

Software for: Domain model explains propagation dynamics and stability of K27 and K36 methylation landscape

1 Software requirements

- MATLAB 2017b or earlier (<https://www.mathworks.com/products/matlab.html>)
- AMICI toolbox (<https://github.com/ICB-DCM/AMICI>, Fröhlich et al. (2017))
- PESTO toolbox (<https://github.com/ICB-DCM/PESTO>, Stapor et al. (2018))

2 Workflow

The code for the analysis is in the folder `HistoneMethylation`. The workflow for the analysis of the manuscript is in the script `main_manuscript.m`.

2.1 Data

The data can be found in folder `data`:

- Untreated: `CAL317318319_WT.mat`
- Inhibitor experiment: `CAL311312313_WT.mat`, `CAL311312313_Inh.mat`
- Recovery experiment: `CAL314315316_WT.mat`, `CAL314315316_Inh.mat`

2.2 Model simulation

The simulation functions for all models can be found in in the folder `simulation`. The required files for the domain models can automatically be generated with `generate_domainModel.m`. The compilation of the simulation function requires the toolbox AMICI.

2.3 Model calibration

The models are calibrated using maximum likelihood estimation. For this, the toolbox PESTO is employed.

The fitting script is `fitting_histones.m`. This script employs the likelihood functions, which are `logLikelihood_histones_hierarchical.m` for using hierarchical optimization (see (Loos et al.,

2018) for more details), and `logLikelihood_histones_standard.m` for the standard approach for optimization. Both likelihood functions allow for normal and Laplace measurement noise (Maier et al., 2017).

2.4 Domain model reduction

For the model reduction of the domain model, different submodels are calibrated and compared using the Bayesian Information Criterion (BIC). The file `domains.mat` comprises the structs `domains` and `modelnames`, which provide the employed domains as string array and the corresponding name of the model. For example, the model accounting for the domains 00, 23, and 32 (as in `domains{1}`) has the name 00_23_32. Thus its results are found in `results_03_23_32_offset1em1.mat`

2.5 Model analysis

The models are visualized in `visualize_histones_fitsForPaper.m` which employs the routine `plot_histones.m`.

Model selection is performed in `analyze_domainModelsUntreated.m`, which employs the routine `get_flux_domainModel.m` to obtain the steady state methylation fluxes for the individual domain models.

The model predictions for the inhibitor experiment are performed in `predict_inhibition.m`

The comparison for generation 2 histones of untreated and cells recovering from EZH2 inhibitor treatment is performed in `modelSelection_untreated_recovery.m` and the model fit is visualized in `visualize_histones_comparison_untreatedRecovery.m`. Similar as for the domain model reduction, the file `diffs.mat` comprises the structs `diffs` and `diffnames`, which provide the indices of the employed differences and the corresponding post-fix of the model. For example, the model accounting for the differences in parameter with index 1 ($k_{00 \rightarrow 01}$) has the post-fix 1. The overall result file then is given by `forwSel_` + the name of the domain model + `_untr_rec_diff` + the post-fix.

References

- Fröhlich, F., Kaltenbacher, B., Theis, F. J., and Hasenauer, J. (2017). Scalable parameter estimation for genome-scale biochemical reaction networks. *PLoS Comput. Biol.*, 13(1):e1005331.
- Loos, C., Krause, S., and Hasenauer, J. (2018). Hierarchical optimization for the efficient parametrization of ODE models. *Bioinformatics*, 34(24):4266–4273.
- Maier, C., Loos, C., and Hasenauer, J. (2017). Robust parameter estimation for dynamical systems from outlier-corrupted data. *Bioinformatics*, 33(5):718–725.

Stapor, P., Weindl, D., Ballnus, B., Hug, S., Loos, C., Fiedler, A., Krause, S., Hross, S., Fröhlich, F., and Hasenauer, J. (2018). PESTO: Parameter ESTimation TOolbox. *Bioinformatics*, 34(4):705–707.