4 GRN Inference Algorithms

Arboretum hosts multiple (currently 2, contributions welcome!) algorithms for inference of gene regulatory networks from high-throughput gene expression data, for example *single-cell RNA-seq* data.

2.4.1 GRNBoost2

GRNBoost2 is the flagship algorithm for gene regulatory network inference, hosted in the Arboretum framework. It was conceived as a fast alternative for GENIE3, in order to alleviate the processing time required for larger datasets (tens of thousands of observations).

GRNBoost2 adopts the GRN inference strategy exemplified by GENIE3, where for each gene in the dataset, the most important feature are a selected from a trained regression model and emitted as candidate regulators for the target gene. All putative regulatory links are compiled into one dataset, representing the inferred regulatory network.

In GENIE3, Random Forest regression models are trained.

2.4.2 GENIE3

We consider GENIE3 as the blueprint of "multiple regression GRN inference" strategy.

2.4.3 DREAM5 benchmark

2.5 Concept and Background

Arboretum was conceived to address the need for a faster alternative for the classic GENIE3 implementation for inferring gene regulatory networks from high-throughput gene expression profiles.

In summary, GENIE3 performs a number of independent learning tasks. This inference "architecture" suggests two approaches for speeding up the algorithm:

1. Speeding up the individual learning tasks.
2. Specifying the task coordination logic so that the tasks can be executed in parallel on distributed hardware.

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2.6 FAQ

2.6.1 Q: How can I use the Dask diagnostics (bokeh) dashboard?

Dask distributed features a nice web interface for monitoring the execution of a Dask computation graph.

By default, when no custom Client is specified, Arboretum creates a LocalCluster instance with the diagnostics dashboard **disabled**:

```
...
local_cluster = LocalCluster(diagnostics_port=None)
client = Client(local_cluster)
...
```

You can easily create a custom LocalCluster, with the dashboard enabled, and pass a custom Client connected to that cluster to the GRN inference algorithm:

```
local_cluster = LocalCluster()  # diagnostics dashboard is enabled
custom_client = Client(local_cluster)

...

network = grnboost2(expression_data=ex_matrix,
                    tf_names=tf_names,
                    client=custom_client)  # specify the custom client
```

By default, the dashboard is available on port `8787`.

For more information, consult:

- Dask web interface documentation
- Running with a custom Dask Client

2.6.2 Q: My gene expression matrix is transposed, what now?

The Python scikit-learn library expects data in a format where rows represent observations and columns represent features (in our case: genes), for example, see the GradientBoostingRegressor API.

However, in some fields (like single-cell genomics), the default is inversed: the rows represent genes and the columns represent the observations.

In order to maintain an API that is as lean is possible, Arboretum adopts the scikit-learn convention (rows=observations, columns=features). This means that the user is responsible for providing the data in the right shape.

Fortunately, the Pandas and Numpy libraries feature all the necessary functions to preprocess your data.

2.7 Troubleshooting