Dynamics on free energy landscapes via relaxation of large kinetic transition networks

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The grouping problem

Energy landscapes studies are performed in three consecutive steps:
1. **Partitioning** of configuration space into cells corresponding to Markov states (usually basins of local minima, [EL])
2. **Construction of the rate matrix** for the master equation [ME] (most conveniently using transition state theory [TST] with harmonic superposition approximation; traditionally by Markov state modeling [MSM] with some treatment of the embedding problem [EMB], more accurately by discrete relaxation path sampling [DRPS])
3. **Extracting observables** from the rate matrix (commonly [DPS] by regrouping of states [RGRP] and a graph transformation [NGT])

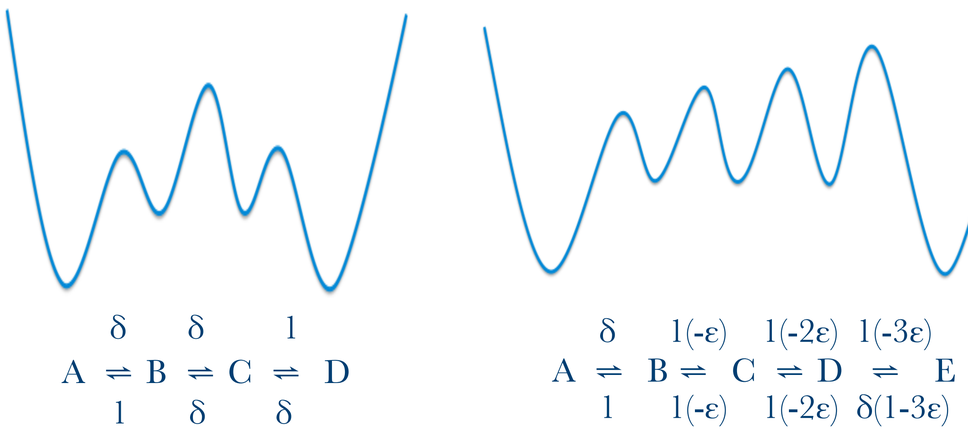
The characteristic properties of the **rate matrices** are
1. **Size**: often of order $>10^5$
2. **Condition number**: very large [SaW]
3. **Sparseness**: the number of relevant transition states is usually about twice the number of the relevant minima

There are two distinct issues of the grouping problem
1. **Calculation problem**: How to efficiently and accurately calculate the rates for the transitions between observables from the rate matrix?
2. **Grouping problem**: How to identify groups of states forming metastable sets, so that a particle stays a long time withing the group before transitioning into another group? This (clustering) problem is also studied in machine learning community [ML].

We propose solutions to both problems
1. **Relaxation approach for extracting observables**, inspired by DRPS
2. A **relaxed recursive regrouping [RRR]**, which is an inproved version of a similar algorithm ("REGROUPFREE" [RGRP]) previously developed in our laboratory.

Breakdown of TST

For pathological cases, flux-based expressions for rates will give nonsensical results



Boundaries between experimentally observed states (defined by a macroscopic quantity, e.g. FRET intensity) rarely coincide exactly with optimal transition states between superbasins. Hence REGROUPFREE will heavily, depend on a regrouping threshold used, making interpretation of results more difficult.

The recursive REGROUPFREE algorithm will also neglect diffusion-like repetitive transitions, which significantly reduce the overall rates.

Relaxation approach

Let us study a system given by a rate matrix of order n with eigenvalues λ_0 .. λ_{n-1}, and eigenvectors ϕ_0 .. ϕ_{n-1}. Using eigenvalue decomposition of the rate matrix the flux expression can be rewritten as (c_i denotes overlap of ϕ_i with state A)

$$k_{BA}^{\mathrm{TST}} = \frac{\partial_t P_A(t)}{P_A(t)}|_{\mathrm{eq}} = -\sum_{i=0}^{n-1} \lambda_i c_i \sum_{a\in A} \phi_{ia}$$

It can be also easily shown that the rate constant based on integration of the **relaxation time** for transition from A in equilibrium to equilibrium between A and B is

$$k_{BA}^{\mathrm{rxn}} = -\frac{(P_B^{\mathrm{eq}})^2}{\sum_{i=1}^{n-1} \frac{c_i}{\lambda_i} \sum_{a\in A} \phi_{ia}}$$

This result is equal to the result previously found by Hummer and Szabo [EXCT].

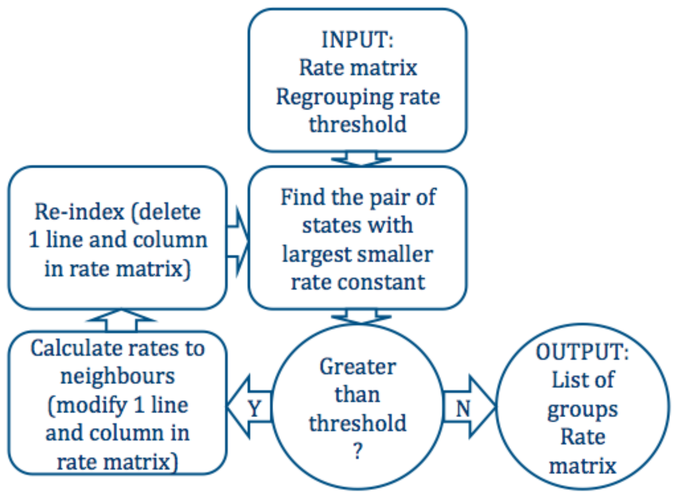
Relaxing algorithm

Since eigenvalue (or singular value) decomposition of rate matrices is very inaccurate due to poor conditioning and expensive due to matrix size, we propose a **numerically stable and cheaper algorithm** for calculating relaxation times. The algorithm is a combination of a linear propagation of population

$$p_i(m\Delta t) = \sum_{j=1}^{n} t_{ij}(\Delta t) p_i[(m-1)\Delta t]$$

(where population in state i at time $m\ \Delta t$, where m is an integer, and $t_{ij}(\Delta t)$ is an element of the transition matrix) and a multiplication of a transition matrix by itself corresponding to doubling the timescale described by the transition matrix. Arbitrarily long timescales can be reliably reached

Relaxed recursive regrouping



Boundary conditions

When extracting a pair of grouped states from the whole matrix, proper boundary conditions must be imposed at the interface between relaxing states and the neighbours:
1. **no-flux boundary conditions**: transitions between relaxing states and neighbours that are not involved in relaxation are disregarded completely = lower bound for the rate.
2. **fast-equilibration boundary conditions**: rates to the neighbours speed up equilibration within relaxing states = upper bound for the rate.

Conclusion

1. We have developed a successful method for calculating rates between grouped states.
2. We have devised a numerically accurate algorithm for relaxation.
3. By imposing different conditions, we can determine the interval for the exact value.
4. We have developed a recursive algorithm scaling almost linearly with size of the studied sparse rate matrix.

References

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