
gpvolve Documentation

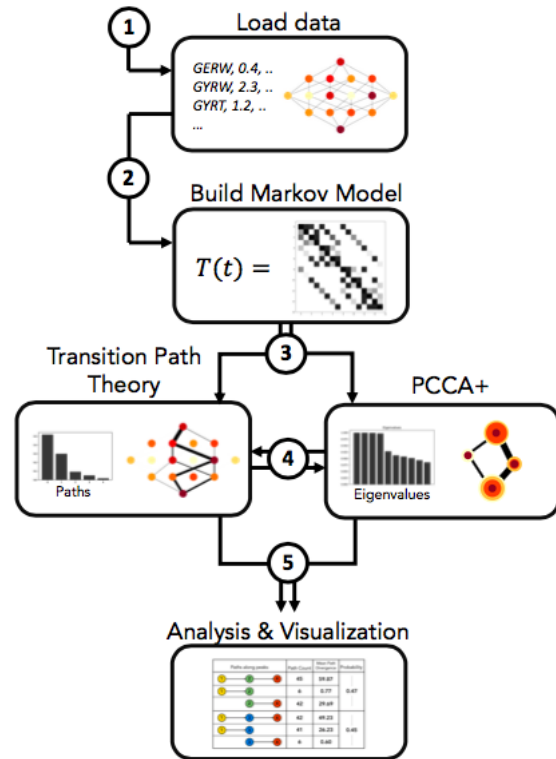
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A Python API for simulating and analyzing evolution in genotype-phenotype space.

GPvolve can be used to:

1. Build a markov state model from a genotype-phenotype-map.
2. Find clusters of genotypes that represent metastable states of the system, using PCCA+.
3. Compute fluxes and pathways between pairs of genotypes and/or clusters of interest, using Transition Path Theory.
4. Visualize the outputs of all of the above.

The core-utilities of this library are built on top of the pyemma and msmtools packages. For a deeper understanding of these tools, we recommend reading the docs and scientific references of the respective libraries (^{1,2,3}).

A rationale for treating fitness landscapes as markov systems can be found in⁴.

Currently, this package works only as an API. There is no command-line interface. Instead, we encourage you use this package inside [Jupyter notebooks](#).

¹ <https://github.com/markovmodel/PyEMMA>

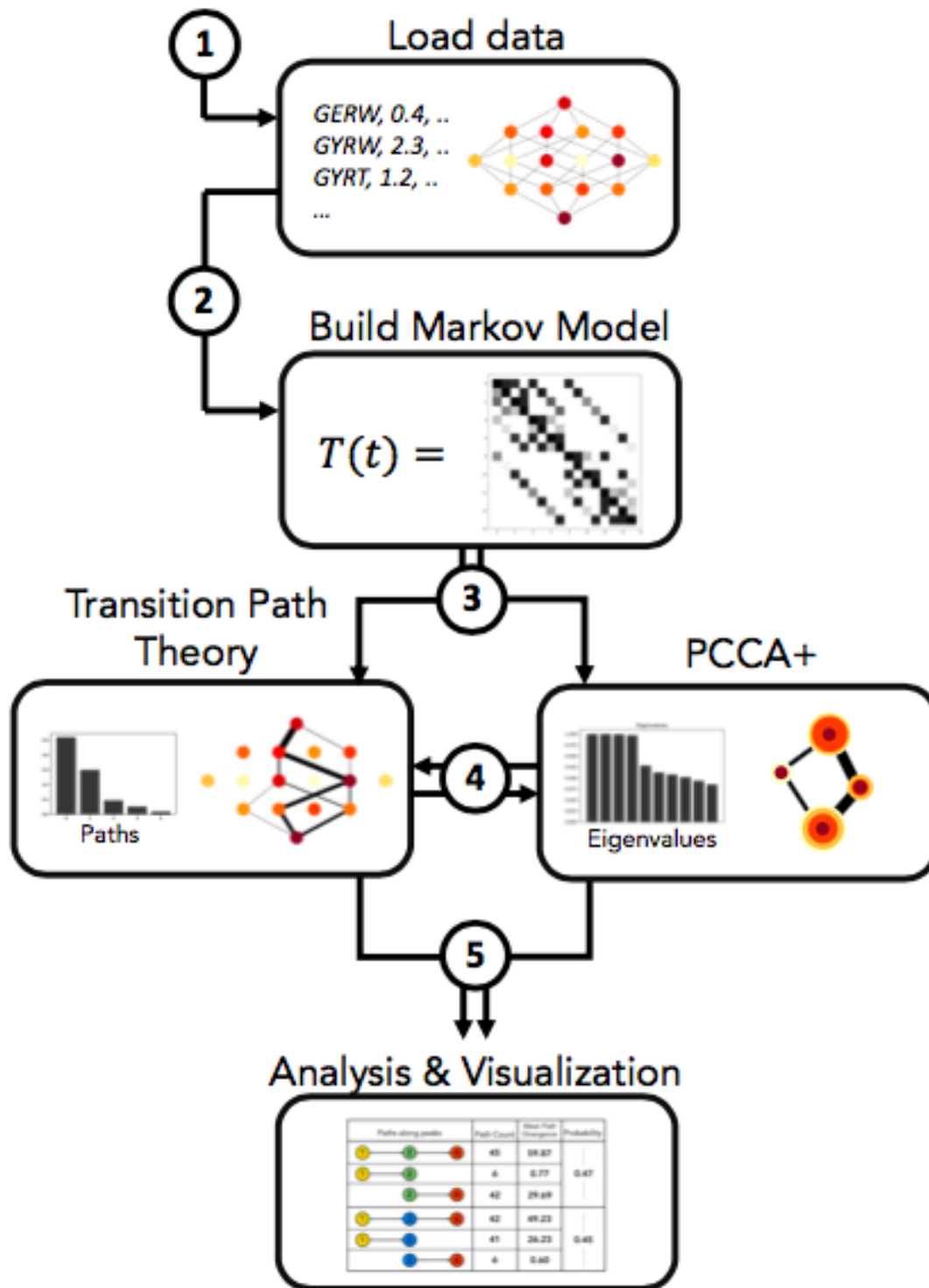
² <https://github.com/markovmodel/msmtools>

³ M K Scherer, B Trendelkamp-Schroer, F Paul, G Pérez-Hernández, M Hoffmann, N Plattner, C Wehmeyer, J-H Prinz and F Noé: PyEMMA 2: A Software Package for Estimation, Validation, and Analysis of Markov Models, J. Chem. Theory Comput. 11, 5525-5542 (2015)

⁴ G Sella, A E Hirsh: The application of statistical physics to evolutionary biology, Proceedings of the National Academy of Sciences Jul 2005, 102 (27) 9541-9546; DOI: 10.1073/pnas.0501865102

1.1 Typical Pipeline

The tools included in the `gpvolve` API can be combined into a computational pipeline which simplifies the repetition of analyzes. We recommend using Jupyter notebooks for this purpose.



In the following example we will go through the 5 steps shown in the figure above. We note that the pipeline is modular, meaning that all steps except step 1 and step 2 can be executed in any desired order.

1.1.1 Example

Import functions.

```
# Import gpvolve functions explicitly.
from gpvolve import GenotypePhenotypeMSM
from gpvolve.fitness import one_to_one
from gpvolve.fixation import mccandlish
from gpvolve.flux import TransitionPathTheory
from gpvolve.visualization import plot_network, plot_matrix
from gpvolve.paths import flux_decomp
from gpvolve.utils import *
from gpvolve.cluster.pcca import PCCA
from gpvolve.cluster.base import GenotypePhenotypeClusters
from gpvolve.cluster.utils import *
from gpvolve.analysis.pathways import *

# Import gpmap for genotype-phenotype data handling
from gpmap.simulate import MultiPeakMountFujiSimulation, MountFujiSimulation

# Helper and plotting functions.
import matplotlib.pyplot as plt
from scipy.sparse import dok_matrix
import pickle
```

Load data.

Simulate 7-site map with 4 fitness peaks. Can also import existing genotype-phenotype data here. See the gpmap Python package for more information (<https://github.com/harmslab/gpmap>)

```
gpm = MultiPeakMountFujiSimulation.from_length(7, peak_n=4, min_dist=2, roughness_
↪width=0.2, field_strength=1)
```

Build Markov model.

First we need to **map a fitness** value onto each phenotype. In this example we simple use phenotype values as fitnesses. The user can also pass their own fitness function here.

```
evovmsm.apply_selection(one_to_one)
```

Building the transition matrix requires the user to define a **fixation probability** function and all its required parameters. Here, we use the fitness function by McCandlish (McCandlish, 2011) and a population size of 10.

```
evovmsm.build_transition_matrix(mccandlish, population_size=10)
```

Transition Path Theory

Having built an evolutionary Markov model of the genotype-phenotype map, we can use Transition Path Theory to compute reactive flux that moves from the wild type to the 7-site mutant.

```
# Compute reactive flux between wild type and 7-site mutant.
tpt = TransitionPathTheory(evovmsm, [0], [127])
```

Now we can use the reactive flux to compute the pathways that go from genotype 0 (0000000) to 127 (1111111) and their relative probabilities.

```
paths = tpt.ReactiveFlux.pathways()
```

Visualize Transition Path Theory output.

```

# Sort path probabilities
path_probabilities = sorted(paths[1], reverse=True)

# Normalize all paths with probability > 0.001.
prob_sum = sum(path_probabilities)
norm_path_probabilities = [prob/prob_sum for prob in path_probabilities if prob/
    ↪prob_sum > 0.001]
x = range(len(norm_path_probabilities))

# Draw figure
figsize=(20,8)
fig, (ax1, ax2) = plt.subplots(1, 2, figsize=figsize)

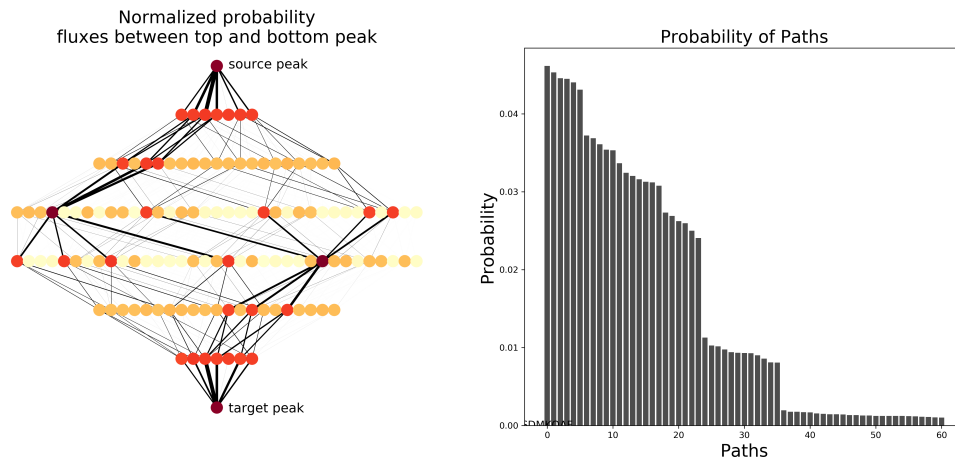
# Plot genotype-phenotype map as network.
plot_network(evomsm, ax=ax1, figsize=figsize, node_size=200, flux=dok_matrix(tpt.net_
    ↪flux/tpt.total_flux))

ax1.set_title("Normalized probability\nfluxes between top and bottom peak", size=20)
ax1.text(1,-0.05, "source peak", size=15)
ax1.text(1,-7.1, "target peak", size=15)

# Plot the probabilities of the most likely paths.
ax2.bar(x, norm_path_probabilities, color='0.3')

ax2.set_xlabel("Paths", size=20)
ax2.set_ylabel("Probability", size=20)
ax2.set_title("Probability of Paths", size=20)

```



Coarse-grain genotype-phenotype map using PCCA+.

Next, we use Robust Perron-Cluster Cluster Analysis (PCCA+) to coarse-grain the genotype-phenotype map.

```

# Cluster genotype-phenotype map into 4 clusters.
pcca = PCCA(evomsm, 4)

```

Since PCCA+ might not return the 4 clusters in the order that we prefer, we have to reorder the clusters.

```

# Find peaks and order them.
peaks = sorted([list(peak)[0] for peak in evomsm.peaks()])

```

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```

# Reorder the pcca clusters according to the peak they contain.
ord_clusters = sort_clusters_by_nodes(pcca.clusters, peaks)

# We simply instantiate a new object for the newly sorted clusters
clustering = GenotypePhenotypeClusters(evomsm, ord_clusters)

# Memberships won't be in order but can be reordered using the command below
reordered_row = pcca.memberships[clustering.order, :]
reordered_mem = reordered_row[:, [0,1,3,2]]
clustering.memberships = reordered_mem

# Check if sorting was correct by finding the peak in each cluster.
string = ""
for i, cluster in enumerate(clustering.clusters):
    for peak in peaks:
        if peak in cluster:
            string = string + "Cluster %s: %s (%s)\n" % (i, clustering.gpmsm.gpm.data.
↪binary[peak], peak)
print(string)

```

```

Cluster 0: 0000000 (0)
Cluster 1: 0001110 (14)
Cluster 2: 1100101 (101)
Cluster 3: 1111111 (127)

```

Visualize the metastability of the coarse-grained genotype-phenotype map.

If we plot the coarse transition matrix, we see that most of the transition probability is located at the diagonal, i.e. transitions that happen within a cluster are more likely than transitions between clusters. The colorbar on the right is in $\log_{10}(\text{transition probability})$.

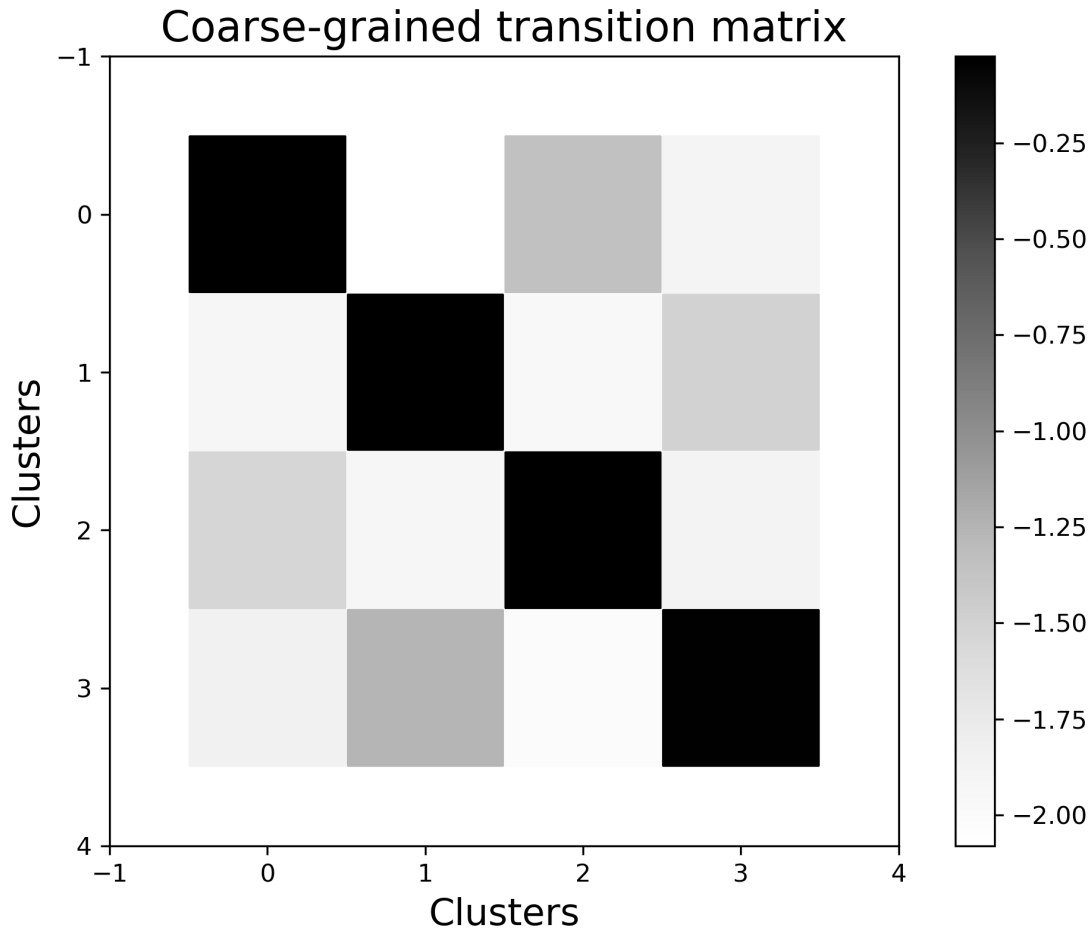
```

# Plot coarse-grained transition matrix.
fig, ax = plt.subplots(figsize=(7,5.5))
header = 17
ax_labels = 15

plot_matrix(clustering.transition_matrix, ax=ax, colorbar=True)
ax.set_title("Coarse-grained transition matrix", size=header)
ax.set_ylabel("Clusters", size=ax_labels)
ax.set_xlabel("Clusters", size=ax_labels)
ax.set_aspect("equal")

plt.tight_layout()

```



Analyze evolutionary mechanisms along fitness peaks.

Finally, we can analyze evolutionary trajectories that pass genotypes of interest. In this example we will look at the trajectories that pass through peak 2 on their way to peak 4 (1-2-4). We split the trajectories into the part between peak 1 and 2 and the part between peak 2 and 4. We find that the sub-trajectories between 2 and 4 are much less constrained than the ones between 1 and 2, which we quantify by calculating the mean path divergence.

```
# First get normalized path probabilities as dict
path_probs = paths_and_probs_to_dict(paths[0], paths[1], normalize=True)
all_paths = list(path_probs.keys())

# Path 1-2-4
paths124 = paths_that_do_not_contain(paths_that_contain(all_paths, [0,14,127], bool_
    and=True), [101])
paths124_probs = {path: path_probs[path] for path in paths124}
mpd124 = mean_path_divergence(evomsm, paths124_probs)
entr124 = entropy(list(paths124_probs.values()))

## Segment 1-2
paths124_12 = get_sub_paths(paths124_probs, 0, 14)
mdp124_12 = mean_path_divergence(evomsm, paths124_12)
## Segment 2-4
paths124_24 = get_sub_paths(paths124_probs, 14, 127)
mdp124_24 = mean_path_divergence(evomsm, paths124_24)
```

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```
print("Path\tPath count\tMean Path Divergence\n%s\t%s\t\t%s\n%s\t%s\t\t%s\n%s\t%s\t\t"
↳ %s" % ("1-2", len(paths124_12), round(mdp124_12,2), "2-4", len(paths124_24),
↳ round(mdp124_24,2), "1-2-4", len(paths124), round(mdp124, 2)))
```

Path	Path count	Mean Path Divergence
1-2	6	0.77
2-4	42	29.69
1-2-4	45	59.88

1.2 Installation and Dependencies

1.2.1 Installation

To get the latest published version, install using pip:

```
pip install gpvolve
```

To install from source, clone this repo and install using pip:

User can clone the github repository and install it locally.

```
git clone https://github.com/harmslab/gpvolve
cd gpvolve
pip install -e .
```

1.2.2 Dependencies

The following dependencies are required for the `gpvolve` package.

- **gmap**: Module for constructing powerful genotype-phenotype map python data-structures.
- **ggraph_**: Module for graphic representation of genotype-phenotype maps built on top of networkx.
- **networkx**: Python package for construction and analysis of networks and graphs.
- **msmttools**: Python package containing tools for construction and analysis of markov models, including Transition Path Theory and PCCA+.
- **numpy**: Python's array manipulation package.
- **cython**: Programming language written in Python with C-like performance.
- **matplotlib**: Python plotting library.

1.3 Writing a fitness function

How to write your own selection function:

```
# code here.
```

1.4 Writing a fixation function

1.5 API documentation

This page lists all modules in the gpvolve library. If you find missing documentation, feel free to open an issue or (better yet) submit a pull request!

1.5.1 gpvolve.markovmodel

1.5.2 gpvolve.fitness

1.5.3 gpvolve.fixation

1.5.4 gpvolve.flux

1.5.5 gpvolve.paths

1.5.6 gpvolve.visualization

1.5.7 gpvolve.utils

1.5.8 gpvolve.cluster.base

1.5.9 gpvolve.cluster.pcca

1.5.10 gpvolve.cluster.from_paths

1.5.11 gpvolve.cluster.utils

1.5.12 gpvolve.analysis.pathways

CHAPTER 2

References
